

Acute Bacterial Meningitis

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In spite of the availability of antibiotics and the introduction of vaccines for immunoprophylaxis, bacterial meningitis remains a common disease worldwide, with high morbidity and mortality. Meningitis can occur at any age and in previously healthy individuals, although some patients have an increased risk of meningitis including: the immunosuppressed patient and patients at the extremes of age; young children, especially infants; and geriatric patients. The clinical triad of meningitis—fever, neck stiffness, and altered mental status—is, unfortunately, present in less than half of adult patients who have bacterial meningitis. Furthermore, certain patient populations, such as infants (especially neonates) and the elderly, often have a subtle presentation with nonspecific signs and symptoms. Analysis of cerebrospinal fluid (CSF) remains the key to diagnosis. The goal of therapy remains the early administration of appropriate antibiotics, although in selected patients, adjuvant therapy with dexamethasone also may be administered.

Etiology

Meningitis, also termed arachnoiditis or leptomeningitis, is an inflammation of the membranes that surround the brain and spinal cord, thereby involving the arachnoid, the pia mater, and the interposed CSF. The inflammatory process extends throughout the subarachnoid space around the brain, the spinal cord, and the ventricles (Fig. 1).

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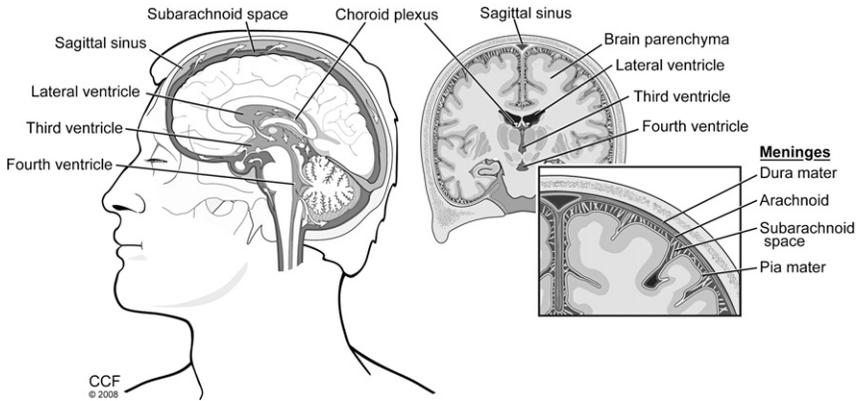


Fig. 1. Anatomy of the central nervous system. (Courtesy of Sharon E. Mace, MD, and Mr. Dave Schumick, of the Cleveland Clinic Center for Art and Photography; with permission.)

Meningitis has been divided into bacterial meningitis and aseptic meningitis. Bacterial or pyogenic meningitis is an acute meningeal inflammation secondary to a bacterial infection that generally evokes a polymorphonuclear response in the CSF. Aseptic meningitis refers to a meningeal inflammation without evidence of pyogenic bacterial infection on Gram's stain or culture, usually accompanied by a mononuclear pleocytosis (Fig. 2). Aseptic meningitis is subdivided into two categories: nonbacterial meningeal infections (typically viral or fungal meningitis), and noninfectious meningeal inflammation from systemic diseases (such as sarcoidosis), neoplastic disease (leptomeningeal carcinomatosis or neoplastic meningitis), or drugs.

Epidemiology

Bacterial meningitis is a common disease worldwide. Meningitis still has high morbidity and mortality in spite of the introduction and widespread use of antibiotics and other advances in medical care [1]. In the United States and in other countries, epidemics of acute meningococcal meningitis are a common occurrence, while in parts of sub-Saharan Africa (meningitis belt) meningococcal meningitis is endemic [2]. In the United States, the overall incidence of meningitis is about 2 to 10 cases per 100,000 population per year [3–5], although the attack rates are very age-specific. The incidence is greatest in pediatric patients, especially infants, with attack rates in neonates at about 400 per 100,000, compared with 1 to 2 per 100,000 in adults and 20 per 100,000 in those less than or equal to 2 years old [6].

Specific pathogens

The relative frequency of the different causative organisms has changed in recent years. The epidemiology of bacterial meningitis has changed

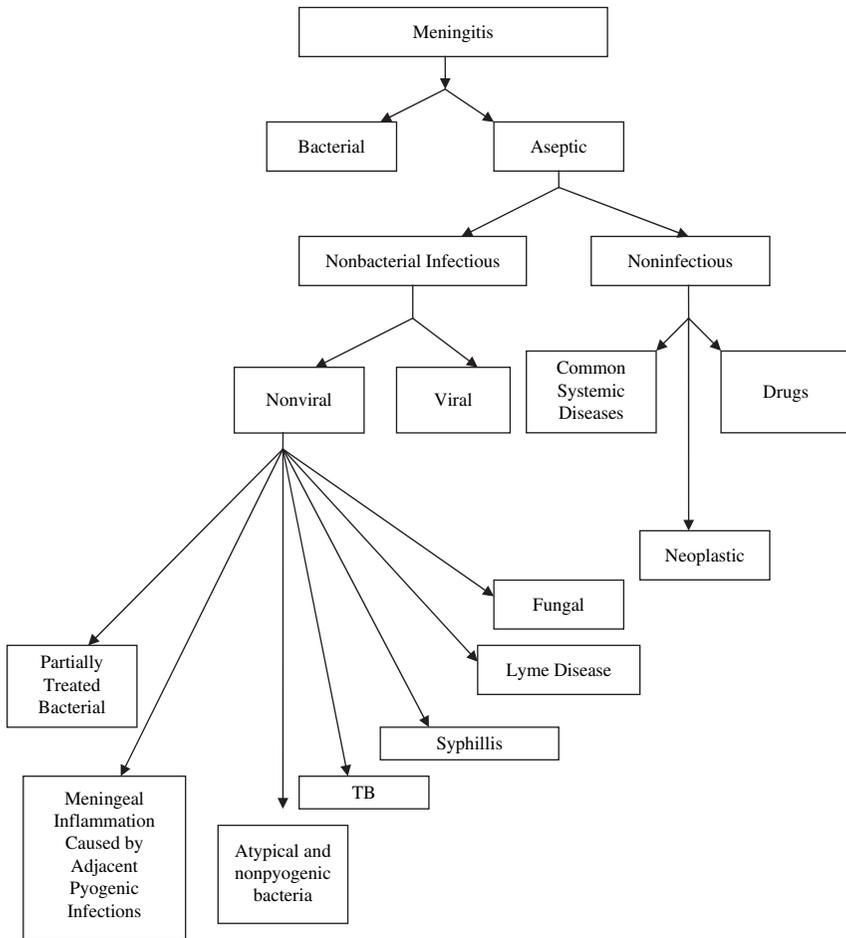


Fig. 2. Causes of meningitis. Bacterial infections of the cerebrospinal fluid (CSF) usually have a positive CSF Gram stain, positive CSF bacterial culture, and increased polymorphonuclear leukocytes in CSF. Aseptic meningitis usually has mononuclear leukocytes in CSF with a negative CSF Gram's stain and negative CSF bacterial culture. (Courtesy of Sharon E. Mace, MD, and Dave Schumick, of the Cleveland Clinic Center for Art and Photography; with permission.)

significantly, primarily because of widespread immunization with new vaccines. The conjugated *Haemophilus influenzae* vaccine (HIB) was introduced in the United States in the early 1990s [7], and in 2000, the *Streptococcus pneumoniae* vaccine was approved by the US Food and Drug Administration (FDA) [8]. Before the introduction of these vaccines, *H influenzae* accounted for nearly half of all bacteria meningitis cases (45%), followed by *S pneumoniae* (18%) and then *Neisseria meningitidis* (14%) [9]. After the introduction of the HIB vaccine, the most common pathogens were *S pneumoniae* (47%), *N meningitidis* (25%), group B streptococcus (12%), and *Listeria monocytogenes* (8%) (Table 1) [4]. It is likely that the most

Table 1
Pathogens responsible for bacterial meningitis

| Before introduction of <i>Haemophilus influenzae</i> type B vaccines ^a | | After introduction of <i>Haemophilus influenzae</i> type B vaccines ^b | |
|--|-----|---|-----|
| <i>H influenzae</i> | 45% | <i>Streptococcus pneumoniae</i> | 47% |
| <i>Streptococcus pneumoniae</i> | 18% | <i>Neisseria meningitidis</i> | 25% |
| <i>N meningitidis</i> | 14% | Group B streptococcus (<i>S agalactiae</i>) | 12% |
| Group B streptococcus (<i>S agalactiae</i>) | 6% | <i>Listeria monocytogenes</i> | 8% |
| <i>Listeria monocytogenes</i> | 3% | <i>H influenzae</i> | 7% |
| Others | 14% | Others | 1% |
| Children <5 years old (>70% <i>H influenzae</i>) | | | |

^a Percentages taken from Wenger JD, Hightower AW, Facklam RR, et al. Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. The Bacterial Meningitis Study Group. *J Infect Dis* 1990;162(6):1316–22.

^b Percentages taken from Schuchat A, Robinson K, Wenger JD, et al. Bacterial meningitis in the United States in 1995. Active surveillance team. *New Engl J Med* 1997;337(14):970–6.

recent addition of the *S pneumoniae* vaccine will change the specific epidemiology of bacterial meningitis again.

H influenzae was previously the most common cause of bacterial meningitis and the most common cause of acquired mental retardation in the United States [7]. *S pneumoniae* has supplanted *H influenzae* as the pathogen causing most bacterial meningitis cases in the United States [4]. *S pneumoniae* is the most frequent cause of bacterial meningitis in adults ages 19 to 59 years and greater than or equal to 60 years, and in infants/very young children excluding neonates (eg, age 1 to 23 months) [4].

N meningitidis was previously the third most common cause of bacterial meningitis in the United States [9] but has now moved into second place behind *S pneumoniae*, and it accounts for 25% of all cases of bacterial meningitis [4]. It remains to be seen whether the widespread use of the pneumococcal vaccines decreases the incidence of *S pneumoniae* meningitis, thereby allowing *N meningitidis* and *L monocytogenes* and other bacteria to become the prevailing pathogens causing bacterial meningitis. The widespread use of the pneumococcal vaccine beginning in infancy has decreased the incidence of invasive disease by *S pneumoniae* by more than 90% [10].

Clinical presentation

Signs and symptoms of meningitis include: fever, headache, stiff neck, confusion or altered mental status, lethargy, malaise, seizures, and vomiting. About 25% of adults have a classic presentation and are not a diagnostic dilemma [6]. Unfortunately, many patients have a less obvious presentation.

Furthermore, certain patients—typically the pediatric patient, especially infants; the elderly; and the immunosuppressed—may not have the classic features of meningitis. These patients often have a subtle presentation and nonspecific clinical signs/symptoms. Patients partially treated with antibiotics in addition to patients at the extremes of age (the very young and the elderly) and the immunocompromised may not have a fever.

The classic triad is fever, neck stiffness, and altered mental status. Yet in an adult study of community-acquired bacterial meningitis, less than half of the patients (44%) had the classic triad. Ninety-five percent of the patients, however, had at least two of the four symptoms of neck stiffness, fever, headache, and altered mental status [11].

A stiff neck or nuchal rigidity is caused by meningeal irritation with resistance to passive neck flexion. Although this finding is a classic sign of meningitis, it may be present only 30% of the time [12].

Positive Kernig's and Brudzinski's signs are hallmarks of meningitis, yet Kernig's and Brudzinski's signs were present in only about half of adults with meningitis [5]. With the patient supine and the thigh flexed to a 90° right angle, attempts to straighten or extend the leg are met with resistance (Kernig's sign). There are two Brudzinski's signs in patients who have meningitis. Flexion of the neck causes involuntary flexion of the knees and hips (Brudzinski's sign). Passive flexion of the leg on one side causes contralateral flexion of the opposite leg (known as Brudzinski's sign or contralateral sign or contralateral reflex).

Confusion suggests possible meningitis, as does an abnormal mental status plus fever. Meningitis also should be in the differential diagnosis when the combination of fever plus a seizure occurs. Seizures occur in 5% to 28% of adults who have meningitis [1,13,14]. Seizures are the presenting symptom in one-third of pediatric patients who have bacterial meningitis [15]. In childhood meningitis, seizures occur more frequently with *S pneumoniae* and *H influenzae* B than with meningococcal meningitis [15].

Petechiae and purpura generally are associated with meningococcal meningitis, although these skin manifestations may be present with any bacterial meningitis [16].

Signs and symptoms in infants can be particularly subtle. They may have only a fever or be hypothermic, or even afebrile. They may not have a stiff neck. The chief complaint of an infant who has meningitis is often nonspecific and includes: irritability, lethargy, poor feeding, fever, seizures, apnea, a rash, or a bulging fontanelle [17].

In geriatric patients, frequently the only presenting sign of meningitis is confusion or an altered mental status [18].

The onset of presentation varies with meningitis. Typically, the adult who has acute bacterial meningitis seeks medical care within a few hours to several days after illness onset. The presentation differs, however, depending on many variables, including: age, underlying comorbidity, immunocompetence, mental competence, ability to communicate, prior antibiotic therapy,

and the specific bacterial pathogen. The onset of viral meningitis or viral meningoencephalitis is also generally acute over hours to days, but sometimes is preceded by a nonspecific febrile illness of a few days' duration.

Patients who have subacute or chronic meningitis present over weeks to months, and even years. Generally, the onset is more gradual, with a lower fever, and there may or may not be associated lethargy or disability. Fungal (eg, *Cryptococcus* and *Coccidioides*) and mycobacterium are typical causes of subacute and chronic meningitis.

The clinical presentation of meningitis also has been categorized as fulminant (10%) or insidious (90%). Patients who have an insidious onset often have been seen by a medical care provider and given a diagnosis of a nonspecific or viral illness days before their diagnosis of meningitis is made and frequently have been partially treated with oral antibiotics for an infection such as otitis, sinusitis, or bronchitis. The delay in diagnosis of meningitis in such patients is up to 2 weeks, with a median of 36 to 72 hours.

Risk factors for bacterial meningitis

Age and demographics

Meningitis can occur at any age and in previously healthy individuals. There are some risk factors that predispose the individual to meningitis, however (Box 1). Host risk factors can be grouped into four categories: age, demographic/socioeconomic factors, exposure to pathogens, and immunosuppression. Patients at the extremes of age: the elderly (age over 60 years) and pediatric patients (young children age younger than 5 years, especially infants/neonates) have an increased susceptibility to meningitis [16,18]. Demographic and socioeconomic factors include: male gender, African American race, low socioeconomic class, and crowding (eg, military recruits and college students in dormitories) [19].

Immunocompromised patients

There is an association between immunosuppression and an increased risk for bacterial meningitis. Immunosuppressive conditions include: diabetes, alcoholism, cirrhosis/liver disease, asplenia or status postsplenectomy, hematologic disorders (eg, sickle cell disease, thalassemia major), malignancy, immunologic disorders (complement deficiency, immunoglobulin deficiency), HIV, and immunosuppressive drug therapy (Table 2) [19,20].

Mechanism of entry into the central nervous system

There are several mechanisms by which organisms gain entry to the CSF, most commonly by means of hematogenous spread, but also by contiguous

Box 1. Risk factors for meningitis**Age**

- Extremes of age: elderly (age >60 years); young children (age <5 years), especially infants/neonates

Demographic/socioeconomic

- Male gender
- African American ethnicity
- Low socioeconomic status
- Crowding: military recruits, crowded dormitories

Exposure to pathogens

- Recent colonization
- Household/close contact with meningitis patient
- Contiguous infection: sinusitis, mastoiditis, otitis media
- Bacterial endocarditis
- Intravenous drug abuse
- Dural defect: status post neurosurgery, central nervous system (CNS) trauma, congenital defect
- Ventriculoperitoneal shunt, other CNS devices
- Cochlear implants

Immunosuppression

- Status post splenectomy
- Hematologic disorders: sickle cell disease, thalassemia major
- Malignancy
- Diabetes
- Alcoholism/cirrhosis
- Immunologic disorder: complement deficiencies, immunoglobulin deficiency
- HIV
- Immunosuppressive drug therapy

spread and infrequently by direct entry. Factors that aid the organism in gaining entry to the CSF include:

- Recent colonization
- Close contact with a patient who has meningitis
- Contiguous infection (eg, sinusitis, mastoiditis, otitis media)
- Hematogenous seeding of the CSF (eg, intravenous drug abuse, bacterial endocarditis)
- Disruption of dura,
- Status post neurosurgery
- Penetrating CNS trauma
- Congenital defects

Table 2
Common bacterial pathogens and empiric therapy based on age, clinical setting, and risk factors

| Age pediatric | Common pathogens | Empiric therapy | Alternative empiric therapy |
|--|---|---|--|
| Neonate (≤ 30 days) | Group B streptococcus Gram negatives: (<i>Escherichia coli</i> , <i>Klebsiella</i>) <i>Listeria</i> | Ampicillin + third generation cephalosporin (cefotaxime) | Ampicillin + aminoglycoside (gentamicin) |
| Children 1–23 months | <i>Streptococcus pneumoniae</i> <i>Neisseria meningitidis</i> Group B streptococcus <i>Haemophilus influenzae</i> <i>Escherichia coli</i> | Third generation cephalosporin (cefotaxime or ceftriaxone) + vancomycin ^a | Meropenem (carbapenem) + vancomycin ^a |
| Children 2–18 years | <i>S pneumoniae</i> <i>N meningitidis</i> | Third generation cephalosporin (cefotaxime or ceftriaxone) + vancomycin ^a | Carbapenem (meropenem) + vancomycin ^a |
| Age adult | | | |
| Young and middle-aged adults (18–50 years) | <i>S pneumoniae</i> <i>N meningitidis</i> | Third generation cephalosporin (cefotaxime or ceftriaxone) + vancomycin ^a | Carbapenem (meropenem) \pm vancomycin ^a |
| Age >50 years (includes elderly) | <i>S pneumoniae</i> <i>N meningitidis</i> <i>Listeria monocytogenes</i> | Third-generation cephalosporin (cefotaxime or ceftriaxone) + vancomycin ^a + ampicillin | Third generation cephalosporin (cefotaxime or ceftriaxone) + vancomycin ^a + trimethoprim-sulfamethoxazole |
| Special considerations | | | |
| Impaired immunity (such as HIV) | <i>S pneumoniae</i> Gram-negative bacilli <i>L monocytogenes</i> | Third generation cephalosporin (ceftazidime) + vancomycin ^a + ampicillin | Carbapenem (meropenem) + vancomycin ^a + trimethoprim-sulfamethoxazole |

| | | | |
|--|---|--|--|
| Status post neurosurgery or penetrating trauma | <i>Staphylococcus aureus</i> Coagulase-negative staphylococci Aerobic gram-negative bacilli (eg, <i>Pseudomonas aeruginosa</i>) | Fourth generation cephalosporin (cefepime) ± vancomycin ^a | Third generation cephalosporin (ceftazidime) + vancomycin ^a or carbapenem (meropenem) + vancomycin ^a |
| Cerebrospinal fluid leak or basilar skull fracture | <i>S pneumoniae</i> Streptococci (various) <i>H influenzae</i> | Third generation cephalosporin (cefotaxime or ceftriaxone) + vancomycin ^a | Carbapenem (meropenem) + vancomycin ^a |
| Cerebrospinal fluid shunt (eg, VP shunt) | Coagulase-negative staphylococci <i>Staphylococcus aureus</i> Aerobic gram-negative bacilli (eg, <i>P aeruginosa</i> , <i>Propionibacterium acnes</i>) | Fourth generation cephalosporin (cefepime) + vancomycin ^a | Third generation cephalosporin (ceftazidime) + vancomycin ^a |

^a Some recommend the addition of rifampin when vancomycin and dexamethasone are coadministered.

- CSF shunts (eg, ventricular shunts)
- Other devices (eg, epidural catheters, Ommaya reservoirs, intracranial monitoring devices, external ventricular drains)

Postoperative neurosurgical patients and patients who have penetrating head trauma are at risk for meningitis caused by staphylococci [21]. Bacterial meningitis in patients who have a ventriculoperitoneal shunt commonly is caused by staphylococci, especially coagulase-negative strains, and gram-negative organisms [21–23]. Patients who have a cochlear implant have a greatly increased risk (greater than 30-fold) of pneumococcal meningitis [24].

Neonatal meningitis

Neonatal (age less than or equal to 1 month) meningitis is caused by the same organisms that cause bacteremia and sepsis in newborns: commonly, group-B β -hemolytic streptococci, gram-negative enteric bacteria, and *L monocytogenes*. After the first few weeks of life, *S pneumoniae* and *H influenzae* emerge as common pathogens also. The pathogenesis of neonatal meningitis probably results from a maternal–fetal infection, either by direct inoculation during the birth process or hematogenously (transplacental). There are predisposing maternal and infant risk factors for neonatal meningitis. Infant factors are prematurity and low birth weight. Maternal factors include: prolonged rupture of membranes, maternal urinary tract infection, chorioamnionitis, and endometritis [25]. Neonatal meningitis is frequently a component of a sepsis syndrome whereby bacteremia seeds the CSF.

Neonates do not have a completely functional immune system, which predisposes them to infections. Multiple factors cause impaired functioning of the polymorphonuclear neutrophils (PMNs), including decreased chemotactic ability of PMNs, decreased adhesion of PMNs to surfaces, and impaired mobility of PMNs. Newborns receive an incomplete range of antibody transmitted across the placenta. Although some IgG is received transplacentally, there is only a small amount of antibody to gram-negative bacteria and no IgM. Under conditions of stress, preliminary data suggest there is decreased phagocytosis of gram-negative bacteria and decreased killing of group B streptococci and *Escherichia coli*. In addition to impaired function of PMNs, most newborns have a functional deficiency of the alternate pathway of the complement system [26].

Geriatric meningitis

The elderly have many risk factors that predispose patients to infections. Numerous chronic illnesses and comorbid conditions, and polypharmacy and immunosuppressive medications, are associated with aging [27]. The decline in immune system function that occurs in the elderly includes a decrease in both T lymphocyte function and cell-mediated immunity [28]. Environmental factors, such as incontinence, indwelling catheters, and impaired

mental status predispose to aspiration and ulcers, which lead to infections that can progress to bacteremia and hematogenous seeding of the meninges [29]. Nursing home residents can be a reservoir for antimicrobial-resistant pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) [29,30].

The elderly often have a subtle clinical presentation of meningitis [18]. The geriatric patient who has meningitis is less likely to have neck stiffness and meningeal signs, and more likely to have mental status changes, seizures, neurologic deficits, and even hydrocephalus [31,32]. The elderly patient who has meningitis may not have a high fever and may even be afebrile. The mental status changes that can occur in geriatric patients who have meningitis frequently are ascribed to other conditions from delirium to psychosis, senility, a transient ischemia attack, or a stroke. Fever, when present, may be mistakenly attributed to pneumonia, a urinary tract infection, viral illness, bronchitis, bacteremia, or sepsis, especially because classic signs and symptoms of meningitis are often lacking in the elderly patient.

Conversely, the geriatric patient also may have false-positive findings of meningitis. Signs and symptoms of meningeal irritation such as nuchal rigidity or a positive Kernig's sign or Brudzinski's sign may be found in healthy elderly people [33]. This false-positive finding is attributed to the presence of limited neck mobility and cervical spine disease. Thus, classic signs and symptoms of meningeal irritation are unreliable in the elderly and make the diagnosis of meningitis more difficult [32–34]. Meningitis in the elderly, as in neonates, (eg, in the extremes of age) frequently is associated with a delay in diagnosis and has a high mortality rate [25,26,32,34].

Pathophysiology

Pathogens enter the CNS either by hematogenous spread (the most common method) or by direct extension from a contiguous site (Fig. 3). Most organisms that cause meningitis are able to colonize the upper respiratory tract by attaching to the host's nasopharyngeal mucosal epithelium. The next step is to evade the host's complement system, which allows invasion into the neighboring intravascular space. The pathogens then cross the blood–brain barrier to enter the CSF. Because the host defense mechanisms within the CSF are poor, the pathogens can proliferate. In attempt to defend against the invading organisms, a cascade of inflammatory events is set into motion by the body's immune defense mechanisms.

The bacteria that cause meningitis have properties that enhance their virulence, which accounts, at least partly, for their ability to cause meningitis. The bacteria: *H influenzae*, *N meningitidis*, and *S pneumoniae*, all make immunoglobulin A proteases. Such proteases inactivate the host's immunoglobulin A by cleaving the antibody. This destruction of immunoglobulin

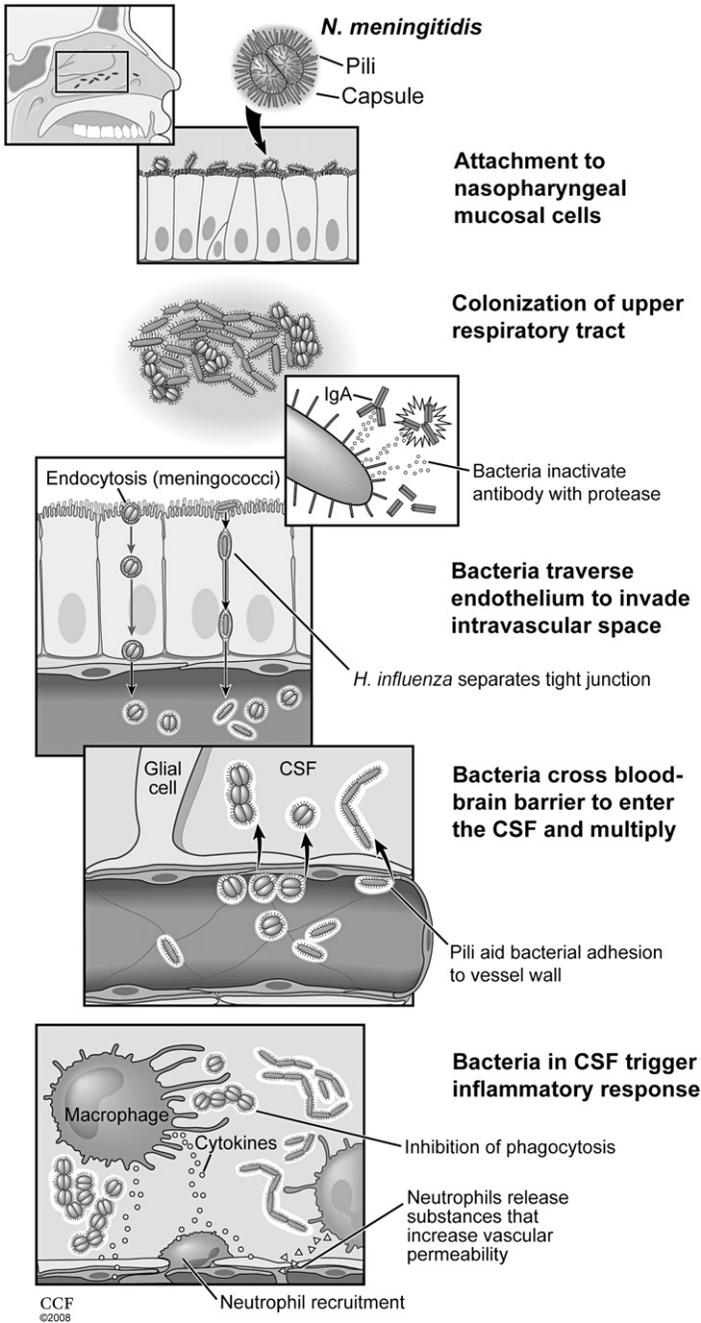


Fig. 3. Pathophysiology of meningitis. (Courtesy of Sharon E. Mace, MD, and Mr. Dave Schumick, of the Cleveland Clinic Center for Art and Photography; with permission.)

A antibody inactivates the host's local antibody defense, which allows bacterial adherence to the nasopharyngeal mucosa and colonization. Adhesion to the host's nasopharyngeal mucosal epithelial cells by *N meningitidis* occurs by means of fimbria or pili. When the ciliated cells of the host are damaged, as occurs from a viral upper respiratory infection or with smoking, their ability to prevent mucosal adhesion by invading bacteria is limited. The pathogens enter the intravascular space by various mechanisms. Meningococci by the process of endocytosis traverse the endothelium in membrane bound vacuoles. *H influenzae* separates the apical tight junctions between epithelial cells to invade the mucosa and gain access to the intravascular space.

Encapsulated bacteria, (eg, *S pneumoniae*, *H influenzae*, and *N meningitidis*) avoid destruction by their host once they are in the bloodstream, because their polysaccharide capsule inhibits phagocytosis and complement-mediated bactericidal activity.

Once the bacteria are in the bloodstream, bacterial adhesion to structures of the blood–brain barrier are aided by structural qualities of the bacteria such as the fimbria with some *E coli strains*, and the pili and fimbria with *N meningitidis*.

Because of poor host defenses in the CSF, the bacteria quickly multiply after gaining entry to the CSF. Multiple factors account for inadequate host defense mechanisms within the CSF, including: low complement levels, low immunoglobulin levels, and decreased opsonic activity, all of which result in the host's inability to destroy the bacteria by phagocytosis.

Bacterial components in the CSF trigger an inflammatory cascade in the host. Proinflammatory cytokines—interleukin (IL)-1, tumor necrosis factor (TNF), and others—are released by various cells including macrophages, microglia, meningeal cells, and endothelial cells. Cytokines, in turn, promote the migration of neutrophils into the CSF by several mechanisms. Cytokines increase the binding affinity of leukocytes for endothelial cells, and induce adhesion molecules that interact with leukocyte receptors.

Once they are in the CSF, neutrophils release substances (eg, prostaglandins, toxic oxygen metabolites, matrix metalloproteinases) that increase vascular permeability and even may cause direct neurotoxicity. The inflammatory cascade leads to abnormalities in cerebral blood flow and cerebral edema. The forces leading to cerebral edema include: vasogenic edema from increased permeability of the blood–brain barrier, cytotoxic edema caused by cellular swelling from the toxic substances released by bacteria and neutrophils, and occasionally from obstruction to CSF outflow at the arachnoid villi. Early in meningitis, cerebral blood flow increases, but later decreases, which can cause further neurologic damage. Local vascular inflammation or thrombosis can cause localized cerebral hypoperfusion. Autoregulation of cerebral blood flow can be impaired. Herniation of the brain and death can result from the increased intracranial pressure.

Management

After stabilization of the patient (including airway, breathing, circulation), the priority in the treatment of acute bacterial meningitis is the prompt administration of an appropriate bactericidal antibiotic(s) that has rapid entry into the subarachnoid space. In the emergency department, the specific pathogen usually is not known, so empiric therapy is the rule. In some cases, an anti-inflammatory agent (eg, dexamethasone, which suppresses the body's usual inflammatory reaction) also is given (see section on adjuvant therapy). Administration of antibiotics should not be delayed. If any delay, however, is expected for any reason, including a CT scan, then blood cultures should be obtained and empiric antibiotics given (see [Table 2](#), [Table 3](#)).

Complications

Acute complications are common with bacterial meningitis ([Box 2](#), [Fig. 4](#)). Patients may have an altered mental status or even be comatose. They may present in shock. About 15% of pediatric patients who had pneumococcal meningitis presented in shock [35]. Shock and/or disseminated intravascular coagulation (DIC) frequently are associated with meningococcal meningitis. Apnea and/or respiratory failure/distress can occur with bacterial meningitis, especially in infants.

Seizures occur in about one-third of patients who have bacterial meningitis [16]. Seizures that persist (longer than 4 days) or begin late tend to be associated with neurologic sequelae. Focal seizures carry a worse prognosis than generalized seizures. Focal seizures should raise concern for complications such as subdural empyema, brain abscess, or increased intracranial pressure, and suggest a need for neuroimaging. Subdural effusions, which are common (occurring in one-third of pediatric patients), are generally asymptomatic, resolve spontaneously, and have no permanent neurologic sequelae. The syndrome of inappropriate antidiuretic hormone (SIADH) can occur, so the electrolytes and fluid status should be monitored closely.

All of these complications—shock, DIC, altered mental status to coma, respiratory distress, seizures, increased intracranial pressure, SIADH, and other symptoms—should be managed with the usual therapy.

Diagnostic evaluation

Lumbar puncture

CSF is essential to confirm the diagnosis and institute specific antibiotic therapy ([Table 4](#)). In most patients who have acute bacterial meningitis, a lumbar puncture (LP) can be done safely without prior neuroimaging studies. The concern is that an LP, in a patient who has increased intracranial pressure, can have adverse effects even death [36]. If a patient presents with an acute fulminating febrile illness consistent with bacterial meningitis, early

antibiotic therapy is warranted, because early therapy is thought to improve the prognosis and decrease morbidity and mortality. When confronted with such a patient, the recommendation is either: immediate LP, then give the initial antibiotic dose; or administer empiric antibiotics, obtain head CT scan, then do the LP. Criteria have been suggested for obtaining a head CT scan prior to the LP in suspected bacterial meningitis. The criteria are:

- Head trauma
- Immunocompromised state
- Recent seizure (within the last 7 days)
- Abnormal level of consciousness
- Focal weakness, abnormal speech
- Abnormal visual fields or gaze paresis
- Inability to follow commands or answer questions appropriately
- A history of any of the following: mass lesions, focal infection, or stroke [37]

An absolute contraindication to an LP is the presence of infection in the tissues near the puncture site. A relative contraindication to an LP is increased intracranial pressure (ICP) from a space-occupying lesion, especially when progressive signs of herniation such as unilateral cranial nerve III palsy or lateralizing signs (hemiparesis), are present [38]. The risk of herniation appears to be greater if the patient has a brain abscess [39,40]. A reduction in pressure in the spinal canal has been associated with seizures, stupor, cardiorespiratory collapse, and even sudden death in patients who have impending herniation [38].

If the procedure is essential (as with suspected meningitis), and because platelet transfusion (for thrombocytopenia) and replacement of clotting factors (for hemophilia and other disorders) can be done prior to the LP, the presence of a coagulopathy is only a relative contraindication [41]. If the patient has a coagulopathy, some experts recommend that the LP be done by experienced clinicians who are less likely to have a difficult or complicated LP that results in localized trauma to the dura. A study in children who had thrombocytopenia secondary to acute lymphoblastic leukemia documented the safety of LP in thrombocytopenic patients (without platelet transfusion prior to the LP), although less than 1% of patients had a platelet count less than or equal to 10×10^9 [42].

Of course, cardiorespiratory instability of the patient is another contraindication, although the ABCs should be dealt with before the LP. Evidence of spinal cord trauma and/or spinal cord compression would be another contraindication to an LP.

When considering bacterial meningitis, CSF should be sent for: Gram's stain and cultures, cell count with differential, glucose, and protein, and other studies as indicated. If an organism can be identified on the Gram's stain then empiric therapy can be based on this finding (see Table 3). CSF findings suggestive of bacterial meningitis are:

- Positive Gram's stain (organism identified on slide)
- Glucose less than 40 mg/dL or ratio of CSF/blood glucose less than 0.40

Table 3
Likely bacterial pathogen and antibiotic of choice based on cerebrospinal fluid Gram's stain results

| Gram stain | | | | | |
|-------------------|-------|------------------------------------|---------------------------------|--|---|
| Positive/negative | | Appearance | | | |
| Gram-positive | | | | | |
| ± | Shape | Appearance | Bacterial pathogen | Antibiotic of choice | Dose |
| + | Cocci | Paired diplococci | <i>Streptococcus pneumoniae</i> | Penicillin G (if sensitive) or chloramphenicol + vancomycin + rifampin | Penicillin: adult 4 million units every 6 h; pediatric 100,000 U/kg every 6 h Chloramphenicol: 50 mg/kg every 6 h (maximum 1 g dose) Vancomycin: adult 1 g every dose; pediatric 15 mg/kg every 8–12 h (maximum 1 g every dose, 4 g/d) Rifampin: adult 600 mg/d; pediatric 5–10 mg/kg every dose given once or twice daily |
| + | Cocci | Single, doubles, tetrads, clusters | Staphylococci | Nafcillin or oxacillin (if methicillin-sensitive) or vancomycin (if methicillin-resistant) | Nafcillin or oxacillin: adult 1–2 g every 6 h; pediatric 25–50 mg/kg every 6 h (maximum 12 g/d) Vancomycin: adult 1 g every dose; pediatric 15 mg/kg every 8–12 h (maximum 1 g every dose, 4 g/d) |

| | | | | | |
|---------------|--------------|---|--|---|--|
| + | Cocci | Pairs and chain | Other streptococci (β hemolytic streptococci) | Penicillin G (if sensitive) or ampicillin | Penicillin: adult 4 million units every 6 h; pediatric 100,000 U/kg every 6 h Ampicillin: 100 mg/kg 6 hrs (maximum 2 g per dose) |
| + | Rods | Single or chains | <i>Listeria monocytogenes</i> | Ampicillin + gentamycin or trimethoprim- sulfamethoxazole | Ampicillin: 100 mg/kg every 6 h (maximum 2 g per dose) Gentamycin: adult 1–2 mg/kg every 8 h; pediatric 2.5 mg/kg every 8–12 h (max 1 g q dose, 4g qd) Trimethoprim- sulfamethoxazole: 5 mg/kg every 12 h (based on trimethoprim component) |
| Gram-negative | | | | | |
| – | Cocci | Kidney or coffee bean appearance cocci or paired diplococci | <i>Neisseria meningitidis</i> | Penicillin G (if sensitive) or chloramphenicol | Penicillin: adult 4 million units every 6 h; pediatric 100,000 U/ kg every 6 h Chloramphenicol: 50 mg/kg every 6 h (maximum 1 every dose) |
| – | Coccobacilli | Coccobacilli or pleomorphic bacilli | <i>Haemophilus influenzae</i> | Ceftriaxone or cefotaxime + meropenem or chloramphenicol | Ceftriaxone: 50 mg/kg every 12 h Cefotaxime: 50 mg/kg every 6 h Meropenem: 40 mg/kg every 8 h (maximum 2 g every dose) Chloramphenicol: 50 mg/kg every 6 h (maximum 1 g every dose) |

(continued on next page)

Table 3 (continued)

| Gram stain | | | | | |
|-------------------|-------|------------|--|---|--|
| Positive/negative | | Appearance | | | |
| Gram-positive | | | | | |
| ± | Shape | Appearance | Bacterial pathogen | Antibiotic of choice | Dose |
| – | Rods | Rods | Enterobacteriaceae: <i>Escherichia coli</i> | Ceftriaxone + gentamycin or meropenem or quinolones | Ceftriaxone: 50 mg/kg every 12 h plus gentamycin: adult 1–2 mg/kg; pediatric 2.5 mg/kg every 8 h Meropenem: 40 mg/kg every 8 h (maximum 2 g every dose) Quinolones: adult 400 mg every 8 h or 600 mg every 12 h (maximum 1200 mg every 6 h) |
| – | Rods | Rods | <i>Pseudomonas aeruginosa</i> | Ceftazidime + tobramycin or meropenem or quinolones | Ceftazidime: 50 mg/kg every 8 h (maximum 2 g every dose) Tobramycin: adult 1–2 mg/kg every 8 h; pediatric 2.5 mg/kg every 8 h Metroponem: 40 mg/kg every 8 h (maximum 2 g per dose) Quinolones: adult 400 mg every 8 h or 600 mg every 12 h (maximum 1200 mg every 6 h) |

Doses are for adults and children > 1 month of age (excludes neonates) who have normal renal and hepatic function and are administered intravenously. Quinolones generally are not recommended in pediatric patients, although the dose used is 5–10 mg/kg every 12 h (maximum 400 mg per dose).

Box 2. Complications and sequelae of bacterial meningitis

Acute complications

- Shock
- Respiratory failure/distress/arrest
- Apnea
- Altered mental status/coma
- Increased intracranial pressure
- Seizures
- Disseminated intravascular coagulation (DIC)
- Subdural effusions
- Subdural abscess
- Intracerebral abscess
- Increased intracranial pressure
- Death

Sequelae

- Seizure disorder
- Impaired intellectual functioning
- Impaired cognition
- Personality changes
- Dizziness
- Gait disturbances
- Focal neurologic deficits:
 - Deafness/sensorineural hearing loss (most common in children who have *H influenzae*)
 - Blindness
 - Paralysis
 - Paresis
- Central nervous system structural sequelae/complications
 - Hydrocephalus
 - Brain abscess
 - Subdural abscess
 - Subdural effusion
 - Subdural empyema
 - Epidural abscess
 - Cerebral thrombosis
 - Cerebral vasculitis

- Protein greater than 200 mg/dL
- WBC greater than 1000/ μ L
- Greater than 80% polymorphonuclear neutrophils
- Opening pressure (OP) of greater than 300 mm

Other diseases from aseptic or viral meningitis to fungal meningitis, brain abscess, or neoplastic disease can give abnormal CSF findings (see [Table 4](#)).

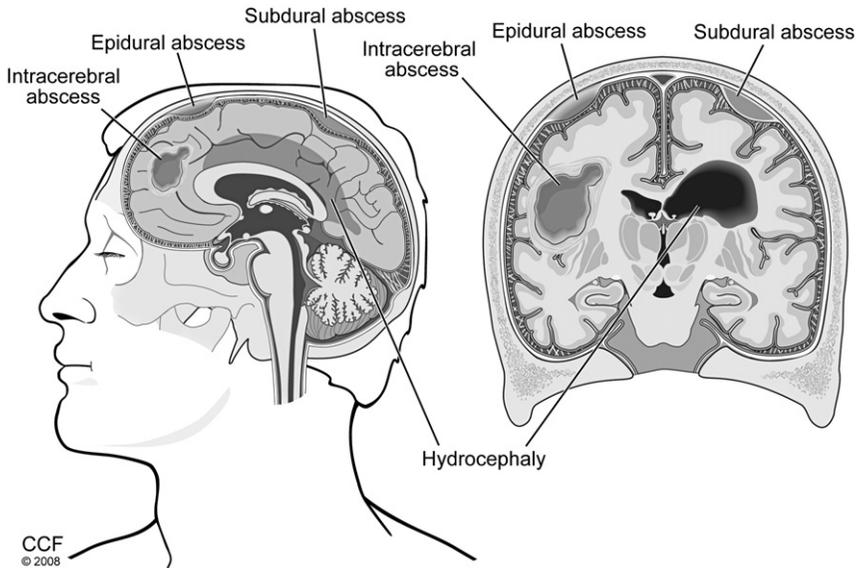


Fig. 4. Central nervous system (CNS) complications of meningitis. Also focal CNS infections in the differential diagnosis for meningitis. (Courtesy of Sharon E. Mace, MD, and Mr. Dave Schumick, of the Cleveland Clinic Center for Art and Photography; with permission.)

One caveat to remember is that the CSF findings in bacterial meningitis may not always yield the classic results. Reasons for a lack of classic CSF findings in bacterial meningitis include:

- Partially treated meningitis (eg, prior antibiotics)
- Time of LP (is it early in course of the disease before the patient mounts a response, or late in the course?)
- The patient's condition (is the patient able to mount a response to the invading organism or is the patient immunosuppressed or has an overwhelming infection?)

Thus, the typical CSF findings may not be present in every patient who has bacterial meningitis and may even show a normal WBC in the CSF and/or lymphocyte predominance, especially if early in the disease (see Table 4) [43]. Therefore, if there is any concern that the clinical diagnosis is meningitis, it is better to treat for bacterial meningitis (specifically, give parental antibiotics and admit for close observation while awaiting culture [CSF and blood] results) [44]. In the past, repeat LP was done routinely to follow the course of bacterial meningitis and to document sterilization of the CSF, but now repeat LP is done only if there is a specific concern or indication [45], such as when a hospitalized patient who has bacterial meningitis on appropriate antibiotics is not improving.

Additional CSF studies may be useful in selected patients. For example, in patients who have partially treated meningitis, bacterial antigen tests,

Table 4
Cerebrospinal fluid results

| Gram's stain | Bacterial meningitis | Viral meningitis | Normal adult | Normal child | Normal term infant | Normal preterm infant |
|---|----------------------|------------------|--------------|--------------|------------------------|-------------------------|
| Gram's Stain | + | – | – | – | – | – |
| White blood cell (WBC) (per μL) | > 1000 | < 1000 | < 5 | 0–7 | 8 (0–22 range) | 9 (0–25 range) |
| WBC type | > 80% polys | 1% to 50% polys | All monos | 0% polys | 61% polys | 57% polys |
| Glucose (mg/dL) | < 40 | > 40 | > 40 | 40–80 | 52 mean (34–119 range) | 50 mean (24–63 range) |
| Glucose ratio cerebrospinal fluid/blood | < 0.4 | > 0.4 | > 0.4 | > 0.5 | 0.44–1.28 | 0.55–1.05 |
| Protein (mg/dL) | < 200 | < 200 | < 50 | 5–40 | 90 mean (20–170 range) | 115 mean (65–150 range) |

Abbreviations: Monos, mononuclear leukocytes; Polys, polymorphonuclear leukocytes.

such as counterimmunoelectrophoresis (CIE), ELISA, or PCR tests on CSF can help identify the pathogen. The sensitivity of different detection tests varies and is in the 60% to 90% range. Newer antigen detection tests are being designed, however, and older ones are being improved, so these tests, especially PCR, may become more useful and widely available in the future [46,47].

When viral meningitis is suspected, testing for viruses by PCR or viral cultures may be done. Similarly when fungal meningitis is a consideration, testing for fungal pathogens by India ink and fungal cultures and antigen testing may be done. Mixing India ink with CSF or other biologic fluids remains a quick and efficacious technique for identifying *Cryptococcus*, although clinical experience is necessary to recognize the encapsulated yeast. A positive India ink test occurs in over 80% of patients who have AIDS and half of non-AIDS patients who have cryptococcal meningitis, according to one author [48], while others report only about a 50% yield [49]. By comparison, cryptococcal antigen is positive in over 90% of patients in the CSF or serum [48–50].

If leptomenigeal meningitis is a possibility, CSF should be sent for cytology. Although it is nonspecific, CSF lactic acid has been used when a patient has had prior antibiotic therapy, which likely makes the CSF culture- and gram stain-negative. With bacterial or fungal meningitis, the CSF lactic acid is elevated, while it is generally normal (normal CSF lactic acid less than 35 mg/dL) with viral infections [51]. Seizures alone generally do not cause abnormalities in the CSF, so abnormal findings on CSF should not automatically be attributed to a seizure [52].

Laboratory studies

Laboratory studies other than CSF include: complete blood cell count (CBC), glucose, electrolytes, serum urea nitrogen (BUN,) creatinine, and blood cultures. The white blood cell (WBC) generally is elevated, and the differential usually has a leftward shift, although patients at the extremes of age (geriatric patients, infants) and the immunosuppressed may have a normal or depressed WBC. The serum glucose is useful to compare with the CSF glucose (CSF/blood glucose ratio). Renal function tests (BUN, creatinine) are useful as indicators of renal perfusion/function and when dosing medications. Electrolyte abnormalities (especially hyponatremia), dehydration, and SIADH may occur in meningitis. Blood cultures may be positive when the CSF is negative, so blood cultures are recommended in all patients who have suspected bacterial meningitis.

A chest radiograph can be valuable in identifying comorbidity (such as heart failure) and may detect a pneumonia, which could suggest a causative organism. About half of patients who have pneumococcal meningitis have pneumonia on radiograph. The urinalysis may reveal a urinary tract infection that led to bacteremia and meningitis, as well as yielding information

on the patient's state of hydration and renal function. In seriously ill patients, urine output should be monitored. An EKG may assist in diagnosing comorbidity and complications from heart failure to septic shock with cardiac dysfunction and dysrhythmias. Other studies, such as an arterial blood gas, an electroencephalogram (EEG), or echocardiogram, depend on the patient's clinical presentation.

Empiric antibiotic therapy

Empiric antibiotic therapy with a broad-spectrum antibiotic that can rapidly enter the subarachnoid space is administered when the specific etiologic agent is unknown. When the exact organism cannot be identified on a Gram's stain smear of CSF, empiric therapy based on the most likely pathogen is given. The likelihood of a given pathogen is determined from clinical clues, such as the patient's age, comorbidity, immunologic status, and the history/physical examination (see Table 2). For example, based on the likely pathogen, what are the empiric antibiotics for meningitis in: a febrile military recruit who has a petechial rash, an elderly confused febrile patient who has a recent urinary tract infection, an HIV patient, or a febrile newborn (see Table 2)?

Most empiric therapy regimens include a third- or fourth-generation cephalosporin plus vancomycin [53,54]. Ampicillin is added in special situations where *Listeria* may be a pathogen (such as the elderly, those who have impaired immunity including patients who have HIV, and newborns). Meropenem is an alternative drug for the cephalosporins, while trimethoprim-sulfamethoxazole is an alternative drug for ampicillin (excluding newborns). If a cephalosporin cannot be administered (for example, with a true allergy), alternative antibiotics are a carbapenem (eg, meropenem) or chloramphenicol plus vancomycin (see Table 2).

Vancomycin penetration into the CNS is mainly dependent upon meningeal inflammation. Dexamethasone, probably because it decreases meningeal inflammation, significantly lowers therapeutic drug levels in the CSF [55,56], which has led to clinical treatment failures in adults [57]. Thus, a concern has been raised regarding vancomycin efficacy when given with dexamethasone, so some recommend adding rifampin whenever there is concurrent administration of vancomycin and dexamethasone.

Rifampin has good CSF penetration and *in vitro* activity against many meningeal pathogens, but when used alone, resistance develops quickly. Therefore, rifampin must be used in combination with other antimicrobial drugs [58]. When dexamethasone is given in the treatment of bacterial meningitis, rifampin generally also is given along with other antimicrobial drugs [58]. This is because of studies indicating dexamethasone is associated with a higher therapeutic failure rates and may decrease the CSF levels of various antibiotics, such as vancomycin (see Tables 2 and 4, and the adjuvant therapy section) [57,58].

Unfortunately, in the emergency department, the specific bacterial pathogen is generally unknown, so empiric therapy is the rule. The CSF Gram's stain, however, may yield an important early clue to the specific pathogen before the CSF culture results are back. The likely pathogen based on the Gram's stain and the current antibiotics of choice are listed in Table 3.

Other empiric therapy for aseptic (nonbacterial) infectious meningitis includes: acyclovir for herpes (HSV-1) meningoencephalitis (usually the CSF shows lymphocytic pleocytosis, increased number of erythrocytes, elevated protein, normal glucose), and amphotericin B and flucytosine for fungal meningitis (eg, cryptococcal meningoencephalitis).

Antibiotic resistance

Antibiotic sensitivity testing of the causative bacterial pathogen is key, so that antibiotic coverage can be tailored to provide optimal narrow coverage. Antibiotic sensitivity testing is also critical because of increasing pathogen resistance to various antibiotics.

There has been an increase in infections with antibiotic resistant strains in recent years. With the pneumococci, resistance to penicillin has occurred. In one series of patients who had pneumococcal meningitis, 25% of isolates were resistant to penicillin, and 9% were resistant to cefotaxime [59]. In other reports, up to about one-third of pneumococci tested had intermediate (14% to 22%) or high resistance (3% to 14%) to penicillin [4,60,61].

With the pneumococci, resistance to cephalosporins is starting to emerge. In the United States, in the prevaccine era, over 40% of *S pneumoniae* isolates were nonsusceptible to penicillin G, and about half of these isolates also were nonsusceptible to a third-generation cephalosporin (ceftriaxone or cefotaxime). These penicillin-nonsusceptible strains also have increased rates of resistance to trimethoprim-sulfamethoxazole, clindamycin, and particularly high resistance to macrolides (greater than 50% resistance). Increased rates of macrolide resistance (greater than 10% resistance) also are noted with the penicillin-susceptible strains [8]. Another study found *S pneumoniae* isolates had 0% to 45% penicillin resistance, 18% to 33% clindamycin resistance, and 33 to 50% erythromycin resistance. This study also noted that antibiotic resistance for *S pyogenes* isolates was 14% to 34% for erythromycin and 0% to 28% for clindamycin [62]. *S pneumoniae* organisms that cause meningitis remain susceptible to vancomycin and moxifloxacin, although decreased susceptibility to penicillin and cefotaxime was noted in some isolates [63].

Many experts recommend adding vancomycin to a third-generation cephalosporin when treating pneumococcal meningitis until the sensitivities are known [53,54,64]. Because of its poor penetration of the blood-brain barrier, monotherapy with vancomycin is not recommended [57].

Resistance to ampicillin has been noted in up to 39% of *H influenzae* isolates, and 36% produced a β -lactamase [65]. Fortunately, so far, *H influenzae* resistance to third-generation cephalosporins (eg, ceftriaxone or cefotaxime)

is rare [66]. Likewise, meningococcus is sensitive to the cephalosporins, and there have been few reports of β -lactamase producing meningococcus in the United States.

Increased resistance to antibiotics has been noted with staphylococci (MRSA), enterococci (vancomycin-resistant enterococci, VRE), pneumococcus (penicillin- and cephalosporin-resistant pneumococci), and *Haemophilus* (ampicillin resistance). Resistance mechanisms to β -lactams, which consists mainly of extended-spectrum β -lactamase (ESBL), have been reported in gram-negative organisms: *Pseudomonas aeruginosa*, *E coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*. The emergence of ESBL-producing pathogens may decrease the effectiveness of the cephalosporins against gram-negative bacilli [67,68].

Some experts are recommending that serious methicillin-susceptible *Staphylococcus aureus* (MSSA) infections including meningitis be treated with a β -lactamase resistant (BLR) β -lactam antimicrobial agent, such as oxacillin or nafcillin rather than vancomycin. This is because most *Staphylococcus aureus* strains produce β -lactamase enzymes and are resistant to penicillin and ampicillin. Oxacillin and nafcillin have been recommended for MSSA infections to decrease the possible emergence of vancomycin- or clindamycin-resistant strains. For MRSA, vancomycin is the drug of choice, with some experts adding rifampin or gentamicin [69].

Recently, polymicrobial infections and multiantibiotic resistance also have been identified [21,70]. Because the sensitivities to antibiotics are evolving, new antimicrobials are being developed, and the incidence of various pathogens as causative agents of meningitis is changing, the physician should be aware of and consider local/hospital trends regarding antibiotics, their sensitivities, and pathogens when considering antibiotic therapy for acute bacterial meningitis. The recommendations in Tables 2 and 3 are based on current reports; they may need modifications in the future as sensitivities/pathogens evolve.

Adjunctive dexamethasone therapy

Clinical trials

The role of corticosteroids in acute bacterial meningitis is controversial. The best answer to whether corticosteroids should be used in acute bacterial meningitis is “it depends” or “sometimes.” The likely bacterial pathogen and the patient’s age are key considerations in determining whether corticosteroids (specifically, dexamethasone) are given. The time of administration of dexamethasone is also critical.

The pathogenesis of bacterial meningitis and animal studies support the use of corticosteroids [71,72], while the results of clinical trials are mixed [73–80]. Animal studies of corticosteroids in experimental pneumococcal meningitis resulted in decreased cerebral edema, lowered CSF pressure, and decreased CSF lactate levels [72]. Bactericidal antibiotics given to

patients who have septic meningitis results in the killing of the invading bacteria and the release of bacterial cell wall components, which in turn leads to the production of proinflammatory cytokines, such as IL-1 and TNF by macrophages and microglial cells in the subarachnoid space. Dexamethasone has several anti-inflammatory effects including: inhibition of the synthesis of IL-1 and TNF, and stabilizing the blood–brain barrier.

The reason why it is recommended that dexamethasone be given 15 to 20 minutes before administering antibiotics is that dexamethasone inhibits the release of IL-1, TNF, and other inflammatory cytokines by microglia and macrophages only if it is given before these cells are activated by the endotoxins released from the killing of bacteria. Once these cells have been induced to produce these inflammatory cytokines, dexamethasone does not affect cytokine (IL-1, TNF, others) production by the body's cells (macrophages, glial cells, and others) [48,81].

The findings regarding corticosteroids as adjunctive therapy in acute bacterial meningitis from various clinical trials are mixed and somewhat dependent on the bacterial pathogen and on the patient's age (pediatric patients versus adults). Two randomized double-blind, placebo-controlled studies of childhood bacterial meningitis documented a lower incidence of long-term hearing loss in infants/children given dexamethasone and a cephalosporin antibiotic versus those given just the antibiotic [73]. A meta-analysis of 11 studies of dexamethasone in infants/children who had bacterial meningitis found:

- With *H influenzae* meningitis, dexamethasone significantly decreased severe hearing loss irrespective of when it was given (eg, before or after antibiotic therapy)
- With pneumococcal meningitis, dexamethasone was effective in reducing hearing loss only if given before antibiotics
- For all pathogens combined, the only benefit of dexamethasone was a decrease in hearing loss with no protection against any other neurologic deficits [79]

Several other studies of dexamethasone in childhood bacterial meningitis noted similar results [74–76].

In adults who had bacterial meningitis, a randomized placebo-controlled, double-blind trial that compared dexamethasone versus placebo in addition to antibiotics found that dexamethasone decreased the incidence of unfavorable outcomes including death [77]. The reduction in unfavorable outcomes was 25% to 15% ($P = .03$) and in mortality was 15% to 7% ($P = .04$). The absolute risk reduction was 10%. Dexamethasone was given either 15 minutes before or simultaneously with antibiotics and continued every 6 hours for 4 days. Benefits were present with pneumococcal meningitis but not with any other bacterial pathogen (including *N meningitidis*) [77].

A study of neonatal (age less than or equal to 30 days) meningitis in which *K pneumoniae* was the main bacterial pathogen showed negative

results with dexamethasone [80]. Therefore, dexamethasone is not recommended in this age group.

Currently, adjunctive dexamethasone is recommended in infants/children older than 6 weeks with *H influenzae* B meningitis and is considered in infants/children older than 6 weeks who have pneumococcal meningitis, and in adults who have proven or suspected pneumococcal meningitis [58]. According to the Red Book, dexamethasone may be beneficial for the treatment of *H influenzae* B meningitis in infants and children if given before or concurrently with the first dose of antibiotics [7]. The dexamethasone dose in children and adults is 0.15 mg/kg per dose intravenously every 6 hours for 2 to 4 days, with the first dose given before or concurrently with the first dose of antibiotics.

Empiric adjunctive dexamethasone therapy?

Because the organism usually is not known definitively when the patient who has bacterial meningitis is in the emergency department, empiric antibiotics are frequently the rule. Similarly, the question of empiric administration of dexamethasone in the emergency department could be argued, with some advocates for [82] and some against [83].

Several concerns regarding the use of dexamethasone have been raised. There is also the logistical necessity of administering dexamethasone either just before or at the same time as the antibiotic. There is concern that clinical signs and symptoms may be masked in the presence of dexamethasone, making it difficult to evaluate the adequacy or inadequacy of the response to therapy [83]. Gastrointestinal (GI) bleeding has been noted to occur in the 1% to 2% of patients with bacterial meningitis who received dexamethasone [83]. A decreased learning ability and decreased spatial memory, and increased hippocampal neuronal apoptosis were noted in two recent animal studies [84,85].

First, the narrow window of opportunity for drug administration should not be an issue if prospectively discussed with nursing/pharmacy/other involved hospital or department personnel, and a mechanism is put into place for rapidly obtaining and giving the medications.

Next, a significant difference in the incidence of GI bleeding between those receiving dexamethasone and those not receiving dexamethasone has not been noted, although the incidence of GI bleeding may be too small (1% to 2%) to detect a difference. One study in adults noted a higher incidence of GI bleeding in the placebo group (5 of 144 patients = 0.03%) versus the dexamethasone group (2 of 157 patients = .01%) [77], while a study in children that monitored for possible adverse effects found no abnormalities [74]. A systematic review of steroids in adults who had acute bacterial meningitis found that adverse events were distributed equally between both groups (eg, steroids versus nonsteroids). They noted

a significant decrease in mortality ($P = .002$) and in neurologic sequelae ($P = .05$) with steroid treatment. They recommended “routine steroid therapy with the first dose of antibiotics” in most adults who had community-acquired bacterial meningitis [82].

An increased number of the therapeutic failures has been noted in some studies when dexamethasone is given with various antibiotics [57]. The therapeutic failures occurring with concomitant dexamethasone administration are a concern. This may, at least in part, be related to a decreased CSF level of antibiotics. The mechanism for this is not entirely clear. It may be that antibiotic therapy failures occur because dexamethasone impairs antibiotic penetration across the blood–brain barrier [57,86]. Another possibility is that dexamethasone decreases the level of antibiotic (eg, vancomycin, ceftriaxone, and rifampin) in the CSF [83]. Several studies did demonstrate decreased level of antibiotics in the CSF when dexamethasone was given in several animal studies [55,56,86], and in a study of adults who had bacterial meningitis receiving vancomycin [57]. Another animal study noted therapeutic failures when dexamethasone was given with ceftriaxone, although the antibiotic pharmacokinetics, including CSF drug levels, were not different between the animals receiving dexamethasone or not receiving dexamethasone.

Negative effects of dexamethasone were reported in a study of neonatal bacterial meningitis. Therefore, coadministration of dexamethasone with antibiotics is contraindicated in neonatal bacterial meningitis.

Furthermore, the two recent studies using different animal models demonstrating decreased learning ability and impaired memory along with molecular signs of neuronal damage are particularly concerning [84,85].

The conclusion is that the various risks and benefits of administering dexamethasone in bacterial meningitis need to be determined on an individual basis until additional evidence/research is forthcoming.

Differential diagnosis

The differential diagnosis of bacterial meningitis includes all the causes of aseptic meningitis, both the infections (mostly viral but also partially treated bacterial meningitis and focal CNS infections) and noninfectious causes: neoplasm, drugs, and systemic diseases. The infectious causes of aseptic meningitis include: partially treated bacterial, viral, fungal, tuberculosis, Lyme disease, syphilis, and meningitis caused by atypical and nonpyogenic bacteria. Meningeal irritation also can be caused by adjacent bacterial infections (such as a brain abscess, subdural empyema or epidural abscess) (see Fig. 1). A CT scan can be valuable in detecting these adjacent infections. Neoplastic disease of the meninges (leptomeningeal carcinomatosis) also can cause meningeal signs and symptoms.

Aseptic meningitis is differentiated into infectious and noninfectious causes. Viral meningitis accounts for most cases of aseptic meningitis. Nonviral infectious causes of aseptic meningitis include the following: partially

treated bacterial meningitis, atypical and nonpyogenic bacterial meningitis, meningitis caused by adjacent pyogenic infections, tuberculous meningitis, syphilitic meningitis, fungal meningitis, and meningitis associated with Lyme disease (see Fig. 2).

Etiologic agents of viral meningitis include: enteroviruses (most common cause: echoviruses, but also coxsackie, and infrequently polio viruses), adenoviruses, herpes simplex, varicella-zoster virus, influenza types A and B, HIV, lymphocytic choriomeningitis virus, and Epstein-Barr virus.

A multicenter study of 3295 children admitted to the hospital with CSF pleocytosis who were treated with parenteral antibiotics noted 3.7% of the patients had bacterial meningitis, and 96.3% had aseptic meningitis [87]. A bacterial meningitis scoring system was devised using the following variables:

- Positive CSF Gram's stain
- CSF absolute neutrophil count greater than or equal to 1000 cells/ μ L
- CSF protein greater than 80 mg/d
- Peripheral blood absolute neutrophil count greater than or equal to 10,000 cells/ μ L
- A history of seizure before or at the time of presentation. The risk of bacterial meningitis was very low (0.1%) in patients with none of these criteria [87]

Atypical bacteria that can cause meningitis include: tuberculosis, *Nocardia*, *Treponema pallidum* (syphilis) and *Borrelia burgdorferi* (Lyme disease). Fungal etiologies for meningitis are in two categories: those that cause disease in immunocompromised patients (such as HIV patients) and those endemic to certain geographic locales. Fungi associated with a specific geographic region are: *Histoplasma*, *Coccidioides*, and *Blastomyces*. Organisms causing meningitis in compromised hosts include

- Fungi: *Candida*, *Cryptococcus*, and *Aspergillus*
- Parasites: *Toxoplasma gondii* and cysticercosis (pork tapeworm)
- Certain viruses

There are reports of these pathogens causing meningitis in immunocompetent individuals as well.

Focal CNS infections that are in the differential for bacterial meningitis include: brain abscess and parameningeal CNS infections (subdural empyema, epidural abscess, spinal abscess) (see Fig. 4). A CT scan can be valuable in detecting these adjacent infections.

Noninfectious etiologies of aseptic meningitis can be grouped into four categories: (1) drugs, (2) carcinomatous meningitis or leptomeningeal carcinomatous (metastases to the meninges), (3) associated systemic diseases, and (4) inflammatory conditions that primarily affect the CNS. The systemic diseases that can cause aseptic noninfectious meningitis are generally an autoimmune hypersensitivity disease and include: systemic lupus erythematosus, sarcoidosis, Behcet's syndrome, Wegner's granulomatosis, and lead

poisoning. Noninfectious CNS inflammatory processes include: granulomatous cerebral vasculitis and chemical meningitis following myelography (with water-soluble nonionic contrast), inflammation following neurosurgery, and inflammation after spinal or epidural anesthesia.

Neoplastic disease can cause meningitis with tumors that leak inflammatory materials into the CSF, with primary CNS tumors, or with metastatic carcinomatous meningitis. Some of the drugs that have been associated with drug hypersensitivity meningitis are: nonsteroidal anti-inflammatory drugs, trimethoprim-sulfamethoxazole, and OKT3 (an antibody against T cells).

Prognosis/sequelae

The annual mortality for bacterial meningitis in the United States was about 6000 prior to the routine use of pneumococcal conjugate vaccine, with about two-thirds of all cases occurring in pediatric patients less than or equal to 18 years of age [59]. A recent report notes half of all acute bacterial cases are in children and infants [4]. In the United States, the annual mortality rate for bacterial meningitis was less than 1000 (708 deaths) reported in 2003 [88]. Although the overall incidence of bacterial meningitis in the United States is decreasing, especially in pediatric patients, the proportion of patients in certain high-risk groups (such as geriatric patients) is increasing [4,34]. Whether this changing age-related trend continues and if it is related to the use of the newer vaccines and widespread immunization and/or other factors including an aging population with higher acuity and increased comorbidity (including immunosuppressed patients) remain to be determined.

The case fatality rates for bacterial meningitis are reported as 4% to 10% in the pediatric population [16], 25% in adults [1], and up to 50% for geriatric patients [34]. Meningitis case fatality rates are estimated at 3% to 7% for *H influenzae* or *N meningitidis* or group B streptococci, 20% to 25% for *S pneumoniae*, and up to 30% to 40% for *L monocytogenes* [4,8,19,81]. Higher fatality rates occur in patients at the extremes of age (the elderly and the infant, especially the neonate) [16,17,32,34,89].

The prognosis varies depending on multiple factors: age, presence of comorbidity, responsible pathogen, and the degree of severity at presentation/neurologic presentation on admission. The severity or degree of neurologic impairment at the time of presentation is a prognostic factor [81,89]. The mortality rate rises with the following clinical parameters:

- Decreased level of consciousness at admission
- Signs of increased intracranial pressure
- Seizures within 24 hours of admission
- Age (older than 50 years or infancy)
- Comorbidity
- Need for mechanical ventilation
- Delay in initiation of treatment [81]

A recent study of community-acquired acute adult bacterial meningitis (51% *S pneumoniae*, 37% *N meningitidis*) noted risk factors associated with a poor prognosis were: advanced age, presence of osteitis or sinusitis, low Glasgow Coma Scale (GCS) on admission, tachycardia, absence of rash, thrombocytopenia, elevated erythrocyte sedimentation rate, low CSF cell count, and positive blood culture [11].

The incidence of sequelae varies with the pathogen, with about 25% of survivors having moderate or severe sequelae [81]. In one report, 40% of survivors had sequelae, including hearing loss and other neurologic sequelae [89], while others cite 60% morbidity [48,59]. Sequelae of bacterial meningitis [90] include: sensorineural hearing loss (particularly common in children who have *H influenzae* infection), decreased intellectual/cognitive function, impaired memory, dizziness, gait disturbances, focal neurologic deficits including paralysis and blindness, hydrocephalus, subdural effusion, and seizures (Box 2).

Chemoprophylaxis

The incidence of transmission of *Meningococcus* among household contacts is about 5%. According to one estimate, the risk for developing meningitis after exposure to a patient with meningococcal meningitis is 500 to 800 times greater than in the general population [91]. Therefore, chemoprophylaxis is indicated for high-risk contacts of patients who have meningitis. Because up to one-third of secondary cases of meningococcal disease develop within 2 to 5 days of illness in the index (initial) case, prompt chemoprophylaxis is indicated.

Individuals considered high-risk who need prophylaxis are: household or close contacts (individuals who slept and ate in the same household with the patient) and intimate nonhousehold contacts who have had mucosal exposure to the patient's secretions (such as a boyfriend or girlfriend). Individuals who have had direct exposure to the patient's secretions through shared utensils or toothbrushes, kissing, and school/daycare contacts in the prior seven days should receive chemoprophylaxis.

Not all health care workers need chemoprophylaxis. Health care workers who are at increased risk and require chemoprophylaxis are those who have had direct mucosal contact with the patient's secretions, as for example, during mouth-to-mouth resuscitation, endotracheal intubation, or suctioning of the airway.

Chemoprophylaxis for meningococcal meningitis is provided by rifampin given in a 600 mg dose for adults, 10 mg/kg every dose for children older than 1 month, 5 mg/kg every dose for neonates (age less than or equal to 30 days) orally every 12 hours for a total of four doses. Those receiving chemoprophylaxis should be counseled to watch for fever, rash, or any other meningial signs/symptoms. They should be hospitalized with appropriate intravenous antibiotics if signs/symptoms of active meningococcal disease

develop, because rifampin alone is not effective against invasive meningococcal disease. Alternative single-dose chemoprophylaxis regimens are ciprofloxacin 500 mg by mouth for adults and ceftriaxone 250 mg intramuscularly (age greater than or equal to 12 years) or 125 mg intramuscularly (age less than 12 years).

Rifampin chemoprophylaxis for *H influenzae* meningitis is warranted for nonpregnant household contacts if there are young children (age younger than 4 years) in the household. The by mouth dose is 600 mg for adults and 20 mg/kg for children once daily for 4 days. Chemoprophylaxis is not given for pneumococcal meningitis.

Immunoprophylaxis

A vaccine against meningococci has been used to immunize adults. Unfortunately, this vaccine does not confer protection in children younger than 2 years because of a poor antibody response in this age group. This vaccine is based the polysaccharide capsule but only confers immunity against four serogroups of meningococci (A, C, Y, W-135). The quadrivalent vaccine has been used for routine immunization by the United States military since the 1980s, for travelers to countries where meningococcal disease is endemic, during meningococcal epidemics, and for elective immunization of college freshman. Currently, there is no licensed vaccine against serogroup β meningococci. The quadrivalent meningococcal conjugate vaccine (MCV4) is recommended:

- For 2- to 10-year old children at increased risk for meningococcal disease, including patients who have asplenia (functional or anatomic), HIV infection, and terminal complement deficiencies
- For travelers to areas where *N meningitidis* is hyperendemic or endemic
- During outbreaks caused by a serotype included in the vaccine [92–94]

A quadrivalent meningococcal conjugate vaccine was approved by the FDA in 2005 for use in adolescents and adults 11 to 55 years of age [93,94].

Despite there being a large number of serotypes of pneumococci, effective pneumococcal vaccines have been developed, because most clinical disease is caused by relatively few serotypes of pneumococci. The pneumococcal vaccines have had a positive effect in decreasing the incidence of all types of invasive pneumococcal diseases including meningitis [10].

Several pneumococcal vaccines are available. A single dose of a polyvalent vaccine effective against 23 serotypes of pneumococci is recommended for elderly or debilitated patients, especially those who have pulmonary disease, sickle cell disease, and those who have impaired splenic function such as patients after splenectomy. Childhood immunization recommendations include a heptavalent conjugated pneumococcal vaccine that is 90% protective with a low incidence of adverse reactions [8].

The HIB vaccine, which confers immunity against *H influenzae* type B, is also part of the childhood immunization recommendation and has been very effective in decreasing the incidence of all types of disease caused by *H influenzae* type B, from pneumonia to meningitis [7].

Summary

Despite advances in medical care including antibiotics and vaccines, meningitis still has a high morbidity and mortality rate, especially in certain high-risk patients. Early diagnosis with the administration of appropriate antibiotics remains the key element of management.

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