Acute Bacterial and Viral Meningitis

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ABSTRACT

Purpose of Review: Most cases of acute meningitis are infectious and result from a potentially wide range of bacterial and viral pathogens. The organized approach to the patient with suspected meningitis enables the prompt administration of antibiotics, possibly corticosteroids, and diagnostic testing with neuroimaging and spinal fluid analysis.

Recent Findings: Acute meningitis is infectious in most cases and caused by a potentially wide range of bacterial and viral pathogens. Shifts in the epidemiology of bacterial pathogens have been influenced by changes in vaccines and their implementation. Seasonal and environmental changes influence the likely viral and rickettsial pathogens.

Summary: The organized approach to the patient with suspected meningitis enables the prompt administration of antibiotics, possibly corticosteroids, and diagnostic testing with neuroimaging and spinal fluid analysis. Pertinent testing and treatment can vary with the clinical presentation, season, and possible exposures. This article reviews the epidemiology, clinical presentation, diagnosis, and treatment of acute meningitis.

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OVERVIEW

Meningitis is a syndrome of fever, headache, and meningismus with inflammation in the subarachnoid space as evidenced by CSF pleocytosis. The time to presentation (acute, subacute, or chronic) and tempo of the illness differ based on the etiology and guide appropriate initial management and treatment. Acute meningitis usually presents within hours to days, whereas chronic meningitis is by definition longer than 4 weeks in duration. Acute meningitis is often infectious with a bacterial or viral cause, with noninfectious etiologies in the differential diagnosis. Despite the widespread availability of effective therapy, the morbidity and mortality of bacterial meningitis remain substantial, which emphasizes the importance of prompt recognition and management of potential cases.

Acute bacterial meningitis affects all ages and was mostly a pediatric disease until the success of the *Haemophilus influenzae* type b vaccine (HIB). Now most cases occur in young and older adults. The most common organisms from the community are *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria monocytogenes*, group B streptococci, and *H. influenzae*. The age, immune status, and predisposing and associated conditions predict the etiologic agent and choice for appropriate initial treatment. Initially, the treatment is broad, with the goal of determining the causative organism for specific therapy.

Viral meningitis outnumbers meningitis of all other causes in the United States.[1] Viral meningitis is caused by predominantly a few viral groups with neurotropism; often enteroviruses, herpes

KEY POINT

■ The average age of the patient with meningitis is 41.9 years.

viruses, arboviruses, or HIV; and rarely mumps. Typically, a CSF pleocytosis with a lymphocytic predominance is present, and bacterial cultures are negative. The broad term "aseptic" is entrenched in the literature to describe these cases but is misleading if the cause is truly infectious.

TABLE 1-1 Empiric Therapy for Acute Meningitis Syndrome

Source or Syndrome	Common Pathogens	Suggested Empiric Therapy[a]
Community Acquired		
Adult or child	*Streptococcus pneumoniae* *Neisseria meningitidis* *Listeria monocytogenes* *Haemophilus influenzae*	Vancomycin + ceftriaxone
Neonate	Group B streptococcus *L. monocytogenes* *S. pneumoniae*	Ampicillin + cefotaxime or aminoglycoside
Immunocompromised (eg, patients with HIV, asplenia, alcoholism, or cancer, or patients older than 60 years)	*S. pneumoniae* *L. monocytogenes* Aerobic gram-negative bacilli (eg, Enterobacteriaceae family)	Vancomycin + ampicillin + extended-spectrum cephalosporin
Adjunctive therapy (community-acquired disease unless contraindicated)		Dexamethasone (before or with first dose of antibiotics)
Identified Focus of Infection		
Maxillary sinusitis or otitis	*Streptococcus* species Gram-negative bacilli *Staphylococcus aureus* *Haemophilus* species	Vancomycin + metronidazole + extended-spectrum cephalosporin
Endocarditis	*Viridians streptococcus* *S. aureus Streptococcus bovis* HACEK group Enterococci	Vancomycin + extended-spectrum cephalosporin
Nosocomial	Gram-negative bacilli Staphylococci species	Vancomycin + extended-spectrum cephalosporin
Penetrating trauma or recent neurosurgical procedure (eg, shunt)	*S. aureus* and other species (especially MRSA) Enterobacteriaceae family *Pseudomonas* species	Vancomycin + metronidazole + extended-spectrum cephalosporin or Vancomycin + meropenem
Encephalitis (eg, seizures, obtundation)	Herpes family (especially herpesvirus type 1)	Acyclovir

HACEK = *Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens*, and *Kingella kingae*; MRSA = methicillin-resistant *Staphylococcus aureus*.

Autoimmune disease (eg, systemic lupus erythematosus), toxic causes (eg, IV immunoglobulin), and cancer (eg, lymphocytic carcinomatosis or paraneoplastic disease) may result in a meningitis syndrome and are more appropriately called ''aseptic.''

The initial management of a patient with suspected meningitis includes blood cultures and antibiotic therapy. Empiric therapy is similar for most patients with community-acquired meningitis with some additional considerations. The most common pathogen, *S. pneumoniae* (pneumococcus), is presumed to be resistant to penicillins. Therefore, vancomycin and ceftriaxone are initial therapy (**Table 1-1**). Based on the patient's age and other host factors, additional antibiotics may be used, as is discussed in more detail below. In addition, corticosteroids should be considered in all patients with acute meningitis presenting from the community setting. The clinical microbiology and epidemiology dictate the other decisions for these patients.

EPIDEMIOLOGY AND ETIOLOGIES OF ACUTE MENINGITIS

The incidence of bacterial meningitis has declined during the past decades, but the mortality of the disease remains high at up to 9.4% for children and approximately 20% or higher in adults, depending on organism and immune status of the patient (**Table 1-2**).[2] An understanding of the epidemiology is necessary to initiate proper empiric therapy. Neurologists are often the consultant contributing to the care in the emergency department or hospital and can suggest an improvement in therapy, proper isolation, prophylaxis of contacts when required, and anticipation and management of the neurologic complications.

KEY POINT

- Empiric antibiotic therapy for suspected bacterial meningitis presumes the cause is penicillin-resistant pneumococcus.

TABLE 1-2 Common Bacterial Meningitis Organisms

Organism	Age	Risk Factors	Proportion of Cases	Case Fatality
Streptococcus pneumoniae	All ages	Immunoglobulin alternative complement deficiency, asplenia, alcoholism	57%	17.9%; higher if immunocompromised
Neisseria meningitidis	Aged 11 to 17 years and younger adults	Multiperson dwellings, travel to sub-Saharan Africa	17% (45% aged 11 to 17 years)	10%
Listeria monocytogenes	Neonates and adults	Cell-mediated immunodeficiencies (eg, steroids, HIV, alcoholism), newborns	4%	18%
Haemophilus influenzae	Children and adults	Newborns	6%	7%
Group B streptococcus	Neonates	86% of cases are in patients aged <2 months	17%	11%
Gram-negative rods (eg, *Escherichia coli*, Klebsiella)	Adults	Nosocomial infection; only 3% from community	33% of all nosocomial meningitis	35% nosocomial; 25% community acquired

S. pneumoniae (pneumococcus) is the most common causative organism of meningitis, responsible for more than half of all cases in all ages except infants younger than 2 months.[2] The risk of clinical disease and mortality from meningitis is increased with immunoglobulin deficiency, sickle cell disease, alcoholism, diabetes, and CSF leaks, and one of these predisposing conditions is present in about one-third of cases.[3] Most adults carry *S. pneumoniae* in the nasopharynx. Dozens of strains have been identified, and not all are prevented by the conjugated vaccine. Over half of patients will have sinusitis or pneumonia at presentation. Meningitis due to vaccine serotypes has declined by 92%, but an increase in nonvaccine strains has limited the potential reduction in pneumococcal cases to 26% over an 8-year period.[2] Newer vaccines provide protection for more serotypes and may potentially impact the disease burden further (**Case 1-1**).

Meningococcus (*N. meningitidis*) is responsible for a large proportion of

Case 1-1

A 60-year-old woman was brought to the emergency department by ambulance. The day before, she had presented to a different emergency department with a ''cold'' and ear pain, and eardrops and analgesics were prescribed. She stayed home from work the next day and later that day was found obtunded by her family. She was awake but not talking or following commands. Her temperature was 40°C (104°F), and she resisted movement of her neck. Erythema and blood were present in her right external ear canal. Ceftriaxone, vancomycin, ampicillin, metronidazole, acyclovir, and dexamethasone 10 mg IV were given. CT scan showed chronic mastoid changes on the right with opacified air cells but no abscess or focal brain lesions. MRI done later showed the same. Lumbar puncture opening pressure was 42 cm H_2O with pleocytosis of 29,310 cells/mL^3 (86% polymorphonuclear [PMN], 4% lymphocytes); laboratory testing values were glucose 9 mg/dL and protein 373 mg/dL. CSF Gram's stain and cultures were negative. Blood cultures grew *S. pneumoniae* that was pansensitive. Ceftriaxone was continued, and all other antimicrobial agents were discontinued once the results of antimicrobial sensitivity testing demonstrated the organism to be pansensitive. Dexamethasone was continued for 4 days. A myringotomy was performed with tube placement in the right ear. The patient improved significantly by day 5 and by day 7 was able to go home with continued IV antibiotics for a total of 14 days. Pneumococcal vaccine, which the patient had not received previously, was given.

Comment. The clinical presentation emphasizes how quickly meningitis can present and that the physical examination focuses on infection. The empiric antimicrobial therapy must be broad, with an understanding that outcome can be improved with the addition of dexamethasone in such patients. The added value of blood cultures allowed for a more simplified course of therapy. Although overall mortality is close to 20%, good outcomes are more likely with prompt, appropriate care. The patient's host immune response will provide future protection against the pneumococcal strain that caused her meningitis, whereas the pneumococcal vaccine protects against many strains to prevent invasive disease in the future.

meningitis cases in adolescents and young adults, nearly equal to pneumococcus, and together these two organisms account for greater than 90% of disease in this age group.[2] *N. meningitidis* also colonizes the nasopharynx and in many patients causes invasive disease shortly after this occurs. Because of this risk, every patient with meningitis should be placed on droplet and contact isolation that can be discontinued if the organism is not *N. meningitidis*.[4] Since invasive disease often occurs in those who are newly colonized, prophylaxis is given to all household, intimate, and other contacts who were directly exposed to patient droplet secretions. For adults, rifampin is preferred at 600 mg every 12 hours for 2 days. Neonates and children younger than 2 years old can be given IM ceftriaxone (125 mg).[4] The Advisory Committee on Immunization Practices since 2005 has recommended the routine vaccination of all adolescents at age 11 to 12 years, and in 2010 added a booster for all adolescents at age 16.

HIB, once the commonest cause of meningitis at nearly 100 cases per 100,000 in young children, has been reduced by over 90% since the implementation of the HIB vaccine.[2,5] In adults and some nonimmunized pediatric cases, *H. influenzae* still accounts for 5% to 7% of bacterial meningitis.

L. monocytogenes is ubiquitous, but outbreaks are often food-borne. Most patients have a preexisting cell-mediated immunity defect, but up to one-third of cases are otherwise healthy. Risk is also increased in third-trimester pregnancy and in newborns. Clinically, a prodromal illness that is seemingly viral or mononucleosislike may present for a few days prior to neuroinvasive disease (**Case 1-2**).

Group B streptococcus (*Streptococcus agalactiae*), like *Listeria*, has the risk of maternal-fetal transmission due to colonization of the female urogenital tract. Transmission occurs via personal contact, and adults might otherwise acquire the disease as well.

Gram-negative rods (mostly *Escherichia coli* and *Klebsiella species*) represent only 3% of meningitis cases from the community but are responsible for 33% of nosocomial cases. Broader therapy to better cover gram-negative organisms, including *Pseudomonas aeruginosa*, is necessary with either ceftazidime or meropenem.

In addition to the epidemiology discussed above, a clinical focus of infection elsewhere in the body can influence the likely pathogen causing the meningitis and therefore alter the choice for empiric therapy. Frontal and maxillary sinusitis or otomastoiditis predisposes to meningitis because of the anatomic proximity to the subarachnoid space, and these pathogens may be anaerobic. Penetrating trauma or neurosurgical procedures obviously breach protective barriers predisposing to infection by skin organisms as well as anaerobes. Broadening of the empiric regimen to include metronidazole with ceftazidime or meropenem is important (**Table 1-1**).

While it is appropriate to emphasize the management of bacterial meningitis, most cases of meningitis are viral with enteroviruses accounting for most. Other neurotropic viruses, such as herpesviruses and arboviruses, occur less frequently. The neurotropic viruses may also cause parenchymal infection resulting in encephalitis, myelitis, or encephalomyelitis and overlap with meningitis. With the exception of the herpes family viruses, specific treatments for viral meningitis are not available, but proper diagnosis is still of clinical value. The identification of a particular cause provides certainty, limits other diagnostic testing, and lessens concerns about potential carcinomatous meningitis. Furthermore, a defined etiology improves the

KEY POINTS

- With meningococcal meningitis, rifampin prophylaxis, 600 mg twice a day for 2 days, should be given to household contacts and those with direct exposure to droplet secretions.
- Immunocompromised states are frequently present in patients who have meningitis due to pneumococcus or *Listeria*.
- One-third of nosocomial meningitis cases are gram-negative rods and require empiric coverage with meropenem or ceftazidime.

KEY POINT

■ Viral meningitis is most often caused by enterovirus and more common in the summer months.

Case 1-2

A 43-year-old woman was brought to the emergency department after a few days of fever at home. The patient's daughter had called the paramedics because of the patient's confusion and inability to respond to questions that morning. The patient had not been feeling well and had headache, body aches, and fever the previous 2 days, self-treated with ibuprofen. Her only other history was HIV infection on antiretroviral therapy with a CD4 count of 250 cells/mL and undetectable viral load. She lived in an urban apartment with her daughter, had not traveled, and had no pets. On examination, she was febrile (temperature 38.4°C [101.2°F]) and awake but unable to follow commands or respond purposefully. She was flushed, and her neck was unable to be flexed. In the emergency department, antibiotic therapy with vancomycin and ceftriaxone was initiated. Ampicillin and acyclovir were added 15 minutes later, but corticosteroids were not given. A CT head scan showed mild ventriculomegaly. Lumbar puncture showed an opening pressure of 28 cm H_2O, a CSF pleocytosis of 443 cells/mL^3 (63% PMNs, 31% lymphocytes, 6% monocytes), glucose concentration of 30 mg/dL, and protein concentration of 113 mg/dL. The Gram's stain showed gram-positive rods with culture positive 2 days later for *L. monocytogenes*. Targeted therapy with ampicillin was continued. Her hospital course was complicated by low serum sodium from syndrome of inappropriate antidiuretic hormone that resolved, and she improved over several days.

Comment. The presentation with profound nuchal rigidity supports a diagnosis of acute bacterial meningitis, but with the patient's obtunded state the diagnosis is really a meningoencephalitis and appropriately raises concern for another process with mass effect, such as abscess, subdural empyema, or focal brain lesion in the context of HIV infection. Thus a CT head scan is performed prior to the lumbar puncture. Antibiotics were started promptly, but with the HIV history, ampicillin should have been given as part of the initial regimen. Acyclovir is appropriate given the obtundation. The CSF profile predicts bacterial meningitis (the glucose alone is greater than 99% predictive) with the mixed pleocytosis potentially misleading, but this is often seen with *L. monocytogenes*, as the Gram's stain demonstrates. With this result, the antibiotic therapy is focused. The decision to forgo steroids until the CT is done is appropriate given the HIV. The benefit of corticosteroids has not been demonstrated when given after antibiotic therapy is initiated. Dexamethasone would also have been acceptable in this case. The CD4 count being greater than 200 cells/mL significantly reduces the odds of opportunistic CNS infection.

public health understanding regarding what agents are causing disease in the area so that preventive interventions can be implemented and health care providers notified (**Table 1-3**).

Enteroviruses are the most common cause of viral meningitis and responsible for approximately 60% of all cases. Enterovirus is a large group of over 70 human viruses that replicate within the gastrointestinal tract and can cause neurologic disease. A few subgroups, including poliovirus, coxsackievirus, echovirus, and numbered enteroviruses, each have at least three or more than 30 serotypes, although 15 of these account for more than 80% of the isolates in the United States. Encephalitis, myelitis,

TABLE 1-3 Viral and Other Culture-Negative (Aseptic) Meningitis

Virus	Other Infections	Toxic or Idiopathic
Enteroviruses	Rickettsial disease (eg, Rocky Mountain spotted fever, ehrlichiosis, anaplasmosis)	Nonsteroidal anti-inflammatories, IV immunoglobulin, muromonab-CD3 (OKT3)
Arboviruses (eg, West Nile virus, St Louis encephalitis virus, dengue virus)	Lyme disease (*Borrelia burgdorferi*)	Subarachnoid hemorrhage
Herpesviruses (eg, herpesvirus types 1 and 2, varicella-zoster virus, Epstein-Barr virus)	Syphilis (*Treponemapallidum*)	Systemic autoimmune disease (eg, sarcoidosis, Behçet disease, systemic lupus erythematosus)
HIV	Leptospirosis	Carcinomatous/ lymphomatous meningitis
Lymphocytic choriomeningitis (hamster and mice exposure)	Psittacosis (bird exposure)	Paraneoplastic or autoimmune (eg, *N*-methyl-D-aspartate receptor)
Mumps	Mycobacterial (tuberculosis)	Dermoid cyst
Measles	Fungal meningitis	Kawasaki disease

and poliomyelitis may occur, but meningitis is by far the most common manifestation of these viruses. Transmitted by contact, these nonenveloped viruses are not easily disrupted with hand washing and can survive on moist surfaces. Transmission is usually fecal-oral and less often respiratory. Year-round cases can occur with a seasonal increase in viral spread and activity in the mid- to late-summer months, causing the number of cases to increase severalfold.

Arboviruses (arthropod borne) are distributed among several families and grouped together because they rely on arthropod vectors to amplify the disease among animal reservoirs in a particular environment (geographically restricted). Humans are not part of the life and amplification cycle and are a ''dead-end host'' if infected by the mosquito or tick. Only a few arboviruses are established in the United States, with the most common being the most recent to arrive, the West Nile virus (WNV). Japanese encephalitis virus and St Louis encephalitis virus are in the same family (Flaviviridae). Prior to the arrival of WNV in 1999, St Louis encephalitis virus was known to cause sporadic cases with occasional epidemic years. In most parts of the United States, disease onset occurs in the mid- to late-summer months because of the activity of the *Culex* mosquito vector until the first hard frost. If infected by a mosquito with WNV, the most common result is asymptomatic infection or transient and mild febrile illness in about 20% of patients. Less than 1% will develop more significant neuroinvasive disease consisting of meningitis, encephalitis, or focal weakness with flaccid paralysis (poliomyelitislike). Meningitis

KEY POINTS

- Genital herpes from herpes simplex virus type 2 can cause meningitis during acute infection and a recurrent lymphocytic meningitis.
- Exposure to hamsters or mice is an important clue to meningitis caused by lymphocytic choriomeningitis virus.

without encephalitis or flaccid paralysis occurs in about 15% of cases. Diagnosis is made by acute and convalescent titers of serum and CSF, with testing provided by state health departments and some commercial laboratories.

HIV is a chronic viral infection, mostly asymptomatic until immunosuppression occurs. At the time of acute HIV infection, a systemic viral illness consisting of pharyngitis, headache, fever, and myalgias that may include meningitis may occur. Approximately 5% to 10% of patients with acute HIV infection may have aseptic meningitis.[6] This can also occur in patients with HIV who interrupt their antiretroviral therapy as HIV replication recurs. Standard ELISA and Western blot analysis for HIV infection detects serum antibodies that may not yet be present in acute infection. Therefore, HIV-RNA (viral load) will demonstrate the presence of virus prior to antibody positivity.

Herpes family viruses, which are neuroinvasive and neurotropic, cause several recognizable syndromes. The most devastating is encephalitis with herpes simplex virus type 1 (HSV1), which causes significant morbidity and mortality even with prompt use of IV acyclovir 10 mg/kg every 8 hours. The presentation of herpes encephalitis may mimic acute bacterial meningoencephalitis, and, if alteration of mental state is present, both entities should be empirically treated with acyclovir until CSF and additional studies allow a narrower differential diagnosis.

Herpes simplex virus type 2 (HSV2) is the primary cause of genital herpes (less often it is HSV1), and at the time of initial genital infection about 33% of women and 11% of men develop a meningitis syndrome.[1] After initial infection, benign recurrent lymphocytic meningitis (also known as Mollaret meningitis) can occur with intermittent reactivation. CSF testing with PCRs for HSV1 and HSV2 should be done to establish the etiologic diagnosis. Patients are prone to recurrent attacks, which can be shortened by treatment with oral antivirals such as valacyclovir (1000 mg orally 2 times daily) or famciclovir (500 mg orally 3 times daily). If recurrences are frequent, one can consider suppressive therapy. Acyclovir can be used, but compliance is difficult because of the need for 5-times-a-day dosing.

Primary infection with varicella-zoster virus (chickenpox), Epstein-Barr virus (mononucleosis), or human herpesvirus type 6 (roseola) may rarely be associated with meningitis during the acute syndrome and is typically self-limited. Diagnosis is based on clinical presentation, and PCR identification of the virus in the CSF may be useful. A more common scenario occurs when patients with shingles report concomitant headache or neck stiffness and a lumbar puncture shows lymphocytic pleocytosis. Treatment should not differ for shingles provided the patient is clinically without signs of altered mentation. Immunocompromised patients are at risk for more widespread viral dissemination, and if clinical signs dictate, IV therapy with acyclovir is reasonable.

Mumps virus was a significant cause of meningitis prior to vaccination programs. The vaccine is protective, but imperfectly so, and smaller outbreaks still occur even among vaccinated individuals. Virtually all patients with mumps virus have respiratory symptoms with headache; about 50% have parotitis with mumps (the other 50% may not have this finding); 10% have meningitis; but over 50% have pleocytosis if CSF is examined. The CSF abnormalities may persist for months. Given these statistics, the clinical suspicion for mumps will greatly improve recognition of the diagnosis, which is made with viral culture and acute and convalescent antibodies for IgM and IgG.

Lymphocytic choriomeningitis virus is uncommon, and human disease is

acquired from direct contact with excrement of virus-infected mice or hamsters. The meningitis can be long-lived and only rarely is fatal.

The list of potential mimics of viral or aseptic meningitis is lengthy; a partial list is shown in **Table 1-3**. Of note, so-called toxic meningitis, due to agents such as muromonab-CD3 (OKT3), IV immunoglobulin, or carbamazepine, is typically PMN at onset but without significant glucose abnormalities. Lymphomatous or carcinomatous meningitis can have very low glucose concentrations, similar to bacterial meningitis.

Rickettsia are technically small pleomorphic bacteria but are obligate intracellular pathogens (like viruses and *Listeria*), rely on vectors to disseminate (like arboviruses), and produce a clinical syndrome more similar to a viral infection. Rickettsial diseases (eg, Rocky Mountain spotted fever [RMSF], ehrlichiosis, and anaplasmosis) are transmitted by a painless tick bite in the endemic areas, particularly in warmer months when tick vectors are active. A maculopapular rash is frequently present with RMSF, but only after 2 to 4 days of illness, and rash is infrequent with the others. Clues to infection with *Ehrlichia* and *Anaplasma* are leukopenia, thrombocytopenia with peripheral neutrophilic response, bandemia, and transaminase elevations. Fevers, myalgias, headache, nausea, and vomiting are common. When meningitis occurs, the pleocytosis can be PMN or lymphocytic predominant. The case fatality rate can be as high as 10% with RMSF. Treatment is initiated with doxycycline or chloramphenicol. **Case 1-3** illustrates this use of empiric doxycycline.

CLINICAL PRESENTATION AND EVALUATIONS

The classic triad of acute meningitis includes fever, neck stiffness, and altered mental status. These three findings at presentation are found in only 44% of patients, although at least two of the four findings of headache, fever, stiff neck, or altered mentation are seen in 95%.[7] An altered level of consciousness is present in two-thirds of patients with bacterial meningitis and is absent in patients with viral meningitis unless coincident encephalitis is present. The absence of nuchal rigidity, Kernig sign, and Brudzinski sign should never be used to exclude the possibility of meningitis.[8] The headache may improve following the initial lumbar puncture regardless of etiology. The headache associated with viral meningitis can be profound and associated with nausea and emesis. Often, opioid analgesics are required to control the pain and may be the primary reason for continued hospitalization.

Lethargy or obtundation is common with acute bacterial meningitis, with up to 20% of patients developing coma, and is more likely with pneumococcal than meningococcal meningitis. Viral etiologies will rarely depress the level of consciousness, but the patient can look ill.

Children are more likely to have a defined syndrome of otitis and upper respiratory tract infection prior to the onset of meningitis. Viral meningitis often follows a few days of a febrile illness and myalgias (primary viremia), which precede the CNS manifestations of the disease. Gastrointestinal upset may be present, with or without diarrhea, with both enteroviruses and arboviruses; therefore, the presence of these symptoms does not differentiate the etiology.

Seizures will occur in about 20% of patients with bacterial meningitis and are associated with a worse prognosis. The clinical presentation of fever, altered mental status, and seizures is typical of herpes simplex virus encephalitis, and acyclovir should be initiated and continued until another etiology is discovered.

KEY POINTS

- Hypoglycorrhachia may be present in lymphomatous meningitis, raising concern for a bacterial infection.
- An altered level of consciousness is common in the course of bacterial meningitis and does not occur in viral meningitis.

Case 1-3

A 38-year-old woman presented in August to her primary doctor for severe headache and malaise of a few days' duration that were not improving. The headache was associated with photophobia and became worse with standing. She also had malaise, anorexia, mild nuchal rigidity, and a temperature of 37.8°C (100°F), with no other symptoms or findings. Her 2-year-old child at home had also been sick recently. They had three pet birds, one of which died 3 months prior. The family had just returned from a vacation in North Carolina, where they walked through grassy areas to get to and from the beach. The patient appeared ill and was sent to the emergency department because of a concern of meningitis. Ceftriaxone and vancomycin were given, and a CT scan was normal. Lumbar puncture revealed a normal opening pressure and CSF had a pleocytosis of 8 cells/μL (88% PMN, 8% lymphocytes), glucose concentration of 55 mg/dL, and protein concentration of 32 mg/dL. The next day the patient appeared sicker, and doxycycline 100 mg IV twice daily was added. Repeat CSF testing now showed a pleocytosis of 443 cells/μL (14% PMN, 85% lymphocytes), glucose concentration of 53 mg/dL, and protein concentration of 47 mg/dL. Based on the repeat CSF differential and negative CSF cultures after 48 hours, antibiotics for bacterial meningitis were stopped. Serologies for RMSF and Lyme antibodies were normal. An arboviral panel (ie, tests for WNV, systemic lupus erythematosus, St Louis encephalitis, eastern equine encephalitis) was sent on blood and CSF cultures to the state laboratory and was negative. CSF testing for reverse-transcriptase PCR for enteroviruses was positive, although type-specific acute and convalescent titers were not done. Doxycycline was stopped once the reverse-transcriptase PCR for enteroviruses was positive and Lyme titers were negative. The patient improved during the next few days and was able to return to home and work the following week.

Comment. The time of year and clinical presentation in an otherwise healthy woman suggest a viral cause in this case. The management by her primary physician and emergency department was excellent in presuming bacterial meningitis. Her ill appearance and CSF PMN-predominant pleocytosis created concern despite the relatively low number of cells and normal glucose concentration. This case illustrates the value of repeat lumbar puncture because it allowed for more specific therapy and discontinuation of IV antibiotics. Based on the travel history, doxycycline for RMSF was prescribed, which also covers psittacosis that may have been contracted from the pet birds.

The presence of a rash may be a clue to the etiology of meningitis. A viral exanthem can be seen with enteroviruses and less often with flaviviruses, such as WNV. Enteroviruses might cause a more telling rash of hand, foot, and mouth disease. Hemorrhagic purpura is practically diagnostic of meningococcemia (with or without meningitis) but can be seen with pneumococcus.

The prompt administration of antibiotics is important; delay is associated with a worse outcome and increased odds of death.[9,10] An organism-specific diagnosis is also important, and delay in performing the lumbar puncture reduces the likelihood of a positive CSF culture.[11] To lessen this trade-off, a sense of urgency to expedite the needed evaluations can help to increase the

diagnostic yield and arrive at a more specific diagnosis more rapidly. Blood cultures should be obtained quickly, prior to antibiotic administration, and will be positive in approximately 50% or more of cases, with some variability based on organism.[12] **Case 1-1** emphasizes the importance of blood cultures.

Neuroimaging should be performed, but the decision of when to do it relies on the presence of clinical criteria. In a pure meningitis syndrome (inflammation limited to the subarachnoid space), or if a ''communicating'' hydrocephalus is present, lumbar puncture does not pose a risk. Meningitis can cause or be associated with brain shift when associated with space-occupying lesions (eg, brain abscess, subdural empyema, stroke, subdural effusion), cerebral edema, or effacement (eg, vasogenic and cytotoxic edema). A rate of complication of brain herniation is often quoted at approximately 1% and as high as 6% in infants and children.[13] Abnormal CT scans were found in 56 of 301 (24%) subjects in a prospective study and were associated with age older than 60 years, immunocompromised states, recent seizure, focal neurologic deficits, or inability to follow two consecutive commands or questions correctly. The absence of these findings had a negative predictive value of 97%, and such patients are deemed safe for lumbar puncture prior to CT.[14]

Lumbar puncture typically finds an elevated opening pressure (greater than 18 cm H_2O), and pressures greater than 40 cm H_2O are more likely to be found in comatose patients with bacterial meningitis. PMN pleocytosis, hypoglycorrhachia, and elevated protein concentrations typify the CSF abnormalities in a bacterial infection. In contrast, viral meningitis has milder abnormalities of protein and glucose concentrations and a mononuclear pleocytosis of usually 100 cells/μL to 1000 cells/μL, although PMNs may predominate in 40% of cases particularly early in the course.[1,15] Contrariwise, approximately 10% of bacterial meningitis cases may have a mononuclear predominance. Differentiating reliably between the two can be challenging, especially with a mixed pleocytosis, as often occurs with *Listeria*.[12] CSF findings that independently predict bacterial meningitis in a suspected patient are a CSF to serum glucose ratio of less than .23 or CSF glucose concentration less than 34 mg/dL, a CSF protein concentration greater than 220 mg/dL, a pleocytosis greater than 2000 cells/μL, or PMNs in CSF greater than 1180 cells/μL.[15] These findings are not altered significantly by pretreatment with antibiotics, although the yield on Gram stain was reduced by 16% (**Table 1-4** and **Table 1-5**).

Gram's stain is reported to be positive in 60% to 90% of cases (with 97% specificity) and is proportional to the concentration of organisms in the sample. With greater than 10^5 colony-forming units (CFUs)/mL, 97% of stains are positive, decreasing to 60% with 10^3 CFUs/mL to 10^5 CFUs/mL; and with less than 10^3 CFUs/mL only 25% of stains will be positive. Culture in bacterial meningitis will provide the identity of the organism in 70% of cases, but when including all cases (eg, viral

TABLE 1-4 CSF Independent Predictors of Bacterial Meningitis With Greater Than 99 Percent Certainty

- Glucose <34 mg/dL
- CSF to serum glucose ratio <0.23
- Protein >220 mg/dL
- Total pleocytosis >2000 cells/μL
- Polymorphonuclear >1180 cells/μL

KEY POINT

- Within hours of antibiotic administration, the yield of bacterial culture falls, but other helpful CSF parameters do not. Blood cultures should be performed prior to antibiotic administration.

KEY POINT

- Serum C-reactive protein and procalcitonin levels can aid in the differentiation of bacterial from viral meningitis.

TABLE 1-5 Tests for Meningitis

▶ **Blood**
Complete blood cell count and differential
Blood cultures (aerobic and anaerobic)
HIV
Rapid plasma reagent
C-reactive protein and procalcitonin
Serum for acute serology (store for paired convalescent sample in 3 to 4 weeks)
Heterophile antibodies (Epstein-Barr virus)[a]
Lyme disease tests: Lyme (*Borrelia burgdorferi*) ELISA and, if positive, confirmatory Western Blot[a]
Rickettsial serologies[a]
▶ **CSF**
Opening pressure
Cell count and differential
Serum and CSF glucose concentration
Protein concentration
Stains: Gram, India ink capsule, acid-fast bacillus
Cultures: aerobic, anaerobic, acid-fast bacillus, fungal
Antibody testing (arboviral)[a]
PCRs: enteroviral, West Nile virus,[a] herpesvirus types 1 and 2
CSF lactate (posttrauma or neurosurgical)

[a] If season, endemic exposure, or context makes diagnosis plausible.

and aseptic) of acute meningitis this value falls to approximately 20%.[10]

Latex agglutination antigen testing is widely available and can identify antigens of common meningitis organisms. Ideally, this would add sensitivity to bacterial culture and reduce the number of cases for which an organism is not identified. However, several studies have examined the added benefit of latex agglutination testing over that of conventional culture and shown its value to be very limited. Many laboratories do not routinely offer the testing, but when available, it is helpful in cases of partially treated bacterial meningitis.[12]

Broad-range bacterial PCR amplifies the species-specific conserved regions of the gene coding for 16S ribosomal RNA (16SrRNA) of the common bacterial meningitis pathogens. The sensitivities vary based on the organism from 61% to 88% with specificities greater than 95%. Higher concentration of organisms in the sample improves the test performance, but this is also true for Gram stain and culture. PCR may be beneficial for pretreated meningitis and can also provide rapid typing of serotypes of meningococcus, helpful for identifying outbreaks.[12] The clinical usefulness of broad-range bacterial PCR is evolving but may reduce the number of cases for which an organism is not identified.

Serum inflammatory markers that are more elevated in bacterial infection than in viral infection have been examined as a means to differentiate bacterial from viral or aseptic meningitis. C-reactive protein (CRP) is synthesized in the liver within hours in response to bacterial infection. Higher levels are more predictive with a wide range of sensitivities reported. A normal CRP for a patient with acute meningitis has a negative predictive value of 97% and can add confidence to the decision to withhold antibiotics when a viral cause is suspected. Procalcitonin levels increase in severe bacterial infection, and levels greater than 5 μg/L in children and greater than 2 μg/L in adults have sensitivities and specificity above 90%

for bacterial meningitis, although false-negatives have been reported.[13] These serum markers can help to add weight to a bacterial or viral diagnosis in addition to conventional CSF parameters but should not be used alone in the decision to treat with antibiotics.

Suspected meningitis that occurs after neurosurgical intervention or penetrating head trauma is a challenge. The presence of CSF pleocytosis, protein, or blood products can occur because the procedure itself reduces the predictive value of routine CSF findings. Furthermore, up to 50% of such patients have already received antibiotics or steroids at the time of lumbar puncture.[13] In this patient population, elevated CSF lactate levels 4.0 mmol/L or greater improved the sensitivity and specificity beyond that of CSF to blood glucose ratios to 88% and 98%, respectively.[13] However, not all cases have lactate levels this high, and some bacterial meningitis cases would be misdiagnosed using this value alone. An elevated CSF lactate value should prompt empiric antibiotic coverage until culture results are available.

The methods for diagnosis of a viral meningitis etiology are similar across pathogens. Viral PCR in CSF amplifies DNA (or by reverse-transcriptase PCR for RNA viruses). Viral culture can still be used, but compared to PCR, the sensitivities are low. Enteroviral PCR amplifies a conserved part of the genome

TABLE 1-6 Antibiotics and Dosing for Bacterial Meningitis

	Dosing	
Antibiotic	**Adult**	**Child**
Ampicillin	12 g daily divided every 4 h	300 mg/kg divided every 6 h
Cefotaxime	8 g to 12 g divided every 4 to 6 h	225 mg/kg to 300 mg/kg divided every 6 to 8 h
Ceftazidime	6 g divided every 8 h	150 mg/kg divided every 8 h
Ceftriaxone	4 g divided every 12 h	80 mg/kg to 100 mg/kg daily divided every 12 h
Chloramphenicol	4 g to 6 g divided every 6 h	75 mg/kg to 100 mg/kg divided every 6 h
Doxycycline	100 mg every 12 h (also for children >45 kg)	2.2 mg/kg every 12 h (for children <45 kg)
Gentamicin	5 mg/kg divided every 8 h	7.5 mg/kg divided every 8 h
Meropenem	6 g every 8 h	120 mg every 8 h
Metronidazole	2 g divided every 8 h	7.5 mg/kg every 6 h
Nafcillin	9 g to 12 g daily divided every 4 h	200 mg/kg divided every 6 h
Penicillin G	24 million U divided every 4 h	0.3 million U divided every 4 to 6 h
Rifampin	600 mg to 1200 mg every 12 h	10 mg/kg every 12 hours (maximum 600 mg/d)
Trimethoprim/sulfamethoxazole	10 mg/kg to 20 mg/kg divided every 6 to 12 h	5 mg/kg IV every 6 to 8 h
Vancomycin	30 mg/kg to 45 mg/kg daily divided every 8 to 12 hours (monitor peak)	60 mg/kg daily divided every 6 to 8 h

KEY POINT

- Acute and convalescent titers remain the best method for finding the causative virus in many cases. Obtain a sample in the first days of illness to compare with a convalescent titer to be obtained later.

and can identify the presence of an enterovirus but does not specify the subtype. For herpes viruses, the utility of PCR is well established, but, in addition, antibodies against specific viral antigens can be measured.

Acute and convalescent (4 weeks later) antibody titers against particular pathogens are a mainstay and reliable means of making an etiologic diagnosis. Unfortunately, this is underutilized. A fourfold rise of pathogen-specific antibody is evidence of a specific immunologic response to that pathogen. For enteroviruses, acute and convalescent titers can determine the precise subtype of enterovirus. With arboviruses, the state health departments provide this testing and are able to track the epidemiology from year to year. With WNV, the IgM antibody can persist for many months after initial infection; thus, the presence in the serum of antibodies to this virus by itself does not prove disease. It is only the incident development of new serum or CSF IgM or IgG titer (or a fourfold rise in titer) between acute and convalescent samples that proves causality.

TABLE 1-7 Specific Antibiotic Therapy for Common Meningitis Organisms

Organism	Suggested Therapy	Alternative Therapy
Streptococcus pneumoniae		
Penicillin minimum inhibitory concentration (MIC) ≤0.1 μg/mL	Penicillin G or ampicillin	Extended-spectrum cephalosporin, chloramphenicol
Penicillin MIC ≤0.1 μg/mL to 1.0 μg/mL	Extended-spectrum cephalosporin	Meropenem, cefepime
Penicillin MIC ≤2.0 μg/mL	Vancomycin plus third-generation cephalosporin	Extended-spectrum cephalosporin plus moxifloxacin
Neisseria meningitidis		
Penicillin MIC <0.1 μg/mL	Penicillin G or ampicillin	Extended-spectrum cephalosporin, chloramphenicol
Penicillin MIC 0.1 μg/mL to 1.0 μg/mL	Extended-spectrum cephalosporin	Chloramphenicol, meropenem
Haemophilus influenzae		
β-Lactamase negative	Ampicillin	Extended-spectrum cephalosporin, chloramphenicol
β-Lactamase positive	Extended-spectrum cephalosporin	Cefepime, chloramphenicol, aztreonam
Listeria monocytogenes		
	Ampicillin or penicillin G	Trimethoprim/sulfamethoxazole
Streptococcus agalactiae		
	Ampicillin or penicillin G	Extended-spectrum cephalosporin
Staphylococcus aureus		
Methicillin-sensitive	Nafcillin or oxacillin	Vancomycin, meropenem
Methicillin-resistant	Vancomycin	Trimethoprim/sulfamethoxazole, linezolid

HIV testing should be routine, especially for patients presenting with an infectious syndrome. HIV ELISA followed by Western blot analysis for confirmation is commonly done in most clinical laboratories. If acute HIV infection is suspected, HIV-RNA quantitation (eg, viral load) is necessary to demonstrate presence of virus prior to antibody formation. If this is the case, repeat antibody testing to HIV antigens performed weeks later will become positive.

TREATMENT

The initial therapy for acute meningitis should include the empiric antibiotic regimens as discussed above and in **Table 1-1**.

In addition, corticosteroids have been shown to reduce morbidity and mortality related to acute bacterial meningitis in children and also improve functional outcome when compared to placebo in adults.[16,17] These studies have only demonstrated the benefit in higher-income countries. Dexamethasone 10 mg IV at the time of or immediately before the first dose of antibiotics and every 6 hours for a total of 4 days should be given to patients with acute-onset, community-acquired meningitis.[16] This therapy should be discontinued if CSF profile or other information confirms a diagnosis other than acute bacterial meningitis. This was done in **Case 1-1**, but in **Case 1-2**, the presence of HIV infection raised concerns about etiologies other than the usual bacterial meningitis organisms.

If a particular bacterial pathogen is determined, antibiotic treatment can be focused and duration of therapy determined (**Table 1-6** and **Table 1-7**). For meningitis due to *S. pneumonia*, lumbar puncture should be repeated after 48 hours of therapy to determine whether culture is negative, although other parameters will still be abnormal. Duration of therapy is at least 7 days regardless of organism and as long as 3 to 4 weeks for *Listeria*.[13] Longer durations of therapy are generally done for more immunocompromised patients and for those with slow clinical response (**Table 1-8**).

TABLE 1-8 Duration of Therapy for Bacterial Meningitis[a]

Pathogen	Duration (Days)
Neisseria meningitidis	7
Haemophilus influenzae	7
Streptococcus pneumoniae	10 to 14
Streptococcus agalactiae	14 to 21
Gram-negative bacilli[b]	21
Listeria monocytogenes	21 or longer

[a] Data from Tunkel AR, et al, Clin Infect Dis.[13]
[b] For neonates, 2 weeks beyond first negative culture or ≥3 weeks, whichever is longer.

CONCLUSION

The presentation of acute meningitis requires an efficient approach to properly manage the initial treatment and evaluation. The primary concern is addressing the possibility of bacterial infection given the potential for morbidity and death. The epidemiology of acute bacterial meningitis is declining, but this also lessens our experience and familiarity with the disease. Viral causes can be seasonal and are less often associated with morbidity but may cause a severe headache and have a slow recovery period. Understanding the rationale for empiric therapy, the role of corticosteroids, and therapy for acute meningitis can limit the burden of the disease.

KEY POINT

- To limit morbidity and mortality from acute community-acquired meningitis, administer dexamethasone 10 mg IV with or before the first dose of antibiotics. If the diagnosis is confirmed, continue the treatment every 6 hours for the next 4 days.

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