Aseptic Meningitis in the Newborn and Young Infant

This is a corrected version of the article that appeared in print.

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When a toxic newborn or young infant presents with fever and lethargy or irritability, it is important to consider the diagnosis of meningitis even if the classic localizing signs and symptoms are absent. Cerebrospinal fluid should be obtained (unless lumbar puncture is clinically contraindicated) to enable initial therapy to be planned. Initial results of cerebrospinal fluid testing may not conclusively differentiate between aseptic and bacterial meningitis, and antimicrobial therapy for all likely organisms should be instituted until definitive culture results are available. Comprehensive therapy, including antibacterial and antiviral agents, should continue until a cause is identified and more specific therapy is initiated, an etiology is excluded or the patient improves considerably and the course of antimicrobial therapy is completed. Group B streptococcus is the most common bacterial etiologic agent in cases of meningitis that occur during the first month after birth. Etiologies of aseptic meningitis include viral infection, partially treated bacterial meningitis, congenital infections, drug reactions, postvaccination complications, systemic diseases and malignancy. Long-term sequelae of meningitis include neuromuscular impairments, learning disabilities and hearing loss. Prompt diagnosis and treatment are essential to improved outcome.

When a newborn or young infant presents with fever and lethargy or irritability, meningitis is a primary concern. Bacterial meningitis has an incidence of about 20 to 100 cases per 100,000 live births during the newborn period.[1] Aseptic meningitis is even more common. Although most types of aseptic meningitis do not cause serious sequelae, some types result in significant morbidity and mortality if not properly diagnosed and treated. Physicians should maintain a high index of suspicion for these treatable causes.

Illustrative Case

A 29-day-old male infant was brought to the office with a history of tympanic fever ranging up to 37.7°C (100.0°F) for two days. He was eating well and had no other symptoms. His tympanic temperature during the office visit was 36.9°C (98.5°F), and the physical examination was normal. The child was discharged with a diagnosis of a viral illness. Two days later, he developed a tympanic temperature of 39.4°C (103.0°F). He was mildly anorectic, more irritable and more somnolent. He had no cough, vomiting or diarrhea.

The prenatal history was remarkable for maternal first-trimester primary genital herpes simplex virus (HSV) infection. The infant's mother tested negative for group B streptococcus. She had no history of intravenous drug use. She had not traveled out of the country and had no known exposure to ticks, cats or undercooked meat. The patient had been delivered by cesarean section because of probable reactivation of maternal genital HSV infection.

Physical examination performed in the emergency department revealed a rectal temperature of 37.5°C (99.6°F); pulse, 174 beats per minute; respiration, 40 per minute; and blood pressure, 97/41 mm Hg. The infant was fussy but consolable and in no acute distress. Physical examination was remarkable only for a clear nasal discharge. His lungs were clear, and the heart examination was normal. He had no bulging fontanelle, rash, petechiae, vesicular lesions, hepatosplenomegaly or neurologic abnormalities.

The cerebrospinal fluid showed a red blood cell count of 15 per mL and a white blood cell count of 1,295 per mL, with a differential of 1 percent neutrophils, 32 percent lymphocytes and 67 percent monocytes. The cerebrospinal fluid glucose level was 35 mg per dL (1.94 mmol per L), with a serum glucose level of 110 mg per dL (6.1 mmol per L) and a cerebrospinal fluid protein measurement of 79 mg per dL (0.79 g per L). His peripheral complete blood cell (CBC) count was 13,600 per mL, with a differential of 32 percent neutrophils, 61 percent lymphocytes and 2 percent monocytes.

Because of the patient's age and the maternal history of genital HSV infection, the infant was admitted to the hospital, and cefotaxime (Claforan), ampicillin and acyclovir (Zovirax) were administered. Clinical improvement was apparent within the first 48 hours. After bacterial cultures were negative for 72 hours, therapy with cefotaxime and ampicillin was discontinued. After cerebrospinal fluid culture for HSV was negative for seven days and the polymerase chain reaction (PCR) test of the cerebrospinal fluid was negative, therapy with acyclovir was discontinued. Stool culture grew coxsackie B virus. The infant recovered and was reaching appropriate developmental milestones at six months of age.

Evaluation of the Newborn or Infant with Suspected Meningitis

HISTORY

When considering the possibility of meningitis in an ill-appearing newborn or infant, the history of the mother and child may help in the determination of possible causative agents and assessment of the severity of the illness. Symptoms to inquire about in the infant include poor feeding, lethargy or irritability, altered sleep pattern, seizures, rash, vomiting, diarrhea or respiratory difficulty.[1] Fever may or may not be present *(Table 1)*. To help identify the cause of meningitis, it is important to consider the season, the patient's exposure to ill persons and travel history, and typical infectious diseases that may be prevalent in the community at the time.[2] In infants younger than three months of age, congenital and perinatal diseases may present with abnormal cerebrospinal fluid findings. The mother should be questioned about any fever or complicating illness occurring during pregnancy or around the time of delivery. In addition, maternal drug-use and sexual histories may give important information. Family physicians have a particular advantage in this area since they may have cared for both the mother and the infant.

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TABLE 1

Signs and Symptoms of Meningitis in Infants

Fever or hypothermia (temperature may also be normal)
Poor feeding

Irritability or lethargy

Seizures

Rash (petechial, vesicular, macular, mucosal)

Tachypnea or apnea

Jaundice

Bulging fontanelle (late)

Vomiting or diarrhea

PHYSICAL EXAMINATION

In the physical examination of a newborn or infant with meningitis, findings may range from completely normal to stupor or even seizures. Important physical findings include lethargy or irritability, fever or hypothermia, petechial, vesicular or macular skin rash, mucosal lesions, tachypnea or apnea[1] *(Table 1)*. Meningeal signs (nuchal rigidity) are not typical in this age group. A bulging fontanelle is frequently absent until late in the course of the disease. The child may be more irritable while being held than while lying still (paradoxic irritability).

LABORATORY DATA

The most important test to perform when meningitis is suspected is the lumbar puncture. The cerebrospinal fluid should be tested for cell counts with differential, Gram stain, glucose determination, protein and bacterial cultures. Some fluid should be saved if further diagnostic studies are needed. Seven or more days may be necessary for definitive results of viral cultures. PCR can provide same-day results for several viruses, including HSV, cytomegalovirus, human immunodeficiency virus (HIV) and the enteroviruses.[3]

Other important laboratory values to obtain during the evaluation include a CBC and bacterial cultures of blood and urine. If possible, the serum glucose level should be obtained before the lumbar puncture, since the procedure itself may cause serum glucose to be elevated.[4] Latex antigen tests for *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, *Neisseria meningitidis* and group B streptococcus may be useful if positive, especially if patients have previously received antibiotics and have negative Gram stains and cultures.[4] Stool cultures may also be indicated. Occasionally, a computed tomographic (CT) scan or magnetic resonance imaging (MRI) is indicated to help identify causative agents. For example, cytomegalovirus, toxoplasmosis, rubella and HSV may show calcifications, while *Staphylococcus aureus, Citrobacter diversus*, *Proteus mirabilis* and other bacteria can cause abscesses.[5,6] *Table 2* summarizes diagnostic tests for suspected meningitis.

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TABLE 2

Diagnostic Tests for Suspected Meningitis

In most cases
Lumbar puncture to obtain CSF for:
Cell count with differential
Gram stain
Glucose level
Protein level
Bacterial cultures
Blood cultures for bacteria
Serum glucose level
Urine culture

When a complete evaluation of the cerebrospinal fluid, including Gram stain, is performed, bacterial meningitis is documented by culture in only 1 to 5 percent of patients with normal values.[4] Normal cerebrospinal fluid values vary with age (***Table 3***). Although cerebrospinal fluid values may help to differentiate bacterial from viral etiologies, culture is still the gold standard. Cerebrospinal fluid values for bacterial and aseptic meningitis may overlap, and all newborns and young infants should receive antibiotic therapy if cerebrospinal fluid values are abnormal or meningitis is suspected. Antiviral therapy should be added if the history, physical examination and laboratory findings suggest a possible viral etiology.

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TABLE 3

Typical Cerebrospinal Fluid Values in Newborns and Young Infants

VALUES	*NORMAL TERM NEWBORN*	*NORMAL INFANT**	*BACTERIAL MENINGITIS*	*VIRAL MENINGITIS*
White blood cells	< 30 per mL	< 10 per mL	200 to 100,000 per mL	25 to 1,000 per mL

VALUES	NORMAL TERM NEWBORN	NORMAL INFANT*	BACTERIAL MENINGITIS	VIRAL MENINGITIS
Neutrophils	< 60 %	< 10 %	80 to 100 %	< 50 %
Glucose	> 60 % of serum	> 50 % of serum	< 40 % of serum	> 40 % of serum
Protein	<70 mg per Dl (1.7 g per L)	<40 mg per dL (0.4 g per L)	100 to 500 mg per dL (1 to 5 g per L)	50 to 100 mg per dL (0.5 to 1 g per L)

**—Six weeks to six months of age.*

Information from Lipton JD, Schafermeyer RW. Evolving concepts in pediatric bacterial meningitis—part I: pathophysiology and diagnosis. Ann Emerg Med 1993;22:1602–15, and Griffith BP, Rooss J. Neurologic infections of the

Etiologies

Results of cerebrospinal fluid culture divide meningitis into two categories: bacterial, in which bacteria are grown from the cerebrospinal fluid, and aseptic, in which no growth of bacteria by standard culture methods is shown.

BACTERIAL ETIOLOGIES

Typical pathogens vary with age (*Table 4*). In the first month of life, group B streptococcus is the most common etiologic agent. Although it usually presents as sepsis in the neonate, it can have a late-onset presentation as meningitis at one to 12 weeks of age.[5] *Escherichia coli* and *Listeria monocytogenes* are other pathogens that cause meningitis in the newborn. After the first month of life, *S. pneumoniae* and *N. meningitidis* become more common pathogens.[1] The widespread use of the *H. influenzae* type b (Hib) vaccine has caused a dramatic decrease in the incidence of this disease (from 2.9 cases per 100,000 in 1986 to 0.2 cases per 100,000 in 1995).[7]

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TABLE 4

Differential Diagnosis of Bacterial Meningitis in Newborns and Young Infants

< 1 month of age

Group B streptococcus

Escherichia coli

Listeria monocytogenes

Streptococcus pneumoniae

One to six months of age

S. pneumoniae

Haemophilus influenzae

Neisseria meningitidis

ASEPTIC ETIOLOGIES

In addition to bacterial causes, aseptic meningitis should be considered in infants with abnormal cerebrospinal fluid values. Aseptic meningitis typically follows a shorter, more benign course than bacterial meningitis. Etiologies include viral infection, partially treated bacterial meningitis, congenital infections, other less common infectious agents, drug reactions, postvaccination complications, systemic diseases and malignancy[2] *(Table 5)*.

TABLE 5
Differential Diagnosis of Aseptic Meningitis
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Among the viral etiologies, enteroviruses account for approximately 85 percent of cases.[2] Enterovirus meningitis usually occurs in the summer and fall, with acute onset of symptoms that last one to two weeks.[2] If Enterovirus is a possibility, a sample of cerebrospinal fluid should be sent for this viral culture.

HSV affects 1,500 to 2,000 neonates each year. Of these, 4 percent acquire the virus congenitally, 86 percent during delivery and 10 percent postnatally.[8] The chance of an infant becoming infected appears to depend on the timing of maternal seroconversion, with the highest risk occurring when the onset of maternal primary herpes is near the time of labor.[9] The typical presentation of neonatal HSV infection follows one of three patterns. The first pattern is localized HSV with herpetic lesions of the skin, eye or mouth; if left untreated, 75 percent of these patients progress to more extensive infection.[8] The second presentation is generalized herpes sepsis, which resembles bacterial sepsis, with alterations in temperature, and lethargy, respiratory distress, anorexia, vomiting and cyanosis.[8] The third presentation is localized central nervous system infection (meningitis or encephalitis), with irritability, bulging fontanelle, seizures, paralysis or coma.[8] When HSV infection is a possibility, samples of the cerebrospinal fluid should be sent for HSV culture and PCR.

Other sexually transmitted diseases may cause congenital or perinatal infection and must be considered in the differential diagnosis since they may require specific therapy. Since its emergence in 1982, HIV infection has been increasing in women and children. An estimated 7,000 infected women give birth to 1,000 to 2,000 infected infants each year.[10] Infected infants may present with opportunistic infections, pneumonitis or neurologic dysfunction.[11] Since antibody tests performed on the infant may also detect maternal antibody, these tests cannot definitively

diagnose HIV in infants. Newer methods for direct detection, including PCR, can identify up to 40 percent of infected infants at birth.[11] The incidence of maternal-to-fetal transmission should decrease with increased maternal prenatal treatment with zidovudine (Retrovir).[12]

Possible infection with cytomegalovirus, syphilis, toxoplasmosis, Lyme disease and tuberculosis may be evaluated with diagnostic tests such as PCR, specific antibody titers and acid-fast stains. Cytomegalovirus is the most common congenital infection. Approximately 40,000 infants born in the United States have cytomegalovirus infection, and 20 percent of these infants experience significant morbidity or mortality.[13] A diagnosis of congenital syphilis should be considered in infants with the physical stigmata of syphilis or in those whose mothers have a known history of inadequately treated syphilis. Each year in the United States, about 3,000 infants are born with congenital toxoplasmosis. Most cases of toxoplasmosis are acquired through ingestion of undercooked meat or oocytes from cat feces. Although congenital Lyme disease is rare, it may cause neurologic symptoms in 20 percent of infants and, in areas where Lyme disease is endemic, should be considered if there is a history of maternal exposure to ticks.[14] With the increasing prevalence of tuberculosis secondary to HIV disease, tuberculous meningitis may become more common and should be considered as a possible etiology.[15]

Table 6 summarizes historic clues that may help the physician diagnose treatable causes of aseptic meningitis.

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TABLE 6

Historical Findings Supporting the Diagnosis of Treatable Causes of Aseptic Meningitis

DISEASE	*MATERNAL ILLNESS*	*STD RISK*	*INTRAVENOUS DRUG USE*	*EXPOSURE TO CAT FECES OR RAW MEAT*	*TICK BITE*	*DAY CARE EXPOSURE*	*CLOSE-CONTACT EXPOSURE*	*SEASONAL*
Cytomegalovirus	X	X				X	X	
Enterovirus	X					X	X	X
Herpes simplex virus	X	X					X	
HIV	X	X	X					
Lyme disease	X				X			X
Syphilis	X	X						
Toxoplasmosis	X			X				
Tuberculosis	X						X	

Treatment

Since the causative agent is usually not known at presentation, all newborns or infants with meningitis should be treated aggressively (*Figure 1*). Patients should be hospitalized, and treatment with intravenous antibiotics should be started. Toxic or unstable patients require intensive-care monitoring. Although bacterial organisms are frequently associated with a more fulminant course, HSV and Enterovirus may also produce viral septic shock. Antibiotics should be administered until all bacterial cultures have been negative for at least 72 hours. Protocols for treatment of bacterial meningitis have been recently published.[16–18] The increasing prevalence of penicillin-resistant *S. pneumoniae* in certain parts of the country offers new challenges in treatment.

View/Print Figure

Diagnosis and Treatment of Meningitis in Infants and Newborns

FIGURE 1.

[corrected (https://www.aafp.org/afp/1999/1101/p1933a.html)] Diagnosis and treatment of meningitis in newborns and infants based on CSF findings. (CSF = cerebrospinal fluid; PCR = polymerase chain reaction; HSV = herpes simplex virus; Ab = antibody; PPD = purified protein derivative).

If HSV infection is a possibility, acyclovir should be added to the treatment regimen. Acyclovir, in dosages of 10 to 15 mg per kg every eight hours for 10 days, has been shown to decrease mortality rates from 49 percent to 17 percent and to reduce neurologic sequelae from 74 percent to 33 percent.[8] Empiric acyclovir therapy is indicated in newborns and infants with typical herpetic skin or mouth lesions, presumed viral encephalitis when no other cause has been identified, sepsis syndrome with negative bacterial cerebrospinal fluid and blood cultures, or sepsis syndrome with either a positive maternal vaginal HSV culture at the time of birth or a history of HSV infection in a parent.[8]

Specific treatment can improve outcomes for other causes of aseptic meningitis *(Table 7)*. Current treatment for Enterovirus meningitis is supportive, and most infants recover completely. Intravenous immune globulin may play a role in management of severe cases.[19] The antiviral drug pleconaril is currently in phase II clinical trials for treatment of adolescents and adults with enteroviral meningitis, and clinical trials for evaluation of treatment of neonatal enteroviral disease are planned for the near future.[20] Treatment for congenital HIV infection is constantly evolving, and infected infants should be managed with the most current antiretroviral regimens.

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TABLE 7

Recommended Treatments for Aseptic Meningitis

ETIOLOGY	*TREATMENT*
Cytomegalovirus	Ganciclovir (Cytovene) (clinical research trial)
Enterovirus	Immune globulin (possibly pleconaril)

ETIOLOGY	*TREATMENT*
Herpes simplex virus	Acyclovir (Zovirax)
Human immunodeficiency virus	Multidrug antiretroviral regimens
Lyme disease	Ceftriaxone (Rocephin)
Syphilis	High-dose penicillin
Toxoplasmosis	Pyrimethamine (Daraprim) and sulfadiazine
Tuberculosis	Multidrug antimycobacterial regimens

Up to 90 percent of symptomatic infants with congenital cytomegalovirus infection experience long-term sequelae.[13] Research trials using ganciclovir are available for newborns and young infants with congenital cytomegalovirus infection.[21] Infants with congenital syphilis who are treated early with high-dose penicillin have a lower risk of long-term sequelae.[6] Treatment with investigational protocols using pyrimethamine (Daraprim) and sulfadiazine may improve the outcomes in infants with congenital toxoplasmosis infection.[6] Congenital Lyme disease can be treated with ceftriaxone (Rocephin).[14] Infection with *Mycobacterium tuberculosis* requires a prolonged regimen of multiple antimycobacterium drugs, and patients with central nervous system disease may still experience complications after this therapy.[15]

Figure 1 offers a suggested protocol for the diagnosis and treatment of meningtitis in newborns and young infants, based on results of bacterial and viral laboratory tests.

Complications

Newborns and young infants with meningitis should be observed carefully for both acute and chronic complications *(Table 8)*. Acute complications include seizures, syndrome of inappropriate antidiuretic hormone (SIADH) and increased intracranial pressure with focal or general neurologic findings.[22] Poor prognostic factors include bacterial rather than viral infection, younger age, focal neurologic findings at admission and the presence of SIADH.[4]

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TABLE 8

Common Complications of Meningitis

Acute complications
Seizures

Syndrome of inappropriate antidiuretic hormone (SIADH) secretion

Hemodynamic instability

Increased intracranial pressure

Subdural effusions

Focal neurologic deficits

Chronic complications

Deafness

Long-term sequelae include seizure disorder, hydrocephalus, sensorineural hearing loss, weakness, paralysis, cranial nerve palsy, learning disabilities, blindness, behavior disorders and speech delay.[4,16,22] Although these sequelae are more common in patients with bacterial meningitis, they may also occur in patients with aseptic meningitis.[22] Close follow-up is needed after hospital discharge for all patients with meningitis. Hearing should be assessed one to two months after discharge, using brainstem auditory evoked response testing. Neuromuscular assessment at the time of discharge should be documented and periodically assessed on an outpatient basis to allow early detection of any deficiencies. Learning disabilities, behavior disorders and speech delay, which can be difficult to diagnose in infants and young children, require close monitoring after discharge and at subsequent well-child visits.

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