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## Bacterial Meningitis in Children

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Meningitis is defined as inflammation of the membranes that surround the brain and spinal cord. Microbiologic causes include bacteria, viruses, fungi, and parasites. Before routine use of pneumococcal conjugate vaccine, bacterial meningitis affected almost 6000 people every year in the United States; about half of all cases occurred in children 18 years old or younger [1]. Approximately 10% of patients with bacterial meningitis die [2], and 40% have sequelae including hearing impairment and other neurologic sequelae [3].

### Epidemiology

The etiology of bacterial meningitis is affected most by the age of the patient. In neonates, the most common etiologic agents are group B streptococci (GBS) and gram-negative enteric bacilli. Although the incidence of early-onset neonatal GBS disease decreased by two thirds after implementation of the Centers for Disease Control and Prevention revised guidelines for intrapartum antibiotic prophylaxis in 2002 [4,5], GBS remains an important cause of late-onset disease, typically manifest as meningitis. *Escherichia coli* and other gram-negative enteric bacilli, including *Klebsiella*, *Enterobacter*, and *Salmonella*, cause sporadic disease except in nosocomial outbreaks and in developing countries [6–8]. Other pathogens that occasionally cause meningitis in neonates, especially during outbreaks, include *Listeria monocytogenes*, *Enterobacter sakazakii* [9,10], and *Citrobacter koseri* (formerly *Citrobacter diversus*). A unique feature of neonatal

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meningitis caused by *C. koseri* is a high association with the development of brain abscesses [11]. Other rare causes of meningitis in neonates include staphylococci, enterococci, and viridans streptococci.

In infants and young children worldwide, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b (Hib) are the most common causes of bacterial meningitis. Among children older than 5 years of age and adolescents, *S. pneumoniae* and *N. meningitidis* are the predominant causes of bacterial meningitis [1,12]. Most of the bacteria responsible for invasive disease, including meningitis, in children have a polysaccharide capsule [13,14].

The incidence of meningitis caused by Hib has decreased markedly in areas of the world where Hib conjugate vaccines are routinely used [15]. Replacement with the other capsular types (*H. influenzae* types a and c to f) has not occurred after the widespread use of Hib vaccines [16]. The incidence of meningitis caused by *S. pneumoniae* and *N. meningitidis* (serotype C) also have been reduced in areas where conjugated vaccines against these pathogens have been introduced.

The highest risk of bacterial meningitis caused by *S. pneumoniae* is in children younger than 2 years old. In 1995, before universal immunization against this pathogen, the estimated incidence of pneumococcal meningitis was more than 20 cases per 100,000 US population in this age group [1]. The seven most common serotypes that cause invasive disease in the United States are 4, 6B, 9V, 14, 19, 18C, and 23 [17]. These serotypes are included in the heptavalent pneumococcal conjugate vaccine, PCV7, which is licensed in the United States. The incidence of invasive disease, including bacterial meningitis, caused by *S. pneumoniae* has been reduced by greater than 90% after the implementation of universal use of this vaccine [18], beginning in infancy.

Most cases of invasive meningococcal disease in the United States are caused by serogroups B, C, Y, and W-135 [19]. Serogroup A strains account for most epidemics, especially in sub-Saharan Africa [20]. Serogroup C predominates in England. The incidence of meningococcal meningitis is greatest in infants younger than 1 year old; a second peak incidence is observed at age 15 to 17 years [21,22]. A conjugate vaccine against meningococcal serogroup C was introduced into the routine immunization schedule in 1999 in England. The use of this vaccine was associated with an overall 81% reduction of serogroup C disease within 2 years of implementation [23]. Continued surveillance has raised concerns about long-term effectiveness in infants vaccinated before 6 months of age [24].

Factors that increase the risk for bacterial meningitis include immunosuppressive states, such as HIV infection, asplenia [25], terminal complement deficiencies, and immunoglobulin deficiencies. Penetrating head injuries, neurosurgical procedures, or the presence of cerebrospinal fluid (CSF) leaks are other risk factors for meningitis. Patients with ventriculoperitoneal shunts are at risk of meningitis caused by staphylococci (especially coagulase-negative strains) and gram-negative organisms, including *Pseudomonas* [26]. Patients with cochlear implants have more than a 30-fold increased incidence of pneumococcal meningitis [27].

## Pathogenesis

Bacteria reach the CNS either by hematogenous spread or by direct extension from a contiguous site. In neonates, pathogens are acquired from nonsterile maternal genital secretions. In infants and children, many of the organisms that cause meningitis colonize the upper respiratory tract. Direct inoculation of bacteria into the CNS can result from trauma, skull defects with CSF leaks, congenital dura defects such as a dermal sinuses or meningomyelocele, or extension from a suppurative parameningeal focus.

After bacteremia, pathogens penetrate the blood-brain barrier to enter the subarachnoid space. Surface bacterial proteins known to facilitate invasion of the blood-brain barrier include *E coli* proteins IbeA, IbeB, and ompA; *S. pneumoniae* protein CbpA; and *N. meningitidis* proteins Opc, Opa, and PilC, a pili protein [28]. Transcellular penetration has been shown for *S. pneumoniae*, GBS, *L. monocytogenes*, and *E coli*.

The intense inflammation elicited by bacterial products, such as gram-negative lipopolysaccharide or gram-positive peptidoglycan, persists after bacteria are destroyed by the host responses and antibiotic therapy [29]. These substances induce production of different inflammatory mediators by CNS astrocytes and ependymal, glial, and endothelial cells. The inflammatory mediators include tumor necrosis factor- $\alpha$ ; interleukin (IL)-1, IL-6, IL-8, and IL-10; macrophage induced proteins 1 and 2; and other mediators including nitric oxide, matrix metalloproteinase-2, and prostaglandins [30-32]. The ensuing granulocyte influx and altered blood-brain barrier permeability result in the release of proteolytic products and toxic oxygen radicals. Accompanying cerebral edema and increased intracranial pressure contribute to neuronal damage and death. Neuronal death is believed to be caused by apoptosis through caspase-dependent and independent pathways [33,34].

## Clinical features

Manifestations of bacterial meningitis depend on the age of the patient. Fever, neck stiffness, and mental status changes are present in less than 50% [35], and Kernig and Brudzinski signs are present in only about 5% of adults with bacterial meningitis [36]. These manifestations are observed even less frequently in children with bacterial meningitis. Signs of meningeal irritation, such as neck stiffness, Brudzinski and Kernig signs, or the tripod phenomenon, in children also are not specific for bacterial meningitis. In one study, bacterial meningitis was present in only about one third of children with signs of meningeal irritation [37]. Seizures occur as the presenting symptom in one third of cases of bacterial meningitis in children. Seizures are more common in children with meningitis caused by *S. pneumoniae* and Hib compared with children with meningococcal meningitis [38]. Petechiae and purpura may accompany meningitis caused by any bacteria, but they are more common in patients with meningococcal meningitis

than patients with meningitis caused by *S. pneumoniae* or *H. influenzae*. Symptoms may be subtle in infants and include fever only, irritability, lethargy, and difficulty feeding. Signs include fever, apnea, seizures, a bulging fontanel, and a rash.

### Diagnosis

A lumbar puncture is necessary for the definitive diagnosis of bacterial meningitis. Analysis of CSF should include Gram stain and cultures, white blood cell (WBC) count and differential, and glucose and protein concentrations. Cyto-centrifugation of the CSF enhances the ability to detect bacteria and perform a more accurate determination of the WBC differential.

Typical findings in the CSF in bacterial meningitis include pleocytosis, usually with a WBC count greater than 1000 cells/mm<sup>3</sup> and predominance of polymorphonuclear leukocytes. In some cases, especially when performed early in the disease, the WBC count can be normal [39], and there may be a lymphocyte predominance. It is common for the polymorphonuclear leukocyte count to increase after 48 hours of diagnosis and then to decrease thereafter [40]. Glucose concentration usually is decreased with a CSF-to-serum glucose ratio of 0.6 or less in neonates and 0.4 or less in children older than 2 months of age, whereas protein concentration usually is elevated [41]. A reduced absolute CSF concentration of glucose is as sensitive as the CSF-to-serum glucose ratio in the diagnosis of bacterial meningitis.

A traumatic lumbar puncture, which introduces blood into the spinal fluid during the procedure, makes interpretation of the CSF cell count difficult. Several methods have been used to distinguish peripheral blood WBCs from true CSF leukocytosis, but none have proved accurate. Caution is recommended when interpreting traumatic lumbar punctures [42,43].

The Gram-stained smear of CSF has a lower limit of detection of about 10<sup>5</sup> colony-forming units/mL. Of patients with untreated bacterial meningitis, 80% to 90% have a positive CSF Gram stain. Unless unusual pathogens, such as anaerobes, are suspected, agar plate cultures of CSF are preferred to liquid media. Routine inoculation of CSF into broth culture is not recommended because isolates recovered by this technique are frequently contaminants [44,45].

With the exception of meningitis caused by gram-negative enteric bacilli, the yield of bacterial CSF cultures decreases soon after antibiotic therapy has been started [46]. The CSF WBC count and glucose and protein concentrations generally remain abnormal for several days, however, after initiating appropriate antibiotic therapy. Some authors recommend using latex agglutination tests to detect bacterial capsular antigens in patients with suspected bacterial meningitis who have been receiving antibiotics at the time the lumbar puncture is performed. These tests are not specific, however, and they identify very few cases of bacterial meningitis not already detected by CSF culture [47]. In the future, more sensitive techniques, such as amplification of the 16S rRNA gene by polymerase chain

reaction, may help to diagnose cases of bacterial meningitis in patients pretreated with antibiotics. Broad-range polymerase chain reaction has shown a sensitivity of 86% and specificity of 97% in detecting multiple organisms simultaneously compared with culture [48]. Real-time polymerase chain reaction techniques are even more sensitive in the clinical setting [49].

The presence of focal neurologic signs, cardiovascular instability, or papilledema in a patient with suspected bacterial meningitis raises the suspicion of increased intracranial pressure. In such cases, neuroimaging should be done before performing a lumbar puncture to avoid possible herniation [50,51]. Blood cultures and antibiotic administration should be done while awaiting results of neuroimaging studies to avoid substantial delays in the initiation of treatment.

### Management

#### *Antibiotic selection*

Factors to consider when selecting the appropriate antibiotic for treating bacterial meningitis include its activity against the causative pathogen and its ability to penetrate and attain effective bactericidal concentrations in the CSF. The integrity of the blood-brain barrier is compromised during meningitis, resulting in increased permeability to most antibiotics.  $\beta$ -Lactam antibiotics achieve concentrations of 5% to 20% of concomitant serum values. Even in the absence of substantial inflammation, penetration of highly lipid-soluble antibiotics, such as rifampin, chloramphenicol, and quinolones, is 30% to 50% of serum concentrations. In contrast, the concentration of vancomycin is less than 5% of the serum concentrations. Experimental models of bacterial meningitis suggest that prompt bacteriologic cure is predictable if antibiotic concentrations that are 10-fold to 30-fold greater than the minimal bactericidal concentration (MBC) for a specific microorganism are attained in CSF.

The pharmacodynamic properties of different antibiotics affect their bacteriologic efficacy. Aminoglycosides and fluoroquinolones exhibit concentration-dependent activity. Their effectiveness is determined by the ratio between the peak concentration or area under the concentration curve of the antibiotic and the MBC of the pathogen [52]. In contrast, the  $\beta$ -lactam antibiotics and vancomycin show concentration-independent activity. The time over the MBC during which the drug concentration exceeds the minimum inhibitory concentration (MIC) seems to determine drug effectiveness. These drugs need to be administered at frequent dosing intervals [53].

#### *Empirical therapy*

Empirical regimens are selected to cover the most likely etiologic agents. Therapy should be modified when the offending organism and its antimicrobial susceptibilities are known. In neonates, during the first 2 to 3 weeks of life,

ampicillin with either an aminoglycoside or cefotaxime is commonly used as initial empirical therapy. For neonates with late-onset meningitis, a regimen containing an antistaphylococcal antibiotic, such as nafcillin or vancomycin, plus cefotaxime or ceftazidime with or without an aminoglycoside is recommended [54].

Recommendations for empirical therapy of bacterial meningitis have been published as a practice guideline by the Infectious Disease Society of America [55]. For children older than 1 month of age, vancomycin plus a third-generation cephalosporin (ceftriaxone or cefotaxime) are recommended for initial therapy. In patients with predisposing factors, such as penetrating trauma, postneurosurgery, or CSF shunt, empirical therapy should include vancomycin plus cefepime or ceftazidime or meropenem. In cases of basilar skull fracture, a regimen containing vancomycin plus ceftriaxone or cefotaxime usually provides adequate empirical therapy.

#### Pathogen-specific antimicrobial therapy

Penicillin G or ampicillin remains the standard therapy for susceptible (MIC  $\leq 0.06$   $\mu\text{g/mL}$ ) strains of *S. pneumoniae* or *N. meningitidis*; a third-generation cephalosporin is a reasonable alternative. A third-generation cephalosporin (ceftriaxone or cefotaxime) is indicated to treat either of these organisms if they are not susceptible to penicillin (MIC  $\geq 0.1$   $\mu\text{g/mL}$ ), but are susceptible to the cephalosporin (MIC  $\leq 0.5$   $\mu\text{g/mL}$ ). Isolates that are not susceptible to penicillin and have a MIC to the third-generation cephalosporin that is 1  $\mu\text{g/mL}$  or

Table 1  
Recommended antimicrobial therapy for selected pathogens in children with bacterial meningitis

Bacteria	Antimicrobial of choice	Alternative therapy
<i>Haemophilus influenzae</i>		
$\beta$ -lactamase negative	Ampicillin	Ceftriaxone, cefotaxime, cefepime, chloramphenicol*, fluoroquinolone
$\beta$ -lactamase positive	Ceftriaxone or cefotaxime	Cefepime, chloramphenicol*, fluoroquinolone
<i>Streptococcus agalactiae</i>	Penicillin G $\pm$ gentamicin or ampicillin $\pm$ gentamicin	Ceftriaxone or cefotaxime
<i>Listeria monocytogenes</i>	Ampicillin $\pm$ gentamicin	Trimethoprim-sulfamethoxazole
<i>Escherichia coli</i> and other Enterobacteriaceae	Ceftriaxone or cefotaxime $\pm$ aminoglycoside	Cefepime or meropenem
<i>Pseudomonas aeruginosa</i>	Ceftazidime + aminoglycoside or cefepime + aminoglycoside	Meropenem $\pm$ aminoglycoside
<i>Staphylococcus aureus</i>		
Methicillin susceptible	Nafcillin or oxacillin	Vancomycin
Methicillin resistant	Vancomycin $\pm$ rifampin	—
<i>Enterococcus</i>		
Ampicillin susceptible	Ampicillin + gentamicin	—
Ampicillin resistant	Vancomycin + gentamicin	—

\* 50% of *H. influenzae* isolates are resistant in certain areas of the world.

greater should be treated with vancomycin plus a third-generation cephalosporin (ceftriaxone or cefotaxime); and the addition of rifampin should be considered. Cefepime and meropenem are alternative therapies for *S. pneumoniae* with intermediate resistance to penicillin (MIC 0.1–1  $\mu\text{g/mL}$ ); a fluoroquinolone, either gatifloxacin or moxifloxacin, is an effective alternative for penicillin-resistant or cephalosporin-resistant isolates.

Vancomycin and rifampin are usually active against cefotaxime-resistant or ceftriaxone-resistant *S. pneumoniae*, although vancomycin-tolerant strains have been described. Vancomycin tolerance is thought to arise from a defect in the bacterium's endogenous cell death pathway that results in defective autolysis. In one study, these isolates represented almost 4% of *S. pneumoniae* nasopharyngeal isolates from children and 10% of meningitis isolates from adults and children. These isolates were associated with increased mortality in the infected children [56].

Antibiotics recommended for other pathogens causing bacterial meningitis in children are summarized in Table 1. Dosages of the most commonly used intravenous antibiotics for therapy of bacterial meningitis in children are presented in Table 2.

Table 2  
Dosages of antibiotics administered intravenously for pediatric patients with bacterial meningitis

Antibiotic	Total daily dose (dosing interval in hours)		
	Neonates, age in days*		
	0–7	8–28	Infants and children
Amikacin**	15–20 mg/kg (12)	30 mg/kg (8)	20–30 mg/kg (8)
Ampicillin	150 mg/kg (8)	200 mg/kg (6–8)	200–300 mg/kg (6)
Cefepime	—	—	150 mg/kg (8)
Cefotaxime	100–150 mg/kg (8–12)	150–200 mg/kg (6–8)	200–300 mg/kg (6–8)
Ceftazidime	100–150 mg/kg (8–12)	150 mg/kg (8)	150 mg/kg (8)
Ceftriaxone	—	—	80–100 mg/kg (12–24)
Chloramphenicol	25 mg/kg (24)	50 mg/kg (12–24)	75–100 mg/kg (6)
Gentamicin**	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)
Meropenem	—	—	120 mg/kg (8)
Nafcillin	75 mg/kg (8–12)	100–150 mg/kg (6–8)	200 mg/kg (6)
Oxacillin	75 mg/kg (8–12)	150–200 mg/kg (6–8)	200 mg/kg (6)
Penicillin G	0.15 mU/kg (8–12)	0.2 mU/kg (6–8)	0.3 mU/kg (4–6)
Rifampin	—	10–20 mg/kg (12)	10–20 mg/kg (12–24)
Tobramycin**	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)
Trimethoprim-sulfamethoxazole	—	—	10–20 mg/kg (6–12)
Vancomycin***	20–30 mg/kg (8–12)	30–45 mg/kg (6–8)	60 mg/kg (6)

\* For neonates weighing <2000 g, refer to Bradley JS, Pocket book of pediatric antimicrobial therapy, 15th edition; \*\* Need to monitor peak and trough serum concentrations; \*\*\* Maintain serum trough concentrations of 15–20  $\mu\text{g/mL}$ .

Adapted from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267–84.

With the use of antibiotics to which the organism exhibits in vitro susceptibility, CSF cultures become sterile in most cases within 24 to 36 hours after initiating therapy [57]. In some cases, a repeat lumbar puncture is indicated 24 to 48 hours after start of therapy because of lack of clinical improvement or when meningitis is caused by resistant *S. pneumoniae* strains or by gram-negative enteric bacilli. The authors also recommend a second lumbar puncture in all neonates because the clinical findings are not helpful in judging success of therapy in this age group, and delayed sterilization of CSF is common.

Duration of therapy depends on the age of the patient, the causative pathogen, and the clinical course. The duration of antibiotic treatment is individualized, and longer regimens than the ones suggested herein might be required for complicated cases. For neonates with GBS meningitis, 14 to 21 days is recommended; for *L. monocytogenes* meningitis, 10 to 14 days is usually satisfactory; and for gram-negative enteric meningitis, a minimum of 3 weeks of therapy usually is provided. Meningococcal meningitis usually is treated for 4 to 7 days; *H. influenzae*, for 7 to 10 days; and *S. pneumoniae*, for 10 to 14 days. Neuroimaging (head CT or MR imaging) is recommended in neonates to determine whether intracranial complications require prolonged therapy or whether surgical intervention is required.

#### *Adjunctive and supportive therapy*

##### *Dexamethasone*

Animal models of bacterial meningitis have shown beneficial effects of dexamethasone administration, including decreasing inflammation, reducing cerebral edema and increased intracranial pressure, and lessening brain damage [53]. In adults with bacterial meningitis, a recently published prospective, randomized, placebo-controlled, double-blind multicenter trial showed that dexamethasone recipients had a lower percentage of unfavorable outcomes, including death, compared with subjects who received placebo. Benefits were evident in the subgroup with pneumococcal meningitis, but not in others [58]. In pediatric patients, several double-blind, placebo-controlled studies to evaluate the use of adjunctive dexamethasone in bacterial meningitis have been conducted. These studies showed a reduction of indices of meningeal inflammatory and decreased audiologic and neurologic sequelae in patients who received dexamethasone compared with patients who received placebo. These beneficial effects were greatest in cases of *H. influenzae* meningitis, especially in regards to hearing outcomes. Clinical benefit was less evident in cases of pneumococcal meningitis; dexamethasone was most beneficial when given with or shortly before the first dose of parenteral antibiotic therapy [59].

Because dexamethasone can decrease antibiotic penetration into the CNS, concerns have been raised that the use of steroids may impede the eradication of highly resistant pneumococcal strains from the CSF [38,60,61]. Clinical data do not support this hypothesis, however, when the combination of vancomycin and a third-generation cephalosporin is used as initial empirical therapy.

Current recommendations support the use of dexamethasone in infants and children with Hib meningitis [55]. For infants and children 6 weeks old and older with pneumococcal meningitis, adjunctive therapy with dexamethasone should be considered after weighing the potential benefits and possible risks. Data are insufficient to recommend dexamethasone therapy in neonates with bacterial meningitis [55].

Recommended dexamethasone dosing regimens range from 0.6 to 0.8 mg/kg daily in two or three divided doses for 2 days to 1 mg/kg in four divided doses for 2 to 4 days [41,55]. For optimal results, the first dose of dexamethasone should be administered before or concomitant with the first parenteral antibiotic dose.

Other adjunctive therapies, such as different anti-inflammatory drugs and compounds including lipopolysaccharide-neutralizing proteins, anticytokine antibodies [62], and anticytotoxic agents [63], have been tested in animal models of bacterial meningitis with varied success [32]. None of these compounds has been evaluated in patients with bacterial meningitis.

##### *Supportive therapy*

Maintenance of adequate cerebral perfusion and management of increased intracranial pressure are crucial to the prevention of potential life-threatening complications of bacterial meningitis. Maintaining normal blood pressure may require infusion of a vasoactive agent, such as dopamine or dobutamine. Fluid restriction is advised only in patients who are not dehydrated and have evidence of inappropriate antidiuretic hormone secretion (hyponatremia). There is no evidence that fluid restriction reduces cerebral edema in children with bacterial meningitis. Fluid restriction in the presence of hypovolemia could result in decreased systemic blood pressure that could compromise cerebral perfusion [64].

Strategies used to reduce increased intracranial pressure include antipyretic agents, avoiding frequent and vigorous procedures such as intubation and tracheal suction, 30° bed head elevation, short-term hyperventilation, mannitol administration, and high-dose barbiturate therapy. Control and prevention of seizures can be attained with anticonvulsant medications; benzodiazepines, phenytoin, and phenobarbital are commonly used for this purpose.

##### **Complications**

The mortality rate for bacterial meningitis in children ranges from 4% to 10% in more recent studies. Case-fatality rate and incidence of neurologic sequelae are greatest in pneumococcal meningitis. Approximately 15% of children with pneumococcal meningitis present in shock [65]. Shock also is a common presentation in cases of meningococcal meningitis, and it can be associated with disseminated intravascular coagulation.

Seizures are a common complication of bacterial meningitis, affecting one third of patients. Seizures that persist for longer than 4 days after diagnosis or

arise for the first time late in the course of the disease are more likely to be associated with neurologic sequelae. Focal seizures have a worse prognosis.

Subdural effusions are present in one third of patients with bacterial meningitis and are associated more commonly with *H. influenzae* and *S. pneumoniae* than with meningococcal meningitis. They are asymptomatic and resolve spontaneously without permanent neurologic sequelae in most cases [66]. Subdural empyema should be suspected when prolonged fever and irritability with or without CSF leukocytosis are present. This is an uncommon complication of bacterial meningitis in infants, occurring in less than 2% of cases. Management consists of surgical drainage and appropriate antibiotic therapy [67].

Brain abscesses are an uncommon complication of bacterial meningitis; they are more likely to occur in newborns infected with *C. koseri* or *Proteus* species. Hydrocephalus, hemorrhage, and infarctions resulting from thromboses are other potential complications of bacterial meningitis in children.

Persistent fevers often are related to nosocomially acquired infection, including infections caused by viruses or infected intravenous catheters. Drug fever, which is commonly associated with  $\beta$ -lactam antibiotics and anticonvulsant therapy, should be suspected when other causes of persistent fever have been excluded. Cranial imaging with CT or MR imaging with gadolinium should be performed in cases of prolonged obtundation, seizures persisting for more than 72 hours after the start of treatment, continued excessive irritability, persistently abnormal CSF indices, and focal neurologic findings and in newborn infants.

### Prognosis

Factors that can affect outcome from bacterial meningitis are age; etiology; CSF findings at the time of diagnosis, including concentration of bacteria or bacterial products, WBC count, and glucose concentration; and the time to sterilization of CSF after start of therapy. Decreased level of consciousness and seizures occurring during hospitalization have been associated with increased mortality and neurologic sequelae in several studies [2,65]. Seizures that are focal or are difficult to control imply an underlying vascular disturbance, such as venous thrombosis or infarction, and are associated with epilepsy and other neurologic sequelae [68].

The most common neurologic sequela of bacterial meningitis is hearing impairment. Some degree of hearing loss occurs in about 25% to 35% of patients with meningitis caused by *S. pneumoniae* and in 5% to 10% of patients with *H. influenzae* and *N. meningitidis* infection. Low glucose concentration in CSF has been shown to correlate with the development hearing impairment in several studies [2,61,69]. Approximately 10% of children develop neuromotor and learning disabilities and speech and behavioral problems as a consequence of bacterial meningitis [70,71].

### Prevention

#### Vaccines

Antibodies directed against the bacterial capsular components of *H. influenzae*, *N. meningitidis*, and *S. pneumoniae* play a major role in development of immunity against these organisms. Immunization with the *Haemophilus*, pneumococcal, and meningococcal conjugate vaccines has had a significant impact on the incidence of invasive diseases in children caused by these organisms.

The routine use of conjugated Hib vaccines in children has been associated with a reduction of more than 99% of invasive disease, including meningitis, in developed countries. Rates of Hib disease have been affected modestly in other areas of the world where the vaccine is not routinely available [14,72].

The heptavalent conjugate pneumococcal vaccine, PCV7, was approved for routine use in infants in 2000. Initial clinical trials showed a reduction of more than 90% in invasive pneumococcal infections in children [73]. Subsequent clinical studies have confirmed the efficacy of conjugated pneumococcal vaccine in children and a concomitant reduction in the incidence of invasive pneumococcal disease in adults, attributed to reduced circulation of the bacteria [18,29,74,75]. Children older than 2 years of age who are at risk of developing invasive pneumococcal disease, such as children with sickle hemoglobinopathy, should receive the conjugate vaccine followed by the 23-valent polysaccharide vaccine. This includes patients with cochlear implants [75].

A quadrivalent meningococcal polysaccharide vaccine against serogroups A, C, Y, and W-135 strains is recommended in the United States for high-risk children older than 2 years, such as children with asplenia or terminal complement deficiencies. In 2000, the Advisory Committee on Immunization Practices recommended that health care providers inform all college students about the risks of meningococcal disease in this population and to make this vaccine available to individuals who want to reduce their risk for meningococcal disease, which is highest in freshmen living in dormitories [76]. Immunogenicity of the vaccines developed against serogroup B meningococci is poor. A major problem of vaccine development for this serogroup is the homology of this bacterium's capsular polysaccharide with components of human neural tissue. Current research is ongoing to improve the immune response to vaccines designed against this serogroup, which is endemic in North America and Europe [77]. A meningococcal serogroup C conjugate vaccine is routinely being administered in the United Kingdom and Canada. The Vaccines and Related Biological Products Advisory Committee of the US Food and Drug Administration voted to recommend licensure of a quadrivalent conjugate meningococcal vaccine (groups A, C, Y, and W-135) for protection against invasive meningococcal disease in adolescents and adults age 11 to 55 years. Clinical trials with this vaccine showed modest immunogenicity in infants [78].

Maternal immunization with GBS (*Streptococcus agalactiae*) conjugate vaccine may represent a future strategy to reduce neonatal GBS streptococcal

disease. Maternal administration of prophylactic antibiotics has an impact on preventing only early-onset GBS disease [79].

### Chemoprophylaxis

Administration of prophylactic antibiotics to asymptomatic contacts of meningitis index cases is indicated to decrease carriage and prevent spread of the disease. Recommendations for chemoprophylaxis in cases of *H. influenzae* and *N. meningitidis* meningitis are provided in Table 3 [80].

Table 3  
Chemoprophylaxis of *Haemophilus influenzae* type b and meningococcal meningitis (*Neisseria meningitidis*)

	<i>H. influenzae</i>	<i>N. meningitidis</i>
Individuals for whom chemoprophylaxis is recommended	All members of the household* with: ≥1 contact <4 years old incompletely immunized, including infants <12 months old without the primary series Immunocompromised child in household, even if >4 years old and fully immunized All susceptible nursery/childcare center contacts when ≥2 cases of Hib invasive disease have occurred within 60 d Index case treated with ampicillin or chloramphenicol if <2 years of age or with a susceptible household contact	All household contacts Childcare/nursery school contacts during 7 d before onset of illness Direct exposure to index case's secretions—kissing, sharing of eating utensils, toothbrushes, close social contact—during 7 d before onset of illness Health care workers who performed unprotected mouth-to-mouth resuscitation, intubation, suction Frequently slept or ate in same dwelling as index case during 7 d before onset of illness
Recommended agents/dosage	Rifampin 20 mg/kg orally once daily × 4 d. Decrease dose to 10 mg/kg/d for infants <1 month old†	Rifampin 10 mg/kg orally once daily × 2 d. Decrease dose to 5 mg/kg/d for infants ≤1 month old† or Ceftriaxone 125 mg for ≤15 years olds or 250 mg for >15 years olds intramuscularly, single dose or Ciprofloxacin 500 mg orally in ≥18 years old, single dose

\* Includes people residing with the index case or nonresidents who spent ≥4 hours with the index case for at least 5 of the 7 days preceding the hospital admission day of the index case.

† Maximum daily dose of 600 mg. Not recommended in pregnant women.

### Summary

Prompt and accurate diagnosis and adequate treatment of bacterial meningitis in children remains a major challenge, as reflected by the continued high morbidity and case-fatality rates of the disease worldwide. Appropriate use of antibiotics, along with adjunctive therapies, such as dexamethasone, has proved helpful in the prevention of neurologic sequelae in children with bacterial meningitis. Better understanding of pathophysiologic mechanisms likely would result in more effective therapies in the future. Use of conjugate vaccines against the most common pathogens has been crucial in preventing bacterial meningitis in children.

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## Distinguishing Among Prolonged, Recurrent, and Periodic Fever Syndromes: Approach of a Pediatric Infectious Diseases Subspecialist

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Approaching the differential diagnosis of a child with a prolonged, recurrent, or periodic fever requires an extensive interview with disciplined dissection of the history. Diagnoses are considered and supported or excluded. Review of systems is used to understand the totality of the condition and to seek certain occurrences specific to diagnoses considered. A careful and complete physical examination is systems based, beginning with growth and ending with a thorough neurologic examination. Laboratory tests rarely establish an unexpected diagnosis. They are used to support or confirm a diagnosis, or to establish “wellness” of major organ systems as predicted by history and physical examination. This article discusses three objectives for the clinician: (1) to categorize patterns of fever illnesses and prioritize differential diagnoses; (2) to diagnose and manage the most frequently encountered prolonged fever syndrome, deconditioning; and (3) to expand knowledge and approach to diagnosing periodic fever syndromes. The approach described in this article represents the honed, 30-year experience of a pediatric infectious diseases subspecialist. Definitions of fever syndromes are shown in Box 1. Figs. 1 and 2 are algorithms to help the pediatrician manage confidently

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