Diphtheria is caused by superficial infection of the respiratory tract or skin with toxin-producing strains of the bacterium *Corynebacterium diphtheriae*. The organisms do not actively invade deep tissue or the blood, but multiply locally, producing diphtheria toxin. This results in necrosis of the mucosal cells and production of a thick, grey pseudomembrane containing fibrin, epithelial cells, bacteria and neutrophils. Diffusion of toxin into the circulation causes toxic neurological and myocardial complications.

The clinical manifestations and epidemiology of infection with *C. diphtheriae* vary between parts of the world and over time, depending on host and environmental factors, some of which are not fully understood. The most important factors are individual and population immunity to the diphtheria toxin mediated by neutralizing antibody; this is induced by immunization with formalin-inactivated toxin (toxoid) and/or natural immunizing events resulting from asymptomatic carriage or low-grade infection (often cutaneous).

**Epidemiology**

Mass immunization with diphtheria toxoid as part of childhood immunization schedules worldwide has led to the virtual disappearance of toxigenic *C. diphtheriae* and of the disease, particularly in developed countries where such programmes have been long established. As a consequence, clinical and laboratory diagnostic skills have declined. In many developed countries, diphtheria is now so uncommon that most clinicians and many microbiologists have never seen a case. However, events in the last decade in Russia and other countries of the former USSR, where diphtheria re-emerged as an epidemic disease (47,808 cases with 1746 deaths were reported in 1994, compared with 198 cases in 1976), suggest that the disease can return when immunization and disease control programmes are disrupted by social, political and other changes. Following major public health efforts, including mass immunization campaigns, the incidence of diphtheria in the former USSR declined during the latter half of the 1990s, though it remains above the low rates noted in the 1970s.

The virtual disappearance of circulating toxigenic *C. diphtheriae* from immunized populations means that the possibility of ‘natural immunizing events’ is precluded, and immunity to the disease relies completely on vaccination. However, vaccine-induced immunity is not necessarily lifelong, and serological surveys in
diphtheria may occur in individuals with an apparently complete immunization history. Increasing international travel and population migration, coupled with continued foci of epidemicity and endemcity in some parts of the world (the former USSR, parts of South America, Africa, the Indian subcontinent and South East Asia), require that a high index of suspicion is maintained, particularly in travellers from these areas and their contacts.

**Clinical features**

The incubation period is usually 2–4 days (range 1–7 days). Clinical manifestations are:

- local in the respiratory tract or skin, resulting from inflammatory reaction and pseudomembrane formation
- systemic, resulting from absorption and dissemination of toxin and leading to effects in distant organs (most notably cardiac and neurological damage, Figure 1).

**Respiratory tract** – the pseudomembranous exudate (Figure 2) adheres to the fauces, and attempts to remove it leave a raw, bleeding surface. The cervical lymph nodes enlarge and there is oedema of the neck, which may be severe and can progress to the condition known as ‘bull-neck’.

Diphtheria of the respiratory tract may be nasal, faucial or proximal pharyngeal (the most common sites), laryngeal or even tracheobronchial. Symptoms range from pharyngitis with low-grade fever in faucial diphtheria, to partial or complete respiratory obstruction caused by extensive pseudomembrane formation in pharyngeal/tracheobronchial diphtheria.

**Cutaneous diphtheria** occurs most commonly in tropical countries. The lesions are often chronic, non-healing, shallow ulcers with rolled edges, usually covered by a hard, grey, adherent membrane. Although *C. diphtheriae* usually produces toxin, systemic toxic manifestations are uncommon. The toxin is absorbed from the lesion slowly and can induce high levels of circulating antibody. The ulcer may act as a reservoir for transmission and spread of the pharyngeal form of the disease.

**Cardiac and neurological toxicity** – the incidence of cardiac and neurological complications is proportional to the severity of the primary (local) infection. Of patients with clinical respiratory tract diphtheria, 10–25% develop myocardial damage and up to 75% neuropathies (Figure 1).

**Systemic manifestations of diphtheria (caused by toxin)**

**Cardiac**

Minor evidence of myocarditis may be apparent in up to 60% of patients; 10–20% develop clinically significant cardiac toxicity.

Myocarditis may present acutely with congestive failure and circulatory collapse, or more slowly with gradually progressive signs and symptoms. Routine ECG monitoring is recommended. Estimation of serum aspartate aminotransferase is also recommended, because increases reflect the intensity of the myocarditis.

ST-T wave changes may be noted on ECG 1–2 weeks after onset of the disease. First-degree heart block can progress to second-degree and third-degree block, bundle-branch block and atrioventricular dissociation, all of which have an ominous prognosis. Mortality in patients with an abnormal ECG is increased 3–4-fold above that in those with a normal ECG, and can be almost 90% in the more severe forms of heart block. Survivors may have permanent conduction defects.

**Neurological**

Neuropathies develop in up to 75% of patients with severe manifestations of diphtheria, but only occasionally in mild forms.

Palatal and posterior pharyngeal wall paralysis is common, usually occurs in the first or second week of the disease, and results in nasal regurgitation of liquids and food. This may be followed by cranial neuropathies, particularly ocular and bulbar palsies, which develop in the second to fourth week after onset of the respiratory infection.

Peripheral neuritis (principally motor) manifests up to 3 months from the onset of the disease. It begins with proximal muscle groups in the extremities and extends distally, varying from mild weakness with reduced reflexes to total paralysis. Respiratory paralysis may necessitate intubation and mechanical ventilation.

Diagnosis

A presumptive clinical diagnosis of respiratory tract diphtheria is based on the presence of pharyngitis with a pseudomembrane. The immunization and travel history of patients and, when possible, their close contacts should always be obtained (though a history of immunization and even a recent booster dose of diphtheria toxoid does not exclude the diagnosis).

**Investigations** – a throat swab and, if possible, samples of the membrane should be collected and sent to the laboratory for culture. It is essential to notify the laboratory that diphtheria is suspected. Samples are plated on specific selective culture media, most commonly a blood tellurite agar, and suspicious colonies are identified by a black or grey appearance on this medium. A range of screening and confirmatory tests and, most importantly, toxin detection are then undertaken. Strains of *C. diphtheriae* may or may not be producers of the potent toxin, and determination of toxigenicity status is probably the most important aspect of laboratory investigation.
Serology has little role in the diagnosis of *C. diphtheriae* infection. However, levels of serum antibody to diphtheria toxoid may be determined by various methods and are useful in assessing individual or population immunity to the organism. Test results may suggest that an individual requires a booster dose of toxoid, or that health authorities should consider mass immunization or the introduction of additional booster doses in routine immunization schedules.

**Differential diagnosis** – other, more common causes of exudative pharyngitis should be considered, including streptococci, infectious mononucleosis, Vincent’s angina and viral respiratory infections.

**Contacts** – close (household and ‘kissing’) contacts of those with suspected diphtheria may be asymptomatic carriers of the organism or at significant risk of developing the disease. Throat swab samples should be taken from these individuals, and they should be followed closely pending the results of laboratory tests. Local public health authorities should always be informed of suspected cases, and may undertake tracing, swabbing and management of contacts (including booster or primary immunization and antimicrobial prophylaxis).

**Management**

The clinical outcome in diphtheria is improved by prompt initiation of specific therapy; therefore, physicians should act on clinical suspicion alone, after collecting appropriate specimens for laboratory diagnosis. There are three components of therapy (Figure 3):
- administration of diphtheria antitoxin (a hyperimmune antiserum produced in horses), to neutralize circulating toxin before it reaches target cells
- administration of antibiotics, to eradicate *C. diphtheriae* (penicillin or erythromycin is recommended)
- supportive management of complications, with particular attention to the airway and cardiac manifestations.

**Prevention**

Diphtheria is a preventable disease. All children should receive a full course of immunization. Adults may require booster doses every 10 years, though this is not commonly applied in practice. Travellers to epidemic or endemic areas should be offered a booster dose of diphtheria toxoid.

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**TREATMENT OF DIPHTHERIA**

**Diphtheria antitoxin (DAT)**

DAT can neutralize only free (non-cell-bound) toxin; therefore, early administration is essential.

The minimum therapeutic dose is unknown; recommendations are based on clinical experience and the assumption that duration of disease and extent of membrane formation indicate the toxin burden. As a guide, doses range from 10,000 units in tonsillar diphtheria of short duration, to 40,000–60,000 units in pharyngeal disease, to 100,000–150,000 units in extensive disease of 3 or more days’ duration.

Recommendations differ on the route of administration (intramuscular vs intravenous), but in severe disease at least some of the dose should be administered intravenously.

About 10% of patients exhibit hypersensitivity to horse proteins; anaphylaxis and serum sickness may result. Administration of antitoxin reduces mortality, however, and the risk of serum sickness is therefore considered acceptable. Patients should be questioned about known allergy and given a test dose of DAT, 1:10–1:100 intracutaneously, under controlled conditions with anti-anaphylactic and supportive measures immediately available. Those who exhibit an immediate reaction should be desensitized using gradually increasing doses of DAT.

Given these complexities and the fact that DAT is not widely available, advice should be sought from an infectious diseases physician.

**Antibiotic therapy**

Antibiotic therapy should be administered to eliminate *Corynebacterium diphtheriae*. This terminates production of new toxin, ameliorates local symptoms and prevents further spread to uninfected contacts. Penicillin, 0.6–1.2 g 6-hourly, or erythromycin, 0.5 g 6-hourly, is recommended. Antibiotic therapy should be continued for 14 days.

**General and supportive measures**

Patients should be nursed in strict isolation and should be attended by staff with documented immunization histories.

Early in the illness, respiratory and cardiac complications are the greatest threat. These can be minimized by close monitoring (including regular ECG) and early intervention (e.g. pacing for conduction disturbances, drugs for arrhythmias). Some experts recommend tracheostomy or intubation at an early stage, to ensure continued patency of a compromised or potentially compromised airway, and mechanical removal of any tracheobronchial membrane.

Before discharge, patients should be documented as culture-negative for *C. diphtheriae* by collection of three swabs at 24-hour intervals. They should also be given a booster dose of diphtheria toxoid; natural infection does not always confer immunity.

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**REFERENCE**


**FURTHER READING**


