Meningitis

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Objectives

After completing this article, readers should be able to:

1. List the typical clinical manifestations of meningitis.
2. Distinguish bacterial, viral, tuberculous, and fungal meningitis based on clinical presentation and cerebrospinal fluid analysis.
3. Describe key management issues for a child who has bacterial meningitis.
4. Recognize the common acute complications of meningitis.
5. Identify the long-term sequelae of meningitis.

Introduction

Since the last review of meningitis in *Pediatrics in Review* in 1998 by Wubbel and McCracken, a number of developments have occurred in the epidemiology and management of meningitis in the pediatric patient. Pneumococcal and meningococcal conjugate vaccines have been implemented, use of enteroviral polymerase chain reaction (PCR) has become routine in most children's hospitals, and additional data concerning the effective use of adjunctive dexamethasone are now available.

Still, meningitis remains one of the most significant infections in children, and morbidity and mortality in the child who has bacterial meningitis has not changed in the last 15 years, despite the availability of newer antibiotics and preventive strategies. It is crucial for pediatricians to remain vigilant in their understanding of the epidemiology, pathogenesis, management, and follow-up of affected patients. Although this article focuses on meningitis, key central nervous system (CNS) pathogens that cause meningoencephalitis or encephalitis also are discussed because clinical symptoms, signs, and laboratory findings in these conditions often overlap.

Abbreviations

BCG:	Bacille Calmette-Guérin
CNS:	central nervous system
CSF:	cerebrospinal fluid
CT:	computed tomography
GBS:	group B *Streptococcus*
GCS:	Glasgow Coma Scale
Hib:	*Haemophilus influenzae* type b
HIV:	human immunodeficiency virus
HSV:	herpes simplex virus
IAP:	intrapartum antimicrobial prophylaxis
IV:	intravenous
PCR:	polymerase chain reaction
SIADH:	syndrome of inappropriate antidiuretic hormone
TB:	tuberculosis
TST:	tuberculin skin test
WBC:	white blood cell

Epidemiology and Etiology

A variety of infectious agents can cause meningitis, including bacteria, viruses, fungi, and mycobacteria. Most pathogens are specific to certain age groups, seasonality, geography, and underlying host factors. In the developed world, meningococcus and pneumococcus currently cause 95% of cases of acute bacterial meningitis in children. Pneumococcal and meningococcal meningitis occur with an annual incidence in the range of 4 to 5 and 2.5 cases per 100,000 children younger than 5 years of age, respectively. Group B *Streptococcus* (GBS) remains the predominant bacterial pathogen in the neonatal population (Fig. 1).

For physicians who trained prior to 1990, the eradication of meningitis caused by *Haemophilus influenzae* type b (Hib) likely remains the most dramatic medical development witnessed during their careers. Since the introduction of Hib conjugate vaccines in 1988, the incidence of invasive disease in the United States has decreased 99%. However, in developing countries, Hib remains an important cause of meningitis.

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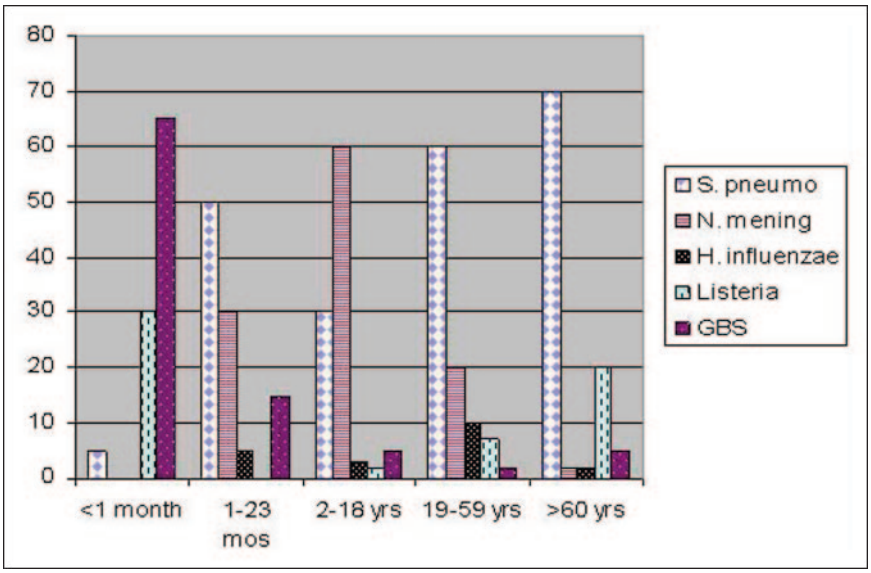

Figure 1. Pathogenic agents of bacterial meningitis in the United States by age group, 1995. Figure derived from Centers for Disease Control and Prevention data. GBS=group B *Streptococcus*, N. mening=*Neisseria meningitidis*, S. pneumo=*Streptococcus pneumoniae*

Although typical bacterial and viral causes of meningitis are the focus of this review, rickettsial infections and certain drugs associated with CNS inflammation also are covered briefly. In addition, tuberculous meningitis is reviewed because delayed diagnosis of this infection is common and can result in significant sequelae. Finally, special pathogens that cause meningitis in the neonate, the immunocompromised host, and patients who have indwelling foreign bodies are discussed.

Neonatal Disease

Neonatal Streptococcal Meningitis

GBS remains the predominant neonatal meningitis pathogen, although sporadic cases related to *Listeria monocytogenes* and gram-negative agents, including *Escherichia coli*, continue to be important.

In most cases, the maternal genital tract is the source of the pathogen for both early- and late-onset disease, the latter often associated with CNS infection. In the era before intrapartum antimicrobial prophylaxis (IAP), 1 to 4 neonatal infections per 1,000 live births were reported, with 75% presenting as early-onset disease (first 7 days after birth). Although IAP has been associated with a greater than 80% reduction in early-onset disease, such cases still occur. Infants typically manifest with signs suggestive of sepsis, often with pneumonia, but less commonly with meningitis, which is noted in 5% to 10% of cases of early-onset GBS disease.

Late-onset disease has not been affected by IAP, and the current incidence estimates suggest approximately 0.3 cases per 1,000 live births, a figure similar to the current incidence of early-onset disease. The typical infant who has late-onset disease is 3 to 4 weeks of age and presents with meningitis or bacteremia, although skeletal infection, adenitis, and cellulitis also occur. The few cases of GBS disease occurring after 3 months of age generally are seen in infants who were born preterm.

Neonatal Gram-negative Meningitis

Gram-negative bacillary meningitis is rare in the pediatric population. It is encountered almost exclusively in neonates, with *E coli* being the most commonly isolated pathogen. The maternal genital tract is the most likely source for infection, although nosocomial sources within the nursery setting also are documented. Similar to GBS meningitis, prematurity, maternal intrapartum infection, and prolonged rupture of membranes are predisposing factors. The unusual predilection of these organisms for CNS infection in neonates may relate to a combination of factors, including less efficient defense mechanisms, deficient transfer of antibodies from mother to baby in the preterm infant of less than 32 weeks' gestation, and an increased ability of bacteria to penetrate the blood-brain barrier.

Environmental sources are well documented for other gram-negative neonatal meningitis pathogens such as *Citrobacter koseri*, *Enterobacter sakazakii*, and *Serratia marcescens*. These pathogens are notable for their association with brain abscesses, although the pathogenesis of this common complication is not well defined.

Neonatal Herpes Simplex (HSV) Infection

HSV in the newborn can present as isolated skin or mucous membrane lesions, encephalitis, or a disseminated process. Seventy-five percent of cases are caused by HSV-2. In most instances, transmission occurs when an infant is delivered vaginally through an infected birth canal, although ascending infection can occur in the face of intact amniotic membranes. Occasionally, horizontal transmission from a caregiver or health-care worker oc-

curs from a nongenital source, usually related to virus transfer from mouth or hands.

Although HSV infection occurs most commonly in infants born to mothers who have active primary infection compared with those who have recurrent genital herpes (≥50% versus ≤5%, respectively), frequently no maternal history or clinical evidence is available to alert the practitioner to this diagnosis. The incubation period is 2 days to 2 weeks, and most infants who develop HSV CNS infection are 2 to 3 weeks of age.

Neonatal *Listeria* Meningitis

Maternal infection usually relates to a food-borne source (unpasteurized milk and soft cheeses, prepared ready-to-eat meats, undercooked poultry, unwashed raw vegetables) and can precipitate abortion, preterm delivery, or early-onset infection. A septic appearance in the neonate is typical in cases of early onset, and a characteristic papular truncal rash has been identified. Such early-onset cases are associated with *Listeria* serotypes Ia, Ib, and IVb. Asymptomatic fecal and vaginal carriage also can occur and result in infection from a transplacental source, ascending infection, or exposure at the time of delivery. Late-onset meningitis may follow exposure at delivery and most often is associated with serotype IVb.

Common Non-neonatal Bacterial Pathogens

Streptococcus pneumoniae

Pneumococcus has emerged as the leading pathogen causing bacterial meningitis in infants and young children in developed countries (Fig. 1). Data from the Centers for Disease Control and Prevention from the year 2000 confirmed 17,000 cases per year of invasive pneumococcal disease among children younger than 5 years of age, including 700 cases of meningitis and 200 deaths in the United States. Children younger than 1 year of age have the highest risk for meningitis, with an estimated incidence of approximately 10 per 100,000 population. The pathogenesis of pneumococcal meningitis occurs primarily through nasopharyngeal colonization, with subsequent bacteremia and seeding of the choroid plexus. Although 90 pneumococcal serotypes are known, 7 serotypes (14, 6B, 19F, 18C, 23F, 4, and 9V) have been noted to account for 78% of invasive strains.

In February 2000, a 7-valent polysaccharide-protein conjugate vaccine (Prevnar®, Wyeth Pharmaceuticals, Philadelphia, Pa.) was incorporated into the universal childhood vaccination schedule. Since implementation, the number of invasive pneumococcal infections caused by vaccine-serogroup isolates among eight United States children's hospitals has decreased more than 75% for children 24 months of age and younger. Serotype replacement (emergence of nonvaccine serotypes) has emerged, and cases of meningitis continue to be identified. In our institution, the incidence of bacteremia has decreased significantly, although pneumococcal meningitis and cases of empyema continue to occur and are related almost exclusively to nonvaccine serotypes. In the last 2 to 3 years, multidrug-resistant serotype 19A has emerged as an important cause of invasive pneumococcal infection.

Neisseria meningitidis

Among the clinical presentations of invasive meningococcal infection, meningitis is the most common. Meningococcal disease generally occurs in otherwise healthy individuals and often has a fulminant presentation with high fatality rates. Secondary cases and outbreaks are well described in the literature.

Between 2,000 and 3,000 cases of invasive meningococcal disease occur each year, with the highest age-specific incidence in children younger than 1 year of age and two thirds of cases seen in children younger than 5 years of age. A second peak in the 8- to 11-year age group was noted in a recent study, and *N meningitidis* is the predominant bacterial agent of meningitis in young adults. Although 98% of invasive meningococcal infections are sporadic, outbreaks can and do occur. A 2005 review of 76 outbreaks in the United States noted that one third were community-based, with the other two thirds occurring in colleges and universities, primary and secondary schools, and nursing homes.

Historically, meningococcus was recognized initially as a cause of meningitis in 1805 after an epidemic occurred in Geneva, Switzerland. Nearly 100 years passed before the importance of nasopharyngeal carriage was recognized; reports now confirm that most invasive infections appear within days of acquiring pathogenic strains.

Nasopharyngeal carriage can be intermittent, with peaks at age 1 year and after age 15 years. An increased risk of colonization is noted with crowding, exposure to active and passive smoking, pneumococcal carriage, and concomitant upper respiratory tract infection. An increased risk for meningococcal infection has been confirmed following outbreaks of influenza A. Other conditions that predispose to meningococcal infection include anatomic or functional asplenia, terminal complement deficiency, laboratory exposure, and travel to epidemic or hyperendemic regions (Saudi Arabia, sub-Saharan Africa).

In 1909, immunologically distinct serogroups of meningococcus were identified; today, at least 13 serogroups have been identified. Predominant pathogenic serogroups include A, B, C, and W-135, and since 1996, B, C, and Y strains have predominated in the United States. In the United Kingdom and other countries where serogroup C conjugate vaccine has been implemented, a nearly 80% reduction in serogroup C cases has occurred, with documented herd immunity sufficient to protect unimmunized children.

Viral, Miscellaneous Infectious, and Noninfectious Pathogens

Aseptic meningitis, defined as a syndrome of meningeal inflammation in which common bacterial pathogens have not been identified, is caused by a variety of infectious and noninfectious agents. A definitive agent is established in one in four patients, and by far the most common agents are viral, with enteroviruses predominating in the pediatric population. In certain parts of the United States, including southern New England and the eastern mid-Atlantic states, the upper Midwest (Minnesota and Wisconsin), and northern California, *Borrelia burgdorferi* is an important cause of CNS infection.

The seasonality of enteroviral meningitis generally is such that the typical pediatric resident who starts training in July becomes adept at recognizing and diagnosing this clinical infection. Most children are not severely ill and often present with a nonspecific febrile illness, although meningeal signs may be present. The typical cerebrospinal fluid (CSF) findings are noted, and many children improve clinically following lumbar puncture.

A large number of enterovirus serotypes are documented, and several viruses can circulate simultaneously in a season. The most common viruses associated with meningitis outbreaks include Coxsackieviruses A9, B2, and B4 and echoviruses 6, 9, 11, and 30.

Enteroviruses are transmitted by the fecal-oral route, and cases of meningitis are recognized most commonly in children younger than 1 year of age. In young neonates who have symptoms and signs consistent with sepsis, a history to elicit maternal symptoms should be sought. Maternal enteroviral infection may precede neonatal infection in up to 70% of infants diagnosed as having enteroviral disease within the first 10 days after birth. Vertical transmission to the infant is well described, as are rare cases of intrauterine transmission. Disseminated disease, with liver, brain, and myocardial involvement, occurs in this age group and is associated with high mortality. Some experts recommend the use of intravenous (IV) immune globulin in treating neonatal enteroviral infection. Studies are ongoing to assess the effectiveness of pleconaril (a new antiviral drug) in such cases. In contrast, uncomplicated enteroviral meningitis in the immunocompetent infant and child has a benign course and generally has no sequelae.

CNS involvement can occur with a variety of other agents, and often the clinical presentation is not restricted to meningitis; meningoencephalitis or encephalitis presentations often predominate. Pathogens such as HSV, *Mycoplasma*, arboviruses, Epstein-Barr virus, rabies virus, human herpesvirus-6, *Ehrlichia* sp, and *Rickettsia rickettsii* are examples of pathogens more likely to cause encephalopathic signs and symptoms.

Cases of noninfectious aseptic meningitis include those that are drug-induced or are related to vasculitis in the setting of systemic lupus erythematosus or Kawasaki disease. The drugs implicated most commonly include nonsteroidal anti-inflammatory agents such as ibuprofen, IV immunoglobulin, and muromonab-CD3 (OKT3) and antimicrobials such as trimethoprim-sulfamethoxazole. Aseptic meningitis can occur in Kawasaki disease; the typical mucocutaneous manifestations of that disease generally direct the clinician to this diagnosis.

Less Common Pathogens

Non–neonatal Gram–negative Bacilli

Meningitis caused by gram-negative bacilli occurs beyond the newborn period, with the pathogens generally being nosocomial in origin. In one study of adults, most patients had predisposing factors, including neurosurgery or head trauma within the past month, presence of a neurosurgical device, or CSF leaks (rhinorrhea).

Mycobacterium tuberculosis

The World Health Organization estimates that 1.3 million annual cases and 450,000 deaths are caused by tuberculosis (TB) globally. A review in 2004 provided an in-depth discussion of tuberculous meningitis, noting that this pathogen is now the most common cause of bacterial meningitis in sub-Saharan Africa, likely related to the prevalence of human immunodeficiency virus (HIV) infection.

Pediatric meningitis caused by *M tuberculosis* tends to be a complication of primary infection in the child 5 years of age or younger. Primary infection occurs after droplet inhalation, with dissemination from the lung to the lymphatics and to the bloodstream. In the United States, most cases of TB arise in lower-income groups and are encountered most commonly in urban cities. This distri-

bution is exemplified by seven states accounting for two thirds of cases. Most cases occur in nonwhite individuals, with African American children being at highest risk. Approximately one quarter of pediatric TB cases in the United States occur in foreign-born children, most commonly in children born in Mexico. Although high latent TB rates are recognized both in immigrants and internationally adopted children, the child traveler also is at risk for infection and disease.

Other risk factors predictive of the development of tuberculous disease include HIV infection; treatment with immunosuppressive medications, including corticosteroids and tumor necrosis factor antagonists such as infliximab or etanercept; and underlying medical conditions, such as lymphoma, diabetes, chronic renal failure, and malnutrition.

Borrelia burgdorferi

Lyme meningitis usually afflicts children living in Lyme-endemic regions such as states in southern New England, the eastern mid-Atlantic, the upper Midwest, and northern California. *B burgdorferi*, a spirochete, is transmitted in most cases by the deer tick *Ixodes scapularis* or *I pacificus*. Although neurologic manifestations of borreliosis can occur at any stage, chronic basilar meningitis occurs most commonly in the early disseminated phase of infection. The seasonality of Lyme meningitis is similar to that of enteroviral meningitis.

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Rickettsia rickettsii

The tick-borne systemic vasculitis of Rocky Mountain spotted fever can have prominent CNS symptoms, and similar to enteroviral and *Borrelia* infections, cases cluster from May through August. The primary vector for *R rickettsii* is the *Dermacentor variabilis* tick in the east and central United States and *D andersoni* in the west. The diagnosis most often is made in children younger than 15 years of age, and the absence of tick bite history and typical exanthema are associated with a delay in diagnosis, with worse outcomes for those children diagnosed after day 5 of symptoms.

Clinical Manifestations of Meningitis

Infants and children who have meningitis can have myriad presentations, depending on the pathogen and the age of the patient. Infants younger than 1 month of age who have viral or bacterial meningitis can present with a constellation of constitutional, nonspecific signs, including fever, hypothermia, lethargy, irritability, and poor feeding. Signs and symptoms of increased intracranial pressure and meningeal inflammation such as vomiting, apnea, and seizures also can occur. Infants who have neonatal enterovirus infection, HSV infection, and bacterial meningitis can present with a similar sepsislike presentation.

Similarly, infants older than 1 month of age and young children present with nonspecific constitutional symptoms such as fever, lethargy, and irritability. Signs and symptoms due to meningeal inflammation and increased intracranial pressure, including mental status changes, vomiting, and seizures, continue to predominate.

Older children and adolescents often experience malaise, myalgia, headache, photophobia, neck stiffness, anorexia, and nausea. However, some patients who have meningitis present with an acute and fulminant onset of sepsis and multiorgan involvement.

History

The history and physical examination are integral parts of the initial evaluation of an infant or child who is presumed to have meningitis. Historical factors of importance in the child who is suspected of having a CNS infection need to be detailed systematically and meticulously (Table 1).

Approximately 20% to 25% of children who have pneumococcal meningitis have a predisposing risk factor. Mechanical risk factors include CNS trauma, cochlear implants, ventricular shunt placement, and a CSF leak. Medical risk factors include immunodeficiency such as HIV infection, asplenia, chronic renal disease, and sickle cell disease. Recent infections such as otitis media, sinusitis, and mastoiditis can predispose a child to bacterial meningitis.

It is important to record a thorough birth history and to inquire about contact with ill individuals, recent travel

Table 1. Historical Features of the Child Who Has Central Nervous System Infection

Important Historical Information	Key Questions
Past Medical History	• Recent illness • Chronic illness • Head/facial trauma
Past Surgical History	• Asplenia • Central nervous system shunts • Cochlear implants
Birth/Perinatal History	• Maternal sexually transmitted infection • Chorioamnionitis • Prolonged rupture of membranes • Perinatal infection
Immunizations	• Full review of vaccines, including dates of pneumococcal and meningococcal vaccines
Medications in past 6 months	• Nonsteroidal anti-inflammatory agents • Immunosuppressive agents • Recent intravenous immune globulin • Antibiotics
Exposures	• Ill contacts • Child care • Vectors, including bites/contact (ticks, mosquitos, cats, bats) • Tuberculosis exposure (institutionalized contacts, contacts in jail, homeless) • Travel (out of the country, wooded area/camping)

history or vector exposures, medication intake (specifically recent antibiotic use), and immunization status. Although identification of the underimmunized infant may not alter the approach to diagnosis and therapy, children who have had invasive pneumococcal infection should complete the full series of doses of pneumococcal vaccine appropriate for age on recovery.

For infants, a birth history, maternal GBS colonization status and treatment, and maternal history of sexually transmitted infection should be elicited, keeping in mind that neonatal HSV infection generally occurs in infants who have no concordant maternal history of HSV.

Infants and children who have bacterial meningitis usually have been healthy previously. It is important for clinicians to ask about and record child care exposure to facilitate chemoprophylaxis in appropriate situations. It is insufficient to review immunization history without personal inspection of the child's record, and the dates of Hib, pneumococcal, and meningococcal vaccines should be documented to ensure proper immunization.

Children who have Lyme meningitis generally reside in or have traveled to the distinct geographic regions where the implicated tick vector is endemic. The tick vector for Rocky Mountain spotted fever is more widespread in the United States, with cases reported from all states except for Maine, Alaska, and Hawaii. A history of being exposed to a tick or living in a wooded endemic area may be a key factor in making this diagnosis. The pediatric patient who has Lyme meningitis tends to be older (mean, 10 years) and has had a longer duration of prodromal symptoms (1 to 2 weeks) compared with the child who has had viral meningitis (1 to 2 days). The patient who has Lyme meningitis also is more likely to have cranial nerve findings, papilledema, and an erythema migrans rash than is the patient who has enteroviral meningitis.

Finally, tuberculous meningitis should be suspected in any patient who has meningitis and a history of close contact with adolescents or adults who have a positive tuberculin skin test (TST) or tuberculous disease or who were born in or traveled to a country at high risk for TB exposure.

Physical Examination

Physical findings that should be assessed quickly include the patient's general appearance and respiratory, cardiovascular, and neurologic status.

Specifically, the initial evaluation should include an assessment of vital signs (including pulse oximetry), an assessment of the cardiopulmonary status (work of breathing, breath sounds, perfusion, and pulses in addition to vital signs), and an assessment of consciousness, using the pediatric Glasgow Coma Scale (GCS) or other validated measure. Altered levels of consciousness can present as irritability, somnolence, lethargy, or coma. Concerning signs and symptoms of increased intracranial pressure include papilledema; diplopia; unilateral or bilateral dilated, poorly reactive pupils; or a bulging fontanelle in infants.

Following the initial assessment, a complete physical examination is essential. The fontanelle in infants should be palpated while the infant is held in a sitting position. Although not sensitive or specific for meningitis as an isolated maneuver, this measure is helpful when combined with all aspects of the evaluation. A head circum-

ference always should be obtained, especially in those who have an open fontanelle. Although meningismus is suggestive of meningeal irritation, this sign generally is not present in the young infant. Instead, paradoxic irritability is the usual sign of meningeal irritation. The infant who has meningitis does not wish to be handled but prefers to remain motionless. Often, the parent has noted this behavior and refrains from holding or rocking the infant. Marked irritability with a high-pitched cry may be noted by the clinician while moving the infant during the physical examination.

In the older child, signs of meningeal irritation should be elicited. To test for the Kernig sign, the patient lies supine and the thigh is flexed at a right angle to the trunk. If knee extension from this position elicits pain, the Kernig sign is positive. In assessing the Brudzinski sign, the patient lies supine and flexes his or her neck. A positive sign occurs if the patient also reflexively flexes the lower extremities, typically at the knees. It is important to note that the absence of Kernig and Brudzinski signs does not exclude meningitis.

The neurologic examination consists of both funduscopic and cranial nerve evaluation because papilledema can be present with Lyme meningitis, and cranial nerve 3, 4, and 6 palsies can be present with bacterial and Lyme meningitis. Bacterial meningitis can present with other focal neurologic deficits, although rarely.

Other body systems should be examined. Besides assessing the patient's perfusion, cardiac examination should include evaluation for jugular venous distention, a sign of possible myocarditis or pericardial effusion. Joint involvement can be present in GBS or meningococcal infection. Exanthems typical for enterovirus, borreliosis (erythema migrans), and invasive meningococcal or pneumococcal disease (petechiae and purpura) may be present. The appearance of vesicles in the infant younger than 6 weeks of age suggests the diagnosis of HSV infection. However, it also is important to recognize that most infants who have HSV CNS disease do not have skin lesions; clinical suspicion should be high for infants who present with a septic appearance and have negative bacterial cultures and refractory seizures in the setting of meningitis.

Diagnosis

All children who are suspected of having meningitis should have their CSF examined unless lumbar puncture is contraindicated. These contraindications include focal neurologic deficits, signs of increased intracranial pressure, uncorrected coagulopathy, and cardiopulmonary compromise. For patients who have signs of increased intracranial pressure, lumbar puncture should be deferred until computed tomography (CT) scan is performed. If a mass lesion, hemorrhage, midline shift, effacement of the basilar cisterns, or effacement of the sulci is noted, lumbar puncture should be deferred and antimicrobial therapy started promptly. It also is important to note that normal findings on CT scan do not exclude increased intracranial pressure, and the patient should be reassessed after lumbar puncture is performed (Fig. 2).

CSF examination should include cell count and differential count, glucose concentration, and protein measurements. These values must be interpreted based on the child's age; normal CSF values for an infant are very different from those of an adult. None of these values should be used in isolation because overlap exists in all categories for all types of meningitis. Serum glucose concentration should be measured to determine the ratio between serum and CSF glucose as a percentage. A Gram stain of the CSF should be performed promptly as well as cultures of the CSF and blood (Table 2).

Serum electrolytes should be measured because the syndrome of inappropriate antidiuretic hormone (SIADH) occurs in bacterial meningitis, although hyponatremia is noted in only 35% of cases. Leukopenia, thrombocytopenia, and coagulopathy may be present in meningococcal and rickettsial infection. The peripheral complete white blood cell (WBC) count may be high in pneumococcal meningitis, but in most cases of pneumococcal meningitis and viral meningitis, the WBC and platelet counts are within normal ranges.

Bacterial meningitis is characterized by CSF pleocytosis (WBC often greater than 1.0×10^3/mcL [1.0×10^9/L]), with a predominance of polymorphonuclear leukocytes. The glucose concentration usually is less than one half of the measured serum value, and the protein value often is greater than 1.0 g/dL (10 g/L). The Gram stain is extremely helpful if positive and may indicate the need to expand antimicrobial coverage, but the clinician should be aware that Gram stain findings never should be used to narrow the spectrum of empiric coverage.

CSF culture remains the gold standard for diagnosing bacterial meningitis. Susceptibility data are critical to adequate therapy and generally are available once identification of a specific bacterial pathogen is confirmed.

Other diagnostic tests may be considered, depending on the patient's clinical presentation and characteristics of the CSF examination. Viral meningitis, for example, is characterized by a lower cell count, often with a WBC count of 0.05 to 0.5×10^3/mcL (0.05 to 0.5×10^9/L). Neutrophil predominance is common early in the course

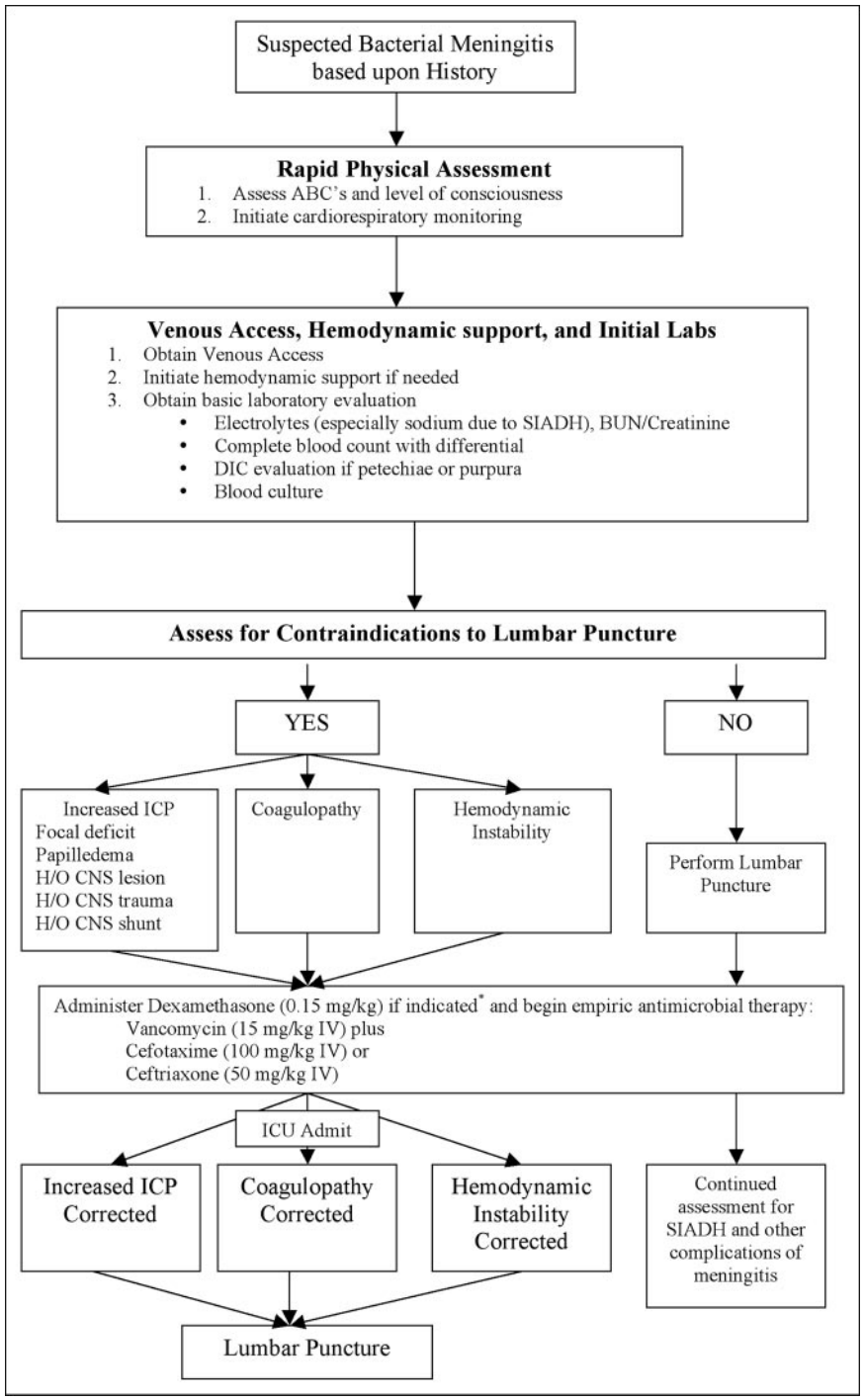

Figure 2. Suggested algorithm for suspected bacterial meningitis. *Meningitis suspected clinically or by cerebrospinal fluid findings. BUN=blood urea nitrogen, CNS=central nervous system, DIC=disseminated intravascular coagulation, H/O=history of, ICP=intracranial pressure, ICU=intensive care unit, IV=intravenous, SIADH=syndrome of inappropriate diuretic hormone.

of infection, shifting to lymphocytic predominance quickly during the illness. Glucose and protein concentrations frequently are normal, although the protein value can be slightly elevated. Gram stain is universally negative. In cases of enteroviral meningitis, enteroviral PCR can confirm the diagnosis and, depending on the child's age and clinical appearance, may be used to guide additional evaluation and management.

For the patient who is suspected of having tuberculous meningitis, based on CSF findings and other epidemiologic clues (Tables 1 and 2), adjunctive testing may be helpful, although culturing of mycobacteria often requires 4 to 6 weeks, during which time treatment should not be delayed. A TST should be performed, recognizing that a negative test result does not exclude disease. Importantly, Bacille Calmette-Guérin (BCG) vaccine can have a variable effect on TST results. Among the 22 countries in which BCG vaccine use is routine, vaccination usually occurs at birth; in Brazil and Russia, the BCG vaccination is repeated at school age. Protection against meningitis and disseminated disease is the ultimate goal, and efficacy rates of 64% and 78%, respectively, have been reported. The prevailing evidence suggests that a positive TST result following BCG vaccine is more likely to represent infection.

In endemic areas, Lyme meningitis is difficult to distinguish from viral meningitis. A higher predominance of CSF monocytes and the relative absence of CSF neutrophils have been noted in Lyme meningitis (mean of 98% and 1%, respectively) compared with enteroviral meningitis (52% monocytes and 47% neutrophils, respectively). The

Table 2. **Cerebrospinal Fluid Analysis***

	Glucose (mg/dL) (mmol/L)	Protein (g/dL) (g/L)	White Blood Cell ($\times 10^3$/mcL) ($\times 10^9$/L)	Differential Count	Gram stain
Healthy newborn	30 to 120 (1.7 to 6.7)	3 to 15 (30 to 150)	<0.03	No PMNs	Negative
Healthy child	40 to 80 (2.2 to 4.4)	2 to 4 (20 to 40)	<0.01	No PMNs	Negative
Bacterial meningitis	<1/2 serum Often <10 (0.6)	>10 (100)	>1.0	>50% PMNs Often >90%	
Enteroviral meningitis	>1/2 serum	4 to 6 (40 to 60)	0.05 to 0.5	>50% PMNs early (<48 h) <50% PMNs later (>48 h)	Negative
Lyme meningitis	>1/2 serum		0.05 to 0.5	Predominance of lymphocytes and monocytes	Negative
Tuberculous meningitis	<1/2 serum Often <10 (0.6)	>10 (100)	0.05 to 0.5	Lymphocyte predominance	Negative

*Values should be used only as a guide, and none should be used in isolation because overlap between values in each of these categories is significant. PMN=polymorphonuclear leukocytes. Adapted from Wubbel L, McCracken GH. *Pediatr Rev.* 1998.

demonstration of serum antibodies against *B burdorferi* in the appropriate clinical setting can confirm infection. Interpretation of CSF antibodies is difficult, and consultation with a Lyme disease expert should be sought when performing this test. CSF PCR for the diagnosis of CNS borreliosis is not recommended at this time.

The Traumatic Lumbar Puncture

It is important to recognize the limitations of lumbar puncture, especially in the face of a traumatic procedure. Frankly bloody CSF should not be used to make clinical decisions, and a lumbar puncture should be attempted again in such situations. Although methods for evaluating CSF obtained from a traumatic lumbar puncture are described in the literature (some suggest correcting the cells by assuming 1 WBC/1,000 red blood cells), we do not recommend using these formulas to guide clinical decisions.

Management

The critical elements of managing pediatric meningitis include prompt initiation of therapy, use of the appropriate antimicrobial with correct dosing and duration, attention to anticipated complications, and appropriate follow-up. Admission to a pediatric intensive care unit is appropriate for children whose GCS scores are less than 8 or who are in shock or have respiratory compromise, focal neurologic findings, or clinical signs of elevated intracranial pressure.

Therapy should not be delayed if CNS infection is suspected. Appropriate antimicrobials are required in bacterial meningitis, HSV encephalitis, Lyme meningitis, tuberculous meningitis, and rickettsial infection, and in all cases, timely diagnosis and correct antimicrobial choice are critical.

If the practitioner cannot perform a lumbar puncture or there are contraindications to CSF examination, a blood culture should be obtained and antibiotics administered promptly. Among common bacterial pathogens, pneumococcus usually can be identified in the CSF up to several hours after the administration of appropriate drugs, whereas sterilization of meningococcus may occur in less than an hour. Therefore, if antimicrobial pretreatment occurs in the setting of meningitis and microbiologic confirmation is not possible, the practitioner needs to continue therapy based on the most likely pathogens. For example, in children whose CSF examination results are abnormal but whose CSF cultures are negative, treatment for meningitis should continue in those cases in which a positive blood culture for *S pneumoniae* or *N meningitidis* is confirmed or in cases in which the clinical scenario is compelling, such as purpura fulminans with CSF pleocytosis.

Antibiotics are not necessary for the older infant and child who have enteroviral meningitis that is confirmed by enteroviral CSF PCR testing. Patients can be sent home if they are afebrile and taking fluids well.

Drug Choice and Duration

The severity of bacterial meningitis necessitates empiric antimicrobial therapy prior to identification of the pathogen. For infants whose CSF is suspicious for bacterial

meningitis, ampicillin (300 mg/kg per day divided every 6 hours) and cefotaxime (200 to 300 mg/kg per day divided every 6 hours) is appropriate. If the child is younger than 4 to 6 weeks of age, acyclovir (60 mg/kg per day divided every 8 hours) should be added if HSV infection is a concern. In the young infant, if the Gram stain suggests pneumococcus, vancomycin (60 mg/kg per day given every 6 hours) should be added.

For children older than 2 months of age, vancomycin (60 mg/kg per day divided every 6 hours) plus ceftriaxone (100 mg/kg per day given in one dose or divided into two doses) or cefotaxime (200 to 300 mg/kg per day divided every 6 hours) should be used for empiric coverage. It is important to emphasize that the results of the Gram stain should not be used to narrow coverage. Once culture and susceptibility data are available, definitive therapy can be selected.

An alternative therapy for children who have had anaphylactic reactions to penicillin or cephalosporins is a carbapenem or a quinolone in addition to vancomycin. Consultation with an infectious disease specialist may be helpful in such cases.

The duration of therapy depends on the organism cultured and the degree of complications. A follow-up CSF examination should be performed in neonates who have gram-negative bacillary meningitis and should be considered for any child who has multidrug-resistant pneumococcal meningitis and those who do not respond appropriately to therapy. Appropriate parenteral antibiotics should be continued for 7 days for meningococcal meningitis and 14 days for *Listeria*, GBS, and pneumococcal meningitis. Lyme meningitis typically is treated with IV ceftriaxone (50 to 75 mg/kg per day given once daily) for 14 to 28 days. Meningitis caused by gram-negative enteric bacilli requires a longer duration of therapy, generally a minimum of 21 days. The duration of treatment for complicated meningitis should be discussed in consultation with infectious disease physicians.

Neonatal HSV CNS infection typically is treated with IV acyclovir (60 mg/kg per day divided every 8 hours) for 21 days. The dosing for non-neonates is 30 mg/kg per day divided every 8 hours IV for 14 to 21 days. A follow-up CSF HSV DNA PCR should be evaluated at day 21 and the course of therapy extended if the result still is positive.

When expanding coverage, it is important to remember that certain antimicrobial agents, such as clindamycin and cephalexin, have poor penetration into the CSF and are not appropriate in the treatment of bacterial meningitis.

Adjunctive Corticosteroids in Bacterial Meningitis

Adjunctive treatment has reduced rates of mortality, severe hearing loss, and neurologic sequelae significantly in adults who have community-acquired bacterial meningitis. For children beyond the neonatal age groups, available data suggest that the use of adjunctive corticosteroids may be beneficial for Hib meningitis and could be considered in cases of pneumococcal meningitis.

The dose of dexamethasone for bacterial meningitis is 0.6 mg/kg per day divided into four doses and administered IV for 4 days. The first dose should be given before or concurrently with antibiotics. Although it will not affect the course of viral meningitis adversely, it is not recommended in such cases. Dexamethasone should be considered when bacterial meningitis is suspected by clinical illness or CSF findings. Consultation with infectious disease experts is recommended.

Supportive Care, Monitoring, and Complications

Shock

Systemic complications of meningitis are common. Studies suggest that up to 70% of children who have bacterial meningitis require fluid resuscitation during initial evaluation and stabilization. Normal saline or lactated Ringer solution is appropriate, and pressor support may be necessary in cases of hemodynamic instability.

Seizures and Focal Complications

Neurologic complications of meningitis should be anticipated. Altered level of consciousness, seizures, increased intracranial pressure, subdural effusions, and focal neurologic deficits are most common. Neurologic effects may manifest as cranial nerve palsy, monoparesis, hemiparesis, gaze preference, visual field defects, aphasia, and ataxia. Focal neurologic deficits usually are the consequence of vascular injuries.

Seizures occur in approximately 20% to 30% of patients who have bacterial meningitis, typically are generalized, and occur within the first 72 hours of illness. Seizures more than 72 hours after the initiation of therapy are less common and more often focal. Such later seizures may signify vascular complications or an intracranial abscess, which increase the risk for long-term neurologic sequelae.

When children present with a focal seizure, focal neurologic deficits, or signs or symptoms of increased intracranial pressure, a CT scan must be obtained before performing a lumbar puncture. Other reasons for CT scan include recent head trauma, the presence of a CNS

shunt, coma or obtundation, and recurrent meningitis. Antibiotic administration should not be delayed in these circumstances. Magnetic resonance imaging may be a more appropriate study to assess complicated meningitis and should be considered in any patient who develops focal neurologic deficits or focal seizures or does not respond to therapy.

Cerebral edema in patients who have bacterial meningitis is caused by a variety of mechanisms that lead to an increase in the intracellular fluid volume of the brain. The increase in intracellular fluid volume leads to a subsequent increase in intracranial pressure. Cerebral edema and the resultant increase in intracranial pressure can cause a variety of signs and symptoms, ranging from headache, nausea, and vomiting to altered mental status, cranial nerve palsies, Cushing triad (bradycardia, hypertension, and abnormal respiratory pattern), and tonsillar herniation. Treatment for patients who are suspected of having cerebral edema depends on the severity and begins with fluid restriction. In the face of cerebral edema that has signs of increased intracranial pressure, diuretics, mannitol, and corticosteroids also can be considered. Invasive measurement of intracranial pressure and serial imaging in patients who have signs and symptoms of increased intracranial pressure also should be considered.

Subdural effusions can complicate the course of 10% to 40% of infants and young children who have bacterial meningitis. Although clinical manifestations can be subtle, patients who have neurologic abnormalities at the time of admission are at a higher risk. Treatment for patients who are improving with therapy and show no signs of increased intracranial pressure is supportive; invasive management typically is not indicated. However, signs of increased intracranial pressure in the presence of a subdural effusion or in cases of suspected subdural empyema indicate the need for neurosurgical drainage.

SIADH

Although SIADH occurs in children who have bacterial meningitis, the true incidence is unclear, with rates reported between 7% and 89%. Prevailing data on the management of SIADH in the setting of meningitis are controversial, although it is clear that over- or underhydration can be associated with adverse outcomes. Vital signs, urine output, and serum electrolytes and osmolality should be assessed initially and monitored every 8 to 12 hours. The diagnosis of SIADH is suggested by a serum sodium concentration less than 135 mEq/L (135 mmol/L), serum osmolarity less than 270 mOsm/kg, urine osmolarity greater than twice the serum osmolarity, urine sodium greater than 30 mEq/L (30 mmol/L), and the absence of clinical findings suggestive of hypovolemia or dehydration. Most experts recommend initial moderate fluid restriction with isotonic fluid, especially if the serum sodium value is less than 130 mEq/L (130 mmol/L). Fluids can be liberalized as the serum sodium returns to normal values, and in most cases, maintenance fluids can be provided by 24 to 48 hours.

Care of the Child Exposed to Meningitis

Practitioners should expect to be deluged with telephone calls after diagnosing meningitis in a child. Meningococcal and Hib disease create an increased risk for secondary infection in contacts.

Secondary cases generally occur among household contacts of a patient who has meningococcal meningitis, and the attack rate is 500 to 800 times that of the general population. Chemoprophylaxis is warranted and should be provided, ideally within 24 hours to high-risk contacts. In addition to household contacts, high-risk contacts include those who attend child care or nursery school with the index cases and those who have intimate contact (including those who have direct contact with a patient's secretions or anyone who frequently has slept or eaten in the same dwelling as the index patient) during the 7 days before the index case's illness. Passengers who are seated next to an infected individual on an airline flight lasting more than 8 hours also are considered at high risk.

Rifampin generally is the drug of choice for chemoprophylaxis in children, and rifampin, ceftriaxone, or ciprofloxacin is appropriate for adult contacts. Specific drug dosing and duration of therapy should take into account the patient's age, weight, and pregnancy status, and practitioners should refer to the *Red Book: 2006 Report of the Committee on Infectious Disease* for detailed recommendations. Age-appropriate immunization should be recommended. In cases in which a meningococcal outbreak has occurred, meningococcal vaccine may be an adjunct if the outbreak is caused by a vaccine serogroup.

Unimmunized or underimmunized children younger than 4 years of age and immunocompromised individuals of all ages who are household contacts of a patient who has Hib invasive disease should be considered to be at increased risk for Hib disease. Rifampin prophylaxis is recommended for all such household contacts regardless of age, and appropriate immunizations for age should be completed. The risk of secondary disease in children attending child care centers with a child who has invasive Hib disease is reported to be rare when all contacts are older than age 2 years. When two or more cases of

invasive Hib disease occur in a child care setting within 60 days, attendees and child care staff should be considered for chemoprophylaxis.

It is equally important to understand that chemoprophylaxis is not recommended for low-risk contacts of a patient who has meningococcal disease, including people who have casual contact or indirect contact or healthcare professionals who have not had direct exposure to the patient's secretions. No specific chemoprophylaxis is necessary for contacts of a patient who has enteroviral or pneumococcal meningitis.

Prognosis

Unfortunately, between 5% and 10% of children who have bacterial meningitis die, and among survivors, the risk of neurologic sequelae is highest in children who have pneumococcal meningitis. Intellectual deficits (intelligence quotient <70), hydrocephalus, spasticity, blindness, and severe hearing loss are the most common sequelae. Hearing loss occurs in approximately 30% of patients, can be unilateral or bilateral, and is more common in pneumococcal than meningococcal meningitis. Accordingly, all children who have bacterial meningitis should have their hearing evaluated before hospital discharge. Developmental follow-up is necessary for all children.

Hearing loss occurs in approximately 30% of patients, can be unilateral or bilateral, and is more common in pneumococcal than meningococcal meningitis.

For neonates, mortality rates of 10% in GBS meningitis and up to 20% in *E coli* meningitis have been noted, and neurologic sequelae are common. Long-term sequelae occur in 30% of those who have GBS disease and 50% of those who have gram-negative meningitis, underscoring the importance of follow-up developmental testing and interventional services.

The prognosis for patients having TB meningitis and neonatal HSV disease is extremely guarded.

Unique Circumstances

Anaerobic Pathogens

Anaerobic meningitis in children generally occurs as a complication of chronic otitis media with mastoiditis, chronic sinusitis, recent craniotomy, abdominal trauma, or abdominal surgery. In addition, congenital defects, including meningorectal fistulae and dermal sinuses with associated dermoid or epidermoid tumors, may predispose a child to meningitis caused by mixed flora, including anaerobes. A dermal sinus is an epithelial cell-lined tract that can extend from the skin and may communicate with epidural or intradural sites, thereby increasing the risk of infection with unusual indolent organisms.

Fungal Meningitis

Fungal meningitis is rare in the pediatric population, generally occurring in the setting of immunosuppression related to HIV infection (*Cryptococcus neoformans*), systemic lupus erythematosus, diabetes, transplantation, or cancer. Fungal meningitis also can occur in the setting of prematurity (*Candida albicans*) or as a complication of neurosurgical procedures.

Ventricular Shunts and Cochlear Implants

Ventricular shunt infection can be caused by a variety of bacteria, particularly *Staphylococcus epidermidis, S aureus*, and gram-negative bacilli and occasionally by yeast. In such cases, removal of the shunt, extraventricular drainage, and appropriate antibiotic therapy before shunt replacement are crucial for cure. In contrast, if meningitis caused by common pathogens such as pneumococcus and meningococcus occurs in a child who has a ventricular shunt, treatment with appropriate antibiotics is required, but shunt removal is not necessary.

It is estimated that more than 10,000 children have had cochlear implantation to restore hearing. Reports confirm that such children have an increased risk of meningitis and that pneumococcus is the most common pathogen isolated. Although the risk of pneumococcal meningitis in the healthy child approximates 4 to 5 per 100,000, rates of 138.2 cases per 100,000 person-years have been reported for children who have cochlear implants. Children who had implants employing silastic wedge positioners (that place the electrode closer to the cochlea) were noted to be at higher risk than children who had other implant models, and the risk of bacterial meningitis persisted beyond 24 months postimplantation for those who had positioners. Implants that have positioners have been withdrawn from the market, but there is not enough information to recommend that children who have such devices undergo surgical re-

moval. Instead, continued vigilance is required in all cases, and use of pneumococcal conjugate vaccines followed by pneumococcal polysaccharide vaccines is recommended for these patients.

Conclusion

The key to a good outcome for those who develop meningitis starts with prompt diagnosis and stabilization of the patient. Practitioners initially should focus on establishing venous access and on initiating supportive care for the hemodynamically unstable patient. In addition, attention to the respiratory and neurologic status should precede initiation of appropriate laboratory studies. The practitioner should know the typical pathogens, understanding that timely and appropriate use of antimicrobials is essential. Empiric therapy should be administered promptly, once testing is complete, and should include a decision about whether adjunctive steroid therapy is appropriate. Antimicrobial therapy should be targeted toward the suspected pathogens. Supportive care and monitoring are imperative, and the practitioner should anticipate and be prepared to treat complications. Although many practitioners are comfortable with the necessary plan of care and monitoring of the pediatric patient who has meningitis, it is essential that such patients be cared for in a facility that has well-trained ancillary support personnel, including pediatric nursing, critical care, infectious disease, and radiologic staff. Once therapy is complete, all children treated for bacterial meningitis should have follow-up hearing testing. Evaluation for neurologic sequelae is necessary for all children treated for CNS infection.

Summary

- Young infants who have meningitis may present with nonspecific clinical manifestations.
- *S pneumoniae* and *N meningitidis* remain the most common causes of bacterial meningitis in the infant and child, and GBS continues to be the most common neonatal pathogen.
- Empiric therapy for suspected bacterial meningitis in a non-neonate includes a combination of parenteral vancomycin and either cefotaxime or ceftriaxone.
- Children whose GCS scores are less than 8, show signs of shock or respiratory compromise, and have focal neurologic findings or clinical signs of elevated intracranial pressure should be admitted to a pediatric intensive care unit.
- Sensorineural hearing loss occurs in 30% of children who have pneumococcal and 10% of those who have meningococcal meningitis.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.aappublications.org.

1. A 14-day-old term newborn girl presents with generalized tonic-clonic seizures. Physical examination shows an unresponsive infant who has occasional facial and right extremity twitches. Rectal temperature is 101.8°F (38.8°C), heart rate is 120 beats/min, respiratory rate is 40 breaths/min, and blood pressure is 88/56 mm Hg. Other than a "full" anterior fontanelle, the rest of the physical examination findings are normal. Cerebrospinal fluid (CSF) examination reveals no organisms on Gram stain, 0.6×10^3/mcL (0.6×10^9/L) white blood cells with 30% polymorphonuclear leukocytes and 70% lymphocytes, 0.7×10^3/mcL (0.7×10^9/L) red blood cells, glucose of 30 mg/dL (1.7 mmol/L), and protein of 8.0 g/dL (80 g/L). Blood glucose is 50 mg/dL (2.8 mmol/L). Intravenous administration of cefotaxime and ampicillin is begun. Of the following, the *most* appropriate addition to therapy at this time is:

   A. Acyclovir.
   B. Dexamethasone.
   C. Isoniazid and rifampin.
   D. None.
   E. Vancomycin.

2. A 2-year-old girl is admitted for treatment of pneumococcal meningitis. She regularly attends a child care facility that cares for children up to the age of 4 years. She has a 2-month-old sibling at home. The parents express concerns about chemoprophylaxis of exposed children and caretakers. Of the following, the individual(s) who should receive chemoprophylaxis with rifampin is(are):

   A. No chemoprophylaxis is necessary for anyone.
   B. Sibling, all children at child care facility, and all caretakers.
   C. Sibling and all children at child care facility.
   D. Sibling and all unimmunized children at child care facility.
   E. Sibling only.

3. A 6-year-old boy is admitted to the hospital with lethargy, headache, photophobia, and fever for 12 hours. His axillary temperature is 102.9°F (39.4°C), heart rate is 120 beats/min, and blood pressure is 110/60 mm Hg. Lumbar puncture shows 0.9×10^3/mcL (0.9×10^9/L) white blood cells with 80% polymorphonuclear leukocytes, glucose of 20 mg/dL (1.1 mmol/L), and protein of 8.0 g/dL (80 g/L). Blood glucose measures 88 mg/dL (4.9 mmol/L). Intravenous antibiotic therapy with ceftriaxone and vancomycin is begun. Six hours later, the laboratory reports that the Gram stain of the cerebrospinal fluid shows gram-negative diplococci. Which of the following is the *most* appropriate next step?

   A. Add ampicillin to the antibiotic regimen.
   B. Add doxycycline to the antibiotic regimen.
   C. Change antibiotic coverage to penicillin G.
   D. Continue current antibiotic regimen.
   E. Discontinue vancomycin and continue cefotaxime.

4. A 4-year-old boy is brought to the emergency department with fever and headache for 2 weeks and increasing lethargy over the last 72 hours. The child was born in Russia and had been adopted at the age of 2 years. His health had been good until this illness. Of note on physical examination is a Glasgow Coma Scale score of 7 and nuchal rigidity. Computed tomography scan of the head shows no space-occupying lesion. CSF examination reveals 0.25×10^3/mcL (0.25×10^9/L) white blood cells with 70% lymphocytes, glucose of 24 mg/dL (1.3 mmol/L), and protein of 25 g/dL (250 g/L). Blood glucose is 90 mg/dL (5.0 mmol/L). Gram stain of the CSF is negative. Antibiotic coverage for which of the following is *most* indicated?

   A. Coccidiomycosis.
   B. Herpes simplex virus meningoencephalitis.
   C. Lyme disease.
   D. Rocky Mountain spotted fever.
   E. Tuberculous meningitis.

Meningitis

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