CHAPTER 86

Neurologic Infections

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INTRODUCTION

Infections of the central nervous system (CNS) are often rapidly progressive and can be fatal if left undiagnosed or treatment is delayed. Prompt diagnosis and treatment are, therefore, crucial to decreasing morbidity and mortality. Patients with CNS infections may require intensive care unit (ICU) admission, most commonly for airway protection and mechanical ventilation due to altered mental status. Similarly, patients with undiagnosed CNS infections may be admitted to the ICU, where intensivists can play a role in diagnosis and optimize outcomes with early and effective therapy.

Identification of the presence or absence of focal neurologic findings is important in patients with suspected neurologic infections as this helps to focus the differential diagnosis and identify patients in whom lumbar puncture (LP) may be contraindicated—at least until neuroimaging is completed. The major neurologic infections encountered in the critically ill include acute bacterial meningitis, encephalitis, brain abscess, subdural empyema, epidural abscess, and suppurative intracranial thrombophlebitis. Neurologic findings may also be the result of primary nonneurologic syndromes, such as sepsis, and are covered in other chapters. Neurologic infections in advanced HIV/AIDS are also covered separately.

The CNS is normally protected by various host defenses, the most important of which is the blood–brain barrier. Once microorganisms gain entry, however, they are able to proliferate rapidly due to low concentrations of immunoglobulins and leukocytes in the CNS. Viral, bacterial, mycobacterial, fungal, or parasitic agents can all cause CNS infection. Patient age, underlying host factors, and epidemiologic exposures including travel, animal or vector exposures, and contacts with infectious cases are important risk factors for acquiring specific infections. Prompt physical examination to identify patients in need of urgent interventions—including endotracheal intubation—should be performed, followed by LP and/or imaging studies. New techniques in the areas of molecular diagnostics and neuroimaging have revolutionized the diagnosis of CNS infections. New therapeutic options, as well as improvements in intensive care support, have also enhanced outcomes in these patients.

MENINGITIS

Meningitis— inflammation of the meninges—may be caused by a wide variety of microorganisms (Table 86.1). Infectious agents gain entry to the CSF via hematogenous, transdural, or transparenchymal routes. It is important to consider noninfectious syndromes in the differential diagnosis of meningitis. Such examples include meningeal carcinomatosis, vasculitic syndromes, or drug effect (e.g., nonsteroidal anti-inflammatory agents, antimicrobials, immunosuppressants, anticonvulsants). Identification of noninfectious conditions is essential, as their therapies differ from those for infectious syndromes; specifically, high-dose corticosteroid therapy may be indicated in some of these cases. Aseptic meningitis refers to inflammation of the meninges not attributed to bacterial infection. Critically ill patients, however, present more commonly with bacterial meningitis by virtue of the more rapid and fulminating presentation.

Acute bacterial meningitis accounts for approximately 1.2 million cases annually worldwide (1). Because untreated bacterial meningitis is universally fatal, early recognition, rapid diagnostic testing, and emergent administration of antimicrobial and adjunctive agents are crucial. The most common meningal pathogens include Streptococcus pneumoniae and Neisseria meningitidis, although specific etiologic agents and their frequencies vary with underlying host factors such as age, immune status, and route of acquisition. The case fatality rate for adults with bacterial meningitis is approximately 15% to 30%, and increases with age (2,3). Transient or permanent neurologic sequelae occur in approximately 25% of survivors (4,5). Recent data suggest that survival has improved following recommendations for the adjunctive use of dexamethasone (6).

PATHOPHYSIOLOGY

Bacterial meningitis develops as a result of several mechanisms and involves complex interactions between pathogen virulence and host immune response. Specific microorganisms that colonize the nasopharynx may invade local tissues and subsequently spread to the bloodstream and CNS (7,8). Bacteremia and subsequent CNS invasion may also develop from sources such as pneumonia or urinary tract infection. Last, direct entry from contiguous infection (e.g., sinusitis or mastoiditis), trauma, neurosurgery, or prosthetic devices such as CSF shunts or cochlear implants also occurs. Inflammation and blood–brain barrier injury result from the release of inflammatory cytokines such as interleukin-1 and tumor necrosis factor (9,10). Vasogenic edema and increased intracranial pressure may ensue with subsequent cerebral ischemia, cytotoxic injury, and cellular apoptosis (11). Host factors including functional or anatomic asplenia, complement deficiency, and congenital or acquired immunodeficiency predispose to bacterial meningitis (Table 86.2). Other risk factors for the development of meningitis include recent close contact with a patient with acute bacterial meningitis, recent travel to areas with endemic meningococcal disease, injection drug use, recent neurotrauma or CSF leak, and otorrhea.

The median duration of symptoms prior to hospital admission in bacterial meningitis is short, averaging approximately 24 hours (12). The classic triad of fever, nuchal rigidity, and change in mental status occurs in less than two-thirds of cases; however, almost all patients have at least one of these findings.
TABLE 86.2 Predisposing Host Factors to Specific Etiologic Agents of Meningitis

<table>
<thead>
<tr>
<th>Common: Host Factors</th>
<th>Uncommon: Specific Etiologic Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulin</td>
<td>D. pneumoniae, S. pneumoniae, N. meningitidis, S. pyogenes</td>
</tr>
<tr>
<td>Asplenia</td>
<td>D. pneumoniae, S. pneumoniae, N. meningitidis, S. pyogenes</td>
</tr>
<tr>
<td>Complement deficiency</td>
<td>D. pneumoniae, S. pneumoniae, N. meningitidis, S. pyogenes</td>
</tr>
<tr>
<td>Corticosteroid excess</td>
<td>L. monocytogenes, C. neoformans, M. tuberculosis</td>
</tr>
<tr>
<td>HIV Infection</td>
<td>L. monocytogenes, C. neoformans, M. tuberculosis</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>S. pneumoniae, N. meningitidis, S. pyogenes</td>
</tr>
<tr>
<td>Fracture of cribriform plate</td>
<td>S. pneumoniae, H. influenzae, S. pyogenes</td>
</tr>
<tr>
<td>Basal skull fracture</td>
<td>S. pneumoniae, H. influenzae, S. pyogenes</td>
</tr>
<tr>
<td>Neurotrauma, postneurosurgery</td>
<td>S. aureus, S. pyogenes, P. aeruginosa, P. aeruginosa</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.

Chapter 86  Neurologic Infections  1009

1009.

The absence of any of these findings effectively excludes the diagnosis. Nuchal rigidity can be detected with passive or active flexion of the neck. Tests, such as the Kernig and Brudzinski signs, are well-described physical examination techniques but are neither sensitive nor specific (14). Jolt accentuation (worsening of headache with horizontal rotation of the head two to three times per second) also lacks sensitivity (15). Photophobia, seizures, focal neurologic deficits, and papilledema may be seen on physical examination. Some patients may not manifest the classic signs and symptoms of bacterial meningitis, particularly neonates and those with underlying immunosuppressive conditions including diabetes mellitus, chronic organ failure, neutropenia, chronic corticosteroid use, organ transplantation, and HIV infection. Ten percent to 25% of patients with bacterial meningitis present with septic shock (16,17).

Certain microorganisms may present with specific physical findings. Meningococcal meningitis may present with characteristic skin manifestations consisting of diffuse petechiae and purpura on the distal extremities. Severe cases are described
as purpura fulminans. Skin findings occur in approximately one-fourth of bacterial meningitis cases, over 90% of which are due to \textit{N. meningitidis} infection (3).

\textit{S. pneumoniae} is the most common cause of bacterial meningitis in adults, accounting for 71% of cases in the United States (2). \textit{S. pneumoniae} serotypes causing bacteremic disease are also those commonly responsible for meningitis. Focal infection is common with contiguous or distant sites, including sinusitis, mastoiditis, pneumonia, otitis media, and endocarditis. The major risk factors for pneumococcal meningitis include asplenia, hypogammaglobulinemia, alcoholism, chronic renal or hepatic disease, malignancy, diabetes mellitus, basal skull fracture with CSF leak, and the presence of a cochlear implant.

\textit{N. meningitidis} commonly causes meningitis in children and young adults. Serogroups B, C, and Y are responsible for most endemic disease in North America (18). Following increasing use of serogroup C and quadrivalent (A, C, Y, W-135) meningococcal vaccines, serogroup B has become the predominant serotype (19). Epidemic disease is most commonly caused by serogroup C, with fewer outbreaks due to serogroup A. In 2000, epidemic W-135 was associated with the Hajj pilgrimage to Mecca in Saudi Arabia (20). Subsequently, meningococcal vaccination has become legally required prior to undertaking this activity. More recent outbreaks have occurred in Gambia and Burkina Faso (21,22). Risk factors for invasive meningococcal disease include nasopharyngeal carriage, terminal complement deficiency, and properdin deficiency (23,24). Although a characteristic rapidly evolving petechial or purpuric rash strongly suggests \textit{N. meningitidis}, a similar rash may be seen in splenectomized patients with overwhelming \textit{S. pneumoniae} or \textit{Haemophilus influenzae} type b infection.

\textit{H. influenzae} previously accounted for a large proportion of cases of bacterial meningitis; however, widespread vaccination against \textit{H. influenzae} type b has now markedly decreased its incidence. Isolation of \textit{H. influenzae} type b in adults suggests the presence of an underlying condition such as sinusitis, otitis media, pneumonia, diabetes mellitus, alcoholism, CSF leak, asplenia, or immune deficiency.

\textit{Listeria monocytogenes} meningitis accounts for only 2% of cases of bacterial meningitis in the United States (2) and is associated with similar mortality rates compared to nonbacterial cases. It occurs in neonates, adults older than 50 years of age, and in those with risk factors including alcoholism, malignancy, pregnancy, and immune suppression secondary to corticosteroid therapy or organ transplantation. It is interesting that this infection is seen infrequently in HIV-infected patients; we postulate this may be due to antibiotic prophylaxis—most non-HIV-infected patients receive prophylaxis (30). \textit{L. monocytogenes} commonly makes up part of the fecal flora of farm animals and can be isolated from soil, water, or contaminated vegetables. Outbreaks have been associated with unpasteurized dairy products such as milk and cheese, as well as vegetables, and processed meats (25–27).

Aerobic gram-negative bacilli can cause meningitis in specific patients. Predisposing risk factors include recent neurosurgery, neonatal status, advanced age, immune suppression, gram-negative bacteremia, and disseminated \textit{Strongyloides stercoralis} hyperinfection syndrome. \textit{Escherichia coli} is a common cause of meningitis in neonates.

\textit{Staphylococcus aureus} and coagulase-negative staphylococci (CoNS) can both cause meningitis, but are less common. Both \textit{Staphylococcus} species exist as part of the normal skin flora, predominantly causing infections following neurosurgery or neurotrauma, or when prosthetic material is present, particularly external ventricular drains or ventriculoperitoneal shunts. Some patients with staphylococcal bacterial meningitis have underlying infective endocarditis, paraspinal or epidural infection, sinusitis, osteomyelitis, or pneumonia.

Other less common causes of bacterial meningitis include Enterococci, viridans group Streptococci, \textit{β}-hemolytic Streptococci, Corynebacterium species (diphtheroids) and \textit{Propionibacterium acnes} (generally only in the setting of prosthetic material), and anaerobic species.

Viruses are the most commonly isolated pathogens in aseptic meningitis. The nonpolio enteroviruses, especially Coxsackie viruses A and B, and echoviruses are common (28), accounting for 85% to 95% of all cases of aseptic meningitis with an identified pathogen (29). Enteroviruses occur worldwide, are transmitted by fecal–oral or respiratory droplet spread, and exhibit summer and fall seasonality in temperate climates. Infants, children, and young adults are commonly affected. Clinical manifestations depend on host age and immune status but generally include abrupt onset of severe headache, fever, nausea, vomiting, photophobia, nuchal rigidity, and malaise. Rash and upper respiratory symptoms are common. Only rarely is illness severe enough to require critical care services.

Arboviruses more commonly cause encephalitis but, rarely, may cause aseptic meningitis. Arboviruses include the flaviviruses (St. Louis encephalitis virus, Colorado tick fever, Japanese encephalitis virus, and West Nile virus), Togaviridae (Eastern equine encephalitis [EEE], Western equine encephalitis [WEE], and Venezuelan equine encephalitis [VEE]), and California serogroup encephalitis viruses, almost all of which are due to La Crosse virus. Arboviruses occur predominantly in the summer and early fall when vector exposure is most likely.

West Nile virus (WNV) came to widespread attention in 1999 when the first North American cases were identified. The virus subsequently spread extensively across North America, and caused three large outbreaks in 2002, 2003, and 2012 (30). WNV infection is asymptomatic in 80% of cases. Symptomatic patients present with West Nile fever (approximately 20%–25%) (31) or neuroinvasive disease (≤1%). WNV fever is a self-limited febrile illness characterized by fever, headache, malaise, myalgias, and often a rash (50%). WNV neuroinvasive disease may present as encephalitis, meningitis, or flaccid paralysis. Meningitis, however, is the least common presentation of neuroinvasive disease. Infections occur in late summer or early fall, as nearly all human infections are due to mosquito bites. Rarely, transmission can occur in utero or via donated blood or organ transplantation.

Lymphocytic choriomeningitis (LCM) virus is a zoonotic infection, transmitted by contact with infected rodent (mouse, rat, hamster) secretions or excretions, or rarely via organ transplantation (32–34), which causes aseptic meningitis (35,36). Presenting manifestations include systemic symptoms of fever, myalgias, and malaise, as well as headache and meningismus, with occasional rash, orchitis, arthritis, myopericarditis, and transient alopecia.

Six of the eight recognized human herpesviruses can cause meningitis. Herpes simplex viruses (HSV) are most commonly
associated with aseptic meningitis during primary genital infection (37). HSV-2 infection is responsible for most infections, however, HSV-1 genital infection and concomitant meningitis can also occur. Meningitis is much less likely in the setting of genital herpes recurrences. Headache, photophobia, and meningismus are common presenting symptoms. Genital lesions are present in 85% of patients with primary HSV-2 meningitis and generally precede meningeal symptoms by several days.

Herpes zoster aseptic meningitis, with or without typical skin lesions, has also been reported, particularly in older patients. Cytomegalovirus (CMV), Epstein–Barr virus (EBV), and human herpesvirus 6 (HHV-6) are all capable of causing aseptic meningitis but occur very rarely, predominantly in immune-suppressed populations.

HIV-associated aseptic meningitis occurs with primary infection in approximately 5% to 10% of patients (37). Cranial neuropathies may be present along with headache, fever, and meningismus. Symptoms are usually self-limited.

Mumps, now rare as a result of universal vaccination programs, was once a relatively common cause of aseptic meningitis. The clinical manifestations include fever, vomiting, headache, and parotitis in approximately 50% of patients. Meningismus, lethargy, and abdominal pain may also be present. Sporadic outbreaks in susceptible individuals continue to occur worldwide including the United States (38–40).

There are a number of less common causes of aseptic meningitis. Spirochetal meningitis may be caused by Treponema pallidum or Borrelia burgdorferi. T. pallidum, the etiologic agent of syphilis, is acquired by sexual contact, placental transfer, or direct contact with active lesions; these include condyloma lata, mucous patches, or the rash of secondary syphilis. Syphilitic meningitis usually occurs during primary or secondary infection, complicating up to 2% of untreated infections during the first 2 years. B. burgdorferi is transmitted by the Ixodes tick and causes Lyme disease. It is the most common vector-borne disease in the United States. Meningitis can occur during the first stage of disease, concurrently with erythema migrans at the tick bite site. Dissemination of the microorganism in the second stage of disease, 2 to 10 weeks following exposure, may also result in aseptic meningitis. Late or chronic disease may include subacute encephalopathy but not meningitis.

Mycobacterium tuberculosis may cause a subacute or chronic form of meningitis. Infection of the meninges results from rupture of a tuberculous focus into the subarachnoid space. In very young patients, concomitant disseminated systemic infection is common. Epidemiologic risk factors include a known prior history of tuberculosis (TB) exposure, residence in an endemic area, contact with an active case, incarceration, homelessness, and HIV infection. Tuberculin skin testing (TST) is negative in over half of patients with tuberculous meningitis (41,42). A negative skin test, therefore, cannot be used to exclude the diagnosis. Newer tests, such as interferon-gamma release assays (IGRA) and nucleic acid amplification tests (NAT) may be available in some centers.

Fungal meningitis, although uncommon, should be considered particularly given the high mortality associated with untreated infection. Cryptococcus neoformans predominantly affects immune-compromised hosts but can also infect the immunocompetent. This encapsulated yeast is distributed worldwide but prefers wet-forested regions with decaying wood and is found in particularly high concentrations in pigeon guano. Risk factors for cryptococcal infection include HIV/AIDS, prolonged corticosteroid therapy, immunosuppression transplantation, malignancy, and sarcoidosis. Clinical presentation is typically indolent, occurring over 1 to 2 weeks, and is characterized by fever, malaise, and headache. Meningismus, photophobia, and vomiting occur in less than one-third of patients. Cryptococcus gattii, a serotype usually restricted to tropical climates, emerged on Vancouver Island, British Columbia (BC), Canada in 1999 and has since been responsible for numerous cases of CNS infection in predominantly immunocompetent hosts in BC and the U.S. Pacific Northwest.

Coccidioides immitis, a dimorphic fungus, is found in soil in the dry desert regions of the southwest United States, Mexico, and Central and South America. Infection results after inhalation of arthroconidia, usually following a dust storm or during building construction. Infection is usually confined to the respiratory system in those with competent immune systems. However, extrapulmonary dissemination to the meninges can occur in patients with immune compromise or during pregnancy. Risk factors for the development of disease include travel to or residence in an endemic region and immune deficiency. Coccidioidal meningitis is universally fatal if untreated.

Less common fungal causes of meningitis include Blastomyces dermatitidis, Histoplasma capsulatum, Sporothrix schenckii, and rarely, Candida species. B. dermatitidis and H. capsulatum are endemic in the Mississippi and Ohio River Valleys. S. schenckii has been reported worldwide, with most cases in the tropical regions of the Americas.

Candida is part of the normal flora of skin and gastrointestinal tract. Candidal CNS infection is most commonly the result of meningeal seeding in candidemic patients. Predisposing risk factors for candidemia include the use of broad-spectrum antibiotics, the presence of indwelling devices such as vascular or urinary catheters, parenteral nutrition, ICU admission, prolonged hospital stay, and immune compromise. Specific risk factors for Candida CNS infection include ventricular shunts, trauma, neurosurgery, or lumbar puncture (43,44). Candida albicans is the most commonly isolated species; however, non-albicans species are becoming more prevalent, particularly in ICU populations.

Meningitis caused by protozoa or helminths are extremely rare. The free-living amoebas Acanthamoeba, Balamuthia, and Naegleria fowleri are associated with fresh water exposure. They are usually acquired by individuals diving into contaminated lakes or swimming pools. N. fowleri can cause a primary amoebic meningoencephalitis. Acanthamoeba and Balamuthia rarely cause meningitis; they commonly present as encephalitis. As for helminths, Angiostrongylus cantonensis (the rat lungworm) is the classic infectious cause of eosinophilic meningitis (>10% eosinophils in the CSF) (Table 86.3). Humans are incidental hosts and develop neurologic symptoms as a result of larval migration through the CNS. A. cantonensis is endemic in Southeast Asia and the Pacific Islands and is acquired by ingesting raw mollusks such as snails or slugs. Gnathostoma spinigerum, acquired by ingestion of raw and undercooked fish and poultry, is not primarily neurotropic like A. cantonensis but may also cause eosinophilic meningitis as a result of migration of larvae up nerve tracts to the CNS. Gnathostomiasis is endemic in Asia, especially Thailand and Japan, and more recently in Mexico. Baylisascaris procyonis, a roundworm infection of raccoons, rarely causes human eosinophilic meningoencephalitis following accidental ingestion of ova from raccoon feces in contaminated water, soil, or foods (45).
**DIAGNOSIS**

Lumbar puncture (LP) should be performed emergently in all patients suspected of having bacterial meningitis unless contraindicated. Unnecessary delays are unfortunately common while neuroimaging is performed to exclude mass lesions. Complications associated with LP are uncommon but may include post-LP headache, infection, bleeding, radicular pain or paresthesias, back pain, and very rarely cerebral herniation (46). A study evaluating the clinical features at baseline associated with abnormal findings on computed tomography (CT) scan, and thus, increased risk of brain herniation, identified an age greater than 40 years, a history of CNS disease such as a mass lesion, stroke, or focal infection; immune compromise such as HIV or immunosuppressive therapy; a history of CNS disease; and greater than or equal to 60 years (47, 48). Based on these findings, guidelines for which adult patients should undergo CT prior to LP have been recommended (Table 86.4) (48).

Nosocomial meningitis is rare in nonneurosurgical patients; nevertheless, LP is often performed in hospitalized patients with unexplained fever and/or decreased level of consciousness.

**TABLE 86.3** Cerebrospinal Fluid Tests in Suspected CNS Infection

<table>
<thead>
<tr>
<th>Routine Tests</th>
<th>Further Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell count and differential</td>
<td>Lactate</td>
</tr>
<tr>
<td>Protein</td>
<td>Viral studies:</td>
</tr>
<tr>
<td>Glucose (preferably with simultaneous serum glucose)</td>
<td>Enterovirus, HSV, WNV, VZV NAT, influenza, EBV, CMV, HHV-6 NAT, (selected cases, rare CNS infections)</td>
</tr>
<tr>
<td>Gram stain</td>
<td>Fungal culture and organism-specific NAT*</td>
</tr>
<tr>
<td>Bacterial culture and sensitivity</td>
<td>VDRL, FTA-Ab, Treponema pallidum, M. tuberculosis NAT*</td>
</tr>
<tr>
<td></td>
<td>Cytology, Cryptococcal antigen test (can send serum as well, sensitivity comparable to CSF)</td>
</tr>
<tr>
<td></td>
<td>Cytospin and flow cytometry if available</td>
</tr>
<tr>
<td></td>
<td>Wet mount if PAM suspected</td>
</tr>
<tr>
<td></td>
<td>Lyme-specific Ab and NAT*</td>
</tr>
</tbody>
</table>

CNS, central nervous system; NAT, nucleic acid amplification test; HSV, herpes simplex virus; WNV, West Nile virus; VZV, varicella zoster virus; AFB, acid-fast bacillus; CSF, cerebrospinal fluid; VDRL, Venereal Diseases Research Laboratory; FTA-Ab, fluorescent treponemal antibody absorption; PAM, primary amoebic meningoencephalitis.

*Experimental, available only in research laboratories.

The yield of performing an LP in the nonneurosurgical population is extremely low and of questionable utility.

CSF analysis is extremely important in the diagnosis of meningitis. Basic laboratory analyses, including cell count and differential, protein, glucose, Gram stain, and bacterial cultures, are most useful in distinguishing between viral, bacterial, tuberculous, and fungal infection (see Table 86.3).

**Bacterial Meningitis**

Bacterial meningitis usually presents with an elevated systemic white blood cell (WBC) count due to neutrophilia and left shift (immature forms such as bands and/or myeloids). Leukopenia is occasionally present in severe infection. Thrombocytopenia may be the result of sepsis, disseminated intravascular coagulation, or meningococcal meningitis alone. Renal and hepatic dysfunction may occur as part of multiorgan failure in severe disease. Blood cultures should always be drawn prior to the administration of antimicrobials, particularly if an LP cannot be performed immediately and are positive in 50% to 80% of cases (3, 12).

CSF analysis in bacterial meningitis classically reveals a neutrophilic pleocytosis with hundreds to thousands of cells and greater than 80% neutrophils. In fact, a low CSF WBC count is usually a marker of poor prognosis in this setting. The CSF glucose concentration is usually low and should always be compared with a simultaneous serum glucose measurement. An abnormal CSF-to-serum glucose ratio (<0.5) is common in bacterial meningitis—and is often much lower than 0.5. Acute illness in diabetics may increase serum glucose levels markedly, making the CSF-to-serum glucose ratio inaccurate. CSF lactate levels may be useful in distinguishing bacterial from aseptic meningitis (49–51). CSF protein and opening pressure are usually elevated in bacterial meningitis (Table 86.5).

Gram staining permits rapid identification of bacterial species—with a sensitivity of 60% to 90% and specificity of close to 100% in patients with bacterial meningitis (3, 51).
Gram stain is more likely to be positive in patients with high bacterial loads. Gram-positive diplococci suggest S. pneumoniae infection, gram-negative diplococci suggest N. meningitidis infection, gram-positive rods suggest L. monocytogenes infection, and small pleomorphic cocciobacilli suggest H. influenzae infection.

CSF bacterial cultures are positive in approximately 80% of cases (5,12). The yield decreases significantly in patients treated with antimicrobials prior to CSF collection. Antigen assays (latex agglutination tests) have been used in these cases, but due to their low sensitivity are no longer routinely offered by many laboratories. Broad-based NAT (52) and 16s rDNA-based gene sequencing (53) may be useful for the diagnosis of culture-negative meningitis.

**Viral Meningitis**

In acute viral meningitis, the CSF cell count is usually in the low hundreds with a lymphocytic predominance. A predominance of neutrophils may be seen in the first 24 hours of disease, occasionally confusing the diagnosis. The CSF glucose concentration is usually within normal range. CSF protein is often mildly elevated, and the opening pressure is usually normal.

Viral cultures and NAT are most commonly used in the diagnosis of viral meningitis, but NAT is more sensitive. Enteroviruses may be cultured from CSF, throat, or rectal swabs, however, CSF NAT testing is both more sensitive and specific. NAT for HSV is also widely available, and in HSV-1 encephalitis, HSV NAT demonstrated a specificity of 99% and sensitivity of 96% when CSF was studied between 48 hours and 10 days from symptom onset (54). False negatives occur mostly within the first 72 hours of infection. The diagnosis of WNV neuroinvasive disease can be made by detection of serum IgM or a fourfold rise in IgG between acute and convalescent titers. WNV NAT of serum and CSF are also available; however, the sensitivity is higher in CSF due to short-lived viremia in humans.

**Other Less Common Causes**

CSF analysis in syphilitic meningitis is characterized by a mild lymphocytic pleocytosis, decreased glucose, and elevated protein. T. pallidum cannot be cultured, so diagnosis must be made using alternate methods, predominantly serology. Direct visualization by darkfield microscopy or direct fluorescent antibody testing may be possible if a primary chancre or skin lesion of secondary syphilis—condyloma lataum or mucous patch—is present. While Treponema-specific enzyme immunoassays (EIA) for IgM and IgG have largely replaced traditional serologic tests, CSF VDRL may be used in the diagnosis of syphilitic meningitis. The specificity is high, but false positives may occur in bloody specimens. The major limitation of CSF VDRL is its low sensitivity, so a negative result should not be used to rule out infection. CSF FTA-Ab is more sensitive; however, false positives are common due to serum antibody leak into the CSF. Last, NAT has been used to detect T. pallidum DNA in the CSF but lacks sensitivity and is not available in all centers (55–57).

Lyme meningitis is characterized by a mild lymphocytic pleocytosis, low glucose, and elevated protein. The CSF concentration of B. burgdorferi antibody, compared to serum levels, is a sensitive and specific diagnostic method. NAT is currently available only in research laboratories and does not differentiate between infection and remnant DNA from prior cured infection (58). CSF oligoclonal bands and B. burgdorferi culture are also available, but neither is sensitive or specific.

The CSF analysis in tuberculosis meningitis demonstrates a lymphocytic pleocytosis, low glucose, and markedly elevated protein and opening pressure. The elevation in protein is particularly marked in the setting of CSF block. Acid-fast bacillus (AFB) smears are generally low yield, but may be optimized by sending large volumes (10–15 mL) of CSF (59). Mycobacterial cultures, although slow growing—taking several weeks—become positive in approximately 70% of cases (59). DNA probes and NAT have recently become available with great improvements in sensitivity and specificity (60). Meningeal biopsy is rarely performed but may show caseating granuloma. Sputum and urine AFB, as well as mycobacterial blood cultures, should also be included as part of the TB workup in these patients. Since CSF AFB microscopy has very low sensitivity and cannot exclude the diagnosis of TB, in most cases the combination of increased WBCs and protein, decreased glucose and negative conventional cultures may be suggestive of TB meningitis, especially in a patient with epidemiologic risk factors for TB (i.e., foreign-born) or positive TST or IGRA, and should prompt consideration of empiric anti-TB therapy.

Cryptococcal meningitis is characterized by a lymphocytic pleocytosis, decreased glucose, and elevated protein. Opening pressures may be markedly elevated. Culture of C. neoformans or C. gattii from the CSF is diagnostic; however, other simpler tests are now available. Detection of serum or CSF cryptococcal antigen (CrAg) is highly sensitive (>90%) (61). India ink was previously regarded as the standard diagnostic test, but due to its low sensitivity it has been largely replaced by antigen testing. Fungal blood cultures may also be useful, as cryptococcal meningitis occurs in the setting of disseminated cryptococcal disease, especially in HIV-infected patients.

Other fungal meningitides are similarly characterized by a lymphocytic pleocytosis, low to normal glucose, and an elevated protein. Coccidioidal meningitis may present with an eosinophilic pleocytosis and peripheral eosinophilia. Fungal cultures are diagnostic and are most useful in Candida or Aspergillus infection. Dimorphic fungal infection may be diagnosed serologically, as isolating these organisms from the CSF is challenging and of low yield (62). Detection of complement-fixing (CF) IgG antibodies or immunodiffusion tests for IgM and IgG in CSF are currently the standard diagnostic tests. Low-titer false positives may occur in the setting of parameningeal foci. As well, false negatives may occur in early disease.

Primary amoebic meningoencephalitis due to N. fowleri results in a neutrophilic pleocytosis, increased red blood cells, low glucose, and an elevated protein. Demonstration of motile trophozoites on a wet mount of CSF or biopsy specimens is diagnostic. The diagnosis of A. cantonensis, G. spinigerum, or B. procyonis requires an appropriate epidemiologic exposure, peripheral blood eosinophilia, and a characteristic eosinophilic pleocytosis. Serologic tests are helpful but performed only in reference laboratories.

**TREATMENT**

The initial management of the patient with suspected meningitis is primarily guided by epidemiologic risk factors and
LP results. The CSF cell count, glucose, and Gram stain are crucial in guiding empiric therapy. If the LP is delayed for any reason, empiric antimicrobial therapy should not be withheld (Table 86.6), as delays in therapy have been associated with adverse clinical outcomes and increased mortality (63–65). The administration of antimicrobials should immediately follow blood culture collection and should not be delayed by neuroimaging or other tests performed prior to LP.

LP should be performed urgently in those with suspected meningitis. A protocol for the management of bacterial meningitis is presented in Figure 86.1. Imaging should be performed prior to LP in specific populations (see Table 86.4) but should not result in delays in antimicrobial therapy. Empiric therapy should be based on age, underlying host factors, and initial CSF Gram stain results, if available (see Table 86.6).

**Bacterial Meningitis**

The choice of antimicrobial therapy in bacterial meningitis is influenced by blood–CSF barrier penetration, effect of meningal inflammation on penetration, and bactericidal efficacy. In general, CSF penetration is enhanced in the setting of meningal inflammation due to increased permeability. Additionally, high lipid solubility, low molecular weight, and low protein binding increase CSF drug levels. Bactericidal efficacy may be decreased in purulent CSF, particularly with aminoglycosides, due to low pH. Penicillins, third-generation cephalosporins, carbapenems, fluoroquinolones, and rifampin achieve high CSF levels and are bactericidal. While antimicrobials may need to be adjusted based on renal and hepatic function, the doses that follow all assume normal renal function. Therapeutic drug monitoring may be required to ensure adequate levels and prevent toxicity (e.g., vancomycin, aminoglycosides). Antimicrobial therapy should also be adjusted based on culture and susceptibility results as soon as possible (Table 86.7). In suspected meningococcal or *H. influenzae* meningitis, droplet isolation (single room, gowns, gloves, surgical masks, eye protection and dedicated equipment) should be enforced until 24 hours of effective antimicrobial therapy have been completed or an alternate diagnosis is reached. Isolation in other cases of meningitis, including pneumococcal meningitis, is not required.

**Streptococcus pneumoniae**

Empiric therapy guidelines for pneumococcal meningitis have been recently modified due to increasing penicillin resistance (66–68). *S. pneumoniae* was once uniformly susceptible to penicillin; however, mutations in penicillin-binding proteins have resulted in varying levels of resistance. Empiric therapy therefore consists of a third-generation cephalosporin and vancomycin until susceptibility results become available (48). The recommendation to add vancomycin, however, is based only on a handful of pneumococcal meningitis cases demonstrating third-generation cephalosporin resistance (minimum inhibitory concentration [MIC] ≥2 μg/mL). It should also be noted that vancomycin penetrates the CSF poorly, particularly when dexamethasone is administered concomitantly, so aggressive dosing is required to achieve target trough serum concentrations. Once MICs are available, therapy should be adjusted accordingly. For isolates with penicillin MIC less than 0.06 μg/mL, penicillin G (4 million units IV every 4 hours) or amoxicillin (2 g IV every 4 hours) should be used. For isolates with a penicillin MIC of 0.12 μg/mL or higher and ceftriaxone MIC below 1 μg/mL, treatment with a third-generation cephalosporin should be continued, either ceftaxime (2 g IV every 6 hours) or ceftriaxone (2 g IV every 12 hours). For isolates with a ceftriaxone MIC greater than or equal to 1 μg/mL, vancomycin and a third-generation cephalosporin are the recommended therapy; some clinicians administer very high doses of third-generation cephalosporins in these cases. Vancomycin should be dosed 15 to 20 mg/kg/dose (based on actual body weight) every 8 to 12 hours. Subsequent dosing should be adjusted based on serum trough vancomycin concentrations (between 15 and 20 μg/mL). A loading dose of 25 to 30 mg/kg (maximum 2 g) may be used to rapidly achieve target concentrations. Meropenem is a reasonable alternative to the above agents and does not carry the theoretical risk of decreasing seizure threshold as with imipenem. The efficacy of linezolid,
daptomycin, dalbavancin, and telavancin may be promising for the treatment of highly resistant pneumococcal strains (69,70). Antimicrobial treatment duration is 10 to 14 days. Dexamethasone should be administered prior to or with the first dose of antimicrobial.

**Neisseria meningitidis**

The empiric treatment of meningococcal meningitis should be a third-generation cephalosporin: cefotaxime (2 g IV every 6 hours) or ceftriaxone (2 g IV every 12 hours); however, therapy should be stepped down to penicillin if susceptibility is confirmed. The duration of treatment is 7 days. Chloramphenicol (25 mg/kg, to a maximum of 1 g IV every 6 hours) is a reasonable alternative in the β-lactam–allergic patient. Meropenem (2 g IV every 8 hours) is another alternative, although there may be cross-reactivity in penicillin-allergic patients. Dexamethasone is not indicated in confirmed meningococcal meningitis.

**Haemophilus influenzae**

Empiric therapy for *H. influenzae* meningitis is a third-generation cephalosporin. Therapy can be narrowed to ampicillin, 2 g IV every 4 hours if susceptibility is confirmed. A total of 7 days of therapy is recommended. Dexamethasone should be administered as adjunctive therapy in children (71).

**Listeria monocytogenes**

*L. monocytogenes* meningitis should be treated with ampicillin 2 g IV every 4 hours. Gentamicin may be added for antimicrobial synergy, but aminoglycosides have poor penetration into CSF and have significant toxicities. When used, gentamicin should be administered as a 2 mg/kg loading dose, followed by 1.7 mg/kg every 8 hours. Trimethoprim/sulfamethoxazole (TMP/SMX), 20 mg/kg/day of the trimethoprim component, divided into 6 to 12 hourly doses, may be used in penicillin-allergic patients. Alternate therapies include meropenem and, potentially, linezolid and rifampin. Third-generation cephalosporins have no activity against *L. monocytogenes*. Treatment duration is 14 to 21 days.

**Aerobic Gram-Negative Bacilli**

Aerobic gram-negative bacilli should be treated empirically with a third-generation cephalosporin or meropenem. Susceptibility results should guide therapy in consultation with an infectious diseases specialist. For *Pseudomonas aeruginosa* infections, ceftazidime or cefepime, 2 g IV every 8 hours, or meropenem, 2 g IV every 8 hours, with tobramycin 2 mg/kg IV every 8 hours, should be used. Ciprofloxacin or aztreonam are acceptable alternatives if the isolate is susceptible. The duration of therapy is prolonged, generally 21 days.
**TABLE 96.7 Specific Therapy of Bacterial Meningitis**

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>β-Lactamase negative</td>
<td>Cefotaxime or ceftriaxone</td>
</tr>
<tr>
<td>β-Lactamase positive</td>
<td>Meropenem</td>
</tr>
<tr>
<td>β-Lactamase negative, ampicillin resistant</td>
<td></td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td></td>
</tr>
<tr>
<td>Penicillin MIC &lt;0.1 μg/mL</td>
<td>Penicillin G or amoxicillin</td>
</tr>
<tr>
<td>Penicillin MIC ≥0.1 μg/mL</td>
<td>Cefotaxime or ceftriaxone</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td>Penicillin MIC ≤0.06 μg/mL</td>
<td>Penicillin G or amoxicillin</td>
</tr>
<tr>
<td>Penicillin MIC ≥0.12 μg/mL</td>
<td>Cefotaxime or ceftriaxone</td>
</tr>
<tr>
<td>Ceftriaxone MIC &lt;0.1 μg/mL</td>
<td>Cefotaxime or ceftriaxone</td>
</tr>
<tr>
<td>Ceftriaxone MIC ≥1.0 μg/mL</td>
<td>Vancomycin + cefotaxime or ceftriaxone</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>Cefotaxime or ceftriaxone unless member of SPICEM group*</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Meropenem or cefazidime or ceftazidime or aztreonam or ciprofloxacin PLUS tobramycin</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Ampicillin or penicillin G</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td>Methicillin-susceptible</td>
<td>Nafcillin</td>
</tr>
<tr>
<td>Methicillin-resistant with vancomycin MIC ≤1 μg/mL</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Methicillin-resistant with vancomycin MIC &gt;1 μg/mL</td>
<td>Trimethoprim/sulfamethoxazole or daptomycin or linezolid + rifampin if susceptible</td>
</tr>
<tr>
<td>Prosthesis associated</td>
<td>Consider adding rifampin to above choices</td>
</tr>
<tr>
<td>Coagulase-negative</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Staphylococci</td>
<td></td>
</tr>
<tr>
<td>Prosthesis associated</td>
<td>Consider adding rifampin</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>Ampicillin or penicillin G</td>
</tr>
</tbody>
</table>

**MIC:** minimum inhibitory concentration. *|SPICEM group: includes *Serrata marcescens, Providencia, Indole-positive Proteus (Proteus vulgaris or perrer), Citrobacter freundii group, Enterobacter spp. and Morganella morganii. These microorganisms carry chromosomal inducible β-lactamases (ampC), which are capable of inactivating third-generation cephalosporins even if reported to be susceptible. Carbapenems (meropenem has greatest cerebrospinal fluid penetration), fluoroquinolones, or trimethoprim/sulfamethoxazole may be used if susceptible. |

Staphylococcus aureus

Staphylococcal meningitis therapy depends on methicillin susceptibility. Methicillin-susceptible strains should be treated with nafcillin 2 g IV every 4 hours, whereas methicillin-resistant (MRSA) strains should be treated with vancomycin, 15 to 20 mg/kg/dose IV every 8 to 12 hours. Subsequent vancomycin dosing should be adjusted based on serum trough vancomycin concentrations (goal trough 15 to 20 μg/mL). A loading dose of 2.5 to 30 mg/kg (maximum 2 g) may be used to rapidly achieve target concentrations. Vancomycin is also recommended in patients with serious penicillin allergies. Infected prostatic material should be removed if possible and antimicrobial therapy continued for 14 days minimum after removal. If removal is not possible, rifampin may be added; however, cure rates are poor with hardware retention. Linezolid, TMP/SMX, daptomycin, telavancin, and dalbavancin may be used as alternate therapies in MRSA meningitis when vancomycin cannot be used or is ineffective (including circumstances of “MIC creep”, when vancomycin MIC >1 μg/mL), however further studies are needed to establish efficacy of these agents. Tigecycline should not be used as therapeutic CSF concentrations are not achieved with standard therapy.

**Adjunctive Therapies**

Adjunctive therapies in bacterial meningitis include corticosteroids, procedures to reduce intracranial pressure, and surgery. Corticosteroid therapy aims to decrease the inflammatory response while allowing antimicrobial therapy to eradicate infection. Although corticosteroid administration may decrease CSF penetration and bactericidal activity of antimicrobials, randomized controlled trials demonstrate benefit with its use (12). In children, the administration of dexamethasone has demonstrated a reduction in the incidence of hearing impairment and severe neurologic complications in *H. influenzae* meningitis (71–73). Adjunctive corticosteroid therapy has also been evaluated in adults, showing a mortality benefit in patients with pneumococcal meningitis (12,72). Based on these results, treatment recommendations suggest dexamethasone, 0.15 mg/kg, be given 10 to 20 minutes before, or at least concomitant with, the first dose of antimicrobial therapy and continued every 6 hours. Dexamethasone should be administered to all patients with suspected bacterial meningitis until Gram stain or culture results are available. Therapy should be continued for 2 to 4 days only if the Gram stain or cultures demonstrate *H. influenzae* in children or *S. pneumoniae* in adults.

Placement of an intracranial pressure monitoring device may be beneficial for patients with bacterial meningitis and elevated intracranial pressure (ICP). Admission to an ICU with expertise in ICP monitoring and management of intracranial hypertension is most appropriate (74). Standard measures—such as CSF drainage, fluid and sodium management, optimization of cerebral perfusion pressure, sedation, temperature control, hyperventilation, and osmotic therapies—should be employed in patients with high ICP (73). Transcranial Doppler ultrasonography and continuous electroencephalography (EEG) monitoring should be applied where possible. Decompressive craniectomy may be considered in patients when maximal medical ICP treatment fails to reduce severe intracranial hypertension. Other surgical interventions may be required, for example, those with basal skull fractures with persistent CSF leaks or dural defects.

**Complications**

Complications of bacterial meningitis can be divided into neurologic and nonneurologic complications. Neurologic complications include seizures, cerebral edema or infarction, cranial nerve palsies, venous sinus thrombosis, brain abscess, subdural empyema, and coma. Late complications include hearing impairment, obstructive hydrocephalus, learning disabilities, sensory and motor deficits, mental retardation, cortical blindness, and seizures. Nonneurologic complications include septic shock, coagulopathy, and the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

**Viral Meningitis**

In general, the treatment for viral meningitis is supportive given its benign and self-limited course. Pleconaril has been evaluated for entero viral meningitis with modest benefit, but
remains experimental (76,77). Intravenous immune globulin has been used in agammaglobulinemic patients with chronic enteroviral meningitis. No specific therapy exists for arboviruses, mumps, or LCM. HIV-associated meningitis should be treated with combination antiretroviral therapy.

It is not clear whether antiviral treatment alters the course of HSV meningitis; nevertheless, primary episodes of genital herpes should be treated as per guidelines. Some physicians extend therapy to 14 days with concomitant meningitis. Intravenous acyclovir, dosed 5 mg/kg every 8 hours, has been used in severe disease. Therapy can be stepped down to an oral agent on discharge. Ganciclovir is the treatment of choice for CMV meningitis in immune-compromised hosts.

Other Less Common Etiologies

Syphilitic meningitis does not respond to benzathine penicillin, which is used to treat most forms of syphilis; it requires a 2-week course of high-dose IV penicillin G: 4 million units every 4 hours. Rapid plasma reagin (RPR) titers should be performed if titers do not decline by fourfold at 6 months after therapy. All HIV patients with syphilitic meningitis should have repeat LP at 6 months following therapy. Patients with penicillin allergy should undergo desensitization, as there are no proven effective alternative therapies for syphilitic meningitis.

The treatment of Lyme meningitis is achieved with ceftriaxone, 2 g daily, or cefotaxime, 2 g IV every 8 hours for 14 to 28 days. Alternate therapy is penicillin, 4 million units every 4 hours, for 14 to 28 days.

The treatment of tuberculous meningitis depends largely on the expected resistance pattern based on country of acquisition and results of susceptibility testing; consultation with an infectious diseases specialist is strongly recommended. In general, standard combination therapy includes isoniazid (INH), rifampin, pyrazinamide, and a fourth drug, either a fluoroquinolone or an injectable aminoglycoside. Ethambutol penetrates CSF poorly and has been largely replaced by fluoroquinolones. If the isolate is fully susceptible, treatment can be narrowed to INH and RIF alone. For drug-resistant TB, therapy should be prescribed by infectious diseases and/or TB services. Treatment should be continued for a minimum of 12 months but may be prolonged for concomitant tuberculoma or in multi–drug-resistant infection. Adjunctive therapy with dexamethasone for the first 2 months has been shown to decrease mortality as well as neurologic deficits and is recommended (78). Pyridoxine, 25 to 50 mg daily, may be administered to prevent INH-related neuropathy.

Therapy for fungal meningitis is complicated by the lack of standardized susceptibility testing and interpretation for many fungi. The area of antifungal therapy, however, is an evolving area with an increasing number of antifungal agents from which to choose.

Cryptococcal meningitis should be treated with a 14-day induction phase of liposomal amphotericin B, 3 to 5 mg/kg/day IV, with or without fluconazole, 100 mg/kg/day PO dosed every 6 hours. Conventional amphotericin B (deoxycholate) may still be used instead of lipid formulations, however, few patients tolerate this therapy. Consolidation therapy with fluconazole, 400 to 800 mg (6 to 12 mg/kg) daily, should be continued for 8 weeks following induction. Maintenance (or suppressive) therapy with fluconazole, 200 mg per day, should be continued in organ transplant recipients for 6 to 12 months or patients with HIV/AIDS until immune reconstitution is achieved. Cryptococcal meningitis may require initial daily therapeutic LPs, an external ventricular drain, or a ventriculoperitoneal shunt to relieve increased intracranial pressure. Echinocandins, such as caspofungin, micafungin, and anidulafungin are not active in cryptococcosis.

The treatment for coccidioidal meningitis is oral fluconazole, 400 mg/day. Some clinicians initiate therapy with a higher dose of 800 mg/day or may add intrathecal amphotericin B. Treatment must be continued lifelong, as relapses are frequently lethal. Newer azoles such as voriconazole or posaconazole may be tried in patients who are refractory to fluconazole, however evidence to support this is limited.

Therapy for H. capsulatum meningitis consists of liposomal amphotericin B or amphotericin B deoxycholate. Fluconazole, 800 mg/day, for an additional 9 to 12 months, may be used to prevent relapse. If relapse does occur, long-term therapy with fluconazole or intraventricular amphotericin B is recommended.

For candidal meningitis, the preferred initial therapy is IV liposomal amphotericin B 3 to 5 mg/kg/day, with or without fluconazole, 25 mg/kg dosed every 6 hours and adjusted to maintain serum levels of 40 to 60 μg/mL. Fluconazole therapy, in susceptible species, may be used for follow-up or suppressive therapy. The duration of therapy is at least 4 weeks after resolution of symptoms. All prosthetic material must be removed to achieve cure.

Primary amoebic meningoencephalitis caused by N. fowleri is usually fatal. A few cases have had good outcomes with early diagnosis and treatment with high-dose intravenous and intrathecal amphotericin B, rifampin and steroids to control cerebral edema. Fluconazole, miltefosine, and azithromycin may be additionally prescribed. Eosinophilic meningitis caused by A. cantonensis and G. spinigerum are treated supportively. Corticosteroids are recommended to decrease the inflammatory response to intracranial larvae. Antihelminthic therapy is relatively contraindicated, as clinical deterioration and death may occur following severe inflammatory reactions to dying larvae.

PREVENTION

Chemoprophylaxis (medications) and immunophrophylaxis (vaccines) are available to prevent infection in close contacts of cases or during outbreaks. Temporary nasopharyngeal carriage with H. influenzae, N. meningitidis, and S. pneumoniae may occur following exposure to an index case and is a risk factor for the development of invasive disease. Chemoprophylaxis is recommended to eliminate nasopharyngeal carriage in individuals at risk.

Prophylaxis is indicated in selected household/close contacts (those having more than 4 hours < 3 feet from the index case), and child-care or preschool contacts within 5 to 7 days before onset of disease, of cases of H. influenzae type b. The recommended therapy is rifampin, 20 mg/kg (usual adult dose of 600 mg daily) for four doses, and should be guided by your local public health department.

Prophylaxis for N. meningitidis is also recommended for close contacts of cases. This includes intimate contacts (e.g.,
kissing and close contacts with greater than or equal to 4 hours of contact 1 week prior to the onset of illness. Most close contacts include housemates, child-care center contacts, cellmates, and/or military recruits. Medical personnel exposed to oropharyngeal secretions during intubation, nasotracheal suctioning, or mouth-to-mouth resuscitation should also receive chemoprophylaxis. Rifampin, 600 mg orally every 12 hours for a total of four doses, or single doses of ciprofloxacin (500 mg orally) or ceftriaxone (250 mg intramuscularly) are all efficacious. It is recommended that ciprofloxacin be avoided in children younger than 16 years of age and in pregnant women, based on joint cartilage injury demonstrated in animal studies. Chemoprophylaxis is not indicated in S. pneumoniae infection.

Vaccination is available for the prevention of H. influenzae serogroup b, N. meningitidis, and S. pneumoniae infections and is part of routine childhood immunization. Unvaccinated children 2 years of age or younger, exposed to an index case, should receive chemoprophylaxis and vaccination.

S. pneumoniae vaccination is available in two preparations: the 23-valent polysaccharide (PPSV23) vaccine and the 13-valent conjugate (PCV13) vaccine. The conjugate vaccine is recommended routinely in all children 23 months of age or less. Adults at high risk of invasive disease—sickle cell disease and other hemoglobinopathies, functional or anatomic asplenia, HIV infection, immune compromise, and chronic medical conditions—and all patients over 65 years of age should receive both PPSV23 and PCV13. Additional specific vaccine recommendations have been published by the United States Advisory Committee on Immunization Practices (79–81). S. pneumoniae vaccination is not indicated as postexposure prophylaxis.

Several different meningococcal vaccines are available in the United States, including both conjugate and polysaccharide vaccines. Conjugate vaccines are preferred due to superior immunogenicity. Quadrivalent and monovalent vaccines are available and should be offered to high-risk populations, including those with specific immune deficiencies (see Table 86.2), those traveling to endemic and epidemic regions, laboratory workers routinely exposed to N. meningitidis, first-year college students living in dormitories, and military recruits. Vaccination during outbreaks of meningococcal disease due to a serogroup contained in a vaccine should be performed in consultation with public health authorities. A pentavalent meningococcal vaccine is currently under development (82).

ENCEPHALITIS

Encephalitis is defined as inflammation of the brain parenchyma. Although encephalitis and meningitis may present with similar clinical findings, the two syndromes are pathophysiologically distinct. The major distinguishing feature is the presence or absence of normal brain function. Patients with meningitis may be drowsy or lethargic but should have normal cerebral function, whereas those with encephalitis generally have altered mental status. Occasionally patients may present with a combination of findings in an overlap syndrome of meningoencephalitis. It is important to distinguish between the two syndromes, as the etiologic agents and treatments may differ.

Encephalitis is most commonly viral or postinfectious (Table 86.8). Viral encephalitis is caused by direct viral invasion of the CNS whereas postinfectious encephalitis is an immune-mediated process. Unfortunately, it may be difficult to differentiate between the two; however, encephalitis with resolving infectious symptoms suggests a postviral cause. The most common viruses causing postinfectious encephalitis include mumps, measles, varicella zoster virus (VZV), rubella, and influenza.

PATHOPHYSIOLOGY

Access to the CNS is highly virus-specific and occurs via hematogenous or neuronal routes. In hematogenous invasion, viral infection is acquired at an initial site of entry, with primary site replication, transient viremia, and CNS seeding. Retrograde transport within motor and sensory axons to the CNS occurs in the neuronal route of entry. After CNS entry, viruses enter neural cells, causing inflammation and cell dysfunction. Clinical manifestations are the result of specific cell-type invasion. Oligodendroglial cell invasion causes demyelination, whereas cortical invasion results in altered mental status, and neuronal invasion may result in focal or generalized seizures. Thus, focal pathology is the result of specific neuronal tropism.

Herpes simplex encephalitis (HSE) is the most common cause of sporadic encephalitis in Western countries, accounting for 20% to 40% of cases (83,84). HSE is caused by type 1 virus in greater than 90% of cases, occurs year-round, and affects all age groups. Two-thirds of cases are due to reactivation of the virus in the trigeminal ganglion, with retrograde transport along the olfactory tract to the orbitofrontal and mediobasal lobes. Untreated HSE has a mortality rate up to 70%, and almost all survivors suffer neurologic sequelae (85,86). Outcomes correlate strongly with the severity of disease at presentation, as well as the time to initiation of anti-viral therapy. Other herpes viruses, such as VZV and HHV-6 can rarely cause encephalitis; however they generally affect immune-compromised patients. VZV encephalitis may occur with or without concomitant cutaneous lesions.

Arboviruses are acquired via vector exposure, mainly mosquitoes and ticks. These include EEE, WEE, St. Louis encephalitis, VEE, California encephalitis (caused in most cases by La Crosse virus), Japanese encephalitis, yellow fever, and WNV. Arbovirus-related encephalitides are geographically specific and most prevalent during the summer and early fall months when mosquitoes and ticks are most active.

West Nile virus, first identified in North America in 1999, causes neuroinvasive disease in less than 1% of exposed individuals. It is, however, now the most commonly diagnosed arboviral CNS infection in the United States (87). Neuroinvasive disease most frequently manifests as encephalitis and occurs in those with comorbid disease (88) such as diabetes mellitus, hypertension, renal disease, malignancy, organ transplantation, alcoholism, and advanced age (89–91). Muscle weakness and flaccid paralysis may present concurrently in patients with encephalitis.

Rabies, a zoonotic disease that requires contact with infected animals, should be considered in all cases of encephalitis. Once CNS infection is established, however, the mortality is essentially 100% although survival with aggressive therapy has recently been described (92,93). Rabies can be acquired from many sources including dogs, cats, raccoons, bats, and
foxes. The history of an animal bite, although useful if present, is absent in most cases of rabies.

Nonviral causes of encephalitis include bacterial, rickettsial, fungal, and parasitic infections. Bacterial causes include *Mycoplasma*, *L. monocytogenes*, *B. burgdorferi* (Lyme disease), *Leptospira* spp., *Brucella*, *Legionella*, *Nocardia*, *T. pallidum* (syphilis), *Salmonella typhi*, mycobacterial species, *Coxiella burnetii* (Q-fever), and *Ehrlichiae*. The most common rickettsial species include *Rickettsia rickettsii* (Rocky Mountain spotted fever) and *Rickettsia typhi* (endemic typhus). Fungal causes include *Cryptococcus* spp, *Aspergillus* spp., *Candida*, *Coccidioides immitis*, *H. capsulatum*, and *B. dermatitidis*. Finally, *Trypanosoma brucei* complex (African sleeping sickness), *malaria*, *Toxoplasma gondii*, *Echinococcus granulosus*, and *Schistosoma* species can cause encephalitis but require epidemiologic exposures or specific risk factors. For example, toxoplasma encephalitis is most common in advanced HIV disease.

**DIAGNOSIS**

Clinical findings of encephalitis include the classic triad of fever, headache, and altered mental status. The onset of symptoms may be acute, subacute, or chronic; the acuity and severity of symptoms at presentation correlate with prognosis.

Encephalitic symptoms may be preceded by a viral prodrome consisting of fever, headache, nausea, vomiting, lethargy, and myalgias.

Disorientation, amnesia, behavioral and speech changes, movement disorders, and focal or diffuse neurologic abnormalities such as hemiparesis, cranial nerve palsies, or seizures are common on presentation; neck stiffness and photophobia may also be noted. VZV, EBV, CMV, and mumps may present with rash, lymphadenopathy, and hepatosplenomegaly. HSE incidence is unrelated to a history of oral or genital lesions.

Laboratory findings may include peripheral leukocytosis or leukopenia. While CSF examination usually reveals a pleocytosis with lymphocytic predominance, neutrophilic predominance may be present early in infection. Red blood cells, in the absence of a traumatic tap, are suggestive of HSV but may be seen in other necrotizing viral encephalitides. Protein levels are usually elevated, and glucose may be normal or slightly decreased. Because viral cultures are rarely positive, molecular methods have become the diagnostic tests of choice. CSF HSV DNA NAT is both sensitive and specific (98% and 94%, respectively) when compared to brain biopsy (94,95), is often positive within the first 24 hours of symptom onset, and remains positive during the first week of antiviral therapy. NAT is available for WNV, VZV, enteroviruses, adenoviruses, rabies, CMV, EBV, and HHV-6 in most reference laboratories. Serology may
be diagnostic if IgM is detected or a fourfold rise in acute and convalescent IgG titers is demonstrated. Corneal or neck (posterior, at the hairline) biopsies and saliva NAT can be diagnostic for rabies. Brain biopsy may be considered in patients with encephalitis if all other tests are nondiagnostic.

Other investigations that may aid in diagnosis include EEG, CT, or magnetic resonance imaging (MRI). EEG is particularly helpful in HSE, showing characteristic focal changes (spiked and slow wave patterns) from the temporal regions in greater than 80% of patients. MRI is the most sensitive imaging modality at detecting early viral encephalitis and may show virus-specific changes (e.g., temporal lobe changes in HSE). CT scans are more available on an urgent basis and are useful in ruling out space-occupying lesions; however, they are rarely able to visualize encephalitic changes. Single photon emission computed tomography (SPECT) imaging has also been used in the diagnosis of HSE (96).

TREATMENT

Unfortunately there are few specific therapies for viral encephalitis. Treatment of HSE with acyclovir, 10 mg/kg IV every 8 hours, is the main exception. Treatment should be initiated as soon as possible, as delays in therapy correlate with mortality. Therapy should be started empirically in all patients with encephalitis until confirmatory testing is available, given the dramatic effect on outcome. Acyclovir should also be considered in VZV encephalitis even though data regarding efficacy are only anecdotal. Supportive ICU care, including intubation and mechanical ventilation, may be required. Ganciclovir—or foscarnet for ganciclovir-resistant strains—is used to treat CMV encephalitis. The role of antivirals for EBV and HHV-6 encephalitides is unproven, but ganciclovir or foscarnet should be considered.

Outcomes are related to multiple factors including host age and immune response, organism virulence, and time to effective therapy. Poor outcomes are more common in younger (<1 year of age) and older (>55 years of age) populations. HSE, Japanese encephalitis, and EEE have the highest mortality rates. HSE mortality approaches 70% without therapy but can be reduced to 10% to 30% with early antiviral treatment (86,96–99). Most patients with HSE recover with significant neurologic deficits (paresis, seizures, cognitive and memory deficits).

BRAIN ABSCESS

Brain abscess is an uncommon but potentially life-threatening infection. Characterized by localized intracranial suppurative collections, brain abscesses are usually the result of direct extension of infection (20%–60%) or hematogenous spread. Mortality rates with treatment have decreased dramatically over the past 60 years with advances in imaging, antimicrobials, and neurosurgical therapies (16). Infection begins as a localized area of cerebritis, with subsequent central necrosis, suppuration, and fibrous capsule formation (Table 86.9).

Solitary abscesses are usually the result of contiguous infection including otitis, mastoiditis, frontal or ethmoid sinusitis, or dental infection. Bullet fragments or other foreign bodies may serve as a nidus of infection and develop into abscesses even years after primary injury. Postneurosurgical brain abscesses may also present in a delayed fashion. Multiple abscesses are more commonly the result of hematogenous seeding from chronic pulmonary, endocardial, skin, intraabdominal, or pelvic infections. A primary site or underlying condition cannot be identified in 20% to 40% of patients with brain abscess.

The location of brain abscess may be suggestive of the source. Temporal lobe (Fig. 86.2) or cerebellar abscesses commonly result from otic infections, frontal lobe abscesses (Fig. 86.3) from sinusitis or dental infection, and abscesses in the distribution of the middle cerebral artery from hematogenous seeding.

The microbiology of brain abscesses is diverse and depends on the primary site of infection, patient age, and underlying host factors (100). Common aerobic species include streptococci (viridans, anginosus group, and microaerophilic species), which are isolated in up to a third of cases (16,101,102). Aerobic gram-negative bacilli—commonly Klebsiella pneumoniae, Pseudomonas spp, E. coli, and Proteus spp—and S. aureus

<table>
<thead>
<tr>
<th>Table 86.9 Risk Factors for Brain Abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otic infection (otitis media, mastoiditis)</td>
</tr>
<tr>
<td>Sinusitis (frontal, ethmoid, sphenoid)</td>
</tr>
<tr>
<td>Dental infection</td>
</tr>
<tr>
<td>Neurosurgical intervention or neurotrauma</td>
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<td>Bacterial endocarditis</td>
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<tr>
<td>Neutropenia</td>
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<tr>
<td>Immune compromise (HIV infection, immunosuppressive therapy, solid organ or hematopoietic stem cell transplantation)</td>
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<tr>
<td>Chronic lung infection (abscess, bronchiectasis, empyema)</td>
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<td>Congenital heart disease</td>
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*HIV, human immunodeficiency virus.*
are common pathogens with contiguous infection. Less common pathogens, such as *Rhodococcus*, *Listeria*, *Nocardia*, mycobacteria, and fungi—including *Candida*, *Cryptococcus*, *Aspergillus*, *Mucorales* (mucormycoses), *Pseudallescheria boydii*, and the dimorphic fungi such as *Histoplasma*, *Coccidioides*, and *Blastomyces*—cause disease in immune-compromised hosts. Postsurgical and posttraumatic abscesses are usually due to *S. aureus* and aerobic gram-negative bacilli. HIV-infected patients with advanced disease commonly present with *T. gondii* infection.

Anaerobes are present in approximately half of brain abscesses (103), although anaerobic cultures may not be routinely performed in all laboratories and, even if performed, may be falsely negative. Anaerobic species identified may originate from the oropharynx with contiguous head and neck infections, or from the abdomen or pelvis when infection is due to hematogenous seeding. Commonly isolated anaerobes include *Peptostreptococcus*, *Bacteroides* spp, *Prevotella* spp, *Propionibacterium*, *Fusobacterium*, *Eubacterium*, *Veillonella*, and *Actinomyces*.

Helminths may occasionally cause localized brain infection in immigrant populations. Neurocysticercosis, intracranial infection with the larval cyst of *Taenia solium* (pork tapeworm), is most common and results from the ingestion of *T. solium* ova. *Entamoeba histolytica*, *Schistosoma japonicum* and *mekongi*, *Paragonimus*, and *Toxocara* have also been described as causes of brain abscess.

The clinical manifestations of brain abscess are relatively nonspecific, resulting in delays in presentation and diagnosis (Table 86.10). The onset may be acute or chronic, and most of the presenting features are related to the size and location of the abscess; systemic toxicity is uncommon. Headache is the most common presenting symptom and is usually localized to the side of the abscess (16). Sudden worsening of headache may be due to rupture of the abscess into the ventricular space. Fever is present in only half of patients and thus is not a reliable sign. Focal neurologic findings can occur in half of patients and seizures, which can be the first manifestation of disease, develop in 25% of cases. Neck stiffness is most commonly seen with occipital abscesses. Altered mental status and vomiting are late signs, indicating the development of elevated intracranial pressure.

Specific presenting features may correlate with abscess location. Patients with frontal lobe abscesses often present with changes in personality or mental status, hemiparesis, speech difficulties, and seizures. Temporal lobe abscesses may cause visual field defects or dysphasia if located in the dominant hemisphere. Patients with cerebellar abscesses may present with ataxia, nystagmus, and dysmetria. Brainstem abscesses usually extend longitudinally, with minimal compressive effect, and therefore present with few classic features. Papilledema occurs late with increased intracranial pressure.

Imaging of the brain parenchyma is the diagnostic test of choice. LP is contraindicated in patients with focal findings or papilledema and should be avoided in patients with suspected

**Table 86.10 Common Presenting Features in Brain Abscess**

<table>
<thead>
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<th>Feature</th>
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<tr>
<td>Headache</td>
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<td>Mental status changes</td>
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<td>Fever</td>
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<td>Focal neurologic deficits</td>
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<tr>
<td>Neck stiffness</td>
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<td>Papilledema, nausea, or vomiting with increased intracranial pressure</td>
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**Figure 86.3** Axial and coronal MRI images of a frontal brain abscess. This 59-year-old diabetic male presented with a 10-day history of confusion, headache, right upper extremity weakness, as well as a generalized tonic-clonic seizure. Axial T2 FLAIR (A) and coronal T1 postgadolinium MRI (B) images are shown above demonstrating a 3.4 × 3.4 × 4.3-cm intra-axial frontal lobe abscess with surrounding edema and mass effect. An urgent craniotomy was performed when the patient’s level of consciousness decreased abruptly. Approximately 8 mL of pus were drained; cultures grew *Streptococcus anginosus*. Blood cultures were negative and the primary source of abscess was never identified.
brain abscess. CT scanning or MRI should be performed with the choice of test depending on the stability of the patient and availability of the imaging technique (CT is generally more available on an urgent basis or after hours). MRI with gadolinium enhancement is more sensitive than CT in detecting early cerebritis and can more accurately estimate the extent of central necrosis, ring enhancement, and cerebral edema. MRI is also better able to visualize the brainstem, cerebellum, and spinal cord and can detect small lesions, which CT may miss.

Blood cultures should be drawn in all patients with suspected or confirmed brain abscess. Abscess specimens should be obtained by stereotactic CT-guided aspiration or surgery to confirm the diagnosis and guide antimicrobial therapy. Bacterial, mycobacterial, and fungal cultures should be requested. Serology may be helpful for specific causes, such as *T. gondii* and neurocysticercosis. In toxoplasma brain abscess, IgG should be positive, as most infections are due to reactivation, not primary infection. A positive IgG antibody, however, is not specific for *T. gondii* brain abscess. Brain biopsy may establish the diagnosis but is not routinely recommended given the risks involved and availability of less invasive diagnostic methods. Empiric therapy without aspiration for microbiologic samples is not advised except in specific situations where there is a high likelihood of a specific pathogen. For example, empiric treatment for toxoplasma infection may be warranted in a patient with advanced HIV (CD4 count <100 cells/μL) not receiving prophylaxis, with multiple lesions and positive IgG *T. gondii* serology. If clinical and radiologic responses are not evident within 7 to 14 days, a microbiologic specimen should be obtained.

The therapy for brain abscess (Fig. 86.4) requires combination medical and surgical therapy for cure, as antimicrobial therapy alone is rarely effective, with the notable exception of toxoplasmosis. Empiric therapy should be initiated after imaging confirms the presence of an intraparenchymal lesion, pending aspiration for definitive diagnosis. Empiric therapy should be directed by the most likely source and respective pathogens.

For patients with presumed otic, mastoid, sinus, or dental sources, or temporal or cerebellar abscesses, treatment with a third-generation cephalosporin (cefotaxime, 2 g IV every 4 hours, or ceftriaxone, 2 g IV every 12 hours) and metronidazole (15 mg/kg IV load, followed by 7.5 mg/kg IV every 8 hours) is appropriate.

For patients with suspected hematogenous spread, an antimicrobial with activity against *S. aureus* should be used. Nafcillin 2 g IV every 4 to 6 hours is appropriate in settings with a low prevalence of methicillin resistance. Vancomycin—25 to 30 mg/kg (maximum 2 g) IV load followed by 15 to 20 mg/kg/dose every 8 to 12 hours, with subsequent adjustment based on serum trough vancomycin concentrations (goal trough between 15 and 20 μg/mL)—should be used where methicillin resistance is common or in penicillin-allergic patients. Vancomycin penetrates the CNS poorly and should be used only when indicated. Metronidazole and/or a third-generation cephalosporin may be added, depending on the clinical setting.

For postneurosurgical or posttrauma patients with brain abscess, vancomycin plus meropenem or a cephalosporin with antipseudomonal activity (such as ceftazidime or cefepime), should be used.

Antimicrobial therapy should be adjusted once culture and susceptibility results are available and continued intravenously for 6 to 8 weeks, guided by clinical response and serial imaging. Longer courses of therapy are generally required if the abscess has not been drained. Therapy should be continued until there is complete resolution of symptoms and CT findings. MRI abnormalities may persist for months—serial MRI studies often lead to prolonged and unnecessary antibiotic use and should be avoided (104). Antifungal therapy must be guided by fungal cultures, is generally prolonged, and should be in combination with surgical therapy.

Neurosurgical consultation should be sought at the time of diagnosis. Aspiration through a burr hole with CT or MRI guidance or complete excision following craniotomy are both appropriate treatment options, although aspiration is generally preferred due to reduced neurologic sequelae (105). Surgical excision is indicated in patients with traumatic brain abscesses, fungal abscesses, and large (>2.5 cm) or multiloculated abscesses. If there is no clinical improvement within 1 week of aspiration, mental status declines, or intracranial pressure or abscess size increase despite therapy, surgical excision is indicated. Antibiotic therapy may be shortened to 4 weeks following surgical excision.

Therapy with dexamethasone should be initiated in patients with significant edema and mass effect. Prophylactic antiseizure medications are also frequently administered. Poor prognostic factors in brain abscess include rapid progression, mental status or neurologic impairment on presentation, and rupture into a ventricle (106,107). The most common neurologic sequelae are seizures. With current advances in medical care however, rates of full recovery have substantially improved to 70% (16).

**SUBDURAL AND EPIDURAL INFECTIONS**

Subdural empyema is an intracranial collection of pus between the dura and arachnoid, while epidural abscesses are located between the dura and overlying skull (intracranial epidural
abscess; ICEA) or vertebral column (spinal epidural abscess; SEA). While all are potentially life-threatening infections, with combined medical and surgical therapy, mortality is now well below 10%, and most survivors do so with complete recovery (108–110).

Spread of infection to the subdural and cranial epidural spaces occurs via emissary veins from local or distant sites, by direct extension of cranial osteomyelitis, or due to inoculation during neurosurgical procedures. Common predisposing infections include otic and sinus infections. Other predisposing conditions include traumatic brain injury with skull fracture, infection of a pre-existing hematoma, chronic pulmonary infection, or preceding meningitis.

SEA is nine times more common than ICEA. The epidural space is larger and predominantly posterior in the lumbar area—thus most SEA occurs in this area. SEA originates when the intervertebral disk (diskitis) or vertebral body (osteomyelitis) become infected via hematogenous seeding. Direct compression of the spinal cord or local vascular damage (thrombosis, thrombophlebitis, vasculitis) may ensue. Most abscesses extend approximately three to five vertebral spaces. Risk factors for the development of SEA include bacteremia, infective endocarditis, injection drug use, chronic indwelling catheterization, diabetes mellitus, decubitus ulcers and other chronic skin conditions, back surgery or procedures—such as epidural catheterization, LP, CT-guided needle biopsies—and blunt or penetrating spinal trauma. Secondary hematogenous spread occurs in 25% to 50% of cases.

Subdural empyema and ICEA are invariably polymicrobial, including streptococci, staphylococci, aerobic gram-negative bacilli, and anaerobes. *S. aureus*, Enterobacteriaceae, and *Pseudomonas* are more common following neurosurgical procedures or neurotrauma. In contrast to this, *S. aureus* is the most common pathogen isolated from SEA—approximately two-thirds of cases—with 90% to 95% being monomicrobial (110). *M. tuberculosis* is a common cause of SEA in patients with a previous history of tuberculosis, residence in an endemic region, or other TB risk factors.

Presenting symptoms of subdural empyema or ICEA include fever and headache. Altered mental status progressing to coma, or focal neurologic signs, most commonly hemiparesis or hemiplegia, may be present on admission. Seizures develop in up to 50% of patients. Other focal findings include cranial nerve palsies, homonymous hemianopsia, dysarthria or dysphasia, and ataxia. A fixed, dilated pupil portends imminent cerebral herniation and requires emergent surgical intervention.

SEA presents classically with fever, back pain, and neurologic deficits, however few patients present with all three symptoms (111–112). Back pain is usually the first symptom, with paresthesias, motor weakness, and sensory changes occurring in the affected nerve roots. Bladder and bowel dysfunction, as well as paralysis, are late signs and should prompt urgent surgical consultation.

Routine blood work may demonstrate a peripheral neutrophilia or elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) (113). Blood cultures should be collected in all patients, especially in SEA as over half of these patients have positive cultures (110).

The diagnostic tests of choice for subdural empyema (Fig. 86.5) or ICEA are contrast CT or MRI—demonstrating typical crescentic or lentiform collections. Imaging of the sinuses, middle ear, and/or mastoids should be performed in the appropriate clinical settings to identify potential sources. For SEA, MRI with gadolinium enhancement is preferred (Fig. 86.6), as CT scanning cannot visualize the spinal cord adequately and is less sensitive at identifying contiguous diskitis or osteomyelitis.

LP is contraindicated in the setting of subdural empyema, ICEA, or SEA; however, studies have shown that CSF analysis is routinely Gram stain-negative and cultures are positive in less than 25% of cases. The highest-yield culture comes from the abscess itself. Ultrasound- or CT-guided drainage should be performed as soon as possible. Bacterial, mycobacterial, and fungal cultures should be requested. Additional studies to diagnose active tuberculosis should be performed (e.g., sputum AFB smears and cultures, and TST or IGRA) in patients with suspected spinal TB.
diagnostic delays (110, 116).

logic outcome are neurologic status prior to surgery as well as deterioration occurs. The most important predictors of neuro-

resolution of the abscess. Repeat imaging should occur at

and should be guided by serial imaging to ensure complete

tive antimicrobial therapy is prolonged, usually 6 to 8 weeks,

the abscess is not evident with medical therapy alone. Defini-

neurologic deterioration occurs at any time, or if resolution of

are, of course, required to guide definitive antimicrobial therapy. Intravenous antimicrobial therapy should be administered for 3
to 6 weeks after drainage, depending on clinical response and serial imaging (108). Prolonged therapy (6–8 weeks) may be

warranted if contiguous osteomyelitis or mastoiditis is present.

The management of SEA similarly includes empiric anti-
microbial therapy with or without surgical decompression, drainage, and/or debridement. Because of the predominance of S. aureus infection, empiric therapy is fairly targeted—vancomycin is preferred to ensure coverage of both methi-
cillin-resistant and methicillin-susceptible strains. Medical therapy alone may be successful when blood or abscess aspi-
rate cultures are available to guide therapy and there are no neurologic deficits on presentation (115). Medical therapy is also appropriate in patients with complete paralysis for more

weakness or hemiparesis may be present. When septic throm-

sigmoid sinus and internal jugular vein thrombosis may present with headache and otitis while sigm-

in the cavernous sinus. Classic symptoms of septic cavernous sinus thrombosis include fever, headache, diplopia, and retro-orbital pain. Posisis, proptosis, and chemos-

may be present. Venous engorgement of the retinal veins and papilledema are commonly present. Septic transverse sinus thrombosis presents with headache and otitis while sig-

may occur rapidly. Upper motor neuron lower extremity weakness or hemiparesis may be present. When septic throm-

is a complication of bacterial meningitis, nuchal rigidity may also be present.

Cranial nerve palsies may result from compression due to increased pressure in the cavernous sinus. MRI demonstrates absence of flow within affected veins and venous sinuses and is the diagnostic test of choice. MR venography can be used to confirm the diagnosis, and sinus imaging should be concomitantly performed. Compared to CT scanning, MRI offers the additional benefits of detecting cere-

basal abscess, cerebral infarction, hemorrhage, or edema.

The treatment of suppurative intracranial thrombophlebitis includes antimicrobials, surgical therapy, and anticoagulation. The choice of antimicrobial therapy depends on patient risk factors, most probable source of infection, and culture results, if available. In antecedent sinusitis, empiric therapy with cefotaxime or ceftriaxone and metronidazole is a reasonable
choice. In cavernous sinus thrombosis, an agent active against *S. aureus* should be included. Antimicrobial therapy should be continued for 6 weeks or until radiographic resolution of thrombosis. Anticoagulation appears to be beneficial in cavernous sinus thrombosis, particularly if used early (119,120).

**Key Points**

**Meningitis**
- Untreated acute bacterial meningitis is universally fatal; early recognition, rapid diagnostic testing, and emergent administration of antimicrobials are crucial.
- The absence of fever, nuchal rigidity, and change in mental status effectively excludes the diagnosis of bacterial meningitis.
- *S. pneumoniae* is the most common cause of acute bacterial meningitis in adults. The incidence of *H. influenzae* type b meningitis in the United States has decreased substantially as a result of widespread vaccination.
- LP should be performed urgently in all patients with suspected meningitis. CSF pleocytosis is the hallmark finding. CSF cultures are positive in the majority of patients with bacterial meningitis if obtained prior to antimicrobial therapy.
- Neuroimaging, to rule out mass lesions, should precede LP in patients with abnormal level of consciousness, focal neurologic deficits, papilledema, a history of CNS disease, immune compromise, or seizure within 1 week of presentation.
- Empiric antimicrobial agents should be administered as soon as possible after blood cultures are collected if neuroimaging is to be performed prior to LP or immediately following CSF collection.
- Dexamethasone has been shown to decrease mortality in adults with *S. pneumoniae* and children with *H. influenzae* meningitis, and as such should be administered empirically in all cases of meningitis, before or concomitant with the first dose of antimicrobial.
- Neurologic complications of meningitis include seizure, cerebral edema or infarction, cranial nerve involvement, venous sinus thrombosis, brain abscess, subdural empyema, and coma. Intracranial pressure monitoring and/or other surgical interventions may be required.

**Encephalitis**
- Encephalitis—inflammation of the brain parenchyma—can most easily be distinguished from meningitis by the finding of altered mental status.
- HSE is the most common cause of sporadic encephalitis in Western countries, accounting for 20% to 40% of cases.
- West Nile virus is the most commonly diagnosed arboviral CNS infection in the United States.
- Clinical findings of encephalitis include the classic triad of fever, headache, and altered mental status.
- Diagnostic tests include CSF analysis and neuroimaging, preferably MRI.

- CSF NAT and/or specific serum tests for plausible etiologies should be pursued.
- Temporal lobe involvement on MRI and EEG are characteristic in HSE.

**Brain Abscess**
- Brain abscess is characterized by focal intracranial supplicative collection as a result of direct extension or hematogenous spread of infection.
- A solitary abscess is usually the result of contiguous infection from otitis, mastoiditis, sinusitis, or dental infection.
- Multiple abscesses commonly result from hematogenous spread from chronic pulmonary, endocardial, skin, intra-abdominal, or pelvic infections.
- Streptococci are the most common bacteria isolated, often in mixed culture with anaerobes. *S. aureus*, enteric gram negatives, and less common microorganisms (including fungi) are also recognized pathogens.
- Clinical manifestations are nonspecific and depend on the size and location of the abscess. Headache is the most common presenting feature. Systemic toxicity is uncommon.
- MRI is more sensitive than CT scanning and is the neuroimaging test of choice.
- Blood and abscess culture results should be used to tailor antimicrobial therapy, which is generally prolonged—4 to 8 weeks—and guided by serial imaging.
- Surgical excision may be indicated in patients with traumatic brain abscesses, fungal abscesses, and large (>2.5 cm) or multiloculated abscesses.
- Combined medical-surgical therapy results in high cure rates. Poor prognostic factors include rapid progression, mental status or neurologic impairment on presentation, and rupture into a ventricle.

**Subdural and Epidural Infections**
- Subdural empyema is a collection of pus between the dura and arachnoid.
- Epidural abscesses form between the dura and overlying skull (ICEA) or vertebral column (SEA).
- Presenting symptoms of subdural empyema and ICEA include fever, headache, and a recent history of contiguous otic, mastoid, sinus, or meningeal infection.
- Risk factors for SEA include bacteremia, infective endocarditis, injection drug use, chronic indwelling catheterization, diabetes mellitus, decubitus ulcers and other chronic skin conditions, back surgery or procedures, and trauma.
- *S. aureus* is the most common pathogen in SEA, however tuberculosis should be considered in those at epidemiologic risk.
- Common presenting features of SEA include fever, back pain, and neurologic deficits.
- Contrast CT or MRI is diagnostic in subdural empyema or ICEA.
- MRI is preferred for the diagnosis of SEA.
- Subdural empyema and ICEA require emergent surgical drainage and prolonged antimicrobial therapy, guided, of course, by surgical culture results.
Management of SEA includes prolonged, 6 to 8 weeks, antimicrobial therapy, serial imaging to ensure resolution of the abscess, and early surgical decompression in selected cases.

Repeat imaging should occur at approximately 4-week intervals or at any time if neurologic deterioration occurs.

**Suppurative Intracranial Thrombophlebitis**

**•** Suppurative intracranial thrombophlebitis—septic venous thrombosis of the cortical veins—is a complication of otic, sinus, mastoid, ophthalmoganglionic, facial, or neurologic (bacterial meningitis, epidural abscess, or subdural abscess) infections.

**•** Microbiology depends on the source of infection, but staphylococci, streptococci, aerobic gram-negative bacilli, and anaerobic bacteria are the most common pathogens.

**•** MRI is the diagnostic test of choice as it offers the additional benefits of detecting cerebritis, intracranial abscess, cerebral infarction, hemorrhage, or edema when compared to CT.

**•** MR venography can be used to confirm the diagnosis.

**•** Sinus imaging should be concomitantly performed.

**•** Management includes antimicrobials, surgical therapy, and anticoagulation if not contraindicated.

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**References**


