HARRISON'S PRINCIPLES OF INTERNAL MEDICINE — 22nd Edition

Acute Meningitis

Chapter 143 | Part 5: Infectious Diseases | Part 5 – Infectious Diseases: Bacterial | DETAILED EDITION

KEY CLINICAL POINTS

1. The classic clinical triad of fever, headache, and nuchal rigidity occurs in >80% of adult cases, though the complete triad is not always present.
2. Dexamethasone should be initiated 20 minutes before or concurrent with the first dose of antibiotics to reduce mortality and hearing loss.
3. Empirical therapy for community-acquired bacterial meningitis includes vancomycin plus a third- or fourth-generation cephalosporin (ceftriaxone, cefotaxime, or cefepime).
4. Acyclovir is added to empirical therapy to cover HSV encephalitis, a leading differential diagnosis.
5. CSF findings in bacterial meningitis include PMN leukocytosis (>100 cells/µL), hypoglycorrhachia (<2.2 mmol/L), elevated protein (>0.45 g/L), and elevated opening pressure (>180 mmH2O).
6. Listeria monocytogenes is an important cause in neonates, pregnant women, and adults >50 years; ampicillin is required in these groups.
7. Mortality rates vary by organism: 3–7% for H. influenzae, N. meningitidis, or GBS; 15% for L. monocytogenes; 20% for S. pneumoniae.
8. Meningococcal contacts require chemoprophylaxis with rifampin, azithromycin, or ceftriaxone.
9. Seizures occur in 15–40% of patients and may be due to focal ischemia, cortical venous thrombosis, or hyponatremia.
10. A CSF/serum glucose ratio <0.4 is highly suggestive of bacterial meningitis but may also be seen in fungal, tuberculous, and carcinomatous meningitis.

FIGURES IN THIS CHAPTER

1. DEFINITION & OVERVIEW

Bacterial meningitis is an acute purulent infection within the subarachnoid space (SAS). It is associated with a central nervous system (CNS) inflammatory reaction that may result in decreased consciousness, seizures, raised intracranial pressure (ICP), and stroke. The meninges, SAS, and brain parenchyma are all frequently involved in the inflammatory reaction (meningoencephalitis).

2. EPIDEMIOLOGY

Bacterial meningitis is the most common form of suppurative CNS infection, with an annual incidence in the United States of ~1.4 cases/100,000 population. The organisms most often responsible for community-acquired bacterial meningitis are Streptococcus pneumoniae (~50%), Neisseria meningitidis (~25%), group B streptococci (~15%), and Listeria monocytogenes (~10%). Haemophilus influenzae type b accounts for <10% of cases of bacterial meningitis in most series. N. meningitidis is the causative organism of recurring epidemics of meningitis every 8–12 years. The incidence of meningitis due to N. meningitidis has decreased with the routine immunization of 11- to 18-year-olds with the quadrivalent (serogroups A, C, W-135, and Y) meningococcal glycoconjugate vaccine, and adolescents and young adults (16–23 years old) with the serogroup B meningococcal vaccine. A pentavalent meningococcal vaccine (serogroups A, B, C, W-135, and Y) has recently become available.

3. ETIOLOGY & PATHOPHYSIOLOGY

The most common bacteria that cause meningitis, S. pneumoniae and N. meningitidis, initially colonize the nasopharynx by attaching to nasopharyngeal epithelial cells. Bacteria are transported across epithelial cells in membrane-bound vacuoles to the intravascular space or invade the intravascular space by creating separations in the apical tight junctions of columnar epithelial cells. Once in the bloodstream, bacteria are able to avoid phagocytosis by neutrophils and classic complement-mediated bactericidal activity because of the presence of a polysaccharide capsule. Bloodborne bacteria can reach the intraventricular choroid plexus, directly infect choroid plexus epithelial cells, and gain access to the CSF. Some bacteria, such as S. pneumoniae, can adhere to cerebral capillary endothelial cells and subsequently migrate through or between these cells to reach the CSF. Bacteria are able to multiply rapidly within CSF because of the absence of effective host immune defenses. Normal CSF contains few white blood cells (WBCs) and relatively small amounts of complement proteins and immunoglobulins. The paucity of the latter two prevents effective opsonization of bacteria, an essential prerequisite for bacterial phagocytosis by neutrophils. Phagocytosis of bacteria is further impaired by the fluid nature of CSF, which is less conducive to phagocytosis than a solid tissue substrate. A critical event in the pathogenesis of bacterial meningitis is the inflammatory reaction induced by the invading bacteria. Many of the neurologic manifestations and complications of bacterial meningitis result from the immune response to the invading pathogen rather than from direct bacteria-induced tissue injury. As a result, neurologic injury can progress even after the CSF has been sterilized by antibiotic therapy. The lysis of bacteria with the subsequent release of cell-wall components into the SAS is the initial step in the induction of the inflammatory response and the formation of a purulent exudate in the SAS. Bacterial cell-wall components, such as the lipopolysaccharide (LPS) molecules of gram-negative bacteria and teichoic acid and peptidoglycans of S. pneumoniae, induce meningeal inflammation by stimulating the production of inflammatory cytokines and chemokines by microglia, astrocytes, monocytes, microvascular endothelial cells, and CSF leukocytes. In experimental models of meningitis, cytokines including tumor necrosis factor alpha (TNF-α) and interleukin 1β (IL-1β) are present in CSF within 1–2 h of intracisternal inoculation of LPS. This cytokine response is quickly followed by an increase in CSF protein concentration and leukocytosis. Chemokines (cytokines that induce chemotactic migration in leukocytes) and a variety of other proinflammatory cytokines are also produced and secreted by leukocytes and tissue cells that are stimulated by IL-1β and TNF-α. In addition, bacteremia and the inflammatory cytokines induce the production of excitatory amino acids, reactive oxygen and nitrogen species (free oxygen radicals, nitric oxide, and peroxynitrite), and other mediators that can induce death of brain cells, especially in the dentate gyrus of the hippocampus. The subarachnoid exudate of proteinaceous material and leukocytes obstructs the flow of CSF through the ventricular system and diminishes the resorptive capacity of the arachnoid granulations in the

dural sinuses, leading to obstructive and communicating hydrocephalus and concomitant interstitial edema. Inflammatory cytokines upregulate the expression of selectins on cerebral capillary endothelial cells and leukocytes, promoting leukocyte adherence to vascular endothelial cells and subsequent migration into the CSF. The adherence of leukocytes to capillary endothelial cells increases the permeability of blood vessels, allowing for the leakage of plasma proteins into the CSF, which adds to the inflammatory exudate. Neutrophil degranulation results in the release of toxic metabolites that contribute to cytotoxic edema, cell injury, and death. During the very early stages of meningitis, there is an increase in cerebral blood flow, soon followed by a decrease in cerebral blood flow and a loss of cerebrovascular autoregulation. Narrowing of the large arteries at the base of the brain due to encroachment by the purulent exudate in the SAS and infiltration of the arterial wall by inflammatory cells with intimal thickening (vasculitis) also occur and may result in ischemia and infarction, obstruction of branches of the middle cerebral artery by thrombosis, thrombosis of the major cerebral venous sinuses, and thrombophlebitis of the cerebral cortical veins. The combination of interstitial, vasogenic, and cytotoxic edema leads to raised ICP and coma. Cerebral herniation usually results from the effects of cerebral edema, either focal or generalized; hydrocephalus and dural sinus or cortical vein thrombosis may also play a role.

Table 1 Table 143-1 Antibiotics Used in Empirical Therapy of Bacterial Meningitis and Focal Central Nervous System Infections

INDICATION	ANTIBIOTIC
Preterm infants to infants <1 month	Ampicillin + cefotaxime
Infants 1–3 months	Ampicillin + cefotaxime or ceftriaxone
Immunocompetent children >3 months and adults <55	Cefotaxime, ceftriaxone, or cefepime + vancomycin
Adults >55 and adults of any age with alcoholism or other debilitating illnesses	Ampicillin + cefotaxime, ceftriaxone, or cefepime + vancomycin
Hospital-acquired meningitis, posttraumatic or postneurosurgery meningitis, neutropenic patients, or patients with impaired cell-mediated immunity	Ampicillin + ceftazidime or meropenem + vancomycin

Table 2 Table 143-2 Cerebrospinal Fluid (CSF) Abnormalities in Bacterial Meningitis

Parameter	Finding
Opening pressure	>180 mmH2O
White blood cells	10/µL to 10,000/µL; neutrophils predominate
Red blood cells	Absent in nontraumatic tap
Glucose	<2.2 mmol/L (<40 mg/dL)
CSF/serum glucose	<0.4
Protein	>0.45 g/L (>45 mg/dL)
Gram's stain	Positive in >60%
Culture	Positive in >80%
PCR	Detects bacterial DNA

3.1 Etiologic Agents

S. pneumoniae (Chap. 151) is the most common cause of meningitis in adults >20 years of age, accounting for nearly half the reported cases. There are a number of predisposing conditions that increase the risk of pneumococcal meningitis, the most important of which is pneumococcal pneumonia. Additional risk factors include coexisting acute or chronic pneumococcal sinusitis or otitis media, alcoholism, diabetes, splenectomy, hypogammaglobulinemia, complement deficiency, and head trauma with basilar skull fracture and cerebrospinal fluid (CSF) rhinorrhea. The mortality rate remains ~20% despite antibiotic therapy. The incidence of meningitis due to N. meningitidis (Chap. 160) has decreased with the routine immunization of 11- to 18-year-olds with the quadrivalent (serogroups A, C, W-135, and Y) meningococcal glycoconjugate vaccine, and adolescents and young adults (16–23 years old) with the serogroup B meningococcal vaccine. A pentavalent meningococcal vaccine (serogroups A, B, C, W-135, and Y) has recently become available. Individuals being treated with complement inhibitors are at increased risk of meningococcal disease and should receive either the quadrivalent vaccine and a serogroup B meningococcal vaccine, or the pentavalent meningococcal vaccine, prior to beginning therapy. Individuals with complement component deficiencies are at increased risk for meningococcal disease and similarly should receive either the quadrivalent and a serogroup B meningococcal vaccine or the pentavalent meningococcal vaccine. The meningococcal vaccines use outer membrane proteins as the vaccine antigens. The serogroup B polysaccharide capsule is poorly immunogenic. The serogroup B meningococcal vaccines do not reduce the risk of bacterial spread of group B meningococcus from vaccinated persons to unimmunized persons as the vaccines do not significantly reduce nasopharyngeal carriage of meningococci, and this remains the major source of person-to-person bacterial transmission. In contrast, nasopharyngeal carriage is reduced in vaccinated individuals who have received the conjugate vaccines that cover groups A, C, W, and Y. The presence of petechial or purpuric skin lesions can provide an important clue to the diagnosis of meningococcal infection. In some patients, the disease is fulminant, progressing to death within hours of symptom onset. Infection may be initiated by nasopharyngeal colonization, which can result in either an asymptomatic carrier state or invasive meningococcal disease. The risk of invasive disease following nasopharyngeal colonization depends on both bacterial virulence factors and host immune defense mechanisms, including the host's capacity to produce antimeningococcal antibodies and to lyse meningococci by both classic and alternative complement pathways. Individuals with deficiencies of any of the complement components, including properdin, are highly susceptible to meningococcal infections. Gram-negative bacilli cause meningitis in individuals with chronic and debilitating diseases such as diabetes, cirrhosis, or alcoholism and in those with urinary tract infections. Gram-negative meningitis can also complicate neurosurgical procedures, particularly craniotomy, and head trauma associated with CSF rhinorrhea or otorrhea. Otitis, mastoiditis, and sinusitis are predisposing and associated conditions for meningitis due to Streptococcus spp., gram-negative anaerobes, Staphylococcus aureus, Haemophilus spp., and Enterobacteriaceae. Meningitis complicating endocarditis may be due to viridans streptococci, S. aureus, Streptococcus bovis, the HACEK group (Haemophilus spp., Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae), or enterococci. Group B streptococcus, or Streptococcus agalactiae (Chap. 153), was previously responsible for meningitis predominantly in neonates, but it has been reported with increasing frequency in individuals aged >50 years, particularly those with underlying diseases. Much of the pathophysiology of bacterial meningitis is a direct consequence of elevated levels of CSF cytokines and chemokines. TNF-α and IL-1β act synergistically to increase the permeability of the blood-brain barrier, resulting in induction of vasogenic edema and the leakage of serum proteins into the SAS. L. monocytogenes (Chap. 156) is an increasingly important cause of meningitis in neonates (<1 month of age), pregnant women, individuals >60 years, and immunocompromised individuals of all ages. Infection is acquired by ingesting foods contaminated by Listeria. Foodborne human listerial infection has been reported from contaminated coleslaw, milk, soft cheeses, and several types of "ready-to-eat" foods, including delicatessen meat and uncooked hotdogs. The frequency of H. influenzae type b (Hib) meningitis in children has declined

dramatically since the introduction of the Hib conjugate vaccine, although rare cases of Hib meningitis in vaccinated children have been reported. More frequently, H. influenzae causes meningitis in unvaccinated children and older adults, and non-b H. influenzae is an emerging pathogen (Chap. 162). S. aureus and coagulase-negative staphylococci (Chap. 152) are important causes of meningitis that occurs following invasive neurosurgical procedures, particularly shunting procedures for hydrocephalus, or as a complication of the use of subcutaneous Ommaya reservoirs for administration of intrathecal chemotherapy.

4. CLINICAL FEATURES

Meningitis can present as either an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days. The classic clinical triad of meningitis is fever, headache, and nuchal rigidity, and these features each occur in >80% of adult cases of acute bacterial meningitis, although the complete classic triad is not always present. A decreased level of consciousness occurs in >75% of patients and can vary from lethargy to coma. Nausea, vomiting, and photophobia are also common complaints. Nuchal rigidity ("stiff neck") is the pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion. Kernig's and Brudzinski's signs are also classic signs of meningeal irritation. Kernig's sign is elicited with the patient in the supine position. The thigh is flexed on the abdomen, with the knee flexed; attempts to passively extend the knee elicit pain when meningeal irritation is present. Brudzinski's sign is elicited with the patient in the supine position and is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees. Although commonly tested on physical examinations, the sensitivity and specificity of Kernig's and Brudzinski's signs are uncertain. Both may be absent or reduced in very young or elderly patients, immunocompromised individuals, or patients with a severely depressed mental status. The high prevalence and of cervical spine disease in older individuals may result in false-positive tests for nuchal rigidity. Seizures occur as part of the initial presentation of bacterial meningitis or during the course of the illness in 15–40% of patients. Focal seizures are usually due to focal arterial ischemia or infarction, cortical venous thrombosis with hemorrhage, or focal edema. Generalized seizure activity and status epilepticus may be due to hyponatremia, cerebral anoxia, or, less commonly, the toxic effects of antimicrobial agents. Raised ICP is an expected complication of bacterial meningitis and the major cause of obtundation and coma in this disease. More than 90% of patients will have a CSF opening pressure >180 mmH2O, and 20% have opening pressures >400 mmH2O. Signs of increased ICP include a deteriorating or reduced level of consciousness, papilledema, dilated poorly reactive pupils, sixth nerve palsies, decerebrate posturing, and the Cushing reflex (bradycardia, hypertension, and irregular respirations). The most disastrous complication of increased ICP is cerebral herniation. The incidence of herniation in patients with bacterial meningitis has been reported to occur in as few as 1% to as many as 8% of cases.

4.1 Specific Clinical Clues

Specific clinical features may provide clues to the diagnosis of individual organisms and are discussed in more detail in specific chapters. The most important of these clues is the rash of meningococcemia, which begins as a diffuse erythematous maculopapular rash resembling a viral exanthem; however, the skin lesions of meningococcemia rapidly become petechial. Petechiae are found on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles. Petechial skin lesions, if present, should be biopsied. The rash of meningococcemia results from the dermal seeding of organisms with vascular endothelial damage, and biopsy may reveal the organism on Gram's stain.

5. DIFFERENTIAL DIAGNOSIS

Viral meningoencephalitis, and particularly herpes simplex virus (HSV) encephalitis (Chap. 142), can mimic the clinical presentation of bacterial meningitis (encephalitis). HSV encephalitis typically presents with headache,

fever, altered consciousness, focal neurologic deficits (e.g., dysphasia, hemiparesis), and focal or generalized seizures. The findings on CSF studies, neuroimaging, and electroencephalogram (EEG) distinguish HSV encephalitis from bacterial meningitis. The typical CSF profile with viral CNS infections is a lymphocytic pleocytosis with a normal glucose concentration, in contrast to the PMN pleocytosis and hypoglycorrhachia characteristic of bacterial meningitis. The CSF HSV PCR has a 96% sensitivity and a 99% specificity when CSF is examined 72 h following symptom onset and in the first week of antiviral therapy. MRI abnormalities (other than meningeal enhancement) are not seen in uncomplicated bacterial meningitis. By contrast, in HSV encephalitis, on T2-weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted MRI images, high-signal-intensity lesions are seen in the orbitofrontal, anterior, and medial temporal lobes in the majority of patients within 48 h of symptom onset. Some patients with HSV encephalitis have a distinctive periodic pattern on EEG. Rickettsial disease (Chap. 192) can resemble bacterial meningitis. Rocky Mountain spotted fever (RMSF) is transmitted by a tick bite and caused by the bacteria Rickettsia rickettsii. The disease may present acutely with high fever, prostration, myalgia, headache, nausea, and vomiting. Most patients develop a characteristic rash within 96 h of the onset of symptoms. The rash is initially a diffuse erythematous maculopapular rash that may be difficult to distinguish from that of meningococcemia. It progresses to a petechial rash, then to a purpuric rash, and if untreated, to skin necrosis or gangrene. The color of the lesions changes from bright red to very dark red, then yellowish-green to black. The rash typically begins in the wrist and ankles and then spreads distally and proximally within a matter of a few hours, involving the palms and soles. Diagnosis is made by immunofluorescent staining of skin biopsy specimens. Ehrlichioses are also transmitted by a tick bite. These are small gram-negative coccobacilli of which two species cause human disease. Anaplasma phagocytophilum causes human granulocytic ehrlichiosis (anaplasmosis), and Ehrlichia chaffeensis causes human monocytic ehrlichiosis. The clinical and laboratory manifestations of the infections are similar. Patients present with fever, headache, confusion, nausea, and vomiting. Twenty percent of patients have a maculopapular or petechial rash. There is laboratory evidence of leukopenia, thrombocytopenia, and anemia, and mild to moderate elevations in alanine aminotransferases, alkaline phosphatase, and lactate dehydrogenase. Patients with RMSF and those with ehrlichial infections may have an altered level of consciousness ranging from mild lethargy to coma, confusion, focal neurologic signs, cranial nerve palsies, hyperreflexia, and seizures. Focal suppurative CNS infections, including subdural and epidural empyema and brain abscess, should also be considered (Chap. 145), especially when focal neurologic findings are present. MRI should be performed promptly in all patients with suspected meningitis who have focal features, both to detect the intracranial infection and to search for associated areas of infection in the sinuses or mastoid bones. A number of noninfectious CNS disorders can mimic bacterial meningitis. Subarachnoid hemorrhage (SAH; Chap. 440) is generally the major consideration. Other possibilities include medication-induced hypersensitivity meningitis; chemical meningitis due to rupture of tumor contents into the CSF (e.g., from a cystic glioma, craniopharyngioma, epidermoid or dermoid cyst); carcinomatous or lymphomatous meningitis; meningitis associated with inflammatory disorders such as sarcoid, systemic lupus erythematosus (SLE), and Behçet's syndrome; pituitary apoplexy; and uveomeningitic syndromes (Vogt-Koyanagi-Harada syndrome). On occasion, subacutely evolving meningitis (see below and Chap. 144) may be considered in the differential diagnosis of acute meningitis. The principal causes include Mycobacterium tuberculosis (Chap. 183), Cryptococcus neoformans (Chap. 221), Histoplasma capsulatum (Chap. 218), Coccidioides immitis (Chap. 219), and Treponema pallidum (Chap. 187).

6. INVESTIGATIONS & DIAGNOSIS

When bacterial meningitis is suspected, blood cultures should be immediately obtained and empirical antimicrobial and adjunctive dexamethasone therapy initiated without delay (Table 143-1). The diagnosis of bacterial meningitis is made by examination of the CSF (Table 143-2). The need to obtain neuroimaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) prior to lumbar puncture (LP)

requires clinical judgment. In an immunocompetent patient with no known history of recent head trauma, a normal level of consciousness, and no evidence of papilledema or focal neurologic deficits, it is considered safe to perform LP without prior neuroimaging studies. If LP is delayed in order to obtain neuroimaging studies, empirical antibiotic therapy should be initiated after blood cultures are obtained. Antibiotic therapy initiated a few hours prior to LP will not significantly alter the CSF WBC count or glucose concentration, nor is it likely to prevent visualization of organisms by Gram's stain or detection of bacterial nucleic acid by polymerase chain reaction (PCR) assay. MRI is preferred over CT because of its superiority in demonstrating areas of cerebral edema and ischemia. In patients with bacterial meningitis, diffuse meningeal enhancement is often seen after the administration of gadolinium. Meningeal enhancement is not diagnostic of meningitis but occurs in any CNS disease associated with increased blood-brain barrier permeability. The classic CSF abnormalities in bacterial meningitis (Table 143-2) are (1) polymorphonuclear (PMN) leukocytosis (>100 cells/µL in 90%), (2) decreased glucose concentration (<2.2 mmol/L [<40 mg/dL] and/or CSF/serum glucose ratio of <0.4 in ~60%), (3) increased protein concentration (>0.45 g/L [>45 mg/dL] in 90%), and (4) increased opening pressure (>180 mmH2O in 90%). CSF bacterial cultures are positive in >70% of patients, and CSF Gram's stain demonstrates organisms in >60%. CSF glucose concentrations <2.2 mmol/L (<40 mg/dL) are abnormal, and a CSF glucose concentration of zero can be seen in bacterial meningitis. Use of the CSF/serum glucose ratio corrects for hyperglycemia that may mask a relative decrease in the CSF glucose concentration. The CSF glucose concentration is low when the CSF/serum glucose ratio is <0.6. A CSF/serum glucose ratio <0.4 is highly suggestive of bacterial meningitis but may also be seen in other conditions, including fungal, tuberculous, and carcinomatous meningitis. It takes 30 min to several hours for the concentration of CSF glucose to reach equilibrium with blood glucose levels; therefore, administration of 50 mL of 50% glucose (D50) prior to LP, as commonly occurs in emergency room settings, is unlikely to alter CSF glucose concentration significantly unless more than a few hours have elapsed between glucose administration and LP. The CSF multiplex PCR pathogen assays, the most common of which is the FilmArray Meningitis/Encephalitis panel (BioFire Diagnostics), detect the nucleic acid of S. pneumoniae, N. meningitidis, Escherichia coli, L. monocytogenes, H. influenzae, and S. agalactiae (group B streptococci). Although these PCR assays have a rapid turnaround time, the sensitivity and specificity for the bacterial meningeal pathogens they test for are not known. The CSF multiplex PCR pathogen assays do not include S. aureus, coagulase-negative staphylococci, and many gram-negative organisms. The PCR assays cannot replace CSF bacteria culture, as culture is required for antimicrobial susceptibility testing. Almost all patients with bacterial meningitis will have neuroimaging studies performed during the course of their illness. MRI is preferred over CT because of its superiority in demonstrating areas of cerebral edema and ischemia. In patients with bacterial meningitis, diffuse meningeal enhancement is often seen after the administration of gadolinium. Meningeal enhancement is not diagnostic of meningitis but occurs in any CNS disease associated with increased blood-brain barrier permeability. Petechial skin lesions, if present, should be biopsied. The rash of meningococcemia results from the dermal seeding of organisms with vascular endothelial damage, and biopsy may reveal the organism on Gram's stain.

Table 3 Table 143-3 Antimicrobial Therapy of Central Nervous System Bacterial Infections Based on Pathogen

ORGANISM	ANTIBIOTIC
Neisseria meningitides	Penicillin-sensitive: Penicillin G or ampicillin; Penicillin-resistant: Ceftriaxone or cefotaxime
Streptococcus pneumoniae	Penicillin-sensitive: Penicillin G; Penicillin-intermediate: Ceftriaxone or cefotaxime or cefepime; Penicillin-resistant: Ceftriaxone (or cefotaxime or cefepime) + vancomycin

ORGANISM	ANTIBIOTIC
Gram-negative bacilli (except Pseudomonas spp.)	Ceftriaxone or cefotaxime
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Staphylococci spp.	Methicillin-sensitive: Nafcillin; Methicillin-resistant: Vancomycin
Listeria monocytogenes	Ampicillin + gentamicin
Haemophilus influenzae	Ceftriaxone or cefotaxime if β-lactamase positive; ampicillin if β-lactamase negative
Streptococcus agalactiae	Penicillin G or ampicillin
Bacteroides fragilis	Metronidazole
Fusobacterium spp.	Metronidazole

7. MANAGEMENT & TREATMENT

Bacterial meningitis is a medical emergency. The goal is to begin antibiotic therapy within 60 min of a patient's arrival in the emergency room. Empirical antimicrobial therapy is initiated in patients with suspected bacterial meningitis before the results of CSF multiplex PCR assays, Gram's stain, and culture are known. Methicillin-resistant S. pneumoniae (Chap. 151) and N. meningitidis (Chap. 160) are the most common etiologic organisms of community-acquired bacterial meningitis. Due to the emergence of penicillin- and cephalosporin-resistant S. pneumoniae, empirical therapy of community-acquired suspected bacterial meningitis in children and adults should include a combination of dexamethasone, a third- or fourth-generation cephalosporin (e.g., ceftriaxone, cefotaxime, or cefepime), and vancomycin, plus acyclovir, as HSV encephalitis is the leading disease in the differential diagnosis, and doxycycline during tick season to treat tick-borne bacterial infections. Ceftriaxone or cefotaxime provides good coverage for susceptible S. pneumoniae, group B streptococci, and H. influenzae and adequate coverage for N. meningitidis. Cefepime is a broad-spectrum fourth-generation cephalosporin with in vitro activity similar to that of cefotaxime or ceftriaxone against S. pneumoniae and N. meningitidis and greater activity against Enterobacter species and Pseudomonas aeruginosa. In clinical trials, cefepime has been demonstrated to be equivalent to cefotaxime in the treatment of penicillin-sensitive pneumococcal and meningococcal meningitis, and it has been used successfully in some patients with meningitis due to Enterobacter species and P. aeruginosa. Cefepime has been associated with seizures, myoclonus, and encephalopathy, any of which may limit its use in critically ill patients. Ampicillin should be added to the empirical regimen for coverage of L. monocytogenes in individuals <3 months of age, those >55, or those with suspected impaired cell-mediated immunity because of chronic illness, organ transplantation, pregnancy, malignancy, or immunosuppressive therapy. Metronidazole is added to the empirical regimen to cover gram-negative anaerobes in patients with otitis, sinusitis, or mastoiditis. In hospital-acquired meningitis, and particularly meningitis following neurosurgical procedures, staphylococci and gram-negative organisms including P. aeruginosa are the most common etiologic organisms. In these patients, empirical therapy should include a combination of vancomycin and ceftazidime or meropenem. Ceftazidime or meropenem should be substituted for ceftriaxone or cefotaxime in neurosurgical patients and in neutropenic patients because ceftriaxone and cefotaxime do not provide adequate activity against CNS infection with P. aeruginosa. Meropenem is a carbapenem antibiotic that is highly active in vitro against L. monocytogenes, has been demonstrated to be effective in cases of meningitis caused by P. aeruginosa, and shows good activity against penicillin-resistant pneumococci. In experimental pneumococcal meningitis,

meropenem was comparable to ceftriaxone and inferior to vancomycin in sterilizing CSF cultures. When S. pneumoniae, H. influenzae, L. monocytogenes, or aerobic gram-negative bacilli (including P. aeruginosa and E. coli) are possible meningeal pathogens, based on predisposing and associated conditions, the combination of vancomycin plus meropenem can be recommended as empiric therapy for bacterial meningitis in children and adults. Meropenem should not be used as monotherapy. A 2-week course of intravenous antimicrobial therapy is recommended for pneumococcal meningitis. Patients with S. pneumoniae meningitis should have a repeat LP performed 24–36 h after the initiation of antimicrobial therapy to document sterilization of the CSF. Failure to sterilize the CSF after 24–36 h of antibiotic therapy should be considered presumptive evidence of antibiotic resistance. Patients with penicillin- and cephalosporin-resistant strains of S. pneumoniae who do not respond to intravenous vancomycin alone may benefit from the addition of intraventricular vancomycin. The intraventricular route of administration is also preferred over the intrathecal route because adequate concentrations of vancomycin in the cerebral ventricles are not always achieved with intrathecal administration. Listeria Meningitis: Meningitis due to L. monocytogenes is treated with ampicillin for at least 3 weeks (Table 143-3). Gentamicin is added in critically ill patients (2 mg/kg loading dose, then 7.5 mg/kg per day given every 8 h and adjusted for serum levels and renal function). The combination of trimethoprim (10–20 mg/kg per day) and sulfamethoxazole (50–100 mg/kg per day) given every 6 h may provide an alternative in penicillin-allergic patients. Staphylococcal Meningitis: Meningitis due to susceptible strains of S. aureus or coagulase-negative staphylococci is treated with nafcillin (Table 143-3). Vancomycin is the drug of choice for methicillin-resistant staphylococci and for patients allergic to penicillin. In these patients, the CSF should be monitored during therapy. If the CSF is not sterilized after 48 h of intravenous vancomycin therapy, then either intraventricular or intrathecal vancomycin, 20 mg once daily, can be added. Gram-Negative Bacillary Meningitis: The third-generation cephalosporins—cefotaxime, ceftriaxone, and ceftazidime—are equally efficacious for the treatment of gram-negative bacillary meningitis, and with the exception of meningitis due to P. aeruginosa, which should be treated with ceftazidime or meropenem (Table 143-3). A 3-week course of intravenous antibiotic therapy is recommended for meningitis due to gram-negative bacilli. Meningococcal Meningitis: Although ceftriaxone and cefotaxime provide adequate empirical coverage for N. meningitidis, penicillin G remains the antibiotic of choice for meningococcal meningitis caused by susceptible strains. Isolates of N. meningitidis should be tested for penicillin and ampicillin susceptibility, and if resistance is found, cefotaxime or ceftriaxone should be substituted for penicillin. A 7-day course of intravenous antibiotic therapy is adequate for uncomplicated meningococcal meningitis. The index case and all close contacts should receive chemoprophylaxis with a 2-day regimen of rifampin (600 mg every 12 h for 2 days in adults and 10 mg/kg every 12 h for 2 days in children >1 year). Rifampin is not recommended in pregnant women. Alternatively, adults can be treated with one dose of azithromycin (500 mg) or one intramuscular dose of ceftriaxone (250 mg). Close contacts are defined as those individuals who have had contact with oropharyngeal secretions, either through kissing or by sharing toys, beverages, or cigarettes. Pneumococcal Meningitis: Antimicrobial therapy of pneumococcal meningitis is initiated with a cephalosporin (ceftriaxone, cefotaxime, or cefepime) and vancomycin. All CSF isolates of S. pneumoniae should be tested for sensitivity to penicillin and the cephalosporins. Once the results of antimicrobial susceptibility tests are known, therapy can be modified accordingly (Table 143-3). For S. pneumoniae meningitis, an isolate of S. pneumoniae is considered to be susceptible to penicillin with a minimal inhibitory concentration (MIC) <0.06 μg/mL and to be resistant when the MIC is >0.12 μg/mL. Isolates of S. pneumoniae that have cephalosporin MICs ≤0.5 μg/mL are considered sensitive to the cephalosporins (cefotaxime, ceftriaxone, cefepime). Those with MICs of 1 μg/mL are considered to have intermediate resistance, and those with MICs ≥2 μg/mL are considered resistant. For meningitis due to pneumococci, with cefotaxime or ceftriaxone MICs ≤0.5 μg/mL, treatment with cefotaxime or ceftriaxone is usually adequate. For MIC >1 μg/mL, vancomycin is the antibiotic of choice. Rifampin can be added to vancomycin for its synergistic effect but is inadequate as monotherapy because resistance develops rapidly when it is used alone. Adjunctive Therapy: The release of bacterial cell-wall components by bactericidal antibiotics leads to the production of the inflammatory cytokines IL-1β and TNF-α

in the SAS. Dexamethasone exerts its beneficial effect by inhibiting the synthesis of IL-1β and TNF-α at the level of mRNA, decreasing CSF outflow resistance, and stabilizing the blood-brain barrier. The rationale for giving dexamethasone 20 min before antibiotic therapy is that dexamethasone inhibits the production of TNF-α by macrophages and microglia only if it is administered before these cells are activated by endotoxin. Dexamethasone does not alter TNF-α production once it has been induced. The result is that dexamethasone has been shown to reduce rates of death and hearing loss with no adverse effects in patients with meningococcal meningitis. One of the concerns for using dexamethasone in adults with bacterial meningitis is that in experimental models of meningitis, dexamethasone therapy increased hippocampal cell injury and reduced learning capacity. This has not been the case in clinical series. The efficacy of dexamethasone therapy in preventing neurologic sequelae is different between high- and low-income countries. Three large randomized trials in low-income countries (sub-Saharan Africa, Southeast Asia) failed to show benefit in subgroups of patients. The lack of efficacy of dexamethasone in these trials has been attributed to late presentation to the hospital with more advanced disease, antibiotic pretreatment, malnutrition, infection with HIV, and treatment of patients with probable, but not microbiologically proven, bacterial meningitis. The results of these clinical trials suggest that patients in sub-Saharan Africa and those in low-income countries with negative CSF Gram's stain and culture should not be treated with dexamethasone.

Table 4 Table 143-1 Antibiotics Used in Empirical Therapy of Bacterial Meningitis and Focal Central Nervous System Infections (Dosing)

ANTIMICROBIAL AGENT	TOTAL DAILY DOSE AND DOSING INTERVAL (CHILD >1 MONTH)	TOTAL DAILY DOSE AND DOSING INTERVAL (ADULT)
Ampicillin	300 (mg/kg)/d, q6h	12 g/d, q4h
Cefepime	150 (mg/kg)/d, q8h	6 g/d, q8h
Cefotaxime	225–300 (mg/kg)/d, q6h	12 g/d, q4h
Ceftriaxone	100 (mg/kg)/d, q12h	4 g/d, q12h
Ceftazidime	150 (mg/kg)/d, q8h	6 g/d, q8h
Gentamicin	7.5 (mg/kg)/d, q8h	7.5 (mg/kg)/d, q8h
Meropenem	120 (mg/kg)/d, q8h	6 g/d, q8h
Metronidazole	30 (mg/kg)/d, q6h	1500–2000 mg/d, q6h
Nafcillin	200 (mg/kg)/d, q6h	12 g/d, q4h
Penicillin G	400,000 (U/kg)/d, q4h	20–24 million U/d, q4h
Vancomycin	45–60 (mg/kg)/d, q6h	45–60 (mg/kg)/d, q6–12h

7.1 Specific Antimicrobial Therapy

Meningococcal Meningitis: Although ceftriaxone and cefotaxime provide adequate empirical coverage for N. meningitidis, penicillin G remains the antibiotic of choice for meningococcal meningitis caused by susceptible strains. Isolates of N. meningitidis should be tested for penicillin and ampicillin susceptibility, and if resistance is found, cefotaxime or ceftriaxone should be substituted for penicillin. A 7-day course of intravenous antibiotic therapy is adequate for uncomplicated meningococcal meningitis. The index case and all close contacts should receive chemoprophylaxis with a 2-day regimen of rifampin (600 mg every 12 h for 2 days in adults and 10 mg/kg every 12 h for 2 days in children >1 year). Rifampin is not recommended in pregnant

women. Alternatively, adults can be treated with one dose of azithromycin (500 mg) or one intramuscular dose of ceftriaxone (250 mg). Close contacts are defined as those individuals who have had contact with oropharyngeal secretions, either through kissing or by sharing toys, beverages, or cigarettes.

7.2 Pneumococcal Meningitis

Antimicrobial therapy of pneumococcal meningitis is initiated with a cephalosporin (ceftriaxone, cefotaxime, or cefepime) and vancomycin. All CSF isolates of S. pneumoniae should be tested for sensitivity to penicillin and the cephalosporins. Once the results of antimicrobial susceptibility tests are known, therapy can be modified accordingly (Table 143-3). For S. pneumoniae meningitis, an isolate of S. pneumoniae is considered to be susceptible to penicillin with a minimal inhibitory concentration (MIC) <0.06 μg/mL and to be resistant when the MIC is >0.12 μg/mL. Isolates of S. pneumoniae that have cephalosporin MICs ≤0.5 μg/mL are considered sensitive to the cephalosporins (cefotaxime, ceftriaxone, cefepime). Those with MICs of 1 μg/mL are considered to have intermediate resistance, and those with MICs ≥2 μg/mL are considered resistant. For meningitis due to pneumococci, with cefotaxime or ceftriaxone MICs ≤0.5 μg/mL, treatment with cefotaxime or ceftriaxone is usually adequate. For MIC >1 μg/mL, vancomycin is the antibiotic of choice. Rifampin can be added to vancomycin for its synergistic effect but is inadequate as monotherapy because resistance develops rapidly when it is used alone. A 2-week course of intravenous antimicrobial therapy is recommended for pneumococcal meningitis. Patients with S. pneumoniae meningitis should have a repeat LP performed 24–36 h after the initiation of antimicrobial therapy to document sterilization of the CSF. Failure to sterilize the CSF after 24–36 h of antibiotic therapy should be considered presumptive evidence of antibiotic resistance. Patients with penicillin- and cephalosporin-resistant strains of S. pneumoniae who do not respond to intravenous vancomycin alone may benefit from the addition of intraventricular vancomycin. The intraventricular route of administration is also preferred over the intrathecal route because adequate concentrations of vancomycin in the cerebral ventricles are not always achieved with intrathecal administration.

7.3 Listeria Meningitis

Meningitis due to L. monocytogenes is treated with ampicillin for at least 3 weeks (Table 143-3). Gentamicin is added in critically ill patients (2 mg/kg loading dose, then 7.5 mg/kg per day given every 8 h and adjusted for serum levels and renal function). The combination of trimethoprim (10–20 mg/kg per day) and sulfamethoxazole (50–100 mg/kg per day) given every 6 h may provide an alternative in penicillin-allergic patients.

7.4 Staphylococcal Meningitis

Meningitis due to susceptible strains of S. aureus or coagulase-negative staphylococci is treated with nafcillin (Table 143-3). Vancomycin is the drug of choice for methicillin-resistant staphylococci and for patients allergic to penicillin. In these patients, the CSF should be monitored during therapy. If the CSF is not sterilized after 48 h of intravenous vancomycin therapy, then either intraventricular or intrathecal vancomycin, 20 mg once daily, can be added.

7.5 Gram-Negative Bacillary Meningitis

The third-generation cephalosporins—cefotaxime, ceftriaxone, and ceftazidime—are equally efficacious for the treatment of gram-negative bacillary meningitis, and with the exception of meningitis due to P. aeruginosa, which should be treated with ceftazidime or meropenem (Table 143-3). A 3-week course of intravenous antibiotic therapy is recommended for meningitis due to gram-negative bacilli.

8. PROGNOSIS & COMPLICATIONS

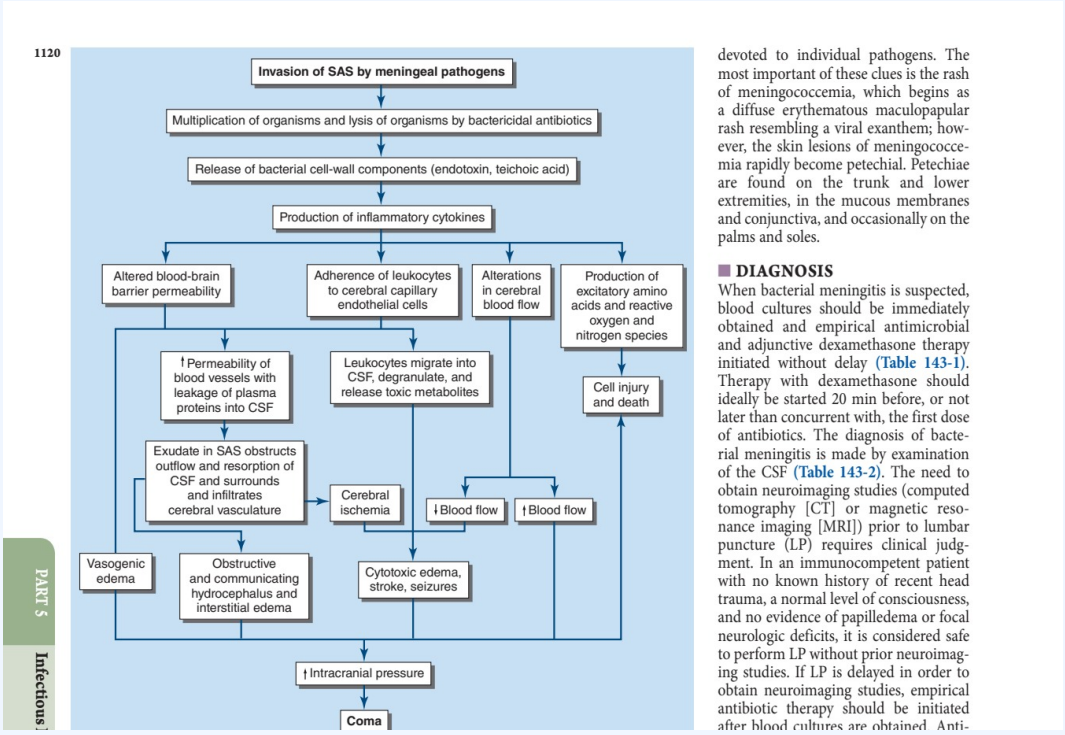
Mortality rate is 3–7% for meningitis caused by H. influenzae, N. meningitidis, or group B streptococci; 15% for that due to L. monocytogenes; 20% for S. pneumoniae. In general, the risk of death from bacterial meningitis increases with (1) decreased level of consciousness on admission, (2) onset of seizures within 24 h of admission, (3) signs of increased ICP, (4) young age (infancy) and age >50, (5) the presence of comorbid conditions including shock and/or the need for mechanical ventilation, and (6) delay in the initiation of treatment. Decreased CSF glucose concentration (<2.2 mmol/L [<40 mg/dL]) and markedly increased CSF protein concentration (>3 g/L [> 300 mg/dL]) have been predictive of increased mortality and poorer outcomes in some series. Moderate or severe sequelae occur in ~25% of survivors, although the exact incidence varies with the infecting organism. Common sequelae include decreased intellectual function, memory impairment, seizures, hearing loss and dizziness, and gait disturbances.

9. SPECIAL CONSIDERATIONS

Ampicillin should be added to the empirical regimen for coverage of L. monocytogenes in individuals <3 months of age, those >55, or those with suspected impaired cell-mediated immunity because of chronic illness, organ transplantation, pregnancy, malignancy, or immunosuppressive therapy. Rifampin is not recommended in pregnant women. The efficacy of dexamethasone therapy in preventing neurologic sequelae is different between high- and low-income countries. Three large randomized trials in low-income countries (sub-Saharan Africa, Southeast Asia) failed to show benefit in subgroups of patients. The lack of efficacy of dexamethasone in these trials has been attributed to late presentation to the hospital with more advanced disease, antibiotic pretreatment, malnutrition, infection with HIV, and treatment of patients with probable, but not microbiologically proven, bacterial meningitis. The results of these clinical trials suggest that patients in sub-Saharan Africa and those in low-income countries with negative CSF Gram's stain and culture should not be treated with dexamethasone.

10. KEY PEARLS & CLINICAL TRAPS

- The classic clinical triad of fever, headache, and nuchal rigidity occurs in >80% of adult cases, though the complete triad is not always present.
- Dexamethasone should be initiated 20 minutes before or concurrent with the first dose of antibiotics to reduce mortality and hearing loss.
- Empirical therapy for community-acquired bacterial meningitis includes vancomycin plus a third- or fourth-generation cephalosporin (ceftriaxone, cefotaxime, or cefepime).
- Acyclovir is added to empirical therapy to cover HSV encephalitis, a leading differential diagnosis.
- CSF findings in bacterial meningitis include PMN leukocytosis (>100 cells/µL), hypoglycorrhachia (<2.2 mmol/L), elevated protein (>0.45 g/L), and elevated opening pressure (>180 mmH2O).
- Listeria monocytogenes is an important cause in neonates, pregnant women, and adults >50 years; ampicillin is required in these groups.
- Mortality rates vary by organism: 3–7% for H. influenzae, N. meningitidis, or GBS; 15% for L. monocytogenes; 20% for S. pneumoniae.
- Meningococcal contacts require chemoprophylaxis with rifampin, azithromycin, or ceftriaxone.
- Seizures occur in 15–40% of patients and may be due to focal ischemia, cortical venous thrombosis, or hyponatremia.
- A CSF/serum glucose ratio <0.4 is highly suggestive of bacterial meningitis but may also be seen in other conditions, including fungal, tuberculous, and carcinomatous meningitis.



Harrison's 22e · Figure 1

FIGURE 143-1 The pathophysiology of the neurologic complications of bacterial SAS, subarachnoid space. — Figure 143-1: The pathophysiology of the neurologic complications of bacterial meningitis. The diagram illustrates the cascade from bacterial invasion of the subarachnoid space (SAS) and multiplication to the release of bacterial cell-wall components (endotoxin, teichoic acid). This triggers the production of inflammatory cytokines (TNF-α, IL-1β), leading to altered blood-brain barrier permeability, cerebral blood flow changes, and leukocyte migration. The resulting exudate obstructs CSF outflow, causing obstructive and communicating hydrocephalus, interstitial edema, vasogenic edema, and cytotoxic edema. These processes lead to increased intracranial pressure (ICP), ischemia, coma, and cerebral herniation.