

## **DIPHTHERIA INFECTION PATHOGENESIS**

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**Annotation:** In this article you will get information about diphtheria, which currently has its place within infection diseases. through this article , you will receive the necessary information about what kind of infection diphtheria itself is , its spread, transmission routes and Prevention.

**Key words:** corynebacteriophages, *diphtheriae* , blood, toxin , infection, pathogenesis.

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Pathogenesis. Susceptible persons may acquire toxigenic diphtheria bacilli in the nasopharynx. The organism produces a toxin that inhibits cellular protein synthesis and is responsible for local tissue destruction and formation of the pseudomembrane that is characteristic of this disease. The toxin produced at the site of the membrane is absorbed into the bloodstream and then distributed to the tissues of the body. The toxin is responsible for major complications such as myocarditis, polyneuropathies, and nephritis, and can also cause thrombocytopenia.

Non-toxin-producing *C. diphtheriae* strains can cause mild to severe exudative pharyngitis. Severe cases with pseudomembranes caused by such strains have been reported rarely; it is possible that these infections were caused by toxigenic strains that were not detected because of inadequate culture sampling. Other manifestations of nontoxigenic *C. diphtheriae* infection include cutaneous lesions, endocarditis, bacteremia, and septic arthritis.

**Clinical Features .** The incubation period for diphtheria is 2 to 5 days, with a range of 1 to 10 days. Disease can involve almost any mucous membrane. In untreated people, organisms can be present in discharges and lesions 2 to 6 weeks after infection. For clinical purposes, it is convenient to classify diphtheria by anatomic site: respiratory (pharyngeal, tonsillar, laryngeal, nasal) and non-respiratory (cutaneous and other mucous membranes) disease.

### **Pharyngeal and Tonsillar Diphtheria**

The most common sites of diphtheria infection are the pharynx and the tonsils. Infection at these sites is usually associated with substantial systemic absorption of toxin. The onset of pharyngitis is gradual. Early symptoms include malaise, sore throat, anorexia, and low-grade fever (less than 101°F). Within 2 to 3 days, a bluish-white membrane forms and extends, varying in size from covering a small patch on the tonsils to covering most of the soft palate. Often by the time a physician is contacted the membrane is greyish-green or, if bleeding has occurred, black. There is a minimal amount of mucosal erythema surrounding the membrane. The membrane is firmly adherent to the tissue, and forcible attempts to remove it cause bleeding. Extensive membrane formation may result in respiratory obstruction.

While some patients may recover at this point without treatment, others may develop severe disease. The patient may appear quite toxic, but the fever is usually not high. Patients with severe disease may develop marked edema of the submandibular areas and the anterior neck along with lymphadenopathy, giving a characteristic “bull neck” appearance. If enough toxin is absorbed, the patient can develop severe prostration, pallor, rapid pulse, stupor, and coma. Death can occur within 6 to 10 days.

#### Laryngeal Diphtheria

Laryngeal diphtheria can be either an extension of the pharyngeal form or can involve only this site. Symptoms include fever, hoarseness, and a barking cough. The membrane can lead to airway obstruction, coma, and death.

#### Anterior Nasal Diphtheria

The onset of anterior nasal diphtheria looks much like the common cold and is usually characterized by a mucopurulent nasal discharge that may become blood-tinged. A white membrane usually forms on the nasal septum. The disease is usually fairly mild because of apparent poor systemic absorption of toxin from this location, and it can be terminated rapidly by diphtheria antitoxin and antibiotic therapy.

#### Cutaneous Diphtheria

Skin infections may be manifested by a scaling rash or by ulcers with clearly demarcated edges and an overlying membrane, but any chronic skin lesion may harbor *C. diphtheriae* along with other organisms. Cutaneous diphtheria is quite common in the tropics and is probably responsible for the high levels of natural immunity found in these populations. Infection with toxigenic strains appears to result less frequently in systemic complications with cutaneous compared to other forms of diphtheria. *C. diphtheriae* isolated from cutaneous cases in the United States typically has been nontoxigenic, although recently a number of imported toxigenic cutaneous cases have been identified.

#### Complications

Most complications of diphtheria, including death, are caused by effects of the toxin. The severity of the disease and complications are generally related to the extent of local disease. The toxin, when absorbed, affects organs and tissues distant from the site of invasion. The most frequent complications of diphtheria are myocarditis and neuritis.

Myocarditis may present as abnormal cardiac rhythms and can occur early in the course of the illness or weeks later. Myocarditis can lead to heart failure and, if it occurs early, it is often fatal.

Neuritis most often affects motor nerves and usually resolves completely. Paralysis of the soft palate is most frequent during the third week of illness. Paralysis of eye muscles, limbs, and the diaphragm can occur after the fifth week. Secondary pneumonia and respiratory failure may result from diaphragmatic paralysis.

Other complications include otitis media and respiratory insufficiency due to airway obstruction, especially in infants.

The estimated overall case fatality ratio for diphtheria is 5% to 10%.

#### Laboratory Testing

Diagnosis of respiratory diphtheria is usually made based on clinical presentation because it is imperative to begin presumptive therapy quickly. Non-respiratory diphtheria, such as cutaneous diphtheria, may not be clinically suspected and therefore diagnosis is typically based on the laboratory finding.

Confirmatory testing for diphtheria includes culture to identify the bacterial species and the Elek test to confirm diphtheria toxin production. Capacity for diphtheria culture may be available at public health or commercial laboratories. CDC's Pertussis and Diphtheria Laboratory routinely performs culture to confirm *C. diphtheriae* and is currently the only laboratory in the United States that tests for toxin production. It is critical to take a swab of the affected area, especially any ulcerations or pseudomembranes. The organism can be cultured on common laboratory media; culture on a selective medium containing tellurite allows for distinguishing *C. diphtheriae* and *C. ulcerans* from other *Corynebacterium* species that normally inhabit the nasopharynx and skin (e.g., diphtheroids). However, further biochemical tests are required to fully identify an isolate as *C. diphtheriae*. If *C. diphtheriae* or *C. ulcerans* are isolated, they must be tested for toxin production.

#### Medical Management

##### Diphtheria Antitoxin

Diphtheria antitoxin, produced in horses, has been used for treatment of respiratory diphtheria in the United States since the 1890s. It typically is not administered in cases of non-respiratory diphtheria and it is not indicated for prophylaxis of diphtheria patient contacts. Diphtheria antitoxin is available only from CDC, through an Investigational New Drug (IND) protocol. Diphtheria antitoxin does not neutralize toxin that is already fixed to tissues, but it will neutralize circulating toxin and prevent progression of disease.

After a provisional clinical diagnosis of respiratory diphtheria is made, appropriate specimens should be obtained for culture and the patient placed in isolation. Persons with suspected diphtheria should be promptly given diphtheria antitoxin and antibiotics in adequate dosage, without waiting for laboratory confirmation. Respiratory support and airway maintenance should also be provided as needed. Consultation on the use of and access to diphtheria antitoxin is available through the duty officer at CDC's Emergency Operations Center at 770-488-7100.

##### Antibiotics

In addition to diphtheria antitoxin, patients with respiratory diphtheria should also be treated with antibiotics. The disease is usually no longer contagious 48 hours after antibiotics have been given. Elimination of the organism should be documented by two consecutive negative cultures taken 24 hours apart, with the first specimen collected 24 hours after therapy is completed.

##### Preventive Measures

Diphtheria disease might not confer immunity. Unvaccinated or incompletely vaccinated persons recovering from diphtheria should begin or complete active immunization with diphtheria toxoid during convalescence.

Vaccination history of close contacts of diphtheria patients should also be assessed: if vaccination history is incomplete or unknown, the contact should receive a dose of diphtheria toxoid-containing vaccine immediately, and the vaccination series should be completed according recommendations from the Advisory Committee on Immunization Practices (ACIP). If the contact is up-to-date according to ACIP recommendations but the last dose was more than 5 years ago, a diphtheria toxoid-containing vaccine should be immediately administered. In addition, close contacts should receive a single intramuscular dose of benzathine penicillin G or

a 7- to 10-day course of oral erythromycin. Benzathine penicillin G should be given to contacts for whom surveillance cannot be maintained for 7 to 10 days. Contacts should be closely monitored and begin diphtheria antitoxin treatment at the first signs of illness.

### **Secular Trends in the United States**

During the 1920s, 100,000 to 200,000 cases of diphtheria (140 to 150 cases per 100,000 population) and 13,000 to 15,000 deaths were reported each year. After diphtheria toxoid-containing vaccines became available in the 1940s, the number of cases gradually declined to about 19,000 in 1945 (15 cases per 100,000 population). A more rapid decrease began with implementation of a universal childhood vaccination program which included diphtheria toxoid-containing vaccines beginning in the late 1940s.

From 1996 through 2018, 14 cases of diphtheria were reported in the United States, an average of less than 1 per year. One fatal case occurred in a 63-year-old male returning to the United States from a country with endemic diphtheria disease.

Within the United States, coverage with diphtheria toxoid childhood vaccines (DTaP) has been consistently high. Among children born during 2016–2017, 93.3% had received at least 3 doses of DTaP vaccine by age 24 months, and 80.6% had received at least 4 doses of DTaP vaccine by age 24 months. Coverage with the adolescent and adult diphtheria toxoid vaccines (Tdap or Td) is variable: Tdap coverage among adolescents age 13 through 17 years reached 90.2% in 2019.

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