CHAPTER 107

Central Nervous System Infections

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PERSPECTIVE

Background

Central nervous system (CNS) infections have always been among the most perplexing and devastating illnesses. "Epidemic cerebrospinal fever," classically described by Viesseux in 1805, was associated with almost universal mortality.[1] The first American epidemic of meningococcal meningitis was recorded in 1806.[2] Since that time, epidemiologic changes have occurred in concert with advances in understanding of disease processes and evolution of effective treatment strategies.

The etiologic spectrum of CNS infection has changed considerably as a result of the development and aggressive use of antibiotics and the epidemic emergence of immune disorders such as infection with the human immunodeficiency virus (HIV). Some of the research on CNS infections has markedly increased in sophistication, which provides insights into pathogenesis, including the role of host mechanisms such as cytokines and other immune components. The pathophysiologic alterations are increasingly understood at the cellular and molecular levels.

Likewise, diagnostic tools have been developed that allow precise pathogen identification, most recently using molecular technologies such as polymerase chain reaction (PCR) tests for viral nucleic acids in cerebrospinal fluid (CSF). The initial treatment methodologies began by demonstrating the efficacy of antiserum treatment by Flexner in 1913 and of antibiotics by Colebrook and Kenny in 1936.[3,4] The mortality rates were decreased further with the use of high-dose penicillin by Dowling and colleagues in the 1940s.[5] Unfortunately, despite historical advances, the morbidity and mortality of these disorders remain considerable, although substantial progress has been made.[6] The use of pneumococcal *Haemophilus influenzae* type b (Hib) and meningococcal vaccines has led to dramatic changes in the incidence of meningitis caused by these bacteria.[7–14]

Definitions

CNS infections comprise a broad spectrum of disease entities. *Meningitis* is defined as inflammation of the membranes of the brain or spinal cord and is also called *arachnoiditis* or *leptomeningitis*. *Encephalitis* denotes inflammation of the brain itself, whereas *myelitis* refers to inflammation of the spinal cord. The terms *meningoencephalitis* and *encephalomyelitis* describe more diffuse inflammatory processes. Collections of infective and purulent materials may form within the CNS as abscesses. Brain abscesses may be intraparenchymal, epidural, or subdural, or may be found in intramedullary or epidural spinal locations.

This chapter focuses on the more common acute and subacute CNS infections. Infections of the nervous system with HIV or human T lymphotrophic virus, rabies virus, polio or hepatitis viruses, *Borrelia burgdorferi* (Lyme disease), *Treponema* organisms (syphilis), parasites, *Rickettsia,* and the chronic and slow infections of the CNS (subacute sclerosing panencephalitis, progressive multifocal leukoencephalopathy, and the prion-mediated spongiform encephalopathies, such as Creutzfeldt-Jakob disease, bovine spongiform encephalopathy, and kuru) are not addressed in detail. Of note, the incidence of neurocysticercosis is on the rise in the United States.[15]

Epidemiology

Bacterial meningitis is a common disease worldwide. Meningococcal meningitis is endemic in parts of Africa, and epidemics commonly occur in other countries, including the United States. A variety of other pathogens are also causative.[16–20] The overall incidence of bacterial meningitis in the United States is 5 to 10 cases per 100,000 people per year.[21] Men are affected more often than women.[21] In the United States, approximately 80% of cases are caused by either *Streptococcus pneumoniae* or *Neisseria meningitidis*.[22] In regions where vaccination is common, the epidemiology of bacterial meningitis has substantially changed.[9–11,14,23] The incidence of bacterial meningitis increases in late winter and early spring, but the disease may occur at any time of the year.

Because most cases are unreported, the actual incidence of viral meningitis is unknown. It is estimated to affect 11 to 27 individuals per 100,000 people.[24] A prominent increase of cases is seen in summer months, which is concurrent with seasonal predominance of the enterovirus group of the picornaviruses.

The same organisms responsible for viral meningitis may also be associated with encephalitis. Encephalitis is, however, far less common, and the ratio of cases of meningitis to encephalitis varies according to the specific pathogen. Arbovirus infection is transmitted by an insect vector, although clinical disease develops in only a small percentage of the people bitten. Before 1999, approximately 19,000 cases of encephalitis were hospitalized in the United States annually. Since then, there has been a rapid increase because of the emergence of

West Nile virus (WNV). In 2003, more than 8000 additional individuals were hospitalized because of WNV alone.[25,26]

Approximately 2000 cases of brain abscess occur in the United States annually.[27] Although CNS abscesses may occur at any age and any time of year, they are more commonly seen in men than women.[28,29] CNS abscesses are associated with local contiguous and remote systemic infections, intravenous (IV) drug use, neurologic surgery, and cranial trauma. Brain abscess secondary to otitis media most often occurs in pediatric or older adult populations. When associated with sinusitis, it most often arises among young adults. Increasingly, CNS abscesses are seen in the immunocompromised population, particularly those with HIV infection, and among bone marrow and solid organ transplant recipients. However, antimicrobial prophylaxis of immunosuppressed patients and more aggressive treatment of otitis and sinusitis have decreased the overall incidence to 0.9 per 100,000 person-years.[27]

PRINCIPLES OF DISEASE

Etiology

Meningitis

Meningeal inflammation may be caused by a variety of disease processes, but the infectious etiologies predominate. Among the bacterial etiologies, *Streptococcus pneumoniae* remains the predominant pathogen in adult patients, followed by *N. meningitidis* and *Listeria monocytogenes*.[30,31] *N. meningitidis* is the predominant organism in adults younger than 45 years. Five major serogroups cause most meningococcal disease worldwide (A, B, C, Y, and W-135). Serogroup A accounts for the majority of cases of meningococcal meningitis in developing nations.[32] Serogroup distribution for invasive disease has changed markedly in the United States, with B, C, and Y now most commonly responsible.[33–36] These pathogens account for the bulk of cases in nontraumatic meningitis, although virtually any organism can be encountered, particularly among patients who are elderly, alcoholic, and immunosuppressed and those who have cancer. Interestingly, higher case fatality has been observed in *N. meningitis* outbreaks versus sporadic cases, likely due to increased virulence of outbreak related strains.[37] Causes of aseptic meningitis, which simply defined is all cases with negative bacterial CSF cultures, are listed in Box 107-1.[38]

Meningeal infection may also occur in association with a dural leak secondary to neurosurgery or neurotrauma. *S. pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and coliform bacteria are seen most commonly in this population.

Viral meningitis may likewise be caused by a variety of etiologic agents.[39] Enteroviruses are statistically encountered most commonly.[40] Unfortunately, precise definition of the etiologic agent is often impossible. Fungal and parasitic meningitides are additional concerns, particularly among immunocompromised patients.[18,19]

Noninfectious meningitides include drug-induced meningitis, carcinomatous meningitis, CNS involvement in serum sickness, vasculitis, systemic lupus erythematosus, Behçet's disease, sarcoidosis, and others. The differentiation of noninfectious from infectious etiologies can often be perplexing.

Encephalitis

Arboviruses and herpes simplex virus (HSV), a human herpes virus (HHV), are the most common causes of epidemic and sporadic cases of encephalitis, respectively. Children are the most vulnerable to infection with these viruses, although adults are also commonly affected. Epidemics of viral encephalitis have been attributed to a wide variety of viral agents. WNV, a flavivirus, first infected humans in the New York City area and rapidly spread to 47 states by 2003.[19,41] Varicella, herpes zoster, HHV 6 and 7, and Epstein-Barr virus have been increasingly reported to be the cause of encephalitis in immunocompetent hosts.[42,43] Vaccinia encephalitis has been recognized in those receiving vaccination for smallpox.[44] Postinfectious encephalomyelitis is also induced by a variety of viral pathogens, most commonly by the measles virus.[45] However, *Mycoplasma pneumoniae* and idiopathic causes are becoming more common in developed countries.

Central Nervous System Abscess

The etiologies of CNS abscess are multiple and reflect the primary infective process and the immune state of the human host. A variety of mixed pathogens may be responsible for intracranial abscesses. Streptococci, particularly the *Streptococcus milleri* group, have been identified in nearly 50% of brain abscesses.[46] Anaerobic bacteria, predominantly *Bacteroides* species, are commonly seen when the primary infectious process is chronic otitis media or pulmonary disease. *S. aureus* and *Propionbacterium acnes* are often identified, particularly after cranial penetration from surgery or trauma.[47,48] The Enterobacteriaceae are an additional common isolate. Opportunistic fungal and parasitic etiologies are often seen in the immunosuppressed, including *Nocardia* species.[46,49] Culture of epidural and subdural abscesses more often yields a single organism, with streptococci most commonly seen when associated with contiguous spread and *S. aureus* and gram-negative rods most commonly encountered after neurologic trauma.[19] Etiologic agents in spinal abscess are similarly varied. *S. aureus* is most commonly encountered (Fig. 107-1).

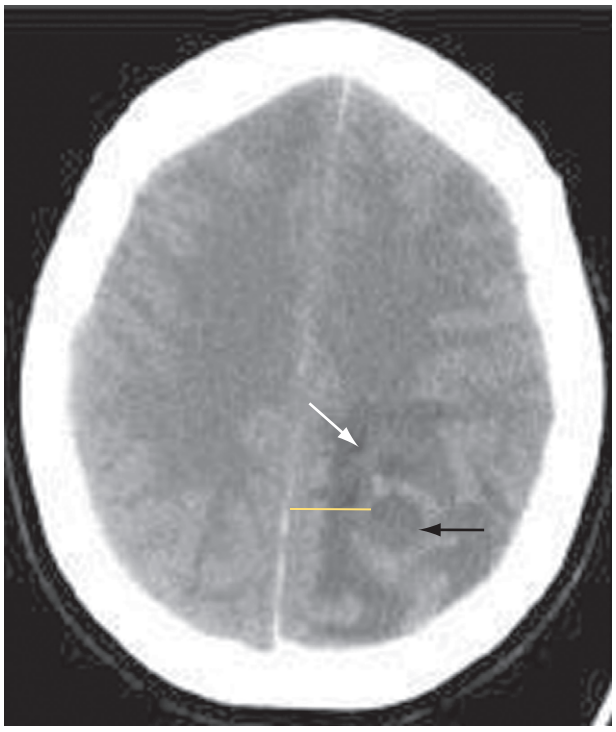

Figure 107-1. Central nervous system abscess: computed tomography scan of an intraparenchymal abscess *(arrows)*.

BOX 107-1 CAUSES OF ASEPTIC MENINGITIS

I. Infectious causes
- 1. Viruses
  - Enteroviruses—polio, coxsackie, ECHO virus
  - Herpes group of viruses
  - Herpes simplex virus types 1 and 2
  - Varicella zoster virus
  - Cytomegalovirus
  - Epstein-Barr virus
  - Human herpes virus 6
  - Respiratory viruses
  - Adenovirus
  - Rhino virus
  - Influenza virus types A and B
  - Arboviruses
  - Mumps virus
  - Lymphocytic choreomeningitis
  - HIV
- 2. Bacteria
  - Partially treated meningitis
  - Parameningeal infection
  - Endocarditis
  - *Mycoplasma pneumoniae*
  - *Mycobacterium tuberculosis*
  - Ehrlichiosis
  - *Borrelia burgdorferi*
  - *Treponema pallidum*
  - *Brucella*
  - Leptospirosis
- 3. Fungi
  - *Cryptococcus neoformans*
  - *Histoplasma capsulatum*
  - *Coccidioides immitis*
  - *Blastomyces dermatitides*
  - *Candida*
- 4. Parasites
  - *Toxoplasma gondii*
  - Neurocysticercosis
  - Trichinosis
  - *Naegleria*
  - *Hartmannella*
  - *Bartonella henselae*
- 5. Rickettsiae
  - Rocky Mountain spotted fever
  - Typhus

II. Noninfectious causes
- 1. Postinfectious/postvaccinial
  - Rubella
  - Varicella
  - Variola
  - Rabies vaccine
  - Pertussis vaccine
  - Influenza vaccine
  - Vaccinia
  - Yellow fever vaccine
- 2. Drugs
  - Nonsteroidal anti-inflammatory drugs
  - Trimethoprim-sulfamethoxazole, amoxicillin
  - Muromunab CD3 (OKT3)
  - Azathioprine
  - Intravenous immunoglobulin
  - Isoniazid
  - Intrathecal methotrexate
  - Intrathecal cytosine arabinoside
  - Allopurinol
  - Carbamazepine
  - Sulfasalazine
- 3. Systemic disease
  - Collagen vascular disorders
  - Systemic lupus erythematosus
  - Wegener's granulomatosis
  - Central nervous system vasculitis
  - Rheumatoid arthritis
  - Kawasaki's disease
  - Sarcoidosis
  - Leptomeningeal cancer
  - Posttransplantation lymphoproliferative disorder
  - Behçet's disease
  - Vogt-Koyabagj syndrome
- 4. Neoplastic disorders
  - Leukemia
  - Carcinomatous meningitis secondary to primary or secondary tumors of the brain
- 5. Inflammation of neighboring structures
  - Brain abscess
  - Epidural abscess
- 6. Miscellaneous
  - Arachnoiditis
  - Migraine
  - Urinary tract infection

Reproduced from Kumar R: Aseptic meningitis: Diagnosis and management. Ind J Pediatr 72:57, 2005.

Pathophysiology

Bacterial Meningitis

The pathogenetic sequence in bacterial meningitis has been well characterized.[18,19,50,51] The first step is nasopharyngeal colonization and mucosal invasion. Although colonization rates vary, virulent microbes use secretion of immunoglobulin A proteases and induce cilio-stasis of mucosal cells. After penetration occurs by a variety of mechanisms, bacterial intravascular survival occurs because of evasion of the complement pathway. The varying capsular properties of each organism protect the bacteria. The third step occurs when the bacteria cross the blood-brain barrier to enter the CSF. The dural venous sinuses, cribriform plate area, and choroid plexus have all been implicated as potential sites of invasion. Although the mechanism of invasion is not completely understood, host defense mechanisms within the CSF are often ineffective; there are low levels of complement, immunoglobulin, and opsonic activity. Bacterial proliferation then occurs, which stimulates a convergence of leukocytes into the CSF.

Meningeal and subarachnoid space inflammation is also associated with the release of cytokines into the CSF, most notably tumor necrosis factor and interleukins 1 and 6.[50,52] This results in increased permeability of the blood-brain barrier, cerebral vasculitis, edema, and increased intracranial pressure (ICP). A subsequent decrease in cerebral blood flow leads to cerebral hypoxia. Glucose transport into the CSF is decreased concomitantly with an increased use of glucose by the brain,

bacteria, and leukocytes, which depresses CSF glucose concentrations. The increased permeability leads to increased CSF proteins.

Viral Meningitis and Encephalitis

Viruses enter the human host through the skin (i.e., insect vectors), through the respiratory, gastrointestinal, or urogenital tract, or by receipt of infected blood products or donor organs.[53,54] Viral replication subsequently occurs outside the CNS, most often followed by hematogenous spread to the CNS. Additional routes into the CNS include retrograde transmission along neuronal axons and direct invasion of the subarachnoid space after infection of the olfactory submucosa.[55,56]

Fortunately, most systemic viral infections do not result in meningitis or encephalitis. The development and subsequent magnitude of viral infection depend on the virulence of the specific virus, the viral inoculum level, and the state of immunity of the human host. The tropism of the virus for specific CNS cell types also influences the focality of disease and its manifestations.[55] Particular viruses may preferentially attack cortical, limbic, or spinal neurons, oligodendria, or ependymal cells. An example is the tropism of HSV for the temporal lobes and the development of temporal lobe seizures and behavioral changes in afflicted patients.

Fungal Meningitis

Fungal meningitis probably develops in much the same way as bacterial meningitis, although this has been incompletely studied. Pulmonary exposure followed by hematogenous spread is the primary pathogenetic mechanism in most cases. Immune system defects or immunosuppressive drugs compromise host defense mechanisms, with ensuing development of CNS infection.

Central Nervous System Abscess

Intraparenchymal brain abscesses, subdural empyema, or intracranial or spinal epidural abscesses form by inoculation of the CNS from contiguous spread of organisms from a sinus, middle ear, or dental infection or metastatic seeding from a distant site, usually from pulmonary infection, endocarditis, or osteomyelitis.[28,47] The primary infection can be identified in 75 to 85% of cases. These conditions may also follow surgery or penetrating cranial trauma, particularly when bone fragments are retained in brain tissue. Otogenic abscesses occur most commonly in the temporal lobe in adults and cerebellum in children, whereas sinogenic abscesses typically occur in frontal areas.[46] Multiple brain abscesses suggest hematogenous spread of organisms, although solitary lesions may also occur. The pulmonary system is the most common source of hematogenous spread.[19]

CLINICAL FEATURES

Symptoms and Signs

Numerous host factors have been implicated in the acquisition of meningitis (Box 107-2).[57] Although these factors alone and in combination increase the risk of meningitis, the disease often occurs in patients with none of these factors.

Many patients with meningitis present with advanced disease; in these patients, the diagnosis of acute meningitis is strongly suspected. The constellation of symptoms that may classically occur in an acute CNS infection consists of fever, headache, photophobia, nuchal rigidity, lethargy, malaise, altered sensorium, seizures, vomiting, and chills.[17,57]

BOX 107-2 HOST FACTORS PREDISPOSING TO MENINGITIS

- Age <5 yr
- Age >60 yr
- Male gender
- Low socioeconomic status
- Crowding (e.g., military recruits)
- Splenectomy
- Sickle cell disease
- Black race
- Alcoholism and cirrhosis
- Diabetes
- Immunologic defects
- Recent colonization
- Dural defect (e.g., traumatic, surgical, congenital)
- Continuous infection (e.g., sinusitis)
- Household contact with meningitis patient
- Thalassemia major
- Intravenous drug abuse
- Bacterial endocarditis
- Ventriculoperitoneal shunt
- Malignancy

Unfortunately, more subtle presentations are also common. Immunosuppressed and geriatric patients present a diagnostic challenge because the classical signs and symptoms of meningitis may not be present. Although some degree of fever is present in most patients, as are headache and neck stiffness, meningitis should be carefully considered in any immunosuppressed patient with symptoms or signs of infectious disease. Often, the only presenting sign of meningitis in the elderly patient is an alteration of mental status. However, a meta-analysis suggested that the absence of fever, stiff neck, and mental status change excludes meningitis in immunocompetent adults.[36]

The presentation of fungal meningitis can be obscure even in the healthy adult population. Headache, low-grade fever, lassitude, and weight loss may be present but often to such a mild degree that the correct diagnosis is not initially considered.[17] This is also true of tuberculous meningitis, which often has a protracted course and a vague nonspecific presentation consisting of fever, weight loss, night sweats, and malaise, with or without headache and meningismus.[16]

The physical findings in meningitis vary, depending on the host, causative organism, and severity of the illness. Nuchal rigidity or discomfort on flexion of the neck is common. Kernig's and Brudzinski's signs are present in approximately 50% of adults.[19] Described in 1882 by Vladimir Kernig, Kernig's sign is present in the patient if the examiner is unable, because of resistance and hamstring pain, to straighten the patient's leg passively to a position of full knee extension when the patient is lying supine with the hip flexed to a right angle. Jozef Brudzinski initially described five signs, two of which are currently utilized.[2] The contralateral sign is present if an attempt to flex the hip passively on one side is accompanied by a similar movement of the other leg. The neck sign is present if attempts to flex the neck passively are accompanied by flexion of the hips. The absence of jolt accentuation of headache with this maneuver may be useful in obviating the need for lumbar puncture (LP) in a patient with low suspicion for meningitis.[58] Deep tendon reflexes may be increased, and ophthalmoplegia may be present, especially of the lateral rectus muscles.

The systemic findings may include an obvious source of infection such as sinusitis, otitis media, mastoiditis, pneumonia, or urinary tract infection. Various manifestations of endocarditis may be present. Arthritis may be seen with *N. meningitidis* and occasionally with other bacteria.[57] Petechiae and cutaneous hemorrhages are widely reported with meningococcemia but also occur with Hib, pneumococcal organisms, *L. monocytogenes*, and echovirus infections, in addition to staphylococcal endocarditis.[57] Endotoxic shock with vascular collapse often develops in severe meningococcal disease, but shock may be present in the advanced stages of any bacterial meningitis. Any determination of a serious systemic infection should encourage rather than dissuade the clinician from considering the possibility of a concomitant CNS infection.

Patients with encephalitis may also have symptoms of meningeal irritation. An alteration of consciousness occurs in virtually all patients. Fever, headache, and a change of personality are also usually present.[56] Hallucinations and bizarre behavior may precede motor, reflex, and other neurologic manifestations by several days, occasionally prompting an initial diagnosis of a psychiatric disorder. Because focal neurologic deficits and seizures occur much more commonly with encephalitis than meningitis, there may also be diagnostic confusion with a brain abscess. Distinguishing the etiologic agent in encephalitis is clinically difficult, although HSV encephalitis results in a higher incidence of dysphasia and seizures.[59] In some patients, WNV produces a myelitis that affects the anterior horn cells of the spinal column, resulting in a flaccid paralysis with a clear sensorium, similar to findings in polio or Guillain-Barré syndrome.[41]

Patients with intracranial abscess may be indistinguishable from those with meningitis or encephalitis. Most patients with intraparenchymal abscess have a subacute course of illness, with symptoms progressing during the course of 2 or more weeks. However, nuchal rigidity and fever are present in fewer than 50% of cases. Focal neurologic deficits are present in most of these patients. A large number of patients exhibit papilledema, which is a rare finding in meningitis. An abrupt neurologic deterioration that results from uncal herniation or rupture into the ventricular system may occur.

Patients with a subdural or epidural abscess most often have headache, fever, and focal signs, although more subtle presentations are common. Most of the patients with spinal abscess typically present with spinal pain and other symptoms and signs of cord compression but not necessarily with fever.[60]

Complications

Bacterial Meningitis

The immediate complications of bacterial meningitis include coma (with loss of protective airway reflexes), seizures, cerebral edema, vasomotor collapse, disseminated intravascular coagulation, respiratory arrest, dehydration, syndrome of inappropriate secretion of antidiuretic hormone, pericardial effusion, and death (Box 107-3).[20] Various delayed complications include multiple seizures, focal paralysis, subdural effusions, hydrocephalus, intellectual deficits, sensorineural hearing loss, ataxia, blindness, bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome), peripheral gangrene, and death.[57]

The case fatality rate for pneumococcal meningitis averages 20 to 25%, with higher fatality rates occurring in patients with serious underlying or concomitant disease or advanced age.[61,62] The prognosis is related to the degree of neurologic impairment on presentation. Overall, 20 to 30% of the survivors of pneumococcal meningitis have some residual neurologic deficit.[57] The case fatality rate for *Listeria* meningitis may be as high as 40%.[31]

BOX 107-3 Complications of Bacterial Meningitis

- Immediate
  - Coma
  - Loss of airway reflexes
  - Seizures
  - Cerebral edema
  - Vasomotor collapse
  - Disseminated intravascular coagulation (DIC)
  - Respiratory arrest
  - Dehydration
  - Pericardial effusion
  - Death
  - Others
- Delayed
  - Seizure disorder
  - Focal paralysis
  - Subdural effusion
  - Hydrocephalus
  - Intellectual deficits
  - Sensorineural hearing loss
  - Ataxia
  - Blindness
  - Bilateral adrenal hemorrhage
  - Death
  - Others

With the advent of antibiotic therapy, the mortality from meningococcal meningitis has markedly decreased to less than 20%, but it remains substantially higher in elderly patients or in those who also have meningococcemia.[62] Although most of the complications and sequelae are less common than with pneumococcal disease, the incidence of Waterhouse-Friderichsen syndrome is dramatically higher when meningococcemia is present.[57] The overall mortality rate in community-acquired gram-negative meningitis has been less than 20% since the introduction of the third-generation cephalosporins.[18]

Viral Meningitis

With rare exceptions, the overall prognosis for complete recovery from viral meningitis is excellent. Various complications related to the systemic effects of the particular virus include orchitis, parotitis, pancreatitis, and various dermatoses. Usually all of these complications resolve without sequelae.[39]

Viral Encephalitis

The outcomes in viral encephalitis are dependent on the infecting agent. Encephalitis caused by Japanese encephalitis virus, Eastern equine virus, and St. Louis encephalitis virus is severe, with high mortality rates and virtually universal neurologic sequelae among survivors.[63] WNV produces encephalitis in only 0.5% of those infected, yet it resulted in 120 deaths in 2003.[26] Western equine virus and California encephalitis virus cause milder infections, and death is rare. The incidence of neurologic sequelae is highly variable and appears to depend on both the host and the infecting agent.[63,64]

The mortality rate from HSV encephalitis before the use of acyclovir was 60 to 70%. Acyclovir treatment has reduced the mortality rate to approximately 30%.[45] Common sequelae observed among survivors include seizure disorders, motor deficits, and changes in mentation.

Tuberculous Meningitis

Death from tuberculous meningitis in the adult age group ranges from 10 to 50% of cases, with the incidence directly proportional to the patient's age and the duration of symptoms before presentation. Focal ischemic stroke may result from the associated cerebral vasculitis. In advanced disease, up to 25% of patients may require some neurosurgical procedure for obstruction (ventriculoperitoneal shunt or drainage).[65] In most patients some neurologic deficit develops, but severe long-term sequelae among survivors are unusual.[16,65]

Fungal Meningitis

Common CNS complications with fungal meningitis include abscesses, papilledema, neurologic deficits, seizures, bone invasion, and fluid collections. Direct invasion of the optic nerve results in ocular abnormalities in up to 40% of patients with cryptococcal meningitis.[17] The mortality rate is high but variable and is related to the timeliness of diagnosis, underlying illness, and therapeutic regimens.

Central Nervous System Abscess

With the early diagnosis afforded by the use of the cranial computed tomography (CT) scan; appropriate antimicrobial therapy; and combined management approaches with surgery, aspiration, and medical therapy, the mortality rate from brain abscess has declined dramatically from approximately 50% to less than 20%.[28,66] Seizure disorder is the most common sequela of intracranial abscess, occurring in 80% of patients.[18] Other neurologic sequelae of intracranial abscesses, including focal motor or sensory deficits or changes in mentation, are common. Complications of spinal abscess primarily result from cord compression, including paralysis, motor and sensory deficits, and bowel and bladder dysfunction. Generalized spread of CNS infection and death may also occur.[60]

DIAGNOSTIC STRATEGIES

Lumbar Puncture

General Considerations

Because the consequences of missing a CNS infection are devastating, CNS infection must be presumed to be present until excluded. The possibility of the diagnosis of meningitis mandates LP unless the procedure is contraindicated by the presence of infection in the skin or soft tissues at the puncture site or the likelihood of brain herniation.[45] Adherence to this principle prevents a delay in diagnosis, which substantially increases the morbidity and mortality of the disease. Some patients have clinically obvious bacterial meningitis, and CSF examination serves primarily to help identify the organism, thereby facilitating the appropriate treatment. Most patients, however, present more of a diagnostic problem, and analysis of the CSF fluid constitutes the critical step in the elucidation of the presence of CNS infection.

Increased Intracranial Pressure

In most patients with bacterial meningitis, LP may be safely performed without antecedent neuroimaging studies. As this may not be the case in other brain pathologies, in many circumstances it is advisable to obtain a CT scan of the head before performing an LP.[67,68] These indications must be carefully weighed against the patient's condition, the probability of meningitis, and the availability of the CT or magnetic resonance imaging (MRI) scan.[18]

It has been conventionally asserted that an LP in the presence of increased ICP may be harmful or fatal to the patient. Although data to address this concern are limited, the presence of focal neurologic signs does appear to be associated with a dramatic increase in complications from LP. These patients may deteriorate precipitously during or after the procedure.[69–72]

Patients with a markedly depressed sensorium that precludes careful neurologic examination or those with a focal neurologic deficit, papilledema, seizures, or evidence of head trauma must be considered to be at risk for a herniation syndrome that may be exacerbated by an LP. If the presentation is an acute, fulminating, febrile illness and bacterial meningitis is the concerning diagnosis, early initiation of antimicrobial therapy is mandatory because of the association of prognosis and time to treatment.[73] The algorithmic alternatives are therefore (1) immediate LP followed by initiation of antibiotic treatment before obtaining the results or (2) initiation of antibiotic treatment followed by a cranial CT scan and then an LP. The latter choice of empirical treatment with antibiotics is now the routine in many institutions, although in some cases a third option could be considered: antibiotics and no LP despite an unremarkable CT scan.[72] This reflects the efficacy of current methodologies of identification of causative organisms by means other than bacteriologic cultures. The controversy emerging regarding not performing LP despite a lack of CT scan findings is based on some reviews and case reports. These describe a fulminant herniation syndrome temporally related to LP in patients with normal CT scans.[70] Increased ICP may not be reliably detected using CT. Clinical signs of increased ICP, rapid change in consciousness, and recent seizures were identified as risk factors predicting deterioration despite a normal CT scan.[72] The risks of ongoing empirical treatment with antibiotics without additional information from CSF analysis appears to be low, as the yield from blood cultures and other diagnostic techniques such as PCR is relatively high. Therefore, this risk may be less than the risks of performing LP in certain very high-risk patients.

Cerebrospinal Fluid Analysis

Opening Pressure

The normal CSF pressure in an adult varies from 50 to 200 mm H_2O. This value applies only to patients in the lateral recumbent position and may increase substantially when the patient is in the sitting position. The pressure is often elevated in bacterial, tuberculous, and fungal meningitides and a variety of noninfectious processes.[56] Pressure may be falsely elevated when the patient is tense or obese or has marked muscle contraction.

Collection of Fluid

At least three sterile tubes each containing at least 1 to 1.5 mL of CSF should be obtained and numbered in sequence. A fourth tube may be desirable should later studies such as viral cultures or a Venereal Disease Research Laboratories (VDRL) test for syphilis become necessary. The fluid should be sent to the laboratory for immediate analysis of turbidity, xanthochromia, glucose, protein, cell count and differential, Gram's stain, bacterial culture, and antigen testing (Table 107-1). In certain cases, an India ink stain, bacteriologic stain for acid-fast bacilli, or VDRL test should be obtained. When only a small amount of fluid can be obtained, the most important studies

Table 107-1 Analysis of Cerebrospinal Fluid

TEST	NORMAL VALUE	SIGNIFICANCE OF ABNORMALITY
Cell count	≤5 WBC/mm^3 ≤1 PMN/mm^3 ≤1 eosinophil/mm^3	Increased WBC counts are seen in all types of meningitis and encephalitis; increased PMN count suggests bacterial pathogen
Gram's stain	No organism	Offending organism identified 80% of time in bacterial meningitis, 60% if patient pretreated
Turbidity	Clear	Increased turbidity with leukocytosis, blood, or high concentration of microorganisms
Xanthochromia	None	Presence of RBCs in spinal fluid for 4 hr before lumbar puncture; occasionally caused by traumatic tap (if protein ≥150 mg/dL) or hypercarotenemia
CSF-to-serum glucose ratio	0.6:1	Depressed in pyogenic meningitis or hyperglycemia; lag time if glucose given IV
Protein	15–45 mg/dL	Elevated with acute bacterial or fungal meningitis; also elevated with vasculitis, syphilis, encephalitis, neoplasms, and demyelination syndromes
India ink stain	Negative	Positive in one third of cases of cryptococcal meningitis
Cryptococcal antigen	Negative	90% accuracy for cryptococcal disease
Lactic acid	≤35 mg/dL	Elevated in bacterial and tubercular meningitis
Bacterial antigen tests	Negative	≥95% specific for organism tested; up to 50% false-negative rate
Acid-fast stain	Negative	Positive in 80% of cases of tuberculous meningitis if ≥10 mL of fluid

CSF, cerebrospinal fluid; PMN, polymorphonuclear; RBC, red blood cell; WBC, white blood cell.

are the cell count with differential, Gram's stain, and bacterial cultures. Ideally, the cell count should be performed on both the first and third or fourth tubes to help differentiate true CSF pleocytosis from contamination of the specimen by a traumatic LP.

Turbidity

The CSF should be assessed immediately for turbidity or cloudiness by the person performing the LP. Because normal CSF is completely clear and colorless and should be indistinguishable from water, any degree of turbidity is pathologic. Leukocytosis is the most common cause of CSF turbidity; counts greater than 200 cells/mm^3 usually cause clinically detectable changes in CSF clarity.[74]

Cell Count and Differential

Normal adult CSF contains no more than 5 leukocytes/mm^3 with at most one granulocyte (polymorphonuclear [PMN] leukocyte)[57,74,75]; therefore, the presence of more than one PMN or a total cell count of more than 5 cells/mm^3 should be considered evidence of CNS infection. In addition, the presence of any eosinophil in the CSF is abnormal, although occasionally basophils may be seen in the absence of disease.[74] Pretreatment with a few doses of antibiotics, although possibly diminishing the yield of Gram's staining and cultures, should not affect the CSF cell counts in meningitis.[18,30,76,77]

The cell counts in bacterial meningitis are usually markedly elevated, sometimes exceeding 10,000 cells/mm^3, and demonstrate a dramatic granulocytic shift.[57] In general, counts exceed 500 cells/mm^3, with a preponderance of PMN leukocytes. However, the initial CSF analysis exhibits lymphocytosis (lymphocyte count >50%) in 6 to 13% of all cases of bacterial meningitis. When only the patients with bacterial meningitis with fewer than 1000 cells/mm^3 are considered, 24 to 32% have a predominance of lymphocytes.[78,79] In addition, the same population of patients often has only a mild disturbance of CSF glucose and protein levels. In well-established viral meningitis and encephalitis, counts are usually less than 500 cells/mm^3, with nearly 100% of the cells being mononuclear.[40] Early (<48 hours) presentations may reveal significant PMN pleocytosis and hence be indistinguishable from presentations in early bacterial meningitis.[80]

Similarly, normal cell counts and differentials, although reassuring, do not absolutely exclude bacterial meningitis.[75] Any patient thought to have a clinical syndrome compatible with meningitis requires hospital admission with frequent reevaluation, repeated LP, and antimicrobial therapy. In some patients who have symptoms or signs of meningitis and have a normal initial CSF analysis, CSF pleocytosis may develop within 24 hours; the causative organism may be cultured from the original "normal" CSF.

Brain abscess and parameningeal infections, such as subdural empyema or epidural abscess, usually display CSF cell counts and differentials similar to those of viral meningitis and encephalitis, although the CSF may also be normal.

A traumatic LP is suggested by the presence of a clot in one of the tubes or the clearing of the CSF and a decreasing red blood cell (RBC) count from tubes one to three. In the presence of a traumatic LP, one may estimate the true degree of CSF white blood cell (WBC) pleocytosis with the formula given in Equation 107-1[74]:

$$\text{True CSF WBC} = \text{measured CSF WBC} - [(\text{CSF RBC} \times \text{blood WBC})/\text{blood RBC}] \quad \text{(Eq. 107-1)}$$

Alternatively, when peripheral cell counts are normal, the CSF from a traumatic LP should contain about 1 WBC per 700 RBCs.

Gram's Stain

A properly performed Gram's stain of a centrifuged specimen of CSF identifies the causative organism approximately 80% of the time in cases of bacterial meningitis.[76] Gram's stain characteristics of the most commonly encountered organisms are described in Table 107-2. The yield from this procedure is diminished by 20 to 30% when there has been prior treatment with antibiotics.[18] Misidentification of gram-positive organisms as gram-negative is also known to occur more commonly among pretreated patients because organisms with damaged walls stain unpredictably.

Table 107-2 Gram's Stain Characteristics of Selected Meningeal Pathogens

PATHOGEN	TYPICAL CHARACTERISTICS
Staphylococci	Gram-positive cocci: singles, doubles, tetrads, clusters
Streptococcus pneumoniae	Gram-positive cocci: paired diplococci
Other streptococci	Gram-positive cocci: pairs and chains
Listeria monocytogenes	Gram-positive rods: single or chains
Neisseria meningitidis	Gram-negative cocci: negative paired diplococci; kidney or coffee bean appearance
Haemophilus influenzae	Gram-negative coccobacilli: "pleomorphic" bacilli
Enterobacteriaceae (including *Escherichia coli*)	Gram-negative rods
Pseudomonas aeruginosa	Gram-negative rods

Xanthochromia

Xanthochromia refers to the yellowish discoloration of the supernatant of a centrifuged CSF specimen. Xanthochromia is abnormal and results from the lysis of RBCs and release of the breakdown pigments oxyhemoglobin, bilirubin, and methemoglobin into the CSF. This process normally begins within 2 hours, and pigments may persist up to 30 days; therefore, early analysis of the LP specimen is essential. If a traumatic tap has introduced enough plasma to raise the CSF protein level to 150 mg/dL or more, blood pigments may cause xanthochromia. If the CSF protein level is less than 150 mg/dL, however, and systemic hypercarotenemia does not exist, xanthochromia of a centrifuged CSF specimen should suggest that subarachnoid hemorrhage has occurred.[74]

Glucose

When the serum glucose is normal, the CSF glucose is usually between 50 and 80 mg/dL. The CSF glucose is normally in a ratio of 0.6:1 to the serum glucose, except with marked systemic hyperglycemia, when the ratio is closer to 0.4:1. Therefore, a CSF-to-serum glucose ratio of less than 0.5 in normoglycemic subjects or 0.3 in hyperglycemic subjects is abnormal and may represent the impaired glucose transport mechanisms and increased CNS glucose use associated with pyogenic meningitis.[57,74] Mild decreases in the CSF glucose level may occur with certain viral and parameningeal processes. However, bacterial or fungal meningitis should be presumed to be the cause of low CSF glucose, termed hypoglycorrhachia, until each is clearly excluded.[81] If the serum glucose level has increased rapidly—for example, after IV administration of 50% dextrose in water—equilibration in the CSF may take up to 4 hours, and therefore the interpretation of CSF-to-serum glucose ratios may be unreliable.

Protein

The normal CSF protein level in adults ranges from 15 to 45 mg/dL. An elevated CSF protein, usually higher than 150 mg/dL, commonly occurs with acute bacterial meningitis.[57] When a traumatic LP has occurred, the CSF protein can be corrected for the presence of blood by subtracting 1 mg/dL of protein for each 1000 RBCs.[74] Elevated CSF protein concentrations can result from any cause of meningitis, subarachnoid hemorrhage, CNS vasculitis, syphilis, viral encephalitis, neoplasms, and demyelination syndromes.[74] A greatly elevated CSF protein level (>1000 mg/dL) in the presence of a relatively benign clinical presentation should suggest fungal disease.[17]

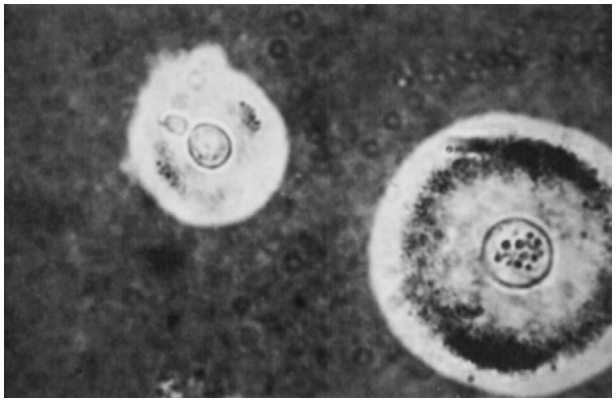

Figure 107-2. India ink staining of the cerebrospinal fluid.

India Ink Preparation

India ink staining of the CSF should be performed when a diagnosis of cryptococcal meningitis is being considered. The demonstration of budding organisms (Fig. 107-2) is virtually diagnostic for cryptococcal disease but occurs in only one third of the cases.[17] A more definitive diagnostic test is the cryptococcal antigen.

Lactic Acid

Although nonspecific, elevations in CSF lactic acid concentrations (>35 mg/dL) are potentially indicative of bacterial meningitis, and lactate may rise prior to the decline in glucose.[82,83] Normal lactate levels (<35 mg/dL) are usually seen in patients with viral meningitides.

Antigen Detection

Counterimmunoelectrophoresis (CIE), latex agglutination, and coagglutination are methods of detecting specific antigens. These tests are particularly useful in patients receiving antibiotic treatment before CSF sampling because the tests depend on the presence of only an antigen and not viable organisms.

The CIE techniques that are performed for the most common bacterial pathogens demonstrate high sensitivity and specificity for bacterial antigens, particularly when performed on CSF, blood, and urine simultaneously. Latex agglutination techniques are, however, more rapid and sensitive and are replacing the use of CIE in many facilities. Although reported results vary, the sensitivities of antigen tests are 50 to 90% for *Neisseria* organisms, 50 to 100% for *S. pneumoniae*, and approximately 80% for *H. influenzae*. A specific agglutination test for cryptococcal antigen is also highly sensitive (90%) and specific. Cultures are always indicated because a negative antigen test does not exclude the possibility of any particular bacterial or fungal etiology.

Antigen and antibody testing is also being used to identify viral and atypical pathogens. These have particular utility in HSV encephalitis. Enzyme-linked immunosorbent assays can detect HSV antibody production.[84] Unfortunately, the appearance of antibody in CSF occurs too late to aid in any therapeutic decision analysis. PCR amplification and the identification of HSV DNA have demonstrated a sensitivity of 95 to 100%

and a specificity of 100% early in the disease and have markedly decreased the need for diagnostic brain biopsy in this disorder.[85–87] PCR has improved the diagnosis of tuberculous meningitis, with a sensitivity of 80 to 85% and a specificity of 97 to 100% and is superior to standard techniques.[88–90] PCR has additionally been shown to be superior in identifying bacteria, enteroviruses, and other viral etiologies in both immunocompromised and immunocompetent patients.[91,92] Reported sensitivities of detection in CSF by PCR for *N. meningitidis*, *H. influenzae*, and *S. pneumoniae* are 88, 100, and 92%, respectively, with nearly 100% specificity.[93,94] The sensitivities of bacteriologic culture are much lower, especially for *N. meningitidis* at 37 to 55% and *H. influenzae* at 50%.[94–96]

In addition, PCR assays have nearly tripled the yield of viral culture in identifying the etiologic agent.[97] In studies of enteroviral meningitis, sensitivities and specificities for PCR ranged from 86 to 100% and 92 to 100%, respectively.[98] PCR has been shown to be at least as sensitive as culture technique in detecting cryptococcal meningitis. Quantitative PCR may be of benefit in monitoring response to therapy in some forms of severe disease.[42]

The growing availability of these molecular techniques does not, however, suggest that they should be routinely employed. Most cases of acute bacterial meningitis are readily diagnosed and treated on the basis of the standard Gram's stain and culture. PCR should be reserved for less clear presentations, patients pretreated with antibiotics, and cases in which concern exists for tuberculous, cryptococcal, and treatable viral CNS infections.[99]

Bacteriologic Cultures

Although results are not available for emergency management, bacteriologic cultures of CSF should be performed. Bacterial culture yields are significantly decreased in patients pretreated with antibiotics. Viral cultures may also be indicated.

Other Tests

A variety of additional, nonspecific tests of CSF have been advocated. These include measuring CSF lactate dehydrogenase, C-reactive protein, and the limulus lysate test; however, none of these have demonstrated a high degree of clinical usefulness. Likewise, the evaluation of CSF chloride as a diagnostic aid for tuberculous meningitis is no longer clinically relevant.

Neuroimaging Techniques

A cranial CT scan or MRI scan is indicated in the evaluation of any patient with presumed CNS infection in whom there is the possibility of an intracranial abscess, intracranial hemorrhage, or mass lesion. In the diagnostic evaluation of acute meningitis, however, a CT scan should not unnecessarily delay LP or antimicrobial therapy. The CT scan may also show hypodense lesions in the temporal lobes in patients with HSV encephalitis, although an MRI scan reveals this abnormality much earlier in the disease process. A contrast-enhanced cranial CT scan or MRI scan is invaluable in the diagnosis of a CNS abscess.[28] MRI scanning is also helpful in the evaluation of other infectious and noninfectious encephalitides.

Additional Investigations

As with other infectious diseases, the complete blood count with differential is a nonspecific adjunct in the diagnostic evaluation of a patient suspected to have a CNS infection. The peripheral cell counts are often normal in the presence of significant disease and may even be depressed, particularly in elderly or immunosuppressed persons. A "normal" leukocyte count and differential should not dissuade the emergency physician from performing a diagnostic LP, obtaining a CT scan, or otherwise pursuing the diagnosis of a CNS infection. Serum C-reactive protein is nonspecific, but a negative test result is potentially helpful.[100] Procalcitonin is emerging as a promising serum marker in infectious disease; however, there is not convincing evidence at this point to advocate its use to attempt to rule out bacterial meningitis.[101]

Even when antimicrobial therapy has already been administered, two or three blood cultures should be obtained for all patients who are being evaluated for a CNS infection. The blood cultures can improve the identification of the causative organisms, especially with pneumococcus and to a lesser degree meningococcus. Although blood cultures are not immediately useful in the acute diagnosis of meningitis in the emergency department, they may be of considerable clinical importance later in the management of the disease. The cultures are helpful in identifying a causative organism in only a small minority of cases of brain abscess.

As many as 50% of patients with pneumococcal meningitis also have evidence of pneumonia on an initial chest radiographic study. This association occurs in fewer than 10% of the cases of meningitis caused by Hib and *N. meningitidis* and in approximately 20% of cases of meningitis caused by other organisms. The identification of a pulmonary infection on chest radiography may assist in identification of causative organisms and appropriate antimicrobial therapy in approximately 10% of cases of brain abscess.[28]

Other ancillary investigations such as echocardiography, cultures of other body fluids, and bone scans may be undertaken as necessary to evaluate coexistent or complicated disease. Serum electrolytes, glucose, urea nitrogen, and creatinine levels should be measured to facilitate the interpretation of the CSF glucose level and to establish the level of renal function and the state of electrolyte balance. Although organism-specific abnormalities are uncommon, hyponatremia has been associated with tuberculous meningitis.

A number of characteristic but not pathognomonic electroencephalographic abnormalities have been associated with HSV type 1 encephalitis. The presence of focal or lateralized electroencephalographic abnormalities in the presence of an encephalitis syndrome should be considered strong evidence supporting a diagnosis of HSV encephalitis.[102]

DIFFERENTIAL CONSIDERATIONS

Patients with meningitis may have symptoms and signs ranging from mild headache with fever to frank coma and shock. To facilitate the discussion of diagnosis and treatment, meningitis may be divided into three clinical syndromes: acute meningitis, subacute meningitis, and chronic meningitis.

Acute meningitis encompasses patients with obvious signs and symptoms of meningitis who are evaluated in less than 24 hours after the onset of their symptoms and who rapidly deteriorate. In many of these patients the diagnosis of meningitis is not in doubt, and the crucial step is to initiate antimicrobial therapy immediately. The most likely pathogens in this syndrome are *S. pneumoniae* and *N. meningitidis*. Although *H. influenzae* has been reported in this context, it is not commonly implicated in the adult population.[20,30]

In the syndrome of subacute meningitis, the symptoms and signs causing the patient to seek care have developed during a period of 1 to 7 days. This syndrome includes virtually all cases of viral meningitis, along with most of the bacterial and

some of the fungal etiologies.[18,19] The differential diagnosis depends on the symptoms and signs at presentation. Among elderly and immunosuppressed individuals, a change in the patient's mental status may be the only presenting sign in meningitis. Even when a fever is present, the patient's change in mental status may be misattributed to another disease outside the CNS, such as pneumonia or urinary tract infection; neck stiffness may be misattributed to degenerative joint disease. The elderly patient is at high risk for meningitis and, rather than constituting a diagnostic endpoint, the identification of an infection outside the CNS in such a patient is a clear indication for LP because of the risk of bacteremic seeding by the involved organisms.

The differential diagnosis of encephalitis and brain abscess occurs in the context of the subacute meningitis syndrome. Brain abscess should be considered, especially if fever is minimal or absent or if there are focal neurologic findings. The presence of fever, altered sensorium, headache, seizures, and personality change is consistent with encephalitis. In addition, diagnoses such as subdural empyema, brain tumor, subarachnoid hemorrhage, subdural hematoma, and traumatic intracranial hemorrhage should be considered. In these circumstances a cranial CT scan should be obtained before performing an LP.

The spectrum of chronic meningitis includes some of the viral meningitides as well as meningitis caused by tubercle bacilli, syphilis, and fungi. Many of the patients in this group have had symptoms for at least 1 week before presentation and generally have a prolonged indolent course marked by difficult and changing diagnoses and multiple therapies.[16,17] Prediction rules have been both derived and validated and have not yet diffused into widespread practice, likely due to limitations in the models, shifts in the epidemiology of the causative organisms, and relatively small sample sizes.[103–105]

MANAGEMENT

Assessment and Stabilization

Septic shock, hypoxemia, seizures, cerebral edema, and hypotension resulting from dehydration require aggressive management. When possible, a thorough history should be obtained from the patient, family members, or ambulance personnel with particular emphasis on preexisting conditions that may complicate the patient's disease. Examples include recent neurosurgery, trauma, a history of leukopenia, immunocompromise, or diabetes mellitus.

Hypotension or shock should be treated as indicated with isotonic crystalloid infusion, high-flow oxygen, and pressors. IV dextrose may be required for hypoglycemia secondary to depletion of glycogen stores. Alcoholic or nutritionally compromised patients should also receive 50 to 100 mg of IV thiamine. In cases of moderate to severe hypotension, central venous pressure monitoring should be initiated and used as a guide for additional IV fluids or vasopressors. In children, after volume resuscitation there does not appear to be evidence to restrict fluids and appropriate maintenance fluids should be instituted.[106]

Active airway management with endotracheal intubation may be required, particularly in cases of coma, recurrent seizures, or severe accompanying pulmonary infection. Cardiac monitoring may also be necessary, particularly in elderly patients, those with known coronary disease, and those with an altered mental status. Seizures are a particularly prominent component of the clinical presentation in patients with a brain abscess but may also occur with any CNS infection, especially when an underlying seizure disorder is present.

If acute cerebral edema or an elevated ICP is present, it should be managed by immediate intubation and adequate ventilation. Osmotic agents such as mannitol or diuretics such as furosemide may be used, but caution should be exercised if shock or uncontrolled hypotension is present. If diuretics or osmotic agents are administered, the emergency physician must ensure that the patient does not become volume depleted and hypotensive.

Definitive Therapy

Bacterial Meningitis

Therapy for bacterial meningitis requires antibiotics that penetrate the blood-brain barrier and achieve adequate CSF concentrations, are bactericidal against the offending organism in vivo, and maintain adequate tissue levels to treat the infection effectively.

Until the pathogenetic organism is identified, broad-spectrum coverage of the most common pathogens is necessary (Table 107-3). Many authorities recommend cefotaxime or ceftriaxone, plus vancomycin to cover potentially resistant organisms.[107] High-dose ampicillin is also added if concern exists about *Listeria*.[107] In patients allergic to penicillin and cephalosporins, meropenem or chloramphenicol plus vancomycin may be effective while awaiting the outcome of desensitization techniques.[107]

After the pathogen is identified, more targeted therapy can be instituted. It is prudent to refer to a current antimicrobial reference to guide therapy in all instances, given rapid changes in etiologic spectrum, drug resistance, and available agents. Duration of treatment varies, and in certain situations (namely epidemics in sub-Saharan Africa), long-acting chloramphenicol or ceftriaxone is effective.[108]

Corticosteroid treatment is additionally recommended in adult acute bacterial meningitis. Animal studies demonstrate the salutary effects of the administration of corticosteroids in experimental pneumococcal meningitis, including reduced brain edema, CSF pressure, and CSF lactate levels.[109] Earlier resolution of the clinical and CSF stigmata of meningitis and a decrease in long-term hearing loss are observed in infants and children given dexamethasone with cefuroxime or ceftriaxone compared with those receiving the antibiotic alone, particularly when *H. influenzae* is the offending agent.[110,111] In adult bacterial meningitis, an absolute risk reduction of 10% for unfavorable outcome is seen when dexamethasone is given either 15 minutes before or concomitantly with antibiotics and continued for 4 days at 6-hour intervals.[112] This benefit was greatest in those with *S. pneumoniae*. Subgroup analyses for different causative organisms did not establish a benefit; however, the study was not designed with adequate power to detect improved outcomes. In addition, amoxicillin and penicillin were the most commonly used initial therapy, due to the process of health care delivery in Europe at the time of that study in which nearly all patients were seen initially in an office-based practice. A recent randomized controlled trial did not demonstrate a benefit of adjuvant dexamethasone in adult patients, even when only those with *S. pneumoniae* were included in a secondary analysis.[113] In the current era of initial empiric parenteral therapy, rising β-lactam resistance, the possibility of the decreased CSF penetration of vancomycin after dexamethasone treatment, and shifts in the likely causative organisms secondary to vaccination campaigns, the true effectiveness of dexamethasone is unclear. The most recent meta-analysis suggests a benefit, but the included studies suffer from one or more of the aforementioned limitations.[114]

Table 107-3 **Recommendations for Empirical Antimicrobial Therapy for Purulent Meningitis Based on Patient Age and Specific Predisposing Condition**

PREDISPOSING FACTOR	COMMON BACTERIAL PATHOGENS	ANTIMICROBIAL THERAPY
Age		
<1 mo	*Streptococcus agalactiae*, *Escherichia coli*, *Listeria monocytogenes*, *Klebsiella* species	Ampicillin plus cefotaxime or ampicillin plus an aminoglycoside
1–23 mo	*Streptococcus pneumoniae*, *Neisseria meningitides*, *S. agalactiae*, *Haemophilus influenzae*, *E. coli*	Vancomycin plus a third-generation cephalosporin[a,b]
2–50 yr	*N. meningitides*, *S. pneumoniae*	Vancomycin plus a third-generation cephalosporin[a,b]
>50 yr	*S. pneumoniae*, *N. meningitides*, *L. monocytogenes*, aerobic gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin[a,b]
Basilar skull fracture	*S. pneumoniae*, *H. influenzae*, group A beta-hemolytic streptococci	Vancomycin plus a third-generation cephalosporin[a,b]
Penetrating trauma	*Staphylococcus aureus*, coagulase-negative staphylococci (especially *Staphylococcus epidermidis*), aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
Post–neurosurgery	Aerobic gram-negative bacilli (including *P. aeruginosa*), *S. aureus*, coagulase-negative staphylococci (especially *S. epidermidis*)	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
Cerebrospinal fluid shunt	Coagulase-negative staphylococci (especially *S. epidermidis*), *S. aureus*, aerobic gram-negative bacilli (including *P. aeruginosa*), *Propionibacterium acnes*	Vancomycin plus cefepime,[c] vancomycin plus ceftazidime,[c] or vancomycin plus meropenem[c]

[a]Ceftriaxone or cefotaxime.
[b]Some experts would add rifampin if dexamethasone is also given.
[c]In infants and children, vancomycin alone is reasonable unless Gram's stains reveal the presence of gram-negative bacilli.
Reproduced from Tunkel AR: Practice guidelines for bacterial meningitis. Clin Infect Dis 39:1267, 2004.

In pediatric meningitis, the evidence that adjunctive dexamethasone is helpful is less compelling. Invasive Hib and pneumococcal infections have drastically been reduced by vaccination.[7,23] A randomized trial of dexamethasone in childhood meningitis in sub-Saharan Africa did not demonstrate a benefit.[115] Current recommendations are organism specific, which presents a major limitation as recommendations are to begin empiric therapy prior to laboratory results in suspicious cases. For Hib, "dexamethasone may be beneficial for treatment of infants and children with Hib meningitis to diminish the risk of neurologic sequelae, including hearing loss, if given before or concurrently with the first dose of antimicrobial agent(s). There probably is no benefit if dexamethasone is given more than 1 hour after antimicrobial agent(s)."[116] For *S. pneumoniae*, "for infants and children 6 weeks of age and older, adjunctive therapy with dexamethasone may be considered after weighing the potential benefits and possible risks. Experts do not agree on a recommendation to use corticosteroids in pneumococcal meningitis; data are not sufficient to demonstrate a clear benefit in children. If used, dexamethasone should be given before or concurrently with the first dose of the antimicrobial agent."[117] The implication for frontline physicians caring for children is that unless the causative organism is known prior to antibiotic treatment, there is probably little role for adjunctive dexamethasone in children.

Viral Meningitis

No specific agents are available for treating most types of viral meningitis. Investigational agents in development may reduce symptoms in enterovirus meningitis[118]; however, with the exception of HSV meningitis, the viral meningitides contracted in the United States are generally characterized by a short, benign, self-limited course followed by a complete recovery. The primary therapeutic consideration in cases of viral meningitis is therefore the validity of the diagnosis. Early cases of viral meningitis may be indistinguishable from bacterial meningitis, and this confusion may not be resolved by CSF analysis; therefore, when any doubt exists about the veracity of the diagnosis, appropriate cultures should be obtained and the patient admitted to the hospital. Antimicrobial therapy for presumed bacterial meningitis may be initiated on the basis of the clinical presentation or may be withheld pending the outcome of close clinical observation and repeated LP in 8 to 12 hours.

Viral Encephalitis

Specific therapy for meningoencephalitis from HHV is available. Acyclovir remains the current choice and is capable of substantially improving the patient's outcome. When the diagnosis of herpes meningoencephalitis is suspected or established, IV acyclovir should be administered in a dose of 10 mg/kg every 8 hours.[81] Ganciclovir, foscarnet, and cidofovir are also effective in HHV infections, and pleconaril has been effective in enteroviral disease. Additional antiviral treatments are in development.[41,42,118]

Tuberculous Meningitis

Early chemotherapeutic intervention in acute tuberculous meningitis improves the patient's prognosis. A strong clinical suggestion of this disease is an adequate indication to begin antituberculous therapy. A standard treatment regimen consists of isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin.[107] Corticosteroids have also been shown to decrease secondary complications.[107,119]

Fungal Meningitis

The treatment of fungal meningitis is complex.[17] Four agents are commonly used: amphotericin B, flucytosine, miconazole, and fluconazole. Of these, amphotericin B, either alone or in combination with flucytosine, is the most commonly recommended initial therapeutic regimen.[107] These diseases are rarely acutely life-threatening but rather are slowly progressive. Prolonged therapy, often with multiple agents, is necessary. The initiation of antifungal therapy is rarely indicated in the emergency department.

Central Nervous System Abscess

The treatment of cerebral abscess is complex, and neurosurgical consultation is indicated. The location, size, and number of abscesses influence the choice of medical management, surgical excision, aspiration, or a combination of these modalities.[46] In general, small multiple abscesses are more appropriately treated medically, whereas large, surgically accessible lesions should be excised. Empirical antimicrobial therapy before identification of specific organisms by aspiration or surgical excision should be guided by the principles of CSF penetration and the coverage of likely pathogens.

Otogenic and sinogenic abscesses are often treated with cefotaxime or ceftriaxone plus metronidazole.[107] Abscesses with traumatic or neurosurgical causes should have antimicrobial coverage for *S. aureus* or methicillin-resistant *S. aureus*. Patients at high risk for tuberculous, fungal, or parasitic abscess should also receive coverage for the suspected etiologic agent. Corticosteroids should be reserved specifically for managing any attendant cerebral edema; in other circumstances, steroid use is associated with increased mortality. In cases where the etiology is bacterial endocarditis, valve replacement is often required.[120]

Chemoprophylaxis

Among household contacts, the incidence of transmission of meningococcus is approximately 5%; therefore, it is recommended that household contacts of bacteriologically confirmed cases receive rifampin (adults, 600 mg; children older than 1 month, 10 mg/kg; children younger than 1 month, 5 mg/kg) orally every 12 hours for a total of four doses.[107] In addition, these contacts should be advised to watch for fever, sore throat, rash, or any symptoms of meningitis. They should be hospitalized with appropriate IV antimicrobial therapy if there are signs that active meningococcal disease is developing because rifampin is ineffective against invasive meningococcal disease. Intimate, nonhousehold contacts who have had mucosal exposure to the patient's oral secretions should also receive rifampin prophylaxis. Health care workers are not at increased risk for the disease and do not require prophylaxis unless they have had direct mucosal contact with the patient's secretions, as might occur during mouth-to-mouth resuscitation, endotracheal intubation, or nasotracheal suctioning. Ciprofloxacin 500 mg by mouth (adults only) and ceftriaxone 250 mg intramuscularly (125 mg intramuscularly for children younger than 15 years) provide single-dose alternatives.[107]

There is no indication for chemoprophylaxis in pneumococcal meningitis. Rifampin prophylaxis for the contacts of patients with Hib meningitis is recommended for nonpregnant household contacts when there are children younger than 4 years of age in the household[107] (adults, 600 mg by mouth; children, 20 mg/kg by mouth daily for 4 days).

Immunoprophylaxis

A quadrivalent vaccine based on the polysaccharide capsule and conferring protection against group A, C, Y, and W-135 meningococci has been in routine use by the U.S. military since the 1980s.[121] However, the capsular polysaccharide vaccines used to immunize adults are neither immunogenic nor protective in children younger than 2 years because of poor antibody response. In addition, no licensed vaccine is currently available against the serogroup B meningococcus.[36] The serogroup B capsular polysaccharide has proved to be poorly immunogenic in both adults and children.[122] The sequence variation of the surface proteins and cross-reactivity of the group B polysaccharide with human tissues have further impeded efforts to develop a successful vaccine. Efforts to enhance the immunogenicity and protective efficacy of meningococcal vaccines have focused on using conjugate methods that link polysaccharides and carrier proteins. Serogroup C and serogroup C + Y conjugate vaccines have been developed and utilized effectively.[123] Current recommendations for the quadrivalent vaccine are evolving. The vaccine is recommended in established meningococcal epidemics and for travelers to countries where meningococcal disease is currently epidemic. Elective vaccination of college freshmen has been recommended by the Advisory Committee on Immunization Practices (ACIP) in the United States and public health authorities in the United Kingdom.[124] The United Kingdom has also implemented universal childhood immunization with a group C conjugate vaccine.[123]

The development of effective pneumococcal vaccines has been hampered by the large number of serotypes of the organism. A small number of serotypes, however, is responsible for most clinical pneumococcal disease, and a 23-valent vaccine effective against many of these principal serotypes has been developed.[125] The recommendations for this polyvalent pneumococcal vaccine are targeted primarily at prevention of pneumonia, despite a potential beneficial effect for meningitis. A single dose of the vaccine should be considered for elderly or debilitated patients, especially those with pulmonary disease, and for patients with impaired splenic function, splenectomy, or sickle cell anemia.[22] A heptavalent conjugated pneumococcal vaccine has also been developed and is recommended for universal childhood immunization by the ACIP.[126] A conjugate vaccine effective against Hib has been developed for use in the pediatric, but not adult, population. It appears to be approximately 90% protective and has a very low incidence of adverse reactions.[7,8,127] Modern childhood immunization against Hib has raised the average age of patients afflicted with *Haemophilus* meningitis to 25 years and decreased the incidence of meningitis of any etiology by 55%.[99]

Vaccination is also available to confer immune protection against Japanese encephalitis virus, and it is recommended for people performing extensive outdoor activities or spending more than 30 days in endemic areas during transmission seasons.[128,129] The reported protective efficacy of the vaccine is approximately 90%. Although there is no current human vaccine for the WNV, vaccines for nonhuman mammals have been developed.[41]

■ DISPOSITION

With the exception of viral meningitis, all but the most chronic CNS infections require initial inpatient evaluation and treatment. Bed rest, analgesics, and the institution of appropriate IV antimicrobials are indicated.

Some patients with suspected viral meningitides merit hospitalization. These include patients with more severe disease, immunocompromise, suspicion of HSV meningitis, or potential nonviral causes. Some authorities manage patients with classical presentations of viral meningitis as outpatients and ensure close follow-up within 24 hours. Others admit all patients until the more serious causes, such as early bacterial meningitis or encephalitis, can be excluded with certainty.

KEY CONCEPTS

- CNS infection should be considered in all patients with headache, neck stiffness, fever, altered sensorium, or diffuse or focal neurologic findings.
- Lumbar puncture with sampling of CSF is the only reliable method of assessing the presence or absence of meningitis. In the absence of contraindications, any suspicion of meningitis mandates performance of LP.
- Early initiation of antimicrobial therapy is mandatory in any case of suspected acute CNS infection. Antibiotic administration must not be delayed for CSF analysis or performance of neuroimaging studies.
- Antibiotic chemoprophylaxis should be assured for close contacts of patients with meningitis resulting from *N. meningitidis* or *H. influenzae*. Single-dose and multiple-dose regimens are available.
- Vaccination against *N. meningitidis* is recommended for certain at-risk populations but does not afford protection against serogroup B infection.
- Concomitant CNS infection should be strongly considered in any patient with another severe systemic infection, such as urinary tract infection or pneumonia.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.