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Europe in children from countries where routine childhood immunizations are not available. Most patients give a history of primary measles infection at an early age (2 years), which is followed after a latent interval of 6–8 years by the development of a progressive neurologic disorder. Some 85% of patients are between 5 and 15 years old at diagnosis. Initial manifestations include poor school performance and mood and personality changes. Typical signs of a CNS viral infection, including fever and headache, do not occur. As the disease progresses, patients develop progressive intellectual deterioration, focal and/or generalized seizures, myoclonus, ataxia, and visual disturbances. In the late stage of the illness, patients are unresponsive, quadriparetic, and spastic, with hyperactive tendon reflexes and extensor plantar responses.

Diagnostic Studies MRI is often normal early, although areas of increased T2 signal develop in the white matter of the brain and brain stem as disease progresses. The EEG may initially show only nonspecific slowing, but with disease progression, patients develop a characteristic periodic pattern with bursts of high-voltage, sharp, slow waves every 3–8 s, followed by periods of attenuated (“flat”) background. The CSF is acellular with a normal or mildly elevated protein concentration and a markedly elevated gamma globulin level (>20% of total CSF protein). CSF antimeasles antibody levels are invariably elevated, and oligoclonal antimeasles antibodies are often present. Measles virus can be cultured from brain tissue using special cocultivation techniques. Viral antigen can be identified immunocytochemically, and viral genome can be detected by in situ hybridization or PCR amplification. **TREATMENT** Subacute Sclerosing Panencephalitis **PART 5 Infectious Diseases** No definitive therapy for SSPE is available. Treatment with isoprinosine (Inosiplex, 100 mg/kg per day), alone or in combination with intrathecal or intraventricular interferon- α , has been reported to prolong survival and produce clinical improvement in some patients but has never been subjected to a controlled clinical trial. ■

■ **PROGRESSIVE RUBELLA PANENCEPHALITIS** This is an extremely rare disorder that primarily affects males with congenital rubella syndrome, although isolated cases have been reported following childhood rubella. After a latent period of 8–19 years, patients develop progressive neurologic deterioration. The manifestations are similar to those seen in SSPE. CSF shows a mild lymphocytic pleocytosis, slightly elevated protein concentration, markedly increased gamma globulin, and rubella virus-specific oligoclonal bands. No therapy is available. Universal prevention of both congenital and childhood rubella through the use of the available live attenuated rubella vaccine would be expected to eliminate the disease. ■ ■ **FURTHER READING** Bernard-Valnet R et al: Advances in treatment of progressive multifocal leukoencephalopathy. *Ann Neurol* 90:865, 2021. Hodzic E et al: Steroids for the treatment of viral encephalitis: A systematic literature review and meta-analysis. *Neurology* 270:3603, 2023. Kaiser JA et al: Twenty years of progress toward West Nile virus vaccine development. *Viruses* 11:823, 2019. Ramachandran PS, Wilson MR:

Metagenomics for neurological infections: Expanding our imagination. *Nat Rev Neurol* 16:547, 2020. Tunkel AR et al: The management of encephalitis: Clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 47:303, 2008. Tyler KL: Acute viral encephalitis. *N Engl J Med* 379:557, 2018. Venkatesan A et al: International Encephalitis Consortium. Case definitions, diagnostic algorithms, and priorities in encephalitis: Consensus statement of the International Encephalitis Consortium. *Clin Infect Dis* 57:1114, 2013.

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Acute Meningitis BACTERIAL MENINGITIS ■ ■ **DEFINITION** Bacterial meningitis is an acute purulent infection within the subarachnoid space (SAS). It is associated with a central nervous system (CNS) inflammatory reaction that may result in decreased consciousness, seizures, raised intracranial pressure (ICP), and stroke. The meninges, SAS, and brain parenchyma are all frequently involved in the inflammatory reaction (meningoencephalitis). ■ ■ **EPIDEMIOLOGY** Bacterial meningitis is the most common form of suppurative CNS infection, with an annual incidence in the United States of ~1.4 cases/100,000 population. The organisms most often responsible for community-acquired bacterial meningitis are *Streptococcus pneumoniae* (~50%), *Neisseria meningitidis* (~25%), group B streptococci (~15%), and *Listeria monocytogenes* (~10%). *Haemophilus influenzae* type b accounts for <10% of cases of bacterial meningitis in most series. *N. meningitidis* is the causative organism of recurring epidemics of meningitis every 8–12 years. ■ ■ **ETIOLOGY** *S. pneumoniae* (Chap. 151) is the most common cause of meningitis in adults >20 years of age, accounting for nearly half the reported cases (1.1 per 100,000 persons per year). There are a number of predisposing conditions that increase the risk of pneumococcal meningitis, the most important of which is pneumococcal pneumonia. Additional risk factors include coexisting acute or chronic pneumococcal sinusitis or otitis media, alcoholism, diabetes, splenectomy, hypogammaglobulinemia, complement deficiency, and head trauma with basilar skull fracture and cerebrospinal fluid (CSF) rhinorrhea. The mortality rate remains ~20% despite antibiotic therapy. The incidence of meningitis due to *N. meningitidis* (Chap. 160) has decreased with the routine immunization of 11- to 18-year-olds with the quadrivalent (serogroups A, C, W-135, and Y) meningococcal glycoconjugate vaccine, and adolescents and young adults (16–23 years old) with the serogroup B meningococcal vaccine. A pentavalent meningococcal vaccine (serogroups A, B, C, W-135, and Y) has recently become available. Individuals being treated with complement inhibitors are at increased risk of meningococcal disease and should receive either the quadrivalent vaccine and a serogroup B meningococcal vaccine, or the pentavalent meningococcal vaccine, prior to beginning therapy. Individuals with complement component deficiencies are at increased risk for meningococcal disease and similarly should receive either the quadrivalent and a serogroup B meningococcal vaccine or the pentavalent meningococcal vaccine. The meningococcal vaccines use outer membrane proteins as the vaccine antigens. The serogroup B polysaccharide capsule is poorly immunogenic. The serogroup B meningococcal vaccines do not reduce the risk of bacterial spread of group B meningococcus from vaccinated persons to unimmunized persons as the vaccines do not significantly reduce nasopharyngeal carriage of meningococci, and this remains the major source of person-to-person bacterial transmission. In contrast, nasopharyngeal carriage is reduced in vaccinated individuals who have received the conjugate vaccines that cover groups A, C, W, and Y. The presence of petechial or purpuric skin lesions can provide an important clue to the diagnosis of meningococcal infection. In some patients, the disease is fulminant, progressing to death within hours of symptom onset. Infection may be initiated by nasopharyngeal colonization,

which can result in either an asymptomatic carrier state or invasive meningococcal disease. The risk of invasive disease following nasopharyngeal colonization depends on both bacterial virulence factors and host immune defense mechanisms, including the host's capacity to produce antimeningococcal antibodies

and to lyse meningococci by both classic and alternative complement pathways. Individuals with deficiencies of any of the complement components, including properdin, are highly susceptible to meningococcal infections. Gram-negative bacilli cause meningitis in individuals with chronic and debilitating diseases such as diabetes, cirrhosis, or alcoholism and in those with urinary tract infections. Gram-negative meningitis can also complicate neurosurgical procedures, particularly craniotomy, and head trauma associated with CSF rhinorrhea or otorrhea. Otitis, mastoiditis, and sinusitis are predisposing and associated conditions for meningitis due to *Streptococcus* spp., gram-negative anaerobes, *Staphylococcus aureus*, *Haemophilus* spp., and *Enterobacteriaceae*. Meningitis complicating endocarditis may be due to viridans streptococci, *S. aureus*, *Streptococcus bovis*, the HACEK group (*Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*), or enterococci. Group B streptococcus, or *Streptococcus agalactiae* (Chap. 153), was previously responsible for meningitis predominantly in neonates, but it has been reported with increasing frequency in individuals aged

■ 50 years, particularly those with underlying diseases. *L. monocytogenes* (Chap. 156) is an increasingly important cause of meningitis in neonates (<1 month of age), pregnant women, individuals >60 years, and immunocompromised individuals of all ages. Infection is acquired by ingesting foods contaminated by *Listeria*. Foodborne human listerial infection has been reported from contaminated coleslaw, milk, soft cheeses, and several types of "ready-to-eat" foods, including delicatessen meat and uncooked hotdogs. The frequency of *H. influenzae* type b (Hib) meningitis in children has declined dramatically since the introduction of the Hib conjugate vaccine, although rare cases of Hib meningitis in vaccinated children have been reported. More frequently, *H. influenzae* causes meningitis in unvaccinated children and older adults, and non-b *H. influenzae* is an emerging pathogen (Chap. 162). *S. aureus* and coagulase-negative staphylococci (Chap. 152) are important causes of meningitis that occurs following invasive neurosurgical procedures, particularly shunting procedures for hydrocephalus, or as a complication of the use of subcutaneous Ommaya reservoirs for administration of intrathecal chemotherapy. ■

■ **PATHOPHYSIOLOGY** The most common bacteria that cause meningitis, *S. pneumoniae* and *N. meningitidis*, initially colonize the nasopharynx by attaching to nasopharyngeal epithelial cells. Bacteria are transported across epithelial cells in membrane-bound vacuoles to the intravascular space or invade the intravascular space by creating separations in the apical tight junctions of columnar epithelial cells. Once in the bloodstream, bacteria are able to avoid phagocytosis by neutrophils and classic complement-mediated bactericidal activity because of the presence of a polysaccharide capsule. Bloodborne bacteria can reach the intraventricular choroid plexus, directly infect choroid

plexus epithelial cells, and gain access to the CSF. Some bacteria, such as *S. pneumoniae*, can adhere to cerebral capillary endothelial cells and subsequently migrate through or between these cells to reach the CSF. Bacteria are able to multiply rapidly within CSF because of the absence of effective host immune defenses. Normal CSF contains few white blood cells (WBCs) and relatively small amounts of complement proteins and immuno globulins. The paucity of the latter two prevents effective opsonization of bacteria, an essential prerequisite for bacterial phagocytosis by neutrophils. Phagocytosis of bacteria is further impaired by the fluid nature of CSF, which is less conducive to phagocytosis than a solid tissue substrate. A critical event in the pathogenesis of bacterial meningitis is the inflammatory reaction induced by the invading bacteria. Many of the neurologic manifestations and complications of bacterial meningitis result from the immune response to the invading pathogen rather than from direct bacteria-induced tissue injury. As a result, neurologic injury can progress even after the CSF has been sterilized by antibiotic therapy. The lysis of bacteria with the subsequent release of cell-wall components into the SAS is the initial step in the induction of the

inflammatory response and the formation of a purulent exudate in the SAS (Fig. 143-1). Bacterial cell-wall components, such as the lipopolysaccharide (LPS) molecules of gram-negative bacteria and teichoic acid and peptidoglycans of *S. pneumoniae*, induce meningeal inflammation by stimulating the production of inflammatory cytokines and chemokines by microglia, astrocytes, monocytes, microvascular endothelial cells, and CSF leukocytes. In experimental models of meningitis, cytokines including tumor necrosis factor alpha (TNF- α) and interleukin 1 β (IL-1 β) are present in CSF within 1–2 h of intracisternal inoculation of LPS. This cytokine response is quickly followed by an increase in CSF protein concentration and leukocytosis. Chemokines (cytokines that induce chemotactic migration in leukocytes) and a variety of other proinflammatory cytokines are also produced and secreted by leukocytes and tissue cells that are stimulated by IL-1 β and TNF- α . In addition, bacteremia and the inflammatory cytokines induce the production of excitatory amino acids, reactive oxygen and nitrogen species (free oxygen radicals, nitric oxide, and peroxynitrite), and other mediators that can induce death of brain cells, especially in the dentate gyrus of the hippocampus.

Much of the pathophysiology of bacterial meningitis is a direct consequence of elevated levels of CSF cytokines and chemokines. TNF- α and IL-1 β act synergistically to increase the permeability of the blood-brain barrier, resulting in induction of vasogenic edema and the leakage of serum proteins into the SAS (Fig. 143-1). The subarachnoid exudate of proteinaceous material and leukocytes obstructs the flow of CSF through the ventricular system and diminishes the resorptive capacity of the arachnoid granulations in the dural sinuses, leading to obstructive and communicating hydrocephalus and concomitant interstitial edema. CHAPTER 143 Inflammatory cytokines upregulate the expression of selectins on cerebral capillary endothelial cells and leukocytes, promoting leukocyte adherence to vascular endothelial cells and subsequent migration into the CSF. The adherence of leukocytes to capillary endothelial cells increases the permeability of blood vessels, allowing for the leakage of plasma proteins into the CSF, which adds to the

inflammatory exudate. Neutrophil degranulation results in the release of toxic metabolites that contribute to cytotoxic edema, cell injury, and death. Contrary to previous beliefs, CSF leukocytes probably do little to contribute to the clearance of CSF bacterial infection. Acute Meningitis During the very early stages of meningitis, there is an increase in cerebral blood flow, soon followed by a decrease in cerebral blood flow and a loss of cerebrovascular autoregulation (Chap. 318). Narrowing of the large arteries at the base of the brain due to encroachment by the purulent exudate in the SAS and infiltration of the arterial wall by inflammatory cells with intimal thickening (vasculitis) also occur and may result in ischemia and infarction, obstruction of branches of the middle cerebral artery by thrombosis, thrombosis of the major cerebral venous sinuses, and thrombophlebitis of the cerebral cortical veins. The combination of interstitial, vasogenic, and cytotoxic edema leads to raised ICP and coma. Cerebral herniation usually results from the effects of cerebral edema, either focal or generalized; hydrocephalus and dural sinus or cortical vein thrombosis may also play a role. ■ ■CLINICAL PRESENTATION Meningitis can present as either an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days. The classic clinical triad of meningitis is fever, headache, and nuchal rigidity, and these features each occur in

■ 80% of adult cases of acute bacterial meningitis, although the complete classic triad is not always present. A decreased level of consciousness occurs in >75% of patients and can vary from lethargy to coma. Nausea, vomiting, and photophobia are also common complaints. Nuchal rigidity (“stiff neck”) is the pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion. Kernig’s and Brudzinski’s signs are also classic signs of meningeal irritation. Kernig’s sign is elicited with the patient in the supine position. The thigh is flexed on the abdomen, with the knee flexed; attempts to passively extend the knee elicit pain when meningeal irritation is present. Brudzinski’s sign is elicited with the patient in the supine

Invasion of SAS by meningeal pathogens Multiplication of organisms and lysis of organisms by bactericidal antibiotics Release of bacterial cell-wall components (endotoxin, teichoic acid) Production of inflammatory cytokines Altered blood-brain barrier permeability Adherence of leukocytes to cerebral capillary endothelial cells Leukocytes migrate into CSF, degranulate, and release toxic metabolites Permeability of blood vessels with leakage of plasma proteins into CSF Exudate in SAS obstructs outflow and resorption of CSF and surrounds and infiltrates cerebral vasculature Cerebral ischemia Blood flow Blood flow Vasogenic edema Obstructive and communicating hydrocephalus and interstitial edema Cytotoxic edema, stroke, seizures PART 5 Infectious Diseases Intracranial pressure Coma FIGURE 143-1 The pathophysiology of the neurologic complications of bacterial meningitis. CSF, cerebrospinal fluid; SAS, subarachnoid space. position and is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees. Although commonly tested on physical examinations, the sensitivity and specificity of Kernig’s and Brudzinski’s signs are uncertain. Both may be absent or reduced in very young or elderly patients, immunocompromised individuals, or patients with a severely depressed mental status. The high prevalence of cervical spine disease in older individuals may result in false-positive tests for nuchal rigidity. Seizures occur as part of the initial presentation of bacterial men

ingitis or during the course of the illness in 15–40% of patients. Focal seizures are usually due to focal arterial ischemia or infarction, cortical venous thrombosis with hemorrhage, or focal edema. Generalized seizure activity and status epilepticus may be due to hyponatremia, cerebral anoxia, or, less commonly, the toxic effects of antimicrobial agents. Raised ICP is an expected complication of bacterial meningitis and the major cause of obtundation and coma in this disease. More than 90% of patients will have a CSF opening pressure >180 mmH₂O, and 20% have opening pressures >400 mmH₂O. Signs of increased ICP include a deteriorating or reduced level of consciousness, papilledema, dilated poorly reactive pupils, sixth nerve palsies, decerebrate posturing, and the Cushing reflex (bradycardia, hypertension, and irregular respirations). The most disastrous complication of increased ICP is cerebral herniation. The incidence of herniation in patients with bacterial meningitis has been reported to occur in as few as 1% to as many as 8% of cases. Specific clinical features may provide clues to the diagnosis of individual organisms and are discussed in more detail in specific chapters

devoted to individual pathogens. The most important of these clues is the rash of meningococemia, which begins as a diffuse erythematous maculopapular rash resembling a viral exanthem; however, the skin lesions of meningococemia rapidly become petechial. Petechiae are found on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles. ■ ■ **DIAGNOSIS** When bacterial meningitis is suspected, blood cultures should be immediately obtained and empirical antimicrobial and adjunctive dexamethasone therapy initiated without delay (Table 143-1). Therapy with dexamethasone should ideally be started 20 min before, or not later than concurrent with, the first dose of antibiotics. The diagnosis of bacterial meningitis is made by examination of the CSF (Table 143-2). The need to obtain neuroimaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) prior to lumbar puncture (LP) requires clinical judgment. In an immunocompetent patient with no known history of recent head trauma, a normal level of consciousness, and no evidence of papilledema or focal neurologic deficits, it is considered safe to perform LP without prior neuroimaging studies. If LP is delayed in order to obtain neuroimaging studies, empirical antibiotic therapy should be initiated after blood cultures are obtained. Antibiotic therapy initiated a few hours prior to LP will not significantly alter the CSF WBC count or glucose concentration, nor is it likely to prevent visualization of organisms by Gram's stain or detection of bacterial nucleic acid by polymerase chain reaction (PCR) assay. Alterations in cerebral blood flow Production of excitatory amino acids and reactive oxygen and nitrogen species Cell injury and death The classic CSF abnormalities in bacterial meningitis (Table 143-2) are (1) polymorphonuclear (PMN) leukocytosis (>100 cells/μL in 90%), (2) decreased glucose concentration (<2.2 mmol/L [<40 mg/dL] and/or CSF/serum glucose ratio of <0.4 in ~60%), (3) increased protein concentration (>0.45 g/L [>45 mg/dL] in 90%), and (4) increased opening pressure (>180 mmH₂O in 90%). CSF bacterial cultures are positive in >70% of patients, and CSF Gram's stain demonstrates organisms in >60%. CSF glucose concentrations <2.2 mmol/L (<40 mg/dL) are abnormal, and a CSF glucose concentration of zero can be seen in bacterial meningitis. Use of the CSF/serum glucose ratio corrects for hyperglycemia that may mask a relative decrease in the CSF glucose concentration. The CSF glucose concentration is low when the CSF/serum glucose ratio is <0.6. A CSF/serum glucose ratio <0.4 is highly suggestive of bacterial meningitis but may also be seen in other conditions, including fungal, tuberculous, and carcinomatous meningitis. It takes from 30 min to several hours for the concentration of CSF glucose to reach equilibrium with blood glucose levels; therefore, administration of 50 mL of 50% glucose (D50) prior to LP, as commonly occurs in emergency room

settings, is unlikely to alter CSF glucose concentration significantly unless more than a few hours have elapsed between glucose administration and LP. The presently available CSF multiplex PCR pathogen assays, the most common of which is the FilmArray Meningitis/Encephalitis panel (BioFire Diagnostics), detect the nucleic acid of *S. pneumoniae*,

TABLE 143-1 Antibiotics Used in Empirical Therapy of Bacterial Meningitis and Focal Central Nervous System Infections^a

INDICATION	ANTIBIOTIC
Preterm infants to infants <1 month	Ampicillin + cefotaxime
Infants 1–3 months	Ampicillin + cefotaxime or ceftriaxone
Immunocompetent children >3 months and adults <55	Cefotaxime, ceftriaxone, or cefepime + vancomycin
Adults >55 and adults of any age with alcoholism or other debilitating illnesses	Ampicillin + cefotaxime, ceftriaxone, or cefepime + vancomycin
Hospital-acquired meningitis, posttraumatic or postneurosurgery meningitis, neutropenic patients, or patients with impaired cell-mediated immunity	Ampicillin + ceftazidime or meropenem + vancomycin

TOTAL DAILY DOSE AND DOSING INTERVAL

CHILD (>1 MONTH)	ADULT	ANTIMICROBIAL AGENT
Ampicillin 300 (mg/kg)/d, q6h	12 g/d, q4h	Cefepime 150 (mg/kg)/d, q8h
6 g/d, q4h	Cefotaxime 225–300 (mg/kg)/d, q6h	12 g/d, q4h
Ceftriaxone 100 (mg/kg)/d, q12h	4 g/d, q12h	Ceftazidime 150 (mg/kg)/d, q8h
6 g/d, q8h	Gentamicin 7.5 (mg/kg)/d, q8hb	7.5 (mg/kg)/d, q8h
Meropenem 120 (mg/kg)/d, q8h	6 g/d, q8h	Metronidazole 30 (mg/kg)/d, q6h
1500–2000 mg/d, q6h	Nafcillin 200 (mg/kg)/d, q6h	12 g/d, q4h
Penicillin G 400,000 (U/kg)/d, q4h	20–24 million U/d, q4h	Vancomycin 45–60 (mg/kg)/d, q6h
45–60 (mg/kg)d, q6–12hb		

^aAll antibiotics are administered intravenously; doses indicated assume normal renal and hepatic function. ^bDoses should be adjusted based on serum peak and trough levels: gentamicin therapeutic level: peak: 5–8 µg/mL; trough: <2 µg/mL; vancomycin therapeutic level: peak: 25–40 µg/mL; trough: 5–15 µg/mL. *N. meningitidis*, *Escherichia coli*, *L. monocytogenes*, *H. influenzae*, and *S. agalactiae* (group B streptococci). Although these PCR assays have a rapid turnaround time, the sensitivity and specificity for the bacterial meningeal pathogens they test for are not known. The CSF multiplex PCR pathogen assays do not include *S. aureus*, coagulase-negative staphylococci, and many gram-negative organisms. The PCR assays cannot replace CSF bacteria culture, as culture is required for antimicrobial susceptibility testing. Almost all patients with bacterial meningitis will have neuroimaging studies performed during the course of their illness. MRI is preferred over CT because of its superiority in demonstrating areas of cerebral edema and ischemia. In patients with bacterial meningitis, diffuse meningeal enhancement is often seen

“ 180 mmH₂O White blood cells 10/µL to 10,000/µL; neutrophils predominate Red blood cells Absent in nontraumatic tap Glucose <2.2 mmol/L (<40 mg/dL) CSF/serum glucose <0.4 Protein 0.45 g/L (>45 mg/dL) Gram’s stain Positive in >60% Culture Positive in >80% PCR Detects bacterial DNA Abbreviation: PCR, polymerase chain reaction.

after the administration of gadolinium. Meningeal enhancement is not diagnostic of meningitis but occurs in any CNS disease associated with increased blood-brain barrier permeability.

Petechial skin lesions, if present, should be biopsied. The rash of meningococcemia results from the dermal seeding of organisms with vascular endothelial damage, and biopsy may reveal the

organism on Gram's stain. ■ ■

DIFFERENTIAL DIAGNOSIS

Viral meningoencephalitis, and particularly herpes simplex virus (HSV) encephalitis (Chap. 142), can mimic the clinical presentation of bacterial meningitis (encephalitis). HSV encephalitis typically presents with headache, fever, altered consciousness, focal neurologic deficits (e.g., dysphasia, hemiparesis), and focal or generalized seizures. The findings on CSF studies, neuroimaging, and electroencephalogram (EEG) distinguish HSV encephalitis from bacterial meningitis. The typical CSF profile with viral CNS infections is a lymphocytic pleocytosis with a normal glucose concentration, in contrast to the PMN pleocytosis and hypoglycorrhachia characteristic of bacterial meningitis. The CSF HSV PCR has a 96% sensitivity and a 99% specificity when CSF is examined 72 h following symptom onset and in the first week of antiviral therapy. MRI abnormalities (other than meningeal enhancement) are not seen in uncomplicated bacterial meningitis. By contrast, in HSV encephalitis, on T2-weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted MRI images, high-signal-intensity lesions are seen in the orbitofrontal, anterior, and medial temporal lobes in the majority of patients within 48 h of symptom onset. Some patients with HSV encephalitis have a distinctive periodic pattern on EEG.

CHAPTER 143 Rickettsial disease (Chap. 192)

can resemble bacterial meningitis. Rocky Mountain spotted fever (RMSF) is transmitted by a tick bite and caused by the bacteria *Rickettsia rickettsii*. The disease may present acutely with high fever, prostration, myalgia, headache, nausea, and vomiting. Most patients develop a characteristic rash within 96 h of the onset of symptoms. The rash is initially a diffuse erythematous maculopapular rash that may be difficult to distinguish from that of meningococcemia. It progresses to a petechial rash, then to a purpuric rash, and if untreated, to skin necrosis or gangrene. The color of the lesions changes from bright red to very dark red, then yellowishgreen to black. The rash typically begins in the wrist and ankles and then spreads distally and proximally within a matter of a few hours, involving the palms and soles. Diagnosis is made by immunofluorescent staining of skin biopsy specimens. Ehrlichioses are also transmitted by a tick bite. These are small gram-negative coccobacilli of which two species cause human disease. *Anaplasma phagocytophilum* causes human granulocytic ehrlichiosis (anaplasmosis), and *Ehrlichia chaffeensis* causes human monocytic ehrlichiosis. The clinical and laboratory manifestations of the infections are similar. Patients present with fever, headache, confusion, nausea, and vomiting. Twenty percent of patients have a maculopapular or petechial rash. There is laboratory evidence of leukopenia, thrombocytopenia, and anemia, and mild to moderate elevations in alanine aminotransferases, alkaline phosphatase, and lactate dehydrogenase. Patients with RMSF and those with ehrlichial infections may have an altered level of consciousness ranging from mild lethargy to coma, confusion, focal neurologic signs, cranial nerve palsies, hyperreflexia, and seizures.

Acute Meningitis

Focal suppurative CNS infections, including subdural and epidural empyema and brain abscess, should also be considered (Chap. 145), especially when focal neurologic findings are present. MRI should be performed promptly in all patients with suspected meningitis who have focal features, both to detect the intracranial infection and to search for associated areas of infection in the sinuses or mastoid bones. A number of noninfectious CNS disorders can mimic bacterial meningitis. Subarachnoid hemorrhage (SAH; Chap. 440) is generally the major consideration. Other possibilities include medication-induced hypersensitivity meningitis; chemical meningitis due to rupture of tumor contents into the CSF (e.g., from a cystic glioma, craniopharyngioma, epidermoid or dermoid cyst); carcinomatous or lymphomatous meningitis; meningitis associated with inflammatory disorders such as sarcoid, systemic lupus erythematosus (SLE), and

Behçet's syndrome; pituitary apoplexy; and uveomeningitic syndromes (Vogt-Koyanagi-Harada syndrome).

On occasion, subacutely evolving meningitis (see below and Chap. 144) may be considered in the differential diagnosis of acute meningitis. The principal causes include *Mycobacterium tuberculosis* (Chap. 183), *Cryptococcus neoformans* (Chap. 221), *Histoplasma capsulatum* (Chap. 218), *Coccidioides immitis* (Chap. 219), and *Treponema pallidum* (Chap. 187). **TREATMENT** Acute Bacterial Meningitis **EMPIRICAL ANTIMICROBIAL THERAPY** (Table 143-1) Bacterial meningitis is a medical emergency. The goal is to begin antibiotic therapy within 60 min of a patient's arrival in the emergency room. Empirical antimicrobial therapy is initiated in patients with suspected bacterial meningitis before the results of CSF multiplex PCR assays, Gram's stain, and culture are known.

S. pneumoniae (Chap. 151) and *N. meningitidis* (Chap. 160) are the most common etiologic organisms of community-acquired bacterial meningitis. Due to the emergence of penicillin- and cephalosporin-resistant *S. pneumoniae*, empirical therapy of community-acquired suspected bacterial meningitis in children and adults should include a combination of dexamethasone, a third- or fourth-generation cephalosporin (e.g., ceftriaxone, cefotaxime, or cefepime), and vancomycin, plus acyclovir, as HSV encephalitis is the leading disease in the differential diagnosis, and doxycycline during tick season to treat tick-borne bacterial infections. Ceftriaxone or cefotaxime provides good coverage for susceptible *S. pneumoniae*, group B streptococci, and *H. influenzae* and adequate coverage for *N. meningitidis*. Cefepime is a broad-spectrum fourth-generation cephalosporin with in vitro activity similar to that of cefotaxime or ceftriaxone against *S. pneumoniae* and *N. meningitidis* and greater activity against *Enterobacter* species and *Pseudomonas aeruginosa*. In clinical trials, cefepime has been demonstrated to be equivalent to cefotaxime in the treatment of penicillin-sensitive pneumococcal and meningococcal meningitis, and it has been used successfully in some patients with meningitis due to *Enterobacter* species and

P. aeruginosa. Cefepime has been associated with seizures, myoclonus, and encephalopathy, any of which may limit its use in critically ill patients. Ampicillin should be added to the empirical regimen for coverage of *L. monocytogenes* in individuals <3 months of age, those

“ 55, or those with suspected impaired cell-mediated immunity because of chronic illness, organ transplantation, pregnancy, malignancy, or immunosuppressive therapy. Metronidazole is added to the empirical regimen to cover gram-negative anaerobes in patients with otitis, sinusitis, or mastoiditis. In hospital-acquired meningitis, and particularly meningitis following neurosurgical procedures, staphylococci and gram-negative organisms including *P. aeruginosa* are the most common etiologic organisms. In these patients, empirical therapy should include a combination of vancomycin and ceftazidime or meropenem. Ceftazidime or meropenem should be substituted for ceftriaxone or cefotaxime in neurosurgical patients and in neutropenic patients because ceftriaxone and cefotaxime do not provide adequate activity against CNS infection with *P. aeruginosa*. Meropenem is a carbapenem antibiotic that is

highly active in vitro against *L. monocytogenes*, has been demonstrated to be effective in cases of meningitis caused by *P. aeruginosa*, and shows good activity against penicillin-resistant pneumococci. In experimental pneumococcal meningitis, meropenem was comparable to ceftriaxone and inferior to vancomycin in sterilizing CSF cultures. When *S. pneumoniae*, *H. influenzae*, *L. monocytogenes*, or aerobic gram-negative bacilli (including *P. aeruginosa* and *E. coli*) are possible meningeal pathogens, based on predisposing and associated conditions, the combination of vancomycin plus meropenem can be recommended as empiric therapy for bacterial meningitis in children and adults. Meropenem should not be used as monotherapy. PART 5 Infectious Diseases

TABLE 143-3 Antimicrobial Therapy of Central Nervous System Bacterial Infections Based on Pathogen

ORGANISM	ANTIBIOTIC
<i>Neisseria meningitidis</i>	Penicillin-sensitive Penicillin G or ampicillin
Penicillin-resistant	Ceftriaxone or cefotaxime
<i>Streptococcus pneumoniae</i>	Penicillin-sensitive Penicillin G
Penicillin-intermediate	Ceftriaxone or cefotaxime or cefepime
Penicillin-resistant	Ceftriaxone (or cefotaxime or cefepime) + vancomycin
Gram-negative bacilli (except <i>Pseudomonas</i> spp.)	Ceftriaxone or cefotaxime
<i>Pseudomonas aeruginosa</i>	Ceftazidime or cefepime or meropenem
Staphylococci spp.	Methicillin-sensitive Nafcillin
Methicillin-resistant	Vancomycin
<i>Listeria monocytogenes</i>	Ampicillin + gentamicin
<i>Haemophilus influenzae</i>	Ceftriaxone or cefotaxime if β -lactamase positive; ampicillin if β -lactamase negative
<i>Streptococcus agalactiae</i>	Penicillin G or ampicillin
<i>Bacteroides fragilis</i>	Metronidazole
<i>Fusobacterium</i> spp.	Metronidazole

Doses are as indicated in Table 143-1.

SPECIFIC ANTIMICROBIAL THERAPY Meningococcal Meningitis (Table 143-3) Although ceftriaxone and cefotaxime provide adequate empirical coverage for *N. meningitidis*, penicillin G remains the antibiotic of choice for meningococcal meningitis caused by susceptible strains. Isolates of *N. meningitidis* with moderate resistance to penicillin have been identified and are increasing in incidence worldwide. CSF isolates of *N. meningitidis* should be tested for penicillin and ampicillin susceptibility, and if resistance is found, cefotaxime or ceftriaxone should be substituted for penicillin. A 7-day course of intravenous antibiotic therapy is adequate for uncomplicated meningococcal meningitis. The index case and all close contacts should receive chemoprophylaxis with a 2-day regimen of rifampin (600 mg every 12 h for 2 days in adults and 10 mg/kg every 12 h for 2 days in children >1 year). Rifampin is not recommended in pregnant women. Alternatively, adults can be treated with one dose of azithromycin (500 mg) or one intramuscular dose of ceftriaxone (250 mg). Close contacts are defined as those individuals who have had contact with oropharyngeal secretions, either through kissing or by sharing toys, beverages, or cigarettes. Pneumococcal Meningitis Antimicrobial therapy of pneumococcal meningitis is initiated with a cephalosporin (ceftriaxone, cefotaxime, or cefepime) and vancomycin. All CSF isolates of

S. pneumoniae should be tested for sensitivity to penicillin and the cephalosporins. Once the results of antimicrobial susceptibility tests are known, therapy can be modified accordingly (Table 143-3). For

S. pneumoniae meningitis, an isolate of *S. pneumoniae* is considered to be susceptible to penicillin with a minimal inhibitory concentration (MIC) $<0.06 \mu\text{g/mL}$ and to be resistant when the MIC is $>0.12 \mu\text{g/mL}$. Isolates of *S. pneumoniae* that have cephalosporin MICs $\leq 0.5 \mu\text{g/mL}$ are considered

sensitive to the cephalosporins (cefotaxime, ceftriaxone, cefepime). Those with MICs of 1 µg/mL are considered to have intermediate resistance, and those with MICs ≥ 2 µg/mL are considered resistant. For meningitis due to pneumococci, with cefotaxime or ceftriaxone MICs ≤ 0.5 µg/mL, treatment with cefotaxime or ceftriaxone is usually adequate. For MIC >1 µg/mL, vancomycin is the antibiotic of choice. Rifampin can be added to vancomycin for its synergistic effect but is inadequate as monotherapy because resistance develops rapidly when it is used alone.

A 2-week course of intravenous antimicrobial therapy is recommended for pneumococcal meningitis. Patients with *S. pneumoniae* meningitis should have a repeat LP performed 24–36 h after the initiation of antimicrobial therapy to document sterilization of the CSF. Failure to sterilize the CSF after 24–36 h of antibiotic therapy should be considered presumptive evidence of antibiotic resistance. Patients with penicillin- and cephalosporin-resistant strains of *S. pneumoniae* who do not respond to intravenous vancomycin alone may benefit from the addition of intraventricular vancomycin. The intraventricular route of administration is preferred over the intrathecal route because adequate concentrations of vancomycin in the cerebral ventricles are not always achieved with intrathecal administration. Listeria Meningitis Meningitis due to *L. monocytogenes* is treated with ampicillin for at least 3 weeks (Table 143-3). Gentamicin is added in critically ill patients (2 mg/kg loading dose, then 7.5 mg/kg per day given every 8 h and adjusted for serum levels and renal function). The combination of trimethoprim (10–20 mg/kg per day) and sulfamethoxazole (50–100 mg/kg per day) given every 6 h may provide an alternative in penicillin-allergic patients. Staphylococcal Meningitis Meningitis due to susceptible strains of *S. aureus* or coagulase-negative staphylococci is treated with nafcillin (Table 143-3). Vancomycin is the drug of choice for methicillin-resistant staphylococci and for patients allergic to penicillin. In these patients, the CSF should be monitored during therapy. If the CSF is not sterilized after 48 h of intravenous vancomycin therapy, then either intraventricular or intrathecal vancomycin, 20 mg once daily, can be added. Gram-Negative Bacillary Meningitis The third-generation cephalosporins—cefotaxime, ceftriaxone, and ceftazidime—are equally efficacious for the treatment of gram-negative bacillary meningitis, with the exception of meningitis due to *P. aeruginosa*, which should be treated with ceftazidime or meropenem (Table 143-3). A 3-week course of intravenous antibiotic therapy is recommended for meningitis due to gram-negative bacilli. ■ ■ADJUNCTIVE THERAPY The release of bacterial cell-wall components by bactericidal antibiotics leads to the production of the inflammatory cytokines IL-1 β and TNF- α in the SAS. Dexamethasone exerts its beneficial effect by inhibiting the synthesis of IL-1 β and TNF- α at the level of mRNA, decreasing CSF outflow resistance, and stabilizing the blood-brain barrier. The rationale for giving dexamethasone 20 min before antibiotic therapy is that dexamethasone inhibits the production of TNF- α by macrophages and microglia only if it is administered before these cells are activated by endotoxin. Dexamethasone does not alter TNF- α production once it has been induced. The results of clinical trials of dexamethasone therapy in meningitis due to *H. influenzae*, *S. pneumoniae*, and

N. meningitidis have demonstrated its efficacy in decreasing meningeal inflammation and neurologic sequelae such as the incidence of sensorineural hearing loss. A prospective European trial of adjunctive therapy for acute bacterial meningitis in adults found that dexamethasone reduced the number of unfavorable outcomes (15 vs 25%, $p = .03$) including death (7 vs 15%, $p = .04$). The benefits were most striking in patients with pneumococcal meningitis. Dexamethasone (10 mg intravenously) was administered 15–20 min before the first dose of an antimicrobial agent, and the same dose was repeated every 6 h for 4 days. These results were confirmed in a second

trial of dexamethasone in adults with pneumococcal meningitis. Therapy with dexamethasone should ideally be started 20 min before, or not later than concurrent with, the first dose of antibiotics. It is unlikely to be of significant benefit if started >6 h after antimicrobial therapy has been initiated. Dexamethasone may decrease the penetration of vancomycin into CSF, and it delays the sterilization of CSF in experimental models of *S. pneumoniae* meningitis. As a result, to assure reliable penetration of vancomycin into the CSF, children and adults are treated with vancomycin in a dose of

45–60 mg/kg per day. Alternatively, vancomycin can be administered by the intraventricular route. In clinical trials, dexamethasone has also been shown to reduce rates of death and hearing loss with no adverse effects in patients with meningococcal meningitis.

One of the concerns for using dexamethasone in adults with bacterial meningitis is that in experimental models of meningitis, dexamethasone therapy increased hippocampal cell injury and reduced learning capacity. This has not been the case in clinical series. The efficacy of dexamethasone therapy in preventing neurologic sequelae is also different between high- and low-income countries. Three large randomized trials in low-income countries (sub-Saharan Africa, Southeast Asia) failed to show benefit in subgroups of patients. The lack of efficacy of dexamethasone in these trials has been attributed to late presentation to the hospital with more advanced disease, antibiotic pretreatment, malnutrition, infection with HIV, and treatment of patients with probable, but not microbiologically proven, bacterial meningitis. The results of these clinical trials suggest that patients in sub-Saharan Africa and those in low-income countries with negative CSF Gram's stain and culture should not be treated with dexamethasone. ■ ■ INCREASED

INTRACRANIAL PRESSURE Emergency treatment of increased ICP includes elevation of the patient's head to 30–45°, intubation, hyperventilation (Paco₂ 25–30 mmHg), and mannitol. Patients with increased ICP should be managed in an intensive care unit; accurate ICP measurements are best obtained with an ICP monitoring device. Treatment of increased ICP is discussed in detail in Chap. 318.

CHAPTER 143 ■ ■ PROGNOSIS Mortality rate is 3–7% for meningitis caused by *H. influenzae*, *N. meningitidis*, or group B streptococci; 15% for that due to *L. monocytogenes*; and 20% for *S. pneumoniae*. In general, the risk of death from bacterial meningitis increases with (1) decreased level of consciousness on admission, (2) onset of seizures within 24 h of admission, (3) signs of increased ICP, (4) young age (infancy) and age >50, (5) the presence of comorbid conditions including shock and/or the need for mechanical ventilation, and (6) delay in the initiation of treatment. Decreased CSF glucose concentration (<2.2 mmol/L [<40 mg/dL]) and markedly increased CSF protein concentration (>3 g/L [>300 mg/dL]) have been predictive of increased mortality and poorer outcomes in some series. Moderate or severe sequelae occur in ~25% of survivors, although the exact incidence varies with the infecting organism. Common sequelae include decreased intellectual function, memory impairment, seizures, hearing loss and dizziness, and gait disturbances. Acute Meningitis

VIRAL MENINGITIS ■ ■ CLINICAL MANIFESTATIONS

Immunocompetent adult patients with viral meningitis usually present with headache, fever, and signs of meningeal irritation coupled with an inflammatory CSF profile (see below). Headache is almost invariably present and often characterized as frontal or retroorbital and frequently associated with photophobia and pain on moving the eyes. Nuchal rigidity is present in most cases but may be mild and present only near the limit of neck antelexion. Constitutional signs can include malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. Patients often have mild lethargy or drowsiness; however, profound alterations in consciousness,

such as stupor, coma, or marked confusion, do not occur in viral meningitis and suggest the presence of encephalitis or other alternative diagnoses. Similarly, seizures or focal neurologic signs or symptoms or neuroimaging abnormalities indicative of brain parenchymal involvement are not typical of viral meningitis and suggest the presence of encephalitis or another CNS infectious or inflammatory process. ■ ■ETIOLOGY Using a variety of diagnostic techniques, including CSF PCR, culture, and serology, a specific viral cause can be found in 60–90% of cases of

TABLE 143-4 Viruses Causing Acute Meningitis in North America COMMON LESS COMMON

Enteroviruses (coxsackieviruses, echoviruses, and the numbered enteroviruses) Varicella-zoster virus Herpes simplex virus 2 Epstein-Barr virus Arthropod-borne viruses (notably WNV) HIV Herpes simplex virus 1 Human herpesvirus 6 Cytomegalovirus Lymphocytic choriomeningitis virus Mumps Zika and other non-WNV arboviruses Abbreviation: WNV, West Nile virus. viral meningitis. The most important agents are enteroviruses (including echoviruses and coxsackieviruses in addition to numbered enteroviruses), varicella-zoster virus (VZV), HSV (HSV-2 > HSV-1), HIV, and arboviruses (Table 143-4). CSF cultures are positive in 30–70% of patients, with the frequency of isolation depending on the specific viral agent. Approximately two-thirds of culture-negative cases of “aseptic” meningitis have a specific viral etiology identified by CSF PCR testing (see below). ■

■EPIDEMIOLOGY Viral meningitis is not a nationally reportable disease; however, it has been estimated that the incidence is at least 75,000 cases per year in the United States. In temperate climates, there is a substantial increase in cases during the nonwinter months, reflecting the seasonal predominance of enterovirus and arthropod-borne virus (arbovirus) infections in the summer and fall, with a peak monthly incidence of about 1 reported case per 100,000 population.

PART 5 Infectious Diseases ■ ■LABORATORY DIAGNOSIS CSF Examination The most important laboratory test in the diagnosis of viral meningitis is examination of the CSF. The typical profile is a pleocytosis, a normal or slightly elevated protein concentration (0.2–0.8 g/L [20–80 mg/dL]), a normal glucose concentration, and a normal or mildly elevated opening pressure (100–350 mmH₂O). Organisms are not seen on Gram’s stain of CSF. The total CSF cell count in viral meningitis is typically 25–500/μL, although cell counts of several thousand/μL are occasionally seen, especially with infections due to lymphocytic choriomeningitis virus (LCMV) and mumps virus. Lymphocytes are typically the predominant cell. Rarely, PMNs may predominate in the first 48 h of illness, especially with infections due to echovirus 9, West Nile virus (WNV), eastern equine encephalitis (EEE) virus, or mumps. A PMN pleocytosis occurs in 45% of patients with WNV meningitis and can persist for a week or longer before shifting to a lymphocytic pleocytosis. PMN pleocytosis with low glucose may also be a feature of cytomegalovirus (CMV) infections in immunocompromised hosts. Despite these exceptions, the presence of a CSF PMN pleocytosis in a patient with suspected viral meningitis in whom a specific diagnosis has not been established should prompt consideration of alternative diagnoses, including bacterial meningitis or parameningeal infections. The CSF glucose concentration is typically normal in viral infections, although it may be decreased in 10–30% of cases due to mumps or LCMV. Rare instances of decreased CSF glucose concentration occur in cases of meningitis due to echoviruses and other enteroviruses, HSV-2, and VZV. As a rule, a lymphocytic pleocytosis with a low glucose concentration should suggest fungal or tuberculous meningitis, *Listeria* meningoencephalitis, or noninfectious disorders (e.g., sarcoid, neoplastic meningitis). A number of tests measuring levels of various CSF proteins, enzymes, and mediators—including C-reactive protein, lactic acid, lactate dehydrogenase, neopterin, quinolinic acid, IL-1β, IL-6, soluble IL-2 receptor, β2-microglobulin, and TNF—have been proposed as potential discriminators between viral and bacterial meningitis or as

markers of specific types of viral infection (e.g., infection with HIV), but they

remain of uncertain sensitivity and specificity and are not widely used for diagnostic purposes.

Polymerase Chain Reaction Amplification of Viral Nucleic Acid Amplification of viral-specific DNA or RNA from CSF using PCR amplification has become the single most important method for diagnosing CNS viral infections. In both enteroviral and HSV infections of the CNS, CSF PCR has become the diagnostic procedure of choice and is substantially more sensitive than viral cultures. HSV CSF PCR is also an important diagnostic test in patients with recurrent episodes of “aseptic” meningitis, many of whom have amplifiable HSV DNA in CSF despite negative viral cultures. The FilmArray Meningitis/Encephalitis panel (BioFire Diagnostics) includes HSV-1, HSV-2, enteroviruses, VZV, human herpesvirus 6 (HHV-6), and human Parechovirus. The panel does not include CMV, WNV, LCMV, or Epstein-Barr virus (EBV). CSF PCR tests are available for WNV but are not as sensitive as detection of WNV-specific CSF IgM. PCR is also useful in the diagnosis of CNS infection caused by *Mycoplasma pneumoniae*, which can mimic viral meningitis and encephalitis. PCR of throat washings may assist in diagnosis of enteroviral and mycoplasmal CNS infections. PCR of stool specimens may also assist in diagnosis of enteroviral infections (see below).

Viral Culture The sensitivity of CSF cultures for the diagnosis of viral meningitis and encephalitis, in contrast to its utility in bacterial infections, is generally poor. In addition to CSF, specific viruses may also be isolated from throat swabs, stool, blood, and urine. Enteroviruses and adenoviruses may be found in feces; arboviruses, some enteroviruses, and LCMV in blood; mumps and CMV in urine; and enteroviruses, mumps, and adenoviruses in throat washings. During enteroviral infections, viral shedding in stool may persist for several weeks. The presence of enterovirus in stool is not diagnostic and may result from residual shedding from a previous enteroviral infection; it also occurs in some asymptomatic individuals during enteroviral epidemics.

Serologic Studies The basic approach to the serodiagnosis of viral meningitis is identical to that for viral encephalitis (see Chap. 142). Serologic studies are important for the diagnosis of arboviruses such as WNV; however, these tests are less useful for viruses such as HSV, VZV, CMV, and EBV that have a high seroprevalence in the general population. CSF oligoclonal γ globulin bands occur in association with a number of viral infections. The associated antibodies are often directed against viral proteins. Oligoclonal bands also occur commonly in certain noninfectious neurologic diseases (e.g., multiple sclerosis) and may be found in nonviral infections (e.g., neurosyphilis, Lyme neuroborreliosis).

Other Laboratory Studies All patients with suspected viral meningitis should have a complete blood count and differential, liver and renal function tests, erythrocyte sedimentation rate (ESR), C-reactive protein, electrolytes, glucose, creatine kinase, aldolase, amylase, and lipase.

Neuroimaging studies (MRI preferable to CT) are not absolutely necessary in patients with uncomplicated viral meningitis but should be performed in patients with altered consciousness, seizures, focal neurologic signs or symptoms (see “Differential Diagnosis” below), atypical CSF profiles, or underlying immunocompromising treatments or conditions. ■ ■

DIFFERENTIAL DIAGNOSIS The most important issue in the differential diagnosis of viral meningitis is to consider diseases that can mimic viral meningitis, including (1) untreated or partially treated bacterial meningitis; (2) early stages of meningitis caused by fungi, mycobacteria, or *Treponema pallidum* (neurosyphilis), in which a lymphocytic pleocytosis is common, cultures may be slow growing or negative, and hypoglycorrhachia may not be present early; (3) meningitis caused by agents such as *Mycoplasma*, *Listeria* spp., *Brucella* spp., *Coxiella* spp., *Leptospira* spp., and *Rickettsia* spp.; (4) parameningeal infections; (5) neoplastic meningitis;

and (6) meningitis secondary to noninfectious inflammatory diseases, including medication-induced hypersensitivity meningitis, SLE and other rheumatologic diseases, sarcoidosis, Behçet's syndrome, and the uveomeningitic syndromes. Studies in children >28 days of age suggest that the presence of CSF protein >0.5 g/L (sensitivity 89%, specificity 78%) and elevated serum procalcitonin levels >0.5 ng/mL (sensitivity 89%, specificity 89%) were clues to the presence of bacterial as opposed to "aseptic" meningitis. A variety of clinical algorithms for differentiating bacterial from aseptic meningitis have been developed. One such prospectively validated system, the bacterial meningitis score, suggests that the probability of bacterial meningitis is 0.3% or less (negative predictive value 99.7%, 95% confidence interval 99.6–100%) in children with CSF pleocytosis who have (1) a negative CSF Gram's stain, (2) CSF neutrophil count <1000 cells/μL, (3) CSF protein <80 mg/dL, (4) peripheral absolute neutrophil count of <10,000 cells/μL, and (5) no prior history or current presence of seizures. ■ ■

SPECIFIC VIRAL ETIOLOGIES Enteroviruses (EVs) (Chap. 210) are the most common cause of viral meningitis, accounting for >85% of cases in which a specific etiology can be identified. Cases may either be sporadic or occur in clusters. EV71 has produced large epidemics of neurologic disease outside the United States, especially in Southeast Asia, but most recently reported cases in the United States have been sporadic. Enteroviruses are the most likely cause of viral meningitis in the summer and fall months, especially in children (<15 years), although cases occur at reduced frequency year-round. Although the incidence of enteroviral meningitis declines with increasing age, some outbreaks have preferentially affected older children and adults. Meningitis outside the neonatal period is usually benign. Patients present with sudden onset of fever; headache; nuchal rigidity; and often constitutional signs, including vomiting, anorexia, diarrhea, cough, pharyngitis, and myalgias. The physical examination should include a careful search for stigmata of EV infection, including exanthems, hand-foot-mouth disease, herpangina, pleurodynia, myopericarditis, and hemorrhagic conjunctivitis. The CSF profile is typically a lymphocytic pleocytosis (100–1000 cells/μL) with normal glucose and normal or mildly elevated protein concentration. However, up to 15% of patients, most commonly young infants rather than older children or adults, have a normal CSF leukocyte count. In rare cases, PMNs may predominate during the first 48 h of illness. CSF reverse transcriptase PCR (RT-PCR) is the diagnostic procedure of choice and is both sensitive (>95%) and specific (>100%). CSF RT-PCR has the highest sensitivity if performed within 48 h of symptom onset, with sensitivity declining rapidly after day 5 of symptoms. RT-PCR of throat washings or stool specimens may be positive for several weeks, and positive results can help support the diagnosis of an acute enteroviral infection. The sensitivity of routine enteroviral RTPCRs for detecting EV71 is low, and specific testing may be required. Treatment is supportive, and patients usually recover without sequelae. Chronic and severe infections can occur in neonates and in individuals with hypo- or agammaglobulinemia.

Arbovirus infections (Chap. 215) occur predominantly in the summer and early fall. Arboviral meningitis should be considered when clusters of meningitis and encephalitis cases occur in a restricted geographic region during the summer or early fall. In the United States, the most important causes of arboviral meningitis and encephalitis are WNV, St. Louis encephalitis virus, and the California encephalitis group of viruses. In WNV epidemics, avian deaths may serve as sentinel infections for subsequent human disease. A history of tick exposure or travel or residence in the appropriate geographic area should suggest the possibility of Colorado tick fever virus or Powassan virus infection, although nonviral tick-borne diseases, including RMSF and Lyme neuroborreliosis, may present similarly. Arbovirus meningitis is typically associated with a CSF lymphocytic pleocytosis, normal glucose concentration, and normal or mildly elevated protein concentration. However, ~45% of patients with WNV meningitis have CSF neutrophilia, which can

persist for a week or more. The rarity of hypoglycorrhachia in WNV infection, the absence of positive Gram's stains, and the negative cultures help distinguish these

patients from those with bacterial meningitis. Definitive diagnosis of arboviral meningitis is based on demonstration of viral-specific IgM in CSF or seroconversion. The prevalence of CSF IgM increases progressively during the first week after infection, peaking at >80% in patients with neuroinvasive disease; as a result, repeat studies may be needed when disease suspicion is high and an early study is negative. CSF RT-PCR tests are available for some viruses in selected diagnostic laboratories and at the Centers for Disease Control and Prevention (CDC), but in the case of WNV, sensitivity (~70%) of CSF RT-PCR is less than that of CSF serology. WNV CSF RT-PCR may be useful in immunocompromised patients who may have absent or reduced antibody responses.

HSV meningitis (Chap. 197) has been increasingly recognized as a major cause of viral meningitis in adults, and overall, it is probably second in importance to enteroviruses as a cause of viral meningitis, accounting for 5% of total cases overall and undoubtedly a higher frequency of those cases occurring in adults and/or outside of the summer-fall period when enterovirus infections are increasingly common. In adults, the majority of cases of uncomplicated meningitis are due to HSV-2, whereas HSV-1 is responsible for 90% of cases of HSV encephalitis. HSV meningitis occurs in ~25–35% of women and ~10–15% of men at the time of an initial (primary) episode of genital herpes. Of these patients, 20% go on to have recurrent attacks of meningitis. Diagnosis of HSV meningitis is usually by HSV CSF PCR because cultures may be negative, especially in patients with recurrent meningitis. Demonstration of intrathecal synthesis of HSV-specific antibody may also be useful in diagnosis, although antibody tests are less sensitive and less specific than PCR and may not become positive until after the first week of infection. Although a history of or the presence of HSV genital lesions is an important diagnostic clue, many patients with HSV meningitis give no history and have no evidence of active genital herpes at the time of presentation. Most cases of recurrent viral or "aseptic" meningitis, including cases previously diagnosed as Mollaret's meningitis, are due to HSV. CHAPTER 143 Acute Meningitis VZV meningitis (Chap. 198) should be suspected in the presence of concurrent chickenpox or shingles. However, it is important to recognize that VZV is being increasingly identified as an important cause of both meningitis and encephalitis in patients without rash. The frequency of VZV as a cause of meningitis is extremely variable, ranging from as low as 3% to as high as 20% in different series. Diagnosis is usually based on CSF PCR, although the sensitivity of this test is not as high as for the other herpesviruses. VZV serologic studies complement PCR testing, and the diagnosis of VZV CNS infection can be made by the demonstration of VZV-specific intrathecal antibody synthesis and/or the presence of VZV CSF IgM antibodies, or by positive CSF cultures. EBV infections (Chap. 199) may also produce aseptic meningitis, with or without associated infectious mononucleosis. The presence of atypical lymphocytes in the CSF or peripheral blood is suggestive of EBV infection but may occasionally be seen with other viral infections. EBV is almost never cultured from CSF. Serum and CSF serology help establish the presence of acute infection, which is characterized by IgM viral capsid antibodies (VCAs), antibodies to early antigens (EAs), and the absence of antibodies to EBV-associated nuclear antigen (EBNA). CSF PCR is another important diagnostic test, although false-positive results may reflect viral reactivation associated with other infectious or inflammatory processes or the presence of latent viral DNA in lymphocytes recruited due to other inflammatory conditions. HIV meningitis should be suspected in any patient presenting with a viral meningitis with known or suspected risk

factors for HIV infection. Meningitis may occur following primary infection with HIV in 5–10% of cases and less commonly at later stages of illness. Cranial nerve palsies, most commonly involving cranial nerves V, VII, or VIII, are more common in HIV meningitis than in other viral infections. Diagnosis can be confirmed by detection of HIV genome in blood or CSF. Seroconversion may be delayed, and patients with negative HIV serologies who are suspected of having HIV meningitis should be monitored for delayed seroconversion. For further discussion of HIV infection, see Chap. 208.

Mumps (Chap. 213) should be considered when meningitis occurs in the late winter or early spring, especially in males (male-to-female ratio 3:1). With the widespread use of the live attenuated mumps vaccine in the United States since 1967, the incidence of mumps meningitis has fallen by >95%; however, mumps remains a potential source of infection in nonimmunized individuals and populations, but also in those who have been vaccinated but may have waning immunity. Rare cases (10–100/100,000 vaccinated individuals) of vaccine-associated mumps meningitis have been described, with onset typically 2–4 weeks after vaccination. The presence of parotitis, orchitis, oophoritis, pancreatitis, or elevations in serum lipase and amylase is suggestive of mumps meningitis; however, their absence does not exclude the diagnosis. Clinical meningitis has been estimated to occur in 10–30% of patients with mumps parotitis. Mumps infection confers lifelong immunity, so a documented history of previous infection excludes this diagnosis. A CSF pleocytosis that can exceed 1000 cells/ μ L is present in 25% of patients with mumps meningitis. Lymphocytes predominate in 75%, although CSF neutrophilia occurs in 25%. Hypoglycorrhachia occurs in 10–30% of patients and may be a clue to the diagnosis when present. Diagnosis is typically made by culture of virus from CSF or by detecting IgM antibodies or seroconversion. CSF PCR is available in some diagnostic and research laboratories.

LCMV infection (Chap. 215) should be considered when aseptic meningitis occurs in the late fall or winter and in individuals with a history of exposure to house mice (*Mus musculus*), pet or laboratory rodents (e.g., hamsters, rats, mice), or their excreta. Some patients have an associated rash, pulmonary infiltrates, alopecia, parotitis, orchitis, or myopericarditis. Laboratory clues to the diagnosis of LCMV, in addition to the clinical findings noted above, may include the presence of leukopenia, thrombocytopenia, or abnormal liver function tests. Some cases present with a marked CSF pleocytosis (>1000 cells/ μ L) and hypoglycorrhachia (<30%). Diagnosis is based on serology and/or culture of virus from CSF.

PART 5 Infectious Diseases TREATMENT Acute Viral Meningitis

Treatment of almost all cases of viral meningitis is primarily symptomatic and includes use of analgesics, antipyretics, and antiemetics. Fluid and electrolyte status should be monitored. Patients with suspected bacterial meningitis should receive appropriate empirical therapy pending culture results (see above). Hospitalization may not be required in immunocompetent patients with presumed viral meningitis and no focal signs or symptoms, no significant alteration in consciousness, and a classic CSF profile (lymphocytic pleocytosis, normal glucose, negative Gram's stain) if adequate provision for monitoring at home and medical follow-up can be ensured. Immunocompromised patients; patients with significant alteration in consciousness, seizures, or the presence of focal signs and symptoms suggesting the possibility of encephalitis or parenchymal brain involvement; and patients who have an atypical CSF profile should be hospitalized. Oral or intravenous acyclovir may be of benefit in patients with meningitis caused by HSV-1 or -2 and in cases of severe EBV or VZV infection. Data concerning treatment of HSV, EBV, and VZV meningitis are extremely limited. Seriously ill patients should probably receive intravenous

acyclovir (15–30 mg/kg per day in three divided doses), which can be followed by an oral drug such as acyclovir (800 mg five times daily), famciclovir (500 mg tid), or valacyclovir (1000 mg tid) for a total course of 7–14 days. Patients who are less ill can be treated with oral drugs alone. Patients with HIV meningitis should receive antiretroviral therapy (Chap. 208). There is no specific therapy of proven benefit for patients with arboviral encephalitis, including that caused by WNV. Patients with viral meningitis who are known to have deficient humoral immunity (e.g., X-linked agammaglobulinemia) and who are not already receiving either intramuscular γ globulin or intravenous immunoglobulin (IVIg) should be treated with these agents.

Intraventricular administration of immunoglobulin through an Ommaya reservoir has been tried in some patients with chronic enteroviral meningitis who have not responded to intramuscular or intravenous immunoglobulin. Vaccination is an effective method of preventing the development of meningitis and other neurologic complications associated with poliovirus, mumps, measles, rubella, and varicella infection. A recombinant zoster vaccine (RSV, Shingrix) contains recombinant VZV glycoprotein E in combination with an adjuvant (AS01B) and has greater efficacy in preventing zoster in adults aged ≥ 70 years than the previously recommended live attenuated vaccine (Zostavax). The Advisory Committee on Immunization Practices recommends the use of the recombinant zoster vaccine in immunocompetent adults aged ≥ 50 years and in immunodeficient or immunosuppressed adults ≥ 19 years of age. ■ ■ **PROGNOSIS** In adults, the prognosis for full recovery from viral meningitis is excellent. Rare patients complain of persisting headache, mild mental impairment, incoordination, or generalized asthenia for weeks to months. The outcome in infants and neonates (<1 year) is less certain; intellectual impairment, learning disabilities, hearing loss, and other lasting sequelae have been reported in some studies. **SUBACUTE MENINGITIS** ■ ■ **CLINICAL MANIFESTATIONS** Patients with subacute meningitis typically have an unrelenting headache, stiff neck, low-grade fever, and lethargy for days to several weeks before they present for evaluation. Cranial nerve abnormalities and night sweats may be present. This syndrome overlaps that of chronic meningitis, discussed in detail in Chap. 144 but is included here because the meningeal pathogens of subacute meningitis can also present as an acute meningitis. ■ ■ **ETIOLOGY** Common causative organisms include *M. tuberculosis*, *C. neoformans*, *H. capsulatum*, *C. immitis*, and *T. pallidum*. Initial infection with

M. tuberculosis is acquired by inhalation of aerosolized droplet nuclei. Tuberculous meningitis in adults does not develop acutely from hematogenous spread of tubercle bacilli to the meninges. Rather, millet seed-sized (miliary) tubercles form in the parenchyma of the brain during hematogenous dissemination of tubercle bacilli in the course of primary infection. These tubercles enlarge and are usually caseating. The propensity for a caseous lesion to produce meningitis is determined by its proximity to the SAS and the rate at which fibrous encapsulation develops. Subependymal caseous foci cause meningitis via discharge of bacilli and tuberculous antigens into the SAS. Mycobacterial antigens produce an intense inflammatory reaction that leads to the production of a thick exudate that fills the basilar cisterns and surrounds the cranial nerves and major blood vessels at the base of the brain. Fungal infections are typically acquired by the inhalation of airborne fungal spores. The initial pulmonary infection may be asymptomatic or present with fever, cough, sputum production, and chest pain. The pulmonary infection is often self-limited. A localized pulmonary fungal infection can then remain dormant in the lungs until there is an abnormality in cell-mediated immunity that allows the fungus to reactivate and disseminate to the CNS. The most common pathogen causing fungal meningitis is *C. neoformans*.

This fungus is found worldwide in soil and bird excreta. *H. capsulatum* is endemic to the Ohio and Mississippi River valleys of the central United States and to parts of Central and South America. *C. immitis* is endemic to the desert areas of the southwest United States, northern Mexico, and Argentina. Syphilis is a sexually transmitted disease that is manifest by the appearance of a painless chancre at the site of inoculation. *T. pallidum* invades the CNS early in the course of syphilis. Cranial nerves VII and VIII are most frequently involved.

■ ■ **LABORATORY DIAGNOSIS** The classic CSF abnormalities in tuberculous meningitis are as follows: (1) elevated opening pressure, (2) lymphocytic pleocytosis (10–500 cells/ μ L), (3) elevated protein concentration in the range of 1–5 g/L, and (4) decreased glucose concentration in the range of 1.1–2.2 mmol/L (20–40 mg/dL). The combination of unrelenting headache, stiff neck, fatigue, night sweats, and fever with a CSF lymphocytic pleocytosis and a mildly decreased glucose concentration is highly suspicious for tuberculous meningitis. The last tube of fluid collected at LP is the best tube to send for a smear for acid-fast bacilli (AFB). If there is a pellicle in the CSF or a cobweb-like clot on the surface of the fluid, AFB can best be demonstrated in a smear of the clot or pellicle. Positive smears are typically reported in only 10–40% of cases of tuberculous meningitis in adults. Cultures of CSF take 4–8 weeks to identify the organism and are positive in ~50% of adults. Culture remains the gold standard to make the diagnosis of tuberculous meningitis. Nucleic acid amplification tests for the detection of *M. tuberculosis* DNA should be sent on CSF if available. The XpertMTB/RIF Ultra and the Xpert MTB/RIF are used most commonly, but the consensus of opinion is that the sensitivity, and thus the risk of false-negative results, has not been defined. The characteristic CSF abnormalities in fungal meningitis are a mononuclear or lymphocytic pleocytosis, an increased protein concentration, and a decreased glucose concentration. There may be eosinophils in the CSF in *C. immitis* meningitis. Large volumes of CSF are often required to demonstrate the organism on India ink smear or grow the organism in culture. If spinal fluid examined by LP on two separate occasions fails to yield an organism, CSF should be obtained by high-cervical or cisternal puncture. The cryptococcal polysaccharide antigen test is a highly sensitive and specific test for cryptococcal meningitis. A reactive CSF cryptococcal antigen test establishes the diagnosis. The detection of the Histoplasma polysaccharide antigen in CSF establishes the diagnosis of a fungal meningitis but is not specific for meningitis due to *H. capsulatum*. It may be falsely positive in coccidioidal meningitis. The CSF complement fixation antibody test is reported to have a specificity of 100% and a sensitivity of 75% for coccidioidal meningitis. The diagnosis of syphilitic meningitis is made when a reactive serum treponemal test (fluorescent treponemal antibody absorption test [FTA-ABS] or microhemagglutination assay–*T. pallidum* [MHA-TP]) is associated with a CSF lymphocytic or mononuclear pleocytosis and an elevated protein concentration, or when the CSF Venereal Disease Research Laboratory (VDRL) test is positive. A reactive CSF FTA-ABS is not definitive evidence of neurosyphilis. The CSF FTA-ABS can be falsely positive from blood contamination. A negative CSF VDRL does not rule out neurosyphilis. A negative CSF FTA-ABS or MHA-TP rules out neurosyphilis.

TREATMENT Subacute Meningitis Empirical therapy of tuberculous meningitis is often initiated based on a high index of suspicion without adequate laboratory support. Initial therapy is a combination of isoniazid (300 mg/d), rifampin (10 mg/kg per day), pyrazinamide (30 mg/kg per day in divided doses), ethambutol (15–25 mg/kg per day in divided doses), and pyridoxine (50 mg/d). When the antimicrobial sensitivity of the *M. tuberculosis* isolate is known, ethambutol can be discontinued. If the clinical response is good, pyrazinamide can be discontinued after 8 weeks and isoniazid and rifampin continued alone for the next 6–12 months. A 6-month course of therapy is acceptable, but therapy should be

prolonged for 9–12 months in patients who have an inadequate resolution of symptoms of meningitis or who have positive mycobacterial cultures of CSF during the course of therapy. Dexamethasone therapy is recommended for HIV-negative patients with tuberculous meningitis. The dose is 12–16 mg/d for 3 weeks, and then tapered over 3 weeks.

Meningitis due to *C. neoformans* in non-HIV, nontransplant patients is treated with induction therapy with amphotericin B (AmB) (0.7 mg/kg IV per day) plus flucytosine (100 mg/kg per day in four divided doses) for at least 4 weeks if CSF culture results are negative after 2 weeks of treatment. Therapy should be extended for a total of 6 weeks in the patient with neurologic complications. Induction therapy is followed by consolidation therapy with fluconazole 400 mg/d for 8 weeks. Organ transplant recipients are treated with liposomal AmB (3–4 mg/kg per day) or AmB lipid complex (ABLC; 5 mg/kg per day) plus flucytosine (100 mg/kg per day in four divided doses) for at least 2 weeks or until CSF culture is sterile. Follow CSF yeast cultures for sterilization rather than the cryptococcal antigen titer. This treatment is followed by an 8- to 10-week course of fluconazole (400–800 mg/d [6–12 mg/kg] PO). If the CSF culture is sterile after 10 weeks of acute therapy, the dose of fluconazole is decreased to 200 mg/d for 6 months to a year. Patients with HIV infection are treated with AmB or a lipid formulation plus flucytosine for at least 2 weeks, followed by fluconazole for a minimum of 8 weeks. HIV-infected patients may require indefinite maintenance therapy with fluconazole 200 mg/d. Meningitis due to *H. capsulatum* is treated with AmB (0.7–1.0 mg/kg per day) for 4–12 weeks. A total dose of 30 mg/kg is recommended. Therapy with AmB is not discontinued until fungal cultures are sterile. After completing a course of AmB, maintenance therapy with itraconazole 200 mg two or three times daily is initiated and continued for at least 9 months to a year. *C. immitis* meningitis is treated with either high-dose fluconazole (1000 mg daily) as monotherapy or intravenous AmB (0.5–0.7 mg/kg per day) for >4 weeks. Intrathecal AmB (0.25–0.75 mg/d three times weekly) may be required to eradicate the infection. Lifelong therapy with fluconazole (200–400 mg daily) is recommended to prevent relapse. AmBisome (5 mg/kg per day) or amphotericin B lipid complex (ABLC; 5 mg/kg per day) can be substituted for AmB in patients who have or who develop significant renal dysfunction. The most common complication of fungal meningitis is hydrocephalus. Patients who develop hydrocephalus should receive a CSF diversion device. A ventriculostomy can be used until CSF fungal cultures are sterile, at which time the ventriculostomy is replaced by a ventriculoperitoneal shunt.

CHAPTER 143 Acute Meningitis Syphilitic meningitis is treated with aqueous penicillin G in a dose of 3–4 million units intravenously every 4 h for 10–14 days. An alternative regimen is 2.4 million units of procaine penicillin G intramuscularly daily with 500 mg of oral probenecid four times daily for 10–14 days. Either regimen is followed with 2.4 million units of benzathine penicillin G intramuscularly once a week for 3 weeks. The standard criterion for treatment success is reexamination of the CSF. The CSF should be reexamined at 6-month intervals for 2 years. The cell count is expected to normalize within 12 months, and the VDRL titer to decrease by two dilutions or revert to non reactive within 2 years of completion of therapy. Failure of the CSF pleocytosis to resolve or an increase in the CSF VDRL titer by two or more dilutions requires retreatment. ■

■ **FURTHER READING** Gundamraj V et al: Viral meningitis and encephalitis: An update. *Curr Opin Infect Dis* 36:177, 2023. Krett JD et al: Neurology of acute viral infections. *Neurohospitalist* 12:632, 2022. Pfefferle S et al: Implementation of the FilmArray ME panel in laboratory routine using a simple sample selection strategy for diagnosis of meningitis and encephalitis. *BMC Infect Dis* 20:170, 2020. Roos KL et al: Acute bacterial meningitis, in *Infections of the Central Nervous System*, 4th ed. Scheld WM, Whitley RJ, Marra (eds). Philadelphia, Wolters Kluwer Health, 2014, pp.

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