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Meningitis, Encephalitis, Brain Abscess, and Empyema

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Acute infections of the nervous system are among the most important problems in medicine because early recognition, efficient decision-making, and rapid institution of therapy can be lifesaving. These distinct clinical syndromes include acute bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess and subdural empyema, and infectious thrombophlebitis. Each may present with a nonspecific prodrome of fever and headache, which in a previously healthy individual may initially be thought to be benign, until (with the exception of viral meningitis) altered consciousness, focal neurologic signs, or seizures appear. Key goals of early management are to emergently distinguish between these conditions, identify the responsible pathogen, and initiate appropriate antimicrobial therapy.

APPROACH TO THE PATIENT

(Fig. 360-1) The first task is to identify whether an infection predominantly involves the subarachnoid space ("meningitis") or whether there is evidence of either generalized or focal involvement of brain tissue in the cerebral hemispheres, cerebellum, or brainstem. When brain tissue is directly injured by a viral infection the disease is referred to as "encephalitis," whereas focal bacterial, fungal, or parasitic infections involving brain tissue are classified as either "cerebritis" or "abscess," depending on the presence or absence of a capsule.

FIGURE 360-1 Algorithm for management of patients with suspected CNS infections. ADEM, acute disseminated encephalomyelitis; CT, computed tomography; MRI, magnetic resonance imaging; PMNs, polymorphonuclear leukocytes; MNCs, mononuclear cells; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; HSV, herpes simplex virus; VZV, varicella-zoster virus; WNV, West Nile Virus; DFA, direct fluorescent antibody; Ag, antigen; VDRL, Venereal Disease Research Laboratory; AFB, acid-fast bacillus; TB, tuberculosis; CXR, chest x-ray; PPD, purified protein derivative; EBV, Epstein-Barr virus; CTFV, Colorado tick fever virus; HHV, human herpesvirus; LCMV, lymphocytic choriomeningitis virus.

Nuchal rigidity 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 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.

Initial management can be guided by several considerations: (1) Empirical therapy should be initiated promptly whenever bacterial meningitis is a significant diagnostic consideration. (2) All patients who have had recent head trauma, are immunocompromised, have known malignant lesions or central nervous system (CNS) neoplasms, or have focal neurologic findings including papilledema or a depressed level of consciousness should undergo computed tomography (CT) or magnetic resonance imaging (MRI) of the brain prior to lumbar puncture (LP). In these cases empirical antibiotic therapy should not be delayed pending test results but should be administered prior to neuroimaging and LP. (3) A significantly depressed mental status (e.g., somnolence, coma), seizures, or focal neurologic deficits only rarely occur in viral ("aseptic") meningitis; patients with these symptoms should be hospitalized for further evaluation and treated empirically for bacterial and viral meningoenkephalitis. (4) Immunocompetent patients with a normal level of consciousness, no prior antimicrobial treatment, and a cerebrospinal fluid (CSF) profile consistent with viral meningitis (lymphocytic pleocytosis and a normal glucose concentration) can often be treated as outpatients, if appropriate contact and monitoring can be ensured. Failure of a patient with suspected viral meningitis to improve within 48 h should prompt a reevaluation including follow-up neurologic and general medical examination and repeat imaging and laboratory studies, often including a second LP.

ACUTE BACTERIAL MENINGITIS

DEFINITION

Bacterial meningitis is an acute purulent infection within the subarachnoid space. It is associated with a CNS inflammatory reaction that may result in decreased consciousness, seizures, raised intracranial pressure (ICP), and stroke. The meninges, the subarachnoid space, and the brain parenchyma are all frequently involved in the inflammatory reaction (*meningoenkephalitis*).

EPIDEMIOLOGY

Bacterial meningitis is the most common form of suppurative CNS infection, with an annual incidence in the United States of >2.5 cases/100,000 population. The epidemiology of bacterial meningitis has changed significantly in recent years, reflecting a dramatic decline in the incidence of meningitis due to *Haemophilus influenzae*, and a smaller decline in that due to *Neisseria meningitidis*, following the introduction and increasingly widespread use of vaccines for both these organisms. Currently, the organisms most commonly responsible for community-acquired bacterial meningitis are *Streptococcus pneumoniae* (~50%), *N. meningitidis* (~25%), group B streptococci (~15%), and *Listeria monocytogenes* (~10%). *H. influenzae* now accounts for <10% of cases of bacterial meningitis in most series.

ETIOLOGY

S. pneumoniae (Chap. 121) 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 CSF rhinorrhea. Mortality remains ~20% despite antibiotic therapy.

N. meningitidis (Chap. 127) accounts for 25% of all cases of bacterial meningitis (0.6 cases per 100,000 persons per year) and for up to 60% of cases in children and young adults between the ages of 2 and 20. 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,

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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 the classic and alternative complement pathways. Individuals with deficiencies of any of the complement components, including properdin, are highly susceptible to meningococcal infections.

Enteric gram-negative bacilli are an increasingly common cause of meningitis in individuals with chronic and debilitating diseases such as diabetes, cirrhosis, or alcoholism and in those with chronic urinary tract infections. Gram-negative meningitis can also complicate neurosurgical procedures, particularly craniotomy.

Group B streptococcus, or *S. agalactiae*, was previously responsible for meningitis predominantly in neonates, but it has been reported with increasing frequency in individuals >50 years of age, particularly those with underlying diseases.

L. monocytogenes (Chap. 123) has become 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 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 adults.

Staphylococcus aureus and coagulase-negative staphylococci (Chap. 120) are important causes of meningitis that follows invasive neurosurgical procedures, particularly shunting

procedures for hydrocephalus, or that occurs 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 immunoglobulins. 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.

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The lysis of bacteria with the subsequent release of cell-wall components into the subarachnoid space is the initial step in the induction of the inflammatory response and the formation of a purulent exudate in the subarachnoid space (Fig. 360-2). 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 (TNF) and interleukin (IL) 1 are present in CSF within 1 to 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 and TNF. 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.

FIGURE 360-2 The pathophysiology of the neurologic complications of bacterial meningitis. SAS, subarachnoid space; CSF, cerebrospinal fluid.

Much of the pathophysiology of bacterial meningitis is a direct consequence of elevated levels of CSF cytokines and chemokines. TNF and IL-1 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 subarachnoid space (Fig. 360-2). 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.

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.

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. 258). Narrowing of the large arteries at the base of the brain due to encroachment by the purulent exudate in the subarachnoid space 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 ("stiff neck"). Each of these signs and symptoms occurs in >90% of cases. Alteration in mental status occurs in >75% of patients and can vary from lethargy to coma. Nausea, vomiting, and photophobia are also common complaints.

Seizures occur as part of the initial presentation of bacterial meningitis or during the course of the illness in 20 to 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 such as high-dose penicillin.

Raised ICP is an expected complication of bacterial meningitis and is 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

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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, but 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 therapy initiated without delay. The diagnosis of bacterial meningitis is made by examination of the CSF (Table 360-1). The need to obtain neuroimaging studies (CT or MRI) prior to 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 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.

TABLE 360-1 Cerebrospinal Fluid (CSF) Abnormalities in Bacterial Meningitis

Opening pressure	>180 mmH ₂ O
White blood cells	10/ μ L to 10,000/ μ L; 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%
Latex agglutination	May be positive in patients with meningitis due to <i>S. pneumoniae</i> , <i>N. meningitidis</i> , <i>H. influenzae</i> type b, <i>E. coli</i> , group B streptococci
Limulus lysates	Positive in cases of gram-negative meningitis
PCR for bacterial DNA	Research test
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Note: PCR, polymerase chain reaction.	

The classic CSF abnormalities in bacterial meningitis (Table 360-1) are (1) polymorphonuclear (PMN) leukocytosis (>100 cells/ μ L 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 >80% 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 CSF glucose concentration to reach equilibrium with blood glucose concentrations; 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 latex agglutination (LA) test for the detection of bacterial antigens of *S. pneumoniae*, *N. meningitidis*, *H. influenzae* type b, group B streptococcus, and *Escherichia coli* K1 strains in the CSF is very useful for making a rapid diagnosis of bacterial meningitis, especially in patients who have been pretreated with antibiotics and in whom CSF Gram's stain and culture are negative. The CSF LA test has a *specificity* of 95 to 100% for *S. pneumoniae* and *N. meningitidis*, so a positive test is virtually diagnostic of bacterial meningitis caused by these organisms. However, the *sensitivity* of the CSF LA test is only 70 to 100% for detection of *S. pneumoniae* and 33 to 70% for detection of *N. meningitidis* antigens, so a negative test does not exclude infection by these organisms. The Limulus amoebocyte lysate assay is a rapid diagnostic test for the detection of gram-negative endotoxin in CSF, and thus for making a diagnosis of gram-negative bacterial meningitis. The test has a specificity of 85 to 100% and a sensitivity approaching 100%. Thus, a positive Limulus amoebocyte lysate assay occurs in virtually all patients with gram-negative bacterial meningitis, but false-positives may occur. CSF polymerase chain

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reaction (PCR) tests are not as useful in the diagnosis of bacterial meningitis as they are in the diagnosis of viral CNS infections. A CSF PCR test has been developed for detecting DNA from bacteria in CSF, but its sensitivity and specificity need to be better characterized before its role in diagnosis can be defined.

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 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 meningococemia 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, can mimic the clinical presentation of bacterial meningitis (see "Encephalitis," below). 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 PMN pleocytosis and hypoglycorrhachia characteristic of bacterial meningitis. MRI abnormalities (other than meningeal enhancement) are not seen in uncomplicated bacterial meningitis. By contrast, in HSV encephalitis parenchymal changes, especially in orbitofrontal and medial temporal lobes, are usually found. Some patients with HSV encephalitis have a distinctive

periodic pattern on EEG (see below).

Rickettsial disease can resemble bacterial meningitis (Chap. 158). 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, and 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 meningococemia. 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 yellowish-green to black. The rash typically begins in the wrist and ankles, and then spreads distally and proximally within a matter of a few hours and involves the palms and soles. Diagnosis is made by immunofluorescent staining of skin biopsy specimens.

Focal suppurative CNS infections (see below), including subdural and epidural empyema and brain abscess, should also be considered, 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. 349) is generally the major consideration. Other possibilities include chemical meningitis due to rupture of tumor contents into the CSF (e.g., from a cystic glioma, craniopharyngioma epidermoid or dermoid cyst); drug-induced hypersensitivity meningitis; carcinomatous or lymphomatous meningitis; meningitis associated with inflammatory disorders such as sarcoid, systemic lupus erythematosus (SLE), and Behçet disease; pituitary apoplexy; and uveomeningitic syndromes (Vogt-Koyanagi-Harada syndrome).

Subacutely evolving meningitis (Chap. 361) may on occasion be considered in the differential diagnosis of acute meningitis. The principal causes include *Mycobacterium tuberculosis* (Chap. 150), *Cryptococcus neoformans* (Chap. 186), *Histoplasma capsulatum* (Chap. 183), *Coccidioides immitis* (Chap. 184), and *Treponema pallidum* (Chap. 153).



TREATMENT

Empirical Antimicrobial Therapy (Table 360-2)

TABLE 360-2 Antibiotics Used in Empirical Therapy of Bacterial Meningitis and Focal CNS Infections^a

<i>Indication</i>	<i>Antibiotic</i>

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

<i>Antimicrobial Agent</i>	<i>Total Daily Dose and Dosing Interval</i>	
	<i>Child (>1 month)</i>	<i>Adult</i>
Ampicillin	200 (mg/kg)/d, q4h	12 g/d, q4h
Cefepime	150 (mg/kg)/d, q8h	6 g/d, q8h
Cefotaxime	200 (mg/kg)/d,	12 g/d, q4h

	q6h	
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, q8h ^b	7.5 (mg/kg)/d, q8h
Meropenem	120 (mg/kg)/d, q8h	3 g/d, q8h
Metronidazole	30 (mg/kg)/d, q6h	1500–2000 mg/d, q6h
Nafcillin	100–200 (mg/kg)/d, q6h	9–12 g/d, q4h
Penicillin G	400,000 (U/kg)/d, q4h	20–24 million U/d, q4h
Vancomycin	60 (mg/kg)/d, q6h	2 g/d, q12h ^b
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^a All antibiotics are administered intravenously; doses indicated assume normal renal and hepatic function.		
^a Doses 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.		

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 Gram's stain and culture are known. *S. pneumoniae* (Chap. 119) and *N.*

meningitidis (Chap. 127) 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 bacterial meningitis in children and adults should include a third-generation cephalosporin (e.g., ceftriaxone or cefotaxime) and vancomycin. Ceftriaxone or cefotaxime provide 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* spp. 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, but its efficacy in bacterial meningitis caused by penicillin- and cephalosporin-resistant pneumococcal organisms, *Enterobacter* spp., and *P. aeruginosa* has not been established. 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, malignancies, or immunosuppressive therapy. In hospital-acquired meningitis,

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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. Ceftazidime should be substituted for ceftriaxone or cefotaxime in neurosurgical patients and in neutropenic patients, as ceftazidime is the only cephalosporin with 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. The number of patients with bacterial meningitis enrolled in clinical trials of meropenem has not been sufficient to definitively assess the efficacy of this antibiotic.

Specific Antimicrobial Therapy (Table 360-3)

Organism	Antibiotic

<i>Neisseria meningitides</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
Penicillin-resistant	(Ceftriaxone or cefotaxime) + vancomycin
Gram-negative bacilli(except <i>Pseudomonas</i> spp.)	Ceftriaxone or cefotaxime
<i>Pseudomonas aeruginosa</i>	Ceftazidime
<i>Staphylococci</i> spp.	
Methicillin-sensitive	Nafcillin
Methicillin-resistant	Vancomycin
<i>Listeria monocytogenes</i>	Ampicillin + gentamicin
<i>Haemophilus influenzae</i>	Ceftriaxone or cefotaxime
<i>Streptococcus agalactiae</i>	Penicillin G or ampicillin
<i>Bacteroides fragilis</i>	Metronidazole
<i>Fusobacterium</i> spp.	Metronidazole

^aDses are as indicated in Table 360-2.

MENINGOCOCCAL MENINGITIS

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, but patients infected with these strains have still been successfully treated with penicillin. 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 ciprofloxacin (750 mg), 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 360-3). For *S. pneumoniae* meningitis, an isolate of *S. pneumoniae* is considered to be susceptible to penicillin with a minimal inhibitory concentration (MIC) < 0.06 µg/mL, to have intermediate resistance when the MIC is 0.1 to 1.0 µg/mL, and to be highly resistant when the MIC > 1.0 µg/mL. Isolates of *S. pneumoniae* that have cephalosporin MICs ≤ 0.5 µg/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. If the 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.

Patients with *S. pneumoniae* meningitis should have a repeat LP performed 24 to 36 h after the initiation of antimicrobial therapy to document sterilization of the CSF. Failure to sterilize the CSF after 24 to 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. A 2-week course of intravenous antimicrobial therapy is recommended for pneumococcal meningitis.

L. MONOCYTOGENES MENINGITIS

Meningitis due to this organism is treated with ampicillin for at least 3 weeks (Table 360-3). Gentamicin is often added (2 mg/kg loading dose, then 5.1 mg/kg per day given every 8 h and adjusted for serum levels and renal function). The combination of trimethoprim [10 to 20 (mg/kg)/d] and sulfamethoxazole [50 to 100 (mg/kg)/d] 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 360-3). 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 intrathecal or intraventricular 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 (Table 360-3). 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 and TNF in the subarachnoid space. Dexamethasone exerts its beneficial effect by inhibiting the synthesis of IL-1 and TNF 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 by macrophages and microglia only if it is administered before these cells are activated by endotoxin. Dexamethasone does not alter TNF production once it has been induced. The results of clinical trials of dexamethasone therapy in children, predominantly with meningitis due to *H. influenzae* and *S. pneumoniae*, 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 301 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 to 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, its potential benefit should be carefully weighed when vancomycin is the antibiotic of choice. Alternatively, vancomycin can be administered by the intraventricular route.

Increased Intracranial Pressure

Emergency treatment of increased ICP includes elevation of the patient's head to 30 to 45°, intubation and hyperventilation (Pa_{CO_2} 25 to 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 intracranial pressure is discussed in detail in Chap. 258.**

PROGNOSIS

Mortality is 3 to 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 VIRAL MENINGITIS

CLINICAL MANIFESTATIONS

Viral meningitis presents as fever, headache, and meningeal irritation coupled with an inflammatory CSF profile (see below). Fever may be accompanied by malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. It is not uncommon to see a mild degree of lethargy or drowsiness. The presence of more profound alterations in consciousness, such as stupor, coma, or marked confusion, should prompt consideration of alternative diagnoses. Similarly, seizures or other focal neurologic signs or symptoms suggest involvement of the brain parenchyma and do not occur in uncomplicated viral meningitis. The headache associated with viral meningitis is usually frontal or retroorbital and often 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 anteflexion. Evidence of severe meningeal irritation, such as Kernig's and Brudzinski's signs, is generally absent.

ETIOLOGY

Enteroviruses account for 75 to 90% of aseptic meningitis cases in most series (Table 360-4). Viruses belonging to the *Enterovirus* genus are members of the family Picornaviridae and include the coxsackieviruses, echoviruses, polioviruses, and human enteroviruses 68 to 71. Using a variety of diagnostic techniques including CSF PCR tests, culture, and serology, a specific viral cause can be found in 75 to 90% of cases of viral meningitis. CSF cultures are positive in 30 to 70% of patients, 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).

TABLE 360-4 Viruses Causing Acute Meningitis and Acute Encephalitis

ACUTE MENINGITIS		
Common	Less Common	Rare
Enteroviruses	HSV-1	Adenoviruses
Arboviruses	LCMV	CMV
HIV	VZV	EBV
HSV-2		Influenza A, B, parainfluenza, mumps, rubella
ACUTE ENCEPHALITIS		

Arboviruses	CMV	Adenoviruses, CTFV, hepatitis C, influenza A, LCMV, parainfluenza, rabies, rotavirus, rubella
Enteroviruses	EBV	
HSV-1	HIV Mumps	
<hr/>		
<p>Note: CMV, cytomegalovirus; CTFV, Colorado tick fever virus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus; VZV, varicella-zoster virus.</p>		

EPIDEMIOLOGY

The exact incidence of viral meningitis in the United States is impossible to determine since most cases go unreported to public health authorities, although a reasonable estimate would be ~75,000 cases per year. In temperate climates, there is a substantial increase in cases during the summer and early fall months, reflecting the seasonal predominance of enterovirus and arthropod-borne encephalitis virus (“arbovirus”) infections, with a peak monthly incidence of about 1 reported case per 100,000 population. The dramatic seasonal predilections of some viruses causing meningitis provide a valuable clue to diagnosis (Table 360-5).

TABLE 360-5 Seasonal Prevalence of Viruses Commonly Causing Meningitis

	<i>Summer/Early Fall</i>	<i>Fall/Winter</i>	<i>Winter/Spring</i>	<i>Nonseasonal</i>
<hr/>				
Arboviruses	LCMV	Mumps	HSV	
Enteroviruses			HIV	
<hr/>				

Note: Abbreviations are as in Table 360-5.

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 lymphocytic pleocytosis (25 to 500 cells/ μ L) a normal or slightly elevated protein concentration [0.2 to 0.8 g/L (20 to 80 mg/dL)], a normal glucose concentration, and a normal or mildly elevated opening pressure (100 to 350 mmH₂O).

Organisms are *not* seen on Gram's or acid-fast stained smears or india ink preparations of CSF. Rarely, PMNs may predominate in the first 48 h of illness, especially in patients with infections due to echovirus 9, West Nile virus or Eastern equine encephalitis virus, or mumps. Recent studies suggest that in some patients with West Nile virus infection, PMN pleocytosis can persist for up to a week before shifting to a lymphocytic pleocytosis.

Despite these exceptions, the presence of a CSF PMN pleocytosis in a patient with suspected viral meningitis should always prompt consideration of an alternative diagnosis including bacterial meningitis or parameningeal infections. The total CSF cell count in viral meningitis is typically 25 to 500/ μ L, although cell counts of several thousand per microliter are occasionally seen, especially with infections due to lymphocytic choriomeningitis virus (LCMV) and mumps virus. The CSF glucose concentration is typically normal in viral infections, although it may be decreased in 10 to 30% of cases due to mumps as well as in cases due to LCMV. Rare instances of decreased CSF glucose concentration occur in cases of meningitis due to echoviruses and other enteroviruses, HSV type 2, and varicella-zoster virus (VZV). As a rule, a lymphocytic pleocytosis with a low glucose concentration should suggest fungal, listerial, or tuberculous meningitis 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, quinolinate, IL-1 β , IL-6, soluble IL-2 receptor, β_2 -microglobulin, and TNF, have been proposed as potential

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discriminators between viral and bacterial meningitis or as markers of specific types of viral infection (e.g., infection with HIV), but 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, PCR has become the diagnostic procedure of choice and is substantially more sensitive than viral cultures. HSV 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. CSF PCR is also used routinely to diagnose CNS viral infections caused by cytomegalovirus (CMV), Epstein-Barr virus (EBV), and VZV.

CSF Culture

The overall results of CSF culture for the diagnosis of viral infection are disappointing, presumably because of the generally low concentration of infectious virus present and the need to customize isolation procedures for individual viruses. For viral isolation, 2 mL of CSF should be brought promptly to the microbiology laboratory, where it should be refrigerated and processed as speedily as possible. CSF specimens for viral isolation should never be stored in a -20°C freezer since viruses are often unstable at this temperature, and most freezers have “frostfree” warm-up cycles that are detrimental to viral stability. Storage for >24 h is probably best done in a -70°C freezer.

Other Sources for Viral Isolation

Viruses may also be isolated from sites and body fluids other than CSF, including throat, 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

For some viruses, including many arboviruses such as West Nile virus (WNV), serologic studies remain a crucial diagnostic tool. Serum serologic studies are less useful for viruses such as HSV, VZV, CMV, and EBV for which the prevalence of antibody seropositivity in the general population is high. Diagnosis of acute viral infection can be made by documenting seroconversion between acute-phase and convalescent sera (typically obtained after 2 to 4 weeks) or by demonstrating the presence of virus-specific IgM antibodies. Documentation of intrathecal synthesis of virus-specific antibodies, as shown by an increased IgG index or the presence of IgM antibodies in CSF, is often significantly more useful than serum serology alone and can provide presumptive evidence of CNS infection. Although serum and CSF IgM antibodies generally persist for only a few months after acute infection, there are exceptions to this rule. For example, WNV IgM has been shown to persist in some patients for >1 year following acute infection. Unfortunately, the delay between onset of infection and the generation by the host of a virus-specific antibody response often means that serologic data are useful mainly for the retrospective establishment of a specific diagnosis, rather than in urgent diagnosis or management.

Agarose electrophoresis or isoelectric focusing of CSF γ -globulins may reveal the presence of oligoclonal bands. These bands have been found in association with a number of viral infections, including infections with HIV, human T cell lymphotropic virus (HTLV) type I, VZV, mumps, subacute sclerosing panencephalitis (SSPE), and progressive rubella panencephalitis. The associated antibodies are often directed against viral proteins. The

finding of oligoclonal bands may be of some diagnostic utility, since typically they are not seen with arbovirus, enterovirus, or HSV infections. Oligoclonal bands are also encountered in certain noninfectious neurologic diseases (e.g., multiple sclerosis) and may be found in nonviral infections (e.g., syphilis, Lyme borreliosis).

Other Laboratory Studies

All patients with suspected viral meningitis should have a complete blood count and differential; liver function tests; and measurement of the erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), and plasma levels of electrolytes, glucose, creatinine, creatine kinase, aldolase, amylase, and lipase. Abnormalities in specific test results may suggest particular etiologic diagnoses. MRI, CT, EEG, evoked response studies, electromyography (EMG), and nerve conduction studies are not necessary in most cases. They are best used selectively when atypical presentations or unusual features present diagnostic problems.

DIFFERENTIAL DIAGNOSIS

The most important issue in the differential diagnosis is the exclusion of nonviral causes that can mimic viral meningitis. The major categories of disease that should always be considered and excluded are (1) bacterial meningitis and other infectious meningitides (e.g., *Mycoplasma*, *Listeria*, *Brucella*, *Coxiella*, and *Rickettsia*); (2) parameningeal infections or partially treated bacterial meningitis; (3) nonviral infectious meningitides where cultures may be negative (e.g., fungal, tuberculous, parasitic, or syphilitic disease); (4) neoplastic meningitis; and (5) meningitis secondary to noninfectious inflammatory diseases such as sarcoid, Behçet's disease, and the uveomeningitic syndromes.

SPECIFIC VIRAL ETIOLOGIES

Enteroviruses (Chap. 175) are the most common cause of viral meningitis (>75% of cases in which a specific etiology can be identified) and should be considered the most likely cause of viral meningitis when a typical case occurs in the summer months, especially in a child (<15 years). However, despite their summer predominance, sporadic cases of enteroviral CNS infection are seen year-round. The physical examination should include a careful search for exanthemata, hand-foot-mouth disease, herpangina, pleurodynia, myopericarditis, and hemorrhagic conjunctivitis, which may be stigmata of enterovirus infections. PCR amplification of enteroviral RNA from CSF has become the diagnostic procedure of choice for these infections.

Arbovirus infections (Chap. 180) typically occur in the summer months, may have clear circumscribed geographic localization, and occur in both endemic and epidemic form, all factors reflecting the ecology of their transmission through infected insect vectors (Fig. 360-2; Tables 360-5 and 360-6). Arboviral meningitis should be considered when clusters of meningitis cases occur in a restricted geographic region during the summer or early fall. WNV infection should be suspected when bird deaths precede clusters of human cases of meningitis or encephalitis in an area known to harbor the virus. 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 diseases producing

meningitis (e.g.,

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Lyme disease) or headache with meningismus (e.g., RMSF) may also present this way.

TABLE 360-6 Features of Selected Arbovirus Encephalitides

<i>Feature</i>	<i>WNV</i>	<i>WEE</i>	<i>EEE</i>	<i>VEE</i>	<i>SLE</i>	<i>CE</i>
Region	All	West, midwest	Atlantic and Gulf coasts	SW, W	All	East and NC
Age	Adults > 60	Infants, adults > 50	Children, adults > 60	Adults	Adults > 60	Children
Deaths	7%	3–15%	50–75%	1%	2–20%	<1%
Sequelae	?	Common	80%	Rare	20%	Rare
Vector	M	M	M	M	M	M
Animal reservoir	B	B	B	H, sm M	B	sm M

Note: WNV, West Nile virus; WEE, Western equine encephalitis (virus); EEE, Eastern equine encephalitis (virus); VEE, Venezuelan equine encephalitis (virus); SLE, systemic lupus erythematosus; CE, California encephalitis (virus); B, bird; H, horse; M, mosquito; NC, north central United States; sm M, small mammal; SW, southwest; W, west.

HSV-2 meningitis (Chap. 163) occurs in ~25% of women and 11% 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. In some series, HSV-2 has been the most important cause of aseptic meningitis in adults, especially women, and overall it is probably second only to enteroviruses as a cause of viral meningitis. Although HSV-2 can be cultured from CSF

during a first episode of meningitis, cultures are invariably negative during recurrent episodes of HSV-2 meningitis. Diagnosis depends on amplification of HSV-2 DNA from CSF by PCR. Almost all cases of recurrent HSV meningitis are due to HSV-2, although rare cases due to HSV-1 have been reported. Most cases of benign recurrent lymphocytic meningitis, including cases previously diagnosed as "Mollaret's meningitis," appear to be due to HSV. Genital lesions may not be present, and most patients give no history of genital herpes. CSF cultures are negative, although HSV DNA can be amplified from CSF by PCR during attacks of meningitis but not during symptom-free intervals.

VZV meningitis should be suspected in the presence of concurrent chickenpox or shingles. However, it is important to recognize that in some series up to 40% of VZV meningitis cases have been reported to occur in the absence of 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. In addition to meningitis, encephalitis (see below), and shingles (see below), VZV can also produce acute cerebellar ataxia. This typically occurs in children and presents with the abrupt onset of limb and truncal ataxia. A similar syndrome occurs less commonly in association with EBV and enteroviral infection. PCR has rapidly become a major tool in the diagnosis of VZV CNS infections. In patients with negative CSF PCR results, 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 may also produce aseptic meningitis, with or without accompanying evidence of the infectious mononucleosis syndrome. The diagnosis may be suggested by the finding of atypical lymphocytes in the CSF or an atypical lymphocytosis in peripheral blood. The demonstration of IgM antibody to viral capsid antigen (VCA), or antibody to the diffuse (D) component of early antigen (EA) in the absence of or preceding detectable antibody to nuclear antigen (EBNA), are indicative of acute EBV infection. EBV is almost never cultured from CSF, but EBV DNA can be amplified from CSF in some patients with EBV-associated CNS infections. HIV-infected patients with primary CNS lymphoma may have a positive CSF PCR for EBV DNA even in the absence of meningoencephalitis.

HIV meningitis should be suspected in any patient with known or identified risk factors for HIV infection. Aseptic meningitis is a common manifestation of primary exposure to HIV and occurs in 5 to 10% of cases. In some patients, seroconversion may be delayed for several months; however, detection of the presence of HIV genome by PCR or p24 protein establishes the diagnosis. HIV can be cultured from CSF in some patients. Cranial nerve palsies, most commonly involving cranial nerves V, VII, or VIII, are more common in HIV meningitis than in other viral infections. →**For further discussion of HIV infection, see Chap. 173.**

Mumps (Chap. 178) should be considered when meningitis occurs in the late winter or early spring, especially in males (male/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%. Rare cases of mumps vaccine-associated meningitis have been reported, but they are not usually seen after vaccination with the attenuated Jeryl-Lynn strain of virus used in the United States. The presence of orchitis, oophoritis, parotitis, pancreatitis, or elevations in serum lipase and amylase are suggestive but can be

found with other viruses, and their absence does not exclude the diagnosis. Clinical meningitis occurs in 5% of patients with parotitis, but only 50% of patients with meningitis have associated parotitis. Mumps infection confers lifelong immunity, so a documented history of previous infection excludes this diagnosis. The presence of hypoglycorrhachia, found in 10 to 30% of patients, may be an additional diagnostic clue, once other causes have been excluded (see above). Up to 25% of patients may have a PMN-predominant CSF pleocytosis, and CSF abnormalities may persist for months. Diagnosis is typically made by isolation of virus from CSF and/or demonstration of seroconversion between acute-phase and convalescent sera.

LCMV infection (Chap. 180) 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), 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%).

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TREATMENT

In the usual case of viral meningitis, treatment is symptomatic and hospitalization is not required. Exceptions include patients with deficient humoral immunity, neonates with overwhelming infection, and patients in whom the clinical or CSF profile suggests the possibility of a bacterial or other nonviral cause of infection. Patients with suspected bacterial meningitis should receive appropriate empirical therapy pending culture results (see above). Patients usually prefer to rest undisturbed in a quiet, darkened room. Analgesics can be used to relieve headache, which is often reduced by the initial diagnostic LP. Antipyretics may help to reduce fever, which rarely exceeds 40°C. Hyponatremia may develop as a result of inappropriate vasopressin secretion [syndrome of inappropriate secretion of antidiuretic hormone (SIADH)], so fluid and electrolyte status should be monitored. Repeat LP is indicated only in patients whose fever and symptoms fail to resolve after a few days, in patients with an initial PMN pleocytosis or hypoglycorrhachia, or if there is doubt about the initial diagnosis.

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 (30 mg/kg per day in three divided doses) for 7 days. Oral acyclovir (800 mg, five times daily), famciclovir (500 mg, tid), or valacyclovir (1000 mg, tid) for a week may be tried in less severely ill patients, although data on efficacy are lacking. Patients with HIV meningitis should receive highly active antiretroviral therapy (Chap. 173).

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.

An experimental drug, pleconaril (Viropharma Inc., VP 63843), has shown efficacy against a variety of enteroviral infections and has good oral bioavailability and excellent CNS penetration. Ongoing clinical trials in patients with enteroviral meningitis suggest that pleconaril decreases the duration of symptoms compared to placebo. Since most cases of enteroviral CNS infection are benign and self-limited, the indications for pleconaril therapy need to be better defined. Antiviral treatment might benefit patients with chronic CNS enteroviral infections in the setting of agammaglobulinemia or those who develop poliomyelitis as a complication of polio vaccine administration.

Vaccination is an effective method of preventing the development of meningitis and other neurologic complications associated with poliovirus, mumps, and measles infection. A live attenuated VZV vaccine (Varivax) is available in the United States. Clinical studies indicate an effectiveness rate of 70 to 90% for this vaccine, but a booster may be required to maintain immunity. An inactivated varicella vaccine is available for transplant recipients.

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.

VIRAL ENCEPHALITIS

DEFINITION

In contrast to viral meningitis, where the infectious process and associated inflammatory response are limited largely to the meninges, in encephalitis the brain parenchyma is also involved. Many patients with encephalitis also have evidence of associated meningitis (meningoencephalitis) and, in some cases, involvement of the spinal cord or nerve roots (encephalomyelitis, encephalomyelorradiculitis).

CLINICAL MANIFESTATIONS

In addition to the acute febrile illness with evidence of meningeal involvement characteristic of meningitis, the patient with encephalitis commonly has confusion, behavioral abnormalities, an altered level of consciousness, and evidence of either focal or diffuse neurologic signs and symptoms. Any degree of altered consciousness may occur, ranging from mild lethargy to deep coma. Patients with encephalitis may have hallucinations, agitation, personality change, behavioral disorders, and, at times, a frankly psychotic state. Focal or generalized seizures occur in many patients with severe encephalitis. Virtually

every possible type of focal neurologic disturbance has been reported in viral encephalitis; the signs and symptoms reflect the sites of infection and inflammation. The most commonly encountered focal findings are aphasia, ataxia, hemiparesis (with hyperactive tendon reflexes and extensor plantar responses), involuntary movements (e.g., myoclonic jerks, tremor), and cranial nerve deficits (e.g., ocular palsies, facial weakness). Involvement of the hypothalamic-pituitary axis may result in temperature dysregulation, diabetes insipidus, or the development of SIADH. Despite the clear neuropathologic evidence that viruses differ in the regions of the CNS they injure, it is often impossible to distinguish reliably on clinical grounds alone one type of viral encephalitis (e.g., that caused by HSV) from others (see “Differential Diagnosis,” below).

ETIOLOGY

In the United States, there are ~20,000 reported cases of encephalitis per year; the actual number is likely to be significantly higher. Hundreds of viruses are capable of causing encephalitis, although only a limited subset is responsible for most cases in which a specific cause is identified (Table 360-4). The same organisms responsible for aseptic meningitis are also responsible for encephalitis, although their relative frequencies differ. The most important viruses causing sporadic cases of encephalitis in immunocompetent adults are HSV-1 (Fig. 360-3), VZV and, less commonly, enteroviruses. Epidemics of encephalitis are caused by arboviruses, which belong to several different viral taxonomic groups including *Alphaviruses* (e.g. Eastern equine encephalitis virus, Western equine encephalitis virus), *Flaviviruses* (e.g., WNV, St. Louis encephalitis virus, Powassan virus), and *Bunyaviruses* (e.g., California encephalitis virus serogroup, LaCrosse virus). Historically, the largest number of cases of arbovirus encephalitis in the United States has been due to St. Louis encephalitis virus and the California encephalitis virus serogroup. However, in 2002, WNV produced the largest epidemic of encephalitis ever recorded in the United States, with 4156 cases and 284 deaths. New causes of viral encephalitis are constantly appearing, as evidenced by the recent outbreak of 257 cases of encephalitis with a 40% mortality rate in Malaysia caused by Nipah virus, a new member of the Paramyxovirus family.

FIGURE 360-3 Coronal FLAIR magnetic resonance image from a patient with herpes simplex encephalitis. Note the area of increased signal in the temporal lobe (left) confined predominantly to the gray matter. This patient had predominantly unilateral disease; bilateral lesions are more common but may be quite asymmetric in their intensity.

LABORATORY DIAGNOSIS

CSF Examination

CSF examination should be performed in all patients with suspected viral encephalitis unless contraindicated by the presence of severely increased ICP. The characteristic CSF profile is indistinguishable from that of viral meningitis and consists of a lymphocytic pleocytosis, a mildly elevated protein concentration, and a normal glucose concentration. A

CSF pleocytosis (>5 cells/ μL) occurs in $>95\%$ of patients with documented viral encephalitis. In rare cases, a pleocytosis may be absent on the initial LP but present on subsequent LPs. Patients who are severely immunocompromised by HIV infection, glucocorticoid or other immunosuppressant drugs, chemotherapy, or lymphoreticular malignancies may fail to mount a CSF inflammatory response. CSF cell counts exceed $500/\mu\text{L}$ in only about 10% of patients with encephalitis. Infections with certain arboviruses (e.g., Eastern equine encephalitis or California encephalitis viruses), mumps, and LCMV may occasionally result in cell counts $>1000/\mu\text{L}$, but this degree of pleocytosis should suggest the possibility of nonviral infections or other inflammatory processes. Atypical lymphocytes in the CSF may be seen in EBV infection and less commonly with other viruses, including CMV, HSV, and enteroviruses. The presence of substantial numbers of PMNs after the first 48 h should prompt consideration of bacterial infection, leptospirosis, amebic infection, and noninfectious processes such as acute hemorrhagic leukoencephalitis. PMN pleocytosis that can persist for up to a week has also been reported in cases of WNV encephalitis. Large numbers of CSF PMNs may be present in patients with viral encephalitis due to Eastern equine encephalitis virus, echovirus 9, and, more rarely, other enteroviruses. About 20% of patients with encephalitis will have a significant number of red blood cells ($>500/\mu\text{L}$) in the CSF in a nontraumatic tap. The pathologic correlate of this finding may be a hemorrhagic encephalitis of the type seen with HSV, Colorado tick fever virus, and occasionally California encephalitis virus. A decreased CSF glucose concentration is distinctly unusual in viral encephalitis and should suggest the possibility of bacterial, fungal, tuberculous, parasitic, leptospiral, syphilitic, sarcoid, or neoplastic meningitis. Rare patients with mumps, LCMV, or advanced HSV encephalitis may have low CSF glucose concentrations.

CSF PCR

CSF PCR has become the primary diagnostic test for CNS infections caused by CMV, EBV, VZV and enteroviruses (see "Viral Meningitis," above). The sensitivity and specificity of CSF PCRs vary with the virus being tested. Recent studies with HSV encephalitis indicate that the sensitivity ($\sim 98\%$) and specificity ($\sim 94\%$) of CSF PCR

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equal or exceed those of brain biopsy. It is important to recognize that CSF HSV PCR results need to be interpreted after considering the likelihood of disease in the patient being tested, the timing of the test in relationship to onset of symptoms, and the prior use of antiviral therapy. A negative HSV CSF PCR test performed in a patient with a high likelihood of HSV encephalitis based on clinical and laboratory tests significantly reduces the likelihood of HSV encephalitis but does not exclude it. There have been several recent reports of initially negative CSF HSV PCR tests that were obtained early (≤ 72 h) following symptom onset, that became positive when repeated 1 to 3 days later. The frequency of positive CSF HSV PCRs in patients with herpes encephalitis also decreases as a function of the duration of illness, with only $\sim 20\%$ of cases remaining positive after ≥ 14 days. PCR results are generally not affected by ≤ 1 week of antiviral therapy. In one study 98% of CSF specimens remained PCR-positive during the first week of initiation of antiviral therapy, but the numbers fell to $\sim 50\%$ by 8 to 14 days and to $\sim 21\%$ by >15 days after initiation of therapy.

The sensitivity and specificity of CSF PCR tests for viruses other than herpes simplex have not been definitively characterized. Enteroviral CSF PCR appears to have a sensitivity and specificity of >95%. The specificity of EBV CSF PCR has not been established, and apparent false-positive results can occur in patients with CNS lymphoma and in patients with inflammatory CSF specimens. In patients with CNS infection due to VZV, CSF antibody and PCR studies should be considered complementary, as several cases with positive serologies and negative PCR studies have been reported. In the case of WNV infection, CSF PCR is considerably less sensitive (~70% sensitivity) than detection of WNV specific CSF IgM in diagnosis of WNV encephalitis.

CSF Culture

Attempts to culture viruses from the CSF in cases of encephalitis are often disappointing. Cultures are invariably negative in cases of HSV-1 encephalitis.

Serologic Studies and Antigen Detection

The basic approach to the serodiagnosis of viral encephalitis is identical to that discussed earlier for viral meningitis. In patients with HSV encephalitis, both antibodies to HSV-1 glycoproteins and glycoprotein antigens have been detected in the CSF. Optimal detection of both HSV antibodies and antigen typically occurs after the first week of illness, limiting the utility of these tests in acute diagnosis. Nonetheless, CSF HSV antibody testing may be of value in selected patients whose illness is >1 week in duration and who are CSF PCR-negative for HSV. Demonstration of WNV IgM antibodies is diagnostic of WNV encephalitis, as IgM antibodies do not cross the blood-brain barrier and their presence in CSF is therefore indicative of intrathecal synthesis.

MRI, CT, EEG

Patients with suspected encephalitis almost invariably undergo neuroimaging studies and often EEG. These tests help identify or exclude alternative diagnoses and assist in the differentiation between a focal, as opposed to a diffuse, encephalitic process. Focal findings in a patient with encephalitis should always raise the possibility of HSV encephalitis. Examples of focal findings include: (1) areas of increased signal intensity in the frontotemporal, cingulate, or insular regions of the brain on T2-weighted, fluid-attenuated inversion recovery (FLAIR), or diffusion-weighted MRI images (Fig. 360-3); (2) temporoparietal areas of low absorption, mass effect, and contrast enhancement on CT; or (3) periodic focal temporal lobe spikes on a background of slow or low-amplitude ("flattened") activity on EEG. Approximately 10% of patients with PCR-documented HSV encephalitis will have a normal MRI, although nearly 90% will have abnormalities in the temporal lobe. CT is less sensitive than MRI and is normal in up to 33% of patients. The addition of FLAIR and diffusion-weighted images to the standard MRI sequences enhances sensitivity. EEG abnormalities occur in >90% of PCR-documented cases of HSV encephalitis; they typically involve the temporal lobes but are often nonspecific. Some patients with HSV encephalitis have a distinctive EEG pattern consisting of periodic, stereotyped, sharp-and-slow complexes originating in one or both temporal lobes and repeating at regular intervals of 2 to 3 s. The periodic complexes are typically noted

between the second and the fifteenth day of the illness and are present in two-thirds of pathologically proven cases of HSV encephalitis.

Significant MRI abnormalities are found in only ~30% of patients with WNV encephalitis, a frequency significantly less than that of HSV encephalitis. When present, abnormalities often involve deep brain structures including the thalamus, basal ganglia, and brainstem rather than the cortex. Patients with VZV encephalitis may show areas of hemorrhagic infarction reflecting the tendency of this virus to produce a CNS vasculopathy rather than a true encephalitis.

Brain Biopsy

Brain biopsy is now generally reserved for patients in whom CSF PCR studies fail to lead to a specific diagnosis, who have focal abnormalities on MRI, and who continue to show progressive clinical deterioration despite treatment with acyclovir and supportive therapy. The isolation of HSV from brain tissue obtained at biopsy was once considered the “gold standard” for the diagnosis of HSV encephalitis, although with the advent of CSF PCR tests for HSV it is rarely necessary to perform brain biopsy for this purpose. The need for brain biopsy to diagnose other forms of viral encephalitis has also declined greatly with the widespread availability of CSF PCR diagnostic tests for EBV, CMV, VZV, and enteroviruses. When biopsy is performed, the tissue is cultured for virus and examined histopathologically and ultrastructurally. Tissue should be taken from a site that appears to be significantly involved on the basis of clinical and laboratory criteria. Although brain biopsy is not an innocuous procedure, the mortality rate is low (<0.2%) and serious complications occur in only 0.5 to 2.0% of cases. Potential morbidity, in addition to that related to general anesthesia, includes local bleeding and edema, the development of a seizure focus, and wound dehiscence or infection.

DIFFERENTIAL DIAGNOSIS

Some of the most common illnesses masquerading as viral encephalitis, as identified in multicenter clinical trials using brain biopsy as a diagnostic standard, were vascular diseases; abscess and empyema; fungal, parasitic, rickettsial, and tuberculous infections; tumors; Reye's syndrome; toxic encephalopathy; subdural hematoma; and SLE. Acute disseminated encephalomyelitis (ADEM), limbic encephalitis, prion diseases, and Hashimoto's encephalopathy are additional considerations. Of the nonviral infections, particular attention should be paid to *Listeria*, *Mycoplasma*, *Leptospira*, *Cryptococcus*, and *Mucor* infections, as well as to toxoplasmosis and tuberculosis.

Meningoencephalitis caused by ameba can also mimic viral encephalitis. Infection caused by *Naegleria fowleri* usually causes an acute syndrome (primary amebic meningoencephalitis), whereas that caused by *Acanthamoeba* and *Balamuthia* more typically produces subacute or chronic granulomatous amebic meningoencephalitis. *Naegleria* thrive in warm iron-rich pools of water including those found in drains, canals, and both natural and man-made outdoor pools. Infection has typically occurred in immunocompetent children with a history of swimming in potentially infected water. The presentation is of an acute encephalitis, with a CSF neutrophilic pleocytosis and hypoglycorrhachia identical to that seen in bacterial meningitis. Motile trophozoites can be

seen in a wet mount of warm fresh CSF. No effective treatment has been identified, and mortality approaches 100%.

There have also been several recent reports of encephalitis caused by the raccoon pinworm *Baylisascaris procyonis*. Clues to the diagnosis include a history of raccoon exposure, and especially of playing in or eating dirt potentially contaminated with raccoon feces. Most patients are children, and many have an associated eosinophilia.

Infection with *Bartonella* species, the agents of cat scratch fever, can also produce a meningoencephalitis. In some recent surveys, *Bartonella* infection has been the most common bacterial infection mimicking viral encephalitis. Infection is transmitted by the bite or scratch of a cat, with an increased risk associated with kittens and feral cats. Patients often develop regional lymphadenopathy; 2 to 4% of infected patients develop encephalopathy, retinitis, or less commonly cranial or peripheral neuropathy. CSF shows a lymphocytic pleocytosis with

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normal glucose in about one-third of cases, the remainder having no abnormalities or only mild protein elevation. Neuroimaging results are nonspecific, and diagnosis is based on serology. Antibiotic therapy is of uncertain value in immunocompetent hosts, although doxycycline (200 mg daily for 3 months) is often tried in patients with CNS disease.

Once nonviral causes of encephalitis have been excluded, the major diagnostic challenge is to distinguish HSV from other viruses that cause encephalitis. This distinction is particularly important because in virtually every other instance the therapy is supportive, whereas specific and effective antiviral therapy is available for HSV, and its efficacy is enhanced when it is instituted early in the course of infection. HSV encephalitis should be considered when clinical features suggesting involvement of the inferomedial frontotemporal regions of the brain are present, including prominent olfactory or gustatory hallucinations, anosmia, unusual or bizarre behavior or personality alterations, or memory disturbance. HSV encephalitis should always be suspected in patients with focal findings on clinical examination, neuroimaging studies, or EEG. The diagnostic procedure of choice in these patients is CSF PCR analysis for HSV. A positive CSF PCR establishes the diagnosis, and a negative test dramatically reduces the likelihood of HSV encephalitis (see above).

The anatomic distribution of lesions may provide an additional clue to diagnosis. Patients with rapidly progressive encephalitis and prominent brainstem signs, symptoms or neuroimaging abnormalities may be infected by flaviviruses (WNV, Japanese encephalitis virus), HSV, rabies or *L. monocytogenes*. Significant involvement of deep gray matter structures including the basal ganglia and thalamus should also suggest possible flavivirus infection. These patients may present clinically with prominent movement disorders (tremor, myoclonus) or Parkinson's disease-like features. Patients with WNV infection can also present with acute poliomyelitis-like areflexic paralysis, as can patients infected with enterovirus 71 and less commonly other enteroviruses. Despite an aggressive World Health Organization poliovirus eradication initiative, cases of wild-type poliovirus-induced poliomyelitis continue to be reported in at least seven countries worldwide: Egypt, Somalia, Niger, Nigeria, India, Pakistan, and Afghanistan. Rare cases continue to occur in the United States in nonvaccinated individuals exposed to vaccine strains of virus that have

reverted to virulence. A recent outbreak of poliomyelitis on Hispaniola (the Dominican Republic and Haiti) has been attributed to vaccine strain–derived viruses that have reverted to virulence after apparently recombining with other circulating enteroviruses. Acute ascending paralysis resembling Guillain-Barré syndrome but associated with CSF pleocytosis can occur with HIV infection, rabies, and WNV infection.

Epidemiologic factors may provide important clues. Particular attention should be paid to the season of the year (Table 360-5); the age of the patient (Table 360-6); the geographic location and travel history (Table 360-6); and possible exposure to animal bites or scratches, rodents, and ticks. Although transmission from the bite of an infected dog remains the most common cause of rabies worldwide, in the United States very few cases of dog rabies occur, and the most common risk factor is exposure to bats—although a clear history of a bite or scratch is often lacking. The classic clinical presentation of encephalitic (furious) rabies is of fever and autonomic hyperactivity with fluctuating mental status. Phobic spasms of the larynx, pharynx, neck muscles, and diaphragm can be triggered by attempts to swallow water (*hydrophobia*) or by inspiration (*aerophobia*). Patients may also present with paralytic (dumb) rabies characterized by acute ascending paralysis. Patients with rabies have a CSF lymphocytic pleocytosis and may show areas of increased T2 signal abnormality in the brainstem, hippocampus, and hypothalamus. Diagnosis can be made by finding rabies virus antigen in brain tissue or in the neural innervation of hair follicles at the nape of the neck. PCR amplification of viral nucleic acid from CSF and saliva or tears may also enable diagnosis. Serology is frequently negative in both serum and CSF in the first week after onset of infection, which limits its acute diagnostic utility. No specific therapy is available, and cases are almost invariably fatal, with isolated survivors having devastating neurologic sequelae.

Morbidity and Mortality Weekly Reports provides regular information about the prevalence of particular viruses causing encephalitis by season and region of the country. State public health authorities provide another valuable resource concerning isolation of particular agents in individual regions. Deaths in crows and other corvid birds in the local area have preceded human infection by WNV during outbreaks in the United States. Details of the occurrence of WNV in mosquitoes, birds, horses, and humans can be found on the Centers for Disease Control and Prevention (CDC) and U.S. Geological Survey (USGS) websites (and <http://westnilemaps.usgs.gov/>).



TREATMENT

Specific antiviral therapy should be initiated when appropriate. Vital functions, including respiration and blood pressure, should be monitored continuously and supported as required. In the initial stages of encephalitis, many patients will require care in an intensive care unit. Basic management and supportive therapy should include careful monitoring of ICP, fluid restriction and avoidance of hypotonic intravenous solutions, and suppression of fever. Seizures should be treated with standard anticonvulsant regimens, and prophylactic therapy should be considered in view of the high frequency of seizures in severe cases of encephalitis. As with all seriously ill, immobilized patients with altered levels of consciousness, encephalitis patients are at risk for aspiration pneumonia, stasis ulcers and decubiti, contractures,

deep venous thrombosis and its complications, and infections of indwelling lines and catheters.

Acyclovir is of benefit in the treatment of HSV and should be started empirically in patients with suspected viral encephalitis while awaiting viral diagnostic studies. Treatment should be discontinued in patients found not to have HSV encephalitis, with the possible exception of patients with severe encephalitis due to VZV or EBV. HSV, VZV, and EBV all encode an enzyme, deoxythymidine (thymidine) kinase, that phosphorylates acyclovir to produce acyclovir-5'-monophosphate. Host cell enzymes then phosphorylate this compound to form a triphosphate derivative. It is the triphosphate that acts as an antiviral agent by inhibiting viral DNA polymerase and by causing premature termination of nascent viral DNA chains. The specificity of action depends on the fact that uninfected cells do not phosphorylate significant amounts of acyclovir to acyclovir-5'-monophosphate. A second level of specificity is provided by the fact that the acyclovir triphosphate is a more potent inhibitor of viral DNA polymerase than of the analogous host cell enzymes.

Adults should receive a dose of 10 mg/kg of acyclovir intravenously every 8 h (30 mg/kg per day total dose) for a minimum of 14 days. Although no studies directly addressing this issue are yet available, repeating the CSF PCR after completion of acyclovir therapy should be considered. Patients with a persisting positive CSF PCR for HSV after completing a standard course of acyclovir therapy should be treated for an additional 7 days, followed by a repeat CSF PCR test. Neonatal HSV CNS infection is less responsive to acyclovir therapy than HSV encephalitis in adults; it is recommended that neonates with HSV encephalitis receive 20 mg/kg of acyclovir every 8 h (60 mg/kg per day total dose) for a minimum of 21 days.

Prior to intravenous administration, acyclovir should be diluted to a concentration ≤ 7 mg/mL. (A 70-kg person would receive a dose of 700 mg, which would be diluted in a volume of 100 mL.) Each dose should be infused slowly over 1 h rather than by rapid or bolus infusion, to minimize the risk of renal dysfunction. Care should be taken to avoid extravasation or intramuscular or subcutaneous administration. The alkaline pH of acyclovir can cause local inflammation and phlebitis (9%). Dose adjustment is required in patients with impaired renal glomerular filtration. Penetration into CSF is excellent, with average drug levels $\sim 50\%$ of serum levels. Complications of therapy include elevations in BUN and creatinine levels (5%), thrombocytopenia (6%), gastrointestinal toxicity (nausea, vomiting, diarrhea) (7%),

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and neurotoxicity (lethargy or obtundation, disorientation, confusion, agitation, hallucinations, tremors, seizures) (1%). Acyclovir resistance may be mediated by changes in either the viral deoxythymidine kinase or DNA polymerase. To date, acyclovir-resistant isolates have not been a significant clinical problem in immunocompetent individuals. However, there have been reports of clinically virulent acyclovir-resistant HSV isolates from sites outside the CNS in immunocompromised individuals, including those with AIDS.

Oral antiviral drugs with efficacy against HSV, VZV, and EBV, including acyclovir, famciclovir, and valacyclovir, have not been evaluated in the treatment of encephalitis either as primary therapy or as supplemental therapy following completion of a course

of parenteral acyclovir. An NIAID/NINDS-sponsored phase III trial of supplemental oral valacyclovir therapy (2 g, tid for 3 months) following the initial 14- to 21-day course of therapy with parenteral acyclovir has recently been initiated by the Collaborative Antiviral Study Group (CASG) in patients with HSV encephalitis (CASG 204); it may help clarify the role of extended oral antiviral therapy.

Both ganciclovir and foscarnet have been shown to be effective in the treatment of CMV-related CNS infections. These drugs are often used in combination. Cidofovir (see below) may provide an alternative in patients who fail to respond to ganciclovir and foscarnet, although data concerning its use in CMV CNS infections are extremely limited.

Ganciclovir is a synthetic nucleoside analogue of 2'-deoxyguanosine. The drug is preferentially phosphorylated by virus-induced cellular kinases. Ganciclovir triphosphate acts as a competitive inhibitor of the CMV DNA polymerase, and its incorporation into nascent viral DNA results in premature chain termination. Following intravenous administration, CSF concentrations of ganciclovir are 25 to 70% of coincident plasma levels. The usual dose for treatment of severe neurologic illnesses is 5 mg/kg every 12 h given intravenously at a constant rate over 1 h. Induction therapy is followed by maintenance therapy of 5 mg/kg every day for an indefinite period. Induction therapy should be continued until patients show a decline in CSF pleocytosis and a reduction in CSF CMV DNA copy number on quantitative PCR testing (where available). Doses should be adjusted in patients with renal insufficiency. Treatment is often limited by the development of granulocytopenia and thrombocytopenia (20 to 25%), which may require reduction in or discontinuation of therapy. Gastrointestinal side effects including nausea, vomiting, diarrhea, and abdominal pain occur in ~20% of patients. Some patients treated with ganciclovir for CMV retinitis have developed retinal detachment, but the causal relationship to ganciclovir treatment is unclear.

Foscarnet is a pyrophosphate analogue that inhibits viral DNA polymerases by binding to the pyrophosphate-binding site. Following intravenous infusion, CSF concentrations range from 15 to 100% of coincident plasma levels. The usual dose for serious CMV-related neurologic illness is 60 mg/kg every 8 h administered by constant infusion over 1 h. Induction therapy for 14 to 21 days is followed by maintenance therapy (60 to 120 mg/kg per day). Induction therapy may need to be extended in patients who fail to show a decline in CSF pleocytosis and a reduction in CSF CMV DNA copy number on quantitative PCR tests (where available). Approximately one-third of patients develop renal impairment during treatment, which is reversible following discontinuation of therapy in most, but not all, cases. This is often associated with elevations in serum creatinine and proteinuria and is less frequent in patients who are adequately hydrated. Many patients experience fatigue and nausea. Reduction in serum calcium, magnesium, and potassium occur in ~15% of patients and may be associated with tetany, cardiac rhythm disturbances, or seizures.

Cidofovir is a nucleotide analogue that is effective in treating CMV retinitis and equivalent or better than ganciclovir in some experimental models of murine CMV encephalitis, although data concerning its efficacy in human CMV CNS disease are limited. The usual dose is 5 mg/kg intravenously once weekly for 2 weeks, then biweekly for 2 or more additional doses, depending on clinical response. Patients must

be prehydrated with normal saline (e.g., 1 L over 1 to 2 h) prior to each dose and treated with probenecid (e.g., 1 g 3 h before cidofovir and 1 g 2 and 8 h after cidofovir). Nephrotoxicity is common; the dose should be reduced if renal function deteriorates.

Intravenous ribavirin (15 to 25 mg/kg per day in divided doses given every 8 h) has been reported to be of benefit in isolated cases of severe encephalitis due to California encephalitis (LaCrosse) virus. Ribavirin might be of benefit for the rare patients, typically infants or young children, with severe adenovirus or rotavirus encephalitis and in patients with encephalitis due to LCMV or other arenaviruses. However, clinical trials are lacking. Hemolysis, with resulting anemia, has been the major side effect limiting therapy.

No specific antiviral therapy of proven efficacy is currently available for treatment of WNV encephalitis. Small groups of patients have been treated with interferon α , ribavirin, and IVIg preparations of non-U.S. origin containing high titer anti-WNV antibody. Evidence is insufficient to establish efficacy of any of these therapies.

SEQUELAE

There is considerable variation in the incidence and severity of sequelae in patients surviving viral encephalitis. In the case of Eastern equine encephalitis virus infection, nearly 80% of survivors have severe neurologic sequelae. At the other extreme are infections due to EBV, California encephalitis virus, and Venezuelan equine encephalitis virus, where severe sequelae are unusual. For example, ~5 to 15% of children infected with LaCrosse virus have a residual seizure disorder, and 1% have persistent hemiparesis. Detailed information about sequelae in patients with HSV encephalitis treated with acyclovir are available from the NIAID-CASG trials. Of 32 acyclovir-treated patients, 26 survived (81%). Of the 26 survivors, 12 (46%) had no or only minor sequelae, 3 (12%) were moderately impaired (gainfully employed but not functioning at their previous level), and 11 (42%) were severely impaired (requiring continuous supportive care). The incidence and severity of sequelae were directly related to the age of the patient and the level of consciousness at the time of initiation of therapy. Patients with severe neurologic impairment (Glasgow coma score 6) at initiation of therapy either died or survived with severe sequelae. Young patients (<30 years) with good neurologic function at initiation of therapy did substantially better (100% survival, 62% with no or mild sequelae) compared with their older counterparts (>30 years); (64% survival, 57% no or mild sequelae). Some recent studies using quantitative CSF PCR tests for HSV indicate that clinical outcome following treatment also correlates with the amount of HSV DNA present in CSF at the time of presentation. Many patients with WNV infection have acute sequelae including cognitive impairment; weakness; and hyper- or hypo-kinetic movement disorders including tremor, myoclonus, and parkinsonism. Improvement in these symptoms may occur over the subsequent 6 to 12 months, although detailed clinical studies of the duration and severity of WNV sequelae are still lacking.

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. 361.

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-size (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. My

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cobacterial 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 to 500 cells/ μ L), (3) elevated protein concentration in the range of 1 to 5 g/L (10 to 500 mg/dL), and (4) decreased glucose concentration in the range of 1.1 to 2.2 mmol/L (20 to 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 to 40% of cases of tuberculous meningitis in adults. Cultures of CSF take 4 to 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. PCR for the detection of *M. tuberculosis* DNA has a sensitivity of 70 to 80% but at the present time is limited by a high rate of false-positive results.

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, absorbed (FTA-ABS) or microhemagglutination-*T. pallidum* (MHA-TP)] is associated with a CSF lymphocytic or mononuclear pleocytosis and an elevated protein concentration, or when the CSF VDRL 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

Empirical therapy of tuberculous meningitis is often initiated on the basis of 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 to 25 mg/kg per day in divided doses), and pyridoxine (50 mg/d). If the clinical response is good, pyrazinamide and ethambutol can be discontinued after 8 weeks and isoniazid and rifampin continued alone for the next 6 to 12 months. A 6-month course of therapy is acceptable, but therapy should be prolonged for 9 to 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 patients who develop hydrocephalus.

Meningitis due to *C. neoformans* is treated with amphotericin B (0.7 mg/kg per day) and flucytosine (100 mg/kg per day in four divided doses) for 2 weeks, followed by an 8- to 10-week course of fluconazole (400 to 800 mg/d). 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 may require indefinite maintenance therapy. Meningitis due to *H. capsulatum* is treated with amphotericin B (0.7 to 1.0 mg/kg per day) for 4 to 12 weeks followed by itraconazole (400 mg/d). Therapy with amphotericin B is not discontinued until fungal cultures are sterile. After completing a course of amphotericin B, maintenance therapy with itraconazole is initiated and continued for at least 6 months to a year. *C. immitis* meningitis is treated with intravenous amphotericin B (0.5 to 0.7 mg/kg per day) for ≥ 4 weeks until CSF fungal cultures are negative. Intrathecal amphotericin B may be required to eradicate the infection. Lifelong therapy with fluconazole is recommended to prevent relapse. Ambisome (4 mg/kg per day) or amphotericin B lipid complex (5 mg/kg per day) can be substituted for amphotericin B 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.

Syphilitic meningitis is treated with aqueous penicillin G in a dose of 3 to 4 million units intravenously every 4 h for 10 to 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 to 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 nonreactive 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 re-treatment.

CHRONIC ENCEPHALITIS

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Clinical Features and Pathology

Progressive multifocal leukoencephalopathy (PML) is a progressive disorder characterized pathologically by multifocal areas of demyelination of varying size distributed throughout the CNS. In addition to demyelination, there are characteristic cytologic alterations in both astrocytes and oligodendrocytes. Astrocytes are tremendously enlarged and contain hyperchromatic, deformed, and bizarre nuclei and frequent mitotic figures.

Oligodendrocytes have enlarged, densely staining nuclei that contain viral inclusions formed by crystalline arrays of JC virus particles. Patients often present with visual deficits (45%), typically a homonymous hemianopia, and mental impairment (38%) (dementia, confusion, personality change). Motor weakness may not be present early but eventually occurs in 75% of cases.

Almost all patients have an underlying immunosuppressive disorder. Prior to the HIV

epidemic, common associated diseases included

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lymphoproliferative disorders, immune deficiency states, myeloproliferative disease, and chronic infectious or granulomatous diseases. More than 60% of currently diagnosed PML cases occur in patients with AIDS. Conversely, it has been estimated that nearly 1% of AIDS patients will develop PML. The basic features of AIDS-associated and non-AIDS-associated PML are identical.

Diagnostic Studies

MRI reveals multifocal asymmetric, coalescing white matter lesions located periventricularly, in the centrum semiovale, in the parietal-occipital region, and in the cerebellum. These lesions have increased T2 and decreased T1 signal, are generally nonenhancing or show only minimal peripheral enhancement, and are not associated with edema or mass effect. CT scans, which are less sensitive than MRI for the diagnosis of PML, often show hypodense nonenhancing white matter lesions.

The CSF is typically normal, although mild elevation in protein and/or IgG may be found. Pleocytosis occurs in <25% of cases, is predominantly mononuclear, and rarely exceeds 25 cells/ μ L. PCR amplification of JC virus DNA from CSF has become an important diagnostic tool. CSF PCR for JC virus DNA has high specificity, but sensitivity has varied among studies. Rare cases of positive CSF PCR for JC virus DNA in the absence of clinical or radiographic evidence of PML have been described in HIV-infected patients. It remains to be established whether these results are false positives or indicate preclinical PML.

A positive CSF PCR for JC virus DNA in association with typical MRI lesions in the appropriate clinical setting is diagnostic of PML. Patients with negative CSF PCR studies may require brain biopsy for definitive diagnosis; JC virus antigen and nucleic acid can be detected by immunocytochemistry, in situ hybridization, or PCR amplification. Detection of JC virus antigen or genomic material should be considered diagnostic of PML only if accompanied by characteristic pathologic changes, since both antigen and genomic material have been found in the brains of normal patients.



TREATMENT

No effective therapy is available. Recent trials in HIV-associated PML failed to show benefit from either cytarabine or cidofovir. Some patients with HIV-associated PML have shown dramatic clinical improvement associated with improvement in their immune status following institution of highly active antiretroviral therapy.

SUBACUTE SCLEROSING PANENCEPHALITIS

SSPE is a rare progressive demyelinating disease of the CNS associated with a chronic infection of brain tissue with measles virus. Most patients give a history of primary measles infection at an early age (2 years), which is followed after a latent interval of 6 to 8 years by the development of insidious intellectual decline and mood and personality changes. Typical signs of a CNS viral infection, including fever and headache, do not occur. Focal

and/or generalized seizures, myoclonus, ataxia, and visual disturbances occur as the disease progresses. The EEG shows a characteristic periodic pattern with bursts every 3 to 8 s of high-voltage, sharp slow waves, followed by periods of attenuated ("flat") background. The CSF is acellular with a normal or mildly elevated protein level and a markedly elevated γ -globulin level (>20% of total CSF protein). CSF antimeasles antibody levels are invariably elevated, and oligoclonal antimeasles antibodies are often present. CT and MRI show evidence of multifocal white matter lesions and generalized atrophy. Measles virus can be cultured from brain tissue, and viral genome can be detected by in situ hybridization or PCR amplification. Treatment with isoprinosine (Inosiplex) (100 mg/kg per day), alone or in combination with intrathecal or intraventricular interferon, 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 to 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 level, markedly increased γ -globulin, and rubella virus-specific oligoclonal bands. No therapy is available.

BRAIN ABSCESS

DEFINITION

A brain abscess is a focal, suppurative infection within the brain parenchyma, typically surrounded by a vascularized capsule. The term *cerebritis* is often employed to describe a nonencapsulated brain abscess.

EPIDEMIOLOGY

A bacterial brain abscess is a relatively uncommon intracranial infection, with an incidence of ~1 in 100,000 persons per year. Predisposing conditions include otitis media and mastoiditis, paranasal sinusitis, pyogenic infections in the chest or other body sites, penetrating head trauma or neurosurgical procedures, and dental infections. In most modern series, an increasing proportion of brain abscesses are not caused by classic pyogenic bacteria, but rather by fungi and parasites including *Toxoplasma gondii*, *Aspergillus* spp., *Nocardia* spp., *Mycobacteria* spp., and *C. neoformans*. These organisms are almost exclusively restricted to immunocompromised hosts with underlying HIV infection, organ transplantation, cancer, or immunosuppressive therapy. In Latin America and in immigrants from Latin America, the most common cause of brain abscess is *Taenia solium* (neurocysticercosis). In India and the Far East, mycobacterial infection (tuberculoma) remains a major cause of focal CNS mass lesions.

ETIOLOGY

A brain abscess may develop (1) by direct spread from a contiguous cranial site of

infection, such as paranasal sinusitis, otitis media, mastoiditis, or dental infection; (2) following head trauma or a neurosurgical procedure; or (3) as a result of hematogenous spread from a remote site of infection. In up to 25% of cases no obvious primary source of infection is apparent (cryptogenic brain abscess).

Up to one-third of brain abscesses are associated with otitis media and mastoiditis, often with an associated cholesteatoma. Otogenic abscesses occur predominantly in the temporal lobe (55 to 75%) and cerebellum (20 to 30%). In some series up to 90% of cerebellar abscesses are otogenic. Common organisms include streptococci, *Bacteroides* spp., *P. aeruginosa*, and Enterobacteriaceae. Abscesses that develop as a result of direct spread of infection from the frontal, ethmoidal, or sphenoidal sinuses and those that occur due to dental infections are usually located in the frontal lobes. Approximately 10% of brain abscesses are associated with paranasal sinusitis, and this association is particularly strong in young males in their second and third decades of life. The most common pathogens in brain abscesses associated with paranasal sinusitis are streptococci (especially *S. milleri*), *Haemophilus* spp., *Bacteroides*