

Meningitis

Douglas Swanson, MD*

*University of Missouri, Kansas City; Division of Infectious Diseases, Children's Mercy Hospitals and Clinics, Kansas City, MO.

Educational Gaps

1. The epidemiology of bacterial meningitis in children is changing.
2. Routine neuroimaging is not necessary for the initial medical evaluation of children with suspected bacterial meningitis who do not have clinical signs of brain herniation.

Objectives After completing this article, the reader should be able to:

1. Describe the causes, clinical manifestations, and general approach to the diagnosis, treatment, and prevention of the different types of meningitis in children of various ages.
2. Understand the indications for neuroimaging, adjunctive corticosteroids, and repeat lumbar puncture in children with bacterial meningitis.
3. Recognize the complications and sequelae of bacterial meningitis in children.

INTRODUCTION

Bacterial meningitis is a severe, life-threatening infection of the central nervous system that requires immediate medical attention. Even with appropriate treatment, morbidity and mortality can be substantial. It is essential for clinicians to recognize the clinical signs and symptoms of meningitis and understand its management and prevention. The focus of this review is acute bacterial meningitis in children, including its causes in different age groups, epidemiology, clinical features, diagnosis, treatment, and sequelae.

ETIOLOGY AND EPIDEMIOLOGY

Acute Bacterial Meningitis

Acute bacterial meningitis has a relatively rapid onset of symptoms, and routine laboratory techniques can usually identify the pathogen. The most common causes have been *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* type b (Hib), group B *Streptococcus* (GBS), and *Listeria monocytogenes* (Table 1). (1)(2)(3) These organisms caused more than 80% of acute bacterial meningitis in children during the 1970s and 1980s. In 1990, conjugate Hib vaccine was introduced. It has almost eliminated Hib meningitis in countries

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TABLE 1. **Estimated Proportions of Organisms Causing Bacterial Meningitis According to Age**

BACTERIA	AGE				
	<1 MONTH [#]	1–<3 MONTHS ⁺	>3–35 MONTHS ⁺	3–9 YEARS ⁺	10–18 YEARS ⁺
<i>Streptococcus pneumoniae</i>	1%–4%	14%	45%	47%	21%
<i>Neisseria meningitidis</i>	1%–3%	12%	34%	32%	55%
Group B <i>Streptococcus</i> *	50%–60%	39%	11%	5%	8%
<i>Listeria monocytogenes</i>	2%–7%	-	-	-	-
<i>Escherichia coli</i>	20%–30%	-	-	-	-
Other bacteria [§]	4%–12%	35%	10%	16%	16%

**Streptococcus agalactiae*.

[#]Data from Gaschignard et al (1) and Heath et al (2).

⁺Data from Nigrovic et al (3).

[§]For children ≥1 month of age, this includes *L. monocytogenes* and *E. coli*. In those 1 to <3 months of group, 32% of other bacteria are Gram-negative bacilli.

where it has been implemented and decreased the overall incidence of acute bacterial meningitis by 55%. Implementation of the heptavalent pneumococcal conjugate vaccine (PCV7) in 2000 resulted in a 59% reduction in rates of pneumococcal meningitis in children younger than 2 years of age. (4) Through herd immunity, the vaccine also protected nonimmunized children and adults. From 1998 to 2007, the overall incidence of bacterial meningitis decreased by 31% from 2.00 cases per 100,000 population to 1.38 cases per 100,000 population. (5) However, mortality from bacterial meningitis remained substantial, and the case fatality rate did not change. In addition, rates of pneumococcal meningitis from non-PCV7–serotype strains began to increase, including cases of meningitis due to drug-resistant strains, such as serotype 19A. (6) In 2010, PCV13 was introduced to respond to the emerging invasive strains of pneumococcus. Currently, *S. pneumoniae* remains the most common cause of acute bacterial meningitis for children older than 1 month.

In developed countries, conjugated vaccines have decreased the incidence of bacterial meningitis in all age groups except children younger than 2 months. The success of the vaccines has shifted the median age of meningitis disease from younger than 5 years of age to 42 years. (5) Nonetheless, the highest incidence of bacterial meningitis remains among children younger than 2 months of age, primarily because the pathogens responsible for meningitis in young infants differ from those causing infection in older children (Table 1). GBS causes 50% to 60% of bacterial meningitis cases among neonates, *Escherichia coli* about 20% of cases, and other Gram-negative bacilli another 10%. (1)(2) These organisms are usually acquired from the maternal genitourinary tract.

Since 1996, the practice of maternal GBS screening and use of intrapartum antimicrobials has become routine in developed countries, resulting in an 86% reduction in early-onset GBS disease in the United States. (7) However, the incidence of late-onset disease has not fallen. Risk factors for acute bacterial meningitis in neonates and older children are highlighted in Table 2. (8)(9)(10)

Aseptic Meningitis

Aseptic meningitis is characterized by clinical signs and symptoms of meningitis without evidence of a bacterial cause by usual laboratory testing methods. Some bacteria that do not grow in routine culture, such as *Mycobacterium tuberculosis* and *Borrelia burgdorferi*, can cause aseptic meningitis. Aseptic meningitis has many infectious and non-infectious causes. The most common are listed in Table 3.

The incidence is uncertain because aseptic meningitis is not a reportable disease. A birth cohort study from Finland found the annual incidence to be 28 per 100,000 persons, with the highest rates in children younger than 4 years of age. (11) Enteroviruses and parechoviruses account for most of all known cases. In temperate climates, infections with these viruses typically occur in the summer and fall seasons. Arboviruses encompass a vast number of viruses from different biologic families that are transmitted by arthropods, especially mosquitoes. The most commonly reported arboviruses causing aseptic meningitis infections in the United States are West Nile virus and La Crosse virus.

Noninfectious causes include medications, autoimmune and auto-inflammatory diseases, and neoplasms. Herpes simplex virus (HSV) is a cause of life-threatening

TABLE 2. Risk Factors for Meningitis (8)(9)(10)

RISK FACTORS IN NEONATES	RISK FACTORS IN CHILDREN
• Preterm birth	• Asplenia (anatomic or functional)
• Low birthweight (<2,500 g)	• Primary immunodeficiency
• Chorioamnionitis	• Human immunodeficiency virus infection
• Endometritis	• Sickle cell anemia
• Maternal Group B <i>Streptococcus</i> colonization	• Cochlear implant
• Prolonged duration of intrauterine monitoring (>12 hrs)	• Cerebrospinal fluid leak
• Prolonged rupture of membranes	• Recent upper respiratory tract infection
• Traumatic delivery	• Day care attendance
• Fetal hypoxia	• Lack of breastfeeding
• Galactosemia	• Exposure to a case of meningococcal or <i>Haemophilus influenzae</i> type b meningitis
• Urinary tract abnormalities	• Penetrating head trauma
• Dermal sinus tract of the spine	• Dermal sinus tract of the spine
	• Travel to an area with endemic meningococcal disease
	• Lack of immunizations

meningoencephalitis in neonates. It is beyond the scope of this review to discuss the clinical features and management of HSV meningoencephalitis.

Chronic Meningitis

Chronic meningitis involves ongoing signs and symptoms of meningitis for 4 or more weeks without clinical improvement. It has many infectious and noninfectious causes (Table 4), each with its own epidemiology. The overall incidence of chronic meningitis is unknown due to limitations in data collection. The epidemiology differs according to the causative agent.

CLINICAL MANIFESTATIONS

History

Neonate and Infant. The clinical manifestations of neonatal bacterial meningitis are generally nonspecific and usually comprise a constellation of signs and symptoms. Although

TABLE 3. Primary Causes of Aseptic Meningitis

COMMON INFECTIOUS CAUSES
• Enteroviruses and parechoviruses
• Arboviruses (especially West Nile virus and La Crosse virus)
• <i>Borrelia burgdorferi</i>
UNCOMMON INFECTIOUS CAUSES
• Herpes simplex virus 2
• Varicella-zoster virus
• Mumps virus
• Human immunodeficiency virus
• <i>Mycobacterium tuberculosis</i>
• <i>Mycoplasma pneumoniae</i>
• Fungi (especially <i>Cryptococcus</i> sp)
NONINFECTIOUS CAUSES
• Medications (eg, nonsteroidal anti-inflammatory drugs, trimethoprim-sulfamethoxazole, isoniazid, intravenous immunoglobulin)
• Autoimmune and auto-inflammatory diseases (eg, sarcoidosis, systemic lupus erythematosus)
• Neoplasm

temperature instability is a common feature, with either fever or hypothermia occurring in about 60% of newborns who have bacterial meningitis, normothermia is not unusual. (12) There is often a report of vomiting and poor feeding. Parents frequently state that their infant is fussy, inconsolable, sleepy, weak, or jittery. Seizures occur in 20% to 50% of infants with the presentation of illness. Neck stiffness is uncommon in neonates. Parents may report that the baby has a “knot on its head” to describe the presence of a bulging fontanelle. Important information to ascertain includes risk factors for meningitis (Table 2), the birth history, trauma, congenital anomalies, and maternal history of sexually transmitted infections (recognizing that there is often no history suggestive of maternal genital HSV in infants with HSV disease).

Older Child. The clinical presentation of meningitis in older children often occurs over a few days and may include a progressive history of fever, headache, lethargy, irritability, confusion, photophobia, nausea, vomiting, back pain, and stiff neck. (13) Sometimes the presenting signs and symptoms are severe and sudden, occurring within a period of hours. About 20% of affected children have a seizure before diagnosis, and about 25% have a seizure during the first few days of hospitalization. The seizures are frequently complex

TABLE 4. **Primary Causes of Chronic Meningitis**

COMMON INFECTIOUS CAUSES

- *Mycobacterium tuberculosis*
- *Treponema pallidum*
- *Borrelia burgdorferi*
- *Cryptococcus* sp
- Human immunodeficiency virus

UNCOMMON INFECTIOUS CAUSES

- *Brucella* sp
- *Nocardia* sp
- *Coccidioides immitis*
- *Histoplasma capsulatum*
- *Toxoplasma gondii*
- Lymphocytic choriomeningitis virus

NONINFECTIOUS CAUSES

- Medications (eg, nonsteroidal anti-inflammatory drugs, trimethoprim-sulfamethoxazole, isoniazid)
- Autoimmune and auto-inflammatory diseases (eg, sarcoidosis, systemic lupus erythematosus)
- Neoplasm

and more common with meningitis due to Hib or *S pneumoniae* than *N meningitidis*. Important historical information to obtain includes risk factors for meningitis (Table 2) and recent medications, including use of antibiotics that might interfere with the ability to isolate a pathogen from blood or cerebrospinal fluid (CSF) culture.

Physical Examination

Neonate and Infant. Vital signs and general appearance should be assessed. Affected infants usually do not like to be moved or examined. Neurologic features of meningitis in infants include inconsolable irritability, lethargy, poor tone, and seizures. (12) Nuchal rigidity is uncommon. The anterior fontanelle is usually full but not often bulging. Poor capillary refill and respiratory difficulty with grunting, tachypnea, and nasal flaring are frequent findings. The infant is less active and often seems apathetic and disinterested in its surroundings. Head circumference should be measured daily to monitor for increased intracranial pressure.

Older Child. The child with meningitis is usually irritable or lethargic on physical examination. Vital signs, including pulse oximetry, should be obtained promptly to help evaluate for hypovolemia, shock, and increased intracranial pressure

(ICP). Cushing triad (hypertension, bradycardia, and respiratory depression) is a late finding of increased ICP. Although the following signs of ICP are uncommon, patients should be screened for papilledema, diplopia, and cranial nerve paralysis. (13) The pediatric Glasgow Coma Scale can be a useful tool to monitor the patient's level of consciousness. Children who are obtunded or comatose upon admission have worse outcomes than those who are not.

Nuchal rigidity, a sign of meningeal inflammation, is demonstrated when the child is unable to flex the neck so that it touches the chest, and by the presence of a Kernig or Brudzinski sign. With the child in the supine position, the Kernig sign is present when the hip and knee are flexed at 90 degrees and the leg cannot be passively extended more than 135 degrees or the patient flexes the opposite knee. The Brudzinski sign occurs when the child is in the supine position and passive flexion of the neck causes the legs to bend at the hip and knee.

DIAGNOSTIC EVALUATION

Blood Tests

Two separate blood cultures and a complete blood cell (CBC) count with differential count should be obtained. If not pretreated with antibiotics, 80% to 90% of children with bacterial meningitis have positive blood cultures. The peripheral white blood cell (WBC) count might be high in bacterial meningitis, but it is frequently within normal limits and may be low in neonates. If the CBC count reveals thrombocytopenia or if petechiae or purpura are present on examination, tests for disseminated intravascular coagulation should be obtained. Serum electrolytes, blood urea nitrogen, creatinine, and glucose should be monitored to assess for syndrome of inappropriate antidiuretic hormone (SIADH), manage fluid administration, adjust antimicrobial doses, and compare the CSF-to-blood glucose ratio. Elevated serum procalcitonin and C-reactive protein values are suggestive of bacterial meningitis but cannot reliably discriminate between bacterial and viral meningitis. (14) However, serial C-reactive protein measurements can be an adjunctive tool to monitor the patient's clinical response and screen for potential complications.

Lumbar Puncture

CSF Evaluation. Unless otherwise contraindicated, a lumbar puncture (LP) should be performed on any child suspected of having bacterial meningitis (Figure). (9)(15) Contraindications to LP include increased ICP, coagulopathy, hemodynamic or respiratory instability, or skin infection over the LP site. If contraindications to LP exist, antimicrobial therapy

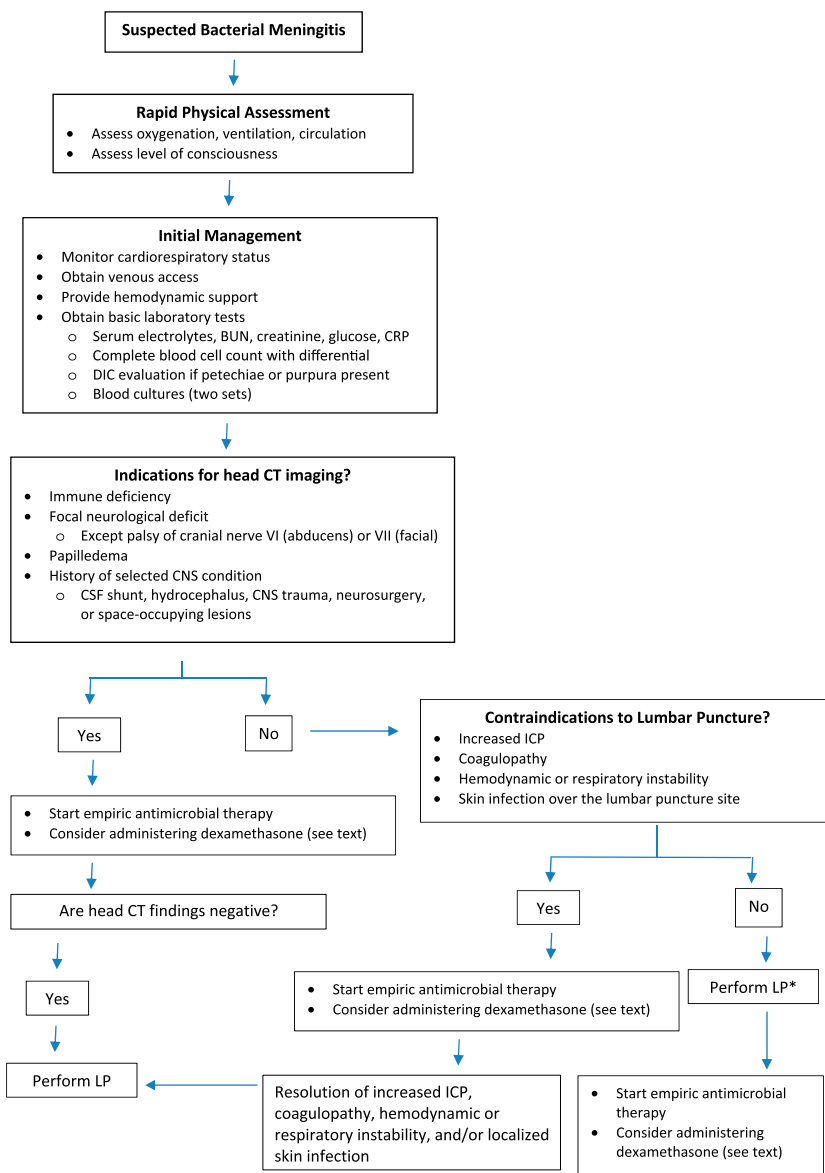


Figure. Algorithm for suspected meningitis. *Do not delay antimicrobial therapy if the lumbar puncture cannot be accomplished. BUN=blood urea nitrogen, CNS=central nervous system, CRP=C-reactive protein, CSF=cerebrospinal fluid, CT=computed tomography, DIC=disseminated intravascular coagulation, ICP=intracranial pressure, LP=lumbar puncture. Adapted from Mann and Jackson (9) and Tunkel et al (15).

should not be delayed; blood cultures should be obtained and empiric antibiotics started promptly. When obtained, CSF should be evaluated for CBC count with differential count, glucose and protein concentrations, Gram stain, and bacterial culture. If the patient has not been pretreated with antibiotics, the typical CSF findings in bacterial meningitis include a neutrophilic pleocytosis (often $>1,000$ WBCs/ μ L), elevated protein, low glucose, and a positive culture for a pathogenic bacterium. However, in rare instances, no or few CSF WBCs may be seen very early in the course of infection. Because of possible misinterpretation of CSF Gram stains, antimicrobial therapy should not be narrowed based on the Gram stain result; empiric broad-spectrum antibiotics should be continued until culture results are known. Table 5 provides the normal

CSF parameters based on age and usual CSF findings based on selected microbial cause of meningitis.

Traumatic Lumbar Puncture. Bleeding into the CSF from a traumatic LP can make it difficult to interpret the CSF cell count. One formula estimates the expected number of CSF WBCs from a traumatic LP by comparing the ratio of (expected CSF WBCs)/(actual CSF red blood cells [RBCs]) to (blood WBCs)/(blood RBCs). The calculated number of expected CSF WBCs is then subtracted from the actual number of CSF WBCs to determine if there is a CSF pleocytosis. A simpler correction method is to subtract 1 to 2 CSF WBCs for every 1,000 CSF RBCs/ mm^3 . However, these formulas are inexact, and clinicians must be cautious when interpreting the results. Empiric antibiotics should be administered while

awaiting culture results for children with a traumatic LP. Furthermore, if the CSF is grossly bloody, attempting a repeat LP is a prudent course.

Antimicrobial Pretreatment. Children with suspected meningitis sometimes receive oral or parenteral antibiotics before a lumbar puncture is performed. CSF cultures remain the reference standard for diagnosing bacterial meningitis, but antibiotic pretreatment decreases the likelihood of obtaining a positive CSF culture. In one study of 128 cases of pediatric meningitis, CSF cultures were negative in 29% of children who were pretreated with oral antibiotics and 44% of children who were pretreated with parenteral antibiotics. (16) Within 1 hour of receiving a third-generation parenteral cephalosporin, three of nine children with meningococcal meningitis had sterile CSF cultures, and all were sterile within 2 hours. With pneumococcal meningitis, CSF cultures usually become sterile by 4 or more hours after parenteral antibiotic pretreatment unless the organisms have decreased susceptibility to beta-lactam antibiotics. Antimicrobial pretreatment does not adversely affect the CSF cell count and is associated with higher CSF glucose and lower protein values than would be expected for untreated bacterial meningitis. However, these changes are unlikely to obscure the diagnosis of bacterial meningitis. (17)

Latex agglutination tests have been used for patients with suspected bacterial meningitis and negative CSF Gram stain and culture. However, these tests have limited benefit, rarely

change the treatment plan, and are no longer routinely recommended for patients pretreated with antibiotics. (14) The overall diagnostic sensitivities for multiplex nucleic acid amplification tests such as polymerase chain reaction (PCR) range from 72% to 92% for Hib, 61% to 100% for *S pneumoniae*, and 88% to 94% for *N meningitidis*. (14) The lower sensitivity results are usually from patients who received antimicrobial pretreatment. Further study is needed to determine if CSF PCR will prove useful in the management of patients with suspected bacterial meningitis who have been pretreated. On the other hand, CSF enteroviral PCR can be a useful tool to identify an alternative diagnosis to bacterial meningitis.

Neuroimaging. Computed tomography (CT) scan of the brain obtained to rule out increased ICP often unnecessarily delays LP. However, abnormal CT scan findings are rare in children without clinical findings of a focal neurologic deficit, papilledema, or coma. (18)(19) In addition, a normal CT scan does not completely confirm that an LP is safe. Clinically stable children with suspected bacterial meningitis and no clinical signs of brain herniation should undergo prompt LP. If a head CT scan is indicated (Figure), blood cultures should be obtained first and antibiotics administered. LP should be performed promptly after CT scan if no contraindication is identified. Although antibiotics are given in advance, routine imaging studies can lead to unnecessary delays in obtaining a diagnostic LP, potentially confounding

TABLE 5. Usual Cerebrospinal Fluid Findings in Healthy Children and Those With Meningitis Caused by Selected Pathogens*

TYPE OF MENINGITIS	GLUCOSE	PROTEIN	WHITE BLOOD CELLS/MM ³	NEUTROPHILS	POSITIVE STAIN [†]
Healthy newborn	30–120 mg/dL (1.7–6.7 mmol/L)	0.03–0.15 g/dL (0.3–1.5 g/L)	<30	20%–60%	NA
Healthy child	40–80 mg/dL (2.2–4.4 mmol/L)	0.02–0.04 g/dL (0.2–0.4 g/L)	<6	None	NA
Bacterial	<1/2 serum	0.1–0.15 g/dL (1–1.5 g/L)	>1,000	>85%–90%	60%
Pretreated bacterial	<1/2 serum to N	0.07–>0.1 g/dL (0.7–>1 g/L)	500–>1,000	>60%	60%
Enteroviral	>1/2 serum	0.04–<0.1 g/dL (0.4–<1 g/L)	<1,000	20%–50% [‡]	NA
Lyme	>1/2 serum	<0.1 g/dL (<1 g/L)	<500	<10%	NA
Fungal	<1/2 serum	>0.1–0.2 g/dL (>1–2 g/L)	<500	<10%–20%	<40%
Tuberculosis	<1/2 serum	>0.1–0.3 g/dL (>1–3 g/L)	<300	<10%–20% [‡]	<30%

N=normal, NA=not applicable

*Values should not be used in isolation because there can be significant overlap in each of the categories.

[†]Gram, silver, or acid-fast bacilli staining for bacteria, fungi, and mycobacteria, respectively.

[‡]Neutrophil predominance can be seen in the early stages of meningitis.

Adapted from Mann and Jackson (9).

and complicating the patient's management. Therefore, CT scan should be used judiciously in children with suspected bacterial meningitis.

DIFFERENTIAL DIAGNOSIS

The signs and symptoms of fever, irritability, lethargy, headache, vomiting, and nuchal rigidity are strongly suggestive of bacterial meningitis. However, other conditions should be considered in the differential diagnosis. Viruses, fungi, mycobacteria, and parasites can sometimes cause meningitis that mimics bacterial meningitis in presentation. Brain abscesses, encephalitis, subdural or epidural abscesses, rickettsial disease, leptospirosis, and neck or retropharyngeal abscesses are other infectious diseases that may mimic acute bacterial meningitis. Noninfectious conditions such as central nervous system autoinflammatory vasculitis, Kawasaki disease, brain tumors, and drug reactions are also considerations in the differential diagnosis. A careful review of the medical history, examination of the CSF, selective laboratory tests, and judicious use of neuroimaging should help discern the final diagnosis if bacterial meningitis is excluded.

MANAGEMENT

Supportive Care

Initial supportive care is usually best provided in an intensive care unit to assure close cardiopulmonary monitoring and management. Serious complications of bacterial meningitis (hypotension, cerebral infarction, seizures, increased ICP) often occur in the first 2 to 3 days of therapy. Fluid and electrolyte resuscitation must be administered to attain appropriate blood pressure and cerebral perfusion. The child's weight, serum electrolytes, urine output, and urine specific gravity should be monitored closely in the first 24 to 36 hours of hospitalization. If the patient does not have hypovolemia or shock upon admission, there may be a role for modest fluid restriction until SIADH can be ruled out, especially if the serum sodium is less than 130 mEq/L (130 mmol/L). SIADH can cause hyponatremia and hypo-osmolality, which could lead to mental confusion, lethargy, seizures, and increased ICP. (20) If SIADH is suspected, serum and urine osmolalities should also be monitored. Fluid restriction can be gradually removed when the sodium concentration reaches 135 mEq/L (135 mmol/L), often within 24 to 48 hours after hospitalization.

Patients should receive a thorough neurologic examination daily and brief directed neurologic examinations several times a day during the first few days of care. Children younger than 18 months of age should have daily head circumference measurements. Mild early signs of increased ICP can be

managed by elevating the head of the bed. However, severe signs of increased ICP (apnea, bradycardia, hypertension, sluggish or dilated pupils) require more aggressive therapy with mannitol and hyperventilation. Generalized seizures occur early in the disease course in 20% to 25% of meningitis cases and can usually be controlled with standard seizure medications, such as fosphenytoin or phenobarbital. Focal seizures, difficult-to-control seizures, or seizures occurring more than 48 hours after admission should prompt a neurology consultation.

Up to one third of children with bacterial meningitis develop a subdural effusion. In most cases, subdural effusions cause minimal symptoms or are asymptomatic and do not require specific treatment. Clinical manifestations of subdural effusions are often subtle or absent. If a subdural empyema develops, drainage is usually necessary. Subdural empyema can present as persistent fever, headache, and nuchal rigidity or new onset of neurologic features, such as seizures, in the setting of appropriate antibiotic treatment.

Antimicrobial Therapy

Antimicrobial agents should be started promptly after LP to decrease the risk of adverse outcomes. As mentioned previously, if a head CT scan is needed before the LP, blood cultures should be obtained first and antibiotics quickly administered (Figure). It is important to determine that the antibiotics administered can achieve good concentrations in the CSF and are bactericidal against the targeted bacterial pathogens.

Neonatal Bacterial Meningitis. Empiric antimicrobial therapy of suspected bacterial meningitis in the neonate has often consisted of ampicillin and gentamicin. (2) However, with increasing resistance of *E coli* and other Gram-negative enteric organisms to ampicillin, some clinicians replace gentamicin with cefotaxime when bacterial meningitis is strongly suspected. Although the use of cefotaxime has been linked to the emergence of cephalosporin-resistant Gram-negative bacilli, this risk must be weighed against the risk of inadequately treating ampicillin-resistant Gram-negative meningitis in the face of suboptimal CSF penetration by gentamicin. When the causative organism and its antibiotic susceptibilities are determined, specific targeted therapy can be provided (Table 6). (8)(15)(20) **For uncomplicated meningitis caused by GBS, *L monocytogenes*, or *S pneumoniae*, 14 days of antibiotics is sufficient.** Twenty-one days of antibiotics is often considered the minimum length of therapy for uncomplicated neonatal meningitis caused by Gram-negative bacilli. Longer antimicrobial treatment courses are necessary for complicated meningitis, such as subdural empyema, ventriculitis, brain abscess, and suppurative venous sinus thrombosis.

Postneonatal Bacterial Meningitis. Empiric antimicrobial therapy of suspected bacterial meningitis for children 1 month of age and older involves vancomycin plus either cefotaxime or ceftriaxone. (8)(15)(20) Vancomycin is used because of the emergence of cephalosporin-resistant pneumococci. It does not need to be continued if the organism is susceptible to penicillin or cephalosporins. When the causative organism and its antibiotic susceptibilities are determined, specific targeted therapy can be provided (Table 6).

For pneumococcal meningitis, clinicians should consider adding rifampin if: 1) the child's condition has worsened after 24 to 48 hours of vancomycin and cephalosporin therapy, 2) a repeat LP reveals the presence of bacteria, 3) the organism has a high cephalosporin minimum inhibitory concentration ($\geq 4 \mu\text{g/mL}$), or 4) dexamethasone has been administered. (21) Care must be taken when treating pneumococcal meningitis to ensure that antimicrobial susceptibility is being interpreted for meningitis and not for nonmeningitic infections.

Vancomycin plus rifampin or vancomycin plus meropenem are possible treatment options for children with serious allergic reactions to penicillins and cephalosporins. Vancomycin should not be administered alone because it

has limited CSF penetration and clinical experience using it as monotherapy for meningitis is limited. Rifampin should not be administered alone because resistance can develop during treatment.

For uncomplicated meningitis, the usual duration of antimicrobial therapy is 10 to 14 days for *S pneumoniae*, 7 to 10 days for Hib, 5 to 7 days for *N meningitidis*, 14 to 21 days for *L monocytogenes*, and a minimum of 3 weeks for Gram-negative bacilli. A pediatric infectious diseases consultation should always be considered, especially for complicated cases, including drug resistance, persistent infection, immunodeficiency, CSF leak, penetrating head trauma, or recent neurosurgery.

Culture-negative CSF. Antibiotics are discontinued for patients with an unremarkable CSF profile and negative blood and CSF cultures. If the child has a positive blood culture, CSF pleocytosis, and negative CSF culture, treatment is usually provided for meningitis as if the CSF culture had been positive. In this circumstance, some experts treat Gram-negative bacteremia and uncomplicated suspected meningitis for only 14 days instead of 21 days. For patients with unconfirmed, uncomplicated, but clinically suspected bacterial meningitis (eg, pretreated with antibiotics), treatment is often 14 days or more of ampicillin and cefotaxime

TABLE 6. **Specific Antibiotics for Selected Pathogens (8)(9)(15)**

PATHOGEN	STANDARD ANTIBIOTIC(S)	ALTERNATIVE ANTIBIOTIC(S)
Group B <i>Streptococcus</i>	Penicillin G or ampicillin \pm gentamicin	Cefotaxime or ceftriaxone
<i>Escherichia coli</i> *	Cefotaxime or ceftriaxone \pm gentamicin	Cefepime or meropenem
<i>Listeria monocytogenes</i>	Penicillin G or ampicillin \pm gentamicin	Trimethoprim-sulfamethoxazole or meropenem
<i>Neisseria meningitidis</i>		
Penicillin-susceptible	Penicillin G or ampicillin	Cefotaxime or ceftriaxone
Penicillin-tolerant	Cefotaxime or ceftriaxone	Cefepime or meropenem
<i>Haemophilus influenzae</i> type b		
Beta-lactamase-negative [†]	Ampicillin	Cefotaxime or ceftriaxone
Beta-lactamase-positive	Cefotaxime or ceftriaxone	Cefepime or meropenem
<i>Streptococcus pneumoniae</i>		
Penicillin-susceptible	Penicillin G or ampicillin	Cefotaxime or ceftriaxone
Penicillin-nonsusceptible Cephalosporin-susceptible	Cefotaxime or ceftriaxone	Cefepime or meropenem
Penicillin-nonsusceptible Cephalosporin-nonsusceptible	Vancomycin + cefotaxime or ceftriaxone \pm rifampin	Vancomycin + meropenem \pm rifampin

*Or other Gram-negative enteric bacilli. Choice of antibiotic is directed by the results of susceptibility testing.

[†]The Committee on Infectious Diseases of the American Academy of Pediatrics recommends, "Initial therapy for children with H influenzae meningitis is cefotaxime or ceftriaxone. Ampicillin should be substituted if the Hib isolate is susceptible." See Addendum to this article in the Supplemental Data tab.

for neonates and 10 days of ceftriaxone for older infants and children. (22) However, the specific management of patients with a CSF pleocytosis and negative blood and CSF cultures needs to be decided on an individual clinical basis; consultation with a pediatric infectious diseases expert is recommended. Sterile CSF pleocytosis sometimes occurs in young febrile infants with urinary tract infections who have not been pretreated with antibiotics. These infants are often not treated for bacterial meningitis and are at very low risk for adverse events. (23)

Adjunctive Therapy

Dexamethasone has been used as adjunctive therapy to modulate the host inflammatory response and prevent neurologic complications of bacterial meningitis, especially hearing loss. However, its use in children with bacterial meningitis has been controversial. A recent subgroup analysis of 2,511 children from a large meta-analysis found that use of dexamethasone significantly reduced hearing loss associated with meningitis caused by Hib, but not meningitis caused by other bacteria. (24) Nonetheless, children in this study from high-income countries who had non-Hib meningitis and received corticosteroids experienced some reduction in severe hearing loss. Therefore, the authors suggested that these children might benefit from corticosteroids because there was no evidence of adverse effects from the treatment. However, the results are inconclusive, and the use of adjunctive dexamethasone for non-Hib meningitis remains controversial. Because Hib meningitis has become rare in developed countries, empiric dexamethasone therapy is harder to justify. In addition, vancomycin was not part of the treatment regimen for most of the studies using adjunctive corticosteroids. Vancomycin has suboptimal CSF penetration, and there is some concern that corticosteroids may further reduce its penetration into the CSF by reducing meningeal inflammation.

The American Academy of Pediatrics (AAP) Committee on Infectious Diseases identifies a potential benefit of dexamethasone for patients with Hib meningitis and indicates that empiric use might be considered for suspected bacterial meningitis in infants and children 6 weeks of age and older after considering the possible risks versus potential benefits. (25) The AAP recognizes that data are insufficient to recommend routine adjunctive corticosteroid therapy for pediatric pneumococcal meningitis. (21) If dexamethasone is used, it should be administered before or at the same time as the first dose of antibiotics. Dexamethasone has no demonstrable benefit if initiated more than 1 hour after antibiotics. The usual dose is 0.15 mg/kg per dose intravenously every 6 hours for 2 days.

Repeat Lumbar Puncture

The AAP Committee on Infectious Diseases recommends a repeat LP after 24 to 48 hours of therapy for all infants with Gram-negative bacilli meningitis to ensure sterility of the CSF. (26) If the CSF culture remains positive, the antimicrobial regimen should be re-evaluated and another LP performed. Some experts recommend a repeat LP after 24 to 48 hours of therapy for all cases of neonatal meningitis to confirm CSF sterilization. (2) In contrast, the United Kingdom National Institute for Health and Clinical Excellence Clinical Guideline 102 recommends against repeat LP in neonates if they are receiving appropriate antibiotic treatment for the causative organism and are making a good clinical recovery. They recommend a repeat LP in neonates with: 1) persistent or re-emergent fever, 2) deterioration in clinical condition, 3) new clinical findings (especially neurologic findings), or 4) persistently abnormal inflammatory markers. (22)

For cases of pneumococcal meningitis, some experts suggest repeating an LP after 48 hours of therapy if: 1) the organism is penicillin-nonsusceptible and cephalosporin susceptibility testing is not yet available, 2) the child's condition is not improved or is worsening, or 3) the patient has received dexamethasone because it can obscure clinical features such as fever, headache, and nuchal rigidity. (21) If the organism is cephalosporin-nonsusceptible, repeat LP at 48 to 72 hours should be considered to verify CSF clearance of the bacteria.

Obtaining an end-of-therapy LP for bacterial meningitis is no longer common practice. (2) However, if one is obtained, the duration of antimicrobial therapy might need to be extended if the CSF has more than 30% neutrophils, the glucose is less than 20 mg/dL (1.1 mmol/L), or the CSF-to-blood glucose ratio is less than 20%.

Prolonged or Returned Fever

Fever usually lasts 4 to 6 days after initiation of appropriate therapy. Return of fever or continued fever for more than 8 days should activate an evaluation for the cause. (8)(20) The discontinuation of adjunctive dexamethasone often results in a return of fever for several days. Suppurative complications, such as subdural empyema, pleural empyema, arthritis, pericarditis, ventriculitis, or brain abscess should be considered and appropriate evaluations performed when indicated. The decision to repeat an LP for CSF analysis and culture should be made on a case-by-case basis. Fever from a hospital-acquired viral infection is not uncommon. A treatment complication (eg, phlebitis from a peripheral intravenous line, catheter-associated urinary tract infection, central line-associated bloodstream infection) is also

a consideration. Drug fever is uncommon and a diagnosis of exclusion. A specific cause for fever is often not found.

Neuroimaging

Neonatal Meningitis. Cranial ultrasonography is often performed early in the course of disease to identify possible hydrocephalus, intraventricular hemorrhage, ventriculitis, extra-axial fluid collections, or other problems. In addition, some experts routinely obtain a head CT scan or magnetic resonance imaging (MRI) with contrast 1 to 3 days before the expected end of therapy, even in apparently uncomplicated cases. (2) Such imaging is designed to identify any potential complications, such as cerebritis or parenchymal abscesses, that would require prolonged antimicrobial therapy. In addition, it might provide prognostic information and indicate the need for early interventional services. Contrast-enhanced neuroimaging with CT scan or MRI is important for infections from *Citrobacter* sp, *Serratia marcescens*, *Proteus mirabilis*, and *Cronobacter* (formerly *Enterobacter*) *sakazakii* because of their tendency to cause brain abscesses.

Postneonatal Meningitis. As noted previously, radiologic studies are used in conjunction with LP in the diagnostic evaluation of bacterial meningitis. Routine neuroimaging with CT scan or MRI is usually not necessary during the management of bacterial meningitis in the older infant and child. However, head CT scan or MRI with contrast is indicated in certain circumstances, including focal neurologic signs, prolonged obtundation, increasing head circumference, seizures after 72 hours of antimicrobial therapy, persistently positive CSF cultures, recurrent meningitis, and infection with Gram-negative bacilli, especially *Citrobacter* sp or *C sakazakii*. (18)(20)

PROGNOSIS AND SEQUELAE

Bacterial meningitis can be a devastating disease. Mortality rates across all pediatric ages range from less than 5% to 15%, depending on the pathogen and when the surveillance was conducted. The patient's prognosis and outcome are affected by many factors, including age, infecting organism, bacterial burden, and clinical status when antibiotics are started. (8)(20) Younger age, greater bacterial burden, and delayed CSF sterilization are all associated with worse prognosis. A decreased level of consciousness at presentation is associated with increased risk for death or neurologic sequelae. The development of seizures more than 72 hours after starting antibiotics has been associated with learning difficulties. Compared to Hib or *N meningitidis*, infection caused by *S pneumoniae* is associated with a poorer outcome. Hearing loss occurs in 20% to 30% of children with

pneumococcal meningitis, approximately 10% with meningococcal meningitis, and approximately 5% with Hib meningitis. Hearing impairment is also associated with CSF glucose less than 20 mg/dL (1.1 mmol/L) at the time of diagnosis. Vestibular injury can result in ataxia and difficulty with balance. Other neurologic sequelae include cognitive and developmental disability, hemiparesis, quadriparesis, cranial nerve palsies, epilepsy, cortical blindness, hydrocephalus, diabetes insipidus, and hypothalamic dysfunction. Paresis generally improves over time and may resolve months or years after the infection.

DISCHARGE CRITERIA

Patients can be considered for discharge to home when they are clinically and neurologically stable, able to tolerate enteral fluids, and have been afebrile for 24 to 48 hours. In selected circumstances, completion of intravenous antimicrobial therapy may be safely managed at home. Candidates for home infusion therapy should meet the previously stated discharge criteria, have received 5 to 7 days of inpatient therapy, and have reliable caretakers with immediate access to transportation and telephone. Advantages of home therapy include avoidance of hospital-acquired infection, return to a normal environment, and decreased treatment costs.

FOLLOW-UP EVALUATIONS

Hearing evaluation should be performed before hospital discharge or soon thereafter. Repeat testing is indicated if the initial evaluation yields abnormal results, and audiology services should be used as needed. Children with recognized neurologic sequelae should be provided appropriate referrals for physical, occupational, and other therapies so they have the opportunity to reach their greatest recovery potential. Even infants and children who appear well upon completion of therapy are at risk for cognitive and developmental delay. Regular routine follow-up evaluations with their primary care clinician are recommended to monitor their behavior, development, and academic progress. Furthermore, infants and young children may be eligible for state-sponsored early intervention services. Children completing antimicrobial therapy at home need close follow-up, preferably from the clinician who was managing their inpatient care.

PREVENTION AND CONTROL

Timely childhood vaccination against Hib, *S pneumoniae*, and *N meningitidis* is the best preventive approach for meningitis

from these organisms. Use of the Hib conjugate vaccines in infants has resulted in a dramatic decrease in the incidence of Hib meningitis. The conjugated vaccines for pneumococcus and meningococcus have been relatively effective in preventing disease from vaccine-related serotypes. Unfortunately, nonvaccine-related serotypes for both pneumococcus and meningococcus continue to cause life-threatening meningitis.

Patients with invasive Hib or meningococcal disease should be placed in droplet precautions until they have received 24 hours of therapy with a third-generation cephalosporin or 4 days of rifampin chemoprophylaxis. In addition, close contacts of patients with Hib and meningococcal disease should be provided antimicrobial prophylaxis. (25) Rifampin is indicated for all household contacts of a patient with invasive Hib infection if at least one of them is younger than age 4 years and is unimmunized or incompletely immunized. Rifampin administration is 20 mg/kg (maximum dose 600 mg) once daily by mouth for 4 days. If two or more cases of invasive Hib disease occur within 60 days at a child care facility or preschool and unimmunized or incompletely immunized children attend, rifampin is recommended for all attendees, regardless of age or vaccine status. All close contacts of patients with meningococcal infection, regardless of vaccine status, should receive chemoprophylaxis with rifampin, ceftriaxone, ciprofloxacin, or azithromycin. The choice of antimicrobial agent depends on the appropriateness for the individual contact.

Finally, daily penicillin prophylaxis is recommended for patients with functional and anatomic asplenia to prevent invasive pneumococcal disease.

Summary

- Based on strong evidence, blood cultures usually recover the causative organism of bacterial meningitis in children not pretreated with antibiotics.
- Based on moderate evidence, pretreatment does not adversely affect the cerebrospinal fluid cell count, but it decreases the positive test result for cerebrospinal fluid culture, especially for meningococcal meningitis. (16)(17)
- Based on some research evidence as well as consensus, children with suspected bacterial meningitis and no clinical signs of brain herniation do not need neuroimaging as part of their initial clinical evaluation. (18)(19)(22)
- Dexamethasone adjunctive therapy in children with pneumococcal meningitis is controversial. (21)
- Some experts recommend neuroimaging toward the end of therapy for all neonates with bacterial meningitis. (2)
- Based on some research evidence as well as consensus, home intravenous antimicrobial therapy may be an option in selected cases of pediatric bacterial meningitis. (15)

CME quiz and references for this article are at <http://pedsinreview.aappublications.org/content/36/12/514.full>.

Parent Resources from the AAP at HealthyChildren.org

- <https://www.healthychildren.org/English/health-issues/conditions/head-neck-nervous-system/Pages/Meningitis.aspx>

PIR Quiz

There are two ways to access the journal CME quizzes:

1. Individual CME quizzes are available via a handy blue CME link in the Table of Contents of any issue.
2. To access all CME articles, click "Journal CME" from Gateway's orange main menu. Use the publications filter at right to refine results to a specific journal.

1. A 1-year-old girl presents to the emergency department with the acute onset of fever, irritability, photophobia, and vomiting. The child has no significant past medical history and the parents report that she is up-to-date with all immunizations, including varicella and the measles, mumps, and rubella vaccines. In the waiting room, the child has a 1-minute generalized tonic-clonic seizure. You are concerned about bacterial meningitis and perform a lumbar puncture (LP). You send the cerebrospinal fluid (CSF) to the laboratory for analysis of glucose, protein, cell count, Gram stain, and bacterial culture. One hour later, the microbiology laboratory technician reports that Gram-positive bacteria have been noted on the CSF Gram stain. Of the following, the most likely organism causing this child's bacterial meningitis is:

- A. *Haemophilus influenzae* type b.
- B. *Listeria monocytogenes*.
- C. *Neisseria meningitidis*.
- D. *Streptococcus pneumoniae*.
- E. *Streptococcus pyogenes*.

2. A 2-week-old male infant presents with a 1-day history of a temperature to 38.9°C (102°F), irritability, and poor feeding. A complete blood cell count, blood culture, urinalysis, and urine culture are obtained. LP is attempted five times without success. Of the following, the next best step in management is:

- A. Administration of parenteral antibiotics.
- B. Computed tomography scan of the brain.
- C. Cranial ultrasonography.
- D. Repeat attempt at LP the following day.
- E. Measurement of serum electrolytes.

3. You are discussing a case of bacterial meningitis with a group of medical students. A 2-year-old boy with fever, headache, irritability, and some emesis was seen by a physician in a walk-in clinic. The child was diagnosed with acute bacterial sinusitis for which he was prescribed amoxicillin. Forty-eight hours later, the child continued to have fevers, headache, and emesis, and his parents took him to the emergency department. You discuss with the students whether LP would be indicated for this child when he is evaluated in the emergency department. One student comments that because the child was already receiving antibiotics, the cerebrospinal fluid (CSF) culture would likely be sterile. Of the following, the most accurate response is that:

- A. Although antibiotic pretreatment decreases the likelihood of obtaining a positive CSF culture, it does not adversely affect the CSF cell count.
- B. Antibiotic pretreatment does not decrease the likelihood of obtaining a positive CSF culture.
- C. Antibiotic pretreatment decreases both the likelihood of obtaining a positive CSF culture and the ability to interpret the CSF cell count.
- D. Antibiotic pretreatment only decreases the likelihood of a positive CSF culture if the etiology of the meningitis is *Streptococcus pneumoniae*.
- E. Antibiotic pretreatment only decreases the likelihood of a positive CSF culture if the lumbar puncture is traumatic.

4. A 2-month-old infant is admitted to the hospital because of fever and new-onset focal seizure activity. A complete blood cell count, blood culture, urinalysis, and urine culture are obtained. LP is also performed and the CSF is sent to the laboratory for glucose, protein, cell count, Gram stain, and bacterial culture. The Gram stain performed on the CSF fluid is suspicious for Gram-positive bacteria. Empiric antimicrobial therapy for suspected bacterial meningitis is initiated. Of the following, which is the best choice for antimicrobial therapy?

- A. Ampicillin plus gentamicin.
- B. Ceftriaxone (or cefotaxime) monotherapy.
- C. Gentamicin plus rifampin.

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: <http://pedsinreview.org>.

To successfully complete 2015 *Pediatrics in Review* articles for AMA PRA Category 1 Credit™, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2017, however, credit will be recorded in the year in which the learner completes the quiz.

- D. Vancomycin monotherapy.
 - E. Vancomycin plus ceftriaxone (or cefotaxime).
5. A 2-week-old male infant in the neonatal intensive care unit, who had been born at 35 weeks' gestation, is evaluated for possible meningitis. Analysis of the CSF reveals a glucose of 17 mg/dL (0.94 mmol/L) and protein of 0.2 g/dL (2 g/L). The CSF Gram stain shows Gram-negative bacilli and within 12 hours, the CSF culture grows *Escherichia coli*. Appropriate parenteral antibiotic therapy is initiated with a plan to complete 2 weeks of intravenous antibiotics. Of the following, which is the best management plan for this child's Gram-negative bacilli meningitis with regard to follow-up LP?
- A. An end-of-therapy LP should be performed for all infants with Gram-negative bacilli meningitis to ensure sterility of the CSF.
 - B. A repeat LP after 24 to 48 hours of therapy should be performed for all infants with Gram-negative bacilli meningitis to ensure sterility of the CSF.
 - C. A repeat LP is indicated in neonates only if they received dexamethasone before or at the same time as the first dose of antibiotics.
 - D. A repeat LP should be performed in Gram-negative bacilli meningitis only if the blood culture grew *Escherichia coli*.
 - E. Weekly LPs should be performed for neonates with Gram-negative bacilli meningitis to ensure there are no complications.

Meningitis
Douglas Swanson
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- A. Obtain laboratory studies for possible bleeding disorder.
- B. Request polysomnography evaluation of her sleep.
- C. Request renal ultrasonography and cystometrography.
- D. Request referral for ophthalmology evaluation.
- E. Submit a report to child welfare.

Parent Resources from the AAP at HealthyChildren.org

- <https://www.healthychildren.org/English/safety-prevention/at-home/Pages/What-to-Know-about-Child-Abuse.aspx>
- Spanish: <https://www.healthychildren.org/Spanish/safety-prevention/at-home/Paginas/What-to-Know-about-Child-Abuse.aspx>

Addendum for Meningitis

Regarding the December 2015 *Pediatrics in Review* article “Meningitis” (*Pediatr Rev.* 2015;36(12):514–526, doi: 10.1542/pir.36-12-514:

The incidence of *Haemophilus influenzae* type b (Hib) invasive disease, including meningitis, has decreased tremendously with the increased use of Hib conjugate vaccine in infants. Unfortunately, there is concern that similar to other vaccine-preventable diseases, such as measles and pertussis, an upsurge in Hib meningitis could follow a decrease in Hib vaccine use. Therefore, it is important for clinicians to recognize possible Hib meningitis promptly and treat it effectively.

The footnote to the listing for *Escherichia coli* in Table 6 of the article on meningitis published in *Pediatrics in Review* clearly states “Or other Gram-negative enteric bacilli. Choice of antibiotic is directed by the results of susceptibility testing.” What may not be clear to all readers is that a very small percentage of Hib that are beta-lactamase-negative still have a sufficiently high minimum inhibitory concentration (MIC) for ampicillin to make Hib resistant to ampicillin. Thus, ampicillin is not considered a preferable antibiotic until susceptibility (based on MIC) is available. This is an essential point because the consequences of initial ineffective therapy can be disastrous.

Out of an abundance of caution, we want to remind readers (and have updated the online version of the article with the notation) that The Committee on Infectious Diseases of the American Academy of Pediatrics recommends, “Initial therapy for children with *H influenzae* meningitis is cefotaxime or ceftriaxone. Ampicillin should be substituted if the Hib isolate is susceptible.”

– Mobeen H. Rathore, MD, FAAP
Pediatrics in Review Editorial Board
AAP Committee on Infectious Diseases



Meningitis

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The online version of this article, along with updated information and services, is located on the World Wide Web at:

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An erratum has been published regarding this article. Please see the attached page for:

<http://pedsinreview.aappublications.org/content/37/4/158.full.pdf>

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