Infectious Disease

Central Nervous System Infections

Meningitis

A positive Gram stain result for bacteria or yeast is seen in only 5% of patients with community-acquired meningitis. Meningitis with a negative Gram stain result is a diagnostic and management challenge because the differential diagnosis includes urgent treatable causes, such as bacterial or fungal meningitis. Bacterial cultures of cerebrospinal fluid (CSF) or blood are needed for antimicrobial sensitivity studies in suspected bacterial meningitis, but results are insufficiently timely to differentiate bacterial from viral meningitis. In situations of clinical uncertainty, rapid diagnostic techniques such as polymerase chain reaction (PCR) for common viruses and arboviral serologies can reduce use of clinically unnecessary cranial imaging or antimicrobial therapy.

Viral Meningitis

Enteroviruses are the most common cause of viral meningitis, usually presenting between May and November in the Western Hemisphere, with symptoms including headache, fever, nuchal rigidity, photophobia, nausea, vomiting, myalgia, pharyngitis, maculopapular rash, and cough. A CSF lymphocytic pleocytosis with normal glucose and mildly elevated protein levels is typical (**Table 1**). Enterovirus PCR confirms the diagnosis. Treatment is supportive with a benign clinical course.

Herpesviruses can cause meningitis year round and include herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6. Of the herpesviruses, HSV-2 is the most common cause of viral meningitis that can sometimes recur (recurrent benign lymphocytic meningitis, also called Mollaret meningitis). The CSF findings resemble enteroviral meningitis. Outcomes for HSV-2 meningitis are generally favorable without requiring acyclovir therapy.

VZV can cause encephalitis, aseptic meningitis, myelitis, and a vasculitis presenting as a stroke. Vesicular lesions clue the diagnosis but may be absent (zoster sine herpete). VZV encephalitis and vasculitis may present with a hemorrhagic CSF. VZV may be detected in the CSF without clinical signs of meningitis or encephalitis, and patients with primary varicella or zoster do not require lumbar puncture (LP) unless they have clinical signs of central nervous system (CNS) involvement. Immunocompromised and older adult patients are at higher risk of VZV meningitis and encephalitis. The diagnosis is confirmed by VZV PCR of the CSF, and therapy is intravenous acyclovir.

TABLE 1. Typical CSF Findings in Patients with Viral and Bacterial Meningitis

CSF Parameter	Viral Meningitis[a]	Bacterial Meningitis
Opening pressure	≤250 mm H_2O	200-500[b] mm H_2O
Leukocyte count	50-1000/μL (50-1000 × 10^6/L)	1000-5000/μL (1000-5000 × 10^6/L)[c]
Leukocyte predominance	Lymphocytes[d]	Neutrophils
Glucose level	>45 mg/dL (2.5 mmol/L)[e]	<40 mg/dL (2.2 mmol/L)[f]
Protein level	<200 mg/dL (2000 mg/L)	100-500 mg/dL (1000-5000 mg/L)
Gram stain	Negative	Positive in 60%-90%[g]
Culture	Negative	Positive in 70%-85%[h]

CSF = cerebrospinal fluid.

[a]Primarily nonpolio enteroviruses (echoviruses and coxsackieviruses) and West Nile virus between June and October; herpes simplex type 2 year round.

[b]Values exceeding 600 mm H_2O suggest the presence of cerebral edema, intracranial suppurative foci, or communicating hydrocephalus.

[c]Range may be <100/μL (100 × 10^6/L) to >10,000/μL (10,000 × 10^6/L).

[d]Neutrophil predominance occurs in 25% of viral meningitis cases, usually early in infection and more likely in young children with enteroviral infection.

[e]A mild hypoglycorrhachia (30-45 mg/dL [1.7-2.5 mmol/L]) can be seen in viral infections such as herpes simplex virus and West Nile virus.

[f]The CSF-to-plasma glucose ratio is ≤0.40 in most patients.

[g]The likelihood of a positive Gram stain correlates with the number of bacteria in the CSF.

[h]The yield of positive results is significantly reduced by previous administration of antimicrobial therapy.

Mosquito-borne viruses such as West Nile virus (WNV), St. Louis encephalitis, and California encephalitis can cause meningitis or encephalitis between June and October in the Western Hemisphere. Neuroinvasive WNV may present with acute flaccid paralysis, potentially leading to persistent weakness or death. The CSF formula resembles enteroviral meningitis. The diagnosis is made by serum or CSF serology (WNV IgM). Treatment is supportive.

Acute HIV infection can present as aseptic meningitis associated with a mononucleosis-like syndrome with fever, rash, and myalgia.

Less common viral causes include mumps, lymphocytic choriomeningitis virus, parainfluenza, adenoviruses, influenza A and B, measles, rubella, poliovirus, rotavirus, and parvovirus B19.

KEY POINTS

- Enteroviruses are the most common cause of viral meningitis, usually presenting with symptoms of headache, fever, nuchal rigidity, photophobia, nausea, vomiting, myalgia, pharyngitis, maculopapular rash, and cough between May and November in the Western Hemisphere.
- Herpesviruses can cause meningitis year round; herpes simplex virus 2 is the most common cause and can recur.
- Neuroinvasive West Nile virus may present with acute flaccid paralysis, which may lead to persistent weakness or death.

Bacterial Meningitis

Bacterial meningitis usually presents with acute meningeal signs (fever, nuchal rigidity) and altered mental status. The incidence of *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* meningitis have decreased; however, *S. pneumoniae* remains the most common cause of community-acquired bacterial meningitis. *N. meningitidis* serogroup B accounts for 40% of infections in the United States because the quadrivalent conjugate vaccine (ACYW-135) does not include serogroup B. Two FDA-approved vaccines that target serogroup B are available in the United States. *Listeria monocytogenes* is an uncommon cause of meningitis in adults; however, the risk increases in patients older than 50 years and those with altered cell-mediated immunity.

Bacterial endocarditis caused by *S. pneumoniae* and *Staphylococcus aureus* can present as purulent meningitis. Clinical clues include a history of valvular disease, a new regurgitant murmur, embolic phenomena, or other stigmata of endocarditis. Injection drug use and hemodialysis are risk factors for *S. aureus*, and alcoholism is a risk factor for *S. pneumoniae* endocarditis. Patients may also present with stroke symptoms secondary to embolic infarction.

Lyme disease, caused by *Borrelia burgdorferi*, can present with a lymphocytic meningitis approximately 2 to 10 weeks after erythema migrans develops. Common clinical features include headache, photophobia, nausea, history of erythema migrans, tick bite in an endemic area, and facial paralysis, which can be unilateral or bilateral.

Treponema pallidum meningitis can occur in the secondary or tertiary phase of syphilis. Headache and meningismus are common, and the CSF usually shows a lymphocytic pleocytosis with an elevated protein level. In tertiary syphilis, neurosyphilis can be asymptomatic or symptomatic. Symptomatic neurosyphilis can present with primarily meningovascular (stroke presentation) or parenchymatous (tabes dorsalis, general paresis) features.

Leptospiral meningitis develops in the immune or second phase of the illness and is classically associated with uveitis, rash, conjunctival suffusion, lymphadenopathy, and hepatosplenomegaly. The CSF formula resembles enteroviral meningitis, and the diagnosis is established by CSF or urine culture or by serology.

Evaluation

All patients with suspected meningitis should promptly undergo LP because a delay is associated with increased costs and a decrease in the yield of the CSF culture. CSF findings characteristic of bacterial meningitis are provided in Table 1. A negative CSF Gram stain result is more common in patients with previous antibiotic therapy or in patients with *L. monocytogenes* or gram-negative bacilli (sensitivity <50%) infections. CSF latex agglutination tests for detecting bacterial antigens are no longer recommended. *S. pneumoniae* antigen detection in the CSF has a 99% sensitivity and specificity. A multiplex PCR assay that can detect 14 pathogens in 1 hour is also now available. If a head CT is indicated before LP (focal neurologic findings, altered mental status, papilledema, new seizure, history of CNS disease, or immunocompromise), imaging should not delay empiric antibiotic therapy, which should be started after promptly obtaining blood cultures. See **Figure 1** for management of suspected bacterial meningitis.

Management

Intravenous antibiotic therapy should be started as soon as possible. If the CSF Gram stain result is negative, initial empiric antibiotic selection is based on age, local epidemiologic patterns of pneumococcal resistance, and the necessity for ampicillin coverage for *L. monocytogenes* (**Table 2**). Despite antibiotic therapy, mortality for bacterial meningitis remains approximately 25%. Adjunctive dexamethasone, given concomitantly with the first dose of antibiotic therapy, reduces morbidity and mortality in adults with pneumococcal meningitis in developed countries. In patients with an identified cause, dexamethasone treatment should be limited to those with *S. pneumoniae* meningitis.

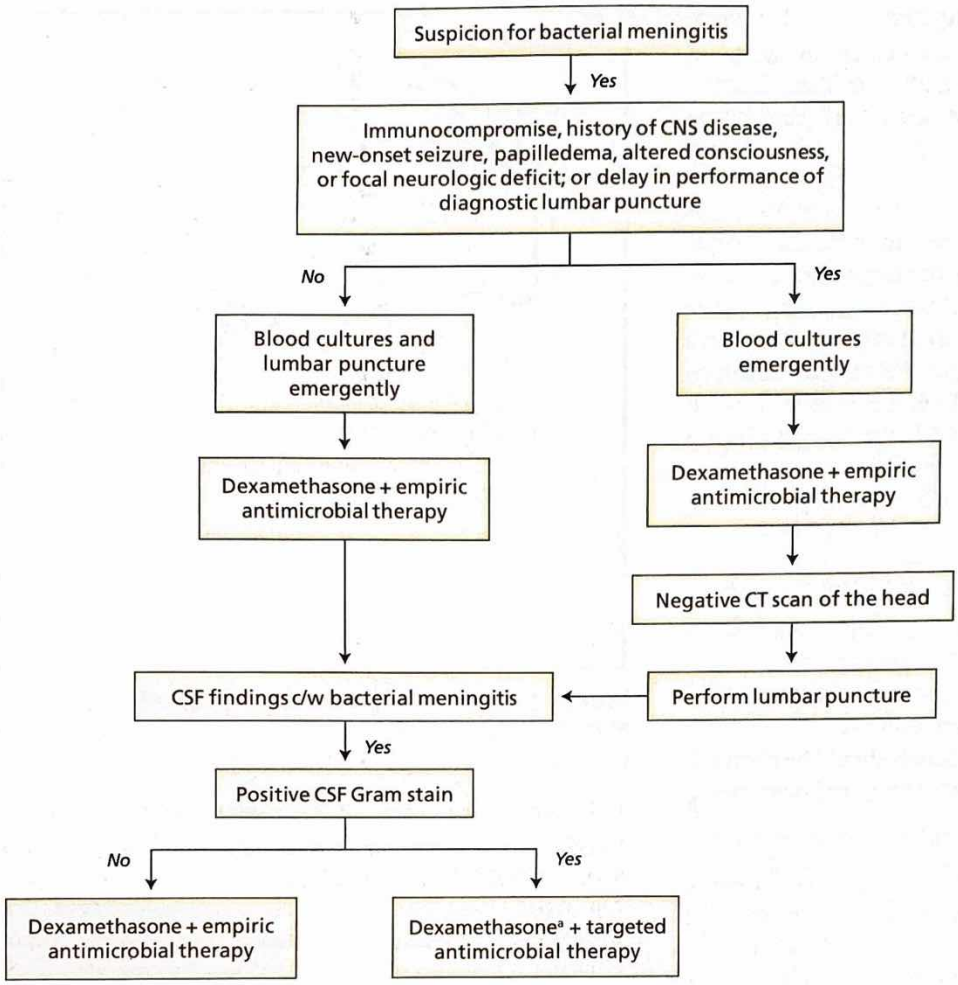

FIGURE 1. Management algorithm for adults suspected of having bacterial meningitis. CNS = central nervous system; c/w = consistent with; CSF = cerebrospinal fluid. [a]Dexamethasone should be continued for 4 days in patients with *Streptococcus pneumoniae* meningitis and stopped in all others.

TABLE 2. Treatment of Bacterial Meningitis

Clinical Characteristics	Empiric Antibiotic Regimen[a]
Immunocompetent host age ≤50 y with community-acquired bacterial meningitis	IV ceftriaxone plus IV vancomycin
Age >50 y or those with altered cell-mediated immunity	IV ampicillin (*Listeria* coverage) plus IV ceftriaxone plus IV vancomycin (in countries with ceftriaxone resistance rate >1%, such as U.S.)
Allergies to β-lactams	IV moxifloxacin instead of cephalosporin IV trimethoprim-sulfamethoxazole instead of ampicillin
Health care–associated ventriculitis or meningitis	IV vancomycin plus either IV ceftazidime, cefepime, or meropenem

IV = intravenous; U.S. = United States.

[a]Adjunctive dexamethasone should be given concomitantly with the first dose of antibiotic therapy and should be continued for 4 days in patients with *Streptococcus pneumoniae* meningitis and stopped in all others.

KEY POINTS

- For diagnosis of bacterial meningitis, the cerebrospinal fluid (CSF) Gram stain result is positive in 60% to 90% of infections; the CSF *Streptococcus pneumoniae* antigen detection test and a multiplex polymerase chain reaction assay are preferred over latex agglutination testing for bacterial antigens.
- Empiric intravenous antibiotic therapy and dexamethasone should be started as soon as possible when community-acquired bacterial meningitis is suspected; ceftriaxone plus vancomycin is indicated for patients 50 years or younger and ampicillin, ceftriaxone, and vancomycin is indicated for patients older than 50 years or with altered cell-mediated immunity.
- Adjunctive dexamethasone reduces morbidity and mortality in adults with pneumococcal meningitis and reduces the risk of neurologic sequelae in bacterial meningitis in developed countries.

Subacute and Chronic Meningitis

Subacute and chronic meningitis are defined by symptom duration between 5 and 30 days and more than 30 days, respectively. The most common infectious causes are *Mycobacterium tuberculosis* and fungi.

Tuberculous Meningitis

Tuberculous meningitis classically presents as basilar meningitis with cranial neuropathies (particularly of cranial nerve VI), mental status changes, and the syndrome of inappropriate secretion of antidiuretic hormone. A history of tuberculosis exposure, an abnormal chest radiograph, a positive tuberculin skin test result, and a positive interferon-γ release assay result are suggestive but can be absent. CSF examination shows a lymphocytic pleocytosis (leukocyte count of 100-500/μL [100-500 × 10^6/L]), elevated protein level, and hypoglycorrhachia. CSF acid-fast bacilli smear is insensitive, and culture results are positive in only 38% to 88% of patients. Culture sensitivity increases when LPs are performed serially for at least 3 days. Nucleic acid amplification testing should be performed when possible, especially when the acid-fast bacilli stain result is negative and suspicion is high, because it might increase diagnostic yield. Antituberculous therapy should be administered for 1 year, and adjunctive glucocorticoids should be given initially because of their association with improved outcomes.

Fungal Meningitis

Fungal pathogens, including *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, and endemic mycoses, are a significant cause of subacute or chronic meningitis syndromes. Fungal meningitis is discussed in the Fungal Infections chapter.

Neurobrucellosis

Neurobrucellosis occurs in 4% to 11% of patients with brucellosis, which is endemic to countries in the Mediterranean, Middle East, and Central America. It may present with meningitis, meningoencephalitis, cranial neuropathies, myelopathy, radiculopathy, or stroke or as a brain abscess. A positive brucellosis culture or serologic test result in the CSF or blood makes the diagnosis. Treatment is combination antibiotic therapy for at least 6 months.

Parasitic Meningitis

Acute primary amebic meningoencephalitis caused by *Naegleria*, *Balamuthia*, and *Acanthamoeba* species is a fatal infection that clinically resembles bacterial meningitis or can present with a chronic granulomatous meningitis. Freshwater exposure during the summer is a key historical clue. Examination of a fresh CSF sample can reveal motile trophozoites, but the CDC should perform confirmatory testing by PCR. Treatment should include miltefosine.

Helminth infections causing eosinophilic meningitis include *Angiostrongylus cantonensis*, *Baylisascaris procyonis*, *Taenia solium* (neurocysticercosis), *Schistosoma* species (schistosomiasis), and *Gnathostoma*. Neurocysticercosis (**Figure 2**) is endemic in Mexico, Central and South America, and Asia. It most commonly presents with seizures or hydrocephalus, and CT scan of the head shows multiple cysts or calcified lesions. Treatment includes managing seizures and increased intracranial pressure and administering adjunctive glucocorticoids and antiparasitic agents for viable cystic lesions. Calcified lesions represent dead parasites and do not require therapy.

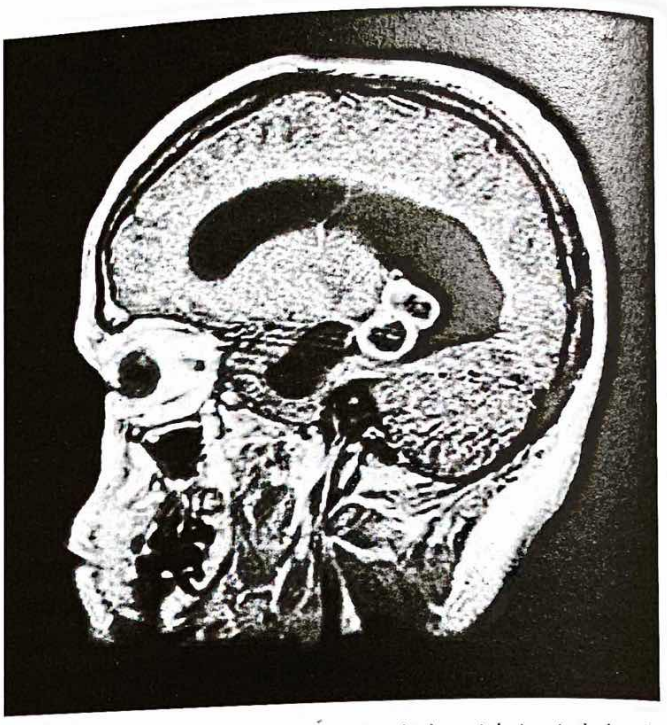

FIGURE 2. Obstructive hydrocephalus and multiple cystic lesions in the lateral ventricle resulting from neurocysticercosis.

Noninfectious Causes

Medications such as NSAIDS, antibiotics, and intravenous immune globulin can occasionally cause aseptic meningitis. Meningeal involvement of leukemia, lymphoma, and metastatic carcinoma can also present as aseptic meningitis, with the CSF cytology showing atypical or immature cells and severe hypoglycorrhachia (<10 mg/dL [0.6 mmol/L]). Systemic lupus erythematosus, Behçet disease, Vogt-Koyanagi-Harada syndrome (uveomeningoencephalitis), and neurosarcoidosis can all present with aseptic meningitis. Finally, chemical meningitis can be seen after intrathecal injections, intracranial hemorrhage, neurosurgical procedures, or spinal anesthesia.

KEY POINTS

- Tuberculous meningitis classically presents as basilar meningitis with cranial neuropathies, mental status changes, and the syndrome of inappropriate secretion of antidiuretic hormone; it should be treated with antituberculous therapy for 1 year with initial adjunctive glucocorticoids.

(Continued)

KEY POINTS *(continued)*

- Freshwater exposure in summertime is a key historical clue in suspected acute primary amebic meningoencephalitis.
- Medications such as NSAIDS, antibiotics, and intravenous immune globulin can occasionally cause aseptic meningitis.

Health Care-Associated Meningitis and Ventriculitis

Health care-associated meningitis and ventriculitis, or nosocomial meningitis, can occur after head trauma or a neurosurgical procedure (craniotomy, LP) or secondary to a device infection (for example, CSF shunt or drain, intrathecal pump, deep brain stimulator). Normal or abnormal CSF cell count, glucose level, and protein level do not reliably confirm or rule out infection in these patients. *Staphylococcus* species and enteric gram-negative bacteria are the most common causes, but up to 50% of infections can have negative culture results. The use of β-D-glucan and galactomannan CSF assays may aid in diagnosing health care-related fungal ventriculitis and meningitis. Empiric antimicrobial therapy is outlined in Table 2 and should be accompanied by device removal, if present.

KEY POINTS

- *Staphylococcus* species and enteric gram-negative bacteria are the most common causes of health care-associated meningitis and ventriculitis, but up to 50% of infections can have negative culture results.
- Empiric intravenous therapy for health care-associated meningitis and ventriculitis is vancomycin plus either ceftazidime, cefepime, or meropenem.

Focal Central Nervous System Infections

Brain Abscesses

Brain abscesses can occur in any patient but are most commonly seen in men. Predisposing conditions in immunocompetent patients can be seen in **Table 3**. Brain abscesses are most commonly caused by anaerobes, aerobic and microaerophilic streptococci, *S. aureus*, and Enterobacteriaceae. Initial empiric therapy is guided by the likely predisposing condition (**Table 4**). Aspiration of the brain abscess for culture is preferred for definitive diagnosis; surgical or stereotactic drainage should be performed if the abscess is large (>2.5 cm). Antibiotic therapy should be given for 4 to 8 weeks with follow-up cranial imaging to ensure resolution of the infection.

Immunosuppressed patients (those with HIV or AIDS, patients undergoing solid organ or bone marrow transplantation) are at risk for developing brain abscesses from several opportunistic infections. See HIV/AIDS and Infections in Transplant Recipients for further discussion.

TABLE 3. Predisposing Conditions for Brain Abscess

Condition	Incidence
Contiguous foci of infection such as sinusitis (frontal lobe) and otitis media (temporal lobe or cerebellum)	~50%
Hematogenous, sometimes with multiple abscesses (odontogenic resulting from viridans streptococci, endocarditis, injection drug use, cardiac right-to-left shunts)	25%
Cryptogenic (most likely odontogenic)	15%
Neurosurgery or penetrating head trauma	10%

KEY POINTS

- Brain abscesses in immunocompetent patients are treated empirically based on the likely predisposing factor, with surgical or stereotactic drainage of abscesses larger than 2.5 cm.
- If the predisposing condition is unknown, empiric intravenous treatment of a brain abscess should include vancomycin plus metronidazole and a third-generation cephalosporin.

Cranial Abscess

Cranial epidural and subdural abscesses can arise from underlying osteomyelitis complicating paranasal sinusitis (Pott puffy tumor) or otitis media or after neurosurgical procedures or head trauma. Rarely, they may arise as a complication of bacterial meningitis. Cranial epidural abscesses usually grow slowly, presenting with subacute to chronic symptoms of headache, localized bone pain, and focal neurologic signs. In contrast, subdural empyema is a rapidly progressive infection with high mortality that represents a neurosurgical emergency. The CSF formula in both parameningeal infections shows neutrophilic pleocytosis and a very high protein level, frequently with negative Gram stain and culture results. Pathogen identification is best achieved by culture of the abscess obtained during surgical drainage.

KEY POINT

- In cranial epidural and subdural abscess, pathogen identification is best achieved by culture of the abscess obtained during surgical drainage.

Spinal Epidural Abscess

Spinal epidural abscess most commonly results from hematogenous dissemination. *S. aureus* accounts for approximately 50% of infections; streptococcus and gram-negative bacilli such as *Escherichia coli* are also implicated. Predisposing factors for bacteremia include endocarditis, injection drug use, long-term intravenous catheters (hemodialysis catheters, central lines), and urinary tract infection. Spinal epidural abscess can also occur after neurosurgical

TABLE 4. Predisposing Conditions, Causative Agents, and Empiric Antimicrobial Therapy in Patients with Bacterial Brain Abscess

Predisposing Condition	Usual Causative Agents	Empiric Antimicrobial Therapy
Otitis media or mastoiditis	Streptococci (aerobic or anaerobic), *Bacteroides* species, *Prevotella* species, Enterobacteriaceae	Metronidazole plus a third-generation cephalosporin[a]
Sinusitis	Streptococci, *Bacteroides* species, Enterobacteriaceae, *Staphylococcus aureus*, *Haemophilus* species	Metronidazole plus a third-generation cephalosporin[a,b]
Dental sepsis	Mixed *Fusobacterium*, *Prevotella*, and *Bacteroides* species; streptococci	Penicillin plus metronidazole
Penetrating trauma or after neurosurgery	*S. aureus*, streptococci, *Pseudomonas*, Enterobacteriaceae, *Clostridium* species	Vancomycin plus an antipseudomonal β-lactam[c]
Lung abscess, empyema, bronchiectasis	*Fusobacterium*, *Actinomyces*, *Bacteroides*, and *Prevotella* species; streptococci; *Nocardia* species	Penicillin plus metronidazole plus a sulfonamide[d]
Endocarditis	*S. aureus*, streptococci	Vancomycin or daptomycin
Hematogenous spread from pelvic, intra-abdominal, or gynecologic infections	Enteric gram-negative bacteria, anaerobic bacteria	Metronidazole plus a third-generation cephalosporin[a,b,c]
Immunocompromised patients HIV-infected patients	*Listeria* species, fungal organisms (*Cryptococcus neoformans*), or parasitic or protozoal organisms (*Toxoplasma gondii*); *Aspergillus*, *Coccidioides*, and *Nocardia* species	Metronidazole plus a third-generation cephalosporin[a,b,c,d,e]; antifungal or antiparasitic agent

[a]Ceftriaxone; the fourth-generation cephalosporin cefepime may also be used.

[b]Add vancomycin if infection caused by methicillin-resistant *Staphylococcus aureus* is suspected. Vancomycin can then be transitioned to antistaphylococcal β-lactam (oxacillin-nafcillin)-penicillin if methicillin-sensitive *S. aureus* is confirmed.

[c]Use ceftazidime, cefepime, or meropenem for *Pseudomonas aeruginosa* pending abscess cultures.

[d]Use trimethoprim-sulfamethoxazole if infection caused by *Nocardia* species is suspected.

[e]Use ampicillin if infection caused by *Listeria* species is suspected. If allergic to penicillin, use trimethoprim-sulfamethoxazole.

NOTE: If predisposing condition is unknown, empiric treatment should include vancomycin plus metronidazole and a third-generation cephalosporin.

procedures (spinal fusion, epidural catheter placement) or paraspinal injection. Patients usually develop localized pain at the site of infection that later radiates down the spine. MRI is the imaging modality of choice to identify location and extent of the abscess. All patients should undergo a baseline laboratory evaluation, including erythrocyte sedimentation rate and C-reactive protein. Blood cultures should be obtained before starting antibiotics. Treatment should be at least 6 weeks of effective antimicrobial therapy. Surgical drainage is indicated in patients with neurologic symptoms or signs (lower extremity weakness, numbness, bladder and bowel dysfunction). Follow-up MRI is not indicated unless the patient has persistent elevation of inflammatory markers, lack of clinical response, or new neurologic symptoms or signs. Tuberculosis (Pott disease) and brucellosis should be considered in patients with negative culture results and appropriate travel history and risk factors.

KEY POINT

- MRI is the imaging modality of choice to identify location and extent of a spinal epidural abscess, and blood cultures should be obtained before starting antibiotic therapy.

Acute Flaccid Myelitis

Acute flaccid myelitis, first reported in 2014, presents as acute-onset limb weakness, often preceded by respiratory illness or fever within the previous 4 weeks. It occurs most often in the pediatric population but has been reported in adults. Several neuroinvasive enteroviruses have been implicated, including EV-A71 and EV-D68. Outbreaks have occurred every 2 years (late summer and early fall) since 2014, and intensive surveillance is ongoing in the United States. Acute flaccid myelitis can progress rapidly and may be complicated by respiratory failure, so all patients should be hospitalized initially for close monitoring. The CDC has developed interim recommendations for management; however, no evidence has shown any current therapies affect outcomes.

Encephalitis

Encephalitis is inflammation of the brain parenchyma. Probable or confirmed encephalitis is defined by the presence of one major (altered consciousness for more than 24 hours) and at least three minor criteria (fever, new-onset seizure, new-onset focal neurologic findings, CSF pleocytosis, and abnormal MRI or electroencephalographic findings) as classified by the International Encephalitis Consortium. The

causative agent is unknown in 37% to 70% of infections, depending if viral PCR and arboviral serologies are performed and autoimmune causes are investigated. The most common known causes are viral (herpes simplex virus types 1 and 6, varicella-zoster virus [VZV], and West Nile virus [WNV]) and autoimmune diseases.

Viral Encephalitis

Herpes Simplex Encephalitis

HSV-1 is the most common cause of sporadic encephalitis in the United States, requiring prompt identification and treatment with intravenous acyclovir. Factors associated with an adverse outcome include older age, abnormal Glasgow Coma Scale score, and delay in starting antiviral therapy. HSV-1 encephalitis commonly presents with fever, seizures, altered mental status, and focal neurologic deficits with unilateral temporal lobe edema, hemorrhage, or enhancement on imaging. The CSF formula usually shows lymphocytic pleocytosis, an elevated protein level, and a normal glucose level. The diagnosis is confirmed by HSV PCR of the CSF (98% sensitivity, 94% specificity). However, false-negative results have been reported; if HSV is suspected, a repeat PCR should be obtained within 1 week while continuing acyclovir therapy. Therapy duration for HSV encephalitis should be 14 to 21 days. Electroencephalography can be helpful in identifying the degree of cerebral dysfunction and specific area of the brain involved and in detecting subclinical seizure activity.

Human herpesvirus 6 can cause severe limbic encephalitis (altered consciousness, focal neurologic signs, seizures, psychosis) in bone marrow transplant recipients. Antiviral agents are often used to treat infection in immunocompromised patients, although data supporting treatment are limited. Cytomegalovirus can cause encephalitis with periventricular enhancement on imaging in immunosuppressed patients (those with AIDS or after transplantation). Diagnosis is by PCR of the CSF for cytomegalovirus, and treatment is parenteral ganciclovir. Cytomegalovirus and Epstein-Barr virus can cause meningoencephalitis in young, immunocompetent patients presenting with infectious mononucleosis syndromes.

Varicella-Zoster Virus Encephalitis

VZV is a commonly underdiagnosed, treatable cause of encephalitis in adults. VZV can present with vasculopathy with a stroke, encephalitis, meningitis, radiculopathy, or myelitis. Patients can present without a vesicular rash, so a CSF VZV PCR should be ordered in all patients with encephalitis. Treatment with intravenous acyclovir for 10 to 14 days is recommended.

Arboviruses

Arboviral CNS infections in the United States are most commonly seen between June and October and include West Nile, Eastern and Western equine encephalitis, St. Louis encephalitis, Powassan, and La Crosse viruses. WNV is the most common cause of epidemic viral encephalitis in the United States; meningitis, acute flaccid paralysis (similar to poliomyelitis), neuropathy, and retinopathy can also occur. Older patients and those who have undergone transplantation or are immunosuppressed have a higher risk of death. WNV affects the thalamus and the basal ganglia; patients present with facial or arm tremors, parkinsonism, and myoclonus. Hypodense lesions or enhancements may be seen in the thalamus, basal ganglia, and midbrain on MRI of the brain. A positive WNV IgM in the CSF or serum confirms the diagnosis; treatment is supportive.

HIV encephalitis is the cause of HIV-associated dementia in later stages of the untreated illness; it can also present as CD8 encephalitis, consisting of perivascular inflammation resulting from infiltration of $CD8^+$ lymphocytes, which may occur as part of an immune reconstitution syndrome, in some cases associated with viral escape (low levels of detectable HIV RNA in CSF).

KEY POINTS

- Herpes simplex virus type 1 is the most common cause of sporadic encephalitis in the United States, presenting with fever, seizures, altered mental status, and focal neurologic deficits; prompt identification and treatment with intravenous acyclovir improves outcomes.
- Varicella-zoster virus (VZV) is a treatable form of encephalitis and may present without vesicular rash, so VZV polymerase chain reaction of the cerebrospinal fluid should be ordered in all patients with encephalitis.
- West Nile virus is the most common cause of epidemic viral encephalitis in the United States and occurs between June and October and may present with acute flaccid paralysis or parkinsonism.

Autoimmune Encephalitis

Autoimmune neurologic diseases can manifest as encephalitis, cerebellitis, dystonia, status epilepticus, cranial neuropathies, and myoclonus. Anti-*N*-methyl-D-aspartate receptor encephalitis is most common and presents with a subacute onset; it was initially described as a paraneoplastic syndrome affecting young women with ovarian teratomas, but it can be associated with other tumors (sex cord stromal tumors, small cell lung cancer) or occur without a tumor. HSV and VZV encephalitis have been reported as triggers for subsequent autoimmune encephalitis. Young women (<35 years) often present after viral-like illness with behavioral changes, headaches, and fever followed by altered mental status, seizures, abnormal movements, and autonomic instability. Treatment includes intravenous glucocorticoids, intravenous immune globulin, tumor removal (if present), and, in some cases, plasmapheresis and rituximab.