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Chapter 128: Central Nervous System Infections

Delaney E. Hart; Christina Koutsari; Michael A. Wankum; Ramy H. Elshaboury

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 36, Central Nervous System Infections.

KEY CONCEPTS

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KEY CONCEPTS

1 The four most common causative pathogens of acute community-acquired bacterial meningitis in the United States are *Streptococcus pneumoniae*, group B *Streptococcus, Neisseria meningitidis*, and *Haemophilus influenzae* type b, although routine vaccinations are having a dramatic effect on the incidence and distribution of these pathogens.

2 In cases of bacterial meningitis, initial findings can include (a) presenting signs and symptoms: fever, headache, nuchal rigidity (the classic triad), Brudzinski's or Kernig's sign, and altered mental status; and (b) abnormal cerebrospinal fluid (CSF) chemistries: elevated white blood cell (WBC) count (>1,000 cells/mm^3 [1.0×10^9/L]), elevated protein (>50 mg/dL [500 mg/L]), and decreased glucose levels (<45 mg/dL [2.5 mmol/L]).

3 Main microbiologic tests that should be obtained include Gram stain and culture of the CSF and blood. In patients with negative CSF Gram stain and culture, molecular testing such as polymerase chain reaction (PCR) has additive value in the pathogen(s) identification.

4 Three primary goals of treatment in meningitis include (a) eradication of infection, (b) amelioration of signs and symptoms, and (c) prevention of the development of neurologic sequelae, such as seizures, deafness, coma, and death.

5 When selecting antibiotics, the clinician must consider the antibiotic concentration at the site of infection and the spectrum of antibacterial activity. Empirical choices should be based on age, predisposing conditions, vaccination history, comorbidities, and local susceptibility patterns.

(a) Either ceftriaxone or cefotaxime with vancomycin is a reasonable initial choice for empirical coverage of community-acquired meningitis in adult patients. (b) Meningitis due to *Listeria monocytogenes* is more common in infants and elderly. Therefore, ampicillin—with or without gentamicin—should be empirically added to antimicrobial regimens in these age groups.

6 Empirical coverage with an appropriate antibiotic should be started as soon as possible when clinical suspicion of meningitis exists. If there is a delay in obtaining a lumbar puncture (even 30-60 minutes), or if the patient is to undergo neuroimaging, the first dose of antibiotic(s) should not be withheld.

7 Antibiotic dosages for the treatment of meningitis should be optimized to ensure adequate CNS therapeutic concentrations.

8 The duration of antibiotic treatment for acute bacterial meningitis has not been standardized. However, it is generally based on the causative organism and the individual case, and may range from 7 to 21 days.

9 Close contacts and relatives of the index case should be assessed for appropriate chemoprophylaxis and vaccinations, particularly for *N. meningitidis* and *H. influenzae* meningitis.

10 Steroid treatment includes dexamethasone of 0.15 mg/kg per dose given four times daily for 2 to 4 days in infants and children with proven or strongly suspected *H. influenzae* type b meningitis. Steroids should be started 10 to 20 minutes prior to, or at least concomitant with, the first dose of antibiotics.

BEYOND THE BOOK

Find the Infectious Diseases Society of America (IDSA) guidelines for the diagnosis and treatment of neurocysticercosis infection. Assume that a male patient who is 90 kg and has normal kidney function requires treatment. Create a treatment regimen with drug, dose (both in mg/kg and in mg), dosing interval, and monitoring parameters for each recommended agent. When are antiparasitic agents used and when are they not given? The purpose of this activity is to enhance your ability to find evidence-based guidelines and apply them to clinical practice.

INTRODUCTION

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Central nervous system (CNS) infections are caused by a variety of pathogens, including bacteria, viruses, fungi, and parasites. CNS infections result from hematogenous spread from a primary infection site, seeding from a parameningeal focus, reactivation from a latent site, trauma, neurosurgery, or CNS congenital defects. Newer diagnostic techniques have enabled more rapid and definitive diagnosis, thus reducing the number of unknown "aseptic meningitis" diagnoses and improving targeted therapy. Bacteria resistant to multiple antibiotics present new challenges in the management of CNS infections. This chapter presents the epidemiology, etiology, pathophysiology, therapy, and prophylaxis of common CNS infections.

EPIDEMIOLOGY

The incidence of acute, community-acquired bacterial meningitis is approximately 0.7 to 0.9 per 100,000 persons annually in developed countries, including the United States and Western Europe.[1] In the United States, this corresponded to approximately 4,100 annual cases of acute community-acquired bacterial meningitis, excluding epidemics, between 2003 and 2007 resulting in approximately 500 deaths.[2] In stark contrast, incidence rates of meningitis in the region of sub-Saharan Africa average 10 to 40 cases per 100,000 people per year.[1] This region, also known as the "meningitis belt," is characterized by seasonal and explosive epidemics putting at least 350 million individuals at risk for meningitis annually.[3]

The estimated incidence of brain abscesses is 0.3 to 1.3 per 100,000 people per year but can be considerably higher in high-risk groups, such as patients with HIV/AIDS.[4] The global reported incidence of encephalitis varies according to the population studied, and due to differences in definitions and research methodology. The reported incidence in western settings ranges from 0.7 to 13.8 per 100,000 for all ages: 0.7 to 12.6 per 100,000 adults and 10.5 to 13.8 per 100,000 children. The incidence peaks in the young and the elderly.[5,6] In the United States, there are approximately 20,000 encephalitis-related hospitalizations and 1,400 deaths per year.[7,8]

ETIOLOGY

1 *Streptococcus pneumoniae* remains the leading cause of acute community-acquired bacterial meningitis in the United States with an incidence rate of 0.3 per 100,000 people in 2010.[9] *Neisseria meningitidis* and *Haemophilus influenzae* type b (Hib) have also been important causes of acute bacterial meningitis but their incidence has decreased substantially in the past several decades, mainly due to introduction of effective vaccinations. *S. pneumoniae* remains the leading cause of bacterial meningitis, followed by Hib, *N. meningitidis*, and other bacterial, viral, and fungal causes.[10]

Hib was the most commonly identified cause of bacterial meningitis until the introduction of the Hib conjugate vaccine in 1987 (at 18 months of age) and 1991 (at 2 months of age) in the United States. Hib vaccination had a profound population-wide effect on incidence of Hib meningitis, and in 2016 Hib was the least common cause of meningitis.[10] Targeted meningococcal vaccinations for high-risk infants, adolescents, and adults have similarly impacted the epidemiology and risk of meningococcal meningitis following the availability of meningococcal vaccines in the United States.[11]

Organisms causing healthcare-associated ventriculitis and meningitis differ markedly from those causing community-acquired bacterial meningitis. The most likely pathogens associated with CSF shunt and drain infections are coagulase-negative staphylococci, *Staphylococcus aureus, Propionibacterium (now Cutibacterium) acnes*, and gram-negative bacilli (including *Escherichia coli*, Enterobacter species, Citrobacter species, Serratia species, and *Pseudomonas aeruginosa*).[12]

Infectious encephalitis is caused by many viruses, bacteria, parasites, and fungi.[5,13,14] Noninfectious processes can also cause encephalitis and, as a result, the etiology remains unknown in 20% or more of encephalitis cases. Viral encephalitis in the United States is often caused by enteroviruses, herpes viruses, and arboviruses.[7,15,16]

ANATOMY AND PHYSIOLOGY OF THE CENTRAL NERVOUS SYSTEM

Meninges

The skull and vertebrae protect the CNS from blunt or penetrating trauma (**Fig. 128-1**). The brain is suspended in these structures by CSF and is surrounded by the meninges. The meninges are made up of three separate membranes: dura mater, arachnoid, and pia mater.[17] Dura mater, or

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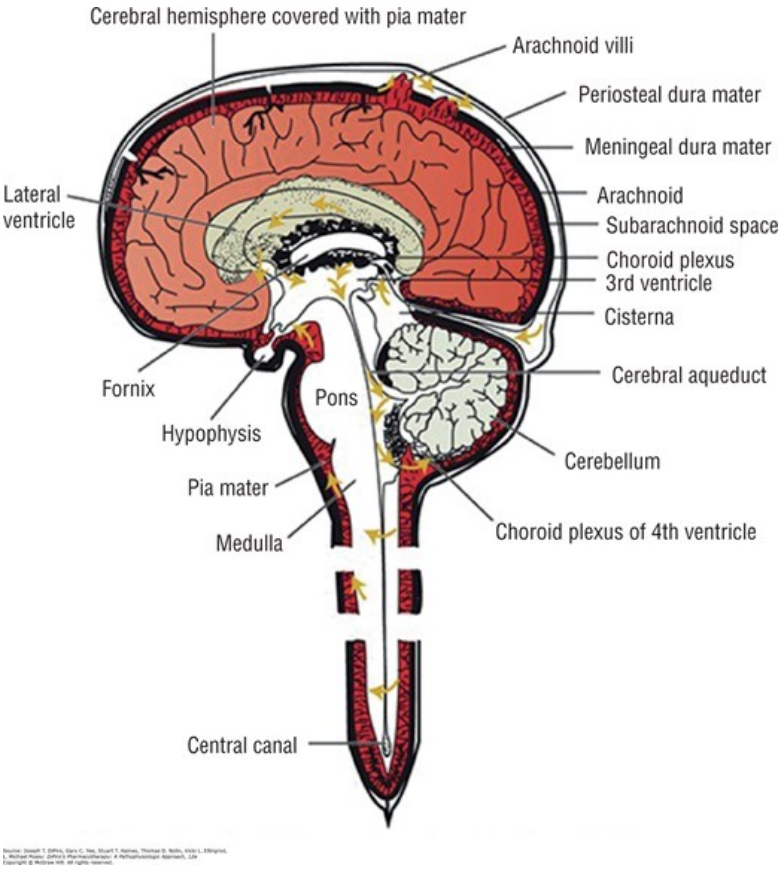
pachymeninges, lies directly beneath and is adherent to the skull. The other two membranes are referred to collectively as leptomeninges. Pia mater lies directly over brain tissue. Arachnoid, the middle layer, lies between the dura mater and the pia mater. The subarachnoid space, located between the arachnoid and the pia mater, is the conduit for CSF. Meningitis refers to inflammation of the subarachnoid space or spinal fluid, whereas encephalitis is an inflammation of the brain tissue itself. Since infectious microorganisms frequently are an underlying cause of these inflammatory processes, the terms “meningitis,” “encephalitis,” and “meningoencephalitis” are frequently used to denote an infectious process.[18]

FIGURE 128-1

Diagram of the central nervous system.



Cerebrospinal Fluid

Approximately 85% of the CSF is produced within the third, fourth, and lateral ventricles by the choroid plexus (Fig. 128-1). CSF volume in the CNS is related to patient age: infants have approximately 40 to 60 mL of CSF, older children have 60 to 100 mL, while adults have 115 to 160 mL. Normally, CSF is produced at the rate of approximately 500 mL/day and flows unidirectionally downward through the spinal cord. The CSF is removed by the arachnoid villi and vertebral venous plexus located in the spinal cord and does not recommunicate with the point of production.[18]

The CSF normally is clear, with a protein content of less than 50 mg/dL (500 mg/L), a glucose concentration of approximately 50% to 60% of the simultaneous peripheral serum glucose concentration, and a pH of approximately 7.4. Also, it typically contains fewer than 5 WBCs per mm^3 (5×10^6/L), all of which should be lymphocytes (Table 128-1).[3,19] As meninges become inflamed, CSF abnormalities can be used diagnostically as markers of CNS infections.

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TABLE 128-1

Mean Values of the Components of Normal and Abnormal Cerebrospinal Fluid

Type	Normal	Bacterial	Viral	Fungal	Tuberculosis
WBC (cells/mm^3 or 10^6/L)	<5 (<30 in newborns)	1,000-5,000	50-1,000	20-500	25-500
Differential[a]	Monocytes	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
Protein (mg/dL)	<50 (500 mg/L)	Elevated	Mild elevation	Elevated	Elevated
Glucose (mg/dL)	45-80 (2.5-4.4 mmol/L)	Low	Normal	Low	Low
CSF/blood glucose ratio	50%-60%	Decreased	Normal	Decreased	Decreased

[a]Data from References *3* and *19*.

Blood–Brain Barrier/Blood–CSF Barrier

Natural barriers to the exchange of drugs and endogenous compounds among the blood, brain, and CSF are the blood–brain barrier (BBB) and the blood–CSF barrier (BCSFB) (**Fig. 128-2**). The BBB consists of tightly joined capillary endothelial cells. Drug entry into brain tissue is accomplished by direct passage through the capillary endothelial cells and further penetration of the glial cells that envelop the capillary structure.[18] Passage of drugs into the CSF is controlled by the BCSFB. This barrier is created by ependymal cells of the choroid plexus, which function as an active-transport system similar to the renal tubular epithelial cells. The inflammatory process associated with meningitis can also inhibit the active-transport system of the choroid plexus.

FIGURE 128-2

Schematic representation of a blood–cerebrospinal fluid barrier capillary, brain tissue capillary, and normal tissue capillary.

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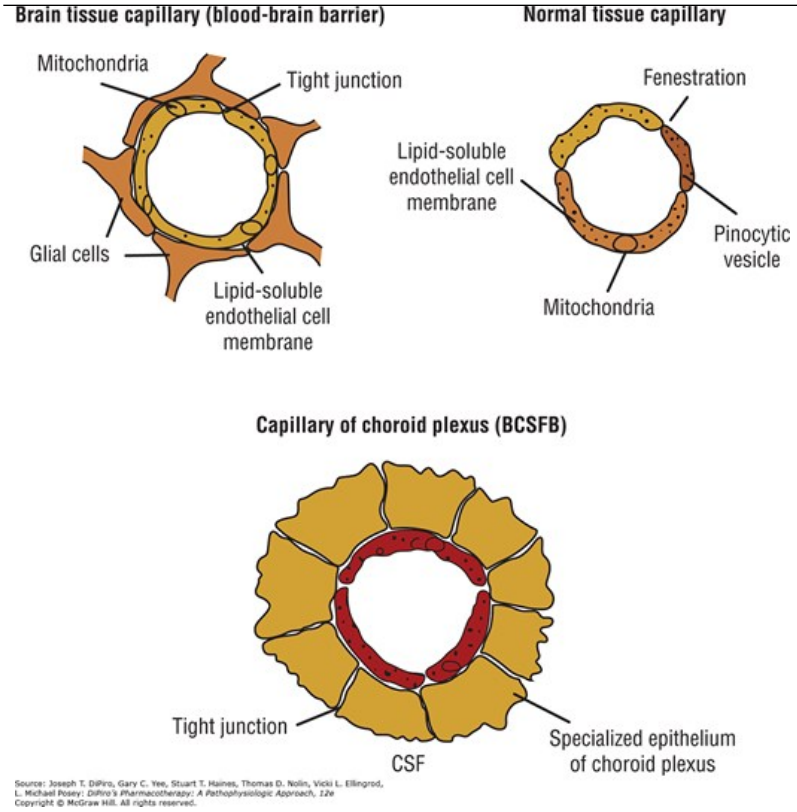

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PATHOPHYSIOLOGY OF THE CNS INFECTION

The development of bacterial meningitis involves four main processes: (1) mucosal colonization and bacterial invasion of the host and CNS; (2) bacterial replication in the subarachnoid space; (3) pathophysiologic alterations resulting in progressive inflammation; and (4) increased intracranial pressure (ICP) and cerebral edema leading to neuronal damage.[3,20] Many bacteria that cause meningitis initially colonize the mucous membranes of the upper respiratory tract. Immunoglobulins (Ig), such as secretory IgA, are found in high concentrations within nasopharyngeal secretions and work to inhibit bacterial colonization. However, this mucus barrier is deteriorated by IgA proteases secreted by bacteria, which allows bacteria to adhere to the host cell surface receptors.

Bacterial pathogens tightly attach to nasopharyngeal epithelial cells and are then phagocytized into the host's bloodstream. Invasion into the bloodstream occurs either transcellularly (passing through the cells) or paracellularly (between cells). After accessing the patient's bloodstream, bacteria must overcome the host's defense mechanisms. Commonly, CNS bacterial pathogens produce an extensive polysaccharide capsule resistant to neutrophil phagocytosis and complement opsonization. Capsular polysaccharides activate the alternate complement pathway, which promotes phagocytosis and clearance of infecting pathogens. Patients unable to activate the alternative complement pathway, such as those with asplenia or sickle cell anemia, are predisposed to bacterial infections caused by encapsulated microorganisms and, therefore, are at increased risk for meningitis. Most cases of acute bacterial meningitis likely occur following bacteremia, but the high incidence of pneumococcal meningitis in patients with sinusitis and otitis media suggests that direct spread to the CNS can also occur.[3]

Although the exact site and mechanism of bacterial invasion into the CNS is unknown, invasion into the subarachnoid space may occur by continuous exposure of the CNS to large bacterial inoculum. Micro-organisms utilize three main mechanisms to directly transit the blood−brain barrier: transcellular route, paracellular route, and lytic mechanism.[21] Host defense mechanisms within the subarachnoid space are inadequate to combat bacterial pathogens. Therefore, bacteria replicate freely within the CSF. Although in most cases of bacterial meningitis the neurological syndrome is caused by the pathogen having invaded into the CNS, some bacteria such as the Shiga toxin-producing *Escherichia coli* (*E. coli*) attack from outside the CNS using toxins.[22]

The effects of meningitis, namely inflammation within the subarachnoid space and the ensuing neurologic damage, are not necessarily a direct result

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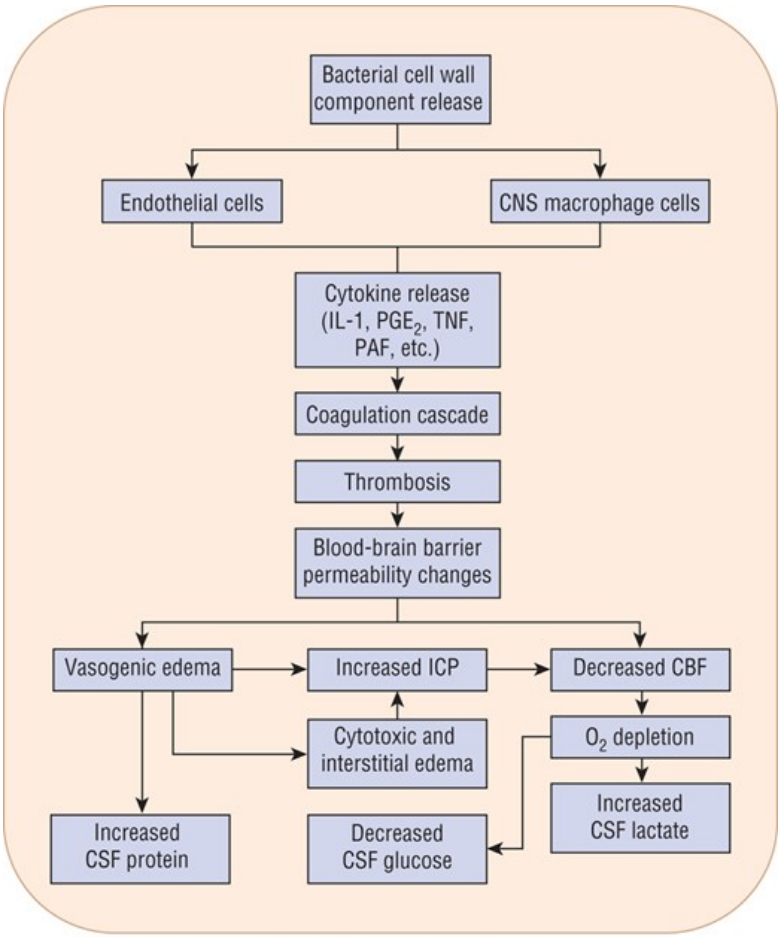
of the pathogens themselves. The neurologic sequelae occur due to the activation of the host's inflammatory pathways, a process induced by the pathogen or its products. Bacterial cell lysis and subsequent death can result in the release of cell-wall components, such as lipopolysaccharide (LPS), lipid A (endotoxin), lipoteichoic acid, teichoic acid, and peptidoglycan, depending on whether the pathogen is gram-positive or gram-negative (**Fig. 128-3**). These cell-wall components cause capillary endothelial cells and CNS macrophages to release cytokines (interleukin-1 [IL-1] and tumor necrosis factor [TNF]) and other inflammatory mediators (IL-6, IL-8, platelet-activating factor [PAF], nitric oxide, arachidonic acid metabolites [eg, prostaglandin and prostacycline], and macrophage-derived proteins). Proteolytic products and toxic oxygen radicals are released from the capillary endothelium, causing an alteration in the permeability of the BBB. Platelet-activating factor activates the coagulation cascade, and arachidonic acid metabolites stimulate vasodilation. These events propagate other sequential events that can lead to cerebral edema, ICP, CSF pleocytosis, decreased cerebral blood flow, cerebral ischemia, and possibly death.

FIGURE 128-3

Hypothetical schema of pathophysiologic events that occur during bacterial meningitis. (CBF, cerebral blood flow; CSF, cerebrospinal fluid; ICP, intracranial pressure; IL-1, interleukin-1; PAF, platelet-activating factor; PGE_2, prostaglandin E_2; TNF, tumor necrosis factor.)



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CLINICAL PRESENTATION AND DIAGNOSIS

Clinical presentation of CNS infections varies with host age, immune status, duration of illness, and the specific pathogen causing the infection.

Signs and Symptoms

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Classic signs and symptoms of acute bacterial meningitis include fever, nuchal rigidity, altered mental status (the classic triad), chills, nausea, vomiting, photophobia, and severe headache. Kernig's and Brudzinski's signs may also be present but are poorly sensitive and frequently absent in children (**Figs. 128-4** and **128-5**). Additionally, clinical signs and symptoms in young children may include bulging fontanelle, apneas, purpuric rash, irritability, refusal to eat, and convulsions. The classic triad occurs in <50% of adult patients with acute bacterial meningitis.[23] However, up to 95% of patients exhibit at least two of the following symptoms: fever, nuchal rigidity, headache, and altered mental status. Purpuric and petechial skin lesions may indicate meningococcal involvement, although lesions may also be present with *H. influenzae* meningitis.[24]

As opposed to acute bacterial meningitis, symptoms of chronic meningitis, defined as 4 weeks of symptoms of meningitis or meningoencephalitis, can be present over weeks and months. Examples include *Mycobacterium tuberculosis* and fungal meningitis (eg, due to Cryptococcus, Histoplasma, or Aspergillus species). Early symptoms of chronic meningitis may include headache, nausea, and decreased memory or comprehension, while later symptoms may include double vision, cranial nerve palsies, unsteady gait, emesis, and confusion.[19]

The clinical manifestations of brain abscess depend on the size and location of the space-occupying lesion. Common symptoms include headache, focal neurologic deficits, motor speech disorder, ataxia, fever, nystagmus, seizures, and vomiting. The clinical course can be indolent or fulminant depending on the virulence of the pathogen.

The classical clinical features of infective encephalitis in adults include fever, abnormal mental status (often with severe headache), nausea, and vomiting. Seizures can also be the initial presenting feature of patients with infectious encephalitic processes affecting the cortex.[5,14] Lastly, ill children cannot often adequately describe symptoms such as headache, whereas infants commonly have nonspecific symptoms similar to those for other acute illnesses including feeding and respiratory difficulties.[13]

Diagnostic Tests

CSF examination is essential for establishing diagnosis of bacterial meningitis, identifying the pathogen, and performing susceptibility testing. CSF polymorphonuclear pleocytosis, an elevated CSF protein of >50 mg/dL (500 mg/L), and a CSF glucose concentration of <50% of the simultaneously obtained peripheral value suggest bacterial meningitis (Table 128-1).[3,19] However, the values for CSF glucose, protein, and WBC found with bacterial meningitis overlap significantly with those with viral, tuberculous, and fungal meningitis (Table 128-1). Therefore, CSF WBC count and CSF glucose and protein concentrations cannot always distinguish the different etiologies of meningitis. CSF culture is the gold standard for diagnosis of bacterial meningitis and is positive in 80% to 90% of patients with community-acquired bacterial meningitis if the CSF sample is obtained before the start of antibiotics.[24] In addition, Gram stain is a rapid, inexpensive, and accurate method to assess the presence of bacteria in CSF. However, the sensitivity of the Gram stain depends on the causative microorganism, so that its aggregate diagnostic yield is 90% in pneumococcal, 70% to 90% in meningococcal, 50% in *H. influenzae*, and only 25% to 35% in *L. monocytogenes* meningitis.[25]

In patients presenting with new-onset seizures, signs of space-occupying lesions, or moderate-to-severe impairment of consciousness, cranial imaging via magnetic resonance imaging (MRI), or cranial computed tomography (CT) should precede a lumbar puncture. MRI is generally preferred, as it more clearly identifies areas of cerebral edemas and has higher specificity and sensitivity than CT.[26] Neuroimaging or CSF cultures should not delay initiation of appropriate antibiotic therapy as doing so can result in a poor outcome in this disease.

In patients with suspected CNS bacterial infection, blood cultures are strongly recommended and should be collected before the first dose of antibiotics. Blood cultures identify the causative organism in 50% to 80% of cases, although the yield decreases by 20% if the patient has received antibiotics.[24] CSF viral cultures are insensitive for the diagnosis of viral encephalitis/meningitis. Patients with suspected encephalitis should have a CSF PCR test for HSV1, HSV2, VZV, and enteroviruses, as this will identify ~90% of cases due to known viral pathogens.[27]

Models have been developed in an attempt to predict the likelihood of acute community-acquired bacterial versus viral meningitis. Expert opinions and guidelines have systematically evaluated these models and identified concerns that limit their use in clinical practice.[24,27] Limitations include <100% sensitivity (risk of false-negative results), application limited to age-specific cohorts in which the models were developed, and ability to only differentiate between acute bacterial versus viral meningitis when in clinical practice other causes are also considered.

CSF lactate may be useful in differentiating between bacterial and other types of meningitis.[12,27] In a meta-analysis of 1,881 adult and pediatric patients, CSF lactate had a sensitivity of 93% and a specificity of 96% in differentiating bacterial from aseptic meningitis, when the specimen was

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collected before antibiotics. However, administration of antibiotics reduced sensitivity to 49%, suggesting that the usefulness of CSF lactate is compromised in patients who have already received antimicrobial therapy.[28] CSF and/or serum procalcitonin (PCT) may be useful markers for bacterial cause in community-acquired and healthcare-associated meningitis.[29,30] However, more studies are needed to confirm the impact of PCT monitoring on clinical outcomes, establish cut-off values, and evaluate cost-effectiveness.

3 Polymerase chain reaction (PCR) techniques can rapidly diagnose CNS infections and may be particularly useful in patients who have received antimicrobial therapy before lumbar puncture, have negative cultures, or when the organism is fastidious or fails to grow in conventional culture.[5,12,27] In addition to individual PCR tests, a multiplex PCR panel can simultaneously and rapidly (within ~1 hour) detect six bacterial, seven viral, and two yeast targets directly from CSF specimens; however, more studies are needed to establish performance in clinical practice.[31] Antimicrobial stewardship programs when combined with rapid diagnostic bloodstream tests have been shown to optimize antimicrobial use, though more data is needed in antimicrobial stewardship initiatives with CNS PCR tests.[32] Routine cultures are necessary for the detection of pathogens not covered by the multiplex PCR panel and for antibiotic susceptibility testing. 16s rRNA molecular testing and next generation sequencing are also emerging as diagnostic tools for CNS infections.[33,34] Ribosomal 16s is part of the 30s ribosomal subunit in bacteria. By identifying species-level 16s sequences, this testing can detect a causative pathogen for patients whose cultures are negative. Due to low positivity, high cost, and slow turnaround time, ribosomal 16s testing should be applied on a case by case basis.[35]

Latex agglutination has little incremental value and is not a recommended routine diagnostic modality for rapid determination of bacterial etiology of meningitis.[12,26,27] More studies are needed to determine whether immunochromatographic antigen testing has incremental value in the diagnosis of bacterial meningitis.

Diagnosis of tuberculous meningitis employs acid-fast stain, culture, and PCR of the CSF. The standard diagnostic tests for fungal meningitis include culture, direct microscopic examination of stained and unstained specimens of CSF, antigen detection of cryptococcal or histoplasma, and antibody assay of serum and/or CSF.

FIGURE 128-4

(A and B) Brudzinski's neck signs. (B) Hip and knee flexion occurs as a result of flexion of the neck. (C to E) Brudzinski's leg signs. (C) Patient's leg is flexed by examiner (*arrow*). (D) The contralateral leg begins to flex—identical contralateral sign (*arrows*). (E) The contralateral leg now begins to extend spontaneously, resembling a little kick (*arrows*).

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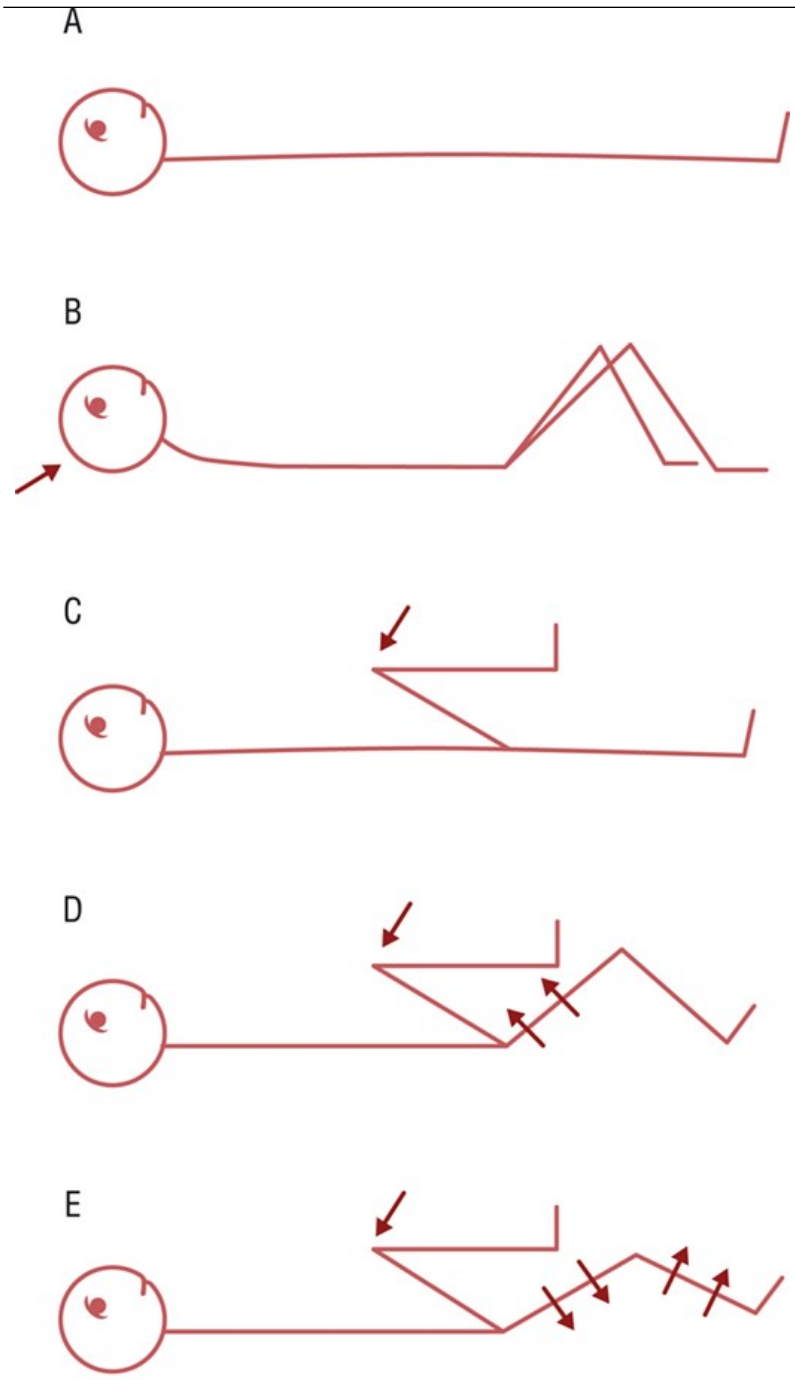

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FIGURE 128-5

Kernig's sign. (A) Knees are raised to form a 90-degree angle relative to the trunk, and the examiner attempts to extend the knees. (B) Once the knee angle reaches approximately 135°, contracture or extensor spasm occurs.

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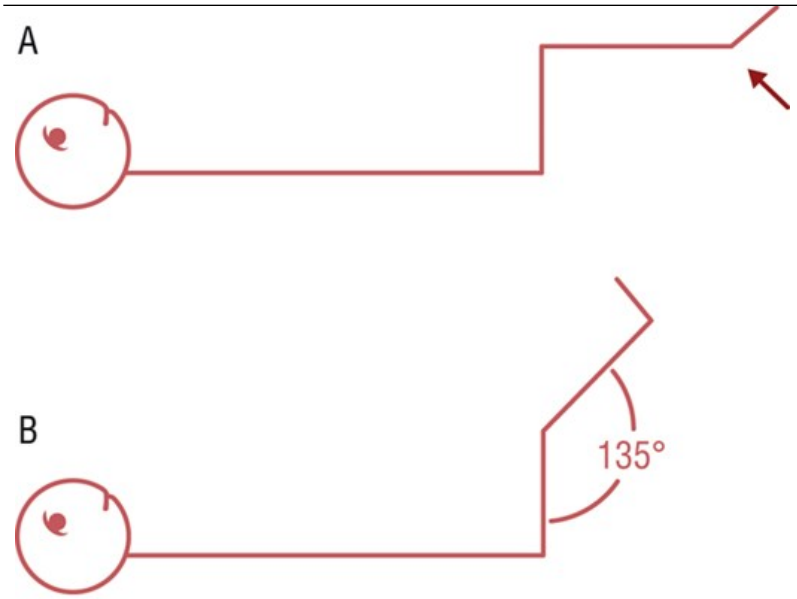

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TREATMENT

Desired Outcome

4 Goals for the treatment of CNS infections should include prompt and effective eradication of infection, amelioration of signs and symptoms, and reduction of morbidity and mortality. Key elements include initiation of appropriate anti-infective and supportive care, and prevention of disease through timely introduction of vaccination and chemoprophylaxis. Understanding appropriate selection of anti-infective agents and the issues surrounding their CNS penetration will assist in meeting the goals of treatment.

General Approach to Treatment, Nonpharmacologic and Supportive Therapy

5 Until a pathogen is identified, prompt empiric antibiotic coverage is needed. Based on the patient's profile (ie, allergies, age, and concurrent medical conditions), extent of antibiotic CNS penetration, spectrum of activity, and local susceptibility patterns, appropriate recommendations should be made. Therapy should last at least 48 to 72 hours or until an infectious process has been ruled out (Tables 128-2 and 128-3).[26,27,36]

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TABLE 128-2

Bacterial Meningitis: Most Likely Etiologies and Empiric Therapy by Age Group

Age	Most Likely Organisms	Empirical Therapy[a]
<1 month	*S. agalactiae* Gram-negative enterics[b] *L. monocytogenes*	Ampicillin + cefotaxime *or* ampicillin + aminoglycoside
1-23 months	*S. pneumoniae* *N. meningitidis* *H. influenzae* *S. agalactiae*	Vancomycin[c] + third-generation cephalosporin (cefotaxime *or* ceftriaxone)
2-50 years	*N. meningitidis* *S. pneumoniae*	Vancomycin[c] + third-generation cephalosporin (cefotaxime *or* ceftriaxone)
>50 years	*S. pneumoniae* *N. meningitidis* Gram-negative enterics[b] *L. monocytogenes*	Vancomycin[c] + ampicillin + third-generation cephalosporin (cefotaxime *or* ceftriaxone)

[a]Data from References 26 and 27.

[b]*E. coli*, *Klebsiella* spp., *Enterobacter* spp. common.

[c]Vancomycin use should be based on local incidence of penicillin-resistant *S. pneumoniae* and until cefotaxime or ceftriaxone minimum inhibitory concentration results are available.

Strength of recommendation: (A) Good evidence to support a recommendation for use; should always be offered. (B) Moderate evidence to support a recommendation for use; should generally be offered.[26]

Quality of evidence: (i) Evidence from one or more properly randomized, controlled trial. (ii) Evidence from one or more well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from one or more center) or from multiple time-series. (iii) Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.[26]

TABLE 128-3

Penetration of Anti-infective Agents into the CSF[a]

Therapeutic Levels in CSF With or Without Inflammation	
Acyclovir	Levofloxacin
Chloramphenicol	Linezolid
Ciprofloxacin	Metronidazole
Fluconazole	Moxifloxacin

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Flucytosine	Pyrazinamide
Foscarnet	Rifampin
Fosfomycin	Sulfonamides
Ganciclovir	Trimethoprim
Isoniazid	Voriconazole
Therapeutic Levels in CSF With Inflammation of Meninges	
Ampicillin ± sulbactam	Imipenem
Aztreonam	Meropenem
Cefepime	Nafcillin
Cefotaxime	Ofloxacin
Ceftazidime	Penicillin G
Ceftriaxone	Piperacillin/tazobactam[b]
Cefuroxime	Pyrimethamine
Colistin	Quinupristin/dalfopristin
Daptomycin	Ticarcillin ± clavulanic acid[b]
Ethambutol	Vancomycin
Nontherapeutic Levels in CSF With or Without Inflammation	
Aminoglycosides	Cephalosporins (second generation)[d]
Amphotericin B	Doxycycline[e]
β-Lactamase inhibitors[c]	Itraconazole[f]
Cephalosporins (first generation)	

[a]Data from Reference *36*.

[b]May not achieve therapeutic levels against organisms with higher MIC, as in *P. aeruginosa*. Tazobactam does not penetrate BBB.

[c]Includes clavulanic acid, sulbactam, and tazobactam.

[d]Cefuroxime is an exception.

[e]Documented effectiveness for *B. burgdorferi*.

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[f]Achieves therapeutic concentrations for *Cryptococcus neoformans* therapy.

6 Acute bacterial meningitis is a neurologic emergency. An empiric antimicrobial therapy should be initiated as soon as possible after a diagnosis is suspected.[26] The first dose of antibiotics should not be withheld, even when lumbar puncture is delayed or neuroimaging is being performed. It is strongly recommended that the time period from suspected diagnosis to initiation of antibiotic treatment should not exceed 1 hour.[27]

Supportive care, particularly early in the course of treatment, is important. Administration of fluids, electrolytes, antipyretics, and analgesics may be indicated for patients presenting with a possible CNS infection. Additionally, venous thromboembolism prophylaxis, antiepileptic therapy, and ICP monitoring may be needed. Patients may require the administration of osmotic diuretics such as mannitol 25% or hypertonic saline to maintain an ICP of less than 15 mm Hg (2 kPa) and a cerebral perfusion pressure of 60 mm Hg (8 kPa) or more. Other supportive care measures may include respiratory and circulatory supports, gastrointestinal (GI) care, and maintaining normal body temperature.

Although supportive treatment may be indicated in certain patients with acute bacterial meningitis, the routine use of adjuvant mannitol, acetaminophen, antiepileptic agents, or hypertonic saline is not recommended according to the European guidelines.[27] Furthermore, therapeutic hypothermia and glycerol are contraindicated because they have been associated with a higher mortality rate.[37,38] However, a Cochrane meta-analysis including 1,272 patients (mostly children under 16 years) demonstrated no effect of glycerol on mortality.[39]

7 Several factors influence the transfer of antibiotic from capillary blood into the CNS. Notably, antibiotic penetration is increased through inflamed meninges due to damage to tight junctions between capillary endothelial cells and reduction of the activity of energy-dependent efflux pumps in the choroid plexus responsible for movement of penicillins and, to a lesser extent, fluoroquinolones and aminoglycosides (Table 128-3). Antibiotics having low molecular weights are passed more easily through biologic barriers than compounds of higher molecular weight. Furthermore, only nonionized antibiotics at physiologic or pathologic pH are capable of diffusion. Highly lipid-soluble compounds penetrate more readily than water-soluble compounds. Antibiotics not extensively bound to plasma proteins provide a larger free fraction of drug capable of passing into the CSF. However, passage of large, polar antibiotics into the CSF may be assisted by a carrier transport system. Antibiotic dosages in the treatment of CNS infections must be optimized to ensure adequate penetration to the site of infection.

Challenges of CSF penetration were traditionally overcome by direct instillation of antibiotics intrathecally or intraventricularly. Advantages of direct instillation, however, must be weighed against the risks of invasive CNS procedures and adverse effects. Intraventricular delivery may be necessary in patients who have shunt infections that are difficult to eradicate or who cannot undergo surgical management.[26] Antimicrobial agents often utilized for bacterial meningitis treatment have adequate CSF penetration, which has limited the need for direct CNS instillation for this type of infection. The Infectious Diseases Society of America (IDSA) guidelines for healthcare-associated meningitis and ventriculitis recommend considering the use of intraventricular antibiotics only in patients who fail or respond poorly to systemic treatment.[12]

8 Although the length of treatment for acute bacterial meningitis is generally based on the causative organism, there is no universally accepted standard (Table 128-4).[12,26,27] Meningitis caused by *S. pneumoniae* has been treated successfully with 10 to 14 days of antibiotic therapy, while cases caused by *N. meningitidis* or *H. influenzae* usually can be treated with a 7-day course. In contrast, a longer duration (21 days or more) has been recommended for patients with *L. monocytogenes*, gram-negative or pseudomonal meningitis. Nonetheless, antibiotic treatments for bacterial meningitis should be individualized, and some patients may require prolonged courses.

TABLE 128-4

Antimicrobial Agents of First Choice and Alternative Choice in the Treatment of Meningitis Caused by Gram-Positive and Gram-Negative Microorganisms

Organism	Antibiotics of First Choice	Alternative Antibiotics	Recommended Duration of Therapy
Gram-Positive Organisms			

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Streptococcus pneumoniae[a]			10-14 days
Penicillin susceptible MIC ≤0.06 mcg/mL (mg/L)	Penicillin G or Ampicillin (A-III)	Cefotaxime (A-III), Ceftriaxone (A-III), Cefepime (B-II), or Meropenem (B-II)	
Penicillin resistant MIC >0.06 mcg/mL (mg/L)	Vancomycin[b,c] + Cefotaxime or Ceftriaxone (A-III)	Moxifloxacin (B-II)	
Ceftriaxone resistant MIC >0.5 mcg/mL (mg/L)	Vancomycin[b,c] + Cefotaxime or Ceftriaxone (A-III)	Moxifloxacin (B-II)	
Staphylococcus aureus			14-21 days
Methicillin susceptible	Nafcillin or Oxacillin (A-III)	Vancomycin (A-III) or Meropenem (B-III)	
Methicillin resistant	Vancomycin[b,c] (A-III)	Trimethoprim-sulfamethoxazole or Linezolid (B-III)	
Group B *Streptococcus*	Penicillin G or Ampicillin (A-III) ± Gentamicin[b,c]	Ceftriaxone or Cefotaxime (B-III)	14-21 days
S. epidermidis	Vancomycin[b,c] (A-III)	Linezolid (B-III)	14-21 days[d]
L. monocytogenes	Penicillin G or Ampicillin ± Gentamicin[b,c,e] (A-III)	Trimethoprim-sulfamethoxazole (A-III), Meropenem (B-III)	≥21 days
Gram-Negative Organisms			
Neisseria meningitis			7-10 days
Penicillin susceptible	Penicillin G or Ampicillin (A-III)	Cefotaxime or Ceftriaxone (A-III)	
Penicillin resistant	Cefotaxime or Ceftriaxone (A-III)	Meropenem or Moxifloxacin (A-I)	

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Haemophilus influenzae			7-10 days
β-lactamase negative	Ampicillin (A-III)	Cefotaxime (A-III), Ceftriaxone (A-III), Cefepime (A-III), or Moxifloxacin (A-III)	
β-lactamase positive	Cefotaxime or Ceftriaxone (A-I)	Cefepime (A-I) or Moxifloxacin (A-III)	
Enterobacteriaceae[f]	Cefotaxime or Ceftriaxone (A-II)	Cefepime (A-III), Moxifloxacin (A-III), Meropenem (A-III), or Aztreonam (A-III)	21 days
Pseudomonas aeruginosa	Cefepime or Ceftazidime (A-II) ± Tobramycin[b,c] (A-III)	Ciprofloxacin (A-III), Meropenem (A-III), Piperacillin plus Tobramycin[a,b] (A-III), Colistin sulfomethate[g] (B-III), Aztreonam (A-III)	21 days

[a]Data from References *12, 26* and *27*.

[b]Direct CNS administration may be considered if failed conventional treatment.

[c]Monitor serum drug levels.

[d]Based on clinical experience; no clear recommendations.

[e]European guidelines recommend adding gentamicin for the first 7 days of treatment.

[f]Includes *E. coli* and *Klebsiella* spp.

[g]Should be reserved for multidrug-resistant pseudomonal or Acinetobacter infections for which all other therapeutic options have been exhausted.

See Table 128-2 footnotes for rating scale of evidence.

PATIENT CARE PROCESS

Patient Care Process for CNS Infections

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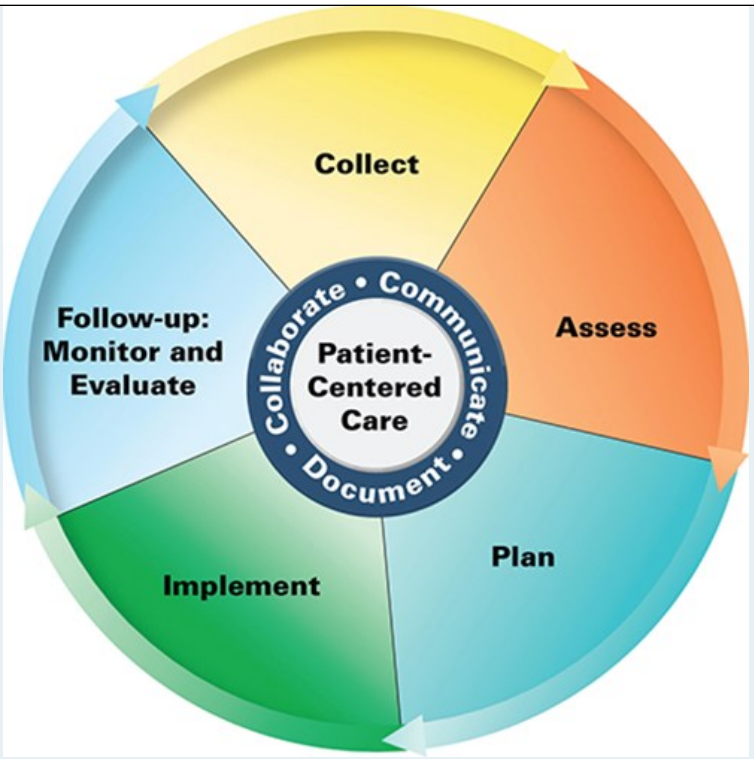

Collect

- Patient characteristics (eg, age, sex, weight, height, pregnancy/breastfeeding status, allergies)
- Patient medical history (personal and family)
- Social history (eg, alcohol/illicit drug use, recent travel, home residence, exposure to animals) and dietary habits including intake of unpasteurized dairy products
- Current medication use including anti-infective and immunomodulating agents
- Vaccination history (eg, PCV13, PPSV23, Hib, MenACWY, MenB, influenza, COVID-19)
- Objective data
    - Vitals (eg, temperature, blood pressure, pulse, respiratory rate), and laboratories (white blood cell count, lactate, procalcitonin, serum creatinine, blood urea nitrogen)
    - Blood/CSF examination, cultures, Gram stain, PCR, 16s rRNA, smear, AFB, serology radiologic imaging (MRI, CT)

Assess

- Presence of risk factors (eg, vaccination history, immunocompromised status, asplenia, recent dental procedure, endocarditis, consumption of unpasteurized dairy products, central venous catheter, CSF shunt)
- Signs and symptoms (eg, temperature >100.4 °F [38 °C], nuchal rigidity, headache, Kernig's and Bruzinski's signs [Figs. 128-4 and 128-5], CSF characteristics [Table 128-1], radiographic evidence, pathogen identification)
- Local susceptibilities of suspected/proven pathogen(s)
- Source control of focal infection (eg, minimally invasive aspiration of brain abscess)

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- Barriers for successful completion of therapeutic regimen
- Candidates for chemoprophylaxis

Plan*

- Evidence-based empiric drug therapy regimen including anti-infective agent(s) with good CNS penetration (Table 128-3), dose, route, frequency, and duration (see Tables 128-2 and 128-5, the sections "Healthcare-Associated Ventriculitis and Meningitis," "Bacterial Brain Abscess," "Viral Encephalitis," and "CNS Infections in Special Populations").
- Definitive anti-infective therapy if specific pathogen identified (Tables 128-4 and 128-5, sections as above)
- Corticosteroid use when indicated
- Monitoring parameters including efficacy (eg, fever, mental status, meningismus, white blood cell count, radiologic resolution of focal infection, drug monitoring) and safety (eg, renal function, drug-drug interactions); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, invasive procedures, drug-specific information)
- Referrals to other providers when appropriate (eg, infectious diseases, neurologist, interventional radiologist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Ensure effective transitions of care
- Schedule follow-up if treatment continues as outpatient (eg, SCr, adherence assessment, radiographic imaging)

Follow-up: Monitor and Evaluate

- Resolution of CNS infection symptoms (eg, fever, nuchal rigidity, headache, altered mental status)
- Presence of adverse effects (eg, acute renal injury, electrolyte abnormalities, QT interval prolongation)
- Patient adherence to treatment plan using multiple sources of information
- Duration of therapy based on evidence-based guidelines, clinical and radiologic progress

*_Collaborate with patient, caregivers, and other healthcare professionals._

TABLE 128-5

Dosing of Anti-infective Agents by Age Group

Agent	Infants and Children	Adults	Monitoring/Comments
Antibacterial			
Ampicillin	75 mg/kg every 6 h	2 g every 4 h	
Aztreonam	40mg/kg every 6-8 h	2 g every 6-8 h	Alternative for severe penicillin allergy
Cefepime	50 mg/kg every 8 h	2 g every 8 h	Consider prolonged infusion

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Cefotaxime	75 mg/kg every 6-8 h	2 g every 4-6 h	Preferred in neonates
Ceftazidime	50 mg/kg every 8 h	2 g every 8 h	
Ceftriaxone	100 mg/kg daily	2 g every 12 h	Avoid in neonates
Ciprofloxacin	10 mg/kg every 8 h	400 mg every 8-12 h	Consider higher doses for *P. aeruginosa*
Colistin	5 mg/kg/day (package insert dosing)	5 mg/kg/day (package insert dosing)	Consider intraventricular doses Only for MDR organisms Monitor renal function
Gentamicin	2.5 mg/kg every 8 h	2 mg/kg every 8 h or 5-7 mg/kg daily	TDM is recommended
Levofloxacin	—	750 mg daily	May prolong QTc
Linezolid	10 mg/kg every 8-12 h	600 mg every 12 h	May cause thrombocytopenia and peripheral neuropathy
Meropenem	40 mg/kg every 8 h	2 g every 8 h	Consider prolonged infusion
Moxifloxacin	—	400 mg daily	May prolong QTc
Oxacillin/Nafcillin	50 mg/kg every 6 h	2 g every 4 h	Nafcillin preferred if renal dysfunction
Penicillin G	0.05 million Units/kg every 4 h	4 million Units every 4 h	
Polymyxin B	—	1.25-1.5 mg/kg every 12 h	Only for MDR organisms No data in pediatric patients
Tobramycin	2.5 mg/kg every 8 h	2.5 mg/kg every 8 h or 5-7 mg/kg daily	TDM is recommended Monitor renal function
Trimethoprim-sulfamethoxazole	5 mg/kg every 6-12 h	5 mg/kg every 6-12 h	Dose based on trimethoprim
Vancomycin	15 mg/kg every 6 h	15-20 mg/kg every 8-12 h	TDM is recommended Monitor renal function
Antifungals			
Conventional Amphotericin B	1 mg/kg daily	0.7-1 mg/kg daily	Monitor renal function Maintain adequate hydration
Lipid amphotericin B	3-5 mg/kg once daily	3-5 mg/kg daily	Monitor renal function Maintain adequate hydration
Flucytosine	25 mg/kg every 6 h	25 mg/kg every 6 h	Consider TDM to avoid bone marrow suppression
Fluconazole	6-12 mg/kg daily	400-800 mg daily	Monitor liver function

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Voriconazole	9mg/kg every 12 h × 2 doses then 8 mg/kg every 12 h	6 mg/kg every 12 h × 2 doses then 4 mg/kg every 12 h	Consider TDM Many drug-drug interactions Monitor liver function
Antivirals			
Acyclovir	10-20 mg/kg every 8 h	10-20 mg/kg every 8 h	Monitor renal function Maintain adequate hydration
Ganciclovir	—	5 mg/kg every 12 h	Monitor renal function
Foscarnet	—	60 mg/kg every 8 h or 90 mg/kgevery 12 h	Monitor renal function Maintain adequate hydration

TDM, therapeutic drug monitoring. Data from References *12, 14, 26 and 27*.

ACUTE BACTERIAL MENINGITIS

Causative Organisms

Streptococcus pneumoniae (Pneumococcus or Diplococcus)

9 *S. pneumoniae* continues to be the leading cause of community-acquired bacterial meningitis in patients 2 months of age or older. It accounts for approximately 40% to 50% of bacterial meningitis cases in the United States, with an overall case fatality rate of ~8% to 22%.[2,9,40] Despite declining rates of pneumococcal meningitis since the introduction of PCV7 and PCV13 vaccinations in 2000 and 2010, respectively, case fatality rate has not significantly changed from the pre-PCV7 era.[2,41] Pneumonia, bloodstream infection, endocarditis, CSF leak secondary to head trauma, splenectomy, alcoholism, sickle cell disease, and bone marrow transplantation may predispose the patient to the development of pneumococcal meningitis. Coma, hearing impairment, and seizures are common neurologic complications due to *S. pneumoniae* meningitis.

5 Based on resistance patterns, penicillin should not be used as empiric therapy if *S. pneumoniae* is suspected. Furthermore, appropriate Clinical Laboratory Standards Institute (CLSI)-approved testing of all CSF isolates for penicillin resistance is recommended. Ceftriaxone and cefotaxime have served as alternatives to penicillin in the treatment of penicillin-nonsusceptible pneumococci. Of note, higher minimum inhibitory concentration (MIC) with cephalosporins and higher cephalosporin resistance rates were noted in penicillin-resistant isolates, with the exception of ceftaroline.[42] Therapeutic approaches to cephalosporin-resistant pneumococci include the addition of vancomycin or, to a lesser extent, rifampin. The combination of vancomycin and ceftriaxone can be used as empirical treatment until antimicrobial susceptibility data are available.[25-27]

Given the limited therapeutic options for penicillin- and cephalosporin-resistant pneumococcal meningitis, newer agents have been evaluated. Meropenem is approved for the treatment of bacterial meningitis in children aged 3 months and older and has shown similar clinical and microbiologic efficacies to cefotaxime or ceftriaxone. Meropenem is recommended as an alternative to a third-generation cephalosporin in penicillin-nonsusceptible isolates. Some caution is warranted with the use of imipenem for CNS infections, given the risk of drug-induced seizures, especially when doses are not properly adjusted for declining renal function. Of note, seizures may be caused by meningitis itself or imipenem, and the cause is often difficult to differentiate. Levofloxacin and moxifloxacin represent additional therapeutic options with favorable activity against multidrug-resistant pneumococci and good penetration into the CSF.[12,43]

Intravenous linezolid, daptomycin, and ceftaroline have also emerged as viable therapeutic options for treating multidrug-resistant gram-positive infections. Linezolid in combination with ceftriaxone has been used to treat limited cases of pneumococcal meningitis with outcomes similar to standard treatment.[44] Further research is required to delineate the clinical utility of therapeutic options such as daptomycin and ceftaroline and determine their place in therapy.[45,46]

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Pneumococcal vaccines help reduce the risk of invasive pneumococcal disease (IPD). Virtually all serotypes of *S. pneumoniae* exhibiting intermediate or complete resistance to penicillin are included in the 23-serotype pneumococcal polysaccharide vaccine (PPSV23). Use of the heptavalent pneumococcal conjugate vaccine (PCV7), introduced in 2000, significantly reduced the incidence of invasive pneumococcal infections, including sepsis and meningitis. However, in the decade following its introduction, rate of invasive disease caused by non-PCV7 strains increased considerably, especially serotype 19A, leading to the development of a newer vaccine with expanded coverage. In 2010, the FDA approved PCV13 to replace PCV7. In the first 3 years after the introduction of PCV13 in the United States, investigators estimated over 30,000 cases of IPD and 3,000 deaths were potentially averted.[47] Between 1998 and 2018, rates of IPD in the United States among children and adults have steadily decreased since PCV7 and PCV13 introductions.[48]

For current recommendations on vaccinations against pneumococcal disease and high-risk groups, refer to Chapter 147, "Vaccines, Toxoids, and Other Immunobiologics" in this book and the current guidelines by the Advisory Committee on Immunization Practices (ACIP).

Neisseria meningitidis (Meningococcus)

1 *N. meningitidis* is a leading cause of bacterial meningitis among children and young adults in the United States and around the world.[2,49] Incidence of meningococcal disease in the United States has been declining from 1.2 cases per 100,000 population in the 1990s to 0.1 cases per 100,000 population in 2018. Incidence peaks in infants <1-year-old (0.93 cases per 100,000 population) with a second peak in adolescents and young adults 16 to 23 years of age (0.23 cases per 100,000 population).[50] Five of the thirteen serogroups of *N. meningitidis* (A, B, C, Y, and W) are primarily responsible for invasive meningococcal disease. The proportion of cases caused by each serogroup varies by age group. Serogroup B causes ~65% of meningococcal disease among children <5 years old.[49]

N. meningitidis is spread by direct person-to-person close contact, including respiratory droplets and pharyngeal secretions. Close contacts of patients contracting meningococcal meningitis are at an increased risk of developing meningitis. Secondary cases of meningitis usually develop within the first week following exposure but may take up to 60 days after contact with the index case.[11] Clusters of disease are associated with crowding as in schools, dormitories, and military barracks. Other significant risk factors for meningococcal disease include complement deficiency, anatomic or functional asplenia, HIV infection, and passive or active smoking.[11]

The presence of petechiae may be the primary clue that the underlying pathogen is *N. meningitidis*.[25] Patients may also have an obvious or subclinical picture of disseminated intravascular coagulation (DIC). Deafness unilaterally or bilaterally may develop early or late in the disease course.

5 Third-generation cephalosporins (ie, cefotaxime and ceftriaxone) are the recommended empiric treatment for meningococcal meningitis (Table 128-4).[26,27] When final culture results are available, penicillin G or ampicillin is recommended for penicillin-susceptible isolates. Meropenem and fluoroquinolones are also suitable alternatives for the treatment of penicillin nonsusceptible meningococci. The recommended duration of therapy is typically 7 days if there is good clinical response.[26] Antimicrobial chemoprophylaxis of close contacts should be started as soon as possible (ideally <24 hours after identification of the index patient). There was an 84% reduction in the risk of invasive meningeal disease for 30 days after the index case when household contacts were given chemoprophylaxis. Ciprofloxacin and rifampin are the two most used chemoprophylactic agents, although antibiotic resistance can develop when meningococcal isolates are exposed to rifampin.[51] For further discussion on who should receive prophylaxis, interested readers can refer to current recommendations by the Centers for Disease Control and Prevention (CDC).[11]

Two types of meningococcal vaccines are available in the United States: two quadrivalent polysaccharide protein conjugate vaccine directed against serogroups A, C, W, and Y and two MenB vaccines directed against serogroup B meningococcal vaccine. The quadrivalent meningococcal conjugate vaccine is recommended for all people 11 to 12 years old with a booster dose at 16 years of age. Among adolescents ages 13 to 17 years old in the United States, 88.9% received ≥1 dose of the MenACWY vaccine in 2019.[52] Additionally, the outer membrane vesicle meningococcal B vaccine (MeNZB) is being assessed for vaccine effectiveness against gonorrhea in young adults, due to the 80% to 90% genetic homology in primary sequences between *N. gonorrhoeae* and *N. meningitidis*.[53] For full details on vaccine availability and vaccination recommendations in various age groups and for those with significant risk factors, refer to Chapter 147, "Vaccines, Toxoids, and Other Immunobiologics" in this book and the current recommendations from the ACIP.

Haemophilus influenzae Type b

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1 Widespread vaccination of infants and children has resulted in a dramatic decline in the global incidence of Hib meningitis from 31 to 5 per 100,000 children aged <5 years in 2000 and 2015, respectively.[54] Similarly, the global Hib meningitis case fatality ratio fell from 44% in 2000 to 23% in 2015. Interested readers can refer to Chapter 147, "Vaccines, Toxoids, and Other Immunobiologics" in this book for information on recommended Hib vaccine dosing and administration schedules. In neonates, infection is acquired intrapartum by aspiration of amniotic fluid or by contact with genital tract secretions containing the organism. In older children and adults, Hib meningitis should suggest the presence of other underlying conditions, including otitis media, epiglottitis, sinusitis, pneumonia, diabetes mellitus, sickle cell, asplenia, alcoholism, and immunodeficiency.

5 Third-generation cephalosporins (cefotaxime and ceftriaxone) are the drugs of choice for empiric therapy for Hib meningitis as they are active against β-lactamase–producing and non-β-lactamase–producing strains. Cefepime and fluoroquinolones are suitable alternatives regardless of β-lactamase activity. Ampicillin can be used if the isolate is susceptible. Beta-lactamase-negative, ampicillin-resistant strains of *H. influenzae* have been described and some experts recommend caution in using ampicillin when the penicillin minimum inhibitory concentration is 1 to 2 mcg/mL.[55] Recommended duration of treatment is 7 days (adults) or 7 to 10 days (children).[26,27]

Dexamethasone is beneficial for treatment of infants and children with Hib meningitis to diminish the risk of hearing loss, if given before or concurrently with the first dose of antimicrobial agent(s).[26,27,56] All invasive (including meningitis) cases should be reported to the local public health department.

9 Chemoprophylaxis is indicated to reduce the risk of secondary invasive Hib disease in close contacts by eliminating nasopharyngeal and oropharyngeal carriages of *H. influenzae*. For prophylaxis, rifampin should be administered orally (once a day for 4 days; 20 mg/kg/dose; maximum, 600 mg). The dose for infants younger than 1 month is not established; some experts recommend lowering the dose to 10 mg/kg.[56,57]

Streptococcus agalactiae (Streptococcus Group B)

Streptococcus group B (GBS) is a leading cause of meningitis in neonates and young infants, with a case fatality rate of 7.3% in pediatric patients and 20.8% in adult patients.[2] Neurologic sequelae include sight or hearing loss and cerebral palsy. Neonates acquire this infection through vertical transmission while passing through the vaginal canal during birth. GBS is an inhabitant of the human GI and genitourinary tracts. Maternal GBS colonization worldwide was shown to be 18% with regional variation from 11% to 35%.[58]

Early onset GBS infection occurs within the first 24 hours of life (range 0-6 days), whereas late-onset disease typically occurs from 7 to 89 days of age.[59] Universal prenatal screening and intrapartum antimicrobial prophylaxis of GBS-colonized pregnant women have significantly decreased the rate of early onset invasive disease.[60] However, late-onset disease cannot be prevented by intrapartum antimicrobial prophylaxis. Recommended agents for intrapartum prophylaxis are penicillin G or ampicillin, cefazolin (if penicillin allergy with low risk of anaphylaxis), clindamycin (if penicillin allergy with high risk of anaphylaxis and GBS isolate is known to be susceptible to clindamycin), or vancomycin (if penicillin allergy with high risk of anaphylaxis and GBS isolate not susceptible, or unknown susceptibility, to clindamycin). Intrapartum antibiotic prophylaxis should be started promptly to achieve the optimal antibiotic treatment window of at least 4 hours before birth.[61]

Maternal immunization represents a non-antibiotic strategy to prevent both early- and late-onset GBS infection and has been a focus of the WHO.[62] There are currently no licensed GBS vaccines, although some promising conjugate vaccine candidates have been tested for safety and immunogenicity in phase I and II trials.

5 Ampicillin plus an aminoglycoside is the treatment of choice for a newborn infant with presumptive early onset GBS meningitis. Empiric treatment for late-onset meningitis differs by postnatal age at the time of evaluation. When group B streptococci are identified in culture, penicillin G is the drug of choice, with ampicillin as an acceptable alternative therapy.[59] For infants with uncomplicated meningitis, 14 days of treatment is satisfactory, but longer periods of treatment may be necessary for patients with prolonged or complicated courses; ventriculitis should be treated for at least 4 weeks. Ampicillin or penicillin G is the recommended agent for confirmed GBS meningitis in adults. Addition of an aminoglycoside could also be considered.[26] Alternative agents are third-generation cephalosporins and vancomycin. For adults with meningitis, the recommended duration of antibiotics is 14 to 21 days.

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Listeria monocytogenes

L. monocytogenes is a facultative anaerobic, gram-positive, diphtheroid-like organism that multiplies intracellularly. Meningitis due to *L. monocytogenes* primarily affects neonates, alcoholic or immunocompromised individuals (including pregnant women), and the elderly. Invasive infections in healthy young individuals remain rare. *L. monocytogenes* is implicated in approximately 10% of meningitis cases in patients older than 65 years of age and carries a case fatality rate of approximately 18% in the United States.[2]

Transmission usually involves colonization of the patient's gastrointestinal tract with the organism, which then penetrates the gut lumen to seed the bloodstream. Soft cheeses and raw produce are common causes of listeriosis outbreaks. Coleslaw, unpasteurized milk, ready-to-eat foods, and raw beef and poultry have also been identified as sources of this foodborne pathogen. Invasive disease includes bacteremia, meningitis, meningoencephalitis, or cerebritis. Infection of the CNS may be diffuse or localized.

5 8 Treatment of *L. monocytogenes* meningitis should consist of penicillin G or ampicillin. The addition of aminoglycoside is also recommended in proven infection for both children and adults. Trimethoprim-sulfamethoxazole and meropenem are recommended alternative agents, whereas there is less clinical experience with linezolid and fluoroquinolones. Despite *in vitro* activity against *L. monocytogenes*, intravenous vancomycin has been associated with high failure rates in patients with *L. monocytogenes* meningitis. Also, third-generation cephalosporins lack *in vitro* activity against *L. monocytogenes*. Patients should be treated for a minimum of 21 days.[26,27]

A national prospective study from France of 252 cases of neurolisteriosis showed significantly greater mortality in patients who received adjunctive dexamethasone within the first 24 hours.[63] This deleterious effect suggests that adjunctive dexamethasone should be avoided in the treatment of neurolisteriosis.

Dexamethasone as an Adjunctive Treatment for Acute Bacterial Meningitis

In addition to antibiotics, dexamethasone is a commonly used adjunctive therapy in the treatment of acute bacterial meningitis to immunomodulate the inflammatory response. Corticosteroids inhibit the production of TNF and IL-1, both potent proinflammatory cytokines.

A systematic review of 25 randomized controlled trials involving 4,121 participants showed that corticosteroid use in bacterial meningitis was associated with lower rates of hearing loss and short-term neurological sequelae in adults and children, but there was no mortality benefit in high-income countries. No beneficial effects were observed in low-income countries. Additionally, subgroup analyses demonstrated a 16% reduction in overall mortality in pneumococcal meningitis and a 66% reduction in severe hearing loss in children with *H. influenzae* meningitis.[64]

1 Routine use of dexamethasone in meningitis is not without controversy. A potential concern is that adjunctive dexamethasone therapy may reduce the penetration of antibiotics into the CSF by inhibiting or reducing meningeal inflammation. Appropriate concentrations of vancomycin in CSF may be obtained even when adjunctive dexamethasone is used, but the small number of subjects studied limits the generalization of these findings.[65] Recommendations by practice guidelines call for the use of adjunctive dexamethasone in infants and children (6 weeks of age and older) with *H. influenzae* meningitis.[26] The recommended intravenous dose is 0.15 mg/kg every 6 hours for 2 to 4 days, initiated 10 to 20 minutes prior to or concomitant with the first dose of antibiotics. In infants and children with pneumococcal meningitis, adjunctive dexamethasone may be considered after weighing the potential benefits and possible risks.[26,56] If pneumococcal meningitis is suspected or proven, adults should receive dexamethasone 0.15 mg/kg (up to 10 mg) every 6 hours for 2 to 4 days with the first dose administered 10 to 20 minutes prior to first dose of antibiotics. It is often difficult to ascertain the responsible pathogen on presentation. Therefore, some clinicians and the European guidelines recommend initiating dexamethasone in all patients (adults and children) presenting with suspected or proven community-acquired bacterial meningitis and consider discontinuation only if pathogens other than *H. influenzae* or *S. pneumoniae* are identified. Another difference between the US and European guidelines is that according to the European guidelines, dexamethasone can still be administered up to 4 hours after initiation of antibiotics.[27] Adjunctive dexamethasone in neurolisteriosis has been associated with reduced survival. Therefore, adjunctive dexamethasone should be discontinued if the meningitis is found to be caused by *L. monocytogenes*.[63]

HEALTHCARE-ASSOCIATED VENTRICULITIS AND MENINGITIS

Healthcare-associated meningitis and ventriculitis, formerly referred to as nosocomial meningitis, is a subclass of bacterial meningitis that largely

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occurs in neurosurgical patients.[12] The disease process in these patients can be more indolent compared to those with community-acquired bacterial meningitis. The most likely pathogens associated with CSF shunt and drain infections are coagulase-negative staphylococci (especially *Staphylococcus epidermidis*), *S. aureus, Propionibacterium* (now *Cutibacterium*) *acnes*, and gram-negative bacilli; including *E. coli*, Enterobacter species, Citrobacter species, Serratia species, and *Pseudomonas aeruginosa*. In the presence of prosthetic devices, some of the microorganisms form biofilms which compromise antibiotic penetration.

Diagnosis of healthcare-associated meningitis and ventriculitis can be challenging and should focus on CSF fluid analysis and culture. However, patients may have only modest abnormalities in CSF cell counts. Additionally, CSF Gram stain may be unreliable—particularly in the setting of systemic antibiotic exposure. If possible, antibiotic therapy should be delayed until CSF can be recovered for culture. A negative CSF culture following antimicrobial therapy is not sufficient to exclude healthcare-associated meningitis or ventriculitis.[66] Use of extended hold cultures is encouraged to increase recovery of slow-growing pathogens such as *C. acnes.* If a CSF drain or shunt is removed due to possible infection, then these components should be cultured as well. Blood cultures may be considered in those with ventriculopleural or ventriculoperitoneal shunts but are recommended in those with ventriculoatrial shunts.[12] 1-3-β-D-glucan may be useful in diagnosing fungal meningitis and ventriculitis because of the low sensitivity of CSF culture for fungal pathogens.[67]

Empiric use of broad-spectrum antibiotic therapy is critical for the treatment of healthcare-associated meningitis and ventriculitis because of the variety of organisms implicated in these cases. Empiric treatment should include intravenous vancomycin coupled with an anti-pseudomonal β-lactam such as meropenem, cefepime, or ceftazidime. All agents should be dosed to maximize CNS penetration.[12] Piperacillin-tazobactam is not recommended given the suboptimal CNS penetration of tazobactam. Continuous infusion vancomycin may optimize vancomycin exposure in the CSF but clinical data remain scant.[68]

Once culture results are available, antibiotic therapy can be tailored. Staphylococcus spp. are important causative pathogens in healthcare-associated meningitis and ventriculitis, particularly among patients with intracranial or spinal hardware. For methicillin-susceptible *S. aureus* (MSSA), the treatment of choice is nafcillin or oxacillin. For methicillin-resistant *S. aureus* (MRSA), vancomycin is preferred. Rifampin may be considered for staphylococcal infections if the isolate is susceptible. Rifampin is indicated when there is hardware present for optimal biofilm penetration. If β-lactam or vancomycin therapy is not possible then clinicians may consider linezolid or trimethoprim-sulfamethoxazole. Daptomycin may also be considered although given its limited CNS penetration aggressive dosing is probably necessary (eg, 10-12 mg/kg/day).[12,69]

5 The treatment of meningitis due to *P. aeruginosa* remains a challenge because antibiotics showing good antibacterial activity, such as antipseudomonal penicillins and aminoglycosides, penetrate the CSF moderately or poorly (Table 128-3). Initially, cases of *P. aeruginosa* meningitis should be treated with an extended-spectrum β-lactam such as ceftazidime or cefepime, or alternatively aztreonam, ciprofloxacin, or meropenem depending on local susceptibility patterns. The addition of an aminoglycoside, usually tobramycin, to one of the aforementioned agents can also be considered. Since aminoglycosides penetrate the CSF poorly, their inclusion is to predominantly aid in the treatment of extracerebral infections.

Multidrug-resistant *P. aeruginosa*, Acinetobacter, and carbapenem-resistant Enterobacterales infections are of concern to clinicians because of the limited therapeutic options available. This concern has led to the reemergence of the use of older antibiotics, such as colistin and polymyxin B. Colistin can be used, both intravenously and intrathecally, in the treatment of multidrug-resistant *P. aeruginosa* or Acinetobacter CNS infections. The use of colistin should be reserved for only the most severe cases.

New cephalosporin-β-lactamase inhibitor combination agents (ceftolozane-tazobactam and ceftazidime-avibactam) have yet to be formally studied in patients with CNS infections, but may represent alternative therapies for multidrug resistant gram-negative organisms. For instance, ceftazidime/avibactam resulted in several successful treatments of meningitis caused by a KPC-producing *Klebsiella pneumoniae*.[70,71] Ceftaroline, a novel cephalosporin with affinity for PBP2a has shown promise in a case series of *S. pneumoniae* and *S. aureus* meningitis as well as three other case reports of MRSA meningitis/ventriculopleural shunt infections.[45,72-74] The pharmacokinetic properties of ceftaroline suggest it is probably reliable for CNS infections, particularly if using every 8-hour dosing.

Other gram-negative organisms causing meningitis, excluding *P. aeruginosa* and Acinetobacter spp., most likely can be treated with a third- or fourth-generation cephalosporin, such as cefotaxime, ceftriaxone, ceftazidime, or cefepime. Ceftazidime, however, may not be the best choice of empiric monotherapy for situations where the offending organism is unknown initially due to lack of reliable gram-positive activity. Cefotaxime should be used in place of ceftriaxone in the neonatal period because of the potential of ceftriaxone to displace bilirubin from its albumin-binding sites.

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Trimethoprim-sulfamethoxazole may offer utility for ventriculitis and meningitis caused by Enterobacterales, given that its penetration into the CSF does not depend on meningeal inflammation. Fluoroquinolones, such as ciprofloxacin, exhibit good penetration into the CSF and are recommended as alternative agents for the treatment of susceptible gram-negative bacilli, including *P. aeruginosa*, when susceptible.

For patients with documented or suspected fungal meningitis or ventriculitis, empiric lipid formulation of liposomal amphotericin B in combination with flucytosine is recommended.[12,75] Once susceptibility is confirmed, fluconazole may be used for Candida spp. recovered from CSF. Echinocandins are large molecules that penetrate poorly into the CNS and are not recommended for fungal meningitis or ventriculitis. For suspected or confirmed Aspergillus spp., the treatment of choice is voriconazole targeting a serum trough level of 2 to 5 mg/L (6 to 14 µmol/L).[12,76]

8 Some patients with meningitis or ventriculitis respond poorly to systemic antibiotic therapy. For these patients intraventricular therapy should be considered. Numerous antimicrobials can be given intraventricularly, including amikacin, amphotericin B deoxycholate, colistimethate sodium, daptomycin, gentamicin, polymyxin B, quinupristin/dalfopristin, tobramycin, and vancomycin. There is no consensus on the optimal dose of intraventricular antimicrobial that should be used; however, some general recommendations are available.[12] If used, intraventricular antibiotic therapy requires vigilance in preparation and administration. Preservative-free product and diluents should be used unless no preservative-free products exist. For patients receiving antimicrobial therapy through a ventricular drain, the drain should be clamped for 15 to 60 minutes to allow antimicrobial equilibration throughout the CSF.

CSF cultures may remain positive for several days or more with a regimen that eventually will be curative. Therapeutic efficacy can be monitored through bacterial colony counts every 2 or 3 days, which should decrease progressively over the period of therapy. Duration of therapy for healthcare-associated meningitis and ventriculitis is based on clinical response and the offending pathogen. For instance, for *P. acnes* and coagulase-negative Staphylococcal spp., IDSA guidelines recommend 10 to 14 days. For *S. aureus* and gram-negative pathogens 14 days or longer is recommended. For those with persistently positive CSF cultures therapy should continue for 10 to 14 days following the last positive culture.[12]

Finally, another important opportunity for antibiotic optimization exists for patients with external ventricular drains (EVDs). Patients with EVD are often given systemic antibiotic therapy (eg, cefazolin) for infection prophylaxis for the duration of EVD placement to prevent ventriculostomy-related infections. However, the Neurocritical Care Society recommended against this practice citing the potential for harm (eg, *Clostridioides difficile* and antimicrobial-resistant pathogens) from the lack of efficacy attributable to antibiotic prophylaxis.[77] Instead the authors recommend administering one dose of antimicrobials prior to EVD insertion, avoiding routine CSF sampling, and using antibiotic-impregnated EVD catheters. Current guidelines also recommend against extended antibiotic prophylaxis following EVD insertion.[12]

BACTERIAL BRAIN ABSCESS

Brain abscess is a life-threatening focal infection of the brain that begins as a localized area of cerebritis and develops into a collection of pus surrounded by a well-vascularized capsule.[78] In immunocompetent patients, bacteria account for >95% of brain abscesses. Bacteria enter the brain either through contiguous spread (eg, following infection in the oropharynx, middle ear, paranasal sinuses, or neurosurgical procedures and cranial trauma), or hematogenous spread due to distant infections (eg, infective endocarditis, congenital heart disease, dental infection, or pulmonary abscess). Abscess occurs most commonly in the frontal lobe, but can occur in any location.[79] Mortality rates have declined significantly in the past 50 years, with 70% of survivors expected to have no to minimal neurologic sequelae, although data on long-term functional and neuropsychological evaluation are lacking.[80]

2 The clinical presentation varies depending on the number, size, and location of the abscess, and diagnosis can be challenging due to this variable presentation. Headache, mental status changes, focal neurologic deficits, and fever are the most common symptoms of brain abscess. Brain imaging is the cornerstone for the diagnosis of brain abscess, with MRI being the preferred modality over contrast-enhanced CT due to better resolution and differentiation of abscesses from tumors. Blood samples should be collected prior to initiation of antibacterial treatment for anaerobic and aerobic cultures, molecular biology, serology, and other diagnostic tests.

The etiology of brain abscess depends on the initial site of infection and the immune state of the host. Abscesses arising from spread of infection from oropharynx, middle ear, and paranasal sinuses are commonly caused by *S. aureus*, streptococci, and oral anaerobes (eg, Actinomyces spp., Bacteroides spp., Fusobacterium spp., or Peptostreptococcus spp.). Dental infections are associated with abscesses caused by Streptococcus spp. and

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Bacteroides fragilis. Staphylococci and Enterobacterales are commonly involved in postoperative abscesses or those following head trauma. *Toxoplasma gondii, Mycobacterium tuberculosis*, Listeria spp., and Nocardia spp. can also cause brain abscesses and are more commonly seen in immunocompromised patients.[79]

5 All lesions equal to or greater than 2.5 cm in diameter should be stereotactically aspirated or surgically excised and specimens should be sent to the microbiology and pathology laboratory.[78,80] Because brain abscesses are commonly polymicrobial, empiric antimicrobial therapy should include antibiotics with activity against gram-positive, gram-negative, and anaerobic organisms. The antimicrobial agents should penetrate into the abscess cavity and remain active in acidic environments. Most commonly the regimen includes a third- or fourth-generation cephalosporin plus metronidazole. Vancomycin should be added when infection caused by MRSA is suspected. Ceftazidime or cefepime can be used if *P. aeruginosa* is suspected. A carbapenem (such as meropenem) could replace the cephalosporin and metronidazole. In immunocompromised patients, the empiric regimen may be supplemented with voriconazole, and trimethoprim-sulfamethoxazole or sulfadiazine to cover fungi and Nocardia while awaiting definitive results. De-escalation of therapy should occur once a causative organism is identified. Repeated neuroimaging should be performed to monitor for abscess resolution or progression.

Prophylactic anticonvulsant therapy and corticosteroids are not routinely recommended.[80] Corticosteroids are not routinely used in brain abscess, and are typically reserved for use in patients with edema causing increased intracranial pressure, brain shift, or increased risk of cerebral herniation. Intravenous antibiotics have traditionally been administered for 6 to 8 weeks, although shorter or longer durations may be used depending on the clinical and radiologic progress. Given the risk of neurotoxicity with prolonged courses of metronidazole, it may be discontinued once anaerobic pathogens have been ruled out. Oral options can consist of ciprofloxacin, metronidazole, trimethoprim-sulfamethoxazole, and amoxicillin but there is no consensus when transition to oral agents can be safely done.

VIRAL ENCEPHALITIS

Encephalitis refers to inflammation of the brain parenchyma in association with clinical evidence of neurologic dysfunction. “Meningoencephalitis” is a term commonly used to describe meningeal inflammation along with encephalitis. Infectious encephalitis should be distinguished from those patients with encephalopathy (eg, due to metabolic disturbances, intoxications, hypoxia, or systemic infections) or noninfectious encephalitis (eg, postimmunization encephalitis or encephalomyelitis), as they have similar clinical presentations.[14] While a confirmed or probable pathogen is identified in less than 50% of cases, viral etiologies are the most commonly diagnosed.[7,15] Collectively, about 20,000 encephalitis-associated hospitalizations are expected per year in the United States, with a case fatality rate of more than 5%. Of those 20,000 hospitalizations, approximately 20% are due to viral pathogens.

The epidemiology of viral encephalitis in the United States has changed dramatically since the mid-1960s due to the introduction of large-scale polio, rubella, varicella-zoster virus, and mumps immunization programs. The most common causes of viral encephalitis/meningoencephalitis in the United States is enteroviruses, followed by herpes viruses and arboviruses.[7,15,16]

Less common causes include adenoviruses, influenza, rotavirus, corona virus, cytomegalovirus (CMV), varicella-zoster virus, Epstein-Barr virus, West Nile Virus (WNV), and lymphocytic choriomeningitis. In recent years, Powassan, Chikungunya, and Zika viruses have emerged as increasing causes of encephalitis in North America. These arboviruses are transmitted via ticks (Powassan) or mosquitoes (Chikungunya and Zika) and have a diverse spectrum of disease. Of these, Powassan virus has seen the largest increase in incidence; prior to 1999 there was an average of 0.7 cases per year in the United States and Canada. In 2003, the CDC included Powassan virus as a reportable disease, resulting in 181 cases reported between 2010 and 2019, with 43 cases reported in 2019 alone.[81]

Zika virus sparked global attention in 2016 after the first cases of brain developmental disorders in newborns were linked to Zika virus infection of their mothers during pregnancy. Epidemiologic and experimental studies have now provided strong support for causality between Zika virus infection during pregnancy and congenital structural abnormalities of the brain.[82] Since 2019 there have been no confirmed reports of Zika disease transmitted by mosquitoes in the United States.[83] Several vaccine candidates for the prevention of Zika disease are in development, although none are approved for use at this time.

Viral encephalitis is acquired primarily by hematogenous spread or, alternatively, by neuronal spread of the causative pathogen. After entry into the

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host, viral replication occurs, resulting in dissemination through the reticuloendothelial system or vasculature. Infection of the capillary endothelial cells and choroid plexus may provide a conduit for CNS infections. Viruses such as polio, HSV, and Varicella-zoster virus may also gain access to the CNS by axonal retrograde transmission from peripheral nerve endings. Once a virus gains access to the CNS, the course of infection depends on the virulence of the particular virus and the host immune response. Subsequent neuronal injury is caused by direct cell damage due to viral replication, but inflammatory and immune-mediated responses also contribute to neurological damage.

2 In contrast with purulent meningitis, host response to viral encephalitis is mediated primarily through cytotoxic T-lymphocytes. Increases in concentrations of IL-1, IL-6, and interferon (INF) α, β, and γ may occur. The clinical syndrome associated with viral encephalitis generally is independent of viral etiology and may vary depending on the patient's age. Common signs in adults include headache, mild fever, nuchal rigidity, malaise, drowsiness, nausea, vomiting, and photophobia. Only fever and irritability may be evident in the infant, and acute bacterial meningitis must be ruled out as a cause of fever when no other localized findings are observed in a child. Duration of symptoms generally is 1 to 2 weeks, and specific manifestations outside the meninges can also occur depending on the viral etiology.

Laboratory examination of the CSF usually reveals a pleocytosis with 100 to 1,000 WBC/mm^3 (0.1×10^9 - 1×10^9/L), which are primarily lymphocytic. However, 20% to 75% of patients with viral encephalitis may have a predominance of polymorphonuclear cells on initial examination of the CSF. On repeat lumbar puncture, 90% of patients presenting initially with a predominance of neutrophils experience a shift to a predominance of mononuclear cells. Other laboratory findings include normal to mildly elevated protein concentrations and normal or mildly reduced glucose concentrations (see Table 128-1).

3 As mentioned earlier, pathogens responsible for viral encephalitis are often unidentified. When clinical signs warrant pathogen identification, appropriate laboratory diagnostic techniques, including PCR and serologic testing, should be undertaken. Molecular methods are preferred to conventional laboratory tests, such as viral cultures and brain biopsy, in the diagnosis of viral encephalitis owing to improved sensitivity and specificity, higher yield, and rapid results.[14,84]

Supportive and symptomatic treatments, including seizure control, hemodynamic management, venous thromboembolism prevention, ICP management, and secondary bacterial infection prevention, are of great importance in patients with viral encephalitis due to limited treatment options. Corticosteroid therapy is generally not recommended in most viral encephalitis cases; however, treatment should be considered for patients with cerebral edema and increased ICP.[14]

Although there are numerous pathogenic causes of viral encephalitis, much of the clinical presentation, diagnosis, and treatment are similar. The most commonly isolated viral etiologies are described here. HSV type 1 (HSV1) and type 2 (HSV2) are considered the most common treatable causes of viral encephalitis. Between 2011 and 2014, HSV encephalitis accounted for 8.3% of viral encephalitis-associated hospitalizations.[7,16] HSV1 is associated with encephalitis in adults, whereas HSV2 is associated predominantly with encephalitis in newborns. Sexually active adults may acquire HSV meningitis during or after an attack of genital or rectal HSV, whereas neonates acquire the virus during passage through the vaginal canal of mothers with active HSV infection. HSV PCR on CSF specimens should be performed for all patients with presumed encephalitis. Repeat testing should be considered for patients with an initial negative test after 3 to 7 days.[14] Establishing the correct diagnosis early is paramount due to mortality rates approaching 70% without treatment and, unlike other viral etiologies, effective therapy is available. As a result, empiric therapy of suspected HSV encephalitis is recommended, while results are pending. Delaying antiviral therapy has been consistently associated with increased mortality. Additionally, a clinical decision to treat may need to be made regardless of test results.

Acyclovir is the drug of choice for HSV encephalitis. In adults with normal renal function, acyclovir is usually administered as 10 mg/kg intravenously every 8 hours for 2 to 3 weeks.[14,84] Higher doses of acyclovir (up to 20 mg/kg intravenously every 8 hours) have been used in neonates and are associated with lower mortality rates.[85] HSV resistance to acyclovir has been reported with increasing incidence, particularly in immunocompromised patients with prior or chronic exposures to acyclovir, ranging from 3.5% to 10%.[86] The alternative treatment for acyclovir-resistant HSV is foscarnet. The dose for patients with normal renal function is 40 to 60 mg/kg every 8 to 12 hours for 3 weeks, with the higher dose typically reserved for HIV-infected individuals.[14,84] Ensuring adequate hydration is imperative to decrease risk of acyclovir- and foscarnet-induced nephrotoxicity. In addition, patients receiving foscarnet should be monitored for seizures related to alterations in plasma electrolyte levels. Adult patients who completed standard initial HSV encephalitis treatment followed by long-term antiviral treatment (an additional 3-month course) of oral valacyclovir did not show improvements in neuropsychological testing 12 months later compared to placebo.[87]

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Although mosquito bites account for nearly all human cases of WNV, transmissions via blood products, organ transplantation, transplacental transfer, and breast milk have been documented.[16,88] Similar to other arboviruses, the incubation period for WNV ranges from 2 to 14 days, although periods of up to 21 days have been observed in immunocompromised patients. Infection with WNV is asymptomatic in most adults or causes a mild flu-like syndrome characterized by fever, malaise, myalgia, and lymphadenopathy. Among 41,762 reported cases of WNV in the United States between 1999 and 2014, the overall mortality rate was approximately 4% (9% in patients with neuroinvasive disease). In 2020, the CDC reported a total of 557 cases of WNV and 38 deaths. CSF examination of WNV encephalitis typically shows pleocytosis and a slightly elevated CSF protein concentration. Several diagnostic methods have been developed for WNV, including a PCR assay and enzyme-linked immunosorbent assay (ELISA) tests. Treatment is typically supportive, including treatment for seizures and increased ICP, and in the majority of cases, the disease is self-limiting.[88]

CMV has emerged as a major cause of morbidity and mortality in immunocompromised patients, including HIV-infected individuals and transplant recipients on immunosuppressant therapy. CNS infections with CMV are often difficult to treat, with higher failure rates and poor outcomes. Combination therapy with ganciclovir and foscarnet is recommended for induction treatment due to the potential for poor outcomes with monotherapy.[14] In adult patients, ganciclovir 5 mg/kg every 12 hours and foscarnet 60 mg/kg every 8 hours (or 90 mg/kg every 12 hours) for 3 weeks or until symptom resolution are recommended during the induction phase, followed by maintenance phase with either induction agent. Some clinicians may use oral valgancyclovir for maintenance treatment of CMV CNS disease, although the use of this agent is not well established. Other interventions that may improve survival outcomes include the initiation of highly active antiretroviral therapy in untreated HIV-infected patients and reduction of immunosuppression intensity in transplant recipients. Although there is no vaccine for the prevention of CMV disease, there are multiple vaccine candidates in the process for FDA approval.

HIV encephalitis is a common CNS complication associated with AIDS. Frequently, patients may complain of headache, photophobia, or stiff neck at the time of presumed seroconversion. As the disease progresses, neurologic symptoms are frequently reported secondary to other opportunistic infections. Diagnosis of viral encephalitis is difficult because mental status and neurologic examinations are not sensitive enough to detect early changes. Direct evidence of HIV encephalitis can be obtained through CSF culture, p24 antigen testing, and qualitative or quantitative PCR for HIV RNA. Diagnostic workup of coinfections, such as HSV, *Toxoplasma gondii, Mycobacterium tuberculosis*, Aspergillus spp., and Cryptococcus spp., should also be performed. See Chapter 148 “Human Immunodeficiency Virus” for a complete discussion of infectious complications in HIV-positive individuals.

CNS INFECTIONS IN SPECIAL POPULATIONS

This section discusses additional pathogens that can cause CNS infections. For discussion on CNS infections caused by Cryptococcus, Histoplasma, and Aspergillus species, the interested reader can refer to Chapter 144, “Invasive Fungal Infections.” CNS infection due to *Treponema Pallidum* (neurosyphilis) is discussed in Chapter 140, “Sexually Transmitted Diseases.”

Bacillus Species

Bacillus anthracis, the causative agent of anthrax, is a nonmotile spore-forming, gram-positive, rod-shaped bacterium. The disease is common in wild and domestic animals. Biodefense experts place *Bacillus anthracis* at or near the top of the list for potential threat agents. It enters the host in the form of spores at the epidermis (cutaneous anthrax), the gastrointestinal epithelium (gastrointestinal anthrax), or the lung mucosa (inhalation anthrax). Anthrax meningitis has been reported with all three clinical forms of anthrax and likely results from hematogenous spread across the blood–brain barrier, generally presenting as hemorrhagic meningitis. Anthrax meningitis is characterized by a fulminant, rapidly progressive clinical course and is nearly always fatal even with treatment. For diagnosis, blood and CSF exam for Gram stain, culture PCR, and toxin assays are recommended.[89]

For the general adult population, empiric treatment for suspected anthrax meningitis should include ≥3 antimicrobial drugs with activity against *B. anthracis*.[89] At least one antimicrobial agent should have bactericidal activity, ≥1 should be a protein synthesis inhibitor for suppression of exotoxin production, and all should have good CNS penetration. A higher percent survival has been observed for patients with anthrax meningitis receiving 3 antimicrobials than those receiving only 2 antimicrobial agents.[90]

5 Empiric regimens that include high doses of intravenous fluoroquinolones (ciprofloxacin preferably, levofloxacin or moxifloxacin) along with a carbapenem (meropenem preferably, doripenem or imipenem/cilastatin) and a protein synthesis inhibitor (e.g., linezolid preferred or clindamycin) are recommended for ≥2 to 3 weeks until clinical criteria for stability are met. Once penicillin susceptibility is confirmed, the carbapenem can be de-

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escalated to intravenous penicillin G or ampicillin.[89] In addition, adjunctive corticosteroids should be considered.

Bacillus cereus is an unusual cause of CNS infections in immunocompromised patients. Occasional outbreaks may occur in the nosocomial setting. One such outbreak was discovered in a cluster of five patients with AML. All patients were started on vancomycin at time of neurological symptom onset, which is a treatment of choice with frequent resistance to beta-lactams and less frequent documented resistance to carbapenems.[91]

Borrelia burgdorferi (Lyme Disease)

Lyme disease (LD) is caused by the spirochete *Borrelia burgdorferi* and is the most common tick-borne infection in North America and Europe.[92] Lyme neuroborreliosis (LNB) is an infectious disorder of the nervous system caused by *B. burgdorferi* and has been reported in up to 15% of patients with untreated LD. CNS involvement may include meningitis, myelitis, cerebral vasculitis, or encephalitis. Clinical manifestations include fever, headache, fatigue, photosensitivity, confusion, hemiparesis, cerebellar ataxia, painful radiculitis, cranial palsy, and Parkinson-like symptoms among others. Poliomyelitis-like syndromes and acute stroke-like symptoms caused by cerebral vasculitis have been documented but are considered rare. Unlike the European LD, the North American LD is also characterized by a skin rash called erythema migrans.[92,93] There is no international consensus for the diagnosis of Lyme neuroborreliosis (LNB). Diagnosis is based on the presence of neurological symptoms without other obvious reasons, CSF analysis (lymphocytic pleocytosis, moderately elevated protein, normal glucose), intrathecal *B. burgdorferi* antibody production, blood and CSF serologic testing (ELISA plus Western blot), and MRI demonstrating areas of inflammation.[92-94] PCR testing for detection of *B. burgdorferi* in CSF has a sensitivity of <30% with an unknown specificity; therefore, it is not routinely recommended. Parenteral treatment with ceftriaxone once daily is recommended as first-line treatment of LNB.

5 Patients with cranial neuropathy without clinical signs of meningitis may be treated with oral amoxicillin, doxycycline, or cefuroxime axetil. European guidelines also recommend oral doxycycline as a first-line option for patients with symptoms confined to the meninges, cranial nerves, nerve roots, or peripheral nerves based on its CSF penetration, ability to achieve CSF concentrations above the MIC, and several studies showing similar short- and long-term efficacy to various parenteral regimens.[93] Alternative parenteral options to ceftriaxone include cefotaxime or penicillin G. For patients intolerant to β-lactams, oral or intravenous doxycycline is suggested.

Mycobacterium tuberculosis

5 *M. tuberculosis* is the primary cause of tuberculous meningitis and remains the most life-threatening form of extrapulmonary tuberculosis. The incidence of tuberculosis, in general, has decreased to 3 cases per 100,000 individuals in the United States in 2016.[95] The guidelines jointly sponsored by the CDC, IDSA, and the American Thoracic Society recommend an initial regimen of four drugs for empirical treatment of drug-susceptible *M. tuberculosis* in adults. The recommended regimen consists of isoniazid, rifampin, pyrazinamide, and ethambutol for the first 2 months, followed by isoniazid plus rifampin for an additional 7 to 10 months, although the optimal duration has not been defined. Furthermore, initial adjunctive corticosteroid therapy tapered over 6 to 8 weeks is recommended, which provides mortality benefit. The recommended therapy for HIV-positive individuals is similar as that for immunocompetent patients.[95,96] In HIV-infected patients with tuberculous meningitis, antiretroviral therapy should not be initiated in the first 8 weeks of antituberculosis therapy to reduce the risk of immune reconstitution syndrome (IRIS). Therapy should be individualized based on susceptibility patterns and evidence-based guidelines including those by the WHO.[97]

Nocardia

Nocardia is an aerobic, gram-positive bacterium. *Nocardia* species represent a ubiquitous group of environmental bacteria that commonly cause opportunistic infections in immunocompromised individuals. Nevertheless, up to 20% of patients with nocardiosis are apparently healthy, although the presence of nocardiosis might reveal a previously unidentified primary immunodeficiency in immunocompetent patients.[98] Pulmonary nocardiosis is the most common clinical presentation and CNS nocardiosis represents the second most frequently involved organ. The usual presentation of CNS infection is single or multiple brain abscesses. CNS symptoms appear gradually and are nonspecific including headache, nausea, vomiting, seizures, and mental status changes. MRI of the brain is the recommended imaging modality. Specific therapeutic recommendations on the basis of prospective controlled trials for nocardiosis are lacking. In addition, *Nocardia* has inconsistent antimicrobial susceptibility patterns *in vitro*.[99] Thus, the management of nocardiosis must be individualized and isolates should undergo antimicrobial testing for treatment decisions. Surgical management may be necessary in many cases.[100]

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According to the 2019 guidelines from the American Society of Transplantation for the treatment of nocardia infections in transplant patients, imipenem/cilastatin coadministered with amikacin alone or in a three-drug regimen with trimethoprim-sulfamethoxazole can be used as empiric therapy for cerebral disease or life-threatening disease. In critically ill patients with significant renal dysfunction where it may be desirable to avoid trimethoprim-sulfamethoxazole and aminoglycosides, treatment with linezolid is an option until susceptibility results are available. Alternative therapies include cefotaxime, ceftriaxone, and minocycline, although some Nocardia species are resistant to these agents, and therefore, use should be guided by susceptibility testing. Nocardiosis appears to be a rare infection in children. Antibiotics reported useful in children are similar to those used in adults. Combined treatment is required until there is evidence of clinical improvement and antimicrobial susceptibility is confirmed. Parenteral therapy is recommended for 3 to 6 weeks followed by appropriate oral therapy for a total of 12 months. After completion of antibiotic therapy, secondary prophylaxis with trimethoprim-sulfamethoxazole can be considered at doses of one double strength tablet daily for adults. However, breakthrough nocardial infections may still occur.[100] Therefore, use of trimethoprim-sulfamethoxazole prophylaxis should not prevent clinicians from considering nocardial infections in differential diagnosis. Patients should be monitored for 1 year after completion of therapy for relapse.

Primary Amoebic Meningoencephalitis (PAM)

Naegleria fowleri is a thermophilic, unicellular parasite that lives in stagnant fresh or brackish waters and causes a rare form of nearly fatal CNS infection known as Primary Amoebic Meningoencephalitis (PAM). Humans acquire PAM when water is insufflated through the nostrils usually while swimming in warm freshwater lakes and rivers. The time from exposure to *N. fowleri* to the onset of symptoms is 1 to 9 days. The pathogen migrates to the brain along the olfactory nerve. Signs and symptoms of PAM include severe frontal headache, fever, nausea, vomiting, seizures, altered mental status, hallucinations, and coma.

Even with early recognition of PAM, progression is rapid and the clinical prognosis is poor. PAM is a rare disease that is almost always fatal. In the United States, there have been 148 PAM infections from 1962 through 2019 with only four survivors. PAM disproportionately affects males and children. Several drug combinations have been used for treatment of PAM.[101] Based on treatment regimens used in survivors, the CDC recommend combination therapy with miltefosine (an oral drug used to treat breast cancer and leishmaniasis), azithromycin, rifampin, fluconazole, and conventional amphotericin B (intravenous and intrathecal) and dexamethasone.

Toxoplasma gondii

Toxoplasmic encephalitis (TE) is caused by the protozoan *T. gondii*. Approximately 11% of the US population 6 years and older have been infected with *T. gondii*. In other parts of the world, up to 95% of populations are infected. The primary routes of transmission are foodborne, animal-to-human (cats serving as the definitive host), and mother-to-child (congenital).[96,102] TE is typically caused by the reactivation of disease in immunocompromised patients, especially those with AIDS, or intrauterine infection in newborns. Clinical manifestations can range from asymptomatic in healthy, nonpregnant patient to headache, seizures, confusion, hemiparesis, cranial nerve abnormalities, or fever in immunocompromised patients. In congenital toxoplasmosis, patients may also present with hydrocephalus, intracerebral calcification, microcephaly, convulsions, or chorioretinitis.[14,96] Definitive diagnosis of TE requires a clinical sample via a brain biopsy; therefore, TE is presumptively diagnosed on the basis of clinical symptoms, positive serology for antitoxoplasma IgG antibodies, and identification of space-occupying lesions on CT, MRI, or other radiologic imaging. In patients with AIDS, MRI typically shows multiple ring-enhancing lesions.

T. gondii can also be detected by PCR in CSF. However, the sensitivity is low (50%) and the result is usually negative once treatment has started.[96,102] First-line treatment for TE in adults consists of pyrimethamine plus sulfadiazine plus leucovorin. Leucovorin is added to the treatment regimen to reduce the likelihood of hematologic toxicity associated with pyrimethamine. In patients who are unable to tolerate sulfadiazine, due to allergies or impaired renal function, clindamycin may be used as an alternative. Other alternative treatment options are available, including trimethoprim-sulfamethoxazole, but have not been extensively studied. Treatment recommendations are the same in pediatric patients; however, several of the alternative regimens have not been studied in children.[96,102] After completion of initial 6-week therapy, chronic maintenance therapy should be initiated and continued based on risk factors and immune status.

EVALUATION OF THERAPEUTIC OUTCOMES

Because of the potential for rapid deterioration associated with CNS infections, the presence of fever, headache, meningismus (eg, nuchal rigidity,

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Brudzinski's, or Kernig's sign), and signs of cerebral dysfunction should be evaluated every 4 hours for the initial 3 days and then daily thereafter. The Glasgow Coma Scale should be used in severely ill patients. Trends in improvement and resolution rather than single evaluations in time are more important in monitoring the signs and symptoms of meningitis. Continued therapy should be based on the assessment of clinical improvement, culture, and susceptibility testing results. Once a pathogen is identified, anti-infective therapy should be tailored to the specific pathogen (Tables 128-4 and 128-5). Throughout the course of treatment, efficacy parameters such as signs and symptoms, microbiologic findings, and CSF examination should be followed to evaluate the success of meeting the desired outcomes. If adjunctive dexamethasone is used, careful monitoring of signs and symptoms of gastrointestinal bleeding and hyperglycemia should be employed. Moreover, the use of dexamethasone may interfere with the interpretation of clinical response to treatment, such as resolution of fever.

ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AFB	acid fast bacillus
AIDS	acquired immunodeficiency syndrome
BBB	blood–brain barrier
BCSFB	blood–cerebrospinal fluid barrier
CBF	cerebral blood flow
CDC	United States Centers for Disease Control and Prevention
CFH	complement factor H
CFU	colony forming unit
CLSI	Clinical and Laboratory Standards Institute
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
DIC	disseminated intravascular coagulation
EFNS	European Federation of Neurological Societies
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EVD	external ventricular drains
FDA	US Food and Drug Administration

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GBS	group B *Streptococcus*
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HSV	herpes simplex virus
ICP	intracranial pressure
IDSA	Infectious Diseases Society of America
Ig	immunoglobulin
IL	interleukin
IPD	invasive pneumococcal disease
INF	interferon
IRIS	immune reconstitution syndrome
LNB	Lyme neuroborreliosis
LPS	lipopolysaccharide
MenACWY	serogroup A, C, W, Y meningococcal vaccine
MenB	serogroup B meningococcal vaccine
MIC	minimum inhibitory concentration
MSSA	methicillin-susceptible *Staphylococcus aureus*
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
PAF	platelet-activating factor
PAM	primary amoebic meningoencephalitis
PBP2a	penicillin binding protein 2a
PCR	polymerase chain reaction
PCT	procalcitonin
PCV7	heptavalent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine

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PGE2	prostaglandin E2
PMN	polymorphonuclear neutrophil
PPSV23	23-valent pneumococcal polysaccharide vaccine
rRNA	ribosomal ribonucleic acid
SNP	single-nucleotide polymorphism
TDM	therapeutic drug monitoring
TE	toxoplasmic encephalitis
TNF	tumor necrosis factor
WBC	white blood cell
WNV	West Nile virus

REFERENCES

1. Brouwer MC, van de Beek D. Epidemiology of community-acquired bacterial meningitis. *Curr Opin Infect Dis.* 2018;31:78–84. [PubMed: 29176349]

2. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998–2007. *N Engl J Med.* 2011;364:2016–2025. [PubMed: 21612470]

3. McGill F, Heyderman RS, Panagiotou S, Tunkel AR, Solomon T. Acute bacterial meningitis in adults. *Lancet* 2016;388:3036–3047. [PubMed: 27265346]

4. Brouwer MC, Coutinho JM, van de Beek D. Clinical characteristics and outcome of brain abscess: systematic review and meta-analysis. *Neurology* 2014;82:806–813. [PubMed: 24477107]

5. Solomon T, Michael BD, Smith PE, et al. Management of suspected viral encephalitis in adults—Association of British Neurologists and British Infection Association National Guidelines. *J Infect.* 2012;64:347–373. [PubMed: 22120595]

6. Granerod J, Cousens S, Davies NW, Crowcroft NS, Thomas SL. New estimates of incidence of encephalitis in England. *Emerg Infect Dis.* 2013;19.

7. Vora NM, Holman RC, Mehal JM, Steiner CA, Blanton J, Sejvar J. Burden of encephalitis-associated hospitalizations in the United States, 1998–2010. *Neurology* 2014;82:443–451. [PubMed: 24384647]

8. Tack DM, Holman RC, Folkema AM, Mehal JM, Blanton JD, Sejvar JJ. Trends in encephalitis-associated deaths in the United States, 1999–2008. *Neuroepidemiology* 2014;43:1–8. [PubMed: 24968857]

9. Castelblanco RL, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the United States from 1997 to 2010: a population-based observational study. *Lancet Infect Dis.* 2014;14:813–819. [PubMed: 25104307]

10. Collaborators GBDM. Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2018;17:1061–1082. [PubMed: 30507391]

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11. Cohn AC, MacNeil JR, Clark TA, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2013;62:1–28. [PubMed: 23515099]

12. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. *Clin Infect Dis.* 2017;64:e34–e65. [PubMed: 28203777]

13. Kneen R, Michael BD, Menson E, et al. Management of suspected viral encephalitis in children—Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group national guidelines. *J Infect.* 2012;64:449–477. [PubMed: 22120594]

14. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2008;47:303–327. [PubMed: 18582201]

15. Bloch KC, Glaser CA. Encephalitis surveillance through the Emerging Infections Program, 1997–2010. *Emerg Infect Dis.* 2015;21:1562–1567. [PubMed: 26295485]

16. Hasbun R, Rosenthal N, Balada-Llasat JM, et al. Epidemiology of meningitis and encephalitis in the United States, 2011–2014. *Clin Infect Dis.* 2017;65:359–363. [PubMed: 28419350]

17. Archibald LK, Quisling RG. Central nervous system infections. In: Layon A.J. ed. *Textbook of Neurointensive Care.* London: Springer-Verlag; 2013:427–517.

18. Bleck T, Greenlee J. *Anatomic Considerations in Central Nervous System Infections.* 5th ed. New York: Churchill Livingstone; 2000.

19. Bennett JE DR, Blaser MA. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* Philadelphia, PA: Elsevier Saunders; 2015.

20. Kim KS. Emerging molecular targets in the treatment of bacterial meningitis. *Expert Opin Ther Targets* 2003;7:141–152. [PubMed: 12667093]

21. Klein RS, Hunter CA. Protective and pathological immunity during central nervous system infections. *Immunity* 2017;46:891–909. [PubMed: 28636958]

22. Magnus T, Rother J, Simova O, et al. The neurological syndrome in adults during the 2011 northern German *E. coli* serotype O104:H4 outbreak. *Brain* 2012;135:1850–1859. [PubMed: 22539260]

23. Levin SN, Lyons JL. Infections of the nervous system. *Am J Med.* 2018;131:25–32. [PubMed: 28889928]

24. Brouwer MC, Thwaites GE, Tunkel AR, van de Beek D. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. *Lancet* 2012;380:1684–1692. [PubMed: 23141617]

25. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clin Microbiol Rev.* 2010;23:467–492. [PubMed: 20610819]

26. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* 2004;39:1267–1284. [PubMed: 15494903]

27. van de Beek D, Cabellos C, Dzupova O, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. *Clin Microbiol Infect.* 2016;22(Suppl 3):S37–S62. [PubMed: 27062097]

28. Sakushima K, Hayashino Y, Kawaguchi T, Jackson JL, Fukuhara S. Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: a meta-analysis. *J Infect.* 2011;62:255–262. [PubMed: 21382412]

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29. Velissaris D, Pintea M, Pantzaris N, et al. The role of procalcitonin in the diagnosis of meningitis: a literature review. *J Clin Med.* 2018;7.

30. Vikse J, Henry BM, Roy J, Ramakrishnan PK, Tomaszewski KA, Walocha JA. The role of serum procalcitonin in the diagnosis of bacterial meningitis in adults: a systematic review and meta-analysis. *Int J Infect Dis.* 2015;38:68–76. [PubMed: 26188130]

31. Leber AL, Everhart K, Balada-Llasat JM, et al. Multicenter Evaluation of BioFire FilmArray Meningitis/Encephalitis Panel for Detection of Bacteria, Viruses, and Yeast in Cerebrospinal Fluid Specimens. *J Clin Microbiol.* 2016;54:2251–2261. [PubMed: 27335149]

32. Beganovic M, McCreary EK, Mahoney MV, Dionne B, Green DA, Timbrook TT. Interplay between Rapid Diagnostic Tests and Antimicrobial Stewardship Programs among Patients with Bloodstream and Other Severe Infections. *J Appl Lab Med.* 2019;3:601–616. [PubMed: 31639729]

33. Srinivasan L, Pisapia JM, Shah SS, Halpern CH, Harris MC. Can broad-range 16S ribosomal ribonucleic acid gene polymerase chain reactions improve the diagnosis of bacterial meningitis? A systematic review and meta-analysis. *Ann Emerg Med.* 2012;60:609–20e2. [PubMed: 22883680]

34. Wilson MR, O'Donovan BD, Gelfand JM, et al. Chronic meningitis investigated via metagenomic next-generation sequencing. *JAMA Neurol.* 2018;75:947–955. [PubMed: 29710329]

35. Aggarwal D, Kanitkar T, Narouz M, et al. Clinical utility and cost-effectiveness of bacterial 16S rRNA and targeted PCR based diagnostic testing in a UK microbiology laboratory network. *Sci Rep.* 2020;10:7965. https://doi.org/10.1038/s41598-020-64739-1. [PubMed: 32409679]

36. Nau R, Seele J, Djukic M, Eiffert H. Pharmacokinetics and pharmacodynamics of antibiotics in central nervous system infections. *Curr Opin Infect Dis.* 2018;31:57–68. [PubMed: 29293475]

37. Mourvillier B, Tubach F, van de Beek D, et al. Induced hypothermia in severe bacterial meningitis: a randomized clinical trial. *JAMA* 2013;310:2174–2183. [PubMed: 24105303]

38. Ajdukiewicz KM, Cartwright KE, Scarborough M, et al. Glycerol adjuvant therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: a double-blind, randomised controlled trial. *Lancet Infect Dis.* 2011;11:293–300. [PubMed: 21334262]

39. Wall EC, Ajdukiewicz KM, Bergman H, Heyderman RS, Garner P. Osmotic therapies added to antibiotics for acute bacterial meningitis. *Cochrane Database Syst Rev.* 2018;2:CD008806. [PubMed: 29405037]

40. Wahl B, O'Brien KL, Greenbaum A, et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. *Lancet Glob Health* 2018;6:e744–e757. [PubMed: 29903376]

41. Jacobs DM, Yung F, Hart E, Nguyen MNH, Shaver A. Trends in pneumococcal meningitis hospitalizations following the introduction of the 13-valent pneumococcal conjugate vaccine in the United States. *Vaccine* 2017;35:6160–6165. [PubMed: 28951086]

42. Pfaller MA, Mendes RE, Duncan LR, Flamm RK, Sader HS. In vitro activities of Ceftaroline and Comparators against Streptococcus pneumoniae isolates from U.S. Hospitals: results from seven years of the AWARE Surveillance Program (2010 to 2016). *Antimicrob Agents Chemother.* 2018;62.

43. Hameed N, Tunkel AR. Treatment of drug-resistant pneumococcal meningitis. *Curr Infect Dis Rep.* 2010;12:274–281. [PubMed: 21308542]

44. Tsuji Y, Hiraki Y, Matsumoto K, et al. Pharmacokinetics and protein binding of linezolid in cerebrospinal fluid and serum in a case of post-neurosurgical bacterial meningitis. *Scand J Infect Dis.* 2011;43:982–985. [PubMed: 21851332]

45. Sakoulas G, Nonejuie P, Kullar R, Pogliano J, Rybak MJ, Nizet V. Examining the use of ceftaroline in the treatment of Streptococcus pneumoniae meningitis with reference to human cathelicidin LL-37. *Antimicrob Agents Chemother.* 2015;59:2428–2431. [PubMed: 25605351]

46. Vivas M, Force E, Garrigos C, et al. Experimental study of the efficacy of daptomycin for the treatment of cephalosporin-resistant pneumococcal meningitis. *J Antimicrob Chemother.* 2014;69:3020–3026. [PubMed: 24962033]

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47. Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the United States: analysis of multisite, population-based surveillance. *Lancet Infect Dis.* 2015;15:301–309. [PubMed: 25656600]

48. Pilishvili T, Gierke R, Farley MM, et al. 1470. Epidemiology of Invasive Pneumococcal Disease (IPD) following 18 years of Pneumococcal Conjugate Vaccine (PCV) use in the United States. *Open Forum Infectious Diseases* 2020;7:S736–S737.

49. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine* 2009;27(Suppl 2):B51–B63. [PubMed: 19477562]

50. Centers for Disease Control and Prevention. Enhanced Meningococcal Disease Surveillance Report 2018. Available at: https://www.cdc.gov/meningococcal/surveillance/index.html#enhanced-reports. Accessed May 2021.

51. Telisinghe L, Waite TD, Gobin M, et al. Chemoprophylaxis and vaccination in preventing subsequent cases of meningococcal disease in household contacts of a case of meningococcal disease: a systematic review. *Epidemiol Infect.* 2015;143:2259–2268. [PubMed: 25916733]

52. Centers for Disease Control and Prevention. Meningococcal conjugate (MenACWY) vaccination coverage among adolescents 13–17 years by State HR, and the United States, National Immunization Survey-Teen (NIS-Teen), 2019. Available at: https://www.cdc.gov/vaccines/imz-managers/coverage/teenvaxview/data-reports/menacwy/dashboard/2019.html. Accessed April 2021.

53. Petousis-Harris H, Paynter J, Morgan J, et al. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. *Lancet* 2017;390:1603–1610. [PubMed: 28705462]

54. Slack MPE. Long term impact of conjugate vaccines on Haemophilus influenzae meningitis: narrative review. *Microorganisms* 2021;9.

55. American Academy of Pediatrics. Haemophilus influenzae Infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. American Academy of Pediatrics; 2018; 367–375.

56. Kimberlin DW BM, Jackson MA, Long SS. *Red Book®: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Elk Grove Village, IL: American Academy of Pediatrics; 2018.

57. Briere EC, Rubin L, Moro PL, et al. Prevention and control of Haemophilus influenzae type b disease: recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep.* 2014;63:1–14. [PubMed: 24572654]

58. Russell NJ, Seale AC, O'Driscoll M, et al. Maternal colonization with Group B Streptococcus and Serotype distribution worldwide: systematic review and meta-analyses. *Clin Infect Dis.* 2017;65:S100–S11. [PubMed: 29117327]

59. Puopolo KM, Lynfield R, Cummings JJ, Committee On F, Newborn, Committee On Infectious D. Management of infants at risk for Group B Streptococcal disease. *Pediatrics* 2019;144.

60. Nanduri SA, Petit S, Smelser C, et al. Epidemiology of invasive early-onset and late-onset Group B Streptococcal disease in the United States, 2006 to 2015: multistate laboratory and population-based surveillance. *JAMA Pediatr.* 2019;173:224–233. [PubMed: 30640366]

61. Prevention of Group B Streptococcal Early-Onset Disease in Newborns: ACOG Committee Opinion, Number 797. *Obstet Gynecol.* 2020;135:e51–e72. [PubMed: 31977795]

62. Vekemans J, Moorthy V, Friede M, et al. Maternal immunization against Group B streptococcus: World Health Organization research and development technological roadmap and preferred product characteristics. *Vaccine* 2019;37:7391–7393. [PubMed: 29398277]

63. Charlier C, Perrodeau E, Leclercq A, et al. Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study. *Lancet Infect Dis.* 2017;17:510–519. [PubMed: 28139432]

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64. Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev.* 2015CD004405.

65. Ricard JD, Wolff M, Lacherade JC, et al. Levels of vancomycin in cerebrospinal fluid of adult patients receiving adjunctive corticosteroids to treat pneumococcal meningitis: a prospective multicenter observational study. *Clin Infect Dis.* 2007;44:250–255. [PubMed: 17173226]

66. Rogers T, Sok K, Erickson T, et al. Impact of antibiotic therapy in the microbiological yield of healthcare-associated ventriculitis and meningitis. *Open Forum Infect Dis.* 2019;6:ofz050. [PubMed: 30899767]

67. Lyons JL, Thakur KT, Lee R, et al. Utility of measuring (1,3)-beta-d-glucan in cerebrospinal fluid for diagnosis of fungal central nervous system infection. *J Clin Microbiol.* 2015;53:319–322. [PubMed: 25378578]

68. Albanese J, Leone M, Bruguerolle B, Ayem ML, Lacarelle B, Martin C. Cerebrospinal fluid penetration and pharmacokinetics of vancomycin administered by continuous infusion to mechanically ventilated patients in an intensive care unit. *Antimicrob Agents Chemother.* 2000;44:1356–1358. [PubMed: 10770777]

69. Kullar R, Chin JN, Edwards DJ, Parker D, Coplin WM, Rybak MJ. Pharmacokinetics of single-dose daptomycin in patients with suspected or confirmed neurological infections. *Antimicrob Agents Chemother.* 2011;55:3505–3509. [PubMed: 21502620]

70. Xipell M, Bodro M, Marco F, Losno RA, Cardozo C, Soriano A. Clinical experience with ceftazidime/avibactam in patients with severe infections, including meningitis and lung abscesses, caused by extensively drug-resistant Pseudomonas aeruginosa. *Int J Antimicrob Agents* 2017;49:266–268. [PubMed: 27979500]

71. Yasmin M, Hanrahan J, Marshall S, et al. Using therapeutic drug monitoring to treat KPC-producing Klebsiella pneumoniae central nervous system infection with Ceftazidime/Avibactam. *Open Forum Infect Dis.* 2020;7:ofaa349. [PubMed: 32964066]

72. Balouch MA, Bajwa RJ, Hassoun A. Successful use of ceftaroline for the treatment of MRSA meningitis secondary to an infectious complication of lumbar spine surgery. *J Antimicrob Chemother.* 2015;70:624–625. [PubMed: 25274007]

73. Kuriakose SS, Rabbat M, Gallagher JC. Ceftaroline CSF concentrations in a patient with ventriculoperitoneal shunt-related meningitis. *J Antimicrob Chemother.* 2015;70:953–954. [PubMed: 25422288]

74. Cies JJ, Moore WS, 2nd, Enache A, Chopra A. Ceftaroline cerebrospinal fluid penetration in the treatment of a ventriculopleural shunt infection: a case report. *J Pediatr Pharmacol Ther.* 2020;25:336–339. [PubMed: 32461749]

75. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;62:e1–e50. [PubMed: 26679628]

76. Patterson TF, Thompson GR, 3rd, Denning DW, et al. Executive Summary: Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;63:433–442. [PubMed: 27481947]

77. Fried HI, Nathan BR, Rowe AS, et al. The insertion and management of external ventricular drains: an evidence-based consensus statement: a statement for healthcare professionals from the Neurocritical Care Society. *Neurocrit Care* 2016;24:61–81. [PubMed: 26738503]

78. Sonneville R, Ruimy R, Benzonana N, et al. An update on bacterial brain abscess in immunocompetent patients. *Clin Microbiol Infect.* 2017;23:614–620. [PubMed: 28501669]

79. Patel K, Clifford DB. Bacterial brain abscess. *Neurohospitalist* 2014;4:196–204. [PubMed: 25360205]

80. Brouwer MC, van de Beek D. Epidemiology, diagnosis, and treatment of brain abscesses. *Curr Opin Infect Dis.* 2017;30:129–134. [PubMed: 27828809]

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81. Doughty CT, Yawetz S, Lyons J. Emerging causes of Arbovirus Encephalitis in North America: Powassan, Chikungunya, and Zika viruses. *Curr Neurol Neurosci Rep.* 2017;17:12. [PubMed: 28229397]

82. Garcez PP, Loiola EC, Madeiro da Costa R, et al. Zika virus impairs growth in human neurospheres and brain organoids. *Science* 2016;352:816–818. [PubMed: 27064148]

83. Centers for Disease Control and Prevention. Zika Virus Statistics and Maps. Available at: https://www.cdc.gov/zika/reporting/index.html. Accessed May 2021.

84. Steiner I, Budka H, Chaudhuri A, et al. Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. *Eur J Neurol.* 2010;17:999–e57. [PubMed: 20236175]

85. Whitley R. Neonatal herpes simplex virus infection. *Curr Opin Infect Dis.* 2004;17:243–246. [PubMed: 15166828]

86. Piret J, Boivin G. Resistance of herpes simplex viruses to nucleoside analogues: mechanisms, prevalence, and management. *Antimicrob Agents Chemother.* 2011;55:459–472. [PubMed: 21078929]

87. Gnann JW, Jr, Skoldenberg B, Hart J, et al. Herpes simplex encephalitis: lack of clinical benefit of long-term valacyclovir therapy. *Clin Infect Dis.* 2015;61:683–691. [PubMed: 25956891]

88. Petersen LR, Brault AC, Nasci RS. West Nile virus: review of the literature. *JAMA* 2013;310:308–315. [PubMed: 23860989]

89. Hendricks KA, Wright ME, Shadomy SV, et al. Centers for Disease Control and prevention expert panel meetings on prevention and treatment of anthrax in adults. *Emerg Infect Dis.* 2014;20.

90. Pillai SK, Huang E, Guarnizo JT, et al. Antimicrobial treatment for systemic anthrax: analysis of cases from 1945 to 2014 identified through a systematic literature review. *Health Secur.* 2015;13:355–64. [PubMed: 26623698]

91. Rhee C, Klompas M, Tamburini FB, et al. Epidemiologic investigation of a cluster of neuroinvasive *Bacillus cereus* infections in 5 patients with acute myelogenous leukemia. *Open Forum Infect Dis.* 2015;2:ofv096. [PubMed: 26269794]

92. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2006;43:1089–1134. [PubMed: 17029130]

93. Mygland A, Ljostad U, Fingerle V, et al. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. *Eur J Neurol.* 2010;17:8–16, e1–e4. [PubMed: 19930447]

94. Garcia-Monco JC, Benach JL. Lyme neuroborreliosis: clinical outcomes, controversy, pathogenesis, and polymicrobial infections. *Ann Neurol.* 2019;85:21–31. [PubMed: 30536421]

95. Nahid P, Dorman SE, Alipanah N, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis.* 2016;63:853–867. [PubMed: 27621353]

96. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed April 2021.

97. Falzon D, Schunemann HJ, Harausz E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. *Eur*

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Respir J. 2017;49.

98. Lafont E, Conan PL, Rodriguez-Nava V, Lebeaux D. Invasive nocardiosis: disease presentation, diagnosis and treatment–Old questions, new answers? *Infect Drug Resist.* 2020;13:4601–4613. [PubMed: 33376366]

99. Restrepo A, Clark NM, Infectious Diseases Community of Practice of the American Society of T. Nocardia infections in solid organ transplantation: Guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation. *Clin Transplant.* 2019;33:e13509. [PubMed: 30817024]

100. Corsini Campioli C, Castillo Almeida NE, O'Horo JC, et al. Clinical presentation, management, and outcomes of patients with brain abscess due to *Nocardia* species. *Open Forum Infect Dis.* 2021;8:ofab067. [PubMed: 33855101]

101. Taravaud A, Fechtali-Moute Z, Loiseau PM, Pomel S. Drugs used for the treatment of cerebral and disseminated infections caused by free-living amoebae. *Clin Transl Sci.* 2021.

102. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Department of Health and Human Services. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf. Accessed April 2021.

SELF-ASSESSMENT QUESTIONS

1. Which of the following pathogen is the leading cause of acute bacterial meningitis in adults in the western societies?
   A. *Streptococcus* group B
   B. *Neisseria meningitides*
   C. *Streptococcus pneumoniae*
   D. *Haemophilus influenzae*
2. The following are true regarding initiation of anti-infective therapy in acute CNS infection, except:
   A. Empiric anti-infective therapy should be initiated as soon as possible after a diagnosis is suspected.
   B. Blood samples should be collected before administration of anti-infective agents.
   C. Supportive care including fluids, electrolytes, antipyretics, and antiemetics should also be given during treatment for possible CNS infections.
   D. Corticosteroids should not be initiated until a final diagnosis of meningitis is confirmed.
3. In children <2 years of age and adults >50 years of age, empiric coverage of which of the following pathogen is recommended?
   A. *Listeria monocytogenes*
   B. *Legionella pneumophila*
   C. *Neisseria meningitidis*
   D. *Mycoplasma pneumoniae*
4. Which of the following supportive agent has been associated with increased mortality in patients with bacterial meningitis?
   A. Mannitol

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B. Glycerol

C. 3% hypertonic saline

D. Levetiracetam

5. In patients with suspected fungal meningitis, which of the following antifungal agent should be avoided during induction therapy due to poor CSF penetration?

A. Flucytocine

B. Itraconazole

C. Fluconazole

D. Voriconazole

6. According to the Infectious Diseases Society of America, the recommended treatment regimen for a 40-year-old patient with suspected acute, community-acquired bacterial meningitis consists of:

A. Cefazolin, vancomycin, and levofloxacin

B. Ceftriaxone and vancomycin

C. Ceftriaxone, ampicillin, and aminoglycoside

D. Ceftriaxone and ampicillin

7. The generally recommended duration of intravenous antibiotic treatment of meningitis caused by *Streptococcus pneumoniaea* is:

A. 7 days

B. 10-14 days

C. 4-6 weeks

D. 12-18 weeks

8. The main rationale for the inclusion of vancomycin to the empiric regimen of non-healthcare-associated bacterial meningitis is for covering possible resistant:

A. *Streptococcus pneumoniae*

B. *Staphylococcus aureus*

C. *Enterococcus facium*

D. *Listeria monocytogenes*

9. Which of the following antipseudomonal agent is not included in the recommended regimen for the treatment of healthcare-associated meningitis and ventriculitis?

A. Meropenem

B. Piperacillin-tazobactam

C. Cefepime

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D. Ceftazidime

10. Adjunctive use of corticosteroids would be indicated for:

A. Brain abscess with significant edema

B. Meningitis due to *Haemophilus influenzae* in children

C. Meningitis due to *Streptococcus pneumoniae* in adults

D. Meningitis due to *Mycobacterium tuberculosis*

E. All of the above

11. Which of the following is NOT one of the most common causes of viral encephalitis in the United States?

A. Arbovirus

B. Herpes simplex virus

C. Zika virus

D. Enterovirus

12. For the treatment of CNS infection due to inhaled *Bacillus anthracis,* CDC recommended:

A. ≥3 antibiotics with activity against *Bacillus anthracis*

B. Anthrax Vaccine Adsorbed

C. Antitoxin (raxibacumab or AIGIV)

D. All of the above

13. According to CDC, the recommended total duration of treatment of Primary Amoebic Meningoencephalitis (PAM) due to *Naegleria fowleri* is:

A. 7 days

B. 14 days

C. 28 days

D. 3 months

14. The recommended treatment regimen of brain abscess due to *Nocardia* may include the following, except:

A. Surgical resection of abscess

B. Ceftriaxone as the core antibiotic agent

C. Combination including trimethoprim-sulfamethoxazole and imipenem

D. At least 12 months duration

15. Which of the following is true of *Toxoplasma* encephalitis and its treatment?

A. *Toxoplasma gondii* is transmitted when water is insufflated through the nostrils usually while swimming in warm freshwater lakes and rivers.

B. It is least common in immunocompromised individuals.

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C. *Toxoplasma* encephalitis is diagnosed using CSF PCR, which has a sensitivity of 99%.

D. Treatment includes a combination of pyrimethamine, sulfadiazine, and leucovorin.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** Streptococcus pneumoniae is the leading cause of acute bacterial meningitis in adults in the western societies. *Neisseria meningitidis* and *Haemophilus influenzae* type b have also been important causes of acute bacterial meningitis but their incidence has decreased substantially over time mainly due to introduction of effective vaccinations. See the "Etiology" section for more information.

2. **D.** Acute CNS infections are a medical emergency and should be treated as such. Blood and CSF samples are useful for pathogen identification and optimization of anti-infective treatment, though sample collection should not delay the administration of anti-infective agents. The European guidelines for acute bacterial meningitis recommend that antibiotics should be administered within an hour from when meningitis is suspected. The IDSA recommends corticosteroids be administered 10 to 20 minutes prior to or concomitant with the first dose of antibiotics. See the "General Approach to Treatment, Nonpharmacologic and Supportive Therapy" and "Dexamethasone as an Adjunctive Treatment for Acute Bacterial Meningitis" sections for more information.

3. **A.** Meningitis due to *L. monocytogenes* primarily affects neonates, alcoholic or immunocompromised individuals (including pregnant women), and the elderly. See the "*Listeria monocytogenes*" section for more information.

4. **B.** Glycerol should be avoided as a supportive care agent in acute bacterial meningitis because it has been associated with a higher mortality rate. See the "General Approach to Treatment, Nonpharmacologic and Supportive Therapy" section for more information.

5. **B.** Itraconazole has poor penetration into the CSF. Refer to Table 128-3 for more information on the penetration of anti-infective agents into the CSF.

6. **B.** The Infectious Diseases Society of America recommends vancomycin plus a third-generation cephalosporin as empiric therapy for suspected acute, community-acquired bacterial meningitis in patients 2 to 50 years old. Refer to Table 128-2 for more information on empiric antimicrobial regimens.

7. **B.** The duration of treatment for bacterial meningitis is often based on causative agent. For bacterial meningitis caused by *Streptococcus pneumoniaea*, the Infectious Diseases Society of America recommends 10 to 14 days of therapy. See Table 128-4 for more information on the duration of antibiotic treatment.

8. **A.** The Infectious Diseases Society of America recommends the addition of vancomycin to ceftriaxone for coverage of potentially cephalosporin-resistant *Streptococcus pneumoniae* isolates in acute, community-acquired, bacterial meningitis. Refer to the "*Streptococcus pneumoniae*" section for more information.

9. **B.** Piperacillin-tazobactam is not included in the recommended regimen for the treatment of healthcare-associated meningitis and ventriculitis because tazobactam does not penetrate the blood–brain barrier (Table 128-3).

10. **E.** Adjunctive use of corticosteroids are indicated for meningitis due to *Haemophilus influenzae* (children), *Streptococcus pneumoniae* (adults), *Mycobacterium tuberculosis*, and brain abscess with significant edema. See "*Haemophilus influenza type b*," "*Streptococcus pneumoniae*," "*Bacterial Brain Abscess*," and "*Mycobacterium Tuberculosis*" sections for more information.

11. **C.** Although Zika virus has been shown to cause encephalitis and congenital brain developmental disorders, it is not a common cause of encephalitis in the United States. There have been no confirmed cases of Zika virus disease in the United States. See the "*Viral Encephalitis*" section for more information.

12. **D.** The Centers for Disease Control and Prevention recommends ≥3 antibiotics with activity against *Bacillus anthracis*, a three-dose subcutaneous series of Anthrax Vaccine Adsorbed, and an antitoxin for the treatment of CNS infection due to inhaled *Bacillus anthracis*. Refer to the "*Bacillus anthracis*" section for more information.

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13. **C.** According to the Centers for Disease Control and Prevention, the recommended treatment duration of Primary Amoebic Meningoencephalitis (PAM) due to *Naegleria fowleri* is 28 days. See the "Primary Amoebic Meningoencephalitis (PAM)" section for more information.

14. **B.** Trimethoprim-sulfamethoxazole is active against most *Nocardia* species and is commonly the core antibiotic used for the treatment of CNS infections. It is used in combination with imipenem or ceftriaxone and, in severe diseases, with a third agent such as linezolid. See the "*Nocardia*" section for more information.

15. **D.** *T. gondii* is transmitted primarily via foodborne, animal-to-human, and mother-to-child routes, and most commonly caused by the reactivation of disease in immunocompromised hosts. Definitive diagnosis of TE requires a clinical sample via a brain biopsy; however, *T. gondii* can also be detected by PCR in CSF, but the sensitivity is low (50%). Refer to the "*Toxoplasma gondii*" section.

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