Diphtheria is an acute infectious disease caused by *Corynebacterium diphtheriae* or, less commonly, *C. ulcerans*. *C. pseudotuberculosis*, which primarily causes infections in sheep and goats, is not discussed here because it only rarely causes a diphtheria-like disease in humans. Infection by toxigenic strains of *C. diphtheriae* causes disease that is mediated by the production of an extracellular protein. Nontoxigenic strains also can cause disease, but it is usually less severe.

Before the discovery of antitoxin at the turn of the 20th century, the “strangling angel of children,” as diphtheria once was called, was a significant cause of mortality in children and adults. Apparent reference to diphtheria can be traced to the 5th century BC in the works of Hippocrates, *Epidemics III*, case 7. In 1821, it was recognized as a specific entity by Brettoneau, who suggested that the disease was caused by a germ and that it could be transmitted from person to person. Brettoneau coined the origin of the modern term *diphtheria* from the Greek root *diphtheria*, which means “skin” or “hide.” In 1883 the causative agent was identified by Klebs in stained smears from diphtheritic membranes; in 1884, Löflller grew the organism on artificial media and showed that in guinea pigs it caused a fatal infection closely resembling human disease.

The toxin was purified in 1889 by Roux and Yersin, who found that toxin alone could cause the disease. Shortly thereafter, Behring and Kitasato discovered antitoxins when they immunized animals with toxins rather than bacteria. The use of antitoxin to treat children with diphtheria at the turn of the 20th century resulted in one of the largest decreases in mortality rates by a therapeutic intervention. In Germany alone, an estimated 45,000 lives were saved each year.

**ETIOLOGY**

*Corynebacteria* (Klebs-Löflller bacilli) are irregularly staining, gram-positive, nonmotile, nonsporulating, pleomorphic bacilli. The club-shaped appearance of the bacillus is not a true morphologic feature, but results from attempting to grow the bacillus on media that are nutritionally inadequate (Löflller media). The organism can be recovered most readily on media containing selective inhibitors that retard the growth of other microorganisms; a sheep blood agar–based medium containing fosfomycin (for selectivity) and Tindale medium (tellurite medium with cystine) are ideal.

*C. diphtheriae* and *C. ulcerans* grow on supplement-free blood agar, chocolate agar, and other standard media. Colonies of *C. diphtheriae* (with the exception of the lipophilic, gray *C. intermedius*) and *C. ulcerans* appear grayish white on Löflller medium. On tellurite medium, three diphtheria colony types can be distinguished: *mitis*, *gravis*, and *intermedius*. *Mitis* colonies are smooth, black, and convex; they do not ferment starch or glycogen and are hemolytic. *Gravis* colonies are gray, radially striate, and semirough; they ferment starch and glycogen and usually are not hemolytic. *Intermedius* colonies are small and smooth and have a black center; they do not ferment starch or glycogen and are not hemolytic. *C. ulcerans* colonies resemble
C. ulcerans can reduce nitrate on Tindale medium and from the three potentially toxigenic diphtheria biotypes by its inability to by its urease activity and ability to liquefy gelatin. Biotype *belfanti*, which does not occur in a toxigenic form, may be distinguished from the three potentially toxigenic diphtheria biotypes by its inability to reduce nitrate on Tindale medium and from *C. ulcerans* by its lack of production of urease. Ribotyping and pulsed-field gel electrophoresis, both of which involve restriction digestion of genomic bacterial DNA, followed by gel electrophoresis and Southern blotting, permit more specific typing within each diphtheria biotype and aid in the epidermiologic study of outbreaks.

*C. diphtheriae* biovars *mitis*, *intermedius*, *gravis*, and *mitis* and *C. ulcerans* all have been observed in a toxigenic form. *Intermedius* was the biotype isolated most commonly in the United States between 1971 and 1981. Of the strains isolated, *intermedius* was found to be toxigenic more often than *mitis* or *gravis*. In the United Kingdom between 1993 and 1998, and similarly in other parts of Europe, the biovar *gravis* has represented most nontoxigenic isolates, followed by *mitis* and *belfanti*. Of the four nontoxigenic isolates obtained during a surveillance study of a U.S. Northern Plains Native American Community in 1996, two were of biotype *mitis* and two were of *gravis*. According to a UK diphtheria reference laboratory, between 1993 and 1998, the toxigenic isolates originating from Asia, Africa, and the Middle East were reported to be of the biotype *mitis* or *gravis*, with the exception of one *intermedius* isolate. Golaz and associates reported similar findings when they surveyed the different biotypes in South Dakota. A significant overall increase in the proportion of nontoxigenic isolates has been observed in Europe and Australia in recent years. The reason for this increase is unclear, but one hypothesis is that increased immunity to toxigenic strains secondary to immunization has altered this epidemiology.

The complete genome sequence of *C. diphtheriae* biotype *gravis* has been elucidated. The genome is approximately 2.48 Mb with a G+C content of 53% and has approximately 2320 predicted coding sequences. Metabolic analysis of the genome has revealed that *C. diphtheriae* has a complete set of enzymes for glycolysis, gluconeogenesis, pentose-phosphate pathways, anaerobic and aerobic respiration, amino acid biosynthesis, and purine nucleotide biosynthetic pathway. Most of the enzymes for the tricarboxylic acid cycle are present, with the exception of an enzyme succinyl coenzyme A (CoA) synthetase that catalyzes the conversion of succinate to succinyl CoA. An alternative enzyme present in *C. diphtheriae* may fulfill this conversion, however. The pyrimidine pathway in *C. diphtheriae* lacks an enzyme that interferes with the production of cytidine; the pathway to the biosynthesis of thymidine is complete. The genome has revealed 13 regions that are unique to *C. diphtheriae* and may serve as pathogenicity islands.

No functional or significant differences have been detected in the exotoxins elaborated by the three strains of *C. diphtheriae* or by *C. ulcerans*. Only strains that are lysogenic for β-prophage or a closely related phage carrying the gene for toxin production produce diphtheria toxin. One or more *tox* gene sequences may exist in the bacterial genome, and the most highly toxigenic strains contain three or more copies. Phage multiplication is not a prerequisite for the production of toxin. The capacity to synthesize toxin depends on genetic and nutritional factors. Toxin-producing cells apparently are cells in which spontaneous induction of the prophage to the phage occurs. The most important factor controlling the yield of toxin is the concentration of inorganic iron in the culture medium. Growth of *C. diphtheriae* in iron-deficient media prolongs the duration of induction lysis and is associated with a high yield of toxin. High concentrations of iron inhibit the production of toxin. Production of toxin also can be increased by the use of ultraviolet radiation. Conversion to a toxigenic strain occurs in nature, as has been shown by restriction enzyme studies of carriers of toxigenic and nontoxigenic strains in Manchester, England.

The ability of a strain of *C. diphtheriae* to elaborate diphtheria toxin can be shown by using several methods. In vivo studies involving necrosis of tissue in guinea pigs has been replaced by the widely used Elek or modified Elek test. Enzyme immunoassay and polymerase chain reaction (PCR) have been used to detect toxigenicity.

**Epidemiology**

Asymptomatic human carriers serve as the reservoir for *C. diphtheriae*. Infection by *C. diphtheriae* is acquired by contact with either a carrier or an individual with active disease. The bacteria may be transmitted via droplets during coughing, sneezing, or talking. Rarely transmission of *C. diphtheriae* occurs from skin lesions or fomites. Some reports suggest that skin carriers of *C. diphtheriae* are more infectious than nose or throat carriers and that skin carriers may serve as potential reservoirs for the initiation of epidemic spread. In areas in which skin infections are endemic, levels of natural immunization may be high. This phenomenon is illustrated particularly well in a survey of tetanus and diphtheria immunity in a rural Kenyan community, where age was not found to be predictive of immunity, and no correlation was found between levels of antibody for tetanus and diphtheria.

Person-to-person transmission of *C. ulcerans* is not known to occur, although *C. ulcerans* was isolated from the siblings of two patients reported in the United Kingdom between 1995 and 1997. Cases of respiratory diphtheria caused by *C. diphtheriae* and *C. ulcerans* have been documented in association with contaminated unpasteurized milk taken from cows with infected teats. *C. diphtheriae* has been isolated from horses, dogs, and other domestic animals. *C. ulcerans* has been reported to infect ground squirrels in the United States, but transmission to humans has not been reported. *C. ulcerans* is a commensal in animals and has been isolated in a wide range of wild and domestic animals.

According to World Health Organization (WHO) reports, diphtheria is distributed worldwide and remains endemic in many developing areas of the world, including Asia, Africa, South America, and the Mediterranean regions. Worldwide, diphtheria epidemics have occurred in a cyclic manner since the 16th century. In 2014, 7321 cases of diphtheria were reported to the WHO, although many others were likely unreported.

In the United States, the incidence and mortality rates from diphtheria in the 1920s were 140 to 150 cases/100,000, with 13,000 to 15,000 deaths each year. The number of cases gradually declined to 15 cases/100,000 population in 1945 with the extensive use of diphtheria toxoid vaccine. From 1970 through 1979, the average number of cases of diphtheria reported annually in the United States was 196. From 1980 to 2004, only 57 cases of diphtheria were reported in the United States. Approximately 75% of the cases were in patients older than 15 years who were unimmunized or inadequately immunized. Only two cases of diphtheria have been reported in the United States between 2004 and 2015. Maintenance of immunity in adults requires a booster vaccination every 10 years. The Centers for Disease Control and Prevention (CDC) estimated in the mid-1990s that fewer than 50% of adults in the United States had received their 10-year boosters and that 40% to 50% of adults were susceptible to diphtheria. In addition, the toxoid vaccine does not provide protection against nontoxigenic strains.

The incidence peaks during the cooler autumn, winter, and spring months. Several epidemics, primarily in the southern United States, have occurred in late summer and fall and corresponded to a high prevalence of *C. diphtheriae* skin infections. Between the years 1971 and 1981, the incidence of diphtheria was highest in the western United States. A 100-fold greater incidence of diphtheria occurs in Native Americans than in the general population. This difference may be attributable to socioeconomic factors more than to race. In 1996, a surveillance study was conducted in a Northern Plains Native American community after *C. diphtheriae* was isolated from the skin of a resident of the community. The woman was a chronic alcoholic admitted to the hospital for detoxification and treatment of severe necrotizing leg ulcers, from which a toxigenic *mitis* biotype was isolated. In the following 4 months, 11 positive cultures were obtained from the community, including four positive throat swabs from asymptomatic household contacts of the index cases. Ribotyping indicated that the isolates were
related closely to each other genetically and to strains obtained from past cases from the same area; they were different from organisms obtained from other parts of the United States and from the former Soviet Union, where an ongoing epidemic was occurring at the time.25,59 A similar study was conducted in a Koorie (Aborigine) community in Victoria, Australia, in 1994, after three cases of nontoxigenic C. diphtheriae endocarditis were diagnosed in the community. After screening 359 asymptomatic (with the exception of four people who had chronic skin ulcers swabbed) contacts of the index cases, 12 produced positive cultures for nontoxigenic C. diphtheriae. Of them, five were of the same biovar gravis clone as the three index cases.6 Evidence that diphtheria is diagnosed more frequently in chronic alcoholics and the indigent than in the general population is significant. In a 1993 to 1994 outbreak in St. Petersburg, Russia, 69% of a total of 42 individuals classified as chronic alcoholics.69 Between 1972 and 1982, three outbreaks occurred in the indigent alcoholic population living in Seattle’s Skid Road.66 Cutaneous infections accounted for 86% of the 1100 total cases. The first outbreak was caused by a single toxigenic intermedius biotype clone, whereas the other two involved nontoxigenic mitis and gravis strains. The incidence was highest in winter and spring.

A major epidemic began in 1990 in the new independent states of the former Soviet Union and spread throughout the area. Between 1990 and 1997, approximately 150,000 cases of diphtheria were reported, with approximately 4000 fatalities.69,109 The epidemic was attributed to decreasing immunization rates and immunity in adults and children and to movement of large numbers of people during the collapse of the former Soviet Union.21,196 Apparently multiple foci of infection existed across the continent. Most of the epidemic isolates from Ukraine and Russia were biotype gravis, but further molecular characterization of the tox genes from these areas revealed distinct epidemic strains in each location.24 A mass immunization program was initiated in Russia in 1993, with a resultant 10% decrease in the number of new cases reported between 1994 and 1995 (vs. two- to threefold increases in the number of cases each year for the preceding 3 years).37 The WHO also held training workshops and assembled laboratory kits to assist in establishing the proper diagnosis of diphtheria. Because cases also began to appear in Europe with increasing frequency during this period, the European Working Group on Diphtheria (ELWGD) and reference laboratories were assembled to assist in an effort to increase routine screening for diphtheria. The ELWGD since has expanded and currently includes 20 participating countries, including representatives in Western and Eastern Europe, the United States, Australia, and Southeast Asia.93 Surveillance from Europe from 2000 to 2009 has documented a decrease in incidence of more than 95% across the region, with the Russian Federation and Latvia accounting for 83% of the cases. In Western Europe, toxigenic C. ulcerans has increasingly been identified, often in association with contact with companion animals.118 More recently there have been documented cases, particularly of cutaneous diphtheria, in refugees and asylum seekers in Europe.

PATHOGENESIS AND PATHOLOGY
Diphtheria is initiated by entry of C. diphtheriae into the nose or mouth, where the bacilli remain localized on the mucosal surfaces of the upper respiratory tract. Occasionally the ocular or genital mucous membranes serve as the site of localization. The bacilli are unable to invade intact skin but may infect preexisting skin lesions. After a 2- to 4-day period of incubation, lysogenized strains may elaborate toxin. The pathogenic effect is mediated through the action of diphtheria toxin (DT), a 140-kDa, monomeric protein that is enzymatically active in the bloodstream. DT is a member of the family of class 1, type A, ADP-ribosylating Clostridium toxins, which also include tetanus and botulinum toxins. These toxins act by catalyzing the ADP-ribosylation of elongation factor 2 (EF-2), an essential subunit of the eukaryotic ribosome. ADP-ribosylation results in the covalent attachment of an ADP-ribose moiety to Cys-53, a residue located in the active site of EF-2. This modification results in a conformational change with subsequent loss of the A subunit into the bloodstream. When it is in the endolysosomal complex, it undergoes a conformational change with subsequent release of the A subunit into the cytoplasm. The A subunit transfers an adenosine diphosphate (ADP)-ribosyl group from nicotinamide adenine dinucleotide (NAD) to elongation factor 2. This ADP-ribosylation inactivates elongation factor 2 and inhibits protein synthesis in the cell. Cholera and pertussis toxins also mediate target protein ribosylation by this mechanism. In addition to the inhibition of cellular protein synthesis, an independent mechanism of cytolysis has been described. In the presence of calcium and magnesium, diphtheria toxin has a nuclease-like activity that causes DNA fragmentation that results in cytolyis.43,53,70,78

Marked toxin-mediated tissue necrosis occurs in the vicinity of C. diphtheriae colonization and induces a robust local inflammatory response. The inflammatory response coupled with the necrotic tissue produces a patchy exudate that initially can be removed. As the infection progresses, the increased production of toxin causes a centrifugal widening of the area of infection, and eventually a fibrinous exudate develops. A tough adherent membrane results from coagulation of the exudate. The color of the pseudomembrane initially is white but, over time, may appear gray. Late in the course of the infection, green or black spots appear on the membrane, representing areas of necrosis. Histologic analysis of the pseudomembrane differs based on the site of formation and maturation of the membrane. Analysis of the pharyngeal pseudomembrane shows fibrin; inflammatory cells, primarily composed of neutrophils, red blood cells, and colonies of organisms; and superficial epithelial cells.

With severe infections, significant vascular congestion, interstitial edema, fibrin exudate, and intense neutrophilic infiltration develop.64 Profuse bleeding can occur when the membrane is torn off. The edematous tissue and the diphtheritic membrane may encroach on the airway. The membrane sloughs spontaneously during the recovery period, although sloughing can occur during the acute phase of the illness, leading to aspiration. Occasionally secondary bacterial infection (classically caused by Streptococcus pyogenes) develops. Respiratory embarrassment or suffocation may occur, with involvement of the larynx or tracheobronchial tree. Bronchopneumonia may develop if the exudate enters the small airways and alveoli. Infection of these sites is an uncommon occurrence, however. Infections of the esophagus and stomach, with pseudomembranous lesions indistinguishable from lesions found in the respiratory tract, have been reported.77

Toxin produced at the site of infection is distributed throughout the body by the bloodstream and the lymphatics. This distribution occurs most readily when the pharynx and tonsils are covered by a diphtheritic membrane. Any organ or tissue can be damaged as a result of diphtheria toxin, but lesions of the heart, nervous system, and kidneys are particularly prominent. Clinical manifestations appear after a variable latent period of 10 to 14 days for myocarditis and 3 to 7 weeks for manifestations in the nervous system, such as peripheral neuritis. In a study of 102 patients who died of diphtheria caused by C. diphtheriae, the hearts appeared dilated, flabby, and pale, with a characteristic “streaky” appearance in the myocardium. The most prominent pathologic findings are necrosis and hyaline degeneration of the myocardium. The myocardium also appears edematous and is infiltrated with mononuclear cells with eosinophilic cytoplasm. In a significant proportion of cases, fatty accumulation in muscle fibers and the conducting system may be observed.68 Burch and associates12 showed mitochondrial damage with depletion of glycogen and accumulation of lipid droplets in the damaged myofibrils. Toxin may be observed within the myocardial cells with fluorescent antibody staining.82 If the patient survives, muscle regeneration and interstitial fibrosis can be seen.

Peripheral neuropathy occurs secondary to C. diphtheriae infections. Histologic studies have shown that affected nerves have significant degeneration of myelin sheaths and axons. Toxic neuritis with fatty degeneration of paranodal myelin can be noted early in the disease course; segmental demyelination occurs later.71 Axonal damage is secondary to the application of external pressure from the swollen Schwann cell cytoplasm and myelin.62

C. diphtheriae infections also can lead to necrosis and hyaline degeneration of the liver, which can lead to hypoglycemia. Adrenal hemorrhage and acute tubular necrosis of the kidney have been known to occur secondary to C. diphtheriae infections.64

CLINICAL MANIFESTATIONS
The signs and symptoms of diphtheria depend on the site of infection, the immunization status of the host, and whether toxin has been
distributed to the systemic circulation. The incubation period is 1 to 6 days (range, 1 to 10 days). Diphtheria can be classified clinically on the basis of the anatomic location of the initial infection and the diphtheritic membrane (nasal, pharyngeal/tonsilar, laryngeal or laryngotracheal, skin, and others) involved. More than one anatomic site may be involved simultaneously.

Nasal diphtheria initially resembles a common cold and is characterized by mild rhinorrhea and a paucity of systemic symptoms. Gradually the nasal discharge becomes serosanguineous and then mucopurulent. A foul odor may be noticed, and careful inspection reveals a white membrane on the nasal septum. In severe cases, the infection may excoriate the nares and upper lip. Nasal diphtheria is a mild form of the disease because absorption of toxin usually is slow from this site. Frequently delayed in establishing an accurate diagnosis of nasal diphtheria occur because of the lack of systemic symptoms. The nasal form of the disease occurs most often in infants.

Pharyngeal and tonsillar diphtheria begin insidiously with anorexia, malaise, low-grade fever, and pharyngitis. Within 1 or 2 days, a membrane appears. The extent of membrane formation correlates with the immune status of the host; in some partially immune individuals, a membrane may not develop. The white or gray adherent membrane may cover the tonsils and pharyngeal walls and extend on to the uvula and soft palate or down on to the larynx and trachea. Attempts to remove the membrane are followed by bleeding. Cervical lymphadenitis varies. In some cases, it is associated with edema of the soft tissues of the neck and may be so severe that it gives the appearance of a “bull neck.” In a 1970 epidemic, “erasure” edema of the neck was noted in patients with pharyngeal diphtheria.16 Patients with erasure edema did not have a classic bull neck appearance, but the edema was characterized by obliteration of the sternocleidomastoid muscle border, the mandible, and the median border of the clavicle. The edema was brawny, pitting, warm to the touch, and tender to palpation. Erasure edema was noted in 29% of immunized patients and 30% of nonimmunized or inadequately immunized patients. It occurred most commonly in children older than 6 years and generally was associated with infection by the gravis or intermedius strain of C. diphtheriae.

The course of pharyngeal diphtheria depends on the degree of elaboration of the toxin and the extent of the membrane. In severe cases, respiratory and circulatory collapse may occur. The pulse rate is increased disproportionately to body temperature, which generally remains normal or slightly elevated. The palate may be paralyzed. This paralysis may be unilateral or bilateral and associated with difficulty swallowing and nasal regurgitation of swallowing fluids.23 Stupor, coma, and death may occur within 7 to 10 days. In less severe cases, recovery may be slow and may be complicated by the development of myocarditis or neuritis. In mild cases, the membrane sloughs off in 7 to 10 days, and recovery is uneventful.

Laryngeal diphtheria generally reflects a downward extension of the membrane from the pharynx. Rarely laryngeal diphtheria is primary and does not reflect an extension of disease from the pharynx. In these cases, toxicity and signs of toxemia generally are less prominent. Two cases of isolated diphtheritic tracheitis have been reported in the literature.1,3,10 The clinical findings of laryngeal diphtheria are indistinguishable from those of other types of infectious group. Noisy breathing, progressive stridor, hoarseness, and a dry, barking cough may be noted. Suprastratal, subcostal, and supraclavicular retractions reflect severe laryngeal obstruction, which may be fatal unless alleviated. Occasionally in a mild case, an acute and fatal obstruction may occur because of a partially detached piece of membrane that occludes the airway. In severe cases of laryngeal diphtheria, the membrane may extend downward and invade the entire tracheobronchial tree.

Cutaneous disease, in contrast to pharyngeal disease, is more common in warmer climates and often is caused by nontoxigenic strains. In some countries with tropical and subtropical climates, such as Uganda, Tanzania, Sri Lanka, and Samoa, C. diphtheriae has been isolated from 60% of skin lesions in children.44 Cutaneous diphtheria is more contagious than respiratory diphtheria. Cutaneous diphtheria may be an important source of person-to-person transmission of diphtheritic organisms and outbreaks in indigenous populations in which overcrowding and poor hygiene are important risk factors.2,20,68 The skin lesions begin as vesicles or pustules that progress to typical ulcers with sharply defined borders, membranous bases, and surrounding erythema and edema. They may be covered with a dark pseudomembrane. The lesions occur most commonly on the legs, feet, and hands. For the first 1 to 2 weeks, the lesions are painful. Spontaneous healing generally takes 6 to 12 weeks, but lesions have been reported to persist for 1 year.68 Conjunctival, auricular, and vulvovaginal diphtheria also may occur. Conjunctival lesions usually are limited to the palpebral conjunctiva, which appears red, edematous, and membranous. Rarely conjunctival lesions have been associated with corneal erosion.66 Diphtheria infections of the ear are characterized by the development of otitis externa with a persistent purulent and frequently foul-smelling discharge.

Clinical presentations other than typical diphtheria have been associated with isolation of the organism from patients with meningitis, endocarditis, osteomyelitis, and hepatitis. In most cases, these infections have occurred in patients with underlying problems, such as structural or valvular heart disease or intravenous drug use, or in individuals from poor socioeconomic backgrounds.70,104

Several cases of septic arthritis caused by nontoxigenic C. diphtheriae have been described.1,63,104 Afghani and Stutman1 reported the case of a 27-month-old child who had septic arthritis of the hip and skin lesions on the lower extremities. In this case, the skin lesions were presumed to be the portal of entry for nontoxigenic C. diphtheriae. Although the child had received four doses of diphtheria and tetanus toxoids and pertussis vaccines, immunization with toxoid does not provide protection against nontoxigenic strains of C. diphtheriae. In this case, the organism was sensitive to penicillin, cefuroxime, cephalothin, and clindamycin but was resistant to oxacillin, an antistaphylococcal antibiotic often used for the treatment of septic arthritis when the causative organism cannot be identified. A similar case was described in an immunocompetent, fully vaccinated 2-year-old child who had skin lesions from which C. diphtheriae was isolated. The skin lesions also were assumed to be the portal of entry for the organism because pan-sensitive C. diphtheriae were isolated from the skin and the articular aspirate.63

Within a 12-month period, in New South Wales, Australia, four cases of septic arthritis complicating endocarditis caused by the nontoxigenic gravis variety of C. diphtheriae were reported. In addition, the same strain caused three cases of endocarditis without the development of septic arthritis. Demographic distribution of these seven cases included a 12-year-old boy who died, five patients who were in their 20s, and a patient who was 49 years old. Three of the patients had underlying cardiac abnormalities, and one had a history of intravenous drug use.104 This same clone of nontoxigenic C. diphtheriae was isolated from three patients in Koorie, an aborigine community in Victoria, Australia, who had endocarditis, and five asymptomatic contacts.7 Two of the three patients with endocarditis were members of the same family, and one of them had a history of alcohol abuse. The third patient had a septic sternoclavicular joint, in addition to endocarditis, with isolation of the same organism. Nontoxigenic C. diphtheriae sepsis can lead to splenic and hepatic abscesses, as reported in a patient with chronic lymphocytic leukemia in British Columbia, Canada.71

Complications secondary to elaborated diphtheria toxin may affect any system, but myocarditis and involvement of the nervous system are most characteristic. Myocarditis may occur after mild and severe cases of diphtheria. Generally it develops in patients in whom administration of antitoxin is delayed. Myocarditis most commonly appears in the second week of the disease, but it can appear as early as the first or as late as the sixth week of illness. Tachycardia, a muffled S1, murmurs, and arrhythmias such as atrioventricular dissociation indicate myocardial involvement. Echocardiography may show left ventricular dysfunction.70,108 Although some cases may result in cardiac failure, most myocardial complications are temporary.

Neurologic complications appear after a variable latent period. Approximately 75% of all patients with severe diphtheria develop neuropathies. The incidence of neurologic sequelae has been shown to correlate with the severity of respiratory symptoms; 20% of all patients with respiratory problems develop polyneuritis. Neurologic complications from diphtheria infections predominantly are bilateral, are motor rather than sensory, and usually resolve completely. Paralysis of the soft palate
is the most common occurrence and generally appears in the third week. It is manifested by a nasal quality in the voice, nasal regurgitation, and difficulty swallowing. Ocular paralysis usually occurs around the fifth week of illness and is characterized by blurring of vision and difficulty with accommodation. Internal strabismus also may be noted. Paralysis of the diaphragm, peripheral neuropathy involving the limbs, and loss of deep tendon reflexes likewise are reported as complications of diphtheria. When they occur, along with an elevated cerebrospinal fluid protein, the syndrome is clinically indistinguishable from Guillain-Barré syndrome.

Rarely, 2 or 3 weeks after the onset of illness, involvement of the vasomotor centers results in hypotension and cardiac failure. Gastritis, hepatitis, nephritis, and hemolytic-uremic syndrome also have been reported as complications of diphtheria.24,25

Information on the effects, if any, of diphtheria on the fetus during pregnancy is sparse. El Seed and associates26 reported a case of pharyngeal diphtheria in a pregnant woman that occurred during the first trimester of pregnancy. Apart from vaginal bleeding, no complications of pregnancy were noted. Severe diphtheritic toxiemia in the mother was characterized by quadriaparesis, from which she fully recovered. A physically normal female infant was delivered at term. In this single case, severe diphtheritic toxemia during pregnancy was not associated with any teratogenic effect in the fetus and did not impair intrauterine fetal growth.

**DIAGNOSIS**

The diagnosis of diphtheria should be based on clinical findings because any delay in initiating therapy poses a serious risk to the patient. Isolation of the organism is used to confirm the clinical diagnosis. Material obtained from beneath the membrane, where organisms are concentrated most highly, or a portion of the membrane itself should be obtained for culture.3,5

*C. diphtheriae* is relatively resistant to drying. The use of a nonnutritive, moisture-reducing transport medium helps prevent the overgrowth of other microorganisms. The laboratory should be notified about the possibility of diphtheria so that appropriate culture media are inoculated. A Löffler slant, a tellurite plate, and a blood agar plate should be inoculated. Tellurite-containing media inhibit the growth of normal oral flora, allowing *C. diphtheriae* to grow into characteristic black colonies. Other corynebacteria, staphylococci, and yeast also can reduce tellurite and grow into black colonies.36 Although examination of direct smears of colonies or diphtheritic lesions remains an important supplement to clinical examination, it often is inaccurate. Screening the colonies from the tellurite plate for catalase, urea, nitrate, pyrazinamidase, and cystinase is important. Most biotypes of *C. diphtheriae* are catalase positive, urease negative, nitrate positive (except biotype *belfanti*), pyrazinamidase negative, and cystinase positive.37

All diphtheria bacilli that are recovered should be tested for toxigenicity. In 1949, the Elek immunoprecipitation assay replaced in vivo testing for toxigenicity using guinea pigs or rabbits.38 The Elek test is based on gel diffusion and immunoprecipitation of toxin from organisms inoculated onto agar adjacent to an antitoxin-containing well. A strain that is positive for toxin is indicated by the formation of a precipitin band between the toxin and antitoxin.44,46 The Elek test takes 48 hours to yield results on the toxigenic nature of a *C. diphtheriae* strain. A modified Elek test that consists of placement of an antitoxin-impregnated disk onto an agar plate surrounded by inoculates of clinical specimen and positive control has been described. In contrast to the conventional Elek test, the modified test has the advantage of using “spot” inoculations of numerous colonies directly from the primary plate. In addition, the modified Elek test has fewer false-positive and false-negative results and yields results more rapidly (16 to 24 hours).45

A rapid enzyme immunoassay is another test for detection of diphtheria toxin. This method uses equine polyclonal antibody to capture the diphtheria toxin and an alkaline phosphatase–labeled monoclonal antibody to detect fragment A of the toxin. It is a rapid test that takes 3 hours and has a limit of detection of 100 pg/mL.47

Rapid testing for diphtheria toxin by PCR specific for the A or B portion of the toxin gene, tox, is sensitive and has produced positive results in specimens stored for 12 months before performing the assay.24,25,91,92,94 The absence of the tox gene by PCR excludes the diagnosis of diphtheria. PCR may give false-positive results, however, because it does not differentiate between partial or nonfunctional tox genes and functional tox gene products. An increasing number of cases of non-toxigenic diphtheria that are positive for the tox gene by PCR have been reported from Ukraine and Russia.95,96

The immune status of patients can be determined by toxin neutralization in Vero cells.60 This method is used frequently, although it is difficult to standardize and relies heavily on individual interpretation of results. Enzyme-linked immunosorbent assay is a more rapid and quite sensitive method, but it detects some nonspecific antibodies; when antitoxin levels are in the low range, the assay may generate falsely elevated results.60 Finally a delayed fluorescence immune assay method was developed by Grimes and associates103 in 1996 and has been reported to have good sensitivity, specificity, and reproducibility.66 Levels of diphtheria antitoxin of 0.01 IU/mL or greater generally are accepted as protective. A skin-testing method, the Schick test, also has been used to assess immunity.

The Schick test was used previously to determine the immune status of the patient. It is not helpful in establishing an early diagnosis because it cannot be read for several days, and currently it is not widely used. In the Schick test, a measured amount of purified diphtheria toxin (0.1 mL) is injected subcutaneously. A hypersensitivity reaction indicates an inadequate presence of antitoxin. A toxoid control also is injected, in the opposite arm, to help distinguish between a reaction to toxin and a reaction to other antigens in the toxin preparation.

Other laboratory studies are of little diagnostic value. The white blood cell count may be normal or elevated. Rarely anemia develops as a result of rapid hemolysis of red blood cells. Examination of cerebrospinal fluid may reveal a minimal elevation of protein and, rarely, a mild pleocytosis in patients with diphtheritic neuritis. Hypoglycemia, glucosuria, or both may occur and reflect hepatic toxicity. An elevation in blood urea nitrogen may develop in patients with acute tubular necrosis. An electrocardiogram should be obtained and may reveal ST-segment and T-wave changes or arrhythmias indicative of myocarditis.

**Differential Diagnosis**

Mild forms of nasal diphtheria in a partially immunized host may resemble the common cold. When the nasal discharge is more serosanguineous or purulent, nasal diphtheria must be distinguished from a foreign body in the nose, sinusitis, adenoiditis, or the stuffles of congenital syphilis. Careful examination of the nose with a nasal speculum, sinus radiographs, and appropriate serologic tests for syphilis are helpful in excluding these disorders.

Tonsillar or pharyngeal diphtheria must be differentiated from streptococcal pharyngitis. Generally streptococcal pharyngitis is associated with more severe pain on swallowing, higher temperature, and a nonadherent membrane limited to the tonsils. In some patients, pharyngeal diphtheria and streptococcal pharyngitis coexist.

Tonsillar and pharyngeal diphtheria also must be differentiated from infectious mononucleosis (lymphadenopathy and splenomegaly are common findings, atypical lymphocytes are generally present, and heterophile antibody may be present), nonbacterial membranous tonsillitis (white blood cell count generally is low, throat cultures reveal normal flora, and the course is unaffected by antibiotics), primary herpetic tonsillitis (presence of gingivitis, stomatitis, and discrete lesions of the tongue and palate may be helpful), Vincent angina (may be indistinguishable), and thrush (constitutional symptoms are absent, and lesions are present on the buccal mucosa and tongue). Tonsillar and pharyngeal diphtheria also must be differentiated from blood dyscrasias such as agranulocytosis and leukemia (complete blood count and bone marrow study are helpful); post-tonsillectomy faucial membrane (membranes are stationary and do not spread); and oropharyngeal dyscrasias such as agranulocytosis and leukemia (complete blood count, and lesions are present on the buccal mucosa and tongue). Tonsillar and pharyngeal diphtheria also must be differentiated from infectious mononucleosis (lymphadenopathy and splenomegaly are common findings, atypical lymphocytes are generally present, and heterophile antibody may be present), nonbacterial membranous tonsillitis (white blood cell count generally is low, throat cultures reveal normal flora, and the course is unaffected by antibiotics), primary herpetic tonsillitis (presence of gingivitis, stomatitis, and discrete lesions of the tongue and palate may be helpful), Vincent angina (may be indistinguishable), and thrush (constitutional symptoms are absent, and lesions are present on the buccal mucosa and tongue). Tonsillar and pharyngeal diphtheria also must be differentiated from blood dyscrasias such as agranulocytosis and leukemia (complete blood count and bone marrow study are helpful); post-tonsillectomy faucial membrane (membranes are stationary and do not spread); and oropharyngeal dyscrasias such as agranulocytosis and leukemia (complete blood count, and lesions are present on the buccal mucosa and tongue).
peripheral and retropharyngeal abscesses; and laryngeal papillomas, hemangiomatis, or lymphangiomatis. A careful history, followed by careful visualization in the hospital under controlled conditions, aids in making a correct diagnosis.

PREVENTION

Diphtheria is prevented on a community-wide basis most effectively by active immunization. Diphtheria toxoid is available in combination with tetanus toxoid as pediatric DT or adult Td and in combination with acellular pertussis as DTaP and Tdap. Combination regimens with DTaP and inactivated poliovirus and hepatitis B (Pediatr) and inactivated poliovirus and Haemophilus influenzae type B (Pentacel) are also available. Pediatric formulations of diphtheria toxoid vaccines contain three to four times more diphtheria toxoid but the same tetanus toxoid in contrast to the adult formulations. Children younger than 7 years should be given the pediatric formulations of vaccine, whereas children older than 7 years should receive the adult Td. Two forms of Tdap are available: Boostrix, which is approved for children beginning at age 10 through 65 years or older, and Adacel, which is approved for individuals 11 to 64 years old.

Primary immunization is carried out conveniently and effectively by giving diphtheria and tetanus toxoids and pertussis vaccine, DTaP, at 2, 4, and 6 months of age, with booster doses given at 15 to 18 months and again when the child is 4 to 6 years of age. Booster doses with the adult type of diphtheria and tetanus toxoids adsorbed (Td) should be given at 10-year intervals to all immunized individuals. Current recommendations are to give Tdap as the first booster dose in patients who are 11 to 12 years old and to anyone older who has not received a dose of Tdap. Td and Tdap contain 2 to 2.5 Lf of diphtheria toxoid per dose in contrast to 7 to 25 Lf in the pediatric diphtheria, tetanus toxoid, and pertussis vaccine preparations (DTaP and DT). Primary immunization of children older than 7 years may be performed with Td. Two doses are given intramuscularly at least 4 weeks apart, with a booster dose provided 1 year later. Children and adults who are severely immunocompromised or undergoing long-term hemodialysis should use the standard immunization schedule, although response may be suboptimal.

Most local and systemic reactions to the diphtheria and tetanus toxoids and whole cell pertussis vaccine (DTP), including fever, were related to the pertussis component. Administration of tetanus and diphtheria toxoids is not followed by the high incidence of reactions associated with the use of pediatric DTP vaccines. At least one study showed that 7.5 Lf toxoid can be given safely to adults without a higher risk for reactions occurring. Primary immunization against diphtheria for infants with progressive neurologic disorders and completion of the primary immunization series in patients who had experienced an untoward reaction to an earlier DTP vaccine injection may be performed with diphtheria and tetanus toxoids rather than diphtheria and tetanus toxoids and pertussis vaccine.

A report of 97 preterm infants who received diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) (94 of these infants also received H. influenzae type B vaccine) showed that most infants tolerated the vaccination without side effects, although a subgroup of infants with very low birth weight (mean, 873 g) had either a recurrence or an increase in the number of apneic and bradycardic episodes in the 48 hours after receiving vaccination. The apneic and bradycardic episodes were present before immunization in every case.

Booster doses of tetanus and diphtheria toxoids should be given at 10-year intervals to all immunized individuals. The CDC Advisory Committee on Immunization Practices now recommends that all adults aged 19 years and older who have not received a dose of Tdap should receive a single dose. A recent update recommends a dose of Tdap during every pregnancy. As mentioned earlier, levels of diphtheria antitoxin of 0.01 IU/mL or greater generally are accepted as protective.

Diphtheria immunization is not always followed by complete protection. Immunization is directed against the phage-mediated toxin, not against infection. Fully immunized individuals may be carriers or may have disease caused by nontoxigenic strains. An investigation conducted during an epidemic in Texas showed no statistical difference in the risk for diphtheria infection developing in individuals with full, lapsed, inadequate, or no previous diphtheria immunization; however, a 30-fold increased risk for development of symptomatic diphtheria in individuals with no immunization and an 11.5-fold increase in individuals with inadequate immunization were noted.

The most important health problem in the United States today is inadequate immunization of the population. Immunization rates in adults are poorer than those in infants and children because of failure to maintain adequate immunity through appropriate booster immunization. A 70% to 80% immunization level is thought to be required to prevent epidemic spread.

Prevention of diphtheria also depends on management of the contacts of known cases. Diphtheria and carriers of the organism and on isolation of patients to minimize the spread of disease. Individuals at risk for contracting the disease from the index case include those who have had close respiratory or physical contact or prolonged close proximity with the infected individual, including members of the index case’s household. Specifically, family members who share body towels and cups or eating utensils, share a bed or a bedroom with more than two people, or take a bath less than once per week have a significantly greater risk for contracting the disease from the infected patient. A history of eczema in the contact also has been associated with a significantly increased risk for contracting diphtheria from the index case. The patient is infectious until diphtheria bacilli no longer can be cultured from the site of infection. Two or three consecutive negative cultures at least 24 hours apart are required, and antibiotic therapy must be complete for 24 hours before the patient is released from isolation. If obtaining cultures is impossible, isolation may be ended after the completion of 14 days of appropriate antibiotic treatment.

Cultures should be taken from the nose and throat of all close contacts, who should be kept under surveillance for 7 days (surveillance as an outpatient is acceptable). Regardless of their immunization status, contacts should be treated with a single intramuscular dose of benzathine penicillin G 600,000 U for individuals weighing less than 30 kg and 1.2 million U for individuals weighing more than 30 kg or a 7-day course of erythromycin 40 to 50 mg/kg per day (maximum 2 g/day) divided into four doses. The immune status of each contact should be determined; individuals for whom immune status is inadequate, including individuals who have had the primary series but more than 5 years has elapsed since they received their last booster dose, should receive an injection of diphtheria toxoid. In addition, patients with diphtheria should be immunized during convalescence because infection may not confer immunity.

Asymptomatic carriers who previously were not immunized against diphtheria should have cultures taken, receive diphtheria toxoid and penicillin or erythromycin (as described earlier), and be seen daily by a physician. Asymptomatic contacts who are found to carry a toxigenic strain should be subjected to the same isolation and treatment measures as the index case. If daily surveillance is impossible, benzathine penicillin is preferred over erythromycin for treatment because failure to adhere to an oral drug regimen is a concern. If a contact is experiencing symptoms when seen, treatment of diphtheria is indicated. It is important to initiate prophylactic therapy in contacts who have not been immunized before the results of culture are received. Management of carriers is described in the next section. Contacts whose occupations involve close contact with unimmunized children or food handling (especially milk) should refrain from working until cultures are confirmed to be negative.

TREATMENT

Treatment of diphtheria is predicated on neutralization of free toxin and eradication of C. diphtheriae or C. ulcerans with antibiotics. Disease caused by C. ulcerans should be treated in the same manner as disease caused by C. diphtheriae. The decision to administer equine antitoxin should be based on the size and site of the membrane, the degree of toxicity, and the duration of illness and should be made clinically as soon as possible.
Antitoxin can neutralize circulating toxin or toxin that is absorbed onto cells, but is ineffective when cells have been penetrated. Early treatment is essential to limit tissue damage. An adequate dose of antitoxin must be administered intravenously as early as possible to neutralize all free toxins. A single dose is used to avoid the risk for developing sensitization from repeated doses of horse serum. Tests for sensitivity to horse serum must be performed before antitoxin is administered. Antitoxin and its indications for use as well as instructions for sensitivity testing and administration are available through the CDC (Emergency Operations Center, 770-488-7100; www.cdc.gov/diphtheria/dait.html). The antitoxin dosage is empirical. Pharyngeal or laryngeal disease of 48 hours’ duration or less should be treated with 20,000 to 40,000 U, nasopharyngeal disease with 40,000 to 60,000 U, and severe pharyngeal or laryngeal diphtheria with 80,000 to 120,000 U of antitoxin. The last dose also should be given to patients with mixed clinical symptoms and to patients with brawny edema or disease of longer than 48 hours’ duration. The value of antitoxin in the treatment of cutaneous disease is debated, but some experts recommend 20,000 to 40,000 U because toxic effects have been reported. The use of intravenous immunoglobulin (IgIV) for therapy of respiratory or cutaneous diphtheria has not been approved or evaluated for efficacy. A human monoclonal antibody to replace equine diphtheria antitoxin is under development and holds promise as a potential therapeutic agent.

Although antibiotics are not a substitute for treatment with antitoxin, they should be given when diphtheria is suspected clinically. Penicillin and erythromycin are still effective against most strains of *C. diphtheriae*. Penicillin and erythromycin also are effective in eradicating group A hemolytic streptococci, which may complicate 30% of cases of diphtheria. Treatment consists of a 14-day course of penicillin or erythromycin. Penicillin may be given as aqueous penicillin G 100,000 to 150,000 U/kg per day in four divided doses intravenously or as procaine penicillin 25,000 to 50,000 U/kg per day (maximum of 1.2 million U) in two divided doses intramuscularly. Patients who are sensitive to penicillin should be given erythromycin in a daily dosage of 40 to 50 mg/kg (maximum of 2 g/d) in four divided doses for 14 days. When the patient is able to tolerate oral medications, erythromycin or penicillin V may be used in place of the intravenous antibiotics.

Follow-up cultures should be obtained at least 2 weeks after antibiotic therapy is completed; if they are positive, erythromycin should be given for an additional 10 days. Some resistance to erythromycin has been observed, but it is uncommon, and its epidemiologic significance is unknown. Penicillin is recommended as first-line treatment in Vietnam, based on sensitivity data. Amoxicillin, rifampin, and clindamycin provided in appropriate dosages also may be effective. Lincomycin and tetracycline have proved to be less effective, and cephalaxin, oxacillin, and colistin have been shown to be ineffective against *C. diphtheriae*. The endpoint of therapy is two or three consecutive negative cultures at least 24 hours apart. In addition to receiving antibiotic therapy, patients with diphtheria should be immunized during convalescence because infection may not confer immunity.

The carrier state has been treated effectively with a single intramuscular dose of benzathine penicillin G 600,000 U for children weighing less than 30 kg or 1.2 million U for individuals weighing 30 kg or greater or oral erythromycin 40 to 50 mg/kg per day for children and 1 g/day for adults for 7 to 10 days. Carriers should have repeat pharyngeal cultures performed a minimum of 2 weeks after antibiotic therapy is complete; if the repeat cultures are positive, carriers should receive an additional course of antibiotics.

Treatment of deep infections caused by nontoxigenic *C. diphtheriae* can be accomplished with a wide variety of susceptible agents. Endocarditis with these organisms treated with either a β-lactam alone or in combination with an aminoglycoside has been associated with favorable outcomes.

**Supportive Treatment**

Bed rest is extremely important and should be required for 2 to 3 weeks. Serial electrocardiograms should be obtained two or three times each week for 4 to 6 weeks to detect myocarditis as early as possible. Absolute bed rest must be enforced if myocarditis is detected, because sudden death has been precipitated by excessive activity. A patient with myocarditis may receive digitalization if congestive heart failure develops. Digitalization for arrhythmias caused by diphtheria may be contraindicated, however. In severe disease, prednisone 1 to 1.5 mg/kg per day for 2 weeks has been shown to lessen the incidence of myocarditis.

Hydration should be maintained, and a high-calorie liquid or soft diet should be provided. Secretions should be suctioned as needed to prevent aspiration. Palatal and pharyngeal paralysis increases the risk for aspiration occurring, so gavage via a nasogastric tube is indicated in these patients.

The quality of the voice and the gag reflex should be checked regularly for assessment of progression of the disease. Laryngeal diphtheria may require relief of obstruction with a tracheostomy. This procedure should be performed before the patient has become exhausted.

Adequate immunity does not develop in at least half of patients who recover from diphtheria, and they remain subject to reinfection. Immunization is indicated after the patient recovers.

**PROGNOSIS**

Many factors affect the prognosis in cases of diphtheria, the most important being the immunization status of the host. Morbidity and mortality rates are increased significantly in patients who are unimmunized or inadequately immunized. The rapidity with which medical care is sought and the diagnosis of diphtheria is suggested has a great impact on outcome. If specific treatment is provided on the first day of disease, the mortality rate may be reduced to less than 1 percent; delay in providing treatment until day 4 may be associated with a 20-fold increase in the mortality rate.

The virulence of the infecting organism and the location of infection are important prognostic factors. Infection with a nontoxigenic *C. diphtheriae* strain may cause disease but does not lead to myocarditis, neuritis, and other toxin-related phenomena. Toxigenic disease may vary from mild to severe. In cases of mild diphtheria, membrane sloughing and full recovery generally occur within 7 days. Disease caused by toxigenic *gravis* strains tends to be more severe and carries a poorer prognosis. Although diphtheria may affect the skin, nasopharynx, and other mucous membranes, involvement of the larynx heralds a more complicated course. Laryngeal diphtheria increases the risk for development of airway obstruction and promotes systemic absorption of the toxin. These patients require close monitoring of respiratory function and for involvement of other organ systems. Laryngeal diphtheria is more likely to be fatal in infants.

Few laboratory parameters indicate the severity of diphtheria. The development of amegakaryocytic thrombocytopenia and leukocytosis with counts of greater than 25,000 cells/mm³ has been associated with a poor outcome.

The prognosis in a patient with diphtheria remains guarded until recovery is complete. At any time during the course of the illness, complications such as laryngeal obstruction, shock, and ventricular fibrillation may occur suddenly and unexpectedly. In patients with myocardial involvement, permanent damage to the heart, specifically fibrosis, may occur and lead to later complications. In addition, potentially severe neurologic manifestations, such as phrenic nerve paralysis, may appear late in the course of the disease.

Persistence of *C. diphtheriae* may be noted in the nasopharynx of 5% to 10% of convalescing patients. Recovery from diphtheria is followed by immunity that is demonstrable for at least 1 year after illness in 50% of patients. Second attacks are rare; nonetheless, immunization should be performed after the patient recovers.

Before the use of antitoxin and the availability of antibiotics, the mortality rate from diphtheria was 30% to 50%. Death was most common in children younger than 4 years old and was the result of suffocation. At present, the worldwide mortality rate is 5% to 10%, with no clear association with age.

**NEW REFERENCES SINCE THE SEVENTH EDITION**


The full reference list for this chapter is available at ExpertConsult.com.

ADDITIONAL READING


