



## Update in the Diagnosis and Management of Central Nervous System Infections

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Central nervous system (CNS) infections presenting to the emergency room include meningitis, encephalitis, brain and spinal epidural abscess, subdural empyema, and ventriculitis. These conditions often require admission to an intensive care unit (ICU) and are complications of ICU patients with neurologic injury, contributing significantly to morbidity and mortality. Nosocomial CNS infections are a serious complication of neurosurgical interventions (craniotomy or ventriculostomy placement), craniocerebral trauma, and invasive neuromonitoring techniques. CNS infections may have acute and chronic neurologic sequelae, including seizures, hydrocephalus, focal neurologic deficits, sensorineural hearing loss, cognitive deficits, and personality change [1]. Reducing morbidity and mortality is critically dependent on rapid diagnosis and, perhaps more importantly, on the timely initiation of appropriate antimicrobial therapy. Those of us in health care continue to be faced with significant challenges to these goals, partly because of structural or administrative limitations in providing immediate antibiotic therapy and because of pharmacokinetic barriers to achieving effective concentrations of antimicrobials at the site of infection, and partly because of changing trends in microbial resistance. New insights into the role of

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inflammation and the immune response in CNS infections have contributed to development of new diagnostic strategies using markers of inflammation, and to the study of agents with focused immunomodulatory activity, which may lead to further adjunctive therapy in human disease.

### Anatomy and inflammation of the central nervous system

Invasive infections of the CNS begin with entry of bacteria between the pia (internal layer in direct contact with brain parenchyma) and arachnoid (middle layer) membranes delimiting the subarachnoid space, a multistep process requiring evasion of host defenses (Fig. 1). Bacteria responsible for meningitis attach to the nasopharyngeal epithelium, and are nearly all capable of secreting IgA proteases that prevent their destruction and allow them to traverse the epithelium and invade the intravascular space [2,3]. Interactions between the bacterial capsular polysaccharide coat and complement regulatory proteins protect pathogenic bacteria from the complement system, increasing their ability to cross the blood-brain barrier (BBB) and enter the cerebrospinal fluid (CSF) [4]. The BBB is a highly specialized structural and biochemical barrier that regulates the entry of molecules into the brain and maintains ionic homeostasis [5,6]. The BBB is composed of nonfenestrated capillaries whose endothelial cells form continuous tight junctions that seal the paracellular cleft between adjacent endothelial membranes and prevent passive diffusion from the intravascular space to the brain parenchyma [5]. Within the CNS, a relatively low concentration of immunoglobulin and weak complement-mediated host defenses enables bacterial replication.

Clinical complications of bacterial CNS infections are largely mediated by host immune responses and leukocyte functions. An estimated 50% of neuronal cell loss occurring in the context of a *Streptococcus pneumoniae*

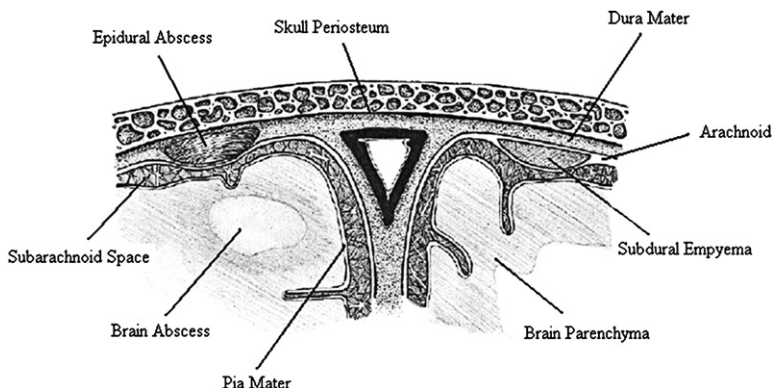


Fig. 1. Coronal view illustrating meningeal layers and common sites of central nervous system infections. (Reproduced from Lewin JJ, LaPointe M, Ziai WC. Central nervous system infections in the critically ill. Journal of Pharmacy Practice 2005;18(1):25-41; with permission.)

meningitis is the result of bacterial toxins (pore-forming pneumolysin, hydrogen peroxide); the other half is mediated by the inflammatory process [7–9]. Endogenous inflammatory mediators, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- $\alpha$ , which are part of the host immune response, are believed to contribute to neurologic injury by stimulating migration of neutrophils into the CSF. Proinflammatory cytokines (IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , IL-6, granulocyte-macrophage colony-stimulating factor), produced by these invading leukocytes, activated endothelial cells, astrocytes, and perivascular macrophages, regulate the extent of brain inflammation by altering brain endothelial cell junction complexes, thereby disrupting the BBB and resulting in the development of vasogenic brain edema, increased intracranial pressure, and disruptions in cerebral blood flow [10–12]. Intercellular adhesion molecules, vascular cellular adhesion molecules, and selectins have been shown to alter tight junction complexes by regulating leukocyte and endothelial cell interactions, and leukocytes themselves increase vascular permeability through interactions with endothelial cells and release of proinflammatory mediators [13–15]. Finally, chemokines and chemoattractant cytokines such as IL-8, monocyte chemoattractant protein-1, and chemokine ligand (CCL2) are proinflammatory mediators that selectively drive leukocytes into brain parenchyma and can regulate BBB permeability by means of expression of specific receptors on brain endothelial cells and by means of production of other proinflammatory agents [16].

Stimulation of the host immune response depends on components of the bacterial cell wall and lipopolysaccharide surface proteins [17]. Because levels of complements, immunoglobulins, and polymorphonuclear leukocytes are lower in the CSF than the serum, opsonic activity is inferior, mandating the use of bactericidal as opposed to bacteriostatic agents [18,19].

On the other side of the coin are factors limiting excessive host immune responses. The TNF-related apoptosis-inducing ligand (TRAIL) appears to modify the inflammatory response and reduce neuronal cell death. Soluble TRAIL levels are elevated in the CSF of patients with bacterial meningitis. In experimental meningitis, using intrathecal administration of pneumococcal cell wall (a TRAIL receptor ligand), TRAIL deficient mice had protracted inflammation, clinical impairment and increased apoptosis in the hippocampus. These changes were reversed by administration of rTRAIL into the subarachnoid space of TRAIL  $-/-$  mice or by transplanting TRAIL-expressing bone-marrow cells into a chimeric mouse model. Therefore, TRAIL is an anti-inflammatory cytokine that limits the lifespan of activated leukocytes, mediates neuronal injury in meningitis, and may have the potential to reduce the acute inflammatory response and improve outcomes in invasive CNS infections [20].

Removing cytokine and chemokine activity with neutralizing antibodies to cytokines and chemokine receptor antagonists, respectively, has been shown experimentally to reduce brain edema formation. This may represent a new strategy for treating vasogenic brain edema, a significant factor

producing morbidity in CNS infections [16,21,22]. Blockade of TNF- $\alpha$ , which plays an important role in cochlear injury, reduced postmeningitic hearing loss, and cochlear injury after *Streptococcus pneumoniae* meningitis [23]. Brain-derived neurotrophic factor, which has marked antiapoptotic effects in hypoxic ischemic injury, has been shown to significantly reduce the extent of three forms of brain cell injury in an experimental meningitis model [24]:

Cortical necrosis in group B streptococcal meningitis

Caspase-3-dependent cell death in *S. pneumoniae* meningitis

Caspase-3-independent hippocampal cell death in group B streptococcal meningitis

These therapies hold promise as adjunctive treatments for bacterial meningitis.

Also of importance is the blood-CSF barrier. The choroid plexi in the ventricles are perfused by unique fenestrated capillaries, with the barrier function here determined by tight junctions between ependymal cells separating these capillaries from the ventricular cavity. The BBB and blood-CSF barrier have different physiology, but they exert the same restraint on CNS drug distribution [25–27]. Altered permeability of these barriers during meningeal inflammation can increase drug penetration into the brain parenchyma and CSF with most antibiotics significantly, especially those that are poorly lipid-soluble [28].

### Evaluating the patient with suspected central nervous system infection

The approach to a patient suspected to have a CNS infection begins with an evaluation of clinical features, which provides critical information leading to etiologic diagnosis [29]. The identification of infectious agents in CNS infection remains highly dependent on the CSF analysis, and occasionally serum or biopsy data. Neuroimaging also plays a crucial role in diagnosis and therapeutic decision-making.

#### *Clinical presentation*

##### *Acute septic meningitis*

This clinical condition constitutes a neurologic emergency, and it is responsible for mortality and morbidity rates as high as 25% and 60%, respectively [30,31]. The classic triad of fever, neck stiffness, and altered mental status has a low sensitivity for diagnosis of bacterial meningitis. In a recent Dutch study of 696 episodes of adult community-acquired acute bacterial meningitis confirmed by CSF cultures, only 44% of cases had the full triad [32]. However, 95% of episodes had at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status. On admission, 14% of patients were comatose, and 33% had focal neurologic

1/3 seize  
1/3 neuro focal

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1-Headache  
2-fever  
3-neck stiff  
4-LOC

95% have 2 of 1-4

CENTRAL NERVOUS SYSTEM INFECTIONS

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1-LOC  
2-seizure  
3-Focal  
4-Shock  
+  
Neuro >  
1000/mm<sup>3</sup>  
=  
Bacterial

deficits. A retrospective French study investigated the accuracy of clinical presentation and relative diagnostic value of CSF parameters in distinguishing between bacterial and viral meningitis in 90 patients with confirmed bacterial meningitis and 54 patients with not previously treated viral meningitis [29]. Logistic regression analysis showed that the presence of severity (defined by one of four findings at admission: altered consciousness, seizures, focal neurologic findings, and shock) and CSF absolute neutrophil count above 1,000/mm<sup>3</sup> were predictive of bacterial meningitis. CSF glucose less than 2 mmol/L and CSF protein above 2 g/L were not predictive.

Other caveats in the clinical diagnosis of meningitis are the potential lack of a febrile response in patients who are elderly, immunocompromised, or inadequately treated with antibiotics. Fever with altered mentation should alert the clinician to the possibility of meningitis in any elderly patient [33]. Nuchal rigidity (30%) and focal cranial nerve palsies, including gaze paresis caused by hydrocephalus, are not uncommon [34]. The occurrence of seizures, reported in 5% to 28% of meningitis cases, indicates cortical irritation, which may be caused by a cortically based complication (eg, empyema, stroke, or venous thrombosis) [35–37]. In a retrospective review of 103 episodes of acute bacterial meningitis in adults, seizure activity was an independent predictor of mortality (34% mortality in patients who had seizures compared with 7% without seizures; odds ratio or OR 17.6,  $P < .001$ ) [37]. Decreased level of consciousness on presentation was also predictive of death (26% versus 2%). Coma can be a consequence of fulminant bacterial meningitis with diffuse cerebral edema leading to cerebral herniation. Multiple cerebral infarcts secondary to vasculitis have also been described [38]. Other manifestations of meningitis may provide clues to the causative organism: petechial or purpurial rash in meningococcal meningitis, ataxia and labyrinthitis in *Haemophilus influenzae* meningitis, and cough, weight loss, night sweats, and cranial nerve deficits in tuberculosis meningitis (TBM). Systemic complications have been reported in 22% of patients: septic shock in 12%, pneumonia in 8%, and disseminated intravascular coagulation in 8% [36]. In a multivariate analysis of 696 episodes of adult bacterial meningitis in the Netherlands treated between 1998 and 2002, risk factors for unfavorable outcome were:

- Advanced age
- Presence of osteitis or sinusitis
- Absence of rash
- Low admission Glasgow Coma Score
- Tachycardia
- Positive blood culture
- Elevated erythrocyte sedimentation rate
- Thrombocytopenia
- Low CSF white cell count [32]

### *Encephalitis*

Encephalitis is an acute inflammation of the brain parenchyma, and it is most commonly caused by viruses such as **mumps, herpes simplex virus (HSV), cytomegalovirus (CMV), varicella zoster virus (VZV), enteroviruses, togaviruses (eastern and western equine viruses), and lymphocytic choriomeningitis virus**. Recent developments in the epidemiology of viral encephalitis include the emergence of West Nile virus (WNV) and monkeypox in North America, and Chandipura viruses in the developed world [39]. An increase in encephalitis caused by **CMV, Epstein-Barr virus (EBV) and human herpes virus (HHV)-6** has occurred because of an increase in immunocompromised states, including HIV, organ transplantation, and cancer chemotherapy [40]. Viruses enter the CNS via reactivation of latent virus within the CNS (see herpes simplex encephalitis section) or by viremia, followed by spread across the blood-brain barrier. In addition, transmission of agents of viral encephalitis through blood transfusions and donated organs increasingly are recognized [39]. Other microorganisms that can cause encephalitis include protozoa, such as *Toxoplasma gondii*, and bacteria, such as *Listeria monocytogenes* and *Mycobacterium tuberculosis*. Immune-mediated conditions, such as acute disseminated encephalomyelitis, paraneoplastic limbic encephalitis, and voltage gated potassium channel limbic encephalitis also cause encephalitis [40].

The pathogenesis of encephalitis includes viral cytopathology (viral destruction of cells), a para/post infectious inflammation, or immune-mediated responses [40]. Although neurons are primarily affected, blood vessels may be involved, causing vasculitis, and associated meningitis, myelitis, radiculitis, and demyelination may also be features.

**Encephalitis should be suspected in a febrile patient who presents with altered mental status or other signs of diffuse cerebral dysfunction**. Clinical presentation often includes a prodrome with **fever, headache, myalgia, and mild respiratory infection**. Changes in level of consciousness with focal neurologic deficits may follow. Seizures, both focal and generalized, are a common manifestation of the encephalitides. Specific viruses can have characteristic presentations, such as parotitis associated with **mumps and herpetic rash with herpes simplex encephalitis (HSE)**. Diplopia, dysarthria, and ataxia can be seen in immunocompromised patients with brainstem HSE [41,42].

HSE is the most important form of treatable encephalitis. It has a predilection for the **temporal and orbitofrontal lobes**, and results in a clinical picture of altered consciousness, memory loss, personality change, and confusion or **olfactory hallucinations**, following a prodrome of headache and fever [43]. HSE is a medical emergency, and it is associated with a high mortality rate and numerous sequelae, such as cognitive and behavioral disorders, seizures, and postinfectious encephalomyelitis [44,45]. Most cases of adult HSE are thought to be caused by **reactivation of HSV-1**, either in the trigeminal ganglion or latent virus in the brain itself [46]. HSV-2, which causes genital herpes in adults, causes meningitis, encephalitis, and

lumbo-sacral radiculitis, mostly in neonates and the immunocompromised, accounting for 10% of HSE. Most cases of recurrent meningitis (previously called Mollaret's meningitis) are thought to be caused by HSV-2 [40].

WNV encephalitis, usually affecting persons over age 55, has a 15% mortality rate [47,48]. Neuroinvasive WNV occurs in approximately 1% to 2% of infections [39]. Neurologic features include movement disorders, sometimes with Parkinsonian features, postural tremor, and myoclonus and cerebellar signs [49–51]. In its most severe form, WNV can cause acute flaccid limb paralysis caused by infection of the anterior horn cells of the spinal cord, causing profound weakness akin to poliovirus infection [52]. This manifestation, referred to as poliomyelitis-like illness, affects 10% of cases with neuroinvasive disease and also occurs in other flavivirus encephalitides (Japanese encephalitis virus and St. Louis encephalitis virus) and enteroviruses [50–53]. The mortality in WNV is caused by respiratory failure 50% of the time; morbidity is also high because of long-term limb weakness and functional disability [52]. Other findings associated with WNV are ophthalmologic disease, such as chorioretinitis and vitritis, and rhabdomyolysis [54,55]. Pediatric WNV infection rates are similar to adults and accounted for 12% of all neuroinvasive cases in the United States in 2004 [56]. Manifestations of neuroinvasive WNV in children are similar to adults [57].

#### *Brain abscess*

Brain abscesses are focal, purulent infections of brain parenchyma. They commonly present with site-specific focal neurologic deficits, such as aphasia and weakness. However, a focal examination may be absent, and signs of increased intracranial pressure may be the only presenting feature [58]. Fever is less common than in meningitis. Neck rigidity may be present in 25% of cases and may indicate associated meningitis [33]. Seizures, often generalized tonic-clonic, occur in up to 40% of cases [59].

#### *Cranial epidural abscess*

Cranial epidural abscess is an extra-axial infection occurring in the virtual space between the dura mater and the skull. It usually occurs in the frontal region, and it can present with headache, fever, and nausea. Neurologic symptoms and complications are quite rare, as the dura mater provides protection to the brain parenchyma, and tight adherence of dura to the overlying skull limits the spread. These infections typically occur as a result of trauma and neurosurgery, but other sources, such as meningitis, sinusitis, and other extra-cranial sources have been implicated. The most common infectious etiologies include streptococci, staphylococci, and anaerobes, and infections are often polymicrobial [60,61].

#### *Subdural empyema*

Subdural empyema is an infection that occurs in the potential space between the dura mater and the arachnoid. It is most commonly situated over

the cerebral convexity, and it can cause an altered level of consciousness, focal neurologic deficits, and seizures. Unlike the epidural space, the subdural space is less restrictive, resulting in a wider spread of empyema, which can cause inflammation of the brain parenchyma, edema, mass effect, elevated intracranial pressure (ICP), septic thrombophlebitis, and venous infarction [60,62]. Subdural empyema is associated with a much more complicated course and worse outcome, as compared with epidural abscess. Sources of infection include the para-nasal sinuses, hematogenous spread by means of emissary veins located in the subdural space, and in the postoperative setting extension of an epidural abscess into the subdural space [60,63].

Infratentorial empyema is a rare complication of bacterial meningitis, often presenting as subacute meningitis with neck stiffness and decreased consciousness [64]. It should be considered in patients with recent history of otitis, sinusitis, or mastoiditis (especially after surgery for these conditions), and suspected meningitis and neurologic findings suggesting a posterior fossa lesion. MRI with diffusion-weighted imaging (DWI) is the preferred method of diagnosis, as CT has failed to visualize infratentorial subdural empyemas in several reported cases, leading to delayed diagnosis. DWI can distinguish subdural empyema from reactive subdural effusion [65]. The mortality rate of this condition is high (34%), based on its subdural location, hydrocephalus, and delay in detection. The treatment is antimicrobial therapy and a low threshold for neurosurgical exploration.

### *Ventriculitis*

Ventriculitis is an infection of the ventricular system of the brain. The ventricles can act as a reservoir of infection and inflammation, resulting in blockade of CSF outflow tracts and hydrocephalus [66]. Ventriculitis occurs as a complication of meningitis in 30% of adult cases, and as many as 90% of neonatal cases [62]. It is clinically relevant when inflammation and bacterial load in the ventricles are significantly higher than in the paraspinal space [67]. It often is thought to be a late complication of meningitis, indicated by failure to improve with conventional therapy for meningitis, but it can occur as a primary process [67,68]. In addition, it is frequently associated with the presence of a CSF shunt, external ventricular drainage (EVD), or other intracranial device. The risk of developing a ventriculitis or meningitis with an EVD in place is reported to be as high as 45%, but more commonly it is reported in the 10% to 15% range, and it depends on the type of EVD, insertion technique, management, and length of time the EVD is in place [69–72]. Hemorrhagic CSF is a risk factor for ventriculostomy-related infections, and hemorrhagic CSF likely contributes to the 10% incidence of such infections in aneurysmal subarachnoid hemorrhage patients who have EVDs, and the 13.7% incidence after intraventricular hemorrhage [71–73]. A protocol of meticulous EVD care has been shown to prolong EVD use and minimize infection rates [74]. Protocol violations and CSF leaks were significant risk factors for infection in this study. Infection has been reported



in 8% to 40% of patients receiving a CSF shunt, with most infections occurring within 1 month of implantation [60].

The most common pathogens involved in EVD and CSF shunt infections are gram-positive organisms, such as *Staphylococcus epidermidis* and *Staphylococcus aureus*. As many as 25% of infections, however, are caused by gram-negative organisms, such as *Escherichia coli*, *Klebsiella* species, *Acinetobacter*, and *Pseudomonas* species. These organisms should be suspected in patients with a ventriculoperitoneal shunt, as a result of contamination of the peritoneal end of the catheter [60].

### Cerebrospinal fluid analysis

CSF analysis is the cornerstone of diagnosis and management of CNS infection. The two major issues that may interfere with appropriate and timely CSF analysis (either by lumbar puncture or shunt tap) are concerns about uncal or cerebellar tonsillar herniation and the need to initiate empiric antibiotics emergently. The availability of CT frequently delays starting antimicrobial therapy [75]. In van de Beek and colleague's study [32], CT was performed before lumbar puncture (LP) in 48% of subjects, and in 63% of those presenting with moderate or severely impaired consciousness or neurologic deficits. In two thirds of subjects who had a CT scan, antimicrobial therapy was not started until after CT results were obtained. It has become common practice to perform CT of the head before performing LP in patients with suspected meningitis, owing to a perception that this is a standard of care or because of litigation [76].

In a prospective study of 301 adults with clinically suspected meningitis, Hasbun and colleagues [76] sought to determine whether clinical characteristics could identify subjects who were unlikely to have abnormalities on CT. Of 78% of subjects who underwent CT before LP, 24% had an abnormal finding and 5% had a mass effect. Abnormal findings on CT were associated with the following clinical features at baseline:

- Age greater than 60 years
- Immunocompromised state
- History of a CNS lesion
- History of seizures within 1 week before presentation
- Abnormal level of consciousness
- Inability to answer two consecutive questions correctly or follow two consecutive commands
- Gaze palsy
- Abnormal visual fields
- Facial palsy
- Arm drift
- Leg drift
- Abnormal language

Of the 96 subjects who had none of these findings, only three had abnormal findings on CT, yielding a negative predictive value of 97%. These three subjects underwent LP without subsequent herniation. There was a significant delay from admission to time of lumbar puncture in patients who first underwent CT, and a trend toward greater delay in administering empiric antibiotic therapy in the group undergoing head CT first [76]. These data and other data support a strategy of obtaining a head CT before lumbar puncture only in patients who have clinical features that increase the likelihood of an intracranial mass lesion or elevated intracranial pressure [77]. These include:

Immunosuppression (to rule out *Toxoplasma* encephalitis or lymphoma)  
Significant alteration in mentation or comatose patient  
Focal neurologic deficits  
Seizures  
Papilledema, poorly reactive pupils, or ocular palsies  
Bradycardia or irregular respirations  
Sedation or muscle paralysis [78]

Even without abnormalities on CT, clinical signs suggestive of increased ICP should caution against use of LP, or suggest use of a 22- or 25-gauge needle to remove the smallest amount of CSF possible and minimize leakage of CSF [77]. In a review of lumbar puncture and brain herniation in acute bacterial meningitis, the incidence of cerebral edema with brain herniation was 5%, accounting for approximately 30% of the mortality [79]. In many reports, the LP was temporally strongly related with the herniation event and most likely causative, although herniation may be a gradual process owing to ongoing CSF leakage from the LP site or cerebral vascular engorgement. The best predictors of when to delay the LP because of risk of herniation were clinical signs of "impending" herniation rather than findings on CT. Aggressive treatment of herniation was noted to produce good outcomes in many cases. Therefore, patients identified as high risk should have blood drawn for culture and empiric antibiotic therapy initiated before undergoing CT. Delaying appropriate antibiotic treatment by even a few hours has been associated with worse outcomes in patients with bacterial meningitis [80]; the diagnostic sensitivity of the CSF should not be diminished by delaying the LP by 1 or 2 hours after initiating antibiotic therapy [81]. CSF counterimmunoelectrophoresis, CSF latex agglutination, and coagulation tests can detect common bacterial antigens in 70% to 100% of patients.

CSF findings in various CNS infections are presented in Table 1. In bacterial meningitis, CSF Gram's stain will indicate organisms in 60% to 90% of cases and positive cultures in 80% of cases [33]. Ninety percent of patients will have a CSF cell count greater than 100 white blood cell count (WBC)/mm<sup>3</sup>, and about 60% have cell counts greater than 1,000 WBC/mm<sup>3</sup> [23].

Table 1  
 Cerebrospinal fluid findings in CNS Infections

CNS infection	Cell count (cells/mm <sup>3</sup> )	Glucose	Protein
Bacterial meningitis	Elevated (100–5,000) PMNs predominate	Decreased	Elevated
Viral meningitis	Elevated (10–500) Lymphocytes predominate	Normal	Elevated
Fungal meningitis	Normal to elevated (0–500) Lymphocytes predominate	Normal to decreased	Elevated
Tuberculous meningitis	Normal to elevated (0–1,000) Lymphocytes predominate	Decreased	Elevated
Brain abscess	Normal to elevated (0–500) Mixed differential	Normal	Elevated
Ventriculitis	Elevated (100–5,000) <sup>a</sup> PMNs predominate	Decreased	Elevated

*Abbreviation:* PMNs, polymorphonuclear leukocytes.

<sup>a</sup> In postneurosurgical patients, or patients with a ventriculostomy, the CSF cell count may be elevated as a result of surgical manipulation and inflammation. Reduction in CSF glucose may be a more sensitive indicator of infection.

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CSF glucose levels are less than 40 mg/dL in 50% to 60% of patients; using a CSF to serum glucose ratio of no more than 0.4 is 80% sensitive and 98% specific in children older than 2 months of age [82]. CSF glucose also may be reduced in fungal, tuberculous, or carcinomatous meningitis. Partial antibiotic treatment may alter the CSF characteristics. The CSF protein level is the most resistant to rapid change, with treatment remaining elevated for 10 days or more [83]. The CSF findings in the case of subdural empyema and epidural abscess (if an LP is performed) typically consist of a polymorphonuclear pleocytosis (10 WBC/mm<sup>3</sup>–500 WBC/mm<sup>3</sup>), normal glucose, increased protein, and often negative Gram's stain and culture [59]. Blood cultures in the presence of meningitis are positive in up to 50% of cases, and a touch preparation of the rash in meningococcal meningitis yields a positive Gram's stain in 70% of cases [60]. Hyponatremia caused by syndrome of inappropriate antidiuretic hormone (SIADH) is common in both meningitis and encephalitis.

Measurement of CSF lactate concentrations is not recommended for suspected community-acquired bacterial meningitis because it is generally nonspecific and provides little additional diagnostic information [82]. In postoperative neurosurgical patients, however, a CSF lactate concentration cut-off of 4 mmol/L was found to be superior to the CSF to serum glucose ratio for diagnosis of bacterial meningitis [84]. The sensitivity was 88% and specificity was 98%. The positive predictive value was 96%; negative predictive value was 94%.

Latex agglutination tests for bacterial antigens are positive in 50% to 100% of cases, depending on the organism. Routine use has been questioned,

however, because bacterial antigen testing does not appear to modify the decision to administer antimicrobials. Additionally, false-positive results have been reported [82]. Hence, they are not recommended for managing bacterial meningitis, but they may be useful for patients pretreated with antibiotics with negative Gram's stain and CSF cultures [82]. Bacterial DNA detection by polymerase chain reaction (PCR) for common meningeal pathogens is available and undergoing further refinements [82]. Broad-range real-time PCR and DNA sequencing for diagnosis of bacterial meningitis allows detection of virtually all pathogenic bacteria and has been shown to have a sensitivity of 86% to 100% and specificity of 98% when compared with culture [85,86].

Laboratory diagnosis of TBM remains challenging for several reasons: less than half of patients have chest X-ray evidence of past or present tuberculosis (TB), only half have a positive tuberculin skin test, and there are many exceptions to the typical CSF profile of a lymphocytic predominant pleocytosis with raised protein and low glucose, especially in HIV-positive patients [87–89]. The acid-fast stain for TB has sensitivity as low as 30%, although repeat CSF sampling and meticulous examination can improve sensitivity to 80% [60]. Finally, culture, the gold standard, is only positive in 40% to 70% of cases and, even with fully automated liquid culture systems, takes from 1 to 3 weeks to a positive result. Several mycobacterial antigen and antibody kits have been designed to improve diagnosis of TBM [87,90], but lack adequate sensitivity and specificity to gain wide acceptance [91]. One biochemical marker elevated in TBM is CSF adenosine deaminase activity (ADA) [92]. For developing countries, which may lack well equipped laboratories, the CSF ADA activity at a cut-off value of 6.97 IU/L has a reported sensitivity and specificity of 85% and 88%, respectively, for distinguishing tubercular from nontubercular or nonmeningitis cases [92]. Specificity is a problem, however, as CSF ADA levels are also elevated in conditions such as lymphoma and sarcoidosis. Molecular diagnosis with commercial nucleic acid amplification tests for diagnosis of TBM have a sensitivity of 60% to 83% and specificity of 98% to 100% [91,93]. Real-time PCR is the fastest system and has greater sensitivity than conventional PCR, but still cannot be used reliably to rule out TBM [94]. Because of their high specificity, however, nucleic acid amplification tests, if available should be the first-line test to rule in TBM [94]. Radioimmunoassay detection of interferon-gamma release measures a major mediator of the immune response in TB, affecting macrophage stimulation and lymphocyte Th1 transformation [95]. Interferon- $\gamma$  assays in CSF were compared with PCR for diagnosis of TBM and had a higher sensitivity (70% versus 65%) with a specificity of 94% [96]. Combination of PCR and interferon- $\gamma$  improved sensitivity to 80% and the incremental value of test combinations such as these shows promise, although further prospective studies should be performed. Currently, careful bacteriology is as good as or better than molecular methods, although the latter are sensitive for longer when anti-TB drugs have been started [92,97].

TB

Several acute-phase reactants have been examined for their usefulness in diagnosing acute bacterial meningitis, including C-reactive protein (CRP) and serum procalcitonin (PCT). CRP measurement may be useful in patients who have CSF findings consistent with meningitis, but negative Gram's stain where the clinician may consider withholding antimicrobial therapy based on the high negative predictive value of a normal CRP in bacterial meningitis (99%) compared with viral meningitis in children (class II-B evidence) [82,98]. Elevated PCT concentrations have been shown to be useful in differentiating between bacterial and viral meningitis in children (cut-off  $>5$   $\mu\text{g/L}$ ; sensitivity 94%; specificity 100%) and adults (cut-off  $>0.2$   $\text{ng/mL}$ ; sensitivity and specificity up to 100%) [99–101]. PCT levels were studied in 50 adults with community-acquired acute bacterial meningitis and no other infection or prior antibiotics [102]. Of 48 patients with a serum PCT level on admission above 0.5  $\text{ng/mL}$ , median serum PCT levels on admission and on day 2 were 4.5 and 2  $\text{mg/mL}$ , respectively ( $P < .0001$ ), compared with median CRP levels of 120 and 156, respectively. Serum PCT levels decreased rapidly (within 24 hours) with appropriate antibiotic treatment, suggesting this test may be valuable in assessing the efficacy of antibiotic therapy and potentially replacing repeat lumbar puncture at 48 to 72 hours [102]. Alternatively, in patients with ventriculitis and a ventricular catheter, PCT levels usually remain within the normal range, even with positive bacterial cultures. Thus, levels do not assist with diagnosis as they do when differentiating between viral and bacterial meningitis [103,104].

Nosocomial ventricular drainage-related infections are often difficult to diagnose because of lower diagnostic value of CSF values, less specific clinical signs of infection, and slow-growing and fastidious microorganisms delaying identification of pathogens and appropriate treatment [105]. Deutch and colleagues [105] applied broad-range real-time polymerase chain reaction (RT-PCR) to CSF samples from 86 patients with in-hospital CSF diversion. Of 16 infected patients with positive CSF by either RT-PCR or CSF culture, five were positive by only cultures and four by only PCR. This evolving diagnostic tool, although not ready for routine clinical use, shows promise as a complement to culture techniques, allowing faster results (about 4 hours) with probable increased sensitivity over cultures after antibiotic treatment and ability to detect bacteria, especially gram-negatives that are difficult to isolate. PCR may be a useful supplement for influencing decisions to initiate or discontinue antibiotics, particularly in previously treated patients [85]. Disadvantages of PCR include inability to identify antibiotic sensitivities, false negative results, and contamination issues.

Early detection of ventriculostomy-related infection in patients with intraventricular hemorrhage (IVH) has been investigated using the ratio of leukocytes to erythrocytes in CSF divided by leukocytes to erythrocytes in peripheral blood (called the cell index) [106]. At the time of IVH onset, the CSF relationship of leukocytes to erythrocytes should be equal to that in peripheral blood; the cell index should be 1. In 6 out of 13 patients

with IVH requiring EVD who did not develop ventriculitis, the cell index fluctuated around 1 over the next 7 days. In seven patients with definitive ventriculitis, the cell index showed a significant rise 3 days before the conventional diagnosis of catheter-related ventriculitis. Antimicrobial therapy led to a rapid decrease of both the cell index and usual infection parameters [106].

Patients who have CNS viral infection may demonstrate normal-to-mild elevation of ICP, CSF lymphocytosis (neutrophils if tested early), WBC counts of  $50/\text{mm}^3$  to  $2,000/\text{mm}^3$ , normal glucose, and elevated protein [59]. HSV-1 encephalitis is typically associated with hemorrhagic CSF and markedly elevated CSF red cell count. CSF culture and serologic testing of acute and convalescent serum may be beneficial. For HSE, PCR in CSF has a sensitivity and specificity of 98% and 94%, respectively. One third of cases remain PCR-positive long after starting acyclovir treatment [107]. Because of the possibility of false negative PCR for HSV with early testing, LP should be repeated at 24-48 hours and treatment continued for 10 days, even if PCR remains negative if features are consistent with HSE [108,109]. PCR has good specificity for CMV (95%) and *Toxoplasma* (100%), but lower sensitivity (79% and 42%, respectively) [59]. In patients with suspected enteroviral meningitis, enteroviral RT-PCR has been found to be more sensitive than viral culture for detecting enteroviruses (sensitivity 86% to 100%; specificity 92% to 100%) [110]. The diagnosis of most important viruses, as well as *Mycoplasma pneumoniae* can be determined by detection of IgM (and IgG) antibodies in CSF (and relative to serum) by an enzyme-linked immunosorbent assay. Oligoclonal bands may be useful to distinguish inflammatory from noninflammatory causes of encephalopathy. Anti-HSV-1 antibody in CSF can be detected at 10 days, with 50% sensitivity if a retrospective diagnosis is considered useful [40].

Immunocompetent patients should be initially tested with PCR for HSV, VZV (both potentially treatable with antiviral therapy), and enterovirus [40]. For immunocompromised patients, EBV and CMV PCR should be added and HHV-6 and HHV-7 considered. Other PCRs to send depend on clinical indication. Quantitative PCR (comparing virus in CSF with that in blood) may be required to determine the significance of a positive PCR assay, especially in HIV patients who may carry infected lymphocytes without representing pathogenic infection.

Findings in viral CNS infection on peripheral blood count are leukocytosis or leucopenia, atypical lymphocytes (EBV), or eosinophilia (eosinophilic encephalitis) [40]. Serum amylase may be elevated in mumps; cold agglutinins occur in mycoplasma, prompting serologic investigations for mycoplasma and Chlamydia; infiltrates on chest X-ray in atypical pneumonia should be followed by investigation for mycoplasma, legionella or lymphocytic choriomeningitis virus. HIV testing has been recommended for uncertain causes of CNS infection [40].

In severely immunosuppressed patients with fungal meningitis, CSF may appear normal, while opening pressure may be high. In cryptococcal meningitis in patients who have HIV, a predominantly lymphocytic pleocytosis with low CSF glucose and high protein levels is common [34]. The encapsulated fungus can be identified by India ink examination of CSF, and serologic detection of cryptococcal antigen is sensitive and relatively specific for CNS cryptococcal infection.

In patients who improve with antimicrobial therapy, repeat LP and CSF analysis to document CSF sterilization is not indicated routinely [82]. Patients who have not responded clinically after 48 hours of appropriate antimicrobial therapy, especially those who have penicillin- or cephalosporin-resistant pneumococcal meningitis, and those who are on adjunctive dexamethasone therapy, should undergo repeat CSF analysis [82,111].

### Neuroimaging of central nervous system infections

In uncomplicated bacterial meningitis, CT scans are usually sufficient for clinical management to exclude cerebral edema, hydrocephalus, and base of skull pathology (eg, fractures, inner ear infection, or mastoiditis). Other findings include subdural effusions, brain stem encephalitis (rhombencephalitis) with *Listeria* infection, and cortical infarcts secondary to vasculitis in up to 20% of cases [112]. CT or MR venography should be considered to diagnose complicating cerebral venous sinus thrombosis.

MR DWI shows parenchymal complications of meningitis, such as infarcts of septic vasculitis earlier than other sequences. Encephalitis, cerebritis, and TB are DWI-hyperintense; neurocysticercosis lesions are DWI-hypointense. Toxoplasmosis is variable, whereas lymphoma shows no restriction of water diffusion [112]. MR angiography can suggest vasculitis. Ventriculitis is detected best by T2 fluid-attenuated inversion recovery (FLAIR) images showing periventricular hyperintensity on ependymal enhancement and irregular intraventricular debris [112].

In TBM, basal enhancement, hydrocephalus, tuberculoma, and infarction are all more common than in pyogenic meningitis, in which subdural collections are more common [113]. Based on a CT study of 94 children with TBM, Kumar and colleagues [113] found that basal meningeal enhancement or tuberculoma was 89% sensitive and 100% specific for diagnosis of TB. Precontrast hyperdensity in the basal cisterns on cranial MRI may be the most specific radiologic sign of TBM in children [114]. In Lyme disease, multifocal nonenhancing patchy lesions on T2 weighted images can be seen [112].

In cases of acute HSV encephalitis, FLAIR or T2-weighted sequences showing asymmetrical changes of necrotizing encephalitis in the first 48 hours may be diagnostic. Diffusion abnormalities disappear within 14 days after symptom onset, while T2 hyperintensities persist [112]. Single photon emission CT may indicate hyperperfusion suggestive of

inflammation and neuronal injury in the temporal and frontal lobes relatively early, although half of scans are normal in the acute stage, and hyperperfusion is a nonspecific finding [59].

Pyogenic abscesses are hyperintense on DWI with reduced apparent diffusion coefficient in contrast to nonpyogenic lesions, which are generally hypointense or mixed-signal. Proton MR spectroscopy showing lactate, cytosolic amino acids, and absence of choline suggests abscess [112]. Extra-axial bacterial empyemas appear slightly hyperintense relative to CSF and hypointense to white matter on T1-weighted imagery and hyperintense on T2-weighted imagery, distinguishing them from sterile effusions and chronic hematomas [112]. Epidural hematomas can be distinguished from subdural empyema by a hypointense rim representing displaced dura. On DWI, subdural empyema is usually hyperintense, whereas epidural hematoma usually has a low or mixed-signal intensity [112].

## Antimicrobial therapy

### *Distribution of drug into the central nervous system*

Antimicrobial distribution into the CNS is influenced by both physical barriers, as well as inherent physiochemical properties of the antimicrobial itself. The major physiochemical factors governing antimicrobial penetration of the CNS are listed in Table 2. Because only the unbound concentration of drug is available for diffusion across the BBB and blood-CSF barrier, highly protein-bound agents have limited ability to penetrate the CNS [115]. The tight junctions within the BBB and blood-CSF barrier limit diffusion of large molecular weight substances (> 500 d). Anti-infectives with larger molecular weights (eg, vancomycin or amphotericin B) have limited ability to penetrate an intact barrier [25,115].

Other factors being held constant, more lipophilic agents (as characterized by a high octanol-to-water partition coefficient) will penetrate the CNS more readily than hydrophilic compounds. Lipophilicity can also

Table 2

#### Physiochemical properties influencing antimicrobial penetration into the CNS

Physiochemical property	Effect on CNS penetration
Lipophilicity	Highly lipophilic drugs more readily penetrate the CNS.
Protein binding	Highly protein bound drugs have reduced CNS penetration.
Molecular weight	Substances > 500–800 Daltons have reduced ability to penetrate the BBB.
Ionization	Polar, ionized compounds are less likely to cross the BBB. Polarity can vary for many drugs with changes in physiologic pH.
Active transport	Specialized active transport cells in the choroid plexus may excrete drugs across the vessel wall.

Data from Refs. [25,26,115].



affect the distribution of drugs within the CNS. Highly lipophilic agents accumulate in the lipid-rich brain structures, with a resultant lower concentration in the CSF and extracellular fluid and potential underestimation of overall CNS penetration when CSF levels are measured [115]. The degree of ionization at physiologic pH also may have an effect on penetration of the BBB. Most drugs are weak acids or weak bases, and as such, polarity can vary depending on the pH. The pH of blood, CSF, and extracellular fluid can change with infection, and this in turn can influence the polarity and, hence, anti-infective penetration of the CNS [115].

The choroid plexus contains specialized active transcellular transport systems involved in the excretion of drugs across the cerebral vessel wall [25]. During active CNS infection, impaired CSF excretion systems may result in higher CSF concentrations of antibiotics. As inflammation diminishes, antibiotic concentrations can decrease accordingly [26].

#### *Timing and appropriateness of initial antimicrobial therapy*

Delayed or inappropriate initial antibiotic therapy has been associated with increased mortality or morbidity for numerous infectious diseases, including community-acquired pneumonia [116], ventilator-associated pneumonia [117], and sepsis [118,119]. A similar observation was noted for infections of the CNS in a retrospective cohort study of 269 subjects with bacterial meningitis and risk factors for adverse outcomes (worsening mental status, hypotension, or seizures), which suggested that early antibiotic therapy can prevent early clinical deterioration and is associated with a reduction in mortality or adverse neurologic sequelae [80].

More recently, two observational studies have confirmed this association. A prospective multicenter observational study of 156 adults hospitalized for pneumococcal meningitis found three factors independently associated with 3-month mortality: simplified acute physiology score II, isolation of a non-susceptible strain, and an interval of greater than 3 hours between hospital admission and administration of antibiotics [120]. In addition, a retrospective cohort of 286 adults with bacterial meningitis assessed the impact of antibiotic timing in relation to the onset of first symptoms, the onset of consciousness disturbance, and the time of admission. In the 125 (43.7%) adults with an unfavorable outcome (Glasgow Outcomes Score or GOS at time of discharge of  $\leq 4$ ), the start of antibiotics was significantly delayed in relation to symptom onset ( $P = .018$ ) and onset of consciousness disturbance ( $P < .001$ ) as compared with those with a favorable outcome (GOS = 5 at discharge). In addition, logistic regression of the subgroup with culture-positive meningitis, revealed that a delay in appropriate antibiotics ( $> 24$  hours after onset of consciousness disturbance) was the most important predictor of an unfavorable outcome (OR = 11.19, 95% confidence interval or CI 4.37–32.57,  $P < .001$ ) [121]. Practice guidelines for the management of bacterial meningitis recommend that patients with purulent

meningitis receive the first dose of antibiotics as soon as possible, and that antibiotic administration **not be delayed for an LP** [82].

The appropriate selection of initial antibiotics is also crucial. In a retrospective review of 109 subjects with community-acquired meningitis, 22 subjects did not receive appropriate initial antibiotic coverage, of whom 100% died, as compared with 23% of patients receiving appropriate therapy ( $P < .001$ ) [122].

### *Antimicrobial selection and dosing*

#### *Meningitis*

Empiric therapy of meningitis must consider the most likely organisms involved, which in turn depend on patient age, immune status, and whether the infection is acquired in the community or nosocomial setting. Recommendations for empiric therapy of meningitis based on patient-specific factors are listed in Table 3. Organism-specific recommendations are provided in Table 4.

***Haemophilus influenzae* accounted for nearly 50%** of bacterial meningitis cases (most being in children) in the United States before the availability and widespread use of the *H. influenzae* type B vaccine [1,123]. Now, *H. influenzae* causes only a small percentage of cases, with the median age of patients with bacterial meningitis shifting from 15 months to 25 years [124]. A 1995 survey performed after the institution of the vaccine indicated that most cases (47%) of **community-acquired bacterial meningitis were caused by *Streptococcus pneumoniae***, followed by *Neisseria meningitidis* (25%), Group B streptococcus (13%), *Listeria monocytogenes* (8%), and *H. influenzae* (7%) [124]. More recent reports point to the growing importance of traditionally nosocomial gram-negative organisms (eg, ***Klebsiella* species, *Serratia* species, *Pseudomonas* species, and *Acinetobacter* species**) [125]. Such trends reflect a shift in the epidemiology of meningitis from a disease of the young and otherwise healthy to a disease of the elderly and immunocompromised. The **immunocompromised are susceptible to meningitis caused by *Listeria monocytogenes* and gram-negative bacilli**, such as those listed previously, in addition to commonly encountered organisms, such as *S. pneumoniae*.

Empiric therapy of meningitis occurring in the setting of neurosurgery, head trauma and CSF leak, and cerebrospinal shunts warrants special consideration. **The most common organisms are *S. aureus* and gram-negative bacilli. Effective source control is critical, which often necessitates surgical removal of foreign materials.** In patients with CSF shunts who are shunt-dependent, removal of the shunt often necessitates placement of a temporary EVD.

For TBM, the Infectious Diseases Society of America and American Thoracic Society recommend a similar regimen as for pulmonary **TB** [126]. This involves an intensive 2-month phase with four drugs (**isoniazid,**

rifampin, pyrazinamide, and ethambutol) followed by a continuation phase for 6 to 9 months.

#### *Ventriculitis and cerebrospinal fluid shunt infections*

Ventriculitis and EVD and CSF shunt infections frequently involve gram-positive organisms, such as *S. epidermidis* and *S. aureus* (including methicillin-resistant *S. aureus* or MRSA). Up to 25% or more of these infections, however, are secondary to gram-negative organisms, such as *E. coli*, *Klebsiella*, *Acinetobacter*, and *Pseudomonas* species. The enteric gram-negative bacilli should be of particular concern in patients who have a ventriculoperitoneal shunt, given the risk of contamination of the peritoneal end of the catheter [60,69].

Initial antibiotic selection should be broad and include coverage for resistant gram-positive organisms (such as MRSA) and resistant gram-negative organisms (such as *Pseudomonas* and *Acinetobacter* species). Vancomycin combined with a cephalosporin with antipseudomonal activity (eg, cefepime or ceftazidime) or vancomycin plus meropenem is recommended. In addition to antimicrobial therapy, any infected hardware should be removed, replaced, or externalized when appropriate.

The presence of inflammation in the setting of bacterial meningitis enhances the ability of a given antimicrobial to penetrate the BBB; however, meningeal inflammation may be less pronounced in ventriculitis [127]. In addition, the ventricles can act as a persistent reservoir of infection and inflammation, resulting in extreme difficulty in eradicating infection and potential blockade of CSF outflow tracts [66]. These characteristics illustrate the challenges of treating ventriculitis and why treatment failures are common. Intraventricular and intrathecal administration of antibiotics may be necessary in some circumstances in an effort to overcome these difficulties [128,129].

#### **Abscess: *S. milleri*, *S. aureus*, *Bacteroides*, *Enterobacteriaceae***

##### *Brain abscess*

The type of pathogen associated with brain abscess varies depending on patient-specific risk factors. Immunocompromised patients and patients undergoing recent neurosurgery or head trauma (especially penetrating brain injury) are at higher risk [130,131]. Brain abscesses are often polymicrobial in nature (up to 60% of cases), with anaerobic bacteria implicated in up to 49% of cases [132,133]. Organisms frequently isolated include *Streptococcus milleri*, *Bacteroides* species, *Enterobacteriaceae*, and *S. aureus*. In addition, immunocompromised individuals are at risk for brain abscess from fungi, *Nocardia*, and *Toxoplasma*. **Immunosupp: *Nocardia*, Toxo, Fungi**

As with other deep-seated infections, optimal treatment involves a combination of antibiotics and surgical intervention to obtain source control. Surgical approaches include stereotactic aspiration or excision of the abscess. Stereotactic aspiration may be preferred if the abscess develops in eloquent areas of the brain unsuitable for excision (eg, brainstem or diencephalic

Table 3  
Recommendations for empiric antimicrobial therapy for bacterial meningitis in adults

Patient-specific factor	Common pathogens	Preferred regimen	Alternative regimens
18–50 years	<i>S. pneumoniae</i> , <i>N. meningitides</i> , <i>H. influenzae</i> (non-immunized patients)	Ceftriaxone <sup>a</sup> 2 g IV q 12 hrs or Cefotaxime <sup>b</sup> 2 g IV q 6 hrs	Meropenem <sup>1</sup> <sup>b</sup> 2 g IV q 8 hrs or Chloramphenicol <sup>c,d</sup> 50 mg/kg–100 mg/kg per day in 4 divided doses or Moxifloxacin <sup>c</sup> 400 mg IV daily
		plus Vancomycin <sup>b,c</sup> 15mg/kg IV q 8–12 hrs	plus Vancomycin <sup>b,c</sup> 15 mg/kg IV q 8–12 hrs
> 50 years	<i>S. pneumoniae</i> , <i>N. meningitides</i> , <i>L. monocytogenes</i> , gram-negative bacilli	Ampicillin <sup>b</sup> 2 g IV q 4 hrs	Ampicillin <sup>b</sup> 2 g IV q 4 hrs or Trimethoprim/Sulfamethoxazole <sup>a</sup> (TMP) 5 mg/kg IV q 6 hrs
		plus Vancomycin <sup>b,c</sup> 15 mg/kg IV q 8–12 hrs	plus Vancomycin <sup>b,c</sup> 15 mg/kg IV q 8–12 hrs
		plus Ceftriaxone <sup>a</sup> 2 g IV q 12 hrs or Cefotaxime <sup>b</sup> 2 g IV q 6 hrs	plus Meropenem <sup>b</sup> 2 g IV q 8 hrs or Moxifloxacin <sup>c</sup> 400 mg IV daily

Impaired immunity	<i>L. monocytogenes</i> , gram-negative bacilli, <i>S. pneumoniae</i> , <i>N. meningitides</i>	Ampicillin <sup>b</sup> 2 g IV q 4 hrs	Ampicillin <sup>b</sup> 2 g IV q 4 hrs or TMP <sup>b</sup> 5 mg/kg IV q 6 hrs
		plus Vancomycin <sup>b,c</sup> 15 mg/kg IV q 8–12 hrs	plus Vancomycin <sup>b,c</sup> 15 mg/kg IV q 8–12 hrs
		Ceftazidime <sup>b</sup> 2 g IV q 8 hrs or Cefepime <sup>b</sup> 2 g IV q 8 hrs	plus Meropenem <sup>b</sup> 2 g IV q 8 hrs or Ciprofloxacin <sup>b</sup> 400 mg IV q 8 hrs
Neurosurgery, head trauma, CSF shunt	Staphylococci, gram-negative bacilli, <i>S. pneumoniae</i>	Vancomycin <sup>b,c</sup> 15 mg/kg IV q 8–12 hrs	Vancomycin <sup>b,c</sup> 15 mg/kg IV q 8–12 hrs
		plus Cefepime <sup>b</sup> 2 g IV q 8 hrs or Ceftazidime <sup>b</sup> 2 g IV q 8 hrs	plus Meropenem <sup>b</sup> 2 g IV q 8 hrs or Ciprofloxacin <sup>b</sup> 400 mg IV q 8 hrs

*Abbreviations:* IV, intravenously; q, every.

<sup>a</sup> Dose adjustments may be indicated in patients with combined hepatic and renal insufficiency.

<sup>b</sup> Dose adjust for renal insufficiency.

<sup>c</sup> Caution in patients with hepatic insufficiency, dose adjustment may be required.

<sup>d</sup> Monitor for bone marrow suppression, including leukopenia, thrombocytopenia, and aplastic anemia.

<sup>e</sup> Monitoring of serum drug levels is recommended to optimize dosing.

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Table 4  
Pathogen-specific recommendations for antimicrobial therapy for bacterial meningitis in adults

Organism	Preferred regimen	Alternative regimen	Duration
<i>S. pneumoniae</i> (PCN MIC < 0.1)	Penicillin G <sup>a</sup> 4 million units IV q 4 hrs or Ceftriaxone <sup>e</sup> 2 g IV q 12 hrs  or Cefotaxime <sup>a</sup> 2 g IV q 6 hrs	Meropenem <sup>a</sup> 2 g IV q 8 hrs or Chloramphenicol <sup>e,d</sup> 50 mg/kg–100 mg/kg per day in 4 divided doses  or Moxifloxacin <sup>c</sup> 400 mg IV daily	10–14 days
<i>S. pneumoniae</i> (PCN MIC ≥ 0.1) (CTX MIC ≤ 0.5)	Ceftriaxone <sup>e</sup> 2 g IV q 12 hrs  or Cefotaxime <sup>a</sup> 2 g IV q 6 hrs	Meropenem <sup>a</sup> 2 g IV q 8 hrs or Moxifloxacin <sup>c</sup> 400 mg IV daily or Vancomycin <sup>a,b</sup> 15 mg/kg IV q 8–12 hrs	10–14 days
<i>S. pneumoniae</i> (PCN MIC ≥ 0.1) (CTX MIC > 0.5)	Vancomycin <sup>a,b</sup> 15 mg/kg IV q 8–12 hrs plus Ceftriaxone <sup>e</sup> 2 g IV q 12 hrs or Cefotaxime <sup>a</sup> 2 g IV q 6 hrs	Vancomycin <sup>a,b</sup> 15 mg/kg IV q 8–12 hrs plus Rifampin <sup>c</sup> 900 mg–1,200 mg IV/PO daily in 2–3 divided doses	10–14 days
<i>N. meningitidis</i>	Penicillin G <sup>a</sup> 4 million units IV q 4 hrs	Ampicillin <sup>a</sup> 2 g IV q 4 hrs or Ceftriaxone <sup>e</sup> 2 g IV q 12 hrs or Cefotaxime <sup>a</sup> 2 g IV q 6 hrs or Chloramphenicol <sup>e,d</sup> 50 mg/kg–100 mg/kg per day in 4 divided doses	7–10 days
<i>H. influenzae</i>	Ceftriaxone <sup>e</sup> 2 g IV q 12 hrs or Cefotaxime <sup>a</sup> 2 g IV q 6 hrs	Chloramphenicol <sup>e,d</sup> 50 mg/kg –100 mg/kg per day in 4 divided doses	7–10 days

<i>L. monocytogenes</i>	Ampicillin <sup>a</sup> 2 g IV q 4 hrs plus Gentamicin <sup>a,b,f</sup> 3 mg/kg–5 mg/kg per day IV in 3 divided doses	TMP <sup>a</sup> 5 mg/kg IV q 6 hrs	21 days
Group B streptococcus	Penicillin G <sup>a</sup> 4 million units IV q 4 hrs  or Ampicillin <sup>a</sup> 2 g IV q 4 hrs	Vancomycin <sup>a,b</sup> 15 mg/kg IV q 8–12 hrs or Ceftriaxone <sup>c</sup> 2 g IV q 12 hrs or Cefotaxime <sup>a</sup> 2 g IV q 6 hrs	14–21 days
<i>Enterobacteriaceae, Klebsiella</i> species	Ceftriaxone <sup>c</sup> 2 g IV q 12 hrs or Cefotaxime <sup>a</sup> 2 g IV q 6 hrs +/- Gentamicin <sup>a,b,f</sup> 3 mg/kg–5 mg/kg per day IV in 3 divided doses or Ciprofloxacin <sup>a</sup> 400 mg IV q 8 hrs	Meropenem <sup>a</sup> 2 g IV q 8 hrs   +/- Gentamicin <sup>a,b,f</sup> 3 mg/kg–5 mg/kg per day IV in 3 divided doses or Ciprofloxacin <sup>a</sup> 400mg IV q 8 hrs	14–21 days
<i>P. aeruginosa, Acinetobacter</i> species	Cefepime <sup>a</sup> 2 g IV q 8 hrs or Ceftazidime <sup>a</sup> 2 g IV q 8 hrs +/- Gentamicin <sup>a,b,f</sup> 3 mg/kg–5 mg/kg per day IV in 3 divided doses or Ciprofloxacin <sup>a</sup> 400 mg IV q 8 hrs	Meropenem <sup>a</sup> 2 g IV q 8 hrs   +/- Gentamicin <sup>a,b,f</sup> 3 mg/kg–5 mg/kg per day IV in 3 divided doses or Ciprofloxacin <sup>a</sup> 400 mg IV q 8 hrs	14–21 days
<i>S. aureus, S. epidermidis</i> (methicillin sensitive)	Nafcillin <sup>c</sup> 2 g IV q 4 hrs or Oxacillin <sup>c</sup> 2 g IV q 4 hrs	Vancomycin <sup>a,b</sup> 15 mg/kg IV q 8–12 hrs +/- Rifampin <sup>c</sup> 900 mg–1,200 mg IV/PO daily in 2–3 divided doses	14–21 days

(continued on next page)

Table 4 (continued)

Organism	Preferred regimen	Alternative regimen	Duration
<i>S. aureus</i> , <i>S. epidermidis</i> (methicillin resistant)	Vancomycin <sup>a,b</sup> 15 mg/kg IV q 8–12 hrs +/- Rifampin <sup>c</sup> 900 mg–1,200 mg IV/PO daily in 2–3 divided doses	Linezolid 600 mg IV/PO q 12 hrs	14–21 days

*Abbreviations:* CTX, cefotaxime; MIC, minimum inhibitory concentration; PCN, penicillin; PO, by mouth.

<sup>a</sup> Dose adjust for renal insufficiency.

<sup>b</sup> Monitoring of serum drug levels is recommended to optimize dosing.

<sup>c</sup> Caution in patients with hepatic insufficiency, dose adjustment may be required.

<sup>d</sup> Monitor for bone marrow suppression, including leukopenia, thrombocytopenia, and aplastic anemia.

<sup>e</sup> Dose adjustments may be indicated in patients with combined hepatic and renal insufficiency.

<sup>f</sup> Once daily dosing of gentamicin has been evaluated in an animal model suggesting superior CNS penetration versus conventional dosing.

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structures) [134]. Given the polymicrobial nature of brain abscess, broad-spectrum empiric therapy is indicated, the choice of which depends largely on risk factors for selected organisms (ie, history, immune status, primary infection site). In patients who are **not immune-suppressed, initial coverage with vancomycin, ceftriaxone (or cefotaxime), and metronidazole is recommended [131]**. Antibiotics should be tailored to the causative organism when microbiologic data become available. Given the frequent implication of anaerobic bacteria, however, metronidazole often is continued, even if an anaerobic source is not identified on culture. This is because of the fastidious nature of anaerobic bacteria resulting in a low yield when cultured.

Patients who have had **recent neurosurgery** or head trauma with a presumed nosocomial source of infection should be treated with a third- or **fourth-generation cephalosporin with antipseudomonal activity (ceftazidime or cefepime), along with vancomycin (to cover MRSA or methicillin-resistant *S. epidermidis*) and metronidazole**. In patients who have **HIV, consideration should be given to empiric therapy to cover *Toxoplasma* with sulfadiazine and pyrimethamine (along with folinic acid)**. Addition of **amphotericin B** should be considered in neutropenic and posttransplant patients to cover fungal sources, such as ***Aspergillus*, *Cryptococcus*, and *Mucoraceae***. If ***Nocardia* is suspected, trimethoprim/sulfamethoxazole should be added to the empiric regimen [131,135]**. In most cases of brain abscess, treatment is continued for 6 to 8 weeks, depending on the clinical and radiographic response.

### *Epidural abscess*

Empiric treatment of cranial epidural abscess consists of broad-spectrum antibiotics, usually in combination with **surgical drainage to prevent progression to subdural empyema. The most common etiologies include streptococci, staphylococci, and anaerobes**. Infections are often polymicrobial [60,61]. Initial treatment with **vancomycin, ceftriaxone (or cefotaxime), and metronidazole** is appropriate in most cases. Substitution of ceftriaxone with ceftazidime, cefepime, or meropenem is suggested where *Pseudomonas aeruginosa* or other resistant gram-negative nosocomial pathogens are suspected, such as after recent neurosurgery or trauma. Meropenem possesses adequate anaerobic coverage, so metronidazole is unnecessary in regimens containing this agent.

Spinal epidural abscess is usually a result of hematogenous spread, with bacteria directly seeding the epidural space. Alternatively, it may be a complication of adjacent discitis or vertebral osteomyelitis. Surgery of the spine, neuraxial anesthesia/analgesia, and LP also have been associated with spinal epidural abscess [60,61,136]. The **most common organism involved is *S. aureus*, occurring in 60% to 90% of cases [136,137]**. Other causative organisms include aerobic and anaerobic streptococcal species, and gram-negative organisms such as ***E. coli* and *P. aeruginosa* [60,61]**. Emergent surgical decompression is often indicated to prevent ensuing neurologic deficits. In addition, empiric antimicrobials, based on the most likely pathogens, should

be initiated immediately. In most instances, vancomycin combined with a cephalosporin with antipseudomonal activity (ceftazidime or ceftipime) or meropenem is indicated until culture results can provide information to optimize therapy. In selected cases where the patient does not have risk factors for nosocomial drug-resistant organisms, empiric therapy with nafcillin (or oxacillin), combined with a third-generation cephalosporin (ceftriaxone or cefotaxime) may be appropriate. Antibiotic coverage should be narrowed once culture data are available, and treatment should continue for 3 to 4 weeks. In the setting of vertebral osteomyelitis or discitis, treatment for 4 to 6 weeks is indicated [60].

### *Subdural empyema*

Successful management of subdural empyema usually requires early surgical evacuation in addition to appropriate antibiotic therapy. Empiric antibiotic selection for subdural empyema is the same as that for intracranial epidural abscess, as the bacteriology of these infections is identical [63].

### *Viral encephalitis*

In most instances, treatment of viral encephalitis is largely supportive and includes optimization of fluid balance and electrolytes; symptomatic treatment of fever, headache, and nausea; airway protection; management of ICP; and management of seizures. For HSE encephalitis, early treatment (within 2 days of onset) with acyclovir (10 mg/kg intravenously every 8 hours for 14 to 21 days) is associated with improved mortality (70% versus less than 20%) and morbidity [138]. Some other herpes viruses (VZV and herpes B virus) also respond to acyclovir. When viral encephalitis is suspected, this therapy usually is started empirically until diagnostic confirmation is obtained (usually by CSF PCR) [138–140]. Dose adjustments are necessary in patients who have renal insufficiency. In addition, adequate hydration should be maintained during treatment, as acyclovir can cause a crystal nephropathy that is usually reversible. Some have recommended to repeat the CSF examination at completion of treatment and continue acyclovir if HSV PCR is still positive, but this approach is still under investigation [40]. Prolonged high dose oral valacyclovir for 3 months after 3 weeks of treatment is also being studied. Oral valacyclovir does not achieve adequate CSF levels to be considered a primary treatment for HSE.

Corticosteroids and mannitol are usually reserved for patients with cerebral edema and intracranial hypertension. However, a nonrandomized retrospective study of 45 subjects with HSE treated with acyclovir found that combination treatment with corticosteroids and acyclovir was an independent predictor of good outcome at 3 months [141]. Further study has been recommended. For VZV encephalitis, steroids are sometimes used to treat the vasculitic component [40].

CMV encephalitis is an opportunistic pathogen most commonly seen in transplant recipients and other immunosuppressed patients [142]. Optimal

treatment of CMV encephalitis has not been studied well. Current recommendations for both CMV and HHV-6 encephalitis call for a combination of ganciclovir (5 mg/kg intravenously every 12 hours) and foscarnet (90 mg/kg intravenously every 12 hours, or 60 mg/kg intravenously every 8 hours) [142–144]. Ganciclovir and foscarnet are associated with severe adverse effects, including renal insufficiency, bone marrow suppression, encephalopathy, and seizures. Both ganciclovir and foscarnet require careful monitoring and dose adjustment in the setting of renal dysfunction [145].

Treatment for severe adenovirus infections have included cidofovir or ribavirin. Patients with life-threatening enterovirus infections have been treated successfully with pleconaril on a compassionate-use basis, and it is deserving of further study [146,147]. Pleconaril is a novel antiviral that inhibits entoviral replication by integrating into the capsid of picornaviruses and preventing the virus from attaching to cellular receptors and uncoating to release RNA into the cell. Treatment of WNV and other flaviviruses with 7 days of interferon alpha has been studied in a randomized, controlled trial of Japanese encephalitis in Vietnamese children, which did not improve outcomes at 3 months [40].

#### *Fungal central nervous system infection*

Fungal infections of the CNS are encountered more commonly as opportunistic infections in the immunosuppressed population. Fungi may cause meningoencephalitis and brain abscess or granuloma. Causative organisms may include *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Candida albicans*, *Sporothrix schenckii*, *Blastomyces dermatidis*, *Zygomycetes* species, and *Aspergillus* species, with the latter two more commonly causing brain abscess [148].

Optimal treatment of CNS fungal infections is ill defined. Although newer antifungal agents have emerged in recent years, the incidence of invasive fungal infections is rising, and outcomes in general are poor [149]. Most treatment regimens consist of an initial induction phase with an amphotericin-based regimen that lasts 2 to 6 weeks, depending on clinical response. This is followed by a chronic suppressive phase with a triazole antifungal with activity against the pathogen being treated (usually fluconazole or voriconazole) that can last anywhere from 6 weeks to lifelong suppression. Optimal treatment also should include management of risk factors for fungal disease, such as hyperglycemia, and the minimization or elimination of immunosuppressants where appropriate.

Although amphotericin B is considered the first-line agent for most CNS fungal infections, it has a large molecular weight and has poor penetration of the BBB. For this reason flucytosine is often added to amphotericin B in the treatment of cryptococcal, *Candida*, and *Aspergillus* CNS infections. The dose of amphotericin B deoxycholate (AmB) is 1 mg/kg intravenously daily, combined with flucytosine 25 mg/kg orally every 6 hours. Higher doses (1.5 mg/kg daily), however, are recommended in the setting of

mucormycosis [150]. Flucytosine requires dose adjustment in the setting of renal insufficiency, and serum levels should be monitored. Levels greater than 100 µg/mL are associated with an increased risk of bone marrow depression, which can be irreversible and result in death [151,152]. The goal peak flucytosine level is 70 µg/mL to 80 µg/mL (drawn 4 hours after a dose at steady state), and the goal trough level is 30 µg/mL to 40 µg/mL.

In patients who have, or have developed renal insufficiency, selection of a lipid-based amphotericin product is recommended. Both liposomal amphotericin B (L-amB) (5 mg/kg/d) and amphotericin B lipid complex (ABLC) (5 mg/kg/d) have been evaluated in a small number of patients, and they appear to have efficacy similar to conventional amphotericin B [153–155]. There are substantial differences between the amphotericin B products with respect to particle size, electrical charge, and volume of distribution, all of which have the potential to influence CNS penetration and antifungal activity. Many animal studies have demonstrated poor distribution of amphotericin products into the CSF; however, brain tissue concentrations appear to be adequate, and CSF concentrations do not appear to correlate with clinical efficacy [156]. An animal model of *C. albicans* CNS infection has demonstrated greater antifungal efficacy with AmB and L-AmB over ABLC and amphotericin B colloidal dispersion, but the clinical relevance of these findings has yet to be demonstrated [157].

Voriconazole represents a promising therapy for managing susceptible CNS fungal infections, in particular invasive aspergillosis. Voriconazole possesses a favorable pharmacokinetic profile with respect to CNS infections, as it penetrates the CSF with a median CSF-to-plasma ratio of 0.5 [158]. Schwartz and colleagues [159] conducted a retrospective analysis of voriconazole in 81 subjects who had CNS aspergillosis, among whom 35% had a complete or partial response. Thirty-one percent of subjects survived for a median time of 390 days. It is worth noting that 31 of the 81 subjects (38%) had neurosurgical intervention for the infection, which in a multivariate analysis was associated with improved survival ( $P = .02$ ), making it difficult to clearly discern the impact of voriconazole on outcomes. Considering that most published estimates of mortality associated with CNS aspergillosis approach 100% [160], however, this study suggests voriconazole is a reasonable option for CNS aspergillosis, and as an alternative for other susceptible CNS fungal infections when an amphotericin-based regimen cannot be tolerated. Initial dosing of voriconazole is 6 mg/kg intravenously every 12 hours for two doses, followed by 4 mg/kg intravenously every 12 hours. Voriconazole is metabolized by the hepatic CYP isoenzymes CYP2C9, CYP2C19, and CYP3A4 and is susceptible to numerous drug interactions, with many combinations being contraindicated. A thorough review of the patient's medication regimen for such interactions is indicated whenever starting a course of therapy.

Posaconazole, an extended spectrum triazole antifungal with in vitro activity against *Candida*, *Aspergillus*, *Zygomycosis*, and *Fusarium* species

has been evaluated in an open-label clinical trial in patients with refractory invasive fungal infections. In the subset of patients evaluated with CNS disease ( $n = 39$ ), the majority had cryptococcal meningitis and underlying HIV infection. Successful outcomes were observed in 14 of 29 (48%) of patients with cryptococcal disease, and 5 of 10 (50%) patients with other fungal infections [161]. Based on this report, as well as animal studies suggesting efficacy [162,163], posaconazole may be considered as an option as salvage therapy in cryptococcal meningitis where other therapies have failed. Currently, posaconazole is only available as an oral medication (200 mg every 6 hours for 7 days, followed by 400 mg twice daily). It is highly lipophilic, with a very large volume of distribution (1,774 L), and is highly protein bound (> 98%). It is an inhibitor of cytochrome P450 3A4, and is therefore subject to numerous clinically significant drug interactions.

Caspofungin is the first of a new class of antifungals (echinocandins) that target the fungal cell wall through inhibition of  $\beta$ -1,3 glucan synthesis. Caspofungin is highly protein-bound and has a large molecular weight and a small volume of distribution, all of which are linked to poor CNS penetration. In addition, animal data suggest that the brain tissue-to-plasma ratio is approximately 0.1 [164]. Hsue and colleagues [165] reported a case of treatment failure associated with the use of caspofungin for meningeal coccidiomycosis. In this report, CSF concentrations were undetectable, despite adequate serum concentrations. Despite some sporadic reports of treatment successes [166,167], use of caspofungin in CNS fungal disease cannot be recommended at this time.

Given the poor CNS penetration of AmB and its significant systemic toxicities, there has been some interest on the use of intrathecal AmB for treating invasive CNS fungal infections. It can be administered through a reservoir device or as an intrathecal or intracisternal injection, and is typically given in conjunction with systemic amphotericin and flucytosine. Dose ranges for intrathecal AmB range from 0.01 mg to 1.5 mg, and intervals range from daily to weekly [168,169]. Adverse effects associated with intrathecal AmB include arachnoiditis, paraplegia, paresthesias, nausea, vomiting, headache, and back pain. Hydrocortisone (15 mg to 25 mg) can be added to the intrathecal mixture in an effort to prevent toxicities. In addition, prophylactic administration of antipyretics and antiemetics may help alleviate some of the toxicities. Because of the invasiveness of intrathecal administration and associated toxicity, intrathecal AmB should be reserved for patients who have not responded to systemic therapy, or those who have relapsed.

## **Therapeutic controversies**

### *Glucocorticoids for bacterial meningitis*

Although it is accepted that inflammatory mechanisms contribute to the morbidity associated with bacterial meningitis, debate continues regarding the appropriate use of anti-inflammatory drugs in particular

glucocorticoids. The rationale for use of steroids is based on experimental data that show that the inflammatory response in the subarachnoid space contributes significantly to the morbidity and mortality of bacterial meningitis [30]. De Gans and colleagues [170] demonstrated in a large prospective randomized, controlled trial that dexamethasone given before or with the first dose of antibiotic and then every 6 hours for 4 days improved the outcome in adults with acute bacterial meningitis, particularly pneumococcal meningitis, without serious adverse effects. Unfavorable outcomes were reduced from 25% to 15% and mortality from 15% to 7% in dexamethasone-treated subjects. On the basis of this study, the Infectious Diseases Society of America Practice Guideline recommends use of dexamethasone (0.15 mg/kg every 6 hours for 2 to 4 days) in patients who have suspected meningitis [82]. Dexamethasone should be continued only in patients with gram-positive diplococci on Gram's stain or *S. pneumoniae* in CSF or blood cultures. It should not be given to patients with prior administration of antibiotics. Generalizability of the study results has been questioned, as initial antibiotic therapy consisted of amoxicillin or penicillin in most patients (77%), and less than 1% of isolates were resistant to penicillin.

A systematic review, including 18 clinical trials and 2,750 people, has since confirmed significant reductions in mortality (risk ratio or RR 0.83, 95% CI 0.71 to 0.99), lower rates of hearing loss (RR 0.65, 95% CI 0.4 to 0.81), and short-term neurologic sequelae (RR 0.42, 95% CI 0.22 to 0.87) overall. Subgroup analysis for causative organisms showed mortality benefit in patients with *S. pneumoniae*, and reduction in hearing loss in children with *H. influenzae* [171].

A major concern is the rapidly rising incidence of highly resistant *S. pneumoniae* requiring combination therapy with vancomycin. Vancomycin penetration into the CNS is largely dependent upon meningeal inflammation, and some experimental studies show that dexamethasone significantly decreases the achievement of therapeutic vancomycin concentrations in the CSF [172,173], resulting in clinical treatment failure in adults [174]. In contrast, more recent data suggests this can be overcome by giving higher doses of vancomycin via continuous infusion (15-mg/kg loading dose followed by 60-mg/kg per day infusion) [175]. Nevertheless, expert opinion recommends adjuvant dexamethasone even in patients with highly resistant pneumococcal isolates [82,176]. There are no data to support adjunctive steroids in patients who have nosocomial and postneurosurgical meningitis, and meningitis related to CSF shunts.

In patients who have TBM, a randomized, double-blind, placebo-controlled study of 545 subjects conducted in Vietnam demonstrated that adjunctive treatment with dexamethasone reduces mortality (31.8% versus 41.3%), but probably does not prevent severe disability (18.2% versus 13.8%) [177]. The prespecified subgroup analysis of patients with HIV demonstrated a nonsignificant reduction in the risk of death, although none were treated with antiretroviral drugs, and the results may not be generalizable to

populations with access to antiretroviral treatment. The results of this trial suggest that for non-HIV patients with TBM, 4 to 8 weeks of dexamethasone (2 to 4 weeks of tapering intravenous steroids followed by tapering oral therapy) should be administered.

#### *Intraventricular and intrathecal antibiotics*

The question of intraventricular antimicrobial therapy arises most commonly in patients with CSF infections who have a CSF shunt or EVD. There is limited evidence for the instillation of antimicrobial agents into the ventricles in difficult-to-eradicate shunt infections or in patients who cannot undergo surgical management [82]. Although no antimicrobial agent is approved by the Food and Drug Administration for intraventricular use, common used agents (depending on the causative organism) include vancomycin, gentamicin, tobramycin, and polymyxins. The usual dose of intraventricular vancomycin is 10 mg to 20 mg per day, continued for a few days after CSF cultures become negative. Potential adverse effects of intraventricular vancomycin include ototoxicity, CSF eosinophilia, seizures, altered mental status, and local tissue irritation [128,178]. In cases of fulminant gram-negative ventriculitis, intraventricular aminoglycosides have been used, although with less encouraging results [178–183]. Toxicities are similar to those of vancomycin. The usual daily dose of intraventricular gentamicin and tobramycin is 5 mg to 10 mg, and that of amikacin is 10 mg to 20 mg [179,182]. Redosing is determined by calculation of the inhibitory quotient (trough CSF concentration divided by the minimum inhibitory concentration of the agent for the isolated pathogen). This number should exceed 10 to 20 for consistent CSF sterilization [184]. Polymyxins (Polymyxin B and colistimethate) have been used in the setting of ventriculitis caused by multi-drug resistant *Acinetobacter* and *Pseudomonas* species, with the most common adverse effect of meningeal irritation being dose-dependent and reversible [185]. Dosing has varied substantially (5 mg–20 mg of colistimethate daily), and as for all of the above regimens, the optimal duration is unknown. It is important to note that preservative-free formulations should always be used for intraventricular administration.

#### *Prophylactic and periprocedural antibiotics for neurosurgical procedures and external ventricular drains*

Nosocomial meningitis accounted for 40% of acute adult bacterial meningitis in a review of 493 episodes, of which 81% occurred within 1 month of neurosurgery or head injury [35]. A recent retrospective study found an overall meningitis rate of 1.52% [74] in 6,243 subjects undergoing craniotomy, among whom 17% did not receive perioperative antibiotics. Independent risk factors for meningitis were CSF leakage, concomitant incision infection, male sex, and duration of surgery. Perioperative antibiotic prophylaxis reduced

incidence of incision infections from 8.8% to 4.6% ( $P < .0001$ ), but did not prevent meningitis. In patients receiving antibiotics, microorganisms were mainly noncutaneous and tended to be less susceptible to prophylactic antibiotics administered. These microorganisms also were associated with a higher mortality rate when compared with meningitis caused by cutaneous organisms. The investigators recommended narrow-spectrum antibiotics be used to prevent surgical site infections without any effect on the risk of meningitis.

Ventriculostomy related infection (VRI) rates are most commonly reported at 5% to 10%, with a range of 0% to 22% [69]. Defining CSF infections in patients with ventriculostomies may imply different management strategies. Critical review of the literature from predominantly retrospective studies found the following categories of VRI to be potentially useful [73]:

Confirmed VRI: positive CSF culture obtained from ventricular or lumbar catheter associated with CSF pleocytosis and clinical symptoms not related to other causes.

Suspected VRI: positive CSF culture and CSF pleocytosis without clinical symptoms or with other likely source of infection.

Contaminant: isolated positive CSF culture in conjunction with negative gram-stain, normal CSF cell counts and absent clinical symptoms.

Some researchers accept CSF pleocytosis or low CSF glucose alone as evidence of CSF infection, although positive cultures are considered the gold standard. Others apply more stringent criteria, requiring an initial sterile CSF culture at time of EVD insertion, requiring two separate CSF cultures on separate days, and assessing number of risk factors in determining whether infections are related to the catheter or not. Risk factors that predispose patients with ventriculostomies to ventriculitis or meningitis are intraventricular hemorrhage, subarachnoid hemorrhage, cranial fracture with CSF leak, craniotomy, systemic infection and catheter irrigation [69]. Because CSF surveillance itself may increase the risk of VRI, clinicians often collect CSF only at time of EVD insertion, removal, and when clinically indicated. The value of routine CSF surveillance has been questioned as it has not been shown to predict VRI before actual positive culture with clinical symptoms [186]. However, some studies do suggest that accessory tests, including cell index, lactate level, and IL-1B may be helpful in diagnosing VRI before the onset of ventriculitis [106,187].

The data on duration of EVD as a risk factor for VRI is controversial; in Lozier's analysis [69], ten studies (2,046 EVDs in 1,698 subjects) reported a positive association, and seven studies (2,199 EVDs in 2,113 subjects) reported no association between duration of catheterization and CSF infection. There is a likely relationship between duration of EVD and infection, but it may not be a continuous rise. Holloway and colleagues [71] reported an increasing risk of infections during the first 10 days of EVD, followed by a significant decrease afterwards despite the population still being at risk. This has been the authors' experience as well.



While EVD duration may not be easily modified, other potential prevention strategies are antibiotic prophylaxis and routine EVD change. The data on antibiotic prophylaxis (none versus periprocedural versus continuous) is conflicting with only one randomized, controlled trial, with the remainder of studies being retrospective or case controlled. Poon and colleagues [188] randomized 228 subjects to either perioperative antibiotics only (ampicillin/sulbactam) or prolonged antibiotics for the duration of the ventricular catheter (ampicillin/sulbactam and Aztreonam). Although CSF infection was not clearly defined in this study, prolonged antibiotic prophylaxis significantly reduced the incidence of both CSF and extracranial infection, but selected resistant or opportunistic pathogens, such as *Candida* and MRSA. The mortality of patients with CSF infection in the continuous antibiotic group was significantly higher than in the perioperative antibiotic-only group. A retrospective study of 308 subjects compared prophylactic antibiotics administered for the duration of the EVDs with periprocedural antibiotics, finding an overall rate of ventriculitis that was almost identical in the two groups [189]. The use of continuous prophylactic antibiotics is therefore discouraged based on the risk of selecting resistant organisms.

It has been argued based on retrospective data that EVDs should be changed around day 5, when the infection risk starts to go up. Based on the majority of retrospective evaluations, however, prophylactic catheter exchange has not been effective in preventing VRI, and has been associated with increased risks of ventriculostomy associated hemorrhage and poor catheter positioning [190]. A prospective randomized study has been recommended to determine whether this common practice has any significant advantage.

Finally, a comment on the efficacy of antimicrobial-impregnated EVDs. A prospective randomized, controlled trial evaluated EVDs impregnated with minocycline and rifampin in 288 subjects (mainly subarachnoid hemorrhage and trauma) requiring EVDs [191]. The antibiotic-impregnated catheters were half as likely to become colonized as the control catheters (17.9% versus 36.7%;  $P < .0012$ ) and seven times less likely to be associated with positive CSF cultures (1.3% versus 9.4%;  $P = .002$ ). Heparin-coated catheters, which have been shown to lower the incidence of bacterial colonization and septicemia in central venous catheters [192], have also been evaluated in a randomized, controlled study of 198 subjects requiring EVDs (again, mostly subarachnoid hemorrhage and trauma), but demonstrated no benefit with regards to catheter colonization when compared with non-heparin-coated EVDs. Finally, a hydrogel-coated EVD, which has a proposed advantage of reducing clot and bacterial adhesion, was evaluated in a prospective randomized trial [193]. This also failed to demonstrate reduction in bacterial colonization. At this time it appears that the antibiotic impregnated EVDs are effective in reducing the likelihood of VRI. A large bore antibiotic impregnated catheter for drainage of intraventricular hemorrhage is not available at present.

## Summary

The management of patients who have CNS infections is challenging. Therapy for CNS infections is evolving in light of changing microbial resistance patterns and with the introduction of new antimicrobial agents. Knowledge of cerebral inflammation, molecular diagnostics, and the evolving microbial epidemiology are important to optimizing therapy in patients with meningitis. Future investigations into the role of selective immunomodulation and other neuroprotective strategies may lead to significant advances in the management of CNS infection.

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