REVIEW ARTICLE

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Acute Bacterial Meningitis

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ABSTRACT

PURPOSE OF REVIEW: **While acute bacterial meningitis is becoming less common in developed countries because of the widespread use of vaccines against *Streptococcus pneumoniae, Neisseria meningitides,* and *Haemophilus influenzae*, bacterial meningitis still occurs worldwide, with peak incidence in young children and the elderly. Bacterial meningitis is usually lethal unless appropriate antibiotics that cross the blood-brain barrier are given. Clinical suspicion of bacterial meningitis begins when patients present with the abrupt onset of fever, headache, and meningismus.**

RECENT FINDINGS: **New technologies are being developed for more rapid identification of the bacterial species causing meningitis. When appropriate, administration of adjunctive dexamethasone with the antibiotics often lessens neurologic sequelae in survivors, which may include aphasia, ataxia, paresis, hearing loss, and cognitive impairment.**

SUMMARY: **Confirmation of the diagnosis of bacterial meningitis comes mainly from examination and culture of CSF obtained from a lumbar puncture. Typically, the CSF shows an elevated neutrophil count, elevated protein, depressed glucose, positive Gram stain, and growth of the bacteria on appropriate culture media. Antibiotic sensitivities of the bacteria determine the appropriate antibiotics, although an educated guess of the best antibiotics to be given promptly must be made until the antibiotic sensitivities return, usually in a few days.**

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INTRODUCTION

Acute bacterial meningitis is a severe life-threatening inflammation of the meninges and subarachnoid space caused by bacteria. The inflammation can also involve the brain cortex and spinal cord owing to their anatomic proximity. The condition requires immediate medical attention and management. Meningeal inflammation causes vasospasm and possible thrombosis of cerebral arterioles and arteries as well as possible cerebral vein occlusions. A variety of inflammatory products of bacteria and neutrophils can cross the pial barrier to cause neuronal necrosis or compress cranial nerves. Acute bacterial meningitis occurs worldwide, develops in individuals of all ages, and causes morbidity and mortality. In 2013, an estimated 16 million cases of acute bacterial meningitis occurred.[1] This article focuses on the clinical characteristics of acute bacterial

meningitis by age group, methods of diagnosis, and the major causative bacteria and on the management of acute bacterial meningitis in children and adults.

CLINICAL FEATURES BY AGE GROUP

This section addresses the clinical features by age group in which bacterial meningitis develops (neonates and infants, children, adults, and adults older than 65 years of age) and their unique characteristics.

Neonates and Infants

In neonates and infants, the symptoms of acute bacterial meningitis may be nonspecific,[2,3] with lethargy, fussiness, sleepiness, jitteriness, anorexia, hypotonia, apnea, jaundice, diarrhea, and general weakness commonly noted by parents (CASE 1-1). Temperature instability with fever or hypothermia is common but not always present. Seizures occur in 15% to 34% of infants.[3] Neck stiffness is uncommon. A bulging anterior fontanelle may develop and is noted by parents as an enlarged swelling on the top of the head, and hydrocephalus develops in 5% of infants.[4] The risk factors for acute bacterial meningitis in neonates and infants are listed in TABLE 1-1.[2,5–9] Because many maternal immunoglobulins do not cross the placenta before 32 weeks, very premature infants are at a higher risk for infections.[3] Neonates have an immature immune system with impaired phagocytic ability of neutrophils and monocytes that also contributes to acute bacterial meningitis.

Children

The manifestations of meningitis may develop over hours or up to a day in children. Classic features include fever, severe headache, lethargy, irritability,

CASE 1-1

A 4-month-old infant boy was noted by his mother to be fussy and less active than usual and was breast-feeding poorly. Soon thereafter, he was noted to have generalized weakness, so his mother took him to the pediatrician. The infant's older sister had reported an earache for several days. The physician confirmed the symptoms and noted the infant's temperature to be slightly elevated but did not detect a stiff neck or spasticity. He was immediately taken to the emergency department, where a lumbar puncture was performed. The lumbar puncture showed a white blood cell count of 350 cells/mm^3 with 80% neutrophils, protein of 280 mg/dL, and glucose of 20 mg/dL (blood glucose was 90 mg/dL). CSF Gram stain demonstrated gram-positive diplococci. A diagnosis of acute bacterial meningitis was made, with a suspicion of *Streptococcus pneumoniae*. The patient was given IV cefotaxime and dexamethasone for 14 days and made a full recovery without neurologic sequelae.

COMMENT

This case demonstrates that young infants may not present with typical signs of bacterial meningitis. The change in this infant's behavior was recognized by his mother, and she promptly took him to the pediatrician, who recognized the findings as suspicious for bacterial meningitis. The patient's CSF findings were typical for pneumococcal meningitis. He had not been vaccinated with the pneumococcal meningitis vaccine.

confusion, photophobia, nausea, vomiting, stiff neck, and back pain.[2] About 20% of children with acute bacterial meningitis will experience a seizure before admission to the hospital. Risk factors for acute bacterial meningitis in children are listed in TABLE 1-2. A medication history should be obtained to exclude recent antibiotic use that could impede isolation of the bacteria from CSF.

On examination, meningeal irritation usually manifests as neck stiffness, especially on anterior-posterior flexion of the chin to the chest. The Kernig sign (painful knee extension after flexing the thigh with the hip and knee at 90-degree angles) and Brudzinski sign (reactive hip and knee flexion when the neck is flexed) have limited specificity and sensitivity.[10]

Adults

Risk factors for acute bacterial meningitis in adults and the elderly are listed in TABLE 1-3. As in children, the classic clinical features of acute bacterial meningitis in adults are headache, neck stiffness, fever, and altered mental status. A prospective nationwide study of 1268 adults with community-acquired bacterial meningitis in the Netherlands found headache in 83%, neck stiffness in 74%, fever in 74%, and impairment of consciousness in 71%.[11] However, some studies of adults have found all the classic features were present in as little as 41% of patients.[12] Of note, patients receiving analgesics or corticosteroids may not have neck stiffness. Occasionally, patients may present with focal neurologic deficits, and a few may have a petechial rash from either meningococcal or pneumococcal meningitis. Complications of acute bacterial meningitis include seizures (17%), ischemic stroke (14% to 25%), hydrocephalus (3% to 5%), subdural empyema (3%), brain abscess (5%), and venous sinus thrombosis (1%).[4]

Adults Older Than 65 Years of Age

Patients older than 65 years of age may have an atypical presentation. Fever is not a constant finding, headache and nuchal rigidity may not be present, and

TABLE 1-1 **Risk Factors for Acute Bacterial Meningitis in Neonates and Infants**

- Preterm birth
- Low birth weight (<2500 g [5.5 lb])
- Chorioamnionitis
- Endometritis
- Maternal Group B streptococci colonization
- Prolonged duration of intrauterine monitoring (>12 hours)
- Traumatic delivery
- Fetal hypoxia
- Galactosemia
- Urinary tract abnormalities
- Dermal sinus tract of spine
- Down syndrome
- Congenital heart disease

nonspecific confusion is common.[5,6] Evaluating a stiff neck can be difficult. About 35% of healthy geriatric individuals have nuchal rigidity, and one study reported only 26% of 93 adults with nuchal rigidity who underwent a lumbar puncture (LP) for suspicion of meningitis actually had meningitis.[13] A 2013 Spanish study compared older adults (older than 65 years of age) with younger adults and found the older adults had fewer cases of meningococci but more *Listeria monocytogenes*, experienced more renal and pulmonary complications, and had a higher mortality rate of 30% versus 12%.[14] CSF findings were similar between the two groups.

HEALTH CARE–ASSOCIATED BACTERIAL MENINGITIS

Most published adult clinical studies are from patients with community-acquired acute bacterial meningitis. However, the incidence of community-acquired acute bacterial meningitis is falling in developed countries in response to wider administration of *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* vaccines. However, meningitis that is not strictly community acquired is being seen in more patients with chronic illnesses and in patients who have experienced trauma or had neurosurgical procedures. These patients are categorized as having health care–associated meningitis (also called nosocomial or hospital-acquired meningitis). These patients often manifest different clinical features and thus are more difficult to diagnose.[7,15–17] Cases often develop as a complication of craniotomy, recent head trauma, CSF leakage, or infected intracranial catheters; develop from spread from the site of a distant infection, such as otitis media, sinusitis, or pneumonia; or occur in patients with immune system compromise, such as from cancer, transplantation, or chemotherapy.

Risk Factors for Acute Bacterial Meningitis in Children TABLE 1-2

- Poverty, malnutrition
- Day care attendance
- Asplenia
- Primary immunodeficiency
- Human immunodeficiency virus (HIV) infection
- Sickle cell anemia
- Cochlear implant
- Central nervous system shunt or CSF leak
- Recent or current respiratory tract infection
- Recent exposure to case of meningococcal or *Haemophilus influenzae* meningitis
- Penetrating head trauma
- Dermal sinus of spine
- Recent travel to country with endemic meningococcal disease
- Lack of immunizations

CSF = cerebrospinal fluid.

TABLE 1-3 **Risk Factors for Acute Bacterial Meningitis in Adults and the Elderly**

Living in groups or retirement homes

Pulmonary disease

- Concurrent pneumonia
- Chronic obstructive pulmonary disease
- Asthma
- Smoking

Malignancy

- Melanoma
- Chronic lymphocytic leukemia
- Advanced cancers
- Chemotherapy
- Metastatic cancers

Chronic sinus or middle ear disease

Diabetes mellitus

Autoimmune disease

- Rheumatoid arthritis
- Systemic lupus erythematosus

Immune deficiency

- Human immunodeficiency virus (HIV) infection
- Primary immunodeficiency, complement C3 deficiency
- Organ transplants
- Asplenia
- Severe anemia
- Alcoholism

Chronic renal disease dialysis, urinary tract infection, or kidney infection, including infected renal stones

Chronic liver disease, cirrhosis

Positive blood cultures

Shock or hypotension

Recent cranial neurosurgery

Indwelling catheters or central venous lines, especially into CSF spaces

CSF = cerebrospinal fluid.

Patients may have an acute or subacute onset of symptoms. Most patients present with a headache, neck stiffness, and fever, but impairment of consciousness is slightly less common. The CSF typically shows a white blood cell count of more than 1000 cells/mm^3, low glucose level (often below 30 mg/dL), and elevated protein (above 100 mg/dL) (TABLE 1-4[18,19]). The CSF Gram stain is positive in about 75% of cases (TABLE 1-4). CSF cultures have grown a wide variety of bacteria that include the common *S. pneumoniae*, but may include *Staphylococcus aureus* or *Staphylococcus epidermidis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and other species. Bacterial cultures should be held for up to 5 to 10 days to detect slow-growing organisms.

Treatment requires broad antibiotic coverage. One recommendation consists of vancomycin in combination with cefepime, ceftazidime, or meropenem.[16] Care must be used in administration of adjunctive corticosteroids as one study reported inadequate antibiotic therapy in 13%, and dexamethasone may then result in worsening of the meningitis since CSF bacteria are not killed.[15]

DIAGNOSIS OF BACTERIAL MENINGITIS

When meningitis is suspected based on the clinical characteristics, the key to diagnosis and establishing the etiology is examination and culture of CSF. For most patients, CSF is obtained via an LP needle placed in the lumbar spine. The lumbar subarachnoid space is chosen because the adult spinal cord parenchyma usually ends about T12 or L1 and only nerve roots are present in the lumbar CSF. In infants, the spinal cord parenchyma may descend to L2. Several risks are involved in placing a needle into the subarachnoid space. If the patient has a bleeding tendency or is anticoagulated, a risk of causing a localized subarachnoid hemorrhage (SAH) or epidural hematoma exists, particularly if the LP needle hits a radicular vein within the subarachnoid space. Thus, individuals with a markedly elevated international normalized ratio (INR) can be at risk of SAH. Likewise, if the patient has thrombocytopenia with a blood platelet level below 20,000/mm^3 to 50,000/mm^3, the subarachnoid bleeding risk may be increased.[20] The American Association of Blood Banks guidelines place the threshold for risk at about 50,000/mm^3,[21] but the British Committee for Standards sets its guidelines at 20,000/mm^3.[22] If time permits, some patients can receive a fresh platelet transfusion before the LP. Rare causes of bleeding include an aneurysm or angioma in the lumbar subarachnoid space. In individuals with an infection of the skin of the lower back, it is possible to introduce the skin bacteria into the CSF via the LP needle.

Finally, a risk of brain herniation exists following removal of CSF from the lumbar space in patients with elevated intracranial pressure. Acute bacterial meningitis causes meningeal inflammation and, consequently, elevated CSF pressure that is reflected in the opening pressure. Opening CSF pressures higher than 200 mm CSF are typical, but opening pressure may be higher than 300 mm CSF. In their classic review of acute bacterial meningitis, Dodge and Swartz[23] found the average CSF pressure to be 307 mm CSF. Typically, CSF pressure continues to elevate for the first 24 to 36 hours before subsiding.

The presumed pathophysiology of brain herniation is that removal of CSF for studies and the subsequent lumbar CSF leakage from the dural opening after removal of the LP needle lowers the CSF pressure in the lumbar space compared to the supratentorial space. This may lead to a downward shifting of one temporal lobe through the midline tentorial opening, causing a herniation syndrome. The temporal lobe pushing the upper brainstem downward with the

KEY POINTS

- Acute bacterial meningitis is a severe life-threatening inflammation of the meninges and subarachnoid space caused by bacteria. The meningeal inflammation can cause vasospasm and even thrombosis of cerebral arterioles, arteries, and draining veins.
- Acute bacterial meningitis causes up to 16 million infections worldwide each year.
- In infants, the symptoms of meningitis may be nonspecific, with lethargy, fussiness, sleepiness, jitteriness, anorexia, hypotonia, apnea, jaundice, diarrhea, and general weakness.
- Because many maternal immunoglobulins do not cross the placenta before 32 weeks, very premature infants are at a higher risk for infections than other children.
- In older children, classic meningitis features include fever, severe headache, lethargy, irritability, confusion, photophobia, nausea, vomiting, stiff neck, and back pain.
- In adults, community-acquired bacterial meningitis may present with headache, neck stiffness, fever, and impairment of consciousness. However, patients may not have all these clinical features.
- Adults older than 65 years of age can have an atypical presentation of meningitis. Fever is not a constant finding, headache and nuchal rigidity may not be present, and nonspecific confusion is common.

TABLE 1-4 **Typical Cerebrospinal Fluid Characteristics in Acute Bacterial Meningitis**

CSF Parameter	Typical Findings	Notes
CSF opening pressure	200–500 mm CSF	Pressure may be lower if patient is an infant/small child or very dehydrated or if bacteria species is atypical.[18]
CSF appearance	Cloudy depending on concentration of white blood cells, bacteria, and protein	
White blood cell count	Usually 1000–3000 white blood cells/mm^3	White blood cell count can be lower if patient is immunosuppressed or taking steroids or if bacteria species is atypical. However, only rarely are white blood cell levels less than 100 white blood cells/mm^3.
White blood cell differential	Predominately neutrophils (polymorphonuclear leukocytes), usually 80–90%	
Glucose concentration	Usually <40 mg/dL, often below 25 mg/dL	Normal CSF glucose is about two-thirds serum level but may be falsely low if the patient recently received IV glucose or has a very high blood glucose level. Many CSF glucose concentrations in bacterial meningitis are less than 25 mg/dL.
Protein concentration	Elevated above normal value for age, often >100 mg/dL	
Gram stain	Average positive >75% but depends on concentration of bacteria in CSF	Concentrations of bacteria in the CSF in patients with acute bacterial meningitis range from 10^3 to 10^8 colony-forming units (CFU)/mL.[18] A positive Gram stain and visualizing bacteria on a Gram stain are related to the concentration of bacteria in CSF and are seen 97% of the time with >10^5 CFU, 60% with 10^3 to 10^5 CFU, and only 25% with <10^3 CFU. When the Gram stain is positive, the specificity is higher than 97%.[19]
Culture positive	<75% but depends on bacteria concentration and whether patient previously received antibiotics	Some strains of bacteria grow poorly on standard culture media, and anaerobic bacteria may not grow at all. Most bacteria in CSF are sterilized when appropriate antibiotics are given 4 or more hours before lumbar puncture. However, *Neisseria meningitidis* can be sterilized in as little as 30 to 60 minutes. False-positive interpretations can occur from cell debris on the smear or contamination of bacteria from the laboratory.

CSF = cerebrospinal fluid.

associated basilar arteries fixed to the hemispheres produces hemorrhages, necrosis, and infarctions of the upper brainstem and sometimes a third nerve palsy. Occasionally, the acute bacterial meningitis swells part of the cerebellum, which encroaches on the fourth ventricle, obstructing the downward flow of CSF into the spinal canal.

The risk of brain herniation is not precisely defined, as brain herniation is well recognized to develop in some cases of acute bacterial meningitis even when no LP was performed. Thus, the actual added risk of herniation following an LP in bacterial meningitis is unclear, but some series found the increased risk to be up to 5%.[24,25] Limited autopsies and comparison of CT scans before and after LP suggest that contributing factors are increased intracranial pressure from preexisting diffuse cerebral edema, asymmetric cerebral hemisphere swelling or masses, or swelling in the posterior fossa.[25] Clinical risk factors from fatal cases suggest that markedly decreased mental status to coma or semicoma, recent generalized seizures, dilated or fixed pupils, papilledema, decorticate or decerebrate posturing, marked respiratory abnormalities, and focal neurologic signs are significant factors.[25] When herniation occurs following the LP, it usually occurs within 5 hours. Emergency management of the herniation syndrome is difficult, but use of hyperosmolar agents and ventricular drainage are thought to be the most helpful.[25,26] Head CT is commonly used before an LP to evaluate increased risks of brain herniation (TABLE 1-5) by detecting a shift of brain compartments, which could increase if the LP is performed.

Lumbar Puncture Technique

When meningitis is suspected, an LP needle with a stylet that enables the straightforward ability to enter the lumbar subarachnoid space is needed to obtain an accurate opening CSF pressure and to gather sufficient CSF for analysis. Most commercial CSF kits come with a 21-gauge LP sharp needle to accomplish this. Smaller-gauge LP needles may bend more easily when passing through the paraspinal muscles to enter the subarachnoid space of a restless and confused patient and may make obtaining an accurate CSF opening pressure more difficult. Although smaller-gauge LP needles do have a lower incidence of post-LP headaches, this concern is less relevant in the patient with headache from meningitis. Very difficult LPs may need to be performed under fluoroscopy.[27] It is recommended to obtain sufficient CSF for all the CSF tests needed. After the LP needle is withdrawn, up to several hundred mL of CSF will flow out of the opening even when the CSF pressure is normal.[28] Obtaining a closing pressure is seldom indicated.

Standard Cerebrospinal Fluid Test Analysis

CSF analysis should be done as quickly as possible for diagnostic information, because white blood cells begin to deteriorate in the CSF after 30 minutes and high white blood cell counts can metabolize CSF glucose, lowering the level. As a general rule, tube 1 has the highest risk of red blood cells from a traumatic LP and contamination of non-CSF bacteria. TABLE 1-4 shows the typical CSF characteristics in acute bacterial meningitis.[18]

Identification of the Etiologic Bacteria

Around the world today, the standard method for identifying etiologic bacteria in CSF is to streak the CSF onto sheep's blood and chocolate agar plates and

KEY POINTS

- More patients are developing health care–associated bacterial meningitis. This meningitis differs from community-acquired bacterial meningitis in that it typically develops in patients with chronic illnesses or following trauma or neurosurgical procedures.
- When meningitis is suspected, the key to diagnosis and establishing the etiology is examination and culture of CSF.
- In lumbar puncture, if a patient has a severe bleeding tendency or is anticoagulated, a risk of causing a spinal hematoma exists if the lumbar puncture needle hits a radicular vein within the lumbar subarachnoid space.
- A small risk of brain herniation exists following removal of CSF from the lumbar space. This usually develops from downward shifting of one temporal lobe through the midline tentorial opening, producing a herniation syndrome.

incubate the plates in 3% to 5% carbon dioxide or to inoculate the CSF into enriched broth media. Growth of the bacteria usually requires 24 to 72 hours in an incubator. The bacteria are then Gram stained and subcultured in special antibiotic media to determine the antibiotic sensitivities. Bacteria that are obligate intracellular organisms and present in low concentrations in the CSF, such as *L. monocytogenes*, often take up to 5 days to grow.

Several alternative diagnostic tests are available to diagnose bacteria.[29] Specific methods to detect bacterial antigens have been developed, such as latex agglutination and coagglutination. These tests work best when examining infected sites, such as CSF, where the bacteria are actively proliferating and shedding polysaccharide. These tests are less sensitive for the detection of bacteria in blood or urine but are rapid and simple to perform and do not require special equipment. Reviews of the technology often comment that when the Gram stain is positive, standard CSF cultures are usually satisfactory, but results are not as rapid as these tests.

Newer technologies, such as multiplex polymerase chain reaction (PCR), and new diagnostic platforms that incorporate proteomics and genetic sequencing might help provide a quicker and more accurate diagnosis. PCR tests are widely used in Europe for the diagnosis of the most common strains of bacterial

TABLE 1-5 **Risk Factors for Cerebral Herniation Following Lumbar Puncture for Bacterial Meningitis**[a]

Clinical Risk Factors

- Stupor or coma
- Dilated or fixed pupils
- Fixed deviation of eyes or absent oculocephalic reflex
- Papilledema
- Recent seizures
- Decorticate or decerebrate posturing
- Hemiparesis
- Hypertension with bradycardia

CT Factors for Increased Risk of Future Brain Herniation

- Lateral shift of cerebral midline structures indicating unequal supratentorial intracranial pressure
- Loss of suprachiasmatic and basilar cisterns indicating the supratentorial pressure is greater than infratentorial; the lateral ventricles may be either large or small
- Obliteration or shift of the fourth ventricle indicating increased posterior fossa pressure
- Obliteration of the superior cerebellar and quadrigeminal plate cisterns with sparing of the ambient cisterns indicating upward cerebellar transtentorial herniation
- Masses in the cerebral hemisphere or cerebellum
- Infarction or occlusion of the superior sagittal sinus or draining veins

CT = computed tomography.
[a] Modified with permission from Joffe AR, J Intensive Care Med.[25] © 2007 The Author.

meningitis. However, PCR requires the laboratory to have a wide variety of PCR primers. Thus, the common causes of acute bacterial meningitis are easy to test for, but assays to detect the uncommon bacterial strains are often unavailable.

New technology may change the speed and accuracy of diagnosing the etiology of acute bacterial meningitis. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry is now being used to quickly identify the specific bacteria in blood cultures.[30] It likely will be adapted for CSF diagnosis. The initial technology is expensive, but it can be used for identification of all types of aerobic and anaerobic bacteria, mycobacteria, viruses, and fungi. Advances in PCR assays and DNA sequencing are allowing accurate and rapid diagnoses of a wide variety of infectious diseases.[31] Since both can detect specific bacterial RNA or DNA, it may be possible for future developments to detect the common RNA mutations seen in bacterial drug resistance.

Another promising new technology is a self-contained pouch into which fresh CSF is introduced. Using PCR technology, the test panel can identify six common bacterial pathogens, plus several common viruses and *Cryptococcus neoformans*.[32] Limitations include the need for standard CSF cultures as not all bacteria are included and the lack of antibiotic sensitivities.

KEY POINTS

- New CSF diagnostic tests are being developed to improve on the standard method of culturing CSF on agar plates.
- *Streptococcus pneumoniae* is the most common cause of community-acquired acute bacterial meningitis in the United States.
- The case fatality rate of pneumococcal meningitis is 10% to 20% in developed countries but much higher (30% to 40%) in developing countries.

Major Bacteria Causing Acute Bacterial Meningitis

This section discusses the most common bacteria causing acute bacterial meningitis.

STREPTOCOCCUS PNEUMONIAE. *S. pneumoniae*, a gram-positive bacterium, is the most common cause of community-acquired acute bacterial meningitis in the United States (58%) and Germany based on epidemiologic studies published in the early 2000s.[33] In children, this has resulted from the dramatic fall in *H. influenzae* and *N. meningitidis* infections following the introduction of childhood *H. influenzae* and meningococcal vaccines. The highest incidence of *S. pneumoniae* meningitis is in young children and older adults. In adults, major risk factors include sinusitis, otitis media, pneumonia, or immunosuppression.[31] The current distribution of cases of community-acquired acute bacterial meningitis has not been published in recent years. However, the widespread administration of pneumococcal vaccines first to children and now to older adults is likely changing this epidemiology. Recent studies show that the incidence of pneumococcal meningitis in young children and the elderly is falling.[4]

Initial antibiotic treatment usually is with ceftriaxone or cefotaxime with vancomycin plus early adjunctive corticosteroids.[4] Recommended doses of the major antibiotics are listed in **TABLE 1-6**.[7,34]

The case fatality rate of pneumococcal meningitis is 10% to 20% in developed countries but much higher (30% to 40%) in developing countries.[35] Up to 30% of survivors living in developed countries have permanent neurologic sequelae, including hearing loss, focal neurologic deficits, and neuropsychological impairment.[35]

The pathogenesis of pneumococcal meningitis is becoming better understood. The pneumococci possess pili that attach to the nasopharynx and likely allow transfer across the epithelial cell via an endosome. The presence of a polysaccharide capsule interferes with phagocytosis. The lack of serum pneumococcal antibodies increases the risk of meningitis. Entry into the subarachnoid space may entail bacterial attachment to cerebral endothelial cells followed by entry past the

blood-brain barrier. In the CSF, the bacteria trigger a cascade of proinflammatory cytokines and chemokines that trigger invasion of neutrophils.[35] The CSF neutrophils poorly engulf and destroy all species of invading bacteria, in part because of low levels of CSF complement that are needed for neutrophils to engulf bacteria.[36,37] As such, in the preantibiotic era, more than 95% of individuals with acute bacterial meningitis died. An alternative route of CSF entry is direct subarachnoid space invasion from pneumococcal sinus and middle ear infections.

The routine use of conjugated pneumococcal vaccines began in 2000 in the United States, other developed countries, and some African countries. These vaccines contain polysaccharides plus differing proteins and induce T-cell–dependent immunization and the development of memory B cells that produce long-lasting immunization protection and reduce carriage rates. The new 13-valent polysaccharide conjugate vaccine demonstrated 75% effectiveness for invasive pneumococcal disease.[38] The Centers for Disease Control and

TABLE 1-6 **Recommended Dosages of Antimicrobial Agents for Acute Bacterial Meningitis for Patients With Normal Renal and Hepatic Function[a]**

Antimicrobial Agent	Dosing for Infants and Children[b]	Dosing for Adults[b]
Amikacin[c,d]	20–30 mg/kg/d (divided every 8 hours)	15 mg/kg/d (divided every 8 hours)
Ampicillin	300–400 mg/kg/d (divided every 6 hours)	12 g/d (divided every 4 hours)
Cefepime	150 mg/kg/d (divided every 8 hours)	6 g/d (divided every 8 hours)
Cefotaxime	200 mg/kg/d (divided every 6–8 hours) (maximum dosage 12 g/d)	8–12 g/d (divided every 4–6 hours)
Ceftazidime	150 mg/kg/d (divided every 8 hours) (maximum dosage 6 g/d)	6 g/d (divided every 8 hours)
Ceftriaxone	100 mg/kg/d (divided every 12 hours) (maximum dosage 4 g/d)	4 g/d (divided every 12 hours)
Ciprofloxacin	30 mg/kg/d (divided every 8–12 hours)	1200 mg/d (divided every 8 hours)
Gentamicin[c,d]	5–7.5 mg/kg/d (divided every 8 hours)	5 mg/kg/d (divided every 8 hours)
Linezolid	Age <12 years 30 mg/kg/d (divided every 8 hours) (maximum single dosage 600 mg)[e] Age ≥12 years 20 mg/kg/d (divided every 12 hours) (maximum single dosage 600 mg)[e]	1200 mg/d (divided every 12 hours)

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Prevention evaluated the 13-valent pneumococcal vaccine for its ability to prevent invasive pneumococcal pneumonia. They found the reduction for children younger than 5 years of age to be 78% and the reduction for adults older than 64 years of age to be 65%.[39] It is increasingly recognized that the widespread use of the pneumococcal vaccine not only protects the recipient but also offers a benefit to nonimmunized individuals through the bystander effect.

NEISSERIA MENINGITIDIS. *N. meningitidis*, a gram-negative bacterium, continues to be a major cause of sporadic and epidemic meningitis despite the availability of effective vaccines. In sub-Saharan African meningococcal outbreaks of serotype A, attack rates can reach more than 1000 cases per 100,000 population each year.[40] The meningococcus can cause severe septic meningococcemia, meningitis, or septic arthritis. It is a commensal organism and pathogen only for humans.

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Antimicrobial Agent	Dosing for Infants and Children[b]	Dosing for Adults[b]
Meropenem	120 mg/kg/d (divided every 8 hours) (maximum dosage 6 g/d)	6 g/d (divided every 8 hours)
Moxifloxacin	Data not established	400 mg/d (divided every 24 hours)
Nafcillin	200 mg/kg/d (divided every 6 hours)	9–12 g/d (divided every 4 hours)
Oxacillin	200 mg/kg/d (divided every 6 hours)	9–12 g/d (divided every 4 hours)
Penicillin G	200,000–400,000 U/kg/d (divided every 4–6 hours) (maximum dosage 24 million U/d)	24 million U/d (divided every 4 hours)
Rifampin	10–20 mg/kg/d (divided every 12–24 hours) (maximum dosage 600 mg/d)	600–900 mg/d (divided every 12 hours)
Tobramycin[c,d]	7.5 mg/kg/d (divided every 8 hours)	5 mg/kg/d (divided every 8 hours)
Trimethoprim-sulfamethoxazole[f]	15–20 mg/kg/d (divided every 6 hours)	10–20 mg/kg/d (divided every 6–12 hours)
Vancomycin[g]	60 mg/kg/d (divided every 6 hours)	30–45 mg/kg/d (divided every 8–12 hours)

[a] Modified with permission from Tunkel AR, et al, Clin Infect Dis.[7] © 2017 The Authors.
[b] Total daily dose (dosing interval in hours).
[c] Need to monitor peak and trough serum concentrations.
[d] Aminoglycosides should be based off ideal body weight in obesity.
[e] Not to exceed the adult dose.
[f] Dosing is based on trimethoprim component.
[g] Maintain serum trough concentrations of 15–20 mcg/mL in adult patients who receive intermittent bolus administration.

N. meningitidis is carried in the nasopharynx and transmitted by direct contact with nasal or oral secretions or through inhalation of large droplet nuclei. The bacteria possess pili that allow attachment and passage through the nasopharynx epithelium. In the blood, bacterial capsules help minimize phagocytic engulfment by macrophages. Individuals with congenital deficiencies of immunoglobulins, such as agammaglobulinemia or complement deficiencies, are at increased risk of meningitis.[40] Antibiotic treatment is with amoxicillin or ampicillin.[4]

Current meningococcal conjugated vaccines contain serotypes A, C, Y, and W-135 capsule polysaccharides, and a new separate serotype B vaccine has been developed. The vaccines are highly effective in children[41] but have not been widely administered in developing countries. To prevent transmission from a patient with meningococcal meningitis to close contacts, chemoprophylaxis with rifampin or ciprofloxacin is effective to eliminate colonization of the nasopharynx (TABLE 1-7).

LISTERIA MONOCYTOGENES. *L. monocytogenes* is a gram-positive, facultatively anaerobic, non–spore-forming motile bacillus that causes about 9% of acute bacterial meningitis cases worldwide.[42,43] It is an intracellular pathogen capable of spreading directly from cell to cell without exposure to CSF. Central nervous system (CNS) infection has the highest incidence in infants, the elderly, and individuals with a malignancy or who are immunocompromised or posttransplantation. Outbreaks can develop from eating contaminated salami, raw vegetables, seafood, unpasteurized milk, or homemade cheese (especially goat cheese), even if stored in a refrigerator (CASE 1-2).[42] Patients with meningitis caused by *L. monocytogenes* may have a delayed presentation with fewer classic signs of meningitis, more confusion, and a milder stiff neck and thus may delay seeking care.[42] The CSF may have a lower white blood cell count

TABLE 1-7 Prophylactic Antibiotic Treatment for Close Contacts of Patients With Meningococcal Meningitis[a]

Antibiotic	Dose	Duration
Rifampicin	Child <1 month of age: 5 mg/kg 2 times a day orally Child ≥3 months to 12 years of age: 10 mg/kg 2 times a day orally Child 12 years: 600 mg 2 times a day orally Nonpregnant adult: 600 mg 2 times a day orally	2 Days
Ciprofloxacin	Adult >18 years: 500 mg orally Pregnant: do not use	Once
Ceftriaxone	Child <15 years: 125 mg IM Adult ≥16 years: 250 mg IM Pregnant: 250 mg IM	Once

[a] Data from van de Beek, et al, Clin Microbiol Infect.[4]

(fewer than 500 cells/mm^3), lower protein elevations, and a glucose level closer to normal.[42] Because of *L monocytogenes*' low bacterial concentration in CSF, the Gram stain is negative more than half the time. When identified, *L monocytogenes* may look more like a coccus than a bacillus. Antibiotic treatment should include ampicillin or amoxicillin as the organism may be resistant to a third-generation cephalosporin; treatment should be administered for 14 to 21 days.[42] Aminoglycosides may also be added if CSF cultures demonstrate cephalosporin resistance. The mortality rate is up to 30% but may be elevated because of preexisting comorbidities.

HAEMOPHILUS INFLUENZAE. *H. influenzae* is a gram-negative encapsulated bacterium that is spread via the respiratory route to an individual who subsequently develops a bacteremia that then invades the meninges. Although *H. influenzae* has several serotypes, the type B serotype represents more than 90% of the meningitis cases. Before the widespread administration of *H. influenza*e type B conjugate vaccines, *H. influenzae* meningitis accounted for 48% of all cases of bacterial meningitis.[44] Most cases occurred in infants and small children, with a 2% to 4% carriage rate in the oropharynx of all children under 5 years of age.[45]

CASE 1-2

A 30-year-old woman presented with a fever, bad headache, and vomiting. History revealed that she loved fresh soft goat cheese; 2 weeks before the onset of symptoms, she had purchased some at a rural roadside stand. The local merchant told her he had obtained the cheese from a farm that pasteurized the goat milk.

On examination, her temperature was 39°C (102.2°F). She was lethargic but could give a reasonable history, had a stiff neck, and was nauseated. Head CT was normal. Lumbar puncture showed an opening pressure of 260 mm CSF, 500 white blood cells/mm^3 (predominance of neutrophils), glucose of 26 mg/dL, protein of 95 mg/dL, and negative Gram stain. CSF polymerase chain reaction (PCR) tests for herpes simplex virus and enteroviruses were negative. She was hospitalized and treated with ampicillin and ceftriaxone. Four days later, her CSF grew *Listeria monocytogenes*. She made a full recovery.

COMMENT

This patient likely consumed goat cheese contaminated with *L. monocytogenes*. Goats can become chronically infected, and many farmers may not realize that simple brief boiling is not the same as pasteurization. Milk is an excellent medium for microbial growth, and pasteurization of milk requires heating milk to 72°C (161.6°F) for about 15 seconds. Pasteurization inactivates major milk-borne pathogens, including *L. monocytogenes*, *Salmonella* species, *Escherichia coli*, *Staphylococcus aureus*, Q fever, brucellosis, diphtheria, and tuberculosis. Since *Listeria* is an intracellular pathogen, CSF titers may be as low as 10^3 to 10^4 per mm^3, which may not be in sufficient concentration to produce a positive CSF Gram stain and may require a prolonged culture time.

H. influenzae meningitis now accounts for less than 7% of cases in developed countries but remains an important cause of childhood meningitis in developing countries that do not administer the vaccine. Clinical features of *H. influenzae* meningitis do not differ from other forms of acute bacterial meningitis, and treatment is usually with ampicillin or amoxicillin or occasionally chloramphenicol.[4]

STAPHYLOCOCCUS AUREUS. *S. aureus* is a gram-positive bacterium that accounts for about 5% of meningitis but has a mortality rate of about 30%.[46] It is usually classified as a major hospital-associated cause of meningitis. Published series show *S. aureus* may be either methicillin sensitive (50%) or methicillin resistant (50%), with resistant bacteria increasing in frequency.[12–14] *S. aureus* meningitis occurs due to two major pathogenic mechanisms: as a postoperative complication or via hematogenous spread.

CASE 1-3

A 45-year-old man fell off his motorcycle while riding without a helmet. He was knocked unconscious for several minutes, and his friends called an ambulance. In the emergency department, he was confused and had a bloody nose and pain in the right leg. X-rays showed a compound depressed skull fracture and a nondisplaced fracture of the right femur. Brain MRI showed a subarachnoid bleed, depressed skull fracture, and blood in the right frontal and maxillary sinuses. The patient was hospitalized and transferred to a regional hospital the following day. At the local hospital, his mental status had returned to normal and his vital signs remained normal. At the regional hospital, a neurosurgeon removed the depressed skull fragments. Ceftriaxone was administered. On the third hospital day, his temperature was elevated to 38.4°C (101.1°F) and he became confused, with worsening headache. Several hours later, the confusion worsened. Repeat brain MRI was unchanged.

A lumbar puncture was performed and was notable for an opening pressure of 300 mm CSF. CSF showed 300 red blood cells/mm^3; white blood cells were 450 cells/mm^3 with 90% neutrophils, glucose level was 20 mg/dL, and protein level was 300 mg/dL. CSF Gram stain showed numerous gram-positive cocci. He was diagnosed with acute bacterial meningitis secondary to bacterial entry associated with a skull fracture. He was started on nafcillin for possible *Staphylococcus aureus* and vancomycin for methicillin-resistant *S. aureus* (MRSA). Bacterial cultures grew MRSA. He survived but had neurologic sequelae.

COMMENT

Compound depressed cranial fractures are depressed fractures with an overlying scalp laceration in continuity with the fracture site; they are usually treated with debridement and surgical elevation. In the United States, the incidence of subsequent staphylococcal infection after head trauma is around 3%, and many such infections are MRSA.[12,13] Currently, no standardized antibiotic regimen is recommended, but vancomycin and nafcillin are commonly given.

In postoperative *S. aureus* meningitis, bacteria are introduced following neurosurgical procedures, CSF leaks, shunt devices, head trauma (CASE 1-3), or brain masses, or spread from adjacent infections. The postoperative form accounts for more than 75% of *S. aureus* meningitis.

In hematogenous *S. aureus* meningitis, spread to the CNS occurs from foci of infections outside the CNS, such as from endocarditis, skin or soft tissue infections, pneumonia, peritonitis, or urinary tract infections. People with hematogenous acquisition often have an underlying disease, such as cardiovascular disease, diabetes mellitus, alcoholism, cirrhosis, malignancy, human immunodeficiency virus (HIV), or primary immune deficiencies; use IV drugs; or are immunosuppressed from chemotherapy. These patients usually present acutely with fever and altered mental status. About half also have headache. Focal neurologic signs depend on the location of the entering infection. Patients have an elevated CSF white blood cell count and protein but may not have a dramatically low glucose level. Positive CSF Gram stains are present in 30% to 50% of patients. Blood cultures are commonly positive in patients in the hematogenous group.

Antibiotic treatment generally includes a combination of vancomycin, nafcillin, and linezolid for 18 to 21 days.[4] For infection acquired following a neurosurgical procedure, correction of the initial source (eg, shunt infection, skull fracture) should be addressed. Overall mortality is 30% to 50%.

ANAEROBIC BACTERIAL MENINGITIS

Bacterial meningitis caused by anaerobic bacteria is uncommon and most often develops in infants whose mothers had amnionitis or other delivery problems and in children and adults with otitis media, sinusitis, pulmonary infections, or CNS shunt infections or who have had recent neurosurgery.[47,48] The most common bacteria are *Bacteroides* species, *Fusobacterium* species, *Clostridium* species, *Peptostreptococcus, Actinomyces, Veillonella,* and *Propionibacterium* species. Usually the CSF in patients with meningitis does not grow both anaerobic and aerobic organisms, which makes it different than brain abscesses. In general, these patients present with similar clinical features and CSF findings to individuals with aerobic acute bacterial meningitis. However, the Gram stain may show organisms, while the CSF aerobic culture may be negative. Recommended antibiotics include metronidazole, chloramphenicol, and meropenem.[48]

CHALLENGES IN SELECTION OF INITIAL ANTIBIOTIC THERAPY

Since not all bacteria are sensitive to every antibiotic and administration of too many types of antibiotics could lead to unnecessary adverse reactions and antibiotic resistance, the clinician must consider several factors before selecting the antibiotics to administer. Patient-related factors to consider include age, duration of symptoms, vaccination status, health status (ie, conditions that could predispose to types of meningitis, such as earache, chronic gastrointestinal or respiratory diseases, or recent head trauma), allergies to certain antibiotics, and recent travel status. The clinician should also determine whether other members of the patient's family, friends, or community are experiencing meningitis or illnesses that could predispose to meningitis. Conversations with infectious disease colleagues, hospital bacterial laboratories, state committees that handle infectious diseases, or the Centers for Disease Control and Prevention may be helpful. If CSF and blood values are available, they may suggest an acute bacterial meningitis or a meningitis that could be fungal, viral, cancerous, or autoimmune.

KEY POINTS

- ***Neisseria meningitidis*** **is a major cause of meningitis in sub-Saharan Africa.**
- ***Listeria monocytogenes*** **causes about 9% of acute bacterial meningitis cases worldwide, with the highest incidence in infants, the elderly, and individuals with a malignancy or who are immunocompromised or posttransplantation.**
- ***Staphylococcus aureus*** **accounts for about 5% of meningitis but has a mortality rate of about 30%. It is classified as a major cause of health care–associated bacterial meningitis.**
- **Bacterial meningitis caused by anaerobic bacteria is uncommon but appears to mainly develop in infants whose mothers had amnionitis or other delivery problems and in children and adults with otitis media, sinusitis, pulmonary infections, CNS shunt infections or who have had recent neurosurgery.**

If the factors considered suggest a pure community-acquired bacterial meningitis, a third- or fourth-generation cephalosporin plus vancomycin and adjunctive dexamethasone is often prescribed. If the patient is immunosuppressed and in those with a history of alcohol abuse or aged 65 years or older, a third- or fourth-generation cephalosporin plus vancomycin and ampicillin may be prescribed, with careful consideration of the safety of administering dexamethasone. If the patient is postsurgical, vancomycin plus nafcillin, and linezolid and possibly a cephalosporin may be considered. If the acute meningitis could be very atypical due to foreign travel, a specific infectious disease consultation is indicated.

ADJUNCTIVE THERAPY FOR ACUTE BACTERIAL MENINGITIS

Despite improved speed of diagnosis and appropriate antibiotic treatment, acute bacterial meningitis still has a complication rate of up to 20%. Dexamethasone is widely given in an attempt to reduce the mortality and morbidity of acute bacterial meningitis. For maximum benefit, dexamethasone must be given early (minutes before or immediately after antibiotics are given) in the meningitis course and must be in high dose, and the administered antibiotics must cross the blood-brain barrier and kill the meningitis bacteria. Administration of corticosteroids when the presumed infectious etiology is incorrect and the antibiotics do not kill the organism may lead to a worse outcome.

In 2015, Brouwer and colleagues[49] reviewed 25 studies with 4121 participants in a Cochrane Review. In high-income countries, the use of corticosteroids was associated with a nonsignificant reduction in mortality but significantly lower rates of severe hearing loss, any hearing loss, and other neurologic sequelae. However, nine studies from low-income countries reported that the use of corticosteroids was associated with no significant benefit.

OUTCOME OF ACUTE BACTERIAL MENINGITIS

The incidence of neurologic sequelae of acute bacterial meningitis is substantial and varies considerably between developed and developing countries. The type and prevalence of neurologic sequelae vary by age and offending bacterium.[6,50] The most commonly reported sequelae are hearing loss, cognitive impairment, and epilepsy.

Acute bacterial meningitis caused by *S. pneumoniae* has the highest case fatality rate, ranging from 20% to 37% in developed countries to 50% in developing countries.[50] Pneumococcal meningitis has a higher incidence of neurologic sequelae than acute bacterial meningitis due to most other pathogens. Focal neurologic deficits are usually caused by cerebrovascular events but occasionally develop from subdural empyemas, cerebral abscesses, CNS bleeding, or severe meningeal inflammation with penetration of toxic inflammatory molecules across the pial barrier, resulting in neuronal necrosis. In children, focal deficits may include aphasia, ataxia, or paresis in up to 10% of survivors. In adults, about 12% experience a cerebral infarction at admission and another 12% develop infarction following admission. If more than one cerebral infarction is noted, a cardioembolic source should be considered, as endocarditis can be a coexisting condition. Cognitive impairment is common, especially in children. One Dutch study found 22% of children underachieved in school following acute bacterial meningitis.[51] While some children's cognitive function ultimately improves, others continue to have difficulty in school. Another Dutch study found 32% of

adult survivors had deficits in intelligence, memory, and executive functioning.[52] Seizures can appear before admission and continue during hospitalization and after discharge. Anticonvulsants are indicated but often can be discontinued 2 to 3 years after illness, as many seizure disorders resolve over time after meningitis.

Hearing loss is usually sensorineural, with a reported incidence of 14% for mild hearing loss (more than 25 dB) and 5% for severe hearing loss (more than 75 dB).[8,50] The hearing loss usually develops in the first few days of the meningitis and is usually caused by bacteria and inflammatory toxins traversing the cochlear aqueduct from the meninges to reach the cochlea.[50] Hearing loss spontaneously improves in 24%, but in some the loss is permanent.[50] Hearing loss is particularly common in pneumococcal meningitis, but the incidence and severity can be reduced by adjunctive dexamethasone.[49] Thus, a hearing evaluation should be performed in all childhood survivors of acute bacterial meningitis.

CONCLUSION

Acute bacterial meningitis occurs worldwide and in all age groups, producing a severe life-threatening illness if not promptly diagnosed and treated with appropriate antibiotics that cross the blood-brain barrier. Acute bacterial meningitis is usually acquired in a community setting but may be acquired following invasive procedures or head trauma (called *health care–associated meningitis* or *nosocomial meningitis*).

In individuals suspected of meningitis, often with new onset of fever, headache, and meningismus, the diagnosis is usually made by an LP and CSF examination. The CSF typically shows a neutrophilic pleocytosis, low glucose level, and elevated CSF protein, and gram-positive or gram-negative bacteria are seen on centrifuged CSF stained with the Gram stain. The diagnosis is confirmed by culture of the CSF or use of newer technology.

Based on the clinical history and CSF Gram stain, immediate decisions are made to give one or more antibiotics that cross the blood-brain barrier. When appropriate, early adjunctive administration of dexamethasone has a small beneficial effect in improving outcome and reducing sequelae in survivors. Patients are usually placed in the intensive care unit of a hospital, where they are monitored carefully for 14 days of antibiotics. Although many patients have a good outcome, some patients (depending on the offending bacteria) may die and others may experience sequelae, commonly hearing loss, cognitive impairment, or seizures.

KEY POINTS

- **Despite rapid diagnosis and appropriate antibiotic treatment, acute bacterial meningitis still has a complication rate of up to 20%.**
- **For maximum benefit, adjunctive dexamethasone must be given early in the meningitis course when administering antibiotics and must be in high dose, and the administered antibiotics must cross the blood-brain barrier and kill the meningitis bacteria.**
- **The incidence of neurologic sequelae of acute bacterial meningitis is substantial. The most commonly reported sequelae are hearing loss, cognitive impairment, and epilepsy.**

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