CHAPTER 108 ■ NEUROLOGIC INFECTIONS

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Infections of the central nervous system (CNS) are often rapidly progressive and can be fatal if left undiagnosed and/or treatment is delayed. Prompt diagnosis and treatment are, therefore, crucial to decreasing morbidity and mortality. Patients with CNS infections commonly require intensive care unit (ICU) support, particularly for airway protection and mechanical ventilation in the presence of an altered mental status. Similarly, patients with undiagnosed CNS infections may be admitted to the ICU, offering intensivists the opportunity to make challenging diagnoses and alter patient outcomes with early and effective therapy.

Identifying the presence or absence of focal neurologic findings is the most important distinction to be made in patients with suspected neurologic infections. This distinction helps to focus the differential diagnosis and identifies patients in whom lumbar puncture 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 bacterial endocarditis and are covered in other chapters. Neurologic infections in advanced HIV/AIDS are also covered separately elsewhere.

The central nervous system is normally protected by various host defenses, the most important of which is the blood–brain barrier. Once micro-organisms gain entry, however, they are able to proliferate rapidly due to the low concentration of immunoglobulins and leukocytes in the CNS. Central nervous system infections can be caused by viral, bacterial, mycobacterial, fungal, or parasitic agents. Patient age, underlying host immune status, and history of preceding infections or neurosurgical procedures.

Empiric antimicrobial agents should be administered as soon as possible after blood cultures are collected if neuroimaging is to be performed prior to lumbar puncture or immediately following cerebrospinal fluid (CSF) collection.

The specific microbiology and choice of empiric therapy in bacterial meningitis depend on patient risk factors, especially age, underlying host immune status, and history of preceding infections or neurosurgical procedures.

Neurologic complications of bacterial meningitis in adults with Streptococcus pneumoniae meningitis and children with Haemophilus influenzae, and should therefore be administered before or concomitant with the first dose of antimicrobial in all cases pending Gram stain and culture results.

Neurologic complications of bacterial meningitis include seizure, cerebral edema, cerebral infarction, cranial nerve involvement, venous sinus thrombosis, brain abscess, subdural empyema, and coma. Intracranial pressure monitoring and/or other surgical interventions may be required.

In suspected meningococcal or Haemophilus influenzae meningitis, droplet isolation should be strictly enforced until 24 hours of effective antimicrobial therapy has been completed or an alternate diagnosis is reached. Isolation in other
cases of meningitis, including pneumococcal meningitis, is not required.

- Aseptic meningitis refers to inflammation of the meninges not attributed to bacterial infection. CSF analysis usually reveals a normal glucose, elevated protein, elevated white blood cell count with lymphocytic predominance, and negative Gram stain and bacterial cultures.

- Viral, mycobacterial, syphilitic, fungal, amoebic, and parameningeal infections should be considered in the differential diagnosis of aseptic meningitis.

Meningitis, or inflammation of the meninges, may be caused by a wide variety of micro-organisms (Table 108.1). 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 such noninfectious conditions is essential, as their therapies differ from those used in the treatment of 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 much more commonly with bacterial meningitis by virtue of the more rapid and fulminant presentation of bacterial as opposed to aseptic meningitis.

### TABLE 108.1

**CAUSES OF ACUTE MENINGITIS**

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
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<tbody>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
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<tr>
<td>Enteroviruses non-polio</td>
<td>Influenza</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV)</td>
<td>Parainfluenza</td>
</tr>
<tr>
<td>Arboviruses (including West Nile virus, St. Louis encephalitis virus)</td>
<td>Lymphocytic choriomeningitis virus (LCMV)</td>
</tr>
<tr>
<td>Herpes simplex virus types 1 and 2 (HSV-2)</td>
<td>Varicella-zoster virus (VZV)</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Treponema pallidum (syphilis)</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Rickettsiae</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Mycoplasma</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Brucella</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>Chlamydia</td>
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<tr>
<td>Staphylococcus aureus</td>
<td>Leptospira</td>
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<tr>
<td>Mycobacterium tuberculosis</td>
<td></td>
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<tr>
<td>Borrelia burgdorferi (Lyme disease)</td>
<td></td>
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<tr>
<td>Streptococcus agalactiae</td>
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<tr>
<td><strong>Fungi</strong></td>
<td></td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>Candida</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>Aspergillos</td>
</tr>
<tr>
<td>Coccioides immitis</td>
<td>Blastomyces dermatitidis</td>
</tr>
<tr>
<td></td>
<td>Sporobolus schenckii</td>
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<tr>
<td><strong>Parasites</strong></td>
<td></td>
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<tr>
<td>Toxoplasma gondii</td>
<td>Naegleria fowleri (free-living amoeba)</td>
</tr>
<tr>
<td>Angiostrongylus cantonensis</td>
<td>Angiostrongylus cantonensis (eosinophilic meningitis)</td>
</tr>
<tr>
<td>Strongyloides stercoralis</td>
<td>Strongyloides stercoralis (hyperinfection syndrome)</td>
</tr>
<tr>
<td><strong>Other infectious syndromes</strong></td>
<td></td>
</tr>
<tr>
<td>Parameningeal focus (brain abscess, subdural empyema, epidural abscess)</td>
<td>Infective endocarditis</td>
</tr>
<tr>
<td><strong>Noninfectious causes</strong></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td>Autimmune diseases (SLE, sarcoid, Behcet)</td>
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<tr>
<td>Intracranial tumor</td>
<td></td>
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<tr>
<td>Stroke</td>
<td>Migraine syndromes</td>
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<tr>
<td>Lupusoma/leukemia</td>
<td></td>
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<tr>
<td>Meningal carcinomatosis</td>
<td></td>
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<tr>
<td>Post procedure (neurosurgery)</td>
<td></td>
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<tr>
<td>Seizure</td>
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SLE, systemic lupus erythematosus.
Some patients may not manifest the classic signs and symptoms of meningitis, and papilledema may be seen on physical examination. Patients often note photophobia, and seizures, focal neurologic deficits, and change in mental status occurs in less than 66% of cases; the classic triad of fever, nuchal rigidity, and otorrhea. The median duration of symptoms prior to admission in bacterial meningitis is impressively short, averaging approximately 24 hours (5). The classic triad of fever, nuchal rigidity, and change in mental status occurs in less than 66% of cases; however, almost all patients have at least one of these findings (6). It bears reiterating that the absence of any of these findings effectively excludes the diagnosis with 99% to 100% sensitivity.

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 (7). In addition to severe headache, patients often note photophobia, and 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, chronic organ failure, neutropenia, chronic corticosteroid use, transplantation, and HIV infection.

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. Skin findings occur in approximately one fourth of bacterial meningitis cases, over 90% of which are due to Neisseria meningitidis infection (8).

As a result of the widespread use of conjugate vaccine for H. influenzae type b in infants, Streptococcus pneumoniae has become the most frequently observed cause of bacterial meningitis, accounting for 47% of total cases (9). S. pneumoniae serotypes causing bacterial disease are also those commonly responsible for meningitis. Focal infection is common with contiguous or distant sites, including sinuses, mastoids, pneumo-


### Table 108.2

<table>
<thead>
<tr>
<th>Predisposing Host Factors to Specific Etiologic Agents of Meningitis</th>
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<tbody>
<tr>
<td>Immunoglobulin deficiency</td>
</tr>
<tr>
<td>Asplenia</td>
</tr>
<tr>
<td>Complement deficiency</td>
</tr>
<tr>
<td>Corticosteroid excess</td>
</tr>
<tr>
<td>HSV infection</td>
</tr>
<tr>
<td>Bacteremia</td>
</tr>
<tr>
<td>Fracture of cribiform plate</td>
</tr>
<tr>
<td>Basal skull fracture</td>
</tr>
<tr>
<td>Neurotrauma, postneurosurgery</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus.
underlying condition such as sinusitis, otitis media, pneumonia, diabetes mellitus, alcoholism, CSF leak, asplenia, or immune deficiency.

**Streptococcus pneumoniae** meningitis carries a mortality rate of 15% to 29% (9,12). 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 transplantation. It is interesting that this infection is seen infrequently in HIV-infected patients for unknown reasons. Pregnant women may be asymptomatic carriers and transmit infection to their infants. *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 cheeses, vegetables, and processed meats (18–20).

**Aerobic Gram-negative bacilli** can cause meningitis in specific groups of patients. Predisposing risk factors include neurosurgical procedures, neonatal status, advanced age, immune suppression, Gram-negative bacteremia, and disseminated *Streptococci stercoralis* infection with hyperinfection syndrome. *Escherichia coli* is a common cause of meningitis in neonates.

**Staphylococcus aureus** or **Staphylococcus epidermidis** can both cause meningitis but are, however, less common than the previously described micro-organisms. Both staphylococcal 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 infectious endocarditis, paraspinal or epidural infection, sinusitis, osteomyelitis, or pneumonia.

Other less common causes of bacterial meningitis include **Enterococci**, viridans group streptococci, beta-hemolytic streptococci, diphtheroids and **Propionibacterium acnes**—generally only in the setting of prosthetic material—and anaerobic species.

### Viral Meningitis

Viruses are the most commonly isolated pathogens in aseptic meningitis. The nonpolio enteroviruses, especially *Coxsackie* viruses A and B, and echoviruses are common, accounting for 85% to 95% of all cases of aseptic meningitis with an identified pathogen (21). 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.

Arboviruses more commonly cause encephalitis but have also been isolated in cases of aseptic meningitis. Arboviruses endemic to North America include the flaviviruses—such as *St. Louis encephalitis virus*, Colorado tick fever, Japanese encephalitis virus, and West Nile virus—and California encephalitis viruses. Arboviruses occur predominantly in the summer and early fall when vector exposure is most likely. *St. Louis encephalitis virus* is mosquito borne and causes epidemic disease in the Mississippi River area. *Japanese encephalitis virus* less commonly causes meningitis, is endemic in Asia, and requires prolonged stays in rural settings for acquisition so is uncommon even in returned travelers.

West Nile virus (WNV) came to widespread attention in 1999 when the first North American cases were identified. Since then, the virus has spread extensively across North America and should be considered in all patients with meningitis, particularly in late summer or early fall. WNV infection is asymptomatic in 80% of cases. The remaining patients present with West Nile neuroinvasive syndrome (approximately 20%; formerly named West Nile fever) or West Nile neurologic syndrome (WNNS; less than 1%). West Nile non-neurologic syndrome is a self-limited febrile illness characterized by fever, headache, malaise, myalgias, and often a rash (50%). WNNS may present as encephalitis, meningitis, or flaccid paralysis. Meningitis, however, is the least common presentation of WNNS.

Lymphocytic choriomeningitis (LCM) virus is a zoonotic disease, transmitted by contact with infected rodents—such as house mice, rats, hamsters—or their feces. Though now rare, LCM virus was one of the first viruses to be associated with aseptic meningitis (4). Infection is more common in the winter months. Presenting manifestations include an influenza-like syndrome and meningoencephalitis, 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, affecting 36% of women and 13% of men with primary genital herpes (22). HSV-2 infection is responsible for most infections; nonetheless, 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 meningoencephalitis are common presenting symptoms. Genital lesions are present in 85% of patients with primary HSV-2 meningitis and generally precede meningeval 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 herpes virus 6 (HHV-6) are all capable of causing aseptic meningitis but occur very rarely, predominantly in immunosuppressed populations.

HIV-associated meningitis can occur with primary infection in approximately 5% to 10% of patients (22). Cranial
neuropathies may be present along with headache, fever, and meningeal irritation. Symptoms are usually self-limited. Meningitis, 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 photophobia in approximately 50% of patients. Meningitis, lethargy, and abdominal pain may also be present.

Other Less Common Infectious Causes

Sporotrichal meningitis may be caused by *Sporotrichum 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 0.1% to 2.4% of untreated infections during the first 2 years (4). *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.

*Mycoabacterium 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 dissemination to extracranial sites 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 is negative in over half of patients with tuberculous meningitis (23,24). A negative skin test, therefore, cannot be used to exclude tuberculous meningitis, as is also the case with other active tuberculous infections. Newer tests, such as the QuantiFERON-TB Gold test, may be available in some centers (25).

Fungal meningitis, although uncommon, should be considered, particularly given the high mortality associated with untreated infection. *Cryptococcus neoformans* predominantly affects immunocompromised hosts but can also infect the immunocompetent. The encapsulated yeast is distributed worldwide and 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 post-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 33% of patients. *Cryptococcus gattii*, a serotype usually restricted to tropical climates, was once a relatively common cause of aseptic meningitis, usually following a dust storm or during building construction. Infection is usually confined to the respiratory system in those with competent immune systems. However, extrapoluminal dissemination to the meninges can occur in patients with immune compromise or during pregnancy. Patients present with headache, vomiting, and altered level of consciousness. Risk factors for the development of disease include travel to or residence in an endemic region and immune deficiency. Coccidiodal meningitis is universally fatal if untreated.

Less common fungal causes of meningitis include *Blastoscyces 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* exists only in yeast form and is part of the normal flora of skin and gastrointestinal tract. CNS involvement is most commonly due to candidemia with subsequent meningeal seeding. Predisposing risk factors for candidemia include the use of broad-spectrum antibiotics, the presence of indwelling devices such as vascular or urinary catheters, parental nutrition, intensive care unit admission, prolonged hospital stay, and immune compromise. Specific risk factors for Candida CNS infection include ventricular shunts, trauma, neurosurgery, or lumbar puncture (26,27). *C. albicans* is the most commonly isolated species; however, nonalbicans species are becoming more prevalent, particularly in immunosuppressed populations (28–30).

Meningitis caused by protozoa or helminths is extremely rare. The free-living amoeba *Acanthamoeba* is a well-known cause of aseptic meningitis. Patients present with headache, vomiting, and altered consciousness. *Naegleria fowleri* is associated with fresh water exposure. They are usually acquired by individuals diving into contaminated lakes or swimming pools. CNS invasion occurs via penetration of the nasal mucosa and ciliated epidermal plate. *N. fowleri* can cause a primary amoebic meningoencephalitis. *Acanthamoeba* and *Balamuthia* rarely cause meningitis; they commonly present as encephalitis.

*Angiostrongylus cantonensis*, the rat lungworm, is the classic infectious cause of eosinophilic meningitis (>10% eosinophils in the CSF) (Table 108.4). 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. *Naegleria fowleri*, 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 the nerve tracts to the CNS. Gnaiaestomiasis 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.

**Diagnosis**

Lumbar puncture (LP) should be performed emergently in all patients suspected of having bacterial meningitis unless...
TABLE 108.4
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>PCR for Enteroviruses, HSV, WNV, VZV, influenza</td>
</tr>
<tr>
<td>Gram stain</td>
<td>AFB stain and Mycobacterial culture</td>
</tr>
<tr>
<td>Bacterial culture and sensitivity</td>
<td>Cryptococcal antigen test (can send serum as well, sensitivity comparable to CSF)</td>
</tr>
<tr>
<td></td>
<td>VDRL, FTA-Abs, T. pallidum PCR</td>
</tr>
<tr>
<td></td>
<td>Cytology</td>
</tr>
<tr>
<td></td>
<td>Cytospin and flow cytometry if available</td>
</tr>
<tr>
<td></td>
<td>Lyme-specific Ab and PCR</td>
</tr>
</tbody>
</table>

CNS, central nervous system; PCR, polymerase chain reaction; 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-Abs, fluorescent treponemal antibody absorption; PAM, primary amoebic meningoencephalitis.

*Experimental, available only in research laboratories.

Contrary to the common belief, lumbar puncture is not contraindicated, although it is commonly unnecessarily delayed while neuroimaging is performed to exclude mass lesions. Complications associated with lumbar puncture are uncommon; however, the incidence of life-threatening brain herniation has been reported to range from less than 1% to 6% (31,32). A recent study evaluating the clinical features at baseline associated with abnormal findings on CT scan, and thus, increased risk of brain herniation, identified: age greater than or equal to 60 years; a history of CNS disease such as a mass lesion, stroke, and focal infection; immune compromise such as HIV or immunosuppressive therapy; a history of seizure less than or equal to 1 week before presentation; and specific abnormal neurologic findings (33). Based on these findings, guidelines for which adult patients should undergo CT prior to LP have been recommended (Table 108.5) (34).

TABLE 108.5
INDICATIONS FOR IMAGING PRIOR TO LUMBAR PUNCTURE IN ADULTS WITH SUSPECTED BACTERIAL MENINGITIS

- Immunocompromised state (HIV/AIDS, immunosuppressive therapy)
- History of CNS disease (mass lesion, stroke, or focal infection)
- New-onset seizure (less than or equal to 1 week of presentation)
- Papilledema
- Abnormal level of consciousness
- Focal neurologic deficit (dilated nonreactive pupil, abnormalities of oculomotor, abnormal visual fields, arm or leg drift)

Nosocomial meningitis is rare in nonneurosurgical patients; nevertheless, lumbar punctures are often performed in hospitalized patients with unexplained fever and/or decreased level of consciousness. The yield of performing an LP in the nonneurosurgical population is extremely low and of questionable utility (35).

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 (Table 108.3).

**Bacterial Meningitis**
Bacterial meningitis usually presents with an elevated systemic white blood cell (WBC) count and left shift (immature forms such as bands and myelocytes). Leukopenia is occasionally present in severe infection. Thrombocytopena may be the result of sepsis, disseminated intravascular coagulation, or meningococcemia alone. Renal and hepatic dysfunction may occur as part of multiorgan failure in severe disease. Blood cultures are often positive and should always be drawn prior to the administration of antimicrobials, particularly if the LP cannot be performed immediately. Approximately 66% of patients with bacterial meningitis have positive blood cultures (8).

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 (less than 0.5) is common in bacterial meningitis—and it 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. In the postoperative neurosurgical patient, elevated CSF
lactate concentrations (greater than or equal to 4.0 mMol/L) have been shown to be superior to CSF-to-blood glucose ratios (36), and initiation of empiric antimicrobial therapy in this setting should be considered pending the results of additional studies (34). CSF protein and opening pressure are usually elevated in bacterial meningitis (Table 108.6).

Gram staining permits rapid identification of bacterial species and is positive in approximately 50% to 60% of patients with bacterial meningitis. The presence of bacteria is virtually 100% specific, but sensitivity is variable. The 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 coccobacilli suggest *H. influenzae* infection.

CSF bacterial cultures are positive in approximately 70% to 95% of cases. 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 polymerase chain reaction (PCR) may be useful for excluding the diagnosis of bacterial meningitis (34) but is unavailable in many centers.

**Viral Meningitis**

In acute viral meningitis, the CSF cell count is usually in the low hundreds with 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 usually mildly elevated, and the opening pressure is usually normal.

Viral cultures and nucleic acid amplification tests are most commonly used in the diagnosis of viral meningitis. Enteroviruses may be cultured from CSF, throat, or rectal swabs, with a sensitivity of 63% to 70%, or identified by nucleic acid amplification testing. Enteroviral PCR is both sensitive and specific. PCR for HSV is also widely available, and in studies of HSV-1 encephalitis, HSV PCR demonstrated a specificity of approximately 100% and sensitivity of 75% to 98% (37,38). False negatives occur mostly within the first 72 hours of infection. The diagnosis of WNV can be made by detection of serum IgM or a fourfold rise in IgG between acute and convalescent titers. WNV PCR of serum and CSF are also available; however, the sensitivity is higher in CSF specimens due to the 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 macous patch—is present. Serologic testing should include nontreponemal (RPR, rapid plasma reagin; VDRL, Venereal Diseases Research Laboratory) and treponemal (TPPA, Treponema pallidum particle agglutination; FTA-Abs, fluorescent treponemal antibody absorption) tests for the diagnosis of active syphilis infection. *Treponema*-specific enzyme immunoassays (EIA) for IgM and IgG are replacing the above traditional serologic tests as the initial laboratory diagnostic test in some centers. CSF VDRL may be used in the diagnosis of syphilitic meningitis. The specificity is high, but false positives occur in bloody specimens. The major limitation of CSF VDRL is its low sensitivity (30% to 70%), so a negative result should not be used to rule out infection in the setting of high clinical suspicion. CSFFTA-Abs are more sensitive; however, false positives are common due to serum antibody leak into the CSF. Last, PCR has been recently used to detect *T. pallidum* DNA in the CSF. Further studies are needed to ascertain the sensitivity and specificity of this test.

Lyme meningitis is characterized by a mild lymphocytic pleocytosis, low glucose, and an elevated protein. The CSF concentration of *B. burgdorferi* antibody, compared to serum levels, is a sensitive and specific diagnostic method. PCR is currently available only in research laboratories, although it will likely become the diagnostic test of choice in the near future. CSF oligoclonal bands and *B. burgdorferi* culture are also available, but neither is sensitive or specific.

The CSF analysis in tuberculous 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 bacilli (AFB) smears are very low yield; only 10% to 22% of cases will be positive (24,39,40). Mycobacterial cultures, although slow growing—taking several weeks—become positive in up to 88% of cases (4). DNA probes and nucleic acid amplification

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**TABLE 108.6**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>WBC Count (cells/mm³)</th>
<th>Predominant cell type</th>
<th>Protein (mg/dL)</th>
<th>Glucose (mg/dL)</th>
<th>Opening Pressure (cm H₂O)</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0–5</td>
<td>Lymphocyte</td>
<td>15–40</td>
<td>50–75</td>
<td>8–20</td>
</tr>
<tr>
<td>Viral</td>
<td>10–500</td>
<td>Lymphocyte</td>
<td>Normal</td>
<td>Normal</td>
<td>9–20</td>
</tr>
<tr>
<td>Bacterial</td>
<td>300–5,000</td>
<td>Neutrophil</td>
<td>&gt;100</td>
<td>&lt;40</td>
<td>20–30</td>
</tr>
<tr>
<td>Tuberculous</td>
<td>50–300</td>
<td>Lymphocyte</td>
<td>&gt;100</td>
<td>&lt;40</td>
<td>18–30</td>
</tr>
<tr>
<td>Cryptococcal</td>
<td>20–500</td>
<td>Lymphocyte</td>
<td>30–200</td>
<td>&lt;40</td>
<td>18–30</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid.

*Neutrophils may predominate in the first 24 hours.*
techniques (mainly PCR) have recently become available with great improvements in sensitivity and specificity. Meningeal biopsy is rarely performed but may show caseating granuloma. Skin testing and QuantiFERON-TB Gold testing have been discussed in the previous section. Sputum and urine AFB, as well as mycobacterial blood cultures, should also be included as part of the TB workup in these patients.

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 (greater than 90%). India ink was previously regarded as the standard diagnostic test, but due to its low sensitivity (50%), it has been largely replaced by antigen testing. Fungal blood cultures may also be useful, as cryptococcal meningitis occasionally occurs in the setting of disseminated cryptococcal infection with cryptococcemia, especially in HIV-infected patients.

Other fungal meningitides are similarly characterized by a lymphocytic pleocytosis, low to normal glucose, and an elevated protein. Coccioidal 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 has been discussed in the previous section. Sputum and urine AFB, as well as mycobacterial blood cultures, should also be included as part of the TB workup in these patients.

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 lumbar puncture 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 108.7), as delays in therapy have been associated with adverse clinical outcomes and increased mortality (41,42). The administration of antimicrobials should immediately follow blood culture collection and should not be delayed by neuroimaging or other tests performed prior to LP.

### Bacterial Meningitis

As noted above, lumbar puncture should be performed urgently in those with suspected meningitis. A protocol for the management of bacterial meningitis is presented in Figure 108.1. Imaging should be performed prior to LP in specific populations (Table 108.3) but should not result in a delay in the initiation of antimicrobial therapy. Empiric therapy should be based on

### Table 108.7

**EMPIRIC THERAPY OF BACTERIAL MENINGITIS BASED ON AGE AND HOST FACTORS**

<table>
<thead>
<tr>
<th>Most common causes</th>
<th>Recommended therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: Preterm to less than 1 month</td>
<td>S. agalactiae, E. coli, L. monocytogenes</td>
</tr>
<tr>
<td>Age: 1 month to 50 years</td>
<td>S. pneumoniae, N. meningitidis, H. influenzae</td>
</tr>
<tr>
<td>Age: greater than 50 years or alcoholism or impaired cellular immunity</td>
<td>S. pneumoniae, L. monocytogenes, C. neoformans</td>
</tr>
<tr>
<td>Post neurosurgery, neurotrauma, or cochlear implant</td>
<td>S. pneumoniae, N. meningitidis, C. neoformans</td>
</tr>
<tr>
<td>Ventriculostomy/meningitis due to infected shunt</td>
<td>S. epidermidis, S. aureus, P. aeruginosa</td>
</tr>
</tbody>
</table>

<sup>a</sup>Vancomycin should be added in centers where S. pneumoniae may be resistant to third-generation cephalosporins

<sup>b</sup>Dexamethasone is efficacious in children with H. influenzae and in adults with S. pneumoniae. The first dose is to be given 15 to 20 minutes prior to or concomitant with first dose of antibiotic. Dose, 0.15 mg/kg IV every 6 hours for 2 to 4 days, discontinue if micro-organisms isolated other than listed above.
Chapter 108: Neurologic Infections

History and physical examination consistent with acute bacterial meningitis

1. Draw blood cultures STAT
2. Contraindicated if intracranial lesion identified
3. Lens identified, treat accordingly, lumbar puncture contraindicated

CT scan if indicated

Perform lumbar puncture: Send for STAT cell count, glucose, protein, Gram stain, culture, and sensitivity. Additional tests as indicated, see Table 108.4

If CSF cloudy, high clinical suspicion, or cell count demonstrates neutrophilic pleocytosis, treat with empiric antimicrobial therapy:
1. Dexamethasone 10 mg IV every 6 h
2. Cefotaxime 2 g IV every 6 h or ceftiraxone 2 g IV every 12 h
3. Vancomycin 1 g IV every 12 h
4. Ampicillin 2 g IV every 4 h if age older than 50 y, chronic alcoholic, immune suppression, or malignancy

Adjust therapy based on Gram stain and culture results, see Table 108.8.

− Gram-positive diplococci are seen on Gram stain or S. pneumoniae is isolated in culture in adults
− H. influenzae is isolated in a child

FIGURE 108.1. Bacterial Meningitis Protocol

Streptococcus pneumoniae. Empiric therapy guidelines for pneumococcal meningitis have been recently modified due to the increasing incidence of penicillin resistance. S. pneumoniae organisms were 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 until susceptibility results become available. Once the minimum inhibitory concentrations (MIC) are available, therapy should be adjusted accordingly. For isolates with penicillin MIC less than 0.1 μg/mL, penicillin G (4 million units IV every 4 hours) or ampicillin (2 g IV every 4 hours) should be used. For isolates with a MIC greater than or equal to 0.1 μg/mL, treatment with a third-generation cephalosporin should be continued; either cefotaxime (2 g IV every 6 hours) or ceftiraxone (2 g IV every 12 hours). For isolates with a ceftiraxone 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 1 g IV every 12 hours, or 500 to 750 mg IV every 6 hours, to a maximum of 2 to 3 g/day, and adjusted based on therapeutic drug monitoring to maintain a trough serum concentration of between 15 and 20 μg/mL. Meropenem is a reasonable alternative to the above agents and does not carry the theoretical risk of decreasing age, underlying host factors, and initial CSF Gram stain results (Table 108.7).

The choice of antimicrobial therapy in bacterial meningitis is influenced by blood-CSF barrier penetration, effect of meningeal inflammation on penetration, and the bactericidal efficacy. In general, CSF penetration is enhanced in the setting of meningeal 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 the low pH. Penicillins, third-generation cephalosporins, carbapenems, fluoroquinolones, and rifampin achieve high CSF levels and are all bactericidal. Antimicrobials should be adjusted based on renal and hepatic function. Therapeutic drug monitoring may be required to ensure adequate levels and prevent toxicity (e.g., vancomycin, aminoglycosides). Antimicrobial therapy should be adjusted based on culture and susceptibility results as soon as possible (Table 108.8). In suspected meningococcal or H. influenzae meningitis, droplet isolation (single room, gowns, gloves, surgical masks, and dedicated patient care equipment) should be strictly 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 (Table 108.9).
indicated in confirmed meningococcal meningitis. Another alternative, although there is a high degree of cross-
resistance, is ampicillin (2 g IV every 6 hours), to a maximum of 2 to 3 g/day, with therapeutic drug monitoring to ensure adequate serum levels—those with \( \geq 1 \mu g/mL \) are achieved. Vancomycin is recommended in patients with penicillin allergy. Infected prosthetic material should be removed if possible and antimicrobial therapy continued for 10 to 14 days after removal. If removal is not possible, rifampin may be added; however, cure rates are poor with hardware retention.

### TABLE 108.8

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Recommended therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>Ampicillin or penicillin G</td>
</tr>
<tr>
<td><em>Penicillium G or ampicillin</em></td>
<td>Cefotaxime or ceftriaxone</td>
</tr>
<tr>
<td><em>Penicillium MIC &gt;0.1 μg/mL</em></td>
<td>Cefotaxime or ceftriaxone</td>
</tr>
<tr>
<td><em>Penicillium MIC ≤0.1 μg/mL</em></td>
<td>Cefotaxime or ceftriaxone</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>Cefotaxime or ceftriaxone plus ampicillin or ceftriaxone</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Meropenem or ertapenem</td>
</tr>
<tr>
<td><em>Listeria monozygotes</em></td>
<td>Ampicillin or penicillin G</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Nafcillin or oxacillin</td>
</tr>
<tr>
<td><em>Prosthesis associated</em></td>
<td>Vancomycin</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>Vancomycin</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 *Klebsiella pneumoniae, Proteus, indole-positive Proteus (P. vulgaris), Citrobacter freundii group, Enterobacter spp., and Morganella morganii.* These micro-organisms carry chromosomal, inducible \( \beta \)-lactamases (ampC), which are capable of inactivating third-generation cefalosporin even if reported to be susceptible. Carbapenems (meropenem has greatest cerebrospinal fluid penetration), fluoroquinolones, or trimethoprim/sulfamethoxazole may be used to treat these micro-organisms, if susceptible. Carbapenems (meropenem has greatest cerebrospinal fluid penetration), fluoroquinolones, or trimethoprim/sulfamethoxazole may be used to treat these micro-organisms, if susceptible.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>3%–13%</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>19%–30%</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>3%–6%</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>15%–29%</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>7%–27%</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>14%–77%</td>
</tr>
</tbody>
</table>

### TABLE 108.9

Mortality rates in bacterial meningitis by pathogen.

**Aerobic Gram-negative bacilli.** Aerobic Gram-negative bacilli should be treated empirically with a third-generation cefalosporin or meropenem. Susceptibility results should be obtained as soon as possible to 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. Cefotaxime and ceftiraxone should not be used as they do not have antipseudomonal activity. Ciprofloxacin or aztreonam are acceptable alternatives if the isolate is susceptible. The duration of therapy is prolonged, generally 21 days.

**Staphylococcus.** Staphylococcal meningitis therapy depends on methicillin susceptibility. Methicillin-resistant strains should be treated empirically with a third-generation cefalosporin—such as linezolid and daptomycin, have not been established. Dexamethasone should be administered prior to or with the first dose of antimicrobial (see Adjunctive Therapy). Treatment duration is 10–14 days.

**Neisseria meningitidis.** The initial treatment of meningococcal meningitis is with a third-generation cefalosporin—for example, cefotaxime (2 g IV every 6 hours) or ceftiraxone (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 beta-lactam-resistant patient. Meropenem (2 g IV every 8 hours) is another alternative, although there is a high degree of cross-reaction in penicillin-allergic patients. Dexamethasone is not indicated in confirmed meningococcal meningitis.
become alternate therapies, but data on efficacy are currently lacking. 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, recent randomized controlled trials suggest benefit with its use. In children, the administration of dexamethasone has demonstrated a reduction in the incidence of hearing impairment and severe neurologic complications in H. influenzae meningitis (43). Adjunctive corticosteroid therapy has also been evaluated in adults, showing a mortality benefit in patients with pneumococcal meningitis (5). 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 therefore be administered to all patients with suspected meningitis until Gram stain or culture results are available. Dexamethasone 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. The potential disadvantage of decreased CSF penetration by non-beta-lactam antimicrobials with concomitant dexamethasone administration has yet to be thoroughly studied. Treatment with adjunctive dexamethasone has not been associated with an increased risk for long-term cognitive impairment (44).

Placement of an intracranial pressure monitoring device may be beneficial for patients with bacterial meningitis and elevated intracranial pressure. Admission to an ICU with expertise in this type of monitoring is most appropriate. Surgical intervention may be required in some patients, for example, those with basal skull fractures with persistent CSF leaks or dural defects. Complications of bacterial meningitis can be divided into neurologic and nonneurologic complications. Neurologic complications include seizures, cerebral edema, cerebral 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 enteroviral meningitis with modest benefit but remains experimental (45,46). Intravenous immunoglobulin 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 at 5 mg/kg every 8 hours, has been used in severe disease. Ganciclovir is the treatment of choice for CMV meningitis in immunocompromised hosts.

**Other Less Common Causes**

Syphilitic meningitis does not respond to benzathine penicillin, which is used to treat most forms of syphilis, and requires a 2-week course of high-dose IV penicillin G (4 million units every 4 hours). RPR titers should be monitored after therapy, and repeat CSF examination should be performed if titers do not decline fourfold in 6 months after therapy. All HIV patients with syphilitic meningitis should have a lumbar puncture repeated 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 ceftaxone, 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 resistance pattern in the community and results of susceptibility testing; consultation with an infectious diseases specialist is recommended. In general, standard combination therapy includes isoniazid (INH), rifampin (RIF), ethambutol (ETB), and pyrazinamide (PZA). ETB may be discontinued once INH and RIF susceptibilities are confirmed. Treatment should be continued for a minimum of 12 months and up to 24 months. Adjunctive therapy with dexamethasone for the first month has been shown to decrease complications and is recommended. Pyridoxine, 25 to 30 mg daily, should also 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 amphotericin B, 0.7 to 1 mg/kg/day IV, with or without flucytosine, 100 mg/kg/day PO dosed every 6 hours. Consolidation therapy with fluconazole, 400 mg daily, should be continued for 8 weeks following induction. Maintenance (or suppressive) therapy with fluconazole, 200 mg per day, should be continued in patients with HIV/AIDS until immune reconstitution is achieved. Cryptococcal meningitis may require daily therapeutic lumbar punctures, an external ventricular drain, or a ventriculoperitoneal shunt to relieve increased intracranial pressure. Therapy is identical in non-HIV/AIDS patients, with the exception that consolidation therapy is continued for 10 weeks; further prolongation may be required in transplant patients. Echinocandins, such as caspofungin and micafungin, are not active in cryptococonosis.

The treatment for coccidioideal meningitis is oral fluconazole, 400 mg daily. Some clinicians initiate therapy with a higher dose of 800 mg per day or may add intrathecal amphotericin B. Treatment must be continued lifelong, as relapses are frequently lethal. Therapy for H. capsulatum meningitis consists of amphotericin B, 0.7 to 1 mg/kg/day to complete a total dose of 35 mg/kg. Fluconazole, 800 mg per 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. Itraconazole should be avoided due to poor CSF penetration. Although very rare, S. schenckii meningitis is treated with amphotericin B. Itraconazole, despite its poor CSF penetration, may be tried after initial therapy for lifelong suppression.
For candidal meningitis, the preferred initial therapy is amphotericin B, 0.7 mg/kg/d, with fluconazole, 25 mg/kg dosed every 6 hr and adjusted to maintain serum levels of 80 to 60 μg/mL. Fluconazole therapy, in susceptible species, may be used for follow-up or suppressive therapy. The duration of therapy should continue for 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 been successfully treated with early diagnosis and treatment with high-dose intravenous and intrathecal amphotericin B or miconazole and rifampin. Eosinophilic meningitis caused by *A. cantonensis* and *G. spinigerum* are treated supportively. Corticosteroids are recommended to decrease the inflammatory response to intracranial larvae. Anthelmintic therapy is relatively contraindicated, as clinical deterioration and death may occur following severe inflammatory reactions to dying larvae.

**Prevention**

Chemoprophylaxis (medications) and immunoprophylaxis (vaccines) are available to prevent infection in contacts of cases or in times of epidemic spread. Temporary nasopharyngeal carriage of *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 some individuals at risk.

Prophylaxis is indicated in household contacts—those residing with the index case or with greater than 4 hours of close contact—and day care contacts—same day care as index case for 5 to 7 days before onset of disease—of cases of *H. influenzae,* if there is an unvaccinated contact less than or equal to 4 years of age in the household, chemoprophylaxis is recommended for all household contacts except pregnant women. Rifampin, 20 mg/kg, with a usual adult dose of 600 mg daily, for four doses, is the recommended therapy.

Prophylaxis for *N. meningitidis* is recommended for close contacts of cases. This includes intimate contacts (e.g., kissing) and close contacts with greater than or equal to 4 hours contact 1 week prior to the onset of illness. Most close contacts include house mates, day 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 ceftaxime (250 mg intramuscularly) are all efficacious.

Corticosteroid therapy is recommended in some instances. If there is no response within 24 hours, antiviral therapy should be considered. Antiviral therapy is recommended for all children less than or equal to 23 months of age and in those at high risk of invasive disease—sickle cell disease and other hemoglobinopathies, functional or anatomic asplenia, HIV infection, immunocompromising conditions, and chronic medical conditions—who are greater than 23 months of age. The polysaccharide vaccine is recommended for all individuals greater than 65 years old and in those greater than 5 years old with the above high-risk conditions, but is of limited immunogenicity and efficacy. Studies of conjugate pneumococcal vaccine in adults are ongoing. *S. pneumoniae* vaccination is not an indicated as postexposure prophylaxis.

*N. meningitidis* vaccine is also available in two forms: conjugate and polysaccharide vaccines. Available conjugate vaccines include a quadrivalent (MCV4) vaccine, as well as the monovalent serogroup C (Men-C) vaccine. Available polysaccharide vaccines include a quadrivalent vaccine containing A, C, Y, and W-135 and a bivalent vaccine with serogroups A and C. *N. meningitidis* vaccination is indicated in high-risk populations, including those with specific immune deficiencies (Table 108.2), 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.

**ENCEPHALITIS**

**Key Points**

- In distinguishing encephalitis from meningitis, the most useful finding is altered mental status.
- Encephalitis is most commonly viral or postinfectious in etiology.
- Herpes simplex encephalitis is the most common cause of sporadic encephalitis in Western countries, accounting for 10% to 20% of cases. Temporal lobe involvement on MRI and electroencephalogram (EEG) are characteristic. PCR is 75% to 98% sensitive, with false negatives occurring predominantly during the first 72 hours of illness. Mortality approaches 70% without therapy but can be significantly reduced with early antiviral therapy.
- 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 108.10). 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
### TABLE 108.10

<table>
<thead>
<tr>
<th>Viral cause</th>
<th>Vector or animal host</th>
<th>Geographic distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha viruses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern equine (EEE)</td>
<td>Mosquitoes</td>
<td>New England</td>
</tr>
<tr>
<td>Western equine (WEE)</td>
<td>Culicidae melanura</td>
<td>West of Mississippi River</td>
</tr>
<tr>
<td>Venezuelan equine (VEE)</td>
<td>Culex spp.</td>
<td>South and Central America</td>
</tr>
<tr>
<td><strong>Flaviviruses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. Louis</td>
<td>Mosquitoes or ticks</td>
<td>Throughout the United States</td>
</tr>
<tr>
<td>West Nile (WNV)</td>
<td>Culex spp.</td>
<td>Americas, Africa, Asia, Middle East, Europe</td>
</tr>
<tr>
<td>Japanese</td>
<td>Culex pipiens and tarsalis</td>
<td>Asia and SE Asia</td>
</tr>
<tr>
<td>Murray Valley</td>
<td>Culex and Aedes spp.</td>
<td>Western Australia</td>
</tr>
<tr>
<td>Tick-borne</td>
<td>ixodes ricinus and persalcati ticks</td>
<td>Russia, Central Europe, China, North</td>
</tr>
<tr>
<td>Louping ill virus</td>
<td></td>
<td>America, British Isles</td>
</tr>
<tr>
<td><strong>Herpes viruses</strong></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td>Herpes simplex virus (HSV-1)</td>
<td>N/A</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Varicella-zoster virus (VZV)</td>
<td>N/A</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>N/A</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>N/A</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Human herpesviruses 6, 7</td>
<td>N/A</td>
<td>Worldwide</td>
</tr>
<tr>
<td><strong>Enteroviruses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polioviruses</td>
<td>N/A</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Coxsackieviruses</td>
<td>N/A</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Echoviruses</td>
<td>N/A</td>
<td>Worldwide</td>
</tr>
<tr>
<td><strong>Adenoviruses</strong></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HFV)</td>
<td>N/A</td>
<td>Worldwide, particularly high prevalence in sub-Saharan Africa, Central and Southeast Asia, Eastern Europe</td>
</tr>
<tr>
<td><strong>Rubies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorado tick fever</td>
<td>Dogs, cats, raccoons, wolves, foxes, bats</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Mumps</td>
<td>N/A</td>
<td>Western United States and Canada</td>
</tr>
<tr>
<td>Measles</td>
<td>N/A</td>
<td>Unvaccinated populations worldwide</td>
</tr>
</tbody>
</table>

N/A: not applicable.

include mumps, measles, varicella-zoster virus, rubella, and influenza.

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 neural tropism.

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

EEE has a high mortality rate and occurs in the New England area, whereas WEE is a much milder illness, occurring west of the Mississippi River. VEE occurs from Florida to South America, whereas St. Louis encephalitis virus is found throughout much of the United States. The California encephalitis viruses mainly affect children in the Midwest and Eastern states. West Nile virus, identified in North America in 1999, causes West Nile neurologic syndrome (WNNs) in less than 1% of exposed individuals. WNNs most commonly manifests as encephalitis and occurs in those with diabetes melitus, alcoholism, and of older age (49). Muscle weakness and flaccid paralysis may present concurrently in patients with encephalitis. Japanese virus encephalitis, occurring principally in Southeast Asia, China, India, and Japan, is the most common viral encephalitis outside of the United States.

Colorado tick fever is prevalent in the western United States, and most affected individuals have a history of camping and
Because viral cultures are rarely positive, molecular methods are elevated, and glucose may be normal or slightly decreased. Other necrotizing viral encephalitides. Protein levels are usually noted. A traumatic tap, are suggestive of HSV but may be seen in other cases of rabies.

Herpes viruses cause disease by primary infection or reactivation. Herpes simplex encephalitis (HSE) is the most common cause of sporadic encephalitis in Western countries, accounting for 10% to 20% of cases (50). 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 medialtemporal lobes. Untreated HSE has a mortality rate of 50% to 75%, and all survivors suffer neurologic sequelae. Outcomes correlate strongly with the severity of disease at presentation, as well as the time to initiation of antiviral therapy. Varicella-zoster encephalitis generally affects immune-compromised patients and may occur with or without concomitant cutaneous lesions.

Nonviral causes of encephalitis include bacterial, rickettsial, fungal, and parasitic infections. Bacterial causes include Mycoplasma, Listeria monocytogenes, Borrelia burgdorferi (Lyme disease), Leptospira spp., Brucella, Legionella, Nocardia, Treponema pallidum (syphilis), Salmonella typhi, and mycobacterial species, Coxiella burnetii (Q-fever), and Ehrlichiae. The most common rickettsial species include R. rickettsii (Rocky Mountain spotted fever) and R. typhi (endemic typhus). Fungal causes include Cryptococcus spp., Aspergillus spp., Candida, Coccidioides immitis, Histoplasma capsulatum, and Blastomyces dermatitidis. Last, Treponema 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.

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. Encephalitis 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 presenting; neck stiffness and photophobia may also be noted. VZV, EBV, CMV, measles, and mumps may present with rash, lymphadenopathy, and hepatitisphenomenal. HSE incidence is unrelated to a history of oral or genital lesions. Laboratory findings may include peripheral leukocytosis or leukopenia. 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. Demonstration of HSV DNA in the CSF by PCR is both sensitive and specific (>75%–98% and 100%, respectively) but may miss cases in the first 72 hours of illness. PCR testing is available for WNV, VZV, enteroviruses, adenoviruses, rabies, CMV, EBV, HHV-6, and HHV-7 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 PCR 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 MRL EEG is particularly helpful in HSE, showing characteristic focal changes (spiked and slow wave patterns) from the temporal regions in 80% of patients. MRI is the most sensitive imaging modality at detecting early viral encephalitis and may show virus-specific changes. 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.

It is most unfortunate that there are few specific tests 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 in this form of VZV disease are only anecdotal. Supportive therapy, including ICU admission with intubation and mechanical ventilation, may be indicated. Ganciclovir or foscarin should be considered in ganciclovir-resistant strains is used to treat CMV encephalitis. The role of antivirals for EBV and HHV-6 encephalitides is unproven, but the International Herpes Management Forum has recommended the use of ganciclovir or foscarin for HHV-6 encephalitis.

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 (less than 1 year of age) and older (greater than 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 28% with early antiviral treatment. Most patients with HSE (62%) recover with significant neurologic deficits (paralysis, seizures, cognitive and memory deficits).

### BRAIN ABSCESS

#### Key Points
- Brain abscess results from focal infection, trauma, or surgery.
- A solitary abscess is usually the result of contiguous infection from otitis, mastoiditis, sinusitis, or dental infection.

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*Data on CMV encephalitis come from several papers related to HIV patients, including International Herpes Management Forum (IHMF) recommendations (Herpes. 2004;11(Suppl 2):95A–104A). Data on HHV-6 are more limited, but antivirals are still suggested by the IHMF (Herpes. 2004;11(Suppl 2):105A–111A).*
Surgical excision may be indicated in patients with traumatic
Blood and abscess culture results should be used to tailor
MRI is more sensitive than CT scanning and is the neu-
Clinical manifestations are nonspecific and depend on the
The microbiology of brain abscess depends on the primary
Multiple abscesses commonly result from hematogenous
20% to 40% of patients with brain abscess.
Weber-Rendu syndrome) and children with congenital cyanotic
hematomas, skin, intra-abdominal, or pelvic infections. For exam-
suppurative collections, brain abscesses are usually the re-
risk factors for brain abscess
Otic infection (otitis media, mastoiditis)
Meningitis (frontal, ethmoid, sphenoid)
Dental infection
Neurosurgical intervention or neurotrauma
Bacterial endocarditis
Neutropenia
Immune compromise (HIV infection, immunosuppressive
therapy)
Chronic lung infection (abscess, bronchiectasis, empyema)
Congenital heart disease

HIV, human immunodeficiency virus.

Brain abscess is an uncommon but potentially life-
Characterized by localized intracranial suppurative collections, brain abscesses are usually the re-
result of extension of focal infection (45%), trauma (10%), or
surgery. Bacteria may also gain entry to the CNS by hematoge-
nous seeding in 25% of cases. Mortality rates with treatment
range from 4.5% to 13%, even with new imaging techniques,
antimicrobials, and surgical therapies (51–53). Infection begins
as a localized area of cerebritis, with subsequent central necro-
sis, suppuration, and fibrous capsule formation (Table 108.11).
Solitary abscesses are usually the result of contiguous infec-
tion 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 initial injury. Postneurosurgical brain abscesses may
also present in a delayed fashion.

Multiple abscesses are more commonly the result of hematogenous seeding from chronic pulmonary, endocar-
dial, skin, intra-abdominal, or pelvic infections. For exam-
ple, patients with hereditary hemorrhagic telangiectasia (Osler-
weber-rendu syndrome) and children with congenital cyanotic
heart disease are predisposed to brain abscesses. A primary site
or underlying condition cannot be identified in approximately
20% to 40% of patients with brain abscess.

The location of the brain abscess may be suggestive of the
source. Temporal lobe or cerebellar abscesses commonly result
from otic infections, frontal lobe abscesses 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 de-
pend on the primary site of infection, age of the patient,
and underlying host factors. Common aerobic species include
strepococci (viridans, anginosus group, and microaerophilic
species), which are isolated in up to 70% of cases (54): Aer-
obic Gram-negative bacilli—commonly Klebsiella pneumo-
niae, Pseudomonas spp., Escherichia coli, and Proteus spp.—
and S. aureus are common pathogens with contiguous in-
fection (55,56). Less common pathogens, such as Rhodococ-
cus, Listeria, Nocardia, mycobacteria, and fungi—including
Candida, Cryptococcus, Aspergillus, agents of zygomycosis,
Penicillium brevispora, and the dimorphic fungi such as
Histoplasma, Coccioides, and Blastomyces—cause disease in
immunosuppressed 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 Toxoplasma gondii infection.

Anaerobes are present in 40% to 100% of brain abscesses
(55), although anaerobic cultures may not be routinely per-
formed 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 Peptococcus,
Peptostreptococcus, Bacteroides spp, Prevotella spp., Propi-
ohimobacterium, Fusobacterium, Eubacterium, Veillonella, and
Actinomyces.

Helminths may occasionally cause localized brain infec-
tion in immigrant populations. Neurocysticercosis, intracranial
TABLE 108.12
COMMON PRESENTING FEATURES IN BRAIN ABSCESS

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Mental status changes</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Focal neurologic deficits</td>
</tr>
<tr>
<td>Neck stiffness</td>
</tr>
<tr>
<td>Papilledema, nausea, or vomiting with increased intracranial pressure</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
</tbody>
</table>

Infection with the larval cyst of *T. solium* or pork tapeworm, *Entamoeba histolytica*, *Schistosoma japonicum* and *mekongi* species, *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 108.12). 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. 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; seizure is, however, a common presenting feature. Focal neurologic findings are relatively uncommon. Neck stiffness occurs in 15% of patients and 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 correlate with abscess location. Patients with frontal lobe abscesses often present with changes in personality or mental status, hemiparesis, motor 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. Lumbar puncture is contraindicated in patients with focal findings or papilledema and should be avoided in patients with suspected brain abscess. Computed tomography (CT) scanning or magnetic resonance imaging (MRI) should be performed, with the choice of test depending on the stability of the patient and availability of the imaging technique. CT scanning with contrast is not as sensitive as MRI but is generally more easily obtained on an urgent basis. 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 lesions 1.5 cm or smaller, which the CT scan 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 *Toxoplasma gondii* and neurocysticercosis. In toxoplasma brain abscesses, IgG should be positive, as most infections are due to...
reactivation and not primary infection. A positive IgG antibody, however, does not prove *T. gondii* is the cause of a 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 generally advised except in specific situations where there is a high likelihood of a specific pathogen. For example, empiric treatment for toxoplasmosis may be warranted in a patient with advanced HIV (CD4 count less than 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 and 14 days respectively, a microbiologic specimen should be obtained.

The therapy for brain abscesses (Fig. 108.4) requires combination medical and surgical therapy for cure, as antimicrobial therapy alone is rarely effective. 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, sinuses, 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 or oxacillin, 2 g IV every 4 hours, is appropriate in settings with a low prevalence of methicillin resistance. Vancomycin, 15 mg/kg IV every 12 hours—adjusted for renal function and monitored with therapeutic drug levels—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; a trough level of 15 to 20 μg/mL should be achieved. Metronidazole and/or a third-generation cephalosporin may be added, depending on the clinical setting.

For postneurosurgical or posttrauma patients with brain abscess, nafcillin, oxacillin, or vancomycin plus meropenem, a third-generation cephalosporin, preferably one with antipseudomonal activity such as ceftazidime, should be used. Antimicrobial therapy should be adjusted once pathogen identification and susceptibility results are available and continued intravenously for 6 to 8 weeks, guided by clinical response and serial imaging. Prolonged oral antimicrobial therapy (2–6 months) is often administered if an appropriate regimen is available, although the efficacy of this approach has not been established. Therapy should be continued until there is complete resolution of symptoms and CT/MRI findings.

Antifungal therapy must be guided by fungal cultures and used in combination with surgical therapy. Candidal brain abscesses should be treated with amphotericin B and flucytosine. The efficacy of fluconazole has not been sufficiently evaluated in this clinical setting to recommend its use. Aspergillus brain abscesses have been historically treated with amphotericin B. However, due to recent data, voriconazole has become the treatment of choice (37), and combination antifungal therapy with voriconazole, plus either an echinocandin or an amphotericin B formulation, is increasingly used. Cerebral zygomycosis is almost invariably fatal, although amphotericin B is the treatment of choice. *P. boydii* demonstrates in vitro resistance to amphotericin B, and, due to the lack of alternative agents, voriconazole is recommended as the antifungal of choice in these cases. Neurosurgical consultation should be sought at the time of diagnosis. Aspiration through a burr hole or complete excision following craniotomy are both appropriate treatment options, although aspiration is generally preferred. Therapeutic aspiration may also be performed with CT or MRI guidance. Surgical excision is indicated in patients with traumatic brain abscesses, fungal abscesses, and large (greater than 2.5 cm) or multiloculated abscesses. If there is no clinical improvement within 1 week of initiation of treatment and aspiration, mental status declines, or intracranial pressure or abscess size increases despite therapy, surgical excision is also indicated. Antibiotic therapy may be shortened to 2 to 4 weeks following surgical excision.
and seizures develop in up to 50% of patients (61). Other focal
logic signs most commonly include hemiparesis or hemiplegia,
mission, is initially characterized by confusion and drowsiness
 tal status, present in approximately 50% of patients on ad-
pulmonary infection within 2 weeks is common. Altered men-
ial pressure. Cerebral infarction may also result from septic
blood or cerebrospinal flow is disrupted by increased intracra-
noid. It is a potentially life-threatening condition, accounts for
pus in the subdural space, the area between the dura and arach-
wont. It is a potentially life-threatening condition, accounts for
spread of infection to the subdural space occurs via the ema-
ry veins or by direct extension of cranial osteomyelitis with
maling epidural abscess. The subdural space lacks
septations, so infection may spread rapidly and progressively.
with chronic otitis media, the middle ear and mastoids are
worminal pressure. Septations, so infection may spread rapidly and progressively.
commando. Presenting symptoms include high fever and uni-
dary, most commonly seizures, occur in 30% to 60% of patients (51).

CRANIAL SUBDURAL EMPYEMA

Key Points

- Cranial subdural empyema and brain abscess share epidemi-
logic risk factors and microbiology.
- Presenting symptoms include high fever, unilateral headache, and a recent history of contiguous otic, mastoid, sinus, or meningeal infection.
- MRI is the diagnostic test of choice.
- Therapy should include prolonged antimicrobials and sur-
gical drainage for cure.

Cranial subdural empyema is an intracranial collection of
pus in the subdural space, the area between the dura and arach-
noid. It is a potentially life-threatening condition, accounts for
in up to 50% to 80% of cases (63). In patients
with contiguous otic, mastoid, sinus, or other sources of infection. Common predisposing infections include otic and sinus
infections in up to 50% to 80% of cases (63). In patients
with chronic otitis media, the middle ear and mastoids are
commonly the predisposing sites of infection. Other predis-
posing conditions include traumatic brain injury with skull
fracture, neurosurgical procedures, infection of a pre-existing
hematoma, chronic pulmonary infection, or preceding menin-
gitis.

Cranial subdural empyema is invariably polymicrobial,
including streptococci, staphylococci, aerobic Gram-negative
bacilli, and anaerobes. S. aureus, Enterobacteriaceae, and Pseu-
domonas are more common following neurosurgical proce-
dures or neurotrauma.

The clinical presentation of cranial subdural empyema can be
rapidly progressive so early diagnosis and treatment are cru-
ical. Presenting symptoms generally include high fever and uni-
lateral headache. A recent history of sinusitis, otitis media, mas-
toiditis, meningeal, cranial surgery or trauma, sinus surgery, or pulmonary infection within 2 weeks is common. Altered men-
tal status, present in approximately 50% of patients on ad-
misson, is initially characterized by confusion and drowsiness
and progresses to coma in most untreated cases. Focal neuro-
logic signs most commonly include hemiparesis or hemiplegia,
and seizures develop in up to 50% of patients (61). Other focal
findings include cranial nerve palsy, homonymous hemianop-
sia, dysarthria or dysphasia, and ataxia. A fixed, dilated pupil
portends imminent cerebral herniation and requires emergent
surgical intervention.

The diagnosis of cranial subdural empyema requires a high
index of suspicion and should be considered in patients pre-
senting with meningeal signs and focal neurologic deficits,
with or without systemic toxicity. A lumbar puncture is con-
traindicated in these cases because of the risk of cerebral
herniation with increased intracranial pressure. The diagnos-
tic imaging tests of choice are contrast CT or MRI, demon-
strating a typical crescentic collection running parallel to the
cranial vault. Midline shift implies significant mass effect.
Gadolinium-enhanced MRI is the most sensitive, visualizing
subdural empyemas too small to be detected by CT. MRI can
also detect falcine, basal, and posterior fossa empyemas as
well as differentiate between subdural empyemas and cystic
hygromas or chronic hematomas, which CT is unable to do
(63). Imaging of the sinuses, middle ear, and/or mastoids should
be performed in the appropriate clinical settings to identify po-
tential sources.

Treatment of cranial subdural empyema requires emergent
gomined medical and surgical therapy. Surgical drainage is
mandatory, as antimicrobials alone cannot effectively cure
empyemas. Cultures are, of course, required to guide antimi-
crobial therapy. Antiseizure treatment and/or prophylaxis may
be warranted, and standard therapy for increased intracranial
pressure should be instituted.

Empiric antimicrobial therapy should be initiated as soon
as aspiration of the empyema is performed, or immediately
on admission in unstable patients. Empiric therapy should
be guided by the most likely source of primary infection. Rec-
ommended therapy includes a third-generation cephalosporin
(cefotaxime, 2 g IV every 4 hours, or ceftazidime, 2 g IV every
12 hours) or meropenem, 2g IV every 8 hours with metron-
idazole (15 mg/kg IV load, followed by 7.5 mg/kg IV every
12 hours). If S. aureus is suspected, nafcillin or oxacillin (2 g
IV every 4 hours) should be used. Vancomycin, 1 g IV every
12 hours or 500 to 750 mg IV every 6 hours, to a maximum of
2 to 3 g/day, should be used in patients with penicillin allergy or
in regions with high prevalence of methicillin resistance. Van-
comycin dosing requires adjustment in patients with renal dys-
function, and serum levels should be monitored; a trough level
of 15 to 20 μg/mL is desired. If Pseudomonas aeruginosa infec-
tion is suspected, ceftazidime, cefepime, or meropenem should
be used in place of other third-generation cephalosporins.
In-
travenous antimicrobial therapy should be administered for
3 to 6 weeks, depending on clinical response and serial imaging.
Prolonged therapy (6–8 weeks) may be warranted if contiguous
osteomyelitis or mastoiditis is present.

Surgical therapy of cranial subdural empyema includes ei-
ther burr hole drainage or craniotomy. Debridement of necrotic
bone and surgical correction of sinus and otic infections are im-
portant adjuvant surgical therapies.

EPIDURAL ABSCESS

Key Points

- Epidural abscesses may be cranial (between the dura and skull) or spinal (overlying the vertebral column).
- Cranial epidural abscesses most commonly occur as a complication of sinusitis or mastoiditis.
- Spinal epidural abscesses commonly occur in the lumbar region and may be caused by vertebral osteomyelitis.
Spinal epidural abscesses are nine times more common than cranial epidural abscesses, and result most commonly from hematogenous seeding of the intervertebral disk or vertebral body. They can also occur as a complication of spinal surgery or spinal/epidural anesthesia.

Risk factors for spinal epidural abscess include injection drug use, diabetes mellitus, bacteremia, infective endocarditis, chronic indwelling catheters, decubitus ulcers, back surgery or procedures, and trauma.

S. aureus is the most common pathogen.

Consider tuberculous in those at epidemiologic risk.

Common presenting features of spinal epidural abscess include fever, back pain, and neurologic deficits.

MRI is the diagnostic test of choice.

Management includes prolonged antimicrobial therapy and early surgical decompression. Surgical intervention is preferred when symptoms have been present for less than 24 hours.

An epidural abscess is a localized collection of pus between the dura and overlying skull (cranial epidural abscess) or vertebral column (spinal epidural abscess). Because severe symptoms may result due to compression of the brain or spinal cord, prompt diagnosis and treatment are crucial.

Cranial epidural abscess is commonly accompanied by subdural empyema, as emissary veins may translocate infection across the cranial dura. The microbiology is therefore identical to that of cranial subdural empyema (see previous section).

Spinal epidural abscess is nine times more common than cranial epidural abscess. The epidural space is a potential space extending from the foramen magnum down the length of the spinal canal. The space is larger in the lumbar area and is predominantly posterior, and thus most spinal epidural abscesses occur in this area. Spinal epidural abscesses most commonly originate when the intervertebral disk (diskitis) or vertebral body (osteomyelitis) become infected via hematogenous seeding. As the abscess extends, it may track longitudinally in the epidural space causing damage via direct compression of the spinal cord or local vascular damage (thrombosis, thrombophlebitis, vasculitis). Most spinal epidural abscesses extend approximately three to five vertebral spaces but can extend the entire length of the spinal canal in some cases.

Risk factors for the development of spinal epidural abscess include injection drug use, diabetes mellitus, bacteremia, infective endocarditis, chronic indwelling venous catheterization, epidural catheterization, decubitus ulcers, chronic skin conditions, paraspinal abscess, back surgery, lumbar puncture, CT-guided needle biopsies, and blunt or penetrating spinal trauma. Secondary hematogenous spread occurs in 25% to 30% of cases.

S. aureus is the most common pathogen isolated from spinal epidural abscesses, accounting for approximately 65% of cases (64). Other implicated microorganisms include Streptococcus; aerobic Gram-negative bacilli, particularly Escherichia coli and Pseudomonas aeruginosa; coagulase-negative staphylococci, usually with previous spinal instrumentation; and anaerobes. Less common pathogens include Actinomyces, Nocardia, and fungi, predominantly Candida. Infections are polymicrobial in 5% to 10% of cases. Mycobacterium tuberculosis makes up approximately 25% of spinal epidural abscesses and should be suspected in patients with a previous history of tuberculosis, residence in a TB-endemic region, or other TB risk factors.

Clinical manifestations in patients with cranial epidural abscess are usually insidious. Headache is the most common presenting feature. Once infection spreads to involve the meningeal subdural space, and brain meninges, focal neurologic signs and symptoms may develop. If the abscess is located near the petrous bone, osteomyelitis of the petrous ridge may result in Gradengro syndrome—cranial nerve V and VI palsies with unilateral pain or otalgia.

Spinal epidural abscess presents classically with fever, back pain, and neurologic deficits. However, all three symptoms are present in only 13% of patients (65). Back pain is usually the first symptom, with paresthesia, 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.

The diagnosis of epidural abscess begins with the identification of risk factors and clinical suspicion. Routine blood work may demonstrate a peripheral leukocytosis or elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). MRI with gadolinium enhancement is the imaging modality of choice for both cranial and spinal epidural abscesses. CT scanning cannot visualize the spinal cord adequately and is less sensitive at identifying contiguous diskitis or osteomyelitis. Blood cultures should be collected in all patients, as they are positive in 62% of patients (64). Lumbar puncture is relatively contraindicated in the setting of epidural abscess; however, studies have shown that CSF analysis is routinely Gram stain-negative, but cultures are positive in 19% of cases. The highest-yield (90%) culture comes from the abscess itself. Ultrasonogram or CT-guided drainage should be performed as soon as possible. Blood, sputum, urine, and usual cultures should be requested. Additional studies to diagnose active tuberculosis should be performed—for example, sputum AFB smears and cultures, urine AFB culture, and tuberculin skin testing or Quantiferon-TB Gold testing—in patients with suspected spinal TB.

The management of epidural abscess requires a combination of medical and surgical therapy. Empiric antimicrobial therapy for cranial epidural abscess should include a third-generation cephalosporin or meropenem plus metronidazole. Nafcillin, oxacillin, or vancomycin may be added if S. aureus is strongly suspected. Surgical drainage is crucial for cure.

The management of spinal epidural abscess similarly requires empiric antimicrobial therapy and surgical decompression, drainage, and debridement. Because of the predominance of S. aureus infection, empiric therapy is fairly targeted; vancomycin if methicillin-resistant S. aureus is likely or if the patient is penicillin-allergic; and nafcillin or oxacillin if the local prevalence of methicillin resistance is low. Early surgical intervention, specifically within the first 24 hours of presentation, results in improved outcomes (66,67). Medical therapy alone may be successful when blood or abscess aspirate cultures are available to guide therapy and there are no neurologic deficits on presentation (68,69). Serial imaging is required in these cases to confirm improvement in abscess size. Surgery should be pursued if neurologic deterioration occurs at any time, or if resolution of the abscess is not evident with medical therapy alone.

Therapy with antimicrobials is prolonged, usually 4 to 8 weeks, and should be guided by serial imaging to ensure complete resolution of the abscess. Repeat imaging should occur at approximately 4-week intervals or at any time if neurologic
deterioration occurs. Although the prognosis is fair, 37% of patients experience residual neurologic deficits. The degree of residual deficit is affected by the duration of neurologic deficit prior to surgery and diagnostic delays of greater than 24 hours (65).

**SUPPURATIVE INTRACRANIAL THROMBOPHLEBITIS**

**Key Points**

- Suppurative intracranial thrombophlebitis is a complication of otic, sinus, mastoid, oropharyngeal, facial, or neurologic (bacterial meningitis, epidual abscess, or subdural abscess) infections.
- Staphylococci, streptococci, aerobic Gram-negative bacilli, and anaerobic bacteria are the most common pathogens.
- Symptoms depend on the location of septic intracranial thrombosis.
- MRI is the diagnostic test of choice.
- Management includes antimicrobials, surgical therapy, and anticoagulation.

Suppurative intracranial thrombophlebitis is septic venous thrombosis of the cortical veins. It may occur as a complication of sinus, muddle ear, mastoid, oropharyngeal, or facial infections. Bacterial meningitis, epidual abscess, or subdural abscess may also result in intracranial suppurative thrombophlebitis. The presence of values in the cerebral sinuses and venous sinuses aids the spread of infection from proximal sites. Anatomically, the location of intracranial infection depends on the original source of infection. In bacterial meningitis, infection is spread via drainage of the meningeal veins into the superior sagittal sinus. The superior sagittal sinus may also be involved following facial, scalp, subdural, and epidural space infections. Orbits media and mastoids are the usual causes of lateral sinus and petrosal sinus thromboses, Paranasal sinus, fa- cial, or oropharyngeal infections may result in cavernous sinus thrombosis. Risk factors for cerebral venous stasis include hy- porcoagulable states—specifically antithombolipid antibody syndrome—volume depletion, polycythemia, pregnancy, the use of oral contraceptives, malignancy, sickle cell disease, and traumatic brain injury (63).

The clinical manifestations of suppurative intracranial thrombophlebitis depend on the originating source of infection. S. aureus is commonly involved following facial infections; otherwise, sinusitis and otitis media pathogenesis cause most infections; these include staphylococci, streptococci, aerobic Gram-negative bacilli, and anaerobes such as Fusobacterium and Bacteroides. Aspergillus and the agents of zygomycosis rarely cause suppurative intracranial thrombophlebitis and are most often seen in patients with diabetes mellitus or immune deficiencies.

The clinical manifestations of suppurative intracranial thrombophlebitis depend on the anatomic site(s) involved. Septic thrombosis of the superior sagittal sinus presents with fever, headache, confusion, nausea, vomiting, and seizures. Mental status depression and progression to coma may occur rapidly. Upper motor neuron lower extremity weakness or hemiparesis may be present. When septic thrombosis 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. Cranial nerves III, IV, V-1, V-2, and VI, as well as the internal carotid artery, travel through the cavernous sinus. Classic symptoms of septic cavernous sinus thrombosis include fever, headache, diplopia, and retro-orbital pain. Depending on the site of involvement, facial or ocular sensory or motor deficits, ptosis, proptosis, chemosis, hypophthalmos, and decreased corneal reflexes may be present. Venous engorgement of the retinal veins and papilledema are commonly present.

Septic transverse sinus thrombosis presents with headache and otitis. Intracranial suppurative thrombophlebitis may also be a complication of aseptic meningitis syndrome with spread of infection around the carotid sheath and surrounding venous plexus; patients with sigmoid sinus and internal jugular vein thrombosis may present with neck pain.

The diagnosis of suppurative intracranial thrombophlebitis is made by MRI, demonstrating absence of flow within the affected veins and venous sinuses. MR venography or angiography can be used to confirm the diagnosis, and sinus imaging should be concomitantly performed. Compared to CT scan- ning, MRI offers the additional benefits of detecting cerebro- tis, intracranial abscess, cerebral infarction, hemorrhage, or edema. Despite its lower sensitivity, CT scanning is commonly performed before MRI, as it is more easily obtained on an ur- gent basis.

The treatment of suppurative intracranial thrombophlebitis includes antimicrobials, surgical therapy, and anticoagulation. The choice of antimicrobial therapy depends on risk factors, the most probable source of infection, and culture results, if available. In antecedent sinusitis, empirical therapy with ceftriaxone or cefotaxime, or metronidazole is a reasonable choice. In cavernous sinus thrombosis, an agent active against S. aureus should be included. Anticoagulation therapy should be continued for 6 weeks or until radiographic resolution of thrombosis. If antimicrobial therapy is ineffective, surgical therapy may be required for drainage of infected sinuses, ligation of the internal jugular vein, or for source control (e.g., oropharyngeal or dental infections). Anticoagulation with heparin is beneficial in cavernous sinus thrombosis, particularly if used early, and should be strongly considered (70). Intracerebral hemorrhage, if small, is not an absolute contraindication to heparin therapy; however, this form of therapy must be individualized. The efficacy of thrombolysis in septic intracranial thrombosis has not been adequately evaluated to suggest its use.

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