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 unhelpful cranial imaging, hospitalization, and 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, myalgias, pharyngitis, maculopapular rash, and cough. Lymphocytic pleocytosis of the CSF with a normal glucose level and mildly elevated protein level is typical (**Table 1**). The diagnosis is confirmed by enterovirus PCR. 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 the need for acyclovir therapy.

VZV can cause encephalitis, aseptic meningitis, myelitis, and a vasculitis presenting as a stroke. Vesicular lesions are a clue to the diagnosis but may be absent (zoster sine herpete). VZV encephalitis and vasculitis may present with a hemorrhagic CSF. VZV may be present in the CSF without meningitis or encephalitis, and patients with primary varicella or zoster do not require lumbar puncture 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 parenteral 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.

CONT.

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, which may lead to persistent weakness or death. The CSF formula resembles enteroviral meningitis. The diagnosis is made by serum or CSF serology (WNV IgM); WNV PCR of the CSF is insensitive. Treatment is supportive.

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

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, myalgias, pharyngitis, maculopapular rash, and cough between May and November.
- 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. Since the introduction of conjugate vaccines, *Haemophilus influenzae* and *Neisseria meningitides* meningitis incidence has decreased, making *Streptococcus pneumoniae* the most common cause of community-acquired bacterial meningitis. *N. meningitides* 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. *Streptococcus agalactiae* is now the third most common cause of bacterial meningitis in adults. *Listeria monocytogenes* is an uncommon cause of meningitis in adults; however, the risk increases in older adults 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 development of erythema migrans. 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. Because the CSF formula resembles enteroviral meningitis, the "rule of 7s" was derived and validated to accurately classify a patient at low risk of having Lyme disease (headache duration <7 days, <70% CSF mononuclear cells, and absence of a seventh facial nerve palsy).

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 undergo lumbar puncture. 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 because of low sensitivity (70%) and specificity, although they may play a role in patients with previous antibiotic therapy or culture-negative meningitis. Multiplex PCR assay for detection of *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, and *L. monocytogenes* has high sensitivity (100%) and specificity (98%) and is increasingly available. If a head CT is indicated before lumbar puncture (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 (10 mg every 6 hours for 4 days)

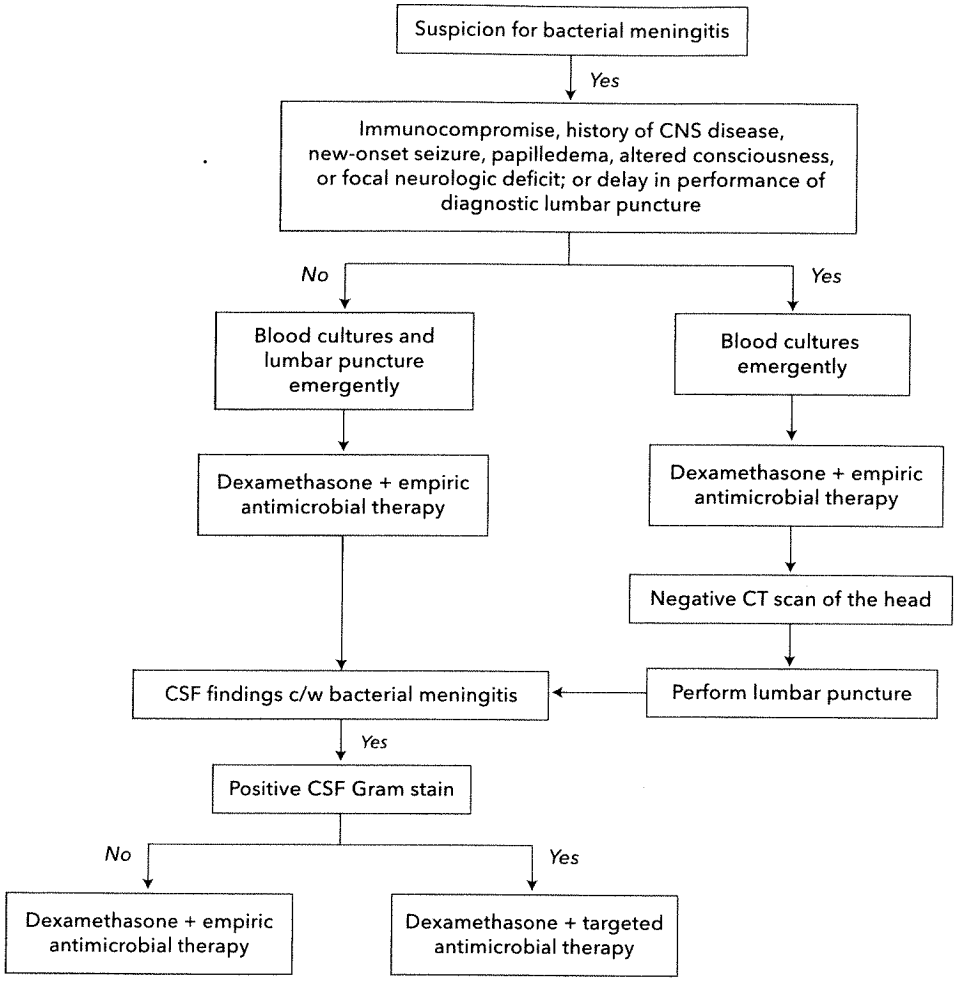

FIGURE 1. Management algorithm for adults suspected of having bacterial meningitis. CNS = central nervous system; c/w = consistent with; CSF = cerebrospinal fluid.

Adapted with permission from Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004;39:1267-84. [PMID: 15494903] Copyright 2004 Oxford University Press.

TABLE 2. Antibiotic Management of Bacterial Meningitis

Clinical Characteristics	Empiric Antibiotic Regimen
Immunocompetent host age <50 y with community-acquired bacterial meningitis	IV ceftriaxone *or* cefotaxime plus IV vancomycin
Patient age >50 y or those with altered cell-mediated immunity	IV ampicillin (*Listeria* coverage) plus IV ceftriaxone *or* cefotaxime plus IV vancomycin
Allergies to β-lactams	IV moxifloxacin instead of cephalosporin
	IV trimethoprim-sulfamethoxazole instead of ampicillin
Hospital-acquired bacterial meningitis	IV vancomycin plus either IV ceftazidime, cefepime, or meropenem
Neurosurgical procedures	IV vancomycin plus either IV ceftazidime, cefepime, or meropenem

IV = intravenous.

reduces morbidity and mortality in adults with pneumococcal meningitis and reduces the risk of neurologic sequelae in bacterial meningitis in developed countries; it should be given concomitantly with the first dose of antibiotic therapy. H

CONT.

KEY POINTS

- For diagnosis of bacterial meningitis, the cerebrospinal fluid Gram stain result is positive in 60% to 90% of infections; latex agglutination testing for bacterial antigens is not recommended because of low sensitivity and specificity.
- Intravenous antibiotic therapy and dexamethasone should be started as soon as possible when bacterial meningitis is suspected; selection of initial empiric antibiotics is based on age, local epidemiologic patterns of pneumococcal resistance, and the necessity for ampicillin coverage for *Listeria monocytogenes*.
- Adjunctive dexamethasone reduces morbidity and mortality in adults with pneumococcal meningitis and reduces the risk of neurologic sequelae in bacterial meningitis in developed countries.

Focal Central Nervous System Infections

Brain Abscesses

Brain abscesses can occur in immunocompetent or immunosuppressed persons and 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, and Enterobacteriaceae. Initial empiric therapy is guided by the likely predisposing condition and is outlined in **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 development of brain abscesses from several opportunistic infections. See HIV/AIDS and Infections in Transplant Recipients for further discussion.

KEY POINT

- Brain abscesses in immunocompetent patients are treated empirically based on the likely predisposing factor with surgical or stereotactic drainage of abscesses greater than 2.5 cm.

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)	25%
Cryptogenic (most likely odontogenic)	15%
Neurosurgery or penetrating head trauma	10%

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 are usually slow growing, presenting with subacute to chronic symptoms of headache, localized bone pain, and focal neurologic signs. In contrast, subdural empyema is a rapidly progressive infection

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, Enterobacteriaceae, *Clostridium* species	Vancomycin plus a third-generation cephalosporin[a,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 plus gentamicin
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]Cefotaxime or 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 or cefepime if infection caused by *Pseudomonas aeruginosa* is suspected. Meropenem can also be used for antipseudomonal coverage.

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

[e]Use ampicillin if infection caused by *Listeria* species is suspected.

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

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, with *S. aureus* accounting 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 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. Although the duration of antibiotic therapy lacks robust supporting data and must be determined on a case-by-case basis, at least 6 weeks of effective antimicrobial therapy is reasonable. 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.

Encephalitis

Encephalitis is inflammation of the brain parenchyma. Possible encephalitis is defined by the presence of one major (altered consciousness for more than 24 hours) and two minor (fever, new-onset seizure, new-onset focal neurologic findings, CSF pleocytosis, and abnormal MRI or electroencephalographic findings) criteria from the International Encephalitis Consortium; probable or confirmed encephalitis requires one major and at least three minor criteria. The causative agent is unknown in 37% to 70% of infections, depending on whether viral PCR is used and autoimmune causes are investigated. The most common known causes are viral (herpes simplex virus types 1 and 6, varicella-zoster virus, and West Nile virus) 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, and delay in starting antiviral therapy. HSV-1 encephalitis presents with fever, seizures, altered mental status, and focal neurologic deficits with unilateral temporal lobe edema, hemorrhage, or enhancement on imaging. Bilateral temporal lobe findings in the insula or cingulate are less commonly seen. 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 encephalitis in transplant recipients. 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

Varicella-zoster virus (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 PCR of the CSF or a serum-to-CSF anti-VZV IgG 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 in summer or fall and include West Nile (WNV), 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. WNV can cause meningitis, encephalitis, acute flaccid paralysis (similar to poliomyelitis), neuropathy, and retinopathy.

H CONT. 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. Diagnosis is confirmed by a positive WNV IgM in the CSF or serum; 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). H

KEY POINTS

- Herpes simplex virus 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 polymerase chain reaction of the cerebrospinal fluid (CSF) or a serum-to-CSF anti-VZV IgG should be ordered in all patients with encephalitis.
- West Nile virus is the most common cause of epidemic viral encephalitis in the United States.

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; 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. 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.

Prion Diseases of the Central Nervous System

Prions cause rare but relentlessly progressive and rapidly fatal neurodegenerative diseases characterized by dementia and ataxia. The cause of disease is an abnormally folded prion protein. In humans, prion diseases occur by three mechanisms: sporadic (spontaneous), familial (genetic), and acquired (infectious or transmissible). In patients of any age presenting with otherwise unexplained rapidly progressive dementia and ataxia, diagnosis of a prion disease should be considered (**Table 5**); the infectious forms are now rare (**Table 6**). Prion diseases have no known therapy.

Sporadic Creutzfeldt-Jakob Disease

Spontaneous (sporadic) disease is the most common form of Creutzfeldt-Jakob disease (CJD), with an incidence of 1 per million worldwide. No environmental risk factors are known. Clinical manifestations include rapidly progressive dementia, usually over 4 to 6 months. Ataxia, myoclonus, and pyramidal and extrapyramidal signs may be observed. Loss of vision is not uncommon, and patients become comatose before dying.

TABLE 5. Criteria for Diagnosis of Probable Prion Disease[a,b]

University of California, San Francisco Criteria (2007)[b]
Rapid cognitive decline
Two of the following signs or symptoms:
Myoclonus
Pyramidal/extrapyramidal dysfunction
Visual dysfunction
Cerebellar dysfunction
Akinetic mutism
Focal cortical signs (for example, neglect, aphasia, acalculia, apraxia)
Typical EEG and/or MRI
Other investigations should not suggest an alternative diagnosis
European MRI-CJD Consortium Criteria (2009)[b]
Progressive dementia
One of the following signs or symptoms:
Myoclonus
Pyramidal/extrapyramidal symptoms
Visual/cerebellar dysfunction
Akinetic mutism
AND
Either
Typical EEG
Elevated CSF protein 14-3-3 (with total disease duration <2 years)
OR
Typical MRI
Routine investigations should not suggest an alternative diagnosis

CJD = Creutzfeldt-Jakob disease; CSF = cerebrospinal fluid; EEG = electroencephalography.

[a]Definitive diagnosis requires neuropathologic confirmation.

[b]Fulfilling one criterion in all categories signifies a probable diagnosis.

TABLE 6. Human Transmissible Spongiform Encephalopathies

Disease Classification	Presentation
Acquired	
Idiopathic only (not environmental)	Sporadic fatal familial insomnia
	Sporadic CJD
Idiopathic/transmissible	Variant CJD (from BSE)
	Kuru
Inherited	Familial CJD
	GSS
	Fatal familial insomnia

BSE = bovine spongiform encephalopathy; CJD = Creutzfeldt-Jakob disease; GSS = Gerstmann-Sträussler-Scheinker syndrome.

The diagnosis can be made by clinical history and MRI; a cerebrospinal fluid analysis positive for either total Tau or 14-3-3 protein may also be useful.

Transmissible Prion Diseases

Variant CJD (vCJD) is the human form of bovine spongiform encephalopathy. It generally affects younger persons (age 15-50 years), frequently presenting with rapidly progressive neuropsychiatric manifestations (depression, withdrawal) and peripheral neuropathy, followed by cerebellar ataxia, involuntary movements, and cognitive decline over a 12-month period. Because vCJD can be transmitted through blood products and tissue, it is a serious public health concern worldwide. Probable vCJD is diagnosed by typical MRI findings ("hockey stick sign" in the posterior thalamus) and tonsil biopsy to detect scrapie-associated prion protein in a patient with a compatible clinical presentation (see Table 5).

Iatrogenic CJD is exceedingly rare, but transmission has been documented with contaminated cadaveric pituitary-derived human growth hormone and gonadotropin, dura mater, stereotactic electroencephalography needles, neurosurgical instruments, corneal transplants, medical instruments, implanted electroencephalography electrodes, and blood transfusions.

Familial Prion Disease

Many mutations have been associated with the prion protein gene. All are autosomally dominant. These include the gradually progressive Gerstmann-Sträussler-Scheinker syndrome and the rapidly progressive fatal familial insomnia.

KEY POINTS

- Prion disease should be included in the differential diagnosis of a patient of any age presenting with otherwise unexplained rapidly progressive dementia and ataxia.
- Spontaneous Creutzfeldt-Jakob disease is the most common form of prion disease and has no known risk factors.

Skin and Soft Tissue Infections

Introduction

Skin infections usually result from epidermal compromise that allows skin colonizers such as *Staphylococcus aureus* and *Streptococcus pyogenes* to become pathogenic. Predisposing conditions include vascular disease, immunodeficiency, neuropathy, previous cellulitis, obesity, skin trauma, tinea pedis, and lymphedema. Infections can be characterized by anatomic involvement and presence or absence of pus. Nonpurulent spreading skin infections include erysipelas, cellulitis, and necrotizing soft tissue infection; purulent skin infections refer to abscesses (**Figure 2**), furuncles, and carbuncles. Purulent skin infections are generally caused by staphylococci, including methicillin-resistant *Staphylococcus aureus* (MRSA); nonpurulent skin infections are usually caused by β-hemolytic streptococci. **Table 7** includes other skin pathogens and their associated risk factors for less common causes of skin infection. Complications of infections include systemic inflammatory response (as in severe cellulitis) or systemic toxin release (as in toxic shock syndrome).

Erysipelas and Cellulitis

Erysipelas refers to infection of the epidermis, upper dermis, and superficial lymphatics. Usually involving the face or lower extremities, this infection is brightly erythematous with distinct elevated borders and associated fever, lymphangitis, and regional lymphadenopathy (see MKSAP 18 Dermatology). Cellulitis refers to infection involving the deeper dermis and subcutaneous fat tissue. Inflammatory signs of infection are similar to erysipelas, but the area of involvement is less well demarcated.

Although the diagnosis of erysipelas or cellulitis is usually established clinically, approximately one third of patients are

FIGURE 2. A cutaneous abscess draining purulent material is shown; it is caused by methicillin-resistant *Staphylococcus aureus* bacteria.

Image credit to the Centers for Disease Control and Prevention/Bruno Coignard, MD; Jeff Hageman, MHS.

TABLE 7. Skin Pathogens and Associated Risk Factors

Pathogen	Risk Factor	Comment
Aeromonas hydrophila	Contact with freshwater lakes, streams, rivers (including brackish water)	Cellulitis nonspecific in clinical appearance; minor trauma to skin usually leads to inoculation of organism
	Contact with leeches	
Vibrio vulnificus, Vibrio parahaemolyticus	Contact with salt water or brackish water	Cellulitis through direct inoculation into skin
	Contact with drippings from raw seafood	Ingestion leads to bacteremia with secondary skin infection
	Consumption of undercooked shellfish (particularly oysters)	Hallmark is hemorrhagic bullae in area of cellulitis lesion(s)
	Liver cirrhosis or chronic liver disease	
Erysipelothrix rhusiopathiae	Contact with saltwater marine life (can also infect freshwater fish)	Cellulitis usually involves the hand or arm, especially in those handling fish, shellfish, or, occasionally, poultry or meat contaminated with bacterium
		Causes erysipeloid disease
Pasteurella multocida	Contact primarily with cats and dogs	Cellulitis occurs as a result of cat scratch or bite
Capnocytophaga canimorsus	Contact primarily with dogs	Cellulitis and sepsis are present, particularly in patients with hyposplenism
Bacillus anthracis	Contact with infected animals or animal products. May be the result of bioterrorism	Edematous pruritic lesion with central eschar; spore-forming organism
Francisella tularensis	Contact with or bite from infected animal (particularly cats); arthropod bites (particularly ticks)	Ulceroglandular syndrome characterized by ulcerative lesion with central eschar and localized tender lymphadenopathy; constitutional symptoms often present
Burkholderia mallei	Contact with tissues or bodily fluids of infected mules or horses	Pustules with suppurative localized lymph nodes or ulcerative nodules at site of inoculation
Clostridium perfringens	Surgery or other significant trauma	Necrotizing infection, often referred to as clostridial myonecrosis or gas gangrene
Mycobacterium marinum	Contact with fresh water or salt water, including fish tanks and swimming pools	Lesion is often trauma associated and often involves the upper extremity; papular lesions become ulcerative at site of inoculation; ascending lymphatic spread can be seen ("sporotrichoid" appearance); systemic toxicity usually absent
Mycobacterium fortuitum	Exposure to freshwater footbaths/pedicures at nail salons, particularly after razor shaving; surgery	Furuncle(s); postoperative wound infection

H CONT.

misdiagnosed. Clinical mimics include contact or stasis dermatitis, lymphedema, erythema nodosum, deep venous thrombosis, thrombophlebitis, lipodermatosclerosis, erythromelalgia, trauma-related inflammation, and hypersensitivity reactions (see MKSAP 18 Dermatology). Blood culture results are positive in approximately 5% of patients with erysipelas and cellulitis and are not routinely indicated; however, cultures should be performed for those who are immunocompromised, exhibit severe sepsis, or have unusual precipitating circumstances, including immersion injury or animal bites. Culture of skin tissue aspirate or biopsy should also be considered for these patients. Radiographic imaging is not helpful for the diagnosis of erysipelas or cellulitis but may be helpful when a deeper necrotizing infection is suspected.

For immunocompetent patients with cellulitis or erysipelas who have no systemic signs or symptoms (mild infection), empiric oral therapy directed against streptococci is recommended as outlined in **Table 8** (see MKSAP 18 Dermatology). Treatment duration for uncomplicated infection can be as short as 5 days but should be extended as necessary until the infection improves. In patients with systemic signs (moderate infection), intravenous treatment is recommended (see Table 8). Treating predisposing factors (such as tinea pedis, edema, and primary skin disorders) may decrease the risk for recurrent infection. Prophylactic antibiotics such as penicillin or erythromycin can be considered in patients with more than three episodes of cellulitis annually.

Patients who are immunocompromised, who have systemic inflammatory response syndrome and hypotension, or who have evidence of deeper necrotizing infection such as bullae and desquamation (severe infection) should receive urgent surgical evaluation for debridement. Initial empiric

TABLE 8. Treatment of Skin Infections

Infection	Treatment
Erysipelas or cellulitis	Mild: Oral penicillin, amoxicillin, cephalexin, dicloxacillin, clindamycin
	Moderate: Intravenous penicillin, ceftriaxone, cefazolin, clindamycin
	Severe: Surgical assessment for possible necrotizing component and empiric intravenous vancomycin plus piperacillin-tazobactam, imipenem, or meropenem
Necrotizing fasciitis	Polymicrobial infection: Surgical assessment/debridement and combination therapy such as vancomycin plus piperacillin-tazobactam or imipenem or meropenem
	Streptococcus pyogenes or *Clostridium perfringens*: Surgical assessment/debridement and penicillin plus clindamycin
	Aeromonas hydrophila: Surgical assessment/debridement and ciprofloxacin plus doxycycline
	Vibrio vulnificus: Surgical assessment/debridement and ceftazidime, ceftriaxone, or cefotaxime plus doxycycline
Furuncle, carbuncle, or abscess	Mild: Incision and drainage
	Moderate: Incision and drainage plus empiric trimethoprim-sulfamethoxazole or doxycycline pending culture and susceptibilities
	Severe: Incision and drainage plus empiric vancomycin, daptomycin, linezolid, telavancin, or ceftaroline pending culture and susceptibilities

H CONT. broad-spectrum antibiotic therapy should be started (see Table 8); then treatment may be adjusted based on culture and sensitivity results from lesion-associated specimens. H

KEY POINTS

HVC
- Blood cultures are positive in approximately 5% of patients with erysipelas and cellulitis and are not routinely indicated; however, cultures should be performed for those who are immunocompromised, exhibit severe sepsis, or have unusual precipitating circumstances, including immersion injury or animal bites.
- Patients with evidence of deeper necrotizing infection such as bullae and desquamation (severe infection) should receive urgent surgical evaluation for debridement and empiric broad-spectrum antibiotic therapy.

Necrotizing Fasciitis

Necrotizing soft tissue infections, which involve subdermal compartments including fascia and possibly muscle, are uncommon but potentially life threatening. In necrotizing fasciitis (NF), infection usually spreads along the superficial fascia. These infections may be monomicrobial or polymicrobial, consisting of a mixture of aerobic and anaerobic bacteria, and are often associated with the production of toxins. In monomicrobial infection, the classically associated pathogen is *Streptococcus pyogenes*; other potential organisms include *Staphylococcus aureus, Streptococcus agalactiae, Aeromonas hydrophila, Vibrio vulnificus,* and *Clostridium perfringens.*

H NF characteristically occurs in the setting of previous skin trauma or infection and most commonly affects the extremities. Risk factors include diabetes mellitus, injection drug use, malignancy, immunosuppression, and liver disease. Patients with liver disease are at particular risk for infection with *V. vulnificus* (**Figure 3**). Patients with diabetes are at risk for NF of the perineum, a polymicrobial infection known as Fournier gangrene that usually results from antecedent genitourinary, traumatic, or anorectal infection.

The initial presentation of NF resembles cellulitis before potentially rapid progression with edema, severe pain, hemorrhagic bullous lesions, skin necrosis, and local crepitus. Systemic toxicity manifests with fever, hypotension, tachycardia, mental status changes, and tachypnea. A hallmark of infection is "woody" induration appreciated by palpation of involved subcutaneous tissues. Necrosis of local nerves may result in anesthesia.

Laboratory study results are individually nonspecific. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is derived from six variables that, when added together, are associated with an increased likelihood of necrotizing skin

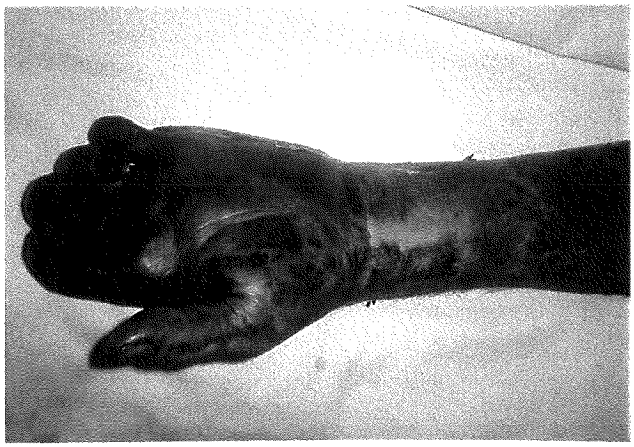

FIGURE 3. Bullous cellulitis characteristic of *Vibrio vulnificus* infection is shown in a patient with cirrhosis; cutaneous necrosis is also evident, most likely associated with disseminated intravascular coagulation.

CONT. infection: C-reactive protein level (>15 mg/dL [150 mg/L]), total leukocyte count (>15,000-25,000/μL [15-25 × 10^9/L), hemoglobin level (<11-13.5 g/dL [110-135 g/L]), sodium level (<135 mEq/L [135 mmol/L]), creatinine level (>1.6 mg/dL [141 μmol/L]), and glucose level (>180 mg/dL [10 mmol/L]). This tool was developed to improve diagnostic accuracy; the reported positive and negative predictive values are 92% and 96%, respectively. However, use of the score has not been prospectively validated in all clinical settings, so operative debridement should be pursued in patients with a high index of clinical suspicion for NF.

Plain radiographs and CT scans may demonstrate gas in soft tissues, but MRI with contrast is more sensitive and can help delineate anatomic involvement. Surgical exploration can confirm the diagnosis of NF. Blood culture(s) obtained before surgery and antibiotic administration or deep intraoperative specimen culture can establish the microbiologic cause.

In confirmed cases of NF, repeated surgical debridement is typically required. Pending culture results, empiric antibiotic treatment includes broad-spectrum coverage for aerobic and anaerobic organisms (including MRSA) and consists of vancomycin, daptomycin, or linezolid plus piperacillin-tazobactam, a carbapenem, ceftriaxone plus metronidazole, or a fluoroquinolone plus metronidazole. Some experts also recommend adding empiric clindamycin because of its suppression of toxin production by staphylococci and streptococci. See Table 8 for treatment of NF caused by *S. pyogenes*, *V. vulnificus*, *A. hydrophila*, or clostridial species. Antimicrobial discontinuation can be considered when the patient is afebrile and clinically stable, and surgical debridement is no longer required.

KEY POINTS

- Necrotizing fasciitis initially resembles cellulitis before rapid progression of subdermal infection manifesting with clinical signs of edema, "woody" induration, severe pain, hemorrhagic bullous lesions, skin necrosis, local crepitus, fever, hypotension, tachycardia, mental status changes, and tachypnea; necrosis of local nerves may result in anesthesia.
- In patients with suspected necrotizing fasciitis, MRI with contrast is more sensitive than plain radiography or CT and can help delineate anatomic involvement.

Purulent Skin Infections

Abscesses are erythematous, nodular, localized collections of pus within the dermis and subcutaneous fat. Furuncles (boils) are hair follicle-associated abscesses that extend into the dermis and subcutaneous tissue. These inflammatory nodules are typically seen on the face, neck, and axilla. Infection that extends subcutaneously to involve several furuncles is known as a carbuncle. This coalescence of abscesses can result in systemic signs of infection.

Primary treatment for abscesses, furuncles, and carbuncles is incision and drainage. Gram stain and culture should be obtained from the purulent drainage when antibiotic administration is planned. Mild lesions without systemic symptoms do not require antibiotic therapy after drainage. For patients with moderate infections who have systemic signs of infection, empiric treatment is recommended (see Table 8). Empiric treatment with parenteral therapy is also recommended in immunocompromised patients, patients with hypotension and systemic inflammatory response syndrome (severe infection), or patients in whom incision and drainage plus oral antibiotics fail. Treatment is adjusted based on sensitivities from culture of the purulent drainage.

If MRSA is the cause of multiple recurrences of purulent skin infection, decolonization with topical intranasal mupirocin and chlorhexidine washes should be considered. Other diagnoses such as hidradenitis suppurativa, pilonidal cysts, or a foreign body should be considered when no microbial cause is identified.

Newer antibiotics for skin and soft tissue infections caused by *Streptococcus* and *Staphylococcus* species (including MRSA) include tedizolid, oritavancin, and dalbavancin. Use of these antibiotics is recommended in consultation with infectious disease specialists.

KEY POINTS

- Primary treatment for abscesses, furuncles, and carbuncles is incision and drainage; mild infections (without systemic symptoms) do not require antibiotic therapy. **HVC**
- For moderate and severe purulent infections associated with systemic symptoms, Gram stain and culture should be performed on the purulent drainage followed by empiric oral antibiotic treatment for moderate infections and empiric intravenous antibiotics for severe infections.

Animal Bites

Bites from cats and dogs represent approximately 1% of emergency department visits in the United States; most wounds (about 80%) will not become infected. Cat bites are more likely to become infected because of deeper puncture wounds created by cats' sharp, slender teeth. The microbiology of infection depends on the microbiota of the animal's mouth and of the patient's skin. Mixed aerobes and anaerobes, including staphylococci, streptococci, *Bacteroides* species, *Porphyromonas* species, *Fusobacterium* species, and *Pasteurella* species, typically compose the bacteria in bite wounds. *Capnocytophaga canimorsus* is a common constituent of canine microbiota and can cause severe infections in patients with asplenia.

Wound management includes irrigation with sterile normal saline. Irrigation also allows for characterization of wound extent and dimensions; signs of inflammation and infection, including edema, erythema, pain, necrosis, lymphangitis, and