DIPHTHERIA

Perspective

Background

In the fifth century BC, Hippocrates provided the first clinical description of what is likely diphtheria, characterized by sore throat, membrane formation, and death through suffocation, but references to the disease date to ancient Syria and Egypt. Epidemics of “throat distemper” occurred throughout the 16th, 18th, and 19th centuries. In 1821, French physician Pierre Bretonneau named the condition diphtherite, from the Greek word for leather, to describe the characteristic pharyngeal membrane. Klebs observed the Corynebacterium diphtheriae microorganism on smears obtained from pharyngeal membranes in 1883, and 1 year later Löffler isolated the organisms in pure cultures. Löffler subsequently demonstrated that diphtheria is a localized infection and postulated that an elaborated toxin caused its systemic effects. In 1888 Roux and Yersin demonstrated that bacteria-free filtrates of diphtheria culture were able to kill guinea pigs.

In 1890, von Behring and Kitasato first demonstrated diphtheria immunization with a heat- and formalin-treated toxin to make toxoid. One year later they administered the first dose of antitoxin to a human with diphtheria. Schick developed the skin test for diphtheria immunity in 1913. During the 1930s and 1940s, toxoid immunization was routinely used. In the 1950s, Freeman found diphtheria immunity in 1913. During the 1930s and 1940s, toxoid immunization nearly eliminates these toxigenic strains in a population, and the disease predominantly affected children. During this time, 80% of people acquired natural immunity to diphtheria by the age of 15 years, and recurrent exposure to toxigenic strains of the bacteria acted as a booster. Because childhood immunization nearly eliminates these toxigenic strains in a population, adult immunity wanes. Thus more adults in industrialized nations are susceptible to diphtheria. By the 1980s the Centers for Disease Control and Prevention (CDC) reported only 0 to 5 cases per year nationwide. Currently, sporadic cases occur primarily in adults, many of whom are not adequately immunized. Three urban outbreaks of predominantly cutaneous diphtheria occurred in Seattle between 1972 and 1982 among a population of urban alcohol abusers. Outbreaks are associated with poor hygiene, crowding, underlying skin disease, contaminated fomites, pyoderma, and the appearance of new C. diphtheriae strains. Even in industrialized nations in which childhood vaccination rates are high, more than 50% of adults older than 40 years lack protective antibodies. The ease of international travel and the epidemic in eastern Europe in the 1990s underscore the importance of aggressive continuation of childhood immunizations and reimmunization of adults.

Epidemiology

Humans are the only known reservoir for C. diphtheriae. Spread is primarily by person-to-person contact through respiratory droplets or by direct contact with skin lesion exudates. Transmission is associated with crowded living conditions. Individuals may spread the disease when they are actively ill, in the convalescent stage after acute illness, or as asymptomatic carriers. Fomites and foods have occasionally been implicated but do not represent a major route of transmission.

Between 1991 and 1996 the first large-scale epidemic of diphtheria in an industrialized country in three decades occurred in the newly independent states of the former Soviet Union, where the disease had previously been well controlled. During the peak of the epidemic, more than 98,000 cases and 3400 deaths were reported. Several factors contributed to this outbreak, including (1) decreased childhood immunity due to vaccine supply interruption and administration of adult-formulation tetanus-diphtheria toxoids (Td) to children, (2) increased adult susceptibility due to waning immunity, (3) poor socioeconomic conditions and increased population movement, and (4) resurgence of more toxigenic strains of diphtheria. Diphtheria remains endemic in many parts of the world and continues to cause sporadic cases and outbreaks.

Immunization against diphtheria is highly effective (Fig. 129-1). Before widespread immunization programs in the United States, the incidence of diphtheria was in excess of 100 cases per 100,000 population, and the disease predominantly affected children. During this time, 80% of people acquired natural immunity to diphtheria by the age of 15 years, and recurrent exposure to toxigenic strains of the bacteria acted as a booster. Because childhood immunization nearly eliminates these toxigenic strains in a population, adult immunity wanes. Thus more adults in industrialized nations are susceptible to diphtheria. By the 1980s the Centers for Disease Control and Prevention (CDC) reported only 0 to 5 cases per year nationwide. Currently, sporadic cases occur primarily in adults, many of whom are not adequately immunized. Three urban outbreaks of predominantly cutaneous diphtheria occurred in Seattle between 1972 and 1982 among a population of urban alcohol abusers. Outbreaks are associated with poor hygiene, crowding, underlying skin disease, contaminated fomites, pyoderma, and the appearance of new C. diphtheriae strains. Even in industrialized nations in which childhood vaccination rates are high, more than 50% of adults older than 40 years lack protective antibodies. The ease of international travel and the epidemic in eastern Europe in the 1990s underscore the importance of aggressive continuation of childhood immunizations and reimmunization of adults.

Principles of Disease

Etiology

Diphtheria is caused by C. diphtheriae, an unencapsulated, nonmotile, gram-positive bacillus named for its shape (korynee, for “club”) and for its characteristic clinical presentation (diptheria, for “leather hide,” referring to the appearance of the leathery pharyngeal membrane). When they are viewed on stained smears, the bacteria look like Chinese characters.

Infection by C. diphtheriae can occur at various sites of the respiratory tract or the skin. Respiratory diphtheria includes faucial (pharyngeal or tonsillar), nasal, and laryngeal (tracheobronchial) types, named for the primary location of infection. Cutaneous diphtheria can occur as a primary skin infection or as a secondary infection of a preexisting wound.
Pathophysiology

The *C. diphtheriae* bacterium produces an exotoxin that contributes to formation of the diphtheritic membrane and is responsible for the systemic effects of infection. The exotoxin is a 62,000-dalton polypeptide produced by bacterial strains lysogenized by the corynephage B tox. The exotoxin inhibits cellular protein synthesis. Circulating exotoxin most profoundly affects the nervous system, heart, and kidneys. The degree of local and systemic toxicity depends on the location and extent of membrane formation. Pharyngeal diphtheria generally has the greatest toxicity and cutaneous diphtheria the least.

The diphtheritic membrane forms as a result of necrosis caused by the local effects of the exotoxin. The membrane is composed of leukocytes, erythrocytes, fibrin, epithelial cells, and bacteria. Initially, the pharynx appears erythematous, but as necrosis occurs, grayish white patches appear and eventually coalesce. The membrane is accompanied by surrounding edema and cervical adenitis. The initial grayish white, filmy appearance changes to a thick, grayish white membrane with sharply defined borders. This membrane adheres to the underlying tissue, and bleeding occurs if removal is attempted.

Systemic effects of diphtheria infection are caused by the circulating exotoxin’s action primarily on the cardiovascular and nervous systems. The exotoxin disrupts cellular protein synthesis and produces a peripheral neuropathy manifested by muscle weakness. About 5% of all patients with symptomatic respiratory infection will have polynuertis, but 75% of patients with severe disease have some form of neuropathy. The muscles of the palate are usually the first to become paralyzed. Less commonly, other cranial nerves, peripheral nerves, and the spinal cord are affected. Degenerative lesions develop in the dorsal root and ventral horn ganglia of the spinal cord and in cranial nerve nuclei. Cortical cells are spared. Proximal muscle groups are affected first. In severe cases, paralysis may develop in the first few days of illness. In general, the paralysis does not last more than 10 days, and complete recovery during a longer time is the rule.

The extent of cardiac complications correlates with the degree of local infection and membrane formation. Signs of myocardial dysfunction usually appear 1 to 2 weeks after the onset of illness. In more severe cases, cardiac symptoms arise earlier in the course of the illness. The exotoxin directly damages myocardial cells, producing myocarditis. Electrocardiographic changes suggestive of myocarditis occur in up to two thirds of patients, but clinical manifestations of myocarditis are less common (10-25%).

Clinical Features

Symptoms and Signs

The average incubation period of respiratory tract diphtheria is 2 to 4 days but may range from 1 to 8 days. Signs and symptoms are often indistinguishable from those of other upper respiratory tract infections. In a series of 676 patients, fever and sore throat were the most frequent presenting complaints (79% and 69%, respectively). Weakness (42%), dysphagia (35%), headache (20%), change of voice (15%), and loss of appetite (10%) were also common. Cough, shortness of breath, nasal discharge, and neck edema occurred in less than 10% of patients. Fever, although common, is usually low grade. Cervical adenopathy is present in approximately one third of patients, and a diphtheritic membrane is observed in more than half of all patients. Of note, however, one report indicated that shortness of breath and neck edema were present in approximately 40% of patients who died of the disease.

In patients with faucial diphtheria, the extent of the membrane usually parallels the clinical toxicity. If the membrane is limited to the tonsils, the disease may be mild; if the membrane covers the entire pharynx, the onset of illness is usually abrupt and the disease severe. Swelling of the cervical lymph nodes and infiltration of tissues of the neck may be so extensive that the patient has a “bull-neck” appearance. Patients with this form of “malignant diphtheria” usually have high fever, severe muscle weakness, vomiting, diarrhea, restlessness, and delirium. Death occurs from respiratory tract obstruction or cardiac failure from myocarditis. Nasal diphtheria arises with a unilateral or bilateral serous or serosanguineous discharge from the nose. A diphtheritic membrane may be visible. These patients do not usually have constitutional symptoms. Treatment is important to prevent a persistent carrier state. Laryngeal (tracheobronchial) diphtheria may begin in the larynx or spread downward from a more cephalad primary site. Respiratory tract edema with subsequent upper airway obstruction may develop.
Patients with cutaneous diphtheria generally do not display systemic toxicity. The skin characteristically has an ulcer with a grayish membrane. Wounds from which C. diphtheriae is cultured are clinically indistinguishable from other chronic skin conditions.1

Complications

The most serious complications of diphtheria are airway obstruction (resulting from membrane formation and edema), congestive heart failure, cardiac conduction disturbances, and muscle paralysis. Mortality in two large series ranged from 2 to 3% overall but was up to 7% in patients with myocarditis and 26% in patients with the malignant form of the disease (with neck swelling).7 Unimmunized and underimmunized children requiring intensive care have higher mortality rates (78%) from myocarditis and often develop renal failure.6 Although systemic infection is rare, endocarditis, mycotic aneurysms, osteomyelitis, and septic arthritis have all been described in immunocompromised hosts.1

Diagnostic Strategies

When C. diphtheriae is suggested, the laboratory should be notified because routine cultures do not identify the organism. Throat or nasopharyngeal swabs should be obtained for respiratory diphtheria, and if it is present, membranous material should be examined. For cutaneous infections, samples should be obtained from skin lesions. Specimens should be collected before antibiotic therapy is initiated and should be transported to the laboratory immediately for rapid inoculation onto tellurite (Tinsdale’s) or Löeffler’s selective culture medium.1 Immunofluorescent staining of a 4-hour culture may provide a rapid diagnosis, but direct staining is frequently unreliable. Definitive identification is made by use of a combination of colony morphology, microscopic appearance, and fermentation reactions.1 C. diphtheriae isolates should be tested for the production of toxin. The Elek immunoprecipitation test for toxin A is technically demanding and subject to misinterpretation by inexperienced users. Polymerase chain reaction (PCR), which is more reliable but not as readily available, can be used to detect the diphtheria toxin structural gene. Newer methods that rapidly detect the toxin by mass spectrometry are not readily available but may be used in the future.9 A positive culture for group A beta-hemolytic streptococcus does not exclude diphtheria as a pathogen because up to 30% of patients with diphtheria test positive for streptococcal coinfection or carrier state.

Several laboratory abnormalities, such as leukocytosis, mild thrombocytopenia, and proteinuria, are common but are neither sensitive nor specific for diphtheria. Electrocardiographic changes are nonspecific and include ST-T wave changes, varying degrees of atrioventricular block, and dysrhythmias. An electrocardiogram may be normal even in the presence of myocarditis. An echocardiogram may show dilated or hypertrophic cardiomyopathy. Cardiac enzymes may be elevated, and serum troponin levels correlate with the severity of myocarditis.10

Differential Considerations

In the absence of a diphtheritic membrane, it may be difficult to differentiate respiratory diphtheria from many other respiratory conditions, especially in the early phase of infection (Box 129-1). In general, the diphtheritic membrane is darker, grayer, more fibrous, and more firmly attached to the underlying tissues than in other conditions that have a membrane-like appearance. Vincent’s angina frequently involves the gingivae, which are unaffected in diphtheria. Acute bacterial epiglottitis generally has a much more rapid onset than diphtheria, and indirect laryngoscopy reveals an erythematous, edematous epiglottis without membrane formation.1

Cutaneous diphtheria is difficult to differentiate from other acute and chronic ulcerative skin lesions. C. diphtheriae can secondarily infect any of these lesions, especially in high-risk patients such as alcoholic, socioeconomically disadvantaged, and unimmunized or underimmunized people.

Management

Patients with clinical evidence of diphtheria should be placed in respiratory isolation and treated presumptively for C. diphtheriae infection. The goals of therapy are to protect the airway, to limit the effects of already produced toxin, and to eliminate future toxin production by terminating the growth of C. diphtheriae. Although the likelihood for the development of airway obstruction from diphtheria is remote for a patient in the United States, the management is identical to that for other forms of airway obstruction. Bronchodilators may be useful in symptomatic patients.10 Patients may be dehydrated from fever and decreased oral intake related to dysphagia or neurologic impairment. Fluid resuscitation should be undertaken cautiously as the toxin’s effect on the myocardium may result in congestive heart failure.1,10

Equine serum diphtheria antitoxin (DAT) should be administered promptly after the clinical diagnosis of respiratory diphtheria is made and before laboratory confirmation.10-12 DAT is not licensed by the Food and Drug Administration (FDA) for use in the United States. The CDC is authorized to distribute DAT to physicians as an investigational new drug. DAT can be obtained by contacting the CDC Emergency Operations Center at 770-488-7100. The diphtheria duty officer can also be contacted at 404-639-3158 during duty hours.12 The size and location of the membrane, the duration of illness, and the patient’s overall degree of toxicity determine the dosage of antitoxin. The CDC recommends 20,000 to 40,000 units for pharyngeal or laryngeal involvement of 48 hours’ duration, 40,000 to 60,000 units for nasopharyngeal lesions, and 80,000 to 120,000 units for systemic disease of 3 days’ duration or more or for diffuse swelling of the neck.12 After conjunctival or intradermal sensitivity skin testing, the antitoxin is administered intravenously. If the patient exhibits sensitivity to the antitoxin, desensitization should be performed. Active immunization against diphtheria should also be initiated because clinical infection does not necessarily confer immunity.10

Antibiotics are beneficial in preventing growth and spread of the organism but are no substitute for antitoxin. Erythromycin 30 to 50 mg/kg/day (up to 2 g) intravenously (IV) or orally in divided doses, aqueous crystalline penicillin 100,000 to 150,000 units/kg/day in four divided doses intramuscularly (IM), and procaine penicillin 25,000 to 50,000 units/kg/day in two divided doses for 14 days given IM are acceptable alternatives.10 Treatment failures are slightly more common with penicillin than with erythromycin. The newer generation macrolides (azithromycin and

<table>
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<th>Differential Diagnosis of Respiratory Diphtheria</th>
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<tr>
<td>Streptococcal or viral pharyngitis</td>
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<td>Tonsillitis</td>
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<td>Vincent’s angina</td>
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<td>Acute epiglottitis</td>
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<td>Mononucleosis</td>
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<td>Laryngitis</td>
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<td>Bronchitis</td>
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<td>Tracheitis</td>
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<td>Monilial infection (thrush)</td>
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<td>Rhinitis</td>
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clarithromycin) have activity similar to that of erythromycin in vitro and may result in better compliance. These agents have not yet been adequately tested in clinical disease. An equivalent daily oral therapy may be substituted when the patient is able to swallow. Negative cultures should be documented after treatment.\(^{10}\)

Myocarditis and neuritis are treated with supportive care and careful monitoring. Patients with electrocardiographic changes of myocarditis have three to four times the mortality rate of those with normal electrocardiograms. The mortality rate for patients with left bundle branch block and atrioventricular block is 60 to 90%. Serial tracings are recommended, and survivors may have permanent conduction abnormalities. No data support the use of steroids.

Cutaneous lesions should be debrided of necrotic tissue and cleansed vigorously. A course of antibiotics is recommended, but the administration of antitoxin for cutaneous lesions is of questionable value. Some experts recommend 20,000 to 40,000 units of antitoxin, but few data support its use in this setting.\(^{1,10}\)

Carriers of C. diphtheriae should receive oral penicillin G or erythromycin for 7 days or intramuscular benzathine penicillin (600,000 units for those weighing less than 30 kg and 1,200,000 units for those weighing more than 30 kg). Active immunization should also be provided to unimmunized and partially immunized carriers. After 2 weeks of therapy is completed, cultures should be obtained; if cultures are positive, erythromycin therapy should be given for 10 additional days.\(^{1}\)

Individuals who have been in close contact with infected patients should have culture specimens taken, and the patient should be kept under surveillance for 7 days. Previously immunized close contacts should receive a booster of diphtheria toxoid if the last booster was more than 5 years earlier. The vaccine should be diphtheria, tetanus, and acellular pertussis (DTaP), diphtheria-tetanus (DT), or tetanus-diphtheria with a lower dose of diphtheria toxoid (Td) as appropriate for age according to the recommended immunization schedule. Close contacts who are not immunized or whose immunization status is unknown should receive the same antimicrobial therapy as carriers (as previously described), have culture specimens taken before and after therapy, and have active immunization initiated. Close contacts who cannot be kept under surveillance should receive benzathine penicillin intramuscularly to ensure compliance and a Td booster (appropriate for age and immunization history). Some practitioners treat this group with 5000 to 10,000 units of antitoxin intramuscularly (at a site separate from the toxoid booster) after sensitivity testing. This is generally not recommended, however, because of the risk of horse serum allergy.\(^{12}\)

A universal program of primary immunization along with regular diphtheria boosters every 10 years is the most effective method for control of diphtheria. For this reason, emergency physicians should routinely administer age-appropriate tetanus and diphtheria toxoids as part of wound management.

Disposition
All patients with possible pharyngeal diphtheria should be isolated and admitted. A monitored setting is recommended for the early detection of arrhythmias. A cardiologist should be consulted for patients with evidence of myocarditis. The CDC should be contacted for all suggested or proven cases of diphtheria.

PERTUSSIS

Perspective

Background

Pertussis is an acute respiratory disease that was first described in 1578 when an epidemic swept through Paris. The name pertussis was first used by Sydenham in 1670 when he described the illness in infants. Pertussis literally means “violent cough,” which is the hallmark of the disease. In China it is known as “the cough of 100 days.” It is also called whooping cough because the severe episodes of coughing are followed by forceful inspiration, which creates the characteristic whooping sound. The causative organism was identified in 1906 by Bordet and Gengou.\(^{13}\) In the prevaccination era, pertussis was a major cause of mortality among infants and children in the United States. A vaccine was developed in the 1940s, but pertussis still remains a significant cause of morbidity and mortality in the United States and worldwide.

Epidemiology

Pertussis is a localized respiratory illness transmitted by aerosolized droplets. It is highly contagious, with attack rates greater than 50% in adults exposed more than 12 years after completion of a vaccination series and up to 90% in susceptible individuals with a household exposure.\(^{14}\) The average incubation period is 7 to 10 days but may range from less than 1 week to 3 weeks. Neither vaccination nor prior infection confers lifelong immunity.

Pertussis remains prevalent worldwide, with 106,207 cases reported to the World Health Organization in 2009 (Fig. 129-2A). In the United States, annual pertussis rates declined sharply after the introduction of the vaccine and reached a nadir of 1010 cases in 1976. Since then, there has been a steady increase in the incidence of pertussis, with 11,647 cases reported in 2003 and 25,616 in 2005 (Fig. 129-2B).\(^{14}\) Waning immunity in the adult population and increased reporting of adult cases may be contributing factors. A 1991 report found evidence of a causal relationship between the vaccine and acute encephalopathy. Although there appears to be no causal relationship between the vaccine and long-term neurologic complications, the report resulted in a decline in the use of the whole-cell pertussis vaccine. The acellular pertussis vaccine has been approved in the United States since 1991 for persons 15 months to 64 years and since 1997 for infants.\(^{14}\)

Although pertussis can occur at any age, it is predominantly a pediatric and adolescent illness. The age-specific attack rates are highest in children younger than 1 year who have not yet received the entire vaccine series. There appears to be a seasonal variation; 50% of cases in the United States occur from June through September.

Principles of Disease

Etiology

Pertussis is caused by organisms of the Bordetella genus, which are small, aerobic, gram-negative cocccobacilli that occur singly or in pairs. Bordetella pertussis and Bordetella parapertussis are primarily responsible for disease in humans. The organisms are fastidious and require nicotinamide and an optimal temperature of 35 to 37° C to grow. Bordetella bronchiseptica, a flagellated, motile organism, causes illness in animals, including kennel cough, and may rarely cause respiratory infection in immunocompromised humans.\(^{15}\)

Pathophysiology

The Bordetella organism adheres preferentially to ciliated respiratory epithelial cells. B. pertussis does not invade beyond the submucosal layer in the respiratory tract and is almost never recovered in the bloodstream. The organism elaborates several toxins that act locally and systemically. These toxins include pertussis toxin, dermonecrotic toxin, adenylate cyclase toxin, and tracheal cytotoxin.\(^{15}\)
Local tissue damage consists of inflammatory changes in the mucosal lining of the respiratory tract, primarily congestion and cellular infiltration with lymphocytes and granulocytes. As the infection progresses, secondary pneumonia or otitis media may occur. Systemic effects of pertussis toxin include sensitization to the lethal effects of histamine and increased secretion of insulin. This hyperinsulinemia can cause hypoglycemia, particularly in young infants.13

Clinical Features
Symptoms and Signs

Pertussis arises in three distinct sequential clinical stages: the catarrhal phase, the paroxysmal phase, and the convalescent phase. The catarrhal or prodromal phase begins after an incubation period of approximately 7 to 10 weeks and lasts approximately 1 to 2 weeks. Infectivity is greatest during the catarrhal phase, when the disease is clinically indistinguishable from other upper respiratory tract infections. Signs and symptoms include rhinorrhea, low-grade fever, malaise, and conjunctival injection, which are clinically indistinguishable from a common upper respiratory tract infection. A dry cough usually begins at the end of the catarrhal phase.13

The paroxysmal phase begins as fever subsides and cough increases and lasts 2 to 4 weeks. Paroxysms of staccato coughing occur 40 to 50 times per day. The patient coughs repeatedly in short exhalations, followed by a single, sudden, forceful inhalation that produces the characteristic “whoop.” Only one third of adults with pertussis develop this whoop, and it is rare in young infants, who may present with apneic episodes and no other symptoms. Paroxysms may be spontaneous, occur more frequently at night,
Bradycardia, hypotension, and cardiac arrest can occur in neonates and young infants with pertussis. Severe pulmonary hypertension has increasingly been recognized in this age group and can lead to systemic hypotension, worsening hypoxia, and increased mortality.\textsuperscript{15,16} Intensive care monitoring is recommended for these patients, regardless of how well they may appear on admission.

### Diagnostic Strategies

The diagnosis of pertussis should be entertained in any patient with prolonged cough with paroxysms, whoops, or post-tussive emesis, regardless of previous vaccination status. Up to 25\% of adults in the United States who have a prolonged cough have serologic evidence of pertussis.\textsuperscript{13}

Ancillary studies are of limited value in the emergency department. During the late catarrhal and early paroxysmal phases, a marked leukocytosis and a characteristic lymphocytosis are often present. The white blood cell (WBC) count of 25,000 to 50,000/mL is not uncommon and may exceed 100,000/mL in infants.\textsuperscript{17} Adults with pertussis frequently do not have the characteristic leukocytosis and lymphocytosis, and some infants and immunocompromised hosts may not be able to mount this response. The chest radiograph may show peribronchial thickening, atelectasis, or pulmonary consolidation.\textsuperscript{18}

Laboratory confirmation of the diagnosis is made by nasopharyngeal culture and PCR, if both are available; sputum and throat swabs are inadequate.\textsuperscript{13} The *Bordetella* organism is fastidious, and isolation requires a nicotinamide or Bordet-Gengou medium impregnated with antibiotics to reduce overgrowth of competing bacteria. The slow-growing hemolytic colonies of *B. pertussis* take 3 to 7 days to appear. A synthetic culture medium is also available. The sensitivity of pertussis cultures is only 15 to 80\% and drops to only 1 to 3\% three weeks after the onset of cough. Direct fluorescent antibody techniques are no longer recommended to identify *B. pertussis*. Adults generally come to medical attention late in the disease, at which time cultures are rarely positive (3.6\%). PCR is much more likely to identify the organism but has a high false-positive rate. Most laboratories use enzyme-linked immunosorbent assay, which rises 2 to 3 weeks after infection or primary immunization. Paired serologic tests showing a twofold increase are the “gold standard” for diagnosis.\textsuperscript{13}

### Differential Considerations

The differential diagnosis includes acute viral upper respiratory tract infection, pneumonia, bronchiolitis, cystic fibrosis, tuberculosis, exacerbation of chronic obstructive pulmonary disease, and foreign body aspiration. The marked leukocytosis may suggest the diagnosis of leukemia.

### Management

#### Acute Treatment

Treatment of pertussis is primarily supportive and includes oxygen, frequent suctioning, appropriate hydration, parenteral nutrition if necessary, and avoidance of respiratory irritants. Patients with suggested pertussis and associated pneumonia, hypoxia, or CNS complications or those experiencing severe paroxysms should also be hospitalized. Children younger than 1 year should also be admitted because they are not yet fully immunized and have the greatest risk for morbidity and mortality. Neonates with pertussis should be admitted to an intensive care unit (ICU) as apnea and significant cardiac complications can occur without warning.\textsuperscript{15,17}

Antibiotic treatment does not appear to significantly reduce the severity or duration of illness when it is started in the

### Complications

The major complications of pertussis are pneumonia superinfection, central nervous system (CNS) sequelae, otitis media, and complications related to the paroxysm of coughing. Pneumonia complicating pertussis is a leading cause of death, especially in infants and young children.\textsuperscript{13-18} Aspiration of gastric contents and respiratory secretions may occur during the paroxysm of coughing, whooping, and vomiting. Secondary pulmonary infection may also be a consequence of decreased respiratory tract clearance related to the actions of the *Bordetella* organism and its toxins on bronchial and lung mucosa. Bacterial (*Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae*, and *Staphylococcus aureus*) and viral (respiratory syncytial virus, cytomegalovirus, and adenovirus) superinfections can complicate pertussis infections. A fever during the paroxysmal phase should alert the physician to a possible superinfection.

CNS complications include seizures and encephalopathy in about 1\%.\textsuperscript{19} The causes are unclear but may include hypoxia, hypoglycemia, cerebral petechia, effects of a toxin, or secondary infection by neurotropic viruses or bacteria. CNS hemorrhages may occur as a consequence of the increased cerebrovascular pressures generated during the paroxysm of coughing. Sudden increases in intrathoracic and intra-abdominal pressures can result in several other complications (Box 129-2).\textsuperscript{13,19}

### Box 129-2 Pertussis Complications

<table>
<thead>
<tr>
<th>Periorbital edema</th>
<th>Pneumothorax</th>
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<tr>
<td>Subconjunctival hemorrhage</td>
<td>Pneumomediastinum</td>
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<tr>
<td>Petechiae</td>
<td>Diaphragmatic rupture</td>
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<tr>
<td>Epistaxis</td>
<td>Umbilical and inguinal hernias</td>
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<tr>
<td>Hemoptysis</td>
<td>Rectal prolapse</td>
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<tr>
<td>Subcutaneous emphysema</td>
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paroxysmal phase and may have only a minimal effect in the catarrhal phase. The primary goal of antibiotic therapy is to decrease infectivity and carriage. Erythromycin estolate ester is the antibiotic of choice at 40 to 50 mg/kg/day (maximum 2 g/day) in two or three divided doses for 14 days. Azithromycin (10 mg/kg on day 1, followed by 5 mg/kg on days 2-5), clarithromycin (15 mg/kg/day in two divided doses), and a 7-day course of erythromycin estolate ester are effective alternatives for patients who do not tolerate 14 days of erythromycin. Trimethoprim-sulfamethoxazole (8 mg/kg/day of trimethoprim) is an alternative for macrolide-allergic patients, but efficacy is unproven. Patients should be considered infectious for 3 weeks after the onset of the paroxysmal phase or until at least 5 days after antibiotics are started. Strict droplet isolation is recommended during this period.

Corticosteroids, especially in young critically ill infants, may reduce the severity and course of illness, but effectiveness is not well established. Beta2-adrenergic agonists do not reduce the frequency or severity of paroxysmal coughing episodes but may be helpful in patients with reactive airway disease. Trials with pertussis immune globulin are limited and to date show no proven benefit. Standard cough suppressants and antihistamines are ineffective.

Postexposure prophylaxis with erythromycin as described previously should be considered for infants younger than 6 months who are household contacts of infected patients. Erythromycin may also be prescribed for any unimmunized person or partially immunized infant with a history of significant exposure to the organism are puncture wounds, lacerations, and abrasions. Tetanus has also been reported in association with chronic skin ulcers, abscesses, and otitis media as well as with foreign bodies, corneal abrasions, childbirth, and dental procedures. Postoperative tetanus has been reported in patients who have undergone intestinal operations and abortions. In these cases the source of bacteria is probably endogenous as up to 10% of humans harbor C. tetani in the colon.

Inadequate primary immunization and waning immunity continue to be the primary risk factors for tetanus in the United States. As tetanus vaccination of children has improved, older people have accounted for an increasing percentage of reported cases.

**TETANUS**

**Perspective**

**Background**

Tetanus is a toxin-mediated disease characterized by severe uncontrolled skeletal muscle spasms. Involvement of the muscles of respiration leads to hypoventilation, hypoxia, and death. Dramatic descriptions of this disease date to ancient Egypt, when physicians recognized a frequent relationship between tissue injury and subsequent fatal spasm.

In 1884, Carle and Rattone produced tetanus in rabbits by injecting material from an acne pustule that came from an infected human. In the same year, Nicolar isolated the strychnine-like toxin from anaerobic soil bacteria. In 1889, Kitasato obtained pure cultures of spor-forming bacteria that caused tetanus on introduction into animals. One year later, Faber proved that tetanus is a toxin-mediated disease when he induced the illness by injecting animals with bacteria-free filtrates of Clostridium tetani cultures. In the 1890s, von Behring and Kitasato discovered tetanus antitoxin in the serum of immune animals and demonstrated its efficacy in preventing disease. Prophylactic injection of this antitoxin provided passive immunity to wounded soldiers during World War I. It was not until 1924 that an effective vaccine was developed by Descombes. Large-scale testing during World War II indicated that the tetanus toxoid confers a high degree of protection against disease.

**Epidemiology**

Despite the availability of an effective vaccine, tetanus remains endemic worldwide. It is more common in warm, damp climates and relatively rare in cold regions. The global annual incidence of reported cases of tetanus has declined steadily with the introduction of vaccination programs (Fig. 129-3A). The World Health Organization reported 9836 cases of tetanus in 2009, but it is estimated that 800,000 to 1 million unreported cases occur a year, with half occurring in neonates. Eighty percent of these cases occur in Africa and Southeast Asia because of low immunization rates and poor hygiene.

Since the introduction of vaccination programs in the United States, the incidence of tetanus has steadily declined from 4 cases per million population in the 1940s to 0.095 case per million population in 2005 (Fig. 129-3B). The highest incidence occurs in people older than 65 years (0.23 case per million population), and the incidence in Hispanic Americans is almost twice that in non-Hispanics. Fifteen percent of cases occur in injection drug users. The overall case fatality rate is 18% but approaches 50% in patients older than 70 years (Fig. 129-4). Cases have been reported in patients who had been fully vaccinated, but in the eight patients from 1998 to 2000, no deaths occurred.

Tetanus typically occurs as a result of a deep penetrating wound. A history of injury is present in more than 70% of patients, but the injury may be trivial in 50% of patients and unapparent in up to 30% of patients. The most common portals of entry for the organism are puncture wounds, lacerations, and abrasions. Tetanus has also been reported in association with chronic skin ulcers, abscesses, and otitis media as well as with foreign bodies, corneal abrasions, childbirth, and dental procedures. Postoperative tetanus has been reported in patients who have undergone intestinal operations and abortions. In these cases the source of bacteria is probably endogenous as up to 10% of humans harbor C. tetani in the colon.

Inadequate primary immunization and waning immunity continue to be the primary risk factors for tetanus in the United States. As tetanus vaccination of children has improved, older people have accounted for an increasing percentage of reported cases.

**Etiology**

*C. tetani* is a spore-forming, motile, slender, rod-shaped, obligate anaerobic bacillus. It stains gram positive in fresh culture but has a variable staining pattern in old cultures and tissue samples. The bacillus can form a single spherical terminal endospore that swells the end of the organism to produce a characteristic drumstick appearance. *C. tetani* is ubiquitous in soil and dust and is also found in the feces of animals and humans. Mature bacilli are highly susceptible to heat and other adverse environmental conditions. Spores are resistant to heating and chemical disinfectants and can survive in soil for months to years. When they are introduced into a wound, spores may not germinate for weeks because of unfavorable tissue conditions. When injury favors anaerobic growth, the spores germinate into mature bacilli. Only these mature bacilli produce the tetanus toxin that causes clinical disease.25-27

**Principles of Disease**

*C. tetani* is a noninvasive organism. The development of clinical tetanus requires a portal of entry for the infecting spores as well as tissue conditions that promote germination and growth in an immunologically susceptible host. Tetanus-prone wounds are those with damaged or devitalized tissue, foreign bodies, or other bacteria. Under these conditions, *C. tetani* produces the neurotoxin that causes clinical illness. Germination and replication of *C. tetani* can occur without clinical signs of a local wound infection.

*C. tetani* produces the neurotoxin tetanospasmin (TS) at the site of tissue injury. TS first binds the motor nerve ending and then moves by retrograde axonal transport and trans-synaptic spread to the CNS.30,31 It binds preferentially to inhibitory (GABAergic and glycineric) neurons and blocks the presynaptic release of these neurotransmitters. Interneurons afferent to alpha motor neurons are affected first.30 Without inhibitory control, the motor neurons undergo sustained excitatory discharge, resulting in the muscle spasm characteristic of tetanus.30

TS may also affect preganglionic sympathetic neurons and parasympathetic centers, resulting in autonomic nervous system dysfunction.31,32 The clinical manifestations include dysrhythmias and wide fluctuations in blood pressure and heart rate. The binding of TS at the synapse is irreversible; recovery occurs only when a new axonal terminal is produced.25

**Clinical Features**

**Symptoms and Signs**

The incubation period for tetanus ranges from 1 day to several months. A shorter incubation period portends a worse prognosis.30 The duration of the incubation period is not useful in making the diagnosis of tetanus because many patients have no history of an antecedent wound. Four types of clinical tetanus have been described.

**Generalized Tetanus.** Generalized tetanus is the most common form of the disease and results in spasms of agonist and antagonist muscle groups throughout the body. The classic initial presenting symptom of trismus (“lockjaw”) is caused by masseter muscle spasm and is present in 50 to 75% of patients. As the other facial muscles become involved, a characteristic sardonic smile (risus sardonicus) appears. Other early symptoms include irritability, weakness, myalgias, muscle cramps, dysphagia, hydrophobia, and drooling. As the disease progresses, generalized uncontrollable muscle spasms can occur spontaneously or as a result of minor stimuli, such as touch or noise. Spasms may result in vertebral and long bone fractures and tendon rupture. Opisthotonos is a prolonged tonic contraction that closely resembles decorticate posturing. Spasms of laryngeal and respiratory muscles can lead to ventilatory failure and death. Autonomic dysfunction is the major cause of death in patients who survive the acute phase and is manifested by tachycardia, hypertension, temperature elevation, cardiac dysrhythmias, and diaphoresis. The illness is progressive, with an increase in symptoms during the first 3 days, persistence of symptoms for 5 to 7 days, and reduction of spasms after 10 days. If the patient survives, recovery is complete after 4 weeks or more. Throughout the course of this horrific illness, patients remain completely lucid unless they are chemically sedated.25-27

**Localized Tetanus.** Localized tetanus is a form of the disease characterized by persistent muscle spasms close to the site of injury. Symptoms may be mild or severe, but mortality is lower than with generalized tetanus. Local tetanus may progress to generalized disease. This form of illness may probably reflect partial immunity to TS and may be present for weeks to months before resolution.25

**Cephalic Tetanus.** Cephalic tetanus is a rare variant of localized tetanus that results in cranial nerve palsies and muscle spasms. The palsy precedes the spasm in 42% of cases, resulting in frequent misdiagnosis. The most commonly involved cranial nerve is the facial nerve (VII), mimicking Bell’s palsy. Most of these cases occur after facial trauma or otitis media. Patients have trismus and palsies of cranial nerve III, IV, VII, IX, X, or XII ipsilateral to the site of local infection. The clinical course is variable. In one third of cases, resolution of symptoms is complete. The remainder progress to generalized tetanus with an overall mortality rate of 15 to 30%.25-29

Neonatal Tetanus. Neonatal tetanus is generalized tetanus of the newborn and occurs almost exclusively in developing countries where maternal immunization is inadequate and contaminated material is used to cut and dress umbilical cords. Symptoms begin during the first week of life and include irritability and poor feeding. Mortality approaches 100% because of the high toxin load for body weight and inadequate medical support in developing countries. Even with limited resources, mortality can be reduced to less than 50% with basic medication and experienced medical and nursing personnel.33 The CDC reported one case of neonatal tetanus in the United States between 1998 and 2000. The infant was born at home to an unimmunized mother. The umbilical cord had been treated with bentonite clay. The child was treated and recovered after 19 days of hospitalization.

**Complications**

Acute respiratory failure, the main cause of morbidity and mortality in tetanus, results from respiratory muscle spasms or laryngospasms and airway obstruction. If the patient survives the acute onset of illness and has adequate ventilatory support, autonomic dysfunction becomes the leading cause of death. Autonomic instability occurs several days after the onset of generalized spasms. Disinhibition of the sympathetic nervous system predominates and causes dysrhythmias, hypertension, myocarditis, and pulmonary edema.34 Dysrhythmias and myocardial infarction are the most common fatal events during this phase.

Forceful tetanic muscle spasms can cause vertebral subluxations and fractures, long bone fractures, and shoulder and temporomandibular joint dislocations. Rhabdomyolysis occasionally occurs and can cause acute renal failure. Renal failure may also result from dehydration and sympathetic nervous system hyperactivity. Renal vein thrombosis may cause renal failure in neonatal tetanus.

Secondary infection may occur in the initial inoculating wound or as a complication arising from invasive treatment modalities, such as mechanical ventilation.35 Hyperthermia may also result from muscle spasms and sympathetic hyperactivity. Prolonged
immobility can lead to deep venous thrombosis and pulmonary embolism. Gastrointestinal complications include peptic ulcers, ileus, intestinal perforation, and constipation. The syndrome of inappropriate secretion of antidiuretic hormone occurs in a small number of patients. Hemolysis has also been reported.

Mortality is a function of the previous immunization status, incubation period, severity and rapidity of onset of symptoms, comorbid disease, age, and sophistication of medical treatment available. With appropriate intensive care treatment, elder patients may fare as well as their middle-aged counterparts.26 Long-term physical complications in survivors are rare. The most common persistent problem may be psychological trauma related to the disease and its treatment.25

**Diagnostic Strategies**

The diagnosis of tetanus should be made on clinical grounds alone. Wound cultures for *C. tetani* are of little value as they are positive in only one third of cases. Even if a positive culture is obtained, it does not indicate whether the bacterium is a toxin-positive strain. There are no laboratory tests to confirm or to exclude the diagnosis of tetanus.25 In 1990 the CDC adopted a clinical case definition for the public health surveillance of generalized tetanus: “acute onset of hypertonia or painful muscular contractions (usually of the muscles of the jaw and neck) and generalized muscle spasms without other apparent medical cause (as reported by a health care professional).26

Lumbar puncture may be indicated to exclude meningitis in the neonate when the diagnosis of tetanus is uncertain. A computed tomography scan is helpful in assessment for intracranial disease. A serum calcium level is helpful to exclude hypocalcemia. Electroencephalography may be useful if the diagnosis of cephalic or localized tetanus is in doubt.25

The spatula test involves touching of the oropharynx with a tongue blade. With a negative test result, the patient gags and expels the tongue blade. With a positive test result, the patient has reflex masseter muscle spasm and bites the spatula. This test is 94% sensitive and 100% specific for tetanus.27

**Differential Considerations**

Strychnine poisoning is the only clinical condition that truly mimics generalized tetanus. Strychnine, like TS, antagonizes glycine release, but unlike TS, it has no effect on γ-aminobutyric acid (GABA) release. Patients have opisthotonos while remaining alert. The annual incidences of tetanus and strychnine poisoning are similar in the United States, and serum and urine tests for strychnine should be performed when tetanus is considered.25

In patients who present with diffuse generalized spasm, the diagnosis of tetanus is less likely to be missed, but ideally the disease should be considered and diagnosed in the early stages to minimize complications and to decrease mortality. Some conditions with clinical similarities to tetanus are listed in **Box 129-3**. Trismus is most commonly caused by intraoral infections. These can be excluded with careful history and physical examination of the oral cavity and teeth. Mandibular dislocation can be ruled out with appropriate radiographs of the mandible and temporomandibular joints. Dystonic reactions can be differentiated from tetanus by medication history and symptoms that are alleviated by benztpine or diphenhydramine. Patients with encephalitis usually exhibit an altered mental status. Meningitis can be excluded by examination of the cerebrospinal fluid (CSF). Rabies should be considered when there are symptoms of brainstem dysfunction, including dysphagia and respiratory muscle dysfunction. A history of exposure to secretions of an infected animal is the most helpful historical point. In addition, rabies does not cause trismus.

**Box 129-3**  **Differential Diagnosis of Tetanus**

<table>
<thead>
<tr>
<th>Acute abdomen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black widow spider bite</td>
</tr>
<tr>
<td>Dental abscess</td>
</tr>
<tr>
<td>Dislocated mandible</td>
</tr>
<tr>
<td>Dystonic reaction</td>
</tr>
<tr>
<td>Encephalitis</td>
</tr>
<tr>
<td>Head trauma</td>
</tr>
<tr>
<td>Hyperventilation syndrome</td>
</tr>
<tr>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>Meningitis</td>
</tr>
<tr>
<td>Peritonsillar abscess</td>
</tr>
<tr>
<td>Progressive fluctuating muscle rigidity (stiff-man syndrome)</td>
</tr>
<tr>
<td>Psychogenic</td>
</tr>
<tr>
<td>Rabies</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Status epilepticus</td>
</tr>
<tr>
<td>Strychnine poisoning</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Temporomandibular joint syndrome</td>
</tr>
</tbody>
</table>

Cephalic tetanus is especially difficult to diagnose when the cranial nerve palsy precedes trismus. The differential diagnosis of cephalic tetanus also includes Bell’s palsy, botulism, cranial nerve palsies, and facial cellulitis with facial nerve compression and ophthalmoplegia.

**Management**

**Acute Treatment**

The four treatment strategies for patients with tetanus should be undertaken simultaneously: aggressive supportive care, elimination of unbound TS, active immunization, and prevention of further toxin production.25,26

**Supportive Care.** Supportive care begins with control of the muscle spasms. Reflex spasms can result from stimulation of the patient, such as that caused by any movement of the patient or loud noises. Avoidance of unnecessary stimulation is recommended. Benzodiazepines are the mainstay of symptomatic therapy for tetanus. These drugs are GABA agonists and indirectly antagonize many of the effects of TS. They have no effect on the inhibition of glycine release by TS. Diazepam is the most extensively studied of these agents, but lorazepam and midazolam are equally effective. Diazepam has a rapid onset of action and a wide margin of safety, and it can be given orally, rectally, or intravenously. It is inexpensive and thus available in most parts of the world. It has a long cumulative half-life and active metabolites that can cause prolonged sedation and respiratory depression. The intravenous formulations of diazepam and lorazepam contain propylene glycol, which, at high doses, can produce lactic acidosis. Gastrointestinal delivery of these agents is limited by motility problems associated with tetanus. Midazolam has a short half-life and does not contain propylene glycol, but it should be given by continuous infusion and is cost-prohibitive in most areas of the world. Propofol infusion is effective, but it is also expensive, and patients may not tolerate the lipid vehicle. Neuroleptics, barbiturates, and intrathecal baclofen have no advantage over benzodiazepines. Dantrolene is a direct muscle relaxant without CNS activity. It has been reported as an adjunctive agent for muscle spasms and may decrease the need for mechanical ventilation.27 Magnesium sulfate infusion has been advocated as both adjuvant and first-line therapy for tetanus. Alone or in combination with other agents, it improves spasm control and may alleviate some of the autonomic instability associated with tetanus toxicity.28
If spasm cannot be controlled with these regimens or if any signs of airway compromise develop, the patient should receive neuromuscular blockade and mechanical ventilation. Although succinylcholine can be used in the initial phase of the disease, the clinician should be aware of the risk of severe hyperkalemia resulting from its use in any neuromuscular disease. This effect does not begin until about 4 days after the onset of disease. Long-acting nondepolarizing agents are preferred, even in the initial phase. Pancuronium has traditionally been used, but it is an inhibitor of catecholamine reuptake and may worsen autonomic instability. Vecuronium and rocuronium are shorter acting and are without significant cardiovascular side effects but require continuous infusion. Whichever agent is used, adequate sedation should be provided, and neuromuscular blockade should be withheld at least once a day to assess the patient’s status. All intubated patients should be considered for early tracheostomy to decrease reflex spasms caused by the endotracheal tube.

Autonomic instability requires monitoring and aggressive treatment. Sym pathetic hyperactivity can be treated with combined alpha- and beta-adrenergic antagonists, such as labetalol and propranolol. The use of beta-antagonists alone can lead to unopposed alpha-activity, resulting in severe hypertension. If beta-antagonists are necessary, a short-acting agent such as esmolol should be used. Because the episodes of the autonomic crises in tetanus are due to catecholamine excess, the use of pure beta-antagonism can result in unopposed alpha-agonism. Clonidine has shown variable success at modulation of sympathetic outflow in these cases. Morphine and magnesium sulfate infusions as well as spinal anesthesia and intrathecal baclofen have been shown to improve autonomic dysfunction. Diuretics should be avoided for blood pressure control as volume depletion can worsen autonomic instability. Bradydysrhythmia should be treated with temporary pacing. Atropine and sympathomimetic drugs should be used with caution as the autonomic instability is essentially due to catecholamine excess.

Elimination of Unbound Tetanospasmin and Active Immunization. Human tetanus immune globulin (HTIG) and Td should be administered as soon as possible to all patients with suspected tetanus. Tetanus immune globulin (TIG) does not neutralize toxin already present in the nervous system, nor does it treat any existing symptoms. HTIG neutralizes any circulating toxin as well as toxin at the site of production and reduces mortality. TIG should be administered at a site separate from the toxoid. Dosage recommendations vary (500-10,000 units of TIG), but multiple injections are stimuli for spasm, and most authorities note that 500 units is as effective as higher doses. Adult and pediatric doses are the same. If the larger doses are used, they should be given in divided injections. Administration of a portion of the TIG proximal to the site of inoculation is often recommended but has not been studied. Protective antibody levels are achieved 48 to 72 hours after administration of TIG. Because the half-life of TIG is 25 days, repeated doses are not needed. The preparation of TIG available in the United States is not licensed for intrathecal administration, which is of no proven benefit.

Prevention of Further Toxin Production. Toxin production is eliminated by treatment of the C. tetani infection. Wound débridement and antibiotic administration can cause a transient release of TS, so these measures should be delayed until after the HTIG is administered. Metronidazole (500 mg orally or IV every 6 hours) is the antibiotic of choice for C. tetani. Pediatric doses of metronidazole depend on age and weight.

Neonates < 1200 g and 0-7 days: 7.5 mg/kg IV or orally every 24 hours
Neonates < 1200 g and 8-28 days: 7.5 mg/kg IV or orally every 12 hours
Neonates > 1200 g and 0-7 days: 7.5 mg/kg IV or orally every 12 hours

Penicillin has traditionally been used to treat tetanus and has good in vitro and in vivo activity against C. tetani, but it also has GABA antagonistic activity and may potentiate the effects of TS. Metronidazole has better penetration than penicillin into devitalized tissue and abscesses and is superior in terms of recovery time and effect on mortality. Macrolides, doxycycline, chloramphenicol, and tetracycline are effective alternatives in metronidazole-allergic patients.

Vaccination

Tetanus toxoid is an inactivated form of TS, and vaccination confers protective antibody levels in nearly 100% of people who receive three doses. Immunity wanes between 5 and 10 years after completion of the series. In high-risk patients such as elders, injection drug users, and patients with human immunodeficiency virus (HIV) infection and other causes of immunocompromise, immunity wanes more quickly and the response to vaccine is less brisk.

Adults with an uncertain history of a complete primary immunization series should receive a primary series. The standard vaccination program consists of a primary series of three tetanus toxoid doses, followed by booster doses every 10 years. Age-specific guidelines for tetanus prophylaxis have been developed by the ACIP and published by the CDC (Tables 129-1 and 129-2).

Tetanus vaccination should be updated for all patients who come to the emergency department for management of a wound, even if the presenting complaint is not wound related. Patients with unknown or uncertain immunization status should be considered to have no previous tetanus immunization. Those younger than 7 years should receive diphtheria-tetanus or DTaP. Patients 7 years of age or older should receive Tdap instead of DTaP because adverse reactions from the larger doses of diphtheria toxoid in DTaP are more common in older individuals.

### Table 129-1

<table>
<thead>
<tr>
<th>DOSE</th>
<th>CUSTOMARY AGE</th>
<th>AGE/INTERVAL</th>
<th>PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary 1</td>
<td>2 months</td>
<td>6 weeks or older</td>
<td>DTaP</td>
</tr>
<tr>
<td>Primary 2</td>
<td>4 months</td>
<td>4-8 weeks after first dose</td>
<td>DTaP</td>
</tr>
<tr>
<td>Primary 3</td>
<td>6 months</td>
<td>4-8 weeks after second dose</td>
<td>DTaP</td>
</tr>
<tr>
<td>Primary 4</td>
<td>15-18 months</td>
<td>6-12 months after third dose</td>
<td>DTaP</td>
</tr>
<tr>
<td>Booster</td>
<td>4-6 years, not needed if fourth vaccination administered after birthday</td>
<td></td>
<td>DTaP</td>
</tr>
<tr>
<td>Additional booster</td>
<td>11-18 years</td>
<td>Every 10 years</td>
<td>Tdap</td>
</tr>
<tr>
<td>Adult booster</td>
<td>&gt;18 years</td>
<td></td>
<td>Tdap or Td</td>
</tr>
</tbody>
</table>

Botulism is a rare life-threatening paralytic illness caused by neu- rotoxins produced by Clostridium botulinum. The disease typically occurs in one of five forms: food-borne botulism, infant botulism, wound botulism, unclassified botulism, and inadvertent botulism. Since the approval of botulinum toxins A and B by the FDA for cosmetic and therapeutic uses in the United States, cases of iatrogenic botulism have been reported.

In 1820, Kerner, a health officer in Germany, first noted an association between sausage ingestion and a paralytic illness. The term botulism comes from the Latin botulus, meaning “sausage,” because of these early descriptions of the disease. van Ermengem investigated an epidemic of botulism in a group of musicians at a funeral in Belgium in 1897. He isolated the organism from ham and demonstrated that an elaborated toxin produced illness on injection into animals. This toxin was later identified as type A toxin. Type B toxin was discovered in 1904.

Botulism first received attention in the United States during World War I, when housewives were encouraged to preserve fruits and vegetables. The recommended methods for home canning did not destroy the spores of C. botulinum. Because these foods were often not adequately heated, epidemics of botulism occurred. Meyer described the circumstances favoring toxin production and the conditions necessary to destroy spores during food processing. Wound botulism was first described in 1943. In 1950 the CDC began surveillance of this form of the disease. Infant botulism, which is now the most common form of the illness, was first described in 1976.

**Epidemiology**

Seven types of toxin (A through G) are produced by C. botulinum. Types A, B, E, and F cause illness in humans, and types C and D cause disease in animals. Type G has been found in soil but has not been definitively linked to human or animal outbreaks. C. botulinum spores are found throughout the United States. Type A is found more commonly in the West and type B in the East. Type E is frequently associated with fish products. A total of 121 cases of botulism were reported to the CDC in 2009; 9% were food-borne botulism, 69% infant botulism, and the rest were wound related or unknown. Despite the ubiquitous nature of botulinum spores and the variety of possible routes of toxin entry, the incidence of disease is low.

Typical food-borne botulism results from the ingestion of pre- formed heat-labile toxin rather than from the ingestion of spores or live bacteria. Food-borne botulism usually results from exposure to home-canned foods that are inadequately preserved and undercooked, but large outbreaks occasionally occur after the ingestion of contaminated food at restaurants or from commercial sources. A variety of preserved foods have been implicated, and botulism has also been reported to result from ingestion of improperly prepared and stored fresh foods.

Infant botulism is the most common form of the illness in the United States. It occurs in children younger than 1 year with a peak incidence between the ages of 6 weeks and 6 months. In contrast to food-borne botulism in adults, infant botulism is caused by the ingestion of spores with in vivo production of toxin. Honey and to a lesser extent corn syrup have been implicated as sources of C. botulinum spores in infant botulism. Soil and vacuum cleaner dust have also been implicated, but the source of ingestion remains unknown in most cases. Types A and B botulinum toxins have been responsible for almost all infant cases. Some investigators have explored a possible relationship between infant botulism and the sudden infant death syndrome, but a 10-year prospective study of 248 infants diagnosed with sudden infant death syndrome revealed no cases attributable to C. botulinum.

Wound botulism once accounted for approximately one botulism case per year, but the increased use of black tar heroin has resulted in a dramatic increase in cases. In 1994, of the 53 adult botulism cases reported to the CDC, 11 cases were wound botulism. All occurred among injection drug users in California. Toxin type A is the most frequent causative agent.

Unclassified, hidden, or adult infectious botulism is a rare illness that is analogous to infant botulism. The Clostridium bac- terium produces its toxin in vivo. Patients with compromised gastric acidity, disturbances of gastrointestinal motility, or abnor- mal gastrointestinal bacterial flora may be susceptible to in vivo production of botulinum toxin. Between 1976 and 1996, 39 cases were reported to the CDC. Toxin types A, B, and F were

**Table 129-2** Summary Guide to Tetanus Prophylaxis in Routine Wound Management

<table>
<thead>
<tr>
<th>HISTORY OF ABSORBED TETANUS TOXOID (DOSES)</th>
<th>CLEAN MINOR WOUNDS</th>
<th>ALL OTHER WOUNDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tdap† or Td</td>
<td>TIG</td>
<td>Tdap† or Td</td>
</tr>
<tr>
<td>Unknown or less than three</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>TIG</td>
<td>Yes</td>
</tr>
<tr>
<td>Three or more†</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Three or more‡</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>


†For children <7 years old, DTaP is preferred. For persons >7 years of age, Tdap is preferred to tetanus toxoid alone. Td is preferable in adults who have previously received one dose of Tdap.

‡If only three doses of fluid toxoid have been received, a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.

§Yes, if >10 years since last dose.

<table>
<thead>
<tr>
<th>TOTAL WOUNDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tdap† or Td</td>
</tr>
<tr>
<td>TIG</td>
</tr>
<tr>
<td>Tdap† or Td</td>
</tr>
<tr>
<td>TIG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clean minor wounds</th>
<th>All other wounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tdap† or Td</td>
<td>TIG</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Three or more‡</td>
<td>No</td>
</tr>
</tbody>
</table>

*Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.

**Perspective**

**Background**

Botulism is a rare life-threatening paralytic illness caused by neu- rotoxins produced by Clostridium botulinum. The disease typically occurs in one of five forms: food-borne botulism, infant botulism, wound botulism, unclassified botulism, and inadvertent botulism. Since the approval of botulinum toxins A and B by the FDA for cosmetic and therapeutic uses in the United States, cases of iatrogenic botulism have been reported.

In 1820, Kerner, a health officer in Germany, first noted an association between sausage ingestion and a paralytic illness. The term botulism comes from the Latin botulus, meaning “sausage,” because of these early descriptions of the disease. van Ermengem
identified in these patients. Of the three cases reported in 2009, two were type F.45

Inadvertent botulism is an iatrogenic form of the disease that occurs in patients who have been treated with injections of botulinum toxin for dystonia and other movement disorders and for cosmetic purposes. Inadvertent generalized weakness as well as unintentional focal weakness may be seen.40

The potential exists for botulinum toxin to be used as an offensive biologic weapon. It is highly potent and easy to produce. The Aum Shinrikyo, responsible for the 1995 sarin gas attack on the Tokyo subway, have produced and dispersed aerosols of botulinum toxin in Japan on at least three occasions between 1990 and 1995. In 1995, Iraq admitted to the United Nations that it had produced 19,000 L of concentrated botulinum toxin and loaded approximately 10,000 L into warheads. These 19,000 L are not fully accounted for and constitute three times the amount needed to kill the entire human population by inhalation.46

**Principles of Disease**

**Etiology**

*C. botulinum* is a strictly anaerobic, large, gram-positive, rod-shaped organism. It forms spores that germinate under certain environmental conditions. The bacteria may then produce a potent exotoxin that is responsible for the disease. Each strain of *C. botulinum* produces a specific toxin type—A, B, C, D, E, F, or G. Only types A, B, E, and rarely F produce disease in humans.39 Botulinum toxins are the most potent known biologic compounds.48 Doses as small as 0.09 to 0.15 µg IV or 0.7 to 0.9 µg inhaled can cause death in a 70-kg human.46,47 The toxins are heat labile. Heating at 85° C for 5 minutes destroys any botulinum toxin. Consequently, heating of toxin-contaminated food just before ingestion prevents food-borne botulism. Spores are highly heat resistant, however, and can survive at a temperature of 100° C for several hours.39

**Pathophysiology**

Food-borne botulism results from ingestion of food that contains preformed toxin. Toxin-contaminated food may have a normal appearance and taste or exhibit signs of food spoilage caused by proteolytic enzymes produced by the type A and B strains. Because of the tremendous potency, one taste can expose a person to enough toxin to cause clinical illness. Digestive enzymes do not destroy preformed toxin. Infant and adult infectious botulism results from in vivo bacterial elaboration of toxin in the gastrointestinal tract. Achlorhydria and recent antibiotic use predispose the gastrointestinal tract to colonization with *C. botulinum*. Wound botulism results from in vivo bacterial elaboration of toxin in a wound. Inadvertent or iatrogenic botulism results from injection of preformed toxin for medical purposes.39,40 Primate studies indicate that aerosolized botulinum toxin can also be absorbed systemically through the respiratory tract.17

The neurotoxin produced by *C. botulinum* is similar in structure and function to the TS toxin produced by *C. tetani*, but the clinical effects differ dramatically. TS targets inhibitory interneurons in the CNS, causing generalized muscle spasm, whereas botulinum toxin targets peripheral neuromuscular junctions and autonomic synapses, thereby causing a flaccid paralysis. When botulinum toxin is absorbed from the entry site, it circulates until it reaches the neurons.30,31 The toxin binds to the presynaptic nerve membrane, becomes internalized, and then inhibits the release of acetylcholine, resulting in neuromuscular blockade. This interference with neurotransmission occurs predominantly at the cholinergic synapses of the cranial nerves, autonomic nerves, and neuromuscular junction. Clinically, this is manifested by cranial nerve palsies, parasympathetic blockade, and descending flaccid paralysis. Once it is affected with type A toxin, the nerve is permanently damaged, and recovery requires axonal regeneration and the formation of new synapses, which may take several months. Recovery after type F toxin is substantially faster.38,41

**Clinical Features**

**Symptoms and Signs**

*Food-borne botulism* is the prototype for understanding of the clinical signs and symptoms of all forms of botulism. Symptoms begin approximately 18 to 36 hours (range, 6 hours to 8 days) after the ingestion of toxin-containing food. A shorter incubation period is associated with a more severe form of illness. Early symptoms include weakness, malaise, lightheadedness, nausea, vomiting, and constipation. These symptoms are generally not severe and occur in fewer than half of the patients.39

Neurologic symptoms may begin at the same time or be delayed in onset for several days. The cranial nerves are first affected. Patients experience diplopia, blurred vision, dysphonia, dysphagia, and dysarthria. Vertigo is also a common symptom. Next, a symmetrical descending muscle weakness occurs, involving the upper and lower extremities and the muscles of respiration. Blockade of the cholinergic fibers of the autonomic nervous system leads to a variety of symptoms. Decreased salivation causes a dry mouth, which may be so severe that the patient complains of a painful tongue and sore throat. Ileus and urinary retention may also occur. In one series of patients with food-borne botulism, all had at least three of the following four symptoms: weakness, dry mouth, double vision, and difficulty speaking. This constellation of symptoms should prompt one to inquire about the ingestion of home-canned or improperly prepared food as well as the presence of similar symptoms in family members or friends.39,41

The patient with botulism is usually alert and afebrile unless secondary infection is present. Postural hypotension may be present. Ocular signs are prominent and include ptosis, extracocular palsies, and markedly dilated and fixed pupils; the absence of ocular abnormalities does not exclude the diagnosis. The oropharynx may be erythematous, with dry mucous membranes.39 The gag reflex is depressed or absent.

Muscle weakness is usually present and varies from mild to severe. Neck muscles are often weak. Upper extremity muscles are affected more than those of the lower extremity. Proximal muscles are weaker than distal muscles. Deep tendon reflexes may be normal, symmetrically decreased, or absent. The sensory examination is normal. The abdomen may be distended with hypoactive bowel sounds. Bladder distention may be apparent on examination. Respirations may be tachypneic and shallow or normal. In advanced illness, signs of respiratory failure may be present.39

Atypical presentations of food-borne botulism have been reported, and certain serotypes produce distinct variations in the pattern of symptoms. Type A disease may be more severe and is more commonly associated with bulbar findings and upper extremity weakness. Type A and type B disease may rarely cause a decreased level of consciousness. Type E is associated with a greater incidence of gastrointestinal symptoms.39

The presentation of *infant botulism* is different from that of food-borne botulism. Constipation is a common presenting complaint, followed by several days to weeks of poor feeding, weak cry, loss of head control, and hypotonia. On physical examination, patients have decreased muscle tone and depressed deep tendon reflexes. Cranial nerve involvement causes alterations in facial expression, ptosis, and extraocular palsies. Respiratory failure occurs in 50% of patients. Fever is absent unless secondary infection is present.43,44
Wound botulism has some notable differences from food-borne botulism. The incubation period is longer, from 4 to 14 days, because the toxin must be produced within the wound after the spores have germinated. If the wound is infected, the patient may be febrile. Gastrointestinal symptoms are notably absent in wound botulism.\textsuperscript{39,41} Recurrent episodes are well described.\textsuperscript{45}

The clinical presentation of unclassified (adult infectious) botulism is similar to that of food-borne botulism, although the mortality rate is significantly greater. Recovery from botulism is slow, and survivors are hospitalized for several weeks to months.\textsuperscript{39,41}

Complications

Complications from botulism are related to respiratory failure and problems associated with prolonged intensive care management. The major cause of death from botulism is respiratory failure resulting from weakness of the respiratory muscles. Aspiration of oral secretions and gastric contents because of loss of protective airway reflexes can occur. In the past 50 years, the overall mortality rate has decreased from 50% to less than 8% with modern intensive care. Mortality rates are higher in wound botulism patients (15-17%) and lower in infant botulism patients (<1%). For those who recover, muscle strength and endurance may not return to normal for up to 1 year, and persistent psychological problems are common.\textsuperscript{39,41}

Diagnostic Strategies

The initial diagnosis of botulism is clinical and should be considered in any patient who presents with the constellation of gastrointestinal, autonomic, and cranial nerve dysfunction. Bilateral cranial nerve involvement and the progression of neurologic findings should increase clinical suspicion. Routine laboratory studies are of no value in the diagnosis. If a lumbar puncture is performed, the CSF in patients with botulism is normal or may show a slight elevation of protein.\textsuperscript{41}

The diagnosis is confirmed by detection of (1) botulinum toxin in the patient’s blood; (2) botulinum toxin or \textit{C. botulinum} in the gastric contents, stool, or wound of the patient; or (3) toxin or organisms in the suspected food source. Because most hospital laboratories are unable to process such specimens, the local health department and CDC should be notified for specific instruction on the handling of specimens. Ideally the specimens should be obtained before administration of antitoxin. Serial measurements of the patient’s vital capacity are helpful in recognizing deteriorating ventilatory function.\textsuperscript{39,41}

Electromyography can detect electrophysiologic abnormalities consistent with the diagnosis of botulism; it may also be useful in differentiation of botulism from other paralytic illnesses. The electromyographic signature of botulism is decreased amplitude of the compound muscle action potential in response to a supramaximal stimulus and facilitation of the muscle action potential with repetitive nerve stimulation. Not all motor units are affected, and normal test results do not exclude the diagnosis.\textsuperscript{39,41}

Differential Considerations

The differential diagnosis of adult botulism includes a wide variety of illnesses. Commonly, the first presenting case is misdiagnosed because early symptoms suggest pharyngitis or gastroenteritis, both of which can affect several members of a single household. Only after one or more cases progress to classic botulism is the diagnosis usually suggested.

Botulism should be differentiated from other illnesses that cause paralysis. In Guillain-Barré syndrome, weakness usually starts distally and ascends, paresthesias may be present, and the CSF protein level may be elevated. Tick paralysis is an ascending paralysis, notable for a lack of bulbar involvement and the presence of a tick. In myasthenia gravis, eye signs are also prominent, but pupillary response is preserved, no autonomic symptoms are present, and weakness responds to the administration of edrophonium or ice applied to the affected muscle group. Of note, minimal improvement in weakness after the administration of edrophonium has been reported in botulism.\textsuperscript{39,41} Poliomyelitis causes fever, asymmetrical neurologic signs, and CSF abnormalities. Diphtheria can be distinguished by the prolonged interval between pharyngitis and neurologic symptoms. Eaton-Lambert syndrome does not usually involve bulbar muscles. Cerebrovascular accidents of the brainstem have an acute onset and asymmetrical, neuroanatomically localizing signs and symptoms.\textsuperscript{56}

Certain toxins should also be considered in the differential diagnosis of botulism. Anticholinergics (atropine, belladonna, jimson weed) cause pupillary dilation and dry, red mucous membranes but also cause delirium with alterations in mental status. Organophosphate insecticides have a characteristic odor, and poisoning causes fever and altered mental status. Dystonic reactions are self-limited and respond to diphenhydramine or benztrapine. Neuro-muscular blockade from the administration of aminoglycosides is distinguished by the medication history. Heavy metal poisoning produces changes in mental status. Magnesium toxicity may mimic botulism, but the history and serum magnesium levels distinguish these entities.\textsuperscript{39,41} In paralytic shellfish poisoning, paresthesias are prominent, a history of shellfish ingestion is present, and recovery occurs within 24 hours.

Infant botulism has a broader differential diagnosis. Common illnesses that mimic the presentation of infant botulism include sepsis, various viral illnesses, dehydration, encephalitis, meningitis, and failure to thrive. Neurologic illnesses such as Guillain-Barré syndrome, myasthenia gravis, and poliomyelitis should also be considered.\textsuperscript{41,43,44} Hypothyroidism, hypoglycemia, diphtheria, and toxin exposures are all part of the differential consideration, as are less common conditions such as inborn errors of metabolism, congenital muscular dystrophy, and cerebral degenerative diseases.

Management

The treatment of botulism consists of supportive care and specific treatment with antitoxin and other medications to block the effects of the toxin. All patients with suggested botulism should be admitted to the hospital and placed in an ICU as respiratory failure may develop rapidly and insidiously. When signs of ventilatory failure develop, early endotracheal intubation should be performed. A decrease in vital capacity to less than 30% of predicted or less than 12 mL/kg is an appropriate criterion for intubation of a patient with botulism.\textsuperscript{39,41} Ileus should be treated with nasogastric suction and urinary retention with an indwelling urinary catheter. Fortunately, the autonomic dysfunction of botulism is much less severe than that of tetanus and rarely requires any intervention.\textsuperscript{39,41}

Saline enemas and cathartics have been recommended by some authors to cleanse the gastrointestinal tract of residual toxin. Cathartics should not be given in the presence of ileus. Magnesium-containing cathartics should be avoided because elevated serum magnesium levels can exacerbate muscle weakness. Special care should be taken with use of gastrointestinal clearance in infants with botulism. Because the source of toxin is outside the gastrointestinal tract in wound botulism, bowel decontamination is not indicated.\textsuperscript{39}

Equine trivalent antitoxin contains antibodies to toxin types A, B, and E. It should be administered intravenously as soon as possible after appropriate laboratory specimens have been obtained. It neutralizes only circulating toxin and has no effect on bound toxin. Early administration prevents the progression of illness,
The clinical presentation ranges from a mild illness to a fulminant, cemia is defined as the presence of cant cause of morbidity and mortality worldwide. Pneumococ-
more than 80 years
rable of binding circulating toxin concentra-
Many times in excess of those reported in botulism patients.
The serum half-life is 5 to 8 days. For these reasons, and contrary to the information in the package insert, only one vial of antitoxin is required. Repeated doses are unnecessary and may increase the risk of hypersensitivity reactions, which occur in approximately 9% of patients.

Equine antitoxin is generally not recommended in infant botu-
lism because efficacy has not been demonstrated and because of the risk of anaphylaxis to horse serum. A human botulism immune globulin (BabyBIG) is pooled plasma from immunized adults with high titers of antibodies to toxins A and B. It was approved by the FDA for the treatment of infant botulism in October 2003. BabyBIG shortens hospital length of stay by a mean of 3.1 weeks and mechanical ventilation by a mean of 1.7 weeks. It can be obtained by calling the California Department of Public Health Infant Botulism Treatment and Prevention Program at 510-231-7600 or 510-540-2646.

Antibiotics are not currently recommended for food-borne botulism and may increase cell lysis and promote toxin release. Because the source of toxin is in vivo production within an infected wound, debridement and antibiotic administration should be considered only after antitoxin has been administered. Otherwise, the use of antibiotics should be limited to treatment of secondary infections (e.g., aspiration pneumonia) that may develop. Antibiotic treatment of both infant and wound botulism has no proven benefit. If an antibiotic is used for any reason in a botulism patient, all attempts should be made to avoid the am-
Guandine hydrochloride may enhance the release of acetylcholine from terminal nerve fibers. For this reason, it has been recommended as an experimental component of botulism therapy.

Disposition
All patients with possible botulism should be admitted to the hospital and placed in an ICU as respiratory failure may develop rapidly and insidiously. An infectious disease specialist should be consulted for management issues. The CDC should be called for assistance in any case of suggested botulism. The CDC can be reached by calling 404-639-3311 (days) and 404-639-2540 (nights, weekends, and holidays). State and local health departments may also be helpful in investigating and preventing major epidemics. Area emergency departments should be alerted so that subsequent cases can be looked for and diagnosed.

PNEUMOCOCCEMIA

Perspective

Background

More than a century after the identification of Streptococcus pneu-
mococci as a pathogen in human disease and more than 80 years after the discovery of antibiotics, pneumococcus remains a signifi-
cant cause of morbidity and mortality worldwide. Pneumococc-
cemia is defined as the presence of S. pneumoniae in the blood. The clinical presentation ranges from a mild illness to a fulminant, life-threatening, systemic syndrome. S. pneumoniae also causes myriad localized infections, including otitis media, pneumonia, meningitis, and, less commonly, endocarditis, septic arthritis, and peritonitis.

S. pneumoniae was discovered in 1881 by Sternberg in the United States and simultaneously by Pasteur in France. By the late 1880s it was referred to as pneumococcus because it was the most common cause of lobar pneumonia. In 1884, Friedländer described pneumococcemia. In 1902, Cole published the first case reports of pneumococcemia, including a patient who had meningitis and arthritis without pneumonia. In the early 20th century, Maynard, Lister, Wright, and others demonstrated a decreased incidence of pneumonia after inoculation of miners with killed pneumococci. In the 1920s, Heidelberg and Avery showed that antibodies to the surface capsular polysaccharide conferred immunity to pneumo-
coccal disease. Two routes to bacteremia were described. Wandel described the migration of S. pneumoniae from the lung to the bloodstream by way of the lymphatic system. In 1964, Robert Austrian described bacteria passing directly from the upper respira-
tory tract (middle ear or sinus) to the subarachnoid space, then through the arachnoid villi and into the venous sinus.

An S. pneumoniae vaccine was initially developed in the 1940s but was not produced commercially because of the availability of penicillin. The first vaccine was not licensed for use in the United States until 1977. This 14-valent pneumococcal vaccine was replaced in 1983 by a 23-valent vaccine for use in people older than 2 years. The heptavalent conjugate vaccine (Prevnar) is now available and licensed for use in infants younger than 2 years and for other high-risk patients.

Epidemiology

S. pneumoniae remains a substantial cause of serious illness despite the availability of antibiotics and vaccines. Pneumococcal infection appears sporadically in normal individuals and in patients with impaired host defenses. Epidemics of pneumococcal infection occur rarely, although bacterial serotypes may cluster by geographic area. Most cases of pneumococcal infections are com-
munity acquired, and the peak incidence is in winter.

Invasive pneumococcal disease (IPD) is defined as isolation of S. pneumoniae from a normally sterile site, such as blood, pleural fluid, or CSF. In 1997 the CDC estimated 15 to 30 cases per 100,000 population annually in the United States for all people, 50 to 83 cases per 100,000 population annually for those older than 65 years, and 160 cases per 100,000 population annually for children younger than 2 years. Rates were threefold to fivefold higher in black adults (49–58 cases per 100,000 population) than in whites. Rates were even higher among Alaskan natives, at 74 and 624 cases per 100,000 population for adults and children younger than 2 years, respectively. The highest incidence in the United States occurred among Apache Native Americans, with an overall annual incidence of 156 and 2396 cases per 100,000 popu-
lation for adults and children younger than 2 years, respectively. The introduction of the heptavalent vaccine for infants has decreased the incidence of IPD by 65 to 84% in children younger than 2 years in all populations studied. This decline is almost entirely attributable to the fact that the vaccine is 97% effective at providing immunity to the seven serotypes included. The IPD in these studies in almost entirely due to nonvaccine serotypes, with particular concern recently attributed to multidrug-resistant sero-
type 19A. Ongoing surveillance will determine the need to change the serotypes included in the vaccine.

Pneumococcal pneumonia occurs in less than 2% of all hospitalized patients with community-acquired pneumonia, but this number increases to 7.3% of patients admitted to the ICU, 11.5% of those with multilobar infiltrates on the chest radiograph, 15% of those with a temperature ≥40°C or ≤35°C, 20% of those with a systolic blood pressure below 90 mm Hg, and 22% of those with HIV infection. Other sources include the meninges (8%) and the
The emergence of antibiotic-resistant strains.

because of the increasing number of elders and AIDS patients and mortality rate from pneumococcemia may increase in the future. The case fatality rate is significantly lower for children. The overall disease, and those with localized infections such as meningitis. 54 young adults and much higher for elders, those with underlying disease in people older than 6 years. Worldwide, 10 capsular types the seven serotypes present in Prevnar account for 80% of invasive illness to fulminant disease, progressing to death within several hours. Occult bacteremia arises as a febrile illness in which the only direct indication of pneumococcemia is a positive blood culture (most often at 24-48 hours). Sepsis is the systemic response to infection, manifested by two or more of the following: (1) temperature higher than 38° C or lower than 36° C, (2) heart rate above 90 beats/minute, (3) respiratory rate of more than 20 breaths/minute or partial pressure of carbon dioxide in arterial gas of less than 32 mm Hg, and (4) WBC count higher than 12,000/mm³, below 4000/mm³, or more than 10% immature (band) forms.58 Patients may present with lethargy, signs of poor tissue perfusion, cyanosis, and hyperventilation or hyperventilation. Either occult bacteremia or sepsis can occur in conjunction with a localized infection.

The history should include a description of symptoms, including fever, chills, cough, shortness of breath, headache, and rash; a review of systems; and any recent use of antibiotics. The shaking chills and fever that occur with pneumococcemia are believed to be caused by a toxin. There should be an assessment of the patient’s social situation, including availability of caregivers, transportation to medical care, and ability to comply with discharge instructions.

In children, the clinical presentation of pneumococcemia is similar to that of other common febrile illnesses. Although signs of focal infection, such as pneumonia, may be present,60 often the only indication of pneumococcemia is fever or other signs of bacterial toxicity.

Most adult patients have fever or hypothermia. Cough, rigors, pleuritic pain, and gastrointestinal symptoms occur in approximately one third of adult patients. Many patients complain of vague, nonspecific constitutional symptoms similar to those of common viral illnesses. Fever (temperature >38.5° C) occurs in 90% of younger patients but in less than 60% of those older than 65 years. Patients with signs of sepsis have an increased risk for a fulminant course with rapid deterioration. Findings on physical examination vary with the site, if any, of primary infection. A focal primary source of infection is more common in adults than in children.54 The physician should evaluate for signs of otitis media, sinusitis, and meningitis. Pneumococcemia is considered primary in 18% of adults and 30% of children, so lack of localized infection as a source does not rule out IPD.

Complications
Cardiovascular collapse can occur with fulminant pneumococcal sepsis. Patients who develop severe illness from pneumococcemia may have end-organ damage from inadequate perfusion, disseminated intravascular coagulopathy (DIC), septic emboli, and other complications. These include respiratory failure, meningitis, hypothermia, gastrointestinal bleeding, hepatic coma, renal failure, and myocardial infarction.

Pneumococcemia occasionally results in hematogenous seeding, which causes peritonitis, arthritis, endocarditis, meningitis, and cellulitis.54 Adults and children with functional or anatomic asplenia may have fulminant pneumococcemia termed overwhelming postsplenectomy infection (OPSI). This is characterized by septic shock, adrenal hemorrhage, and DIC. Although the true incidence of OPSI is unknown, studies demonstrate that it is substantial and that the risk for it does not decrease over time after splenectomy. Most invasive pneumococcal infections occur in the first 2 years after splenectomy, and about two thirds occur between 5 and 20 years. OPSI may initially arise with symptoms indistinguishable from those of common viral illnesses.51 The 100-fold increased incidence of pneumococcal bacteremia and meningitis in children with sickle cell disease is probably primarily due to splenic dysfunction, but complement abnormalities may also play a role.62

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Diagnosis and Management of Pneumococcal Infections

**Diagnostic Strategies**

The only test specific for pneumococcal infection is a blood culture that grows *S. pneumoniae*. Ancillary testing of adults with suggested bacteremia should include a complete blood count with differential, blood cultures, urine culture and sensitivity, electrolyte values, glucose concentration, serum creatinine level, and blood urea nitrogen level. A chest radiograph may demonstrate pneumonia as the source of infection. Sputum Gram's stain, culture, and sensitivity testing, if pneumococcal infection is suspected, are of questionable value in the emergency department but may be useful for continued inpatient care. For sputum specimens to be of value, they should be collected before antimicrobial therapy is instituted; however, therapy should not be significantly delayed for the sole purpose of obtaining sputum. Antigen testing of urine for pneumococcal polysaccharide is up to 100% sensitive in IPD.

If the patient appears to be toxic or has signs of respiratory compromise, an arterial blood gas analysis and a coagulation profile should be obtained. If signs of meningitis or alterations in mental status are present, a lumbar puncture should be performed. Gram's stain of theuffy coat may be positive in cases of overwhelming pneumococcal sepsis. The WBC count is usually elevated. A normal or low WBC count is suggestive of more serious disease, as are hypoxemia and hypercarbia. Musher and colleagues demonstrated an increased mortality rate in patients with serum creatinine levels higher than 2.0 mg/dL, bilirubin levels higher than 1.5 mg/dL, and albumin levels below 2.5 g/dL.

**Differential Considerations**

Pneumococcemia in its more benign presentation should be differentiated from other febrile illnesses, such as viral infections. The combination of clinical findings and culture results enables the emergency physician to distinguish between bacteremia and sepsis of other origins. The presence of fever and shock, with or without a distinct rash, suggests the possibility of sepsis caused by *H. influenzae*, *Neisseria meningitidis*, and other streptococcal types. The presence of confirmed pneumococcemia does not exclude other diagnoses, such as influenza and lung cancer.

**Management**

**Acute Treatment**

Management of pneumococcal infection consists of stabilization of life-threatening conditions, eradication of the infection, and treatment of predisposing or coexisting conditions. All septic patients should be managed with early goal-directed therapy (see Chapter 138). The decision to initiate antibiotic therapy for pneumococcal infection is often made with limited objective data, which include the clinical findings, age of the patient, underlying conditions, and possible preliminary laboratory studies.

Elimination of the *S. pneumoniae* organism by prompt initiation of antibiotics is essential to reduce the morbidity and mortality of pneumococcal infection. Antibiotic administration should be managed with early goal-directed therapy (see Chapter 138). The decision to initiate antibiotic therapy for pneumococcemia is often made with limited objective data, which include the clinical findings, age of the patient, underlying conditions, and possible preliminary laboratory studies.

**Disposition**

Disposition of the patient depends on three factors: the patient's age, the overall clinical condition, and the presence of coexisting illnesses. Toxic-appearing patients of any age should be promptly treated with antibiotics and admitted to the hospital. Patients with underlying or coexisting conditions and those with an unclear course of illness should also be admitted.

Children who are febrile and appear well at the time of the initial examination are unlikely to have serious sequelae. A large randomized, controlled trial involving 37,868 infants showed that IPD is rare in children who have received the heptavalent pneumococcal vaccine. Children were observed for 3 years. There was only one case of bacteremic pneumonia in a patient who had
CDC Recommendations for the Use of the 23-Valent Pneumococcal Vaccine, 2010

Box 129-4

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<th>Immunocompetent adults with chronic illnesses</th>
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<tr>
<td>Cardiovascular (excluding hypertension)</td>
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<td>Chronic lung disease</td>
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<td>Diabetes mellitus</td>
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<td>Alcoholism</td>
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<td>Chronic liver disease including cirrhosis</td>
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<td>Cerebrospinal fluid leaks</td>
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<td>Those 65 years of age or older</td>
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<td>Immunocompromised adults, including those with</td>
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<td>Splenic dysfunction or asplenia, including sickle cell disease</td>
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<td>and other hemoglobinopathies</td>
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<td>Congenital or acquired immunodeficiencies, including those</td>
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<td>using immunosuppressive drugs</td>
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<td>Hodgkin's disease, lymphoma, or leukemia</td>
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<td>Multiple myeloma</td>
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<td>Generalized malignant disease</td>
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<td>Chronic renal failure or nephrotic syndrome</td>
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<td>Alcoholism</td>
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<td>Organ transplantation associated with immunosuppression</td>
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<td>Adults and children older than 2 years with asymptomatic HIV</td>
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<td>infections</td>
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<td>Children older than 2 years with chronic illness</td>
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<td>Anatomic or functional asplenia (including sickle cell disease)</td>
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<td>Nephrotic syndrome</td>
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<td>Cerebrospinal fluid leak</td>
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<td>Other conditions associated with immunosuppression</td>
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<td>Persons living in special environments or social settings with</td>
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<td>an identified increased risk (e.g., certain Native American</td>
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<td>The vaccine is not indicated for children having only recurrent</td>
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<td>upper respiratory tract disease, such as otitis media and</td>
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<td>sinusitis</td>
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CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus.

received all four doses of vaccine and two cases in children who had received one dose; one of these children had acute myelogenous leukemia after entering the study and was receiving immunosuppressive chemotherapy. The heptavalent vaccine contains serotypes responsible for only approximately 85% of pneumococcal disease in infants and children. The decision to treat a febrile child with antibiotics and discharge should be based on clinical findings, medical history, ability of the parents to follow the discharge instructions, and availability of timely follow-up.

Vaccination

The pneumococcal vaccine is effective in preventing infection; the currently available 23-valent vaccine contains the purified polysaccharide antigens of the serotypes that cause 70 to 80% of pneumococcal infections in the United States. Although the overall protective efficacy of the vaccine is only 39 to 63%, it is safe, inexpensive, and of substantial value for well-defined groups at risk. Unfortunately, the 23-valent pneumococcal vaccine has limited immunogenicity in children younger than 2 years. The heptavalent conjugate vaccine links the polysaccharide to proteins, resulting in an improved immunogenic response in children younger than 2 years.

The CDC recommendations for the use of the 23-valent vaccine are given in Box 129-4. The CDC and the American Academy of Pediatrics (AAP) recommendations for the use of the heptavalent vaccine are listed in Box 129-5.

The ACIP for pneumococcal vaccine and the AAP recommend that revaccination be strongly considered at 2 to 6 years of age or older for people who are most likely to have a rapid decline of pneumococcal antibodies (e.g., patients with renal failure, transplant recipients, and patients with nephrotic syndrome) and for those at risk for fatal infection (e.g., asplenic patients). Children 10 years of age or younger with nephrotic syndrome, sickle cell anemia, or asplenia should be considered for revaccination after 3 to 5 years. Other preventive measures for pneumococcal disease include passive immunization with immunoglobulins for patients with congenital or acquired immunodeficiency diseases and daily antibiotic prophylaxis for children with functional or anatomic asplenia.

MENINGOCOCCEMIA

Perspective

Background

Few clinical situations in emergency medicine produce greater anxiety for the physician than meningococcal infection. Virtually all experienced emergency physicians have had a patient who appeared relatively well on initial presentation, only to be moribund and in critical condition with fulminating infection several hours later. “Epidemic cerebrospinal fever” was initially described in 1805 by Vieusseux in Geneva. Weichselbaum identified the causative bacterial agent in 1887. Throughout the 19th and first half of the 20th centuries, epidemics occurred periodically in most regions of the world. “Serum therapy” was introduced in France in 1907 and in the United States in 1913 as the first specific treatment of meningococcal disease. The introduction of sulfonamide therapy in 1937 replaced serotherapy and dramatically improved the outcome of meningococcal infection. Sulfonamide prophylaxis was also effective at eradication of the carrier state and was used to prevent the epidemics that occurred in military barracks. Not surprisingly, in the 1940s, sulfonamide resistance began to emerge. In 1963 an outbreak of resistant meningococcal disease occurred in the United States, which spurred efforts to develop a vaccine for this devastating infection. Subsequent worldwide resistance has resulted in continued efforts to develop safe and effective vaccines.

Epidemiology

Humans are the only reservoir for Neisseria meningitidis. As of 2004, 1400 to 2800 cases of meningococcal infection were reported to the CDC annually. The incidence of disease has decreased in the United States since the licensing of the first conjugated meningococcal vaccine in 2005 (Fig. 129-5). Of the more
than 13 serogroups, groups A, B, C, Y, and W-135 cause most of the infections. More than 95% of cases occur sporadically, with occasional outbreaks, most notably on college campuses in dormitories or in other crowded living situations. More than half of the cases in infants are caused by serogroup B, for which there is no effective vaccine. Serogroups C, Y, and W-135 cause 35% of meningococcal disease in patients older than 11 years. Although grouping is important for tracking of the disease, all groups are capable of causing the same spectrum of clinical disease.

The incidence of meningococcal disease peaks in the winter and falls in the summer. Superimposed on this annual variation are cyclic peaks of disease every 5 to 15 years. Approximately every 10 years, massive outbreaks of serogroup A occur in sub-Saharan Africa (the “meningitis belt”). The last outbreak was in 2007. During nonepidemic periods, children younger than 5 years have the highest incidence of infection. During epidemics, the incidence increases among children aged 5 to 9 years, an observation that may be of value in predicting the beginning of an epidemic. Crowded living conditions increase the risk for spread of meningococcal disease. The incidence of disease and the carrier state are cyclic and are higher mortality rate (up to 70%) than meningitis alone of meningococcal disease is inversely proportional to the levels of antibodies after exposure to the bacteria. In children, the incidence of meningococcal disease is inversely proportional to the levels of antibodies against N. meningitidis.

**Principles of Disease**

**Etiology**

Meningococcal disease is caused by *N. meningitidis*, a fastidious, aerobic, gram-negative diplococcus. *N. meningitidis* is an encapsulated organism classified into at least 13 serogroups on the basis of the capsular polysaccharides.

**Pathophysiology**

*N. meningitidis* attaches to nonciliated epithelial cells in the nasopharynx by a number of adhesion factors. Once it is attached, it may either remain on the epithelial surface, causing an asymptomatic carrier state, or produce mild symptoms of an upper respiratory tract infection. In certain patients, the bacteria enter the bloodstream and cause symptoms and signs of localized infection, bacteremia, sepsis, or fulminant infection. The precise host and microorganism characteristics that determine whether clinical disease develops are not fully understood, but the presence of bactericidal antibodies is protective. Complement deficiency may play a role in a host’s inability to fight this infection. The capsule is required for *N. meningitidis* to adhere to epithelium, but only unencapsulated meningococci enter epithelial cells; capsular biosynthesis has been shown to stop as the bacteria enter the epithelial cell. The release of lipo-oligosaccharide and endotoxin by autolysis of the *N. meningitidis* cell is the initial event in the development of meningococcal sepsis. The exogenous mediators appear to stimulate the release of endogenous mediators, including tumor necrosis factor, interleukin-1, and the host’s complement system. All of the major pathophysiologic events of meningococcal sepsis are caused by the host’s inflammatory response to the organism. The complement-activating products and other chemical mediators cause functional and histologic damage to the microvasculature, resulting in increased vascular permeability, pathologic vasoconstriction and vasodilation, loss of thromboresistance, DIC, and profound myocardial dysfunction.

After exposure to *N. meningitidis*, protective antibodies develop. Immunity in children is conferred initially by maternal antibodies that pass through the placenta and later by the development of antibodies after exposure to the bacteria. In children, the incidence of meningococcal disease is inversely proportional to the levels of antibodies against *N. meningitidis*.

**Clinical Features**

**Symptoms and Signs**

The clinical presentation of meningococcemia ranges from a mild febrile illness to fulminant disease progressing to death within hours. Most patients have fever on presentation. Other initial complaints include headache, irritability, lethargy, myalgias, emesis, diarrhea, cough, and rhinorrhea. Anywhere from 27 to 77% of patients will present with the classic hemorrhagic skin lesions. These patients can rapidly progress to purpura fulminans, with hypotension, adrenal hemorrhage, and multiorgan failure. The following categories detail the five patterns of presentation.

Occult Bacteremia. This condition arises as a febrile illness in which the only direct indication of meningococcemia is a positive blood culture, with results available most often 24 to 48 hours after the clinical evaluation. In its mildest form, meningococcal bacteremia cannot clinically be distinguished from more benign febrile illnesses. Initial diagnoses in these patients include common childhood infections, such as otitis media, acute viral upper respiratory infections, and gastroenteritis. For some patients the illness resolves after treatment with an oral regimen of antibiotics; others experience spontaneous resolution without antibiotic treatment. *N. meningitidis* accounts for less than 1% of occult bacteremia cases, but these patients are much more likely to develop meningitis (up to 58%) than are those with *S. pneumoniae*. Also, despite the total absence of clinical clues to meningococcal infection at initial presentation, some untreated patients subsequently deteriorate rapidly.

**Meningococcal Meningitis.** Patients with meningococcal meningitis may present similarly to patients with meningitis of other origins, with headache, photophobia, vomiting, fever, and signs of meningeal inflammation. This classic constellation triad of fever, neck stiffness, and altered mental status is present in less than 30% of patients. Infants and small children may present with fever, irritability, and vomiting as the only complaints. More than half of patients with meningococcal meningitis have rash on presentation, and 20% present with seizures. Onset of symptoms is less abrupt (usually during 24 hours) and prognosis is better for patients with meningococcal meningitis than for patients with meningococcemia without clinical signs of meningitis.

**Meningococcal Septicemia.** Patients with meningococcal septicemia present with lethargy, poor tissue perfusion, cyanosis, and hypoventilation or hyperventilation. Hemorrhagic skin lesions are present in 28 to 77% of patients, but a macular or maculopapular rash may also occur and be mistaken for a variety of viral exanthems. Petechiae generally appear on the extremities and may appear under pressure points, such as the elastic bands of socks and underwear. They may progress to involve almost any body surface, including the mucosa and sclera, but typically spare the palms, soles, and head. Macular lesions may progress to purpura and ecchymoses in fulminant meningococcemia. The purpurae are not a coalescence of petechiae but a distinct entity that more specifically characterizes meningococcemia. *Purpura fulminans*, the most dreaded and advanced form of meningococcal septicemia, occurs most often in children and is usually associated with DIC. This condition is characterized by rapidly spreading ecchymoses and gangrene of the extremities. Evidence of mucosal and gastrointestinal bleeding as well as oozing from intravenous sites may be noted on examination. Clinical signs of meningitis and CSF pleocytosis may not be present, even when diplococci are isolated from the CSF. This is probably because the systemic progression of the disease is so rapid that it precludes a host meningeal inflammatory response to the organism in the CSF. Shock results from both intravascular volume loss and congestive heart failure, probably related to myocarditis. Renal failure, coma, and bilateral adrenal hemorrhage often occur.

**Fever and a Nonblanching Rash.** Up to 30% of patients present without signs of meningitis or septicemia. They are typically admitted for fever and a nonblanching rash and no other specific findings. If they are untreated, meningitis or fulminant septicemia and shock can develop.

**Chronic Meningococcemia.** This syndrome is characterized by fever, rash, and arthritis in conjunction with a positive blood culture for *N. meningitidis*. Headache and upper respiratory symptoms are often present. This is the rarest form of meningococcal disease, accounting for 1 to 2% of cases. It may progress to meningitis, endocarditis, or fulminant meningococcemia regardless of treatment.

### Complications

Myocarditis with congestive heart failure is a common complication of meningococcemia and is the primary cause of death in more than half of patients. Many of the inflammatory mediators released during sepsis cause myocardial dysfunction, and the severity of sepsis is related to the degree of impairment of myocardial contractility. The acidosis, hypoglycemia, hypokalemia, hypocalcemia, hypophosphatemia, and hypoxia that accompany meningococcemia also contribute to the myocardial dysfunction. Treatment with cardiac glycosides is beneficial, but patients may become unresponsive to positive inotropic medications.

Acute respiratory failure occurs from capillary leak in the patient who requires volume resuscitation. It is also likely that intrapulmonary DIC contributes to the pulmonary edema, and patients frequently require mechanical ventilation. Renal failure is common secondary to impaired renal perfusion; acute tubular necrosis may develop. If meningitis accompanies meningococcemia, focal neurologic signs as well as seizures may occur but are less common than with pneumococcal meningitis. Vasculitis in severe cases of meningococcal septicemia may result in skin lesions that necessitate plastic surgery and loss of digits or limbs from gangrene. Purulent or immune complex arthritis and pericarditis with tamponade may also occur.

Poor prognostic indicators in meningococcemia include seizures, shock, agitation, hypothermia, hyperpyrexia, metabolic acidosis, thrombocytopenia, hypocalcemia, hypophosphatemia, metabolic acidosis, and elevated lactate. Intraosseous infusion can be lifesaving in septic shock and can reduce the time to normalize the lactic acid level. Aminoglycosides given as intravenous bolus doses may cause serious complications and should be avoided if possible. The CSF pleocytosis is absent in meningococcemia, but the diagnosis can be established if the CSF Gram stain is positive for *N. meningitidis*.

Acute renal failure may develop due to the presence of DIC, hypocalcemia, or severe sepsis, which can reduce the glomerular filtration rate. Hypotension, shock, and acute renal failure are associated with a poor outcome. The diagnosis of meningococcemia is usually made by obtaining blood cultures and performing a Gram stain of the blood or blood culture. The patient may also have a positive result from a rapid diagnostic test for meningococcal antigen in the blood. The diagnosis of meningococcemia is confirmed by obtaining a CSF sample and performing a Gram stain or culturing the organism. The CSF pleocytosis is usually present, with a predominance of polymorphonuclear leukocytes. Gram-negative meningococcal meningitis is associated with an increased risk of meningococcemia and meningococcal septicemia. The CSF pleocytosis is usually present, with a predominance of polymorphonuclear leukocytes. Gram-negative meningococcal meningitis is associated with an increased risk of meningococcemia and meningococcal septicemia. The CSF pleocytosis is usually present, with a predominance of polymorphonuclear leukocytes.
diplococci may be seen on microscopy. Early in the disease or with fulminant disease, the CSF may be free of inflammatory cells. Serologic evidence of DIC is frequently present.69,71,72

A chest radiograph is useful in evaluation for pneumonia and acute respiratory distress syndrome. An echocardiogram helps assess for myocardial dysfunction and pericardial effusion.

**Differential Considerations**

It is difficult to distinguish the clinical signs of meningococcemia from those of bacteremia caused by *S. pneumoniae*, other streptococcal groups, *H. influenzae*, and *Neisseria gonorrhoeae*. A hemorrhagic rash is more commonly associated with meningococcal disease.76 The differential diagnosis of meningococcemia also includes viral exanthems, Rocky Mountain spotted fever, typhus, typhoid fever, endocarditis, vasculitis syndromes (polyarteritis nodosa and Henoch-Schönlein purpura), toxic shock syndrome, acute rheumatic fever, dengue fever, drug reactions, idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura.71

In one study of 184 children hospitalized with fever and petechiae, 24 (11%) had proven *N. meningitidis*. The remainder showed evidence of viral or other organisms. These data were acquired before the initiation of a vaccination program.77

**Management**

**Acute Treatment**

Morbidity and mortality in meningococcemia are reduced with prompt recognition and immediate initiation of antibiotic therapy. Delays in initiation of therapy for the completion of diagnostic studies or admission to an inpatient unit should be avoided. To simplify selection of a treatment strategy, patients can be divided into three general groups:

1. *Bacteremia or sepsis is suggested on the basis of clinical findings; however, the organism has not been identified*. These patients should receive broad-spectrum antibiotics; the selection is based on factors that include the most likely organism or organisms, the patient’s age and immune status, the presence of coexisting disorders, and the local patterns of antibiotic resistance. A narrower spectrum agent is selected after positive identification of the organism and its sensitivities.
2. *N. meningitidis growth is reported from prior blood cultures*. The treatment regimen for occult bacteremia is guided by the patient’s age, history, physical examination, general appearance, and ancillary test results. The antibiotic selected at the time of the initial visit may be sufficient to treat the meningococcal bacteremia subsequently identified by the laboratory. The decision to hospitalize the patient is based on the findings at the time of reevaluation and the risk of sequelae. Regardless of the patient’s clinical appearance, most physicians would draw blood for repeated cultures, consider lumbar puncture, and admit the patient to the hospital until results of repeated cultures are obtained.
3. *Bacteremia or sepsis is suggested and *N. meningitidis* is identified*. The antibiotic regimen is focused narrowly.

The standard antibiotic regimen for laboratory-proven meningococcemia is penicillin G, 4 million units every 4 hours IV for adults, and penicillin, 250,000 to 300,000 units/kg/day in divided doses every 4 hours IV for children, up to a maximum of 20 million units. Penicillin resistance in *N. meningitidis* remains low in the United States but has been reported in Spain and the United Kingdom.69,71,77

Although it is appropriate first-line therapy, penicillin is rarely given as the initial agent in patients with suspected meningococcal sepsis or meningitis. Ceftriaxone (initial dose of 100 mg/kg IV, followed by daily dosage of 100 mg/kg in divided doses every 12 hours, up to a maximum of 4 g) and cefotaxime (100 mg/kg/day IV in divided doses every 6 hours, up to a maximum of 12 g) are appropriate initial antibiotics as well. The cephalosporins offer the advantages of safety, rapid onset of action, and excellent coverage for *S. pneumoniae* and *H. influenzae*. Chloramphenicol (50-100 mg/kg/day divided every 6 hours to a maximum of 4 g/day) should be considered in penicillin- and cephalosporin-allergic patients.69 Intramuscular ceftriaxone is occasionally administered to children with suspected bacteremia who are treated as outpatients while culture results are pending. Several reports have demonstrated the efficacy of ceftriaxone (80-100 mg/kg IV) in a single daily dose; however, twice-daily dosing remains the standard recommendation at this time. In addition to the obvious advantage of extended dosing intervals, ceftriaxone-treated patients have a more rapid sterilization of the CSF and a lower incidence of hearing loss than conventionally treated patients do.

Patients with fulminant meningococcemia require prompt airway management, intravenous fluid resuscitation, and vasopressor support. Fluid requirements may be high because of third spacing of fluid, and in the setting of frequent myocardial dysfunction, intensive cardiovascular monitoring is required. Electrolyte and acid-base abnormalities should be corrected. If the patient is oliguric or anuric, hemodialysis may be necessary to correct these abnormalities. Fresh frozen plasma should be considered for patients with bleeding complications.69,72

The role of steroids for the treatment of meningococcemia without meningitis remains controversial. Although corticosteroids were once widely recommended for the treatment of the adrenal insufficiency associated with fulminant meningococcemia, more recent studies demonstrate that adrenal function is not impaired in all patients. If a patient has persistent shock despite vigorous fluid resuscitation and vasopressor therapy, glucocorticoid therapy may be considered and adrenal function tested.78

The use of corticosteroids in patients with bacterial meningitis is currently recommended for adults and children but not for neonates. The most recent clinical data show that corticosteroid administration before antibiotic administration decreases mortality rates in adults and long-term neurologic sequelae in adults and children. Dexamethasone (0.4-0.6 mg/kg/day every 6 hours for 4 days) should be given to patients with bacterial meningitis. The first dose should be given before the first dose of antibiotics if possible.79

Plasmapheresis, blood exchange, and extracorporeal membrane oxygenation have been described with favorable outcome, but data are limited.22

**Disposition**

All patients with possible or confirmed meningococcemia should be admitted to the hospital, preferably to an ICU because these patients can decompensate rapidly and without warning. A possible exception is the well-appearing child who has culture-proven *N. meningitidis* and has been taking appropriate antibiotics as an outpatient. This child should have a lumbar puncture to determine CSF involvement if one was not performed at the initial evaluation. Antibiotics should be continued on an inpatient basis, but an ICU may not be necessary if the child appears well.

**Antibiotic Prophylaxis and Vaccination**

Patients with meningococcemia should be placed in respiratory isolation for at least 24 hours. Close contacts should receive antibiotic prophylaxis. Household, nursery school, and daycare
center contacts should receive prophylaxis promptly. Intimate contacts and health care workers with intimate exposure (e.g., mouth-to-mouth resuscitation, intubation, or suctioning) should receive rifampin, 10 mg/kg (up to 600 mg) orally every 12 hours for four doses. The dose for infants younger than 1 month is 5 mg/kg. Patients should be warned that rifampin discolors the urine and secretions; contact lenses should be removed to avoid permanent staining. Intramuscular ceftriaxone (125 mg for children younger than 15 years and 250 mg for those older than 12 years) is effective against group A strains. This is an alternative for pregnant women and for people in whom compliance with an oral regimen cannot be ensured. Ciprofloxacin (500 mg orally) is another alternative for adults.

Meningococcal vaccine should be considered an adjunct to prophylaxis in epidemics and for close contacts in sporadic cases if one of the serotypes contained in the vaccine is identified as the causative agent. The currently available vaccine is a quadrivalent vaccine containing purified capsular polysaccharides for groups A, C, Y, and W-135. Unfortunately, the polysaccharides other than A are poorly immunogenic for children younger than 2 years. In addition, no vaccine exists for group B, a serogroup that causes a significant portion of meningococcal infection in the United States. The quadrivalent vaccine is not recommended for routine use but should be administered to children 2 years of age and older in high-risk groups, such as those with functional or anatomic asplenia and those with terminal complement deficiency. In 2000 the CDC ACIP recommended that college students, especially those living in dormitories, and their parents be advised of the risks of meningococcal disease and be offered vaccination. In August 2007 the ACIP recommended that all persons aged 11 to 18 years receive the vaccine. The vaccine is currently administered to U.S. military recruits. Consideration should be given to vaccination of people traveling to endemic areas of the world, such as sub-Saharan Africa.

**TOXIC SHOCK SYNDROME**

**Perspective**

**Background**

Toxic shock syndrome (TSS) is a toxin-mediated systemic inflammatory response syndrome that was first described by Todd and colleagues in 1978. They reported a series of seven children aged 8 to 17 years who had high fever, rash, headache, confusion, conjunctival injection, edema, vomiting, diarrhea, renal failure, hepatic dysfunction, DIC, and shock. *S. aureus* was cultured from various body sites but not from the blood in five of the seven cases.

The disease gained notoriety in the early 1980s when many cases were reported in association with tampon use in young, healthy menstruating women. The term toxic shock syndrome was coined to describe the constellation of signs and symptoms. Investigators noted positive vaginal cultures for *S. aureus*, recurrence of illness during subsequent menses, and the value of antistaphylococcal antibiotics in preventing recurrences. In response to the growing concern about TSS, changes were made to reduce the absorbency and composition of tampons. Nonmenstrual cases were also recognized in both men and women as a result of a variety of predisposing conditions, and a case definition was published in 1982 (Box 129-6).

In the late 1980s, several reports described group A streptococcus (GAS) infection associated with shock and multisystem organ failure. This has been called streptococcal toxic shock syndrome because it shares so many features with staphylococcal TSS. Box 129-7 shows the case definition for streptococcal TSS.

**Epidemiology**

The peak incidence of TSS occurred in 1980, when 890 cases were reported, 91% of which were associated with tampon use. Since then, the reduction in cases of the menstrual form of TSS has followed an active effort to decrease the absorbency of tampons and to change their composition. Menstruation remains the most common setting for TSS, but nonmenstrual TSS accounts for just under half of the reported cases. TSS has also been reported in association with barrier contraceptives and childbirth. Nonmenstrual TSS occurs in people of all ages and in both sexes. The CDC reported an average of about 200 cases a year (about 1 case per 100,000 population) from 1994 to 2001, with a steady increase in the incidence of streptococcal TSS and a slight decrease in the incidence of staphylococcal TSS. The age and sex distribution reflects the association with menses. In 2003, 294 cases were reported, but a steady decline continues to occur, with 182 cases reported in 2007. Streptococcal TSS accounts for a little more than half of the cases.

Nonmenstrual staphylococcal TSS is associated with superinfection of various skin lesions, including burns, surgical sites, dialysis catheters, and lung (influenza associated). It may also occur in association with staphylococcal respiratory infections or even with colonization by a toxigenic strain of the organism.
**Clinical Case Definition**

Hypotension: systolic blood pressure ≤90 mm Hg for adults or below fifth percentile by age for children younger than 16 years

Multisystem involvement—two or more of the following:
- Renal: creatinine >2 mg/dL (177 μmol/L) for adults or more than twice the upper limit of normal for age or more than twofold elevation above baseline for patients with preexisting renal disease
- Hematologic: platelets <100,000/mm³ or DIC, defined as prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products
- Hepatic: total bilirubin, AST, and ALT at least twice the upper limit of normal for laboratory, or a twofold increase in patients with preexisting liver disease
- Acute respiratory distress syndrome: defined by acute onset of pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia
- Generalized erythematous maculopapular rash that may desquamate
- Soft tissue necrosis, including necrotizing fasciitis, myositis, or gangrene

**Laboratory Criteria for Diagnosis**

Isolation of GAS

**Case Classification**

*Probable*: a case that meets the clinical case definition in the absence of another identified cause of the illness and with isolation of GAS from a nonsterile site

*Confirmed*: a case that meets the clinical case definition and with isolation of GAS from a normally sterile site (e.g., CSF or joint, pleural, or pericardial fluid)

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**Box 129-7**

*Clinical Case Definition* of Streptococcal Toxic Shock Syndrome

**Box 129-8**

*Risk Factors for Toxic Shock Syndrome*

Use of superabsorbent tampons
- Postoperative wound infections
- Postpartum period
- Nasal packing
- Cancer
- Common bacterial infections
- Alcohol abuse
- Infection with influenza A virus
- Infection with varicella virus
- Diabetes mellitus
- Human immunodeficiency virus infection
- Chronic cardiac disease
- Chronic pulmonary disease
- Nonsteroidal anti-inflammatory use (may mask symptoms rather than be a risk factor)

ALT, serum alanine transaminase; AST, serum aspartate transaminase; CSF, cerebrospinal fluid; DIC, disseminated intravascular coagulation; GAS, group A streptococcus.

**Clinical Features**

**Symptoms and Signs**

The clinical presentations of streptococcal TSS and staphylococcal TSS are similar. The primary difference is that an identifiable infectious source is virtually always present with streptococcal TSS, and colonization alone may be the source in staphylococcal TSS.

TSS should be considered in any patient who presents with sudden-onset fever, rash, hypotension, and evidence of end-organ damage, such as respiratory failure or altered mental status. Patients may have a prodromal illness with fever, chills, nausea, vomiting (25%), watery diarrhea (14-30%), headache (10%), myalgias, and pharyngitis, which can last 2 to 3 days before progression to frank sepsis and organ dysfunction. Other patients may become abruptly symptomatic within hours. Rapid progression is more typical of streptococcal TSS. Patients may complain of pain at a site of infection more often with streptococcal TSS.84 Risk factors for TSS are listed in Box 129-8.

The fever is usually high and abrupt in onset, although septic patients may have hypothermia on presentation. The classic rash is a nonpruritic, diffuse, blanching, macular erythoderma. It develops in the first few days of the illness and initially may be faint, evanescent, and mistaken for the flush associated with a fever. The rash is usually diffuse but may be localized to the trunk, extremities, or perineum. After about a week, a fine flaking desquamation occurs on the face, trunk, and extremities, followed by full-thickness peeling of the palms, soles, and fingers. This classic rash progression is much more common in staphylococcal TSS and is present in less than 10% of patients with streptococcal TSS.80 Patients with streptococcal TSS may have a scarlet fever–like rash.

without an obvious infectious source. Streptococcal TSS is classically associated with more severe soft tissue infections, such as necrotizing fasciitis and myositis, as well as with pneumonia, peritonitis, myopericarditis, and osteomyelitis.84-87

The mortality rate from staphylococcal TSS has declined since the disease was first described. The case fatality rate in 1980 was 10%, and it was less than 3% in the past several years. Streptococcal TSS remains a highly fatal disease, with a mortality rate of 30 to 70%.84-87

**Principles of Disease**

**Etiology**

Staphylococcal TSS is caused by colonization or infection with toxigenic strains of *S. aureus*. This strain produces toxic shock syndrome toxin 1 (TSST-1). *S. aureus* has been detected in virtually all cases of both forms of the illness. *S. aureus* has been isolated from the vagina or cervix in 98% of women with menstrual TSS, compared with a colonization rate of less than 10% of unaffected women. Because the organism is often not invasive, the blood cultures are often negative. Streptococcal TSS is caused by invasive infection with toxigenic strains of GAS.82-84

**Pathophysiology**

The shock and multiorgan dysfunction associated with TSS are caused by the effects of various exotoxins produced by *S. aureus* and GAS. *S. aureus* produces TSST-1 and enterotoxin B, TSST-1 is identified in more than 90% of menstrual cases and 60% of nonmenstrual cases. Other toxins may play a role in nonmenstrual TSS. Antibodies to these toxins are protective against disease. GAS produces streptococcal pyrogenic exotoxins A (SPEA) and B (SPEB). These exotoxins are absorbed into the bloodstream through inflamed or traumatized mucous membranes or from areas of focal infection. Absorbed toxins act as superantigens, inducing mononuclear cells to synthesize and to release cytokines, tumor necrosis factor alpha (TNF-α), and interleukins, which begin the cascade of systemic vasculitis and the multisystem manifestations of the disease. Host immune factors are important in the pathogenesis of TSS. GAS is an invasive organism, and circulating GAS organisms induce the production of TNF-α and other cytokines by mononuclear cells.84,85
rash, petechiae, or maculopapular lesions. Mucosal involvement may also occur, including conjunctival and scleral hemorrhages, “strawberry tongue,” and mucosal ulceration.

The patient’s mental status is frequently abnormal, out of proportion to the degree of hypotension. Confusion, somnolence, agitation, and combativeness are present in 55% of patients with streptococcal TSS and in even more patients with staphylococcal TSS.

Other findings on physical examination may include pharyngeal and conjunctival erythema and peripheral edema. Vaginal mucosal erythema and purulent vaginal discharge may be present in menstrual TSS but are not required for the diagnosis to be made. As multiple organ systems become involved, a wide constellation of signs and symptoms may be seen. Gastrointestinal involvement is manifested by vomiting, diarrhea, and severe abdominal pain. Hepatomegaly may be present. Acute respiratory distress syndrome develops in more than half of patients and is manifested by rales on pulmonary examination and hypoxia. Comparisons between staphylococcal and streptococcal TSS are presented in Table 129-3.

### Complications

Complications of TSS include acute respiratory distress syndrome (55%), shock (95%), gangrene, DIC, and a constellation of neuropsychiatric symptoms. Renal failure occurs in 80% of patients but is irreversible in 10%. Less common findings in staphylococcal TSS include rhabdomyolysis, seizures, pancreatitis, pericarditis, and cardiomyopathy. Women with the menstrual form of TSS may experience one or more recurrent episodes; recurrences of the nonmenstrual form are rare. Complication rates are higher with streptococcal TSS. Rhabdomyolysis occurs in up to 63% of patients with streptococcal TSS and is usually related to the underlying soft tissue infections.

### Diagnostic Strategies

The case definition for TSS does not require a positive culture for *S. aureus*, but isolation of *Streptococcus* organisms is a criterion for diagnosis. These case definitions (see Boxes 129-6 and 129-7) are useful to the clinician, but they are neither specific nor foolproof. Specific tests are not required to exclude other diseases, but if such tests are obtained, the results of these studies should be negative.

No specific laboratory changes are associated with TSS, but many abnormalities are common. Either leukocytosis or leukopenia can occur, but a marked bandemia is common. Elevated creatinine levels and hemoglobinuria occur in most patients. Laboratory evidence of renal dysfunction occurs before hypotension in half of the patients. Hypoalbuminemia (85%) and life-threatening hypocalcemia (79%) are prominent initially and persist throughout the course of the disease. Other abnormalities include anemia, thrombocytopenia, prolonged prothrombin and activated partial thromboplastin times (60-71%), hyperbilirubinemia, elevated transaminase levels (63%), and sterile pyuria.

Blood cultures are positive for bacteria in approximately 60% of cases associated with GAS but are rarely positive in staphylococcal TSS. Gram's stains and cultures from wounds may identify the organism. Culture of the cervix or vagina is positive in 90% of menstruation cases associated with TSS even in the absence of local infection.

Chest radiography may reveal evidence of acute respiratory distress syndrome or a pulmonary source of the organism. Plain radiographs of any infected skin or soft tissue site typically show only soft tissue swelling but may reveal evidence of a retained foreign body or air in the soft tissue. A lack of air in the soft tissue does not rule out a necrotizing soft tissue infection.

An electrocardiogram may reveal evidence of ischemia, arrhythmias, and varying degrees of atrioventricular block in association with sepsis. A blood gas analysis may indicate metabolic acidosis secondary to hypotension or hypoxia. A lumbar puncture should be performed in febrile patients with altered mental status to evaluate for meningitis. It is prudent to wait for the results of a coagulation profile before the lumbar puncture is performed because these patients may have DIC at presentation. The CSF is normal in patients with TSS.

### Differential Considerations

The differential diagnosis includes any severe febrile illness with exanthems associated with hypotension. Other diseases to consider include heat stroke, cellulitis, Kawasaki disease, staphylococcal scalded skin syndrome, scarlet fever, drug reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), Rocky Mountain spotted fever, clostridial gas gangrene, leptospirosis, meningococcemia, gram-negative sepsis, atypical measles, and viral illnesses.

Kawasaki disease occurs almost exclusively in children, usually does not progress to shock, lacks multisystem involvement, is manifested with a protracted fever, and is associated with thrombocytosis later in its course. Staphylococcal scalded skin syndrome is manifested with a desquamating rash acutely, whereas the desquamation of TSS occurs in the convalescent phase. Staphylococcal scalded skin syndrome does not progress to shock, is not associated with multisystem illness, and lacks mucous membrane involvement. Scarlet fever differs in its clinical course by lack of shock and multisystem involvement, positive cultures for GAS, and a rise in the convalescent titer. Stevens-Johnson syndrome usually occurs after drug administration, has characteristic mucous membrane lesions, and lacks desquamation. TEN may be difficult to distinguish from TSS; TEN patients are typically febrile, are in shock, and can progress to multisystem failure. The desquamation of TEN occurs early in the course of the disease, and it usually occurs after administration of a drug. Rocky Mountain spotted fever occurs after a tick bite, has a distinctive rash, and is associated with a severe headache without an altered mental status or hypotension. Leptospirosis occurs in endemic areas and may be distinguished by positive serologic studies and cultures. The rash of meningococcemia is characterized by petechiae and purpura occurring anywhere on the skin.
Management

Patients with TSS should receive aggressive fluid resuscitation with crystalloids and may require up to 10 to 15 L/day. Supplemental oxygen should be provided to all septic patients, regardless of initial pulse oximetry. This allows maximum tissue oxygenation and reduces acidosis. Patients should be placed in a monitored setting. Assisted ventilation may be necessary in patients with acute respiratory distress syndrome.

The source of bacteria, such as tampons, nasal packs, and other foreign bodies, should be removed. Prompt surgical consultation should be obtained to debride wounds. If specimens are sent for culture, the laboratory should be informed of the suspected diagnosis.

Patients who do not respond to fluid resuscitation require vasoressors such as norepinephrine, dopamine, phenylephrine, and epinephrine.

Antibiotics should be initiated early in the treatment of TSS as the clinical presentation of the disease is similar whether the source is staphylococcal or streptococcal. For septic patients without an identified organism, broad-spectrum antibiotics should be administered. Although the penicillinase-resistant penicillins (nafcillin, oxacillin) have been widely used in the treatment of TSS, most clinicians recommend clindamycin as a first-line agent. Clindamycin is a potent suppressor of bacterial toxin synthesis; it also facilitates phagocytosis of streptococci by inhibiting M protein synthesis, decreases monocyte synthesis of cytokines, and has a longer postantibiotic effect than the β-lactams. The dose is 600 to 900 mg IV every 8 hours. (The pediatric dose is 20–40 mg/kg/day divided every 6–8 hours.)

Patients who do not respond to massive fluid resuscitation, antibiotics, and vasoressors should be considered for intravenous immune globulin treatment, especially if pulmonary edema develops and mechanical ventilation is required. Pooled immune globulin has high titer for antibodies to TSST-1 and other exotoxins, and significant improvement has been reported with its use. If it is used, the recommended dose is 1 to 2 g/kg on day 1 administered intravenously during several hours, followed by 400 to 500 mg/kg/day for up to 5 days.

The value of corticosteroids in TSS is still unresolved. They are not currently recommended for treatment of staphylococcal or streptococcal TSS but should be given to patients thought to have adrenal insufficiency related to underlying disease or chronic steroid use.

Disposition

All patients thought to have TSS should be admitted to an ICU. Prompt surgical consultation should be obtained for patients with a wound source.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.