Chapter 36: Central Nervous System Infections

INTRODUCTION

- Central nervous system (CNS) infections include a wide variety of clinical conditions and etiologies: meningitis, meningoencephalitis, encephalitis, brain and meningeal abscesses, and shunt infections. The focus of this chapter is meningitis.

PATHOPHYSIOLOGY

- 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.
- The critical first step in the acquisition of acute bacterial meningitis is nasopharyngeal colonization of the host by the bacterial pathogen. Most cases of acute bacterial meningitis probably 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.
- CNS infections may be caused by a variety of bacteria, fungi, viruses, and parasites. The most common causes of bacterial meningitis are *Streptococcus pneumoniae*, group B *Streptococcus*, *Neisseria meningitidis, Haemophilus influenzae*, and *Listeria monocytogenes.*
- A common characteristic of most CNS bacterial pathogens (eg, *H. influenzae, Escherichia coli*, *N. meningitidis*) is the presence of an extensive polysaccharide capsule that is resistant to neutrophil phagocytosis and complement opsonization.
- The neurologic sequelae of meningitis occur due to the activation of host inflammatory pathways. Bacterial cell lysis causes the release of cell wall components such as lipopolysaccharide, lipid A (endotoxin), lipoteichoic acid, teichoic acid, and peptidoglycan, depending on whether the pathogen is gram-positive or gram-negative.
- These cell wall components cause capillary endothelial cells and CNS macrophages to release cytokines (interleukin-1, tumor necrosis factor, and other inflammatory mediators). Proteolytic products and toxic oxygen radicals cause an alteration of the blood–brain barrier, whereas platelet-activating factor activates coagulation, and arachidonic acid metabolites stimulate vasodilation. These events lead to cerebral edema, elevated intracranial pressure, cerebrospinal fluid (CSF) pleocytosis, decreased cerebral blood flow, cerebral ischemia, and death.
- Passive and active exposure to cigarette smoke and the presence of a cochlear implant that includes a positioner both increase the risk of bacterial meningitis.

CLINICAL PRESENTATION

- Signs and symptoms of acute bacterial meningitis include fever, nuchal rigidity, altered mental status, chills, vomiting, photophobia, and severe headache. Up to 95% of patients exhibit at least two of the following symptoms: fever, nuchal rigidity, headache, and altered mental status. Kernig and Brudzinski signs may be present but are poorly sensitive and frequently absent in children.
- Clinical signs and symptoms in young children may include bulging fontanelle, apnea purpuric rash, and convulsions.
- Purpuric and petechial skin lesions typically indicate meningococcal involvement, although the lesions may be present with *H. influenzae* meningitis. Rashes rarely occur with pneumococcal meningitis.
- Meningitis causes changes in CSF fluid, and these changes can be used as diagnostic markers of infection (**Table 36-1**).

- CSF culture is the gold standard for diagnosis of bacterial meningitis and is positive in 80%–90% of patients with community-acquired bacterial meningitis if the CSF sample is obtained before the start of antimicrobial therapy.
- Gram stain is a rapid, inexpensive, and accurate method to assess the presence of bacteria in CSF. However, prior antibiotic therapy may cause the Gram stain and CSF culture to be negative, but the antibiotic therapy rarely affects CSF protein or glucose. The sensitivity of the Gram stain depends on the causative microorganism, so that its aggregate diagnostic yield is 90% in pneumococcal meningitis, 70%–90% in meningococcal, 50% in *H. influenza*, and only 25%–35% in *L. monocytogenes* meningitis.
- 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.

TABLE 36-1

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)	1000–5000	50–1000	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]Initial cerebrospinal fluid (CSF), while blood cell (WBC) count may reveal a predominance of polymorphonuclear neutrophils (PMNs). In CNS infection due to tuberculosis, “therapeutic paradox” may occur in which a lymphocytic predominance becomes neutrophilic during antituberculous treatment.

TREATMENT

- Goals of Treatment: Eradication of infection with amelioration of signs and symptoms preventing morbidity and mortality.
- Key elements include initiating appropriate antimicrobials, providing supportive care, and preventing disease through timely introduction of vaccination and chemoprophylaxis.
- 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.

Pharmacologic Treatment

- Empiric antimicrobial therapy should be instituted as soon as possible to eradicate the causative organism (**Table 36-2**). Antimicrobial therapy should last at least 48–72 hours or until the diagnosis of bacterial meningitis can be ruled out. The first dose of antibiotic should not be withheld even when lumbar puncture is delayed or neuroimaging is being performed. The time period from suspected diagnosis to initiation of antibiotic treatment should not exceed 1 hour.
- Continued therapy should be based on the assessment of clinical improvement, cultures, and susceptibility testing results. Once a pathogen is identified, antibiotic therapy should be tailored to the specific pathogen.
- With increased meningeal inflammation, there will be greater antibiotic penetration (**Table 36-3**). Problems of CSF penetration can be 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 the surgical components of therapy.

- See **Table 36-4** for antimicrobial agents of first choice and alternatives for treatment of meningitis caused by gram-positive and gram-negative microorganisms.
- Meningitis caused by *S. pneumoniae* has been treated successfully with 10–14 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 enduring courses.

TABLE 36-2

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] + 3rd generation cephalosporin (cefotaxime *or* ceftriaxone)
2–50 years	*N. meningitidis* *S. pneumoniae*	Vancomycin[c] + 3rd generation cephalosporin (cefotaxime *or* ceftriaxone)
>50 years	*S. pneumoniae* *N. meningitidis* Gram-negative enterics[b] *L. monocytogenes*	Vancomycin[c] + ampicillin + 3rd generation cephalosporin (cefotaxime *or* ceftriaxone)

[a]All recommendations are A-III.

[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.

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.

TABLE 36-3

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

Therapeutic Levels in CSF With or Without Inflammation of Meninges	
Acyclovir	Levofloxacin
Chloramphenicol	Linezolid
Ciprofloxacin	Metronidazole
Fluconazole	Moxifloxacin
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 of Meninges	
Aminoglycosides	Cephalosporins (second generation)[d]
Amphotericin B	Doxycycline[e]

β-Lactamase inhibitors[c]	Itraconazole[f]
Cephalosporins (first generation)	

[a]Using recommended CNS dosing and compared to MIC of target pathogens.

[b]May not achieve therapeutic levels against organisms with higher MIC, as in *P. aeruginosa.* Tazobactam does not penetrate the blood-brain barrier.

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

[d]Cefuroxime is an exception.

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

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

TABLE 36-4

Antimicrobial Agents of First Choice and Alternative Choice for Treating Meningitis Caused by Gram-Positive and Gram-Negative Microorganisms

Organism	Antibiotics of First Choice	Alternative Antibiotics	Recommended Duration of Therapy
Gram-Positive Organisms			
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-III)	
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]European Guidelines recommend considering the addition of rifampin to vancomycin therapy.

[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 36-2** footnotes for rating scale of evidence.

Dexamethasone as an Adjunctive Treatment for Meningitis

- In addition to antibiotics, dexamethasone is a commonly used adjunctive therapy in the treatment of acute bacterial meningitis to immunomodulate the inflammatory response.
- Recommendations by the Infectious Diseases Society of America (IDSA) call for the use of adjunctive dexamethasone in infants and children (6 weeks of age and older) with *H. influenzae* meningitis. The recommended intravenous dose is 0.15 mg/kg every 6 hours for 2–4 days, initiated 10–20 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. If pneumococcal meningitis is suspected or proven, adults should receive dexamethasone 0.15 mg/kg (up to 10 mg) every 6 hours for 2–4 days with the first dose administered 10–20 minutes prior to first dose of antibiotics.

Neisseria meningitidis (Meningococcus)

- *N. meningitidis* is a leading cause of bacterial meningitis among children and young adults in the United States and around the world. It is spread by direct person-to-person close contact, including respiratory droplets and pharyngeal secretions.
- The presence of petechiae may be the primary clue that the underlying pathogen is *N. meningitidis*. Patients may also have an obvious or subclinical picture of disseminated intravascular coagulation (DIC).
- Deafness unilaterally, or more commonly bilaterally, may develop early or late in the disease course.
- Third-generation cephalosporins (ie, cefotaxime and ceftriaxone) are the recommended empiric treatment for meningococcal meningitis. Penicillin G or ampicillin is recommended for penicillin-susceptible isolates. The recommended duration of therapy is typically 7 days if there is good clinical response.
- Antimicrobial chemoprophylaxis of close contacts should be started as soon as possible (ideally <24 hours after identification of the index patient). In general, rifampin, ceftriaxone, and ciprofloxacin are recommended for prophylaxis; however, there is an increase in rifampin-resistant and ciprofloxacin-resistant isolates.
- For full details on vaccine availability and vaccination recommendations in various age groups and for those with significant risk factors, readers are referred to the current recommendations from the Advisory Committee on Immunization Practices.

Streptococcus pneumoniae (Pneumococcus or Diplococcus)

- *Streptococcus* group B (GBS) is a leading cause of neonatal meningitis in the United States and around the world.
- Neurologic sequelae include sight or hearing loss and cerebral palsy.
- Universal prenatal screening and intrapartum antimicrobial prophylaxis of GBS-colonized pregnant women decreases the rate of early onset invasive disease. Recommended agents for intrapartum prophylaxis are penicillin or ampicillin, cefazolin (if penicillin allergy and not at high risk

for anaphylaxis), or vancomycin (if penicillin allergy and at high risk for anaphylaxis).

- Ampicillin plus an aminoglycoside is the treatment of choice for a newborn infant with presumptive early-onset GBS meningitis. For empirical therapy of late-onset meningitis, ampicillin and an aminoglycoside or cefotaxime is recommended. Ampicillin or penicillin G is the recommended agent in adults. Addition of an aminoglycoside could also be considered. 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. For adults, the recommended duration of antibiotics is 14–21 days.
- Refer to Chapter 52 for information on pneumococcal vaccines.

Haemophilus influenzae

- Widespread vaccination of infants and children has effectively decreased the incidence of bacterial meningitis due to Hib in children between the ages of 1 month and 5 years, resulting in a significant decline in all cases of bacterial meningitis.
- Third-generation cephalosporins (cefotaxime and ceftriaxone) are the drugs of choice for empirical therapy for *H. influenzae* type b 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.
- Recommended duration of treatment is 7 days (adults) or 7–10 days (children).
- 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).
- Chemoprophylaxis with rifampin is indicated to reduce the risk of secondary invasive Hib disease in close contacts by eliminating nasopharyngeal and oropharyngeal carriages of *H. influenzae*. Rifampin should be administered orally, once a day for 4 days (20 mg/kg/dose; maximum, 600 mg). For information on who should receive prophylaxis (adults and children), refer to the recommendations of the American Academy of Pediatrics.
- Refer to Chapter 52 for information on *H. influenzae* vaccination.

Listeria monocytogenes

- *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.
- Treatment of *L. monocytogenes* meningitis should consist of penicillin G or ampicillin. The addition of aminoglycoside is also recommended in proven infection in both children and adults. Patients should be treated a minimum of 21 days.
- **Trimethoprim–sulfamethoxazole** and **meropenem** may be effective alternatives because adequate CSF penetration is achieved with these agents.

See Chapter 124, Central Nervous System Infections, authored by Christina Koutsari, Thomas J. Dilworth, Jessica S. Holt, Ramy H. Elshaboury, and John C. Rotschafer, for a more detailed discussion of this topic.