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Invasive Meningococcal Disease in Childhood

Anne F. Brayer, MD,* Sharon G. Humiston, MD, MPH*

**Objectives** After completing this article, readers should be able to:

1. Describe the epidemiology of meningococcal disease, including predisposing host and environmental factors.
2. Recognize early and key clinical features of meningococcal meningitis and severe meningococcal sepsis.
4. Identify the most common complications and prognosis for meningococcal disease.
5. Be familiar with current vaccination recommendations in the United States.

**Introduction**

Neisseria meningitidis remains a serious bacterial threat to the well-being of children. Since the introduction of immunization against Haemophilus influenzae and Streptococcus pneumoniae, the risk of serious illness from these organisms has decreased sharply among immunized children, and it is hoped that widespread use of meningococcal conjugate vaccine will lead to the same outcome. The meningococcus causes a variety of disease entities, but this review focuses primarily on its two major manifestations: severe meningococcal septicemia (SMS), sometimes confusingly called “meningococcemia,” and meningococcal meningitis (MM).

**Epidemiology**

**Prevalence**

Annually, meningococcal disease has affected as many as 3,000 people in the United States. Although outbreaks of illness tend to receive major media attention, fewer than 5% of cases occur during outbreaks. The prevalence of the asymptomatic carrier state varies from less than 2% in children younger than 2 years of age to as high as 10% to 40% among adolescents and young adults. The highest carrier prevalence is among those living in close quarters, such as college students and military recruits.

Based on data from the United States Active Bacterial Core Surveillance sites, the estimated average annual incidence of meningococcal disease is 0.53 cases per 100,000 population, with the annual incidence decreasing from 0.92 per 100,000 population in 1998 to 0.33 cases per 100,000 population in 2007. Incidence rates are highest in infants younger than 1 year of age (5.38 cases per 100,000 population), decline steadily through late school age, and rise again in adolescence. There has been seasonal variation in incidence, with peaks in late winter and spring.

**Causes**

Factors related to the organism, host, and environment determine which individual becomes ill with a particular organism. The causative agent is the aerobic gram-negative diplococcus *N meningitidis*, which is a natural commensal organism living in the nasopharynx of humans, its only host. Its immunologically relevant components are its outer membrane and the polysaccharide capsule. The membrane is the site of the lipopolysaccharide molecule, the endotoxin.
that triggers the immune response. Capsular polysaccharide composition varies, and it is on this basis that the 13 distinctive serogroups of the organism are identified. Virtually all invasive disease is caused by meningococci in one of five serogroups: A, B, C, Y, and W-135. Groups B, C, and Y cause the bulk of disease in North America. Micropilli, or fimbriae on the outer surface of the capsule, are the basis for adhesion to the nasopharyngeal epithelium. Most commonly, adhesion leads to colonization and is an immunizing event for the host, producing asymptomatic carriage. Systemic infection occurs in fewer than 1% of asymptomatic carriers when changes in the mucosal barrier or host immune factors permit bloodstream invasion.

Predisposing Conditions: The Host
Children younger than 2 years of age have a nearly fivefold greater risk of contracting meningococcal disease than the general adult population. Defects in the host defense mechanisms, both congenital and acquired, predispose to bacterial invasion. Acute viral respiratory infections are believed to be predisposing factors. Because invasion by the organism triggers a response from virtually every branch of the host immune system, most immunodeficiency states increase disease risk. The complement system is of major importance in host defense against invasion, and the presence of a complement deficiency is an important risk factor.

Risk Factors: The Environment
Environmental factors that affect individual risk of invasive disease can be divided into those that promote person-to-person spread of the organism and those that affect the function of the nasopharyngeal mucosal barrier. Crowded living conditions (eg, residential camps, college dormitories, military barracks) predispose to transmission of the organism. The rate of secondary infection among household contacts is up to 800 times that in the general population. Transmission occurs by short-range exposure (eg, droplet aerosolization or direct contact with secretions); effective transmission requires close person-to-person contact.

Both active and passive exposure to tobacco smoke greatly increase the risk of illness through disruption of the mucosal barrier and by a variety of immunosuppressive effects. Tobacco smoke also contributes to increased transmission of the organism by increasing production of respiratory droplets. Asymptomatic carriage rates are substantially higher among smokers. Children who are exposed to smoke have a relative risk 3.5 to 7.5 times that of the general population. There appears to be a positive dose-response relationship between passive smoke exposure and risk. Child care attendance actually may reduce the risk of invasive disease among children who live with smokers, possibly by reducing the amount of time the child spends in close contact with asymptomatic carriers.

Pathophysiology
Mechanism of Disease Process
Infection with *N. meningitidis* produces a variety of disease manifestations, but the two most common and devastating are MM and SMS. There are two critical events in the pathogenesis of meningococcal disease: penetration of the organism through the nasopharyngeal mucosa and replication in the bloodstream. Once penetration occurs, the response to replication defines the course. If replication is rapid and overwhelms host defenses, SMS is the result. If replication can be held in partial check by immune mechanisms, localizing disease such as meningitis or other suppurrative complications develop. Why some individuals develop SMS while others develop MM is unclear.

**COLONIZATION AND INVASION.** Following exposure, the organism colonizes the host nasopharynx. *N. meningitidis* produces virulence factors, including the polysaccharide capsule and its associated structures that promote adhesion to mucosal cells, proteases that destroy host secretory (immunoglobulin A) antibodies, and mucosal ciliary inhibitors. Hosts who have fully functioning immune systems typically destroy the organism shortly after exposure or establish an asymptomatic carrier state. In either case, humoral immunity is produced. In hosts who have impaired mucosal barriers (eg, those who have acute viral illnesses) or are immunocompromised, invasion through the mucosa, survival in the bloodstream, and rapid multiplication of the organism set the stage for severe disease.

Until the maturation of an individual’s ability to mount an immune response (after the first postnatal year), the innate immune system, particularly complement, provides the primary defense against *N. meningitidis*. This mechanism explains the high peak of incidence during late infancy, as passive immunity provided by maternal antibody subsides. Acquisition of both antibody- and cell-mediated immunity occurs throughout childhood, accounting for the drop in disease incidence during that period.

**THE INFLAMMATORY RESPONSE AND MICROVASCULAR INJURY.** The host inflammatory immune response that follows penetration of primary defenses is intimately
involved in the pathogenesis and clinical manifestations of meningococcal disease. The host immune/inflammatory response leads to phagocytosis and activation of pro-inflammatory cytokine pathways. The result of the activation of the inflammatory cascade is an assault on the host’s own capillary endothelium. The immune-mediated microvascular injury produces the four general manifestations of disease caused by meningococcal infection: capillary leak, vasomotor instability, disordered coagulation, and myocardial dysfunction. These pathologic mechanisms, in turn, account for the various organ and system failures.

Specific Organ Systems Involved
The specific result of immune-mediated microvascular injury is impairment and ultimately failure of most of the major organ systems.

Myocardial function is impaired in SMS, with decreased stroke volume resulting in diminished cardiac output. In children, diminished stroke volume can be compensated for transiently by increased heart rate, but tachycardia causes increased metabolic demand. Myocardial ischemia with elevated cardiac troponin concentrations ensues. Impaired myocyte contractility likely results from numerous factors, including hypoxia, acidosis, and electrolyte disturbances. Impaired contractility also correlates with elevated cytokine and nitrous oxide concentrations.

Central nervous system impairment occurs by two distinct mechanisms, either or both of which may be present. In MM, inflammatory changes to vascular permeability and the blood-brain barrier, as well as polymorphonuclear infiltrates, produce the clinical picture of meningitis and direct inflammation of brain. Increased cerebrospinal fluid (CSF) production and decreased reabsorption, along with cerebral edema, produce rapidly elevated intracranial pressure (ICP). These changes result in diminished consciousness, confusion, and ultimately respiratory compromise if brain herniation occurs. By contrast, patients who have SMS and are in rapidly progressive shock experience reduced perfusion, tissue acidosis, and ultimately cerebral infarction, end-organ effects similar to those produced in other body systems.

The characteristic evolving rash of meningococcal disease is the result of damage to capillaries and the endothelium of small end-arteries. Vasculitis, with extravasation of red blood cells (and viable organisms) from leaking capillaries, produces the initial petechial exanthem. With progression, micro- and macroscopic thrombi form in end-arteries and arterioles, producing varying degrees of ischemia and, ultimately, necrosis and gangrenous changes.

Other organs that are notably affected by microvascular injury and its consequences include the lungs, where capillary leak and infiltration with neutrophils produce both intra-alveolar fluid and thickening of the pulmonary interstitium. These changes lead to initial tachypnea, followed by frank respiratory failure with pulmonary edema.

Renal blood flow suffers during SMS, in direct proportion to the degree of shock. Oliguria or anuria may follow, and in severe cases, permanent kidney damage from acute tubular necrosis may occur.

Splanchnic blood flow is reduced and thrombi forming in the mesenteric or gastric distributions can produce submucosal ischemia and hemorrhage similar to that seen on the skin; some patients may complain of severe abdominal pain. In rare cases, the lesions may erode and form ulcers.

Vascular injury also contributes to hepatocellular damage, infarction, and hemorrhage of the adrenal glands (Waterhouse-Friderichsen syndrome) and virtually every other organ and system.

Clinical Aspects
The term “meningococcemia” can be confusing, although it is still widely used. SMS expresses the systemic manifestations of the organism reproducing in the blood and differentiates this rapidly progressive septic state from localized (although still serious) disease. Only about 50% of patients who develop meningococcal bacteremia (ie, whose blood cultures grow the organism) actually have isolated meningitis (purulent inflammation of the meninges); 10% to 15% have SMS alone; and 40% typically have a mixed picture. Too often, clinicians associate petechiae only with meningitis and waste valuable time diagnosing and managing it, while the real culprit, fulminant sepsis, progresses rapidly.

SMS
SMS is characterized by sudden onset, rapid progression, and an absence of localizing findings. The presentation is usually more severe than in meningitis or other manifestations and the case fatality rate is high (40% to 50%). Most patients who develop SMS have no known immunocompromise.

PRESENTING SYMPTOMS AND PHYSICAL FINDINGS.
Meningococcal septicemia begins with an acute onset of high fever, shaking chills, and myalgias that may be expressed as extremity or back pain, particularly in ado-
lescents. Patients presenting with these symptoms before the onset of rash may be misdiagnosed as having “viral syndrome” and discharged.

Within 6 hours, however, patients who have SMS invariably deteriorate rapidly. The rash that develops may initially resemble a viral exanthem, although it is more classically petechial. The rash often becomes hemorrhagic and may coalesce to form widespread purpuric lesions. Purpura fulminans, aggressive spread of purpura to large areas with ischemic necrosis, may develop. Patients who have purpura fulminans are likely to have sudden drops in blood pressure and acute adrenal hemorrhage (Waterhouse-Friderichsen syndrome).

**VITAL SIGNS.** Patients who have early SMS can present with normal blood pressure and warm extremities. Especially in young children, tachycardia may be the sole sign of impending disaster. Falling blood pressure is a late sign. Vital sign abnormalities (eg, elevated heart rate and temperature, widened pulse pressure) may be subtle. Altered mental status of any degree may signal poor brain perfusion.

**CLINICAL CLUES FOR EARLY DIAGNOSIS.** One reason that mortality rates from meningococcus infection have been difficult to decrease is that early diagnosis and treatment continue to evade clinicians. Yung and McDonald (see http://www.mja.com.au/public/issues/178_03_030203/yun10460_fm.html) have summarized early clinical clues:

- **Patient age, contact with a person who has meningococcal disease**
- **Concern level of the presenting adult**
- **Physical signs and symptoms, especially if the illness evolves rapidly:**
  - Rash: Any rash appearing in the context of a sudden febrile illness should raise concern. Unlike viral syndromes that have a several-day prodrome before development of the rash, the meningococcal rash is typically present within 24 hours of any symptomatology. Clinicians should be aware that the first petechiae may be intraoral or conjunctival or be hidden in skinfolds and that the early rash may not be petechial.
  - True rigors (ie, prolonged [10 to 20 minutes] shaking chill that cannot be stopped voluntarily)
  - Severe pain in the neck, back, or extremities, which may manifest in younger children as refusal to walk
  - Vomiting, especially in association with headache or abdominal pain, in the absence of diarrhea

Most pediatricians see many children who have these symptoms, and most such children have a simple viral syndrome. However, the presence of several of these findings in a previously well patient, coupled with a rapid progression, should trigger alarm. Yung’s review suggests that fever and a petechial or hemorrhagic rash is always SMS until proven otherwise. Further, although no single finding is an indication for immediate treatment, clinicians should always give serious consideration to meningococcal disease when one or more of the signs are present. When in doubt, clinicians should refer patients for aggressive fluid management and early administration of antibiotics.

**MM**

In the 50% of patients who have meningitis caused by *N meningitidis* but do not have fulminant sepsis, signs and symptoms are those of typical bacterial meningitis. These patients are (or have been) bacteremic, and progression to SMS is an ever-present possibility.

**PRESENTING SYMPTOMS AND PHYSICAL FINDINGS.** Patients who have MM usually have a 1- to 3-day nonspecific prodrome resembling viral illness, with low-grade fever and upper respiratory tract symptoms. Signs and symptoms in MM include:

- **Vital signs:** In MM, rising ICP may produce the Cush- ing triad (bradycardia, hypertension, and respiratory depression). This picture contrasts with that seen in SMS patients, who tend to exhibit tachycardia and eventually hypotension.
- **Meningismus:** In patients older than 3 years, the classic signs of Kernig and Brudzinski may be elicited,* but these signs rely on a cooperative patient who has near-normal mental status. Infants and toddlers who have MM may not have classic signs of meningeal inflammation. Children who are verbal may complain of worsening headache with neck flexion.
- **Mental status:** Patients’ mental status may range from normal to obtunded. They may be lethargic or irritable.
- **Other neurologic signs:** Adolescent patients may develop sudden and severe headache, often with photophobia. Younger infants may demonstrate a bulging fontanelle.
- **Skin:** A petechial rash is sometimes present. Centrally

*The Kernig sign is present when the supine patient with the thigh flexed onto the abdomen complains of pain on passive extension of the leg. The best known of Brudzinski’s five meningeal signs is produced in the supine patient when passive neck flexion produces spontaneous flexion of the hips and knees.
mediated vasospasm may lead to decreased peripheral perfusion.

- Gastrointestinal complaints: Nausea and vomiting are common.
- Myalgias: Muscle aches and especially back pain are common.

**DIAGNOSTIC STUDIES.** In the case of fulminant meningococcal disease, laboratory test results may return too late or may fall within normal ranges early in a precipitous course to be of any value. Blood cultures obtained when intravenous access is obtained are helpful, but clinicians should not delay antibiotics or fluids for the sake of cultures or other testing.

Culture of the organism from a normally sterile site is the gold standard for bacteriologic diagnosis, but because of appropriate early administration of antibiotics, cultures may be falsely negative. When CSF is available, Gram stain is highly sensitive and specific and continues to be a fast and accurate test. Antigen detection assays of CSF, but not serum or urine, are of some use but have high false-negative rates. Polymerase chain reaction analysis of blood specimens has promise but is neither widely available nor timely. If the patient’s condition and time permit, a Gram stain and culture of aspirates from the edges of purpuric lesions may be diagnostic.

**Detection of Meningitis**

A lumbar puncture should always be deferred if the patient has signs of airway problems, shock, elevated ICP, or coagulopathy, until the patient has been fully stabilized. When obtained, CSF should be sent for complete blood count and differential white blood cell (WBC) count, total protein concentration, and glucose assessment. WBC counts are elevated in most patients who have meningitis, although when disease is severe and rapidly progressive, CSF WBC counts are low or even normal; this finding is a negative prognostic sign. In such patients, markedly low glucose and elevated protein values are associated with the diagnosis of meningitis; these ancillary tests add little information when they are only mildly abnormal. A negative lumbar puncture result is an ominous, not a reassuring finding in patients who have meningococcal sepsis.

**Immune and Metabolic Determinations**

Blood laboratory tests in patients who have SMS or MM are useful less for diagnostic purposes than for following the degree of immune response and metabolic injury. A complete blood count may be difficult to interpret. Because of the rapid progress of SMS, the WBC count may be normal. A very low WBC count suggests overwhelming sepsis, as does the presence of toxic granulations. The hematocrit also may be low, normal, or high, depending on the stage of progression and the patient’s volume status. The platelet count may be the fastest means of learning about the extent to which the patient has disseminated intravascular coagulation, although the count may be normal early in the course. Other coagulation parameters should be determined through the use of standard measures, and products of fibrinolysis, fibrin dimmers, or fibrins split products should be monitored.

Standard metabolic panels are used to detect abnormalities in electrolytes and acid-base status. Arterial blood gas determination may be useful, particularly after fluid resuscitation, as an indirect measure of pulmonary extracellular fluid. Elevated serum lactate correlates well with other measures of rapidly advancing sepsis and may be rapidly available.

**Differential Diagnosis**

Meningococcal disease may be confused with “viral syndrome,” influenza, upper respiratory tract infections, and other causes of abdominal pain. In the patient who has early MM or other localizing disease, other invasive bacterial infections enter the differential diagnosis. In evaluating the patient who develops rash, clinicians should consider viral causes such as enteroviruses (in summer), parvovirus, human herpesvirus 6, and rickettsial diseases (particularly when headache is present).

**Management**

**Initial Stabilization and Treatment (Table 1)**

The first step in managing meningococcal clinical syndromes is to recognize them and be prepared to treat early and aggressively. Patients suspected of having meningococcal infections should be referred for evaluation in an emergency care facility and preferably transported via emergency medical services to allow for prompt delivery of intravenous fluids and airway management. Vital signs should be monitored frequently throughout this phase.

**FLUIDS.** Patients should be given large isotonic fluid boluses (20 mL/kg) over the first 5 minutes, using either manual “push” with a large-volume syringe on a three-way stopcock or a high-volume infusion pump. Giving 60 to 100 mL/kg in the first hour is associated with improved survival. Altered mental status may result either from shock or meningitis with associated elevations in ICP.
VASOACTIVE AGENTS. Once a patient has received at least 60 mL/kg of fluid, consideration should be given to starting an inotropic/vasoactive agent such as dopamine or dobutamine. Starting these drugs sooner is of questionable value; they work best when the intravascular fluid volume has been maximized. In most cases of SMS, initial fluid boluses alone are insufficient to produce more than transient stabilization. This fact highlights the importance of transfer to a facility that can provide ongoing intensive care.

AIRWAY MANAGEMENT. Although most patients who have meningococcal disease, even those who have SMS, present with spontaneous respirations, delivery of large intravenous fluid volumes may lead to pulmonary edema. Once circulatory status has been optimized with fluid and inotrope use, early elective intubation is recommended.

ANTIBIOTICS. *N meningitidis* remains sensitive to penicillin, and if the diagnosis is certain, penicillin is effective treatment for both SMS and MM. Usually the cause of sepsis or meningitis is not certain early in the treatment course, so broad-spectrum antibiotics effective against *N meningitidis* and other potential pathogens are indicated (eg, ceftriaxone, cefotaxime, vancomycin).

CORTICOSTEROIDS. Children who have SMS have lower overall cortisol and higher corticotrophin concentrations than do those who have meningitis only; this deficiency is associated with more profound and refractory shock. Physiologic doses (1 mg/kg intravenously every 6 hours) of hydrocortisone may be beneficial in children who have SMS and respond poorly to vasopressors. High-dose corticosteroids or dexamethasone have not been shown to be effective for treating septic shock. For MM, high-dose or high-potency corticosteroids have not been adequately studied, but experience with pneumococcal and *H influenzae* disease suggests their efficacy. In these latter conditions, dexamethasone administered early in the course reduces opening pressure, lowers concentrations of inflammatory mediators in the CSF, and reduces hearing loss and other neurologic sequelae. Most authorities recommend dexamethasone administration when MM is suspected.

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**Table 1. Initial Treatment and Stabilization of a Patient Who Has Meningococcal Disease**

<table>
<thead>
<tr>
<th>Airway, Breathing, Circulation (ABCs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>As soon as the diagnosis of meningococcal disease is suspected, assure the ABCs:</td>
</tr>
<tr>
<td>● Assure a protected airway.</td>
</tr>
<tr>
<td>● Supply high-flow oxygen by 100% nonrebreather mask.</td>
</tr>
<tr>
<td>● Secure large-bore intravenous (IV) access, ideally at least two lines.</td>
</tr>
<tr>
<td><strong>Deliver IV Fluids and Antibiotics</strong></td>
</tr>
<tr>
<td>● Use the first IV line for large volumes of isotonic crystalloid or colloid and IV antibiotics.</td>
</tr>
<tr>
<td>● Place an intraosseous line if unable to place peripheral lines promptly.</td>
</tr>
<tr>
<td><strong>Avoid Delays</strong></td>
</tr>
<tr>
<td>● If a blood culture can be obtained from the initial access site, send it, but <em>do not delay</em> antibiotics for the sake of cultures.</td>
</tr>
<tr>
<td>● <em>Do not</em> perform a lumbar puncture in a patient suspected of having meningococcal disease until airway/breathing, access, and antibiotics are assured.</td>
</tr>
<tr>
<td>● Administer antibiotics immediately after initial fluid resuscitation in any suspected case of meningococcal disease.</td>
</tr>
<tr>
<td>● Prehospital antibiotic use has been shown to reduce case fatality rate, so administer before transport if possible.</td>
</tr>
<tr>
<td>● Use a third-generation cephalosporin if there is a history of anaphylaxis to penicillin.</td>
</tr>
<tr>
<td>● Many individuals and institutions continue to worry about the &quot;sudden release of endotoxin&quot; following initial antibiotic treatment. This concern should not be used as a rationale for delaying antibiotics until arrival at definitive care.</td>
</tr>
<tr>
<td><strong>Transport</strong></td>
</tr>
<tr>
<td>● Generally it is best to use at least basic life support-level transport with IV access and isotonic saline running, unless to do so would cause significant delay.</td>
</tr>
<tr>
<td>● Be sure that the airway will remain stable during transport.</td>
</tr>
</tbody>
</table>
Admission and Transfer Considerations

All patients who have known or suspected meningococcal disease must be admitted to a hospital that has intensive care capabilities. When such admission requires transport, the patient must be adequately stabilized before transport.

Table 2. Hospital Care

<table>
<thead>
<tr>
<th>Metabolic Derangement</th>
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<tbody>
<tr>
<td>Look for and correct abnormalities of:</td>
</tr>
<tr>
<td>● Glucose</td>
</tr>
<tr>
<td>● Potassium</td>
</tr>
<tr>
<td>● Calcium</td>
</tr>
<tr>
<td>● Magnesium</td>
</tr>
<tr>
<td>● pH (correct metabolic acidosis if severe)</td>
</tr>
<tr>
<td>Adequate Ventilation</td>
</tr>
<tr>
<td>Provide adequate ventilation to avoid central</td>
</tr>
<tr>
<td>nervous system acidosis; severe acidosis is</td>
</tr>
<tr>
<td>itself an indication for early and elective</td>
</tr>
<tr>
<td>intubation.</td>
</tr>
<tr>
<td>Transfusions</td>
</tr>
<tr>
<td>● Administer red blood cells to patients who</td>
</tr>
<tr>
<td>have anemia</td>
</tr>
<tr>
<td>● Administer fresh frozen plasma early in</td>
</tr>
<tr>
<td>response to laboratory findings of abnormal</td>
</tr>
<tr>
<td>coagulation</td>
</tr>
<tr>
<td>● Platelet transfusions may be necessary,</td>
</tr>
<tr>
<td>although the consumption rate in early stages</td>
</tr>
<tr>
<td>is so high that this procedure can be futile</td>
</tr>
<tr>
<td>Monitor Pressures</td>
</tr>
<tr>
<td>Although it should never be an early priority,</td>
</tr>
<tr>
<td>a Swan-Ganz catheter can provide a wealth of</td>
</tr>
<tr>
<td>information about central venous and</td>
</tr>
<tr>
<td>pulmonary capillary wedge pressure as well as</td>
</tr>
<tr>
<td>cardiac output.</td>
</tr>
</tbody>
</table>

Hospital Care (Table 2)

Children who require airway management, show signs of increased ICP, or are in a persistent state of shock after initial fluid resuscitation require care in a pediatric intensive care unit. Other children may be cared for on a general pediatric unit. All patients must be closely monitored for end-organ malfunction, including pulmonary edema, myocardial dysfunction, gastrointestinal edema or ischemia, and renal insufficiency. Metabolic derangements (electrolyte disturbances, acidosis) and hematologic complications (thrombocytopenia, coagulation disorders) are not uncommon and may require treatment. Children manifesting extensive purpura should be monitored for progressive necrosis and compartment syndrome. Consultation with plastic or orthopedic surgeons may be necessary.

A total of 5 to 7 days of intravenous antibiotic coverage is generally sufficient (Table 3). Patients treated with penicillin also require treatment with oral rifampin to eradicate the nasopharyngeal carriage state. Children should be considered contagious and require isolation with droplet precautions for 24 hours after initiation of antibiotic coverage (including rifampin).

Cutting-edge Therapies

Human bacterial permeability-increasing protein, naturally produced in neutrophils, binds endotoxin and has bactericidal effects. Early trials using the recombinant form of this protein showed reduced mortality and improved functional outcome. Interfering with the sepsis cascade further down the line by modifying the sequence leading to coagulopathy has shown some benefit, but not without significant risks of exacerbation of bleeding.

Table 3. Treatment Regimens for Invasive Meningococcal Disease

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosing for Meningitis (5 to 7 Days)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>100 mg/kg per day IV in one or two divided doses; maximum, 4 g/day</td>
<td>May be used in patients who have nonanaphylaxis penicillin allergy</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>225 to 300 mg/kg per day IV in three or four divided doses; maximum, 12 g/day</td>
<td>May be used in patients with nonanaphylaxis penicillin allergy</td>
</tr>
<tr>
<td>Penicillin G*</td>
<td>250,000 to 300,000 U/kg per day IV; maximum, 24 million U/day, in four or six divided doses</td>
<td>Use when sensitivity to penicillin is known</td>
</tr>
<tr>
<td>Chloramphenicol*</td>
<td>75 to 100 mg/kg per day IV; maximum dose, 2 to 4 g/day, in four divided doses</td>
<td>Use in patients who have penicillin allergy with anaphylaxis</td>
</tr>
</tbody>
</table>

*Patients treated with antibiotics other than third-generation cephalosporins should also receive chemoprophylaxis to eradicate nasopharyngeal carriage.

IV = intravenous
Prognosis

The mortality rate for SMS approaches 50%, while that for MM alone is approximately 10%. A hallmark study by Stiehm and Damrosch (1) identified the following factors as predictors of poor outcome:

- Presence of petechiae for less than 12 hours before medical presentation
- Presence of shock (systolic blood pressure, ≤70 mm Hg)
- Absence of meningitis (<20 WBC/mm³) in CSF
- Blood leukocyte count normal or low (<10,000 WBC/mm³)
- Erythrocyte sedimentation rate normal or low (<10 mm/hour)

Infections with serogroup C appear to be associated with a higher mortality. Most children who survive invasive meningococcal disease make a full recovery. Common sequelae (occurring in 10% to 20% survivors) include hearing loss, brain damage, renal failure, and limb amputation. All children who survive SMS or MM should be tested for hearing impairment.

Prevention

Vaccines

In comparison with pure polysaccharide vaccines, conjugate vaccines tend to be more effective, have longer duration of immunity, and produce herd immunity through eradication of asymptomatic carriage. For these reasons, development of meningococcal conjugate vaccine (MCV4) offering protection against four capsular groups (A, C, Y, and W-135) may be a great breakthrough in preventing meningococcal disease in the United States. MCV4 is routinely recommended at 11 to 12 years of age; unvaccinated adolescents through 18 years of age should receive a dose at the earliest opportunity. Vaccination is also recommended (2) for persons ages 2 to 55 years who are at increased risk for meningococcal disease, including those who have:

- Problems with immunity to N meningitidis (persons who have terminal complement component deficiencies or anatomic or functional asplenia). The Advisory Committee on Immunization Practices (ACIP) recommends that persons who have human immunodeficiency virus infection be vaccinated.
- Increased exposure (microbiologists routinely exposed to isolates of N meningitidis and travelers to or residents of countries in which N meningitidis meningitis is hyperendemic or epidemic).
- Risk due to living conditions or behavior (military recruits, college freshmen living in dormitories).

Although MCV4 is licensed for children as young as 2 years of age, it is not routinely recommended for healthy children ages 2 to 10 years. MCV4 is neither licensed nor recommended for use in the age group that has the highest incidence of meningococcal disease: infants. A meningococcal vaccine for United States infants is currently under investigation. (3)

Common symptoms following receipt of MCV4 include local pain, headache, and fatigue. MCV4 can be administered concomitantly with other vaccines, including tetanus-diphtheria or tetanus-diphtheria-acellular pertussis. Meningococcal vaccine is contraindicated for persons who have had an allergic reaction to a previous dose of vaccine or any vaccine component. A personal history of Guillain-Barré syndrome is listed as a contraindication in the MCV4-D package insert; the MCV4-CRM package insert indicates that data are insufficient to assess the risk. The ACIP’s 2011 General Recommendations do not include this as either a precaution or contraindication.

Table 4. Chemoprophylaxis Regimens for High-risk Contacts

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifampin</strong></td>
<td></td>
<td></td>
<td>Drug of choice for most patients</td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>5 mg/kg every 12 hours</td>
<td>2 days</td>
<td>Not recommended for pregnant women; may interfere with medications (anticoagulants, oral contraceptives, anticonvulsants)</td>
</tr>
<tr>
<td>≥1 month</td>
<td>10 mg/kg (maximum, 600 mg)</td>
<td>2 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>orally every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15 years</td>
<td>125 mg intramuscularly</td>
<td>Single dose</td>
<td></td>
</tr>
<tr>
<td>≥15 years</td>
<td>250 mg intramuscularly</td>
<td>Single dose</td>
<td></td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 month</td>
<td>20 mg/kg (maximum, 500 mg)</td>
<td>Single dose</td>
<td>Not recommended for pregnant women, for routine use in those &lt;18 years of age, or in communities that have reported fluoroquinolone-resistant strains of N meningitidis</td>
</tr>
<tr>
<td></td>
<td>orally</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Azithromycin</strong></td>
<td>10 mg/kg (maximum, 500 mg)</td>
<td>Single dose</td>
<td>Not recommended routinely</td>
</tr>
</tbody>
</table>

Table 4. Chemoprophylaxis Regimens for High-risk Contacts
Summary

- Based on strong surveillance data, (4) the incidence of invasive meningococcal disease has decreased in the past decade. Children younger than 2 years of age remain at highest risk.
- Based on multiple clinical studies and consensus, (5)(6)(7)(8)(9) *Neisseria meningitidis* produces a variety of disease manifestations, but the two most common and devastating are MM and SMS. Because these manifestations present subtly and progress rapidly, clinicians still must be watchful for patients who might be developing meningococcal disease and treat them aggressively.
- Based on multiple research studies, (5)(7)(10) despite improved understanding of meningococcal disease, no intervention has proved more effective at reducing morbidity and mortality than penicillin and the aggressive management of shock.
- Based on surveillance data and clinical research, (4)(11)(12)(13)(14)(15) it seems likely that prevention through routine vaccination should significantly diminish disease burden, and a meningococcal vaccine may soon be licensed for use during infancy.

Revaccination

Persons who received MCV4 at ages 11 through 12 years should receive a one-time booster at age 16 years. Persons who received their first dose at ages 13 through 15 years should receive a one-time booster at ages 16 through 18 years. For details on revaccinating high-risk children, please refer to the most recent “Recommended Immunization Schedule for Persons Aged 7 Through 18 Years—United States,” available at the Centers for Disease Control Prevention website: http://www.cdc.gov/vaccines/recs/schedules/child-schedule.htm.

For an excellent list of Internet links to parent and clinician resources on meningococcal vaccination, please see http://immunize.org/mening/#resources.

Treatment of Contacts (Table 4)

Household contacts of patients who have meningococcal disease should be treated to eradicate nasopharyngeal carriage of the organism. Those who have child care contact and those who have direct exposure to an index case’s oral secretions (such as personnel providing mouth-to-mouth resuscitation) during the 7 days before the onset of illness also require chemoprophylaxis. Risk factors, ciprofloxacin, azithromycin, or ceftriaxone should be used for contacts.

References

**PIR Quiz**

Quiz also available online at http://pedsinreview.aappublications.org.

6. In an infectious disease seminar for medical students, you are addressing the risk factors that increase the likelihood that transmission from carriers will result in meningococcal disease. You correctly state that among the following groups, the risk of disease is **highest** among:

A. Healthy schoolchildren.
B. Healthy nonsmoking adults.
C. Household contacts of an index case.
D. Toddlers in child care centers.
E. Vaccinated students living in college dormitories.

7. While taking a weekend call, you receive a call from the mother of a previously healthy, fully immunized 14-month-old boy who has had cold symptoms for the past 2 days. Late this morning, he developed a temperature of 40.0°C, malaise, and discomfort, and she now sees raised red spots scattered over his trunk. He is alert and interactive but very fussy. The **most** appropriate next step is to:

A. Arrange for him to be seen in the office first thing tomorrow morning.
B. Call in a prescription for high-dose oral amoxicillin.
C. Immediately arrange to transfer him to the nearest emergency department.
D. Order a complete blood count and differential count.
E. Recommend an antipyretic and close observation at home.

8. A previously healthy adolescent arrives by ambulance to your emergency department. He has become very ill over the past few hours. A quick physical examination reveals fever, tachycardia, a stiff neck, and widely scattered petechiae. He is also becoming progressively more obtunded. You establish an intravenous line, draw a blood culture, order electrolyte assessment and a complete blood count, and administer a fluid bolus. The **most** appropriate next step is to:

A. Administer intravenous ceftriaxone.
B. Obtain a chest radiograph.
C. Order a computed tomography scan of the head.
D. Perform a Gram stain on an aspirate of a purpuric lesion.
E. Perform a lumbar puncture.

9. A 2-year-old boy is diagnosed with meningococcal meningitis. Intravenous penicillin was administered on admission, droplet precautions were begun immediately, and he received oral rifampin the next morning. No special resuscitative procedures were ever required. To reduce the risk of secondary cases, prophylaxis with oral rifampin is necessary for:

A. Grandparents who live out of state and visited him in the hospital.
B. His companions in child care.
C. Laboratory personnel who drew blood samples.
D. Nurses who delivered routine bedside care.
E. Physicians who examined the patient.

10. Meningococcal conjugate vaccine is routinely recommended:

A. At age 4 to 5 years.
B. At the earliest opportunity between 11 and 18 years.
C. At 12 months.
D. For all infants at birth.
E. For children of all ages who have cellular immune deficiencies.