# DIPHTHERIA

## Introduction

Diphtheria is an acute bacterial infection caused by toxigenic strains of Corynebacterium diphtheriae.

It is a serious disease because of its potential lethality.

Historically it was a major killer of young people, however with modern vaccination programs, it is now extremely rare in countries that have these programs.

There is a small potential it may be seen in immigrants who have not undergone vaccination.

### *History:*

The Corynebacterium diphtheria organism was discovered in 1884 by two German bacteriologists, Edwin Klebs (1834 – 1912) and Friedrich Loffler (1852 – 1915).

The first antitoxin to diphtheria was discovered in 1890 by Emil von Behring and Shibasaburo Kitasato. Behring received the **1901 Nobel Prize** for Physiology or Medicine for the discovery.


*One of the first bottles (1895) of diphtheria antitoxin produced at the Hygienic Laboratory, (National Institute of Health).*

Diphtheria vaccine was developed in the 19040s, which brought about a dramatic decline in the number of cases of diphtheria.

## Epidemiology

Diphtheria occurs worldwide and is more prevalent in winter months in temperate zones

**An epidemic occurred in the Russian Federation in 1990 which involved all of the countries of the former Soviet Union and Mongolia.**

**Disruption of vaccination programs following the collapse of the Soviet Union resulted in the re-emergence of diphtheria throughout the Newly Independent States. From 1991 to 1996, there were more than 140 000 cases and more than 4000 deaths. Cases also occurred in neighboring European countries and in visitors to the area. Mass vaccination eventually brought the epidemic under control and has declined after a peak in 1995. Over 70% of cases were aged 15 years or older.** [3]

Diphtheria is now a very rare infection in Australia but may occur in unimmunized people who are recent travelers, or their contacts.

The last reported case in Victoria occurred in 1991.

Importation of the infection from other affected countries remains a possibility in Australia with the potential to affect *unimmunized* children and adults as well as adults with *waning immunity* post-vaccination.

## Pathology

### *Organism*

- Corynebacterium diphtheriae, an aerobic, non-encapsulated, non-sporing, non-motile gram-positive bacillus
- The organisms are often arranged into small groups or pallisades.
- There are 3 biotypes, gravis, mitis and intermedius.

### *Pathophysiology*

Diphtheria is an acute bacterial infection caused by toxigenic strains of Corynebacterium diphtheriae.

Toxin production results when the bacteria are infected by a bacteriophage containing the diphtheria toxin gene (tox +). Nontoxigenic forms are designated tox-.

The toxin causes:

- Local tissue destruction and an extensive exudative membrane formation.

- Cardiac toxicity
- Neurotoxicity

Diphtheria (non-cutaneous) has an overall case fatality rate of 5-10% with higher rates in children under five years and adults over 40 years of age.

*Risk Factors:*

Risk factors for diphtheria include:

- Non-immunization is the greatest risk factor, (especially for age < 12 years)
- Travel to endemic areas or regions with current epidemics
- Large scale population movements, this may have been a contributing factor in the explosive spread of the epidemic in the Newly Independent States of the former Soviet Union, in the 1990s.
- Low socioeconomic status
- Overcrowded conditions, eg: homeless shelters, prisons.

## Transmission

- Transmission is by droplet spread from the respiratory tract.
- Rarely transmission may occur via contact with articles soiled with respiratory discharges.

## Incubation Period

- This is two to five days but may occasionally be longer.

## Reservoir

- Humans.
- Carriers are usually asymptomatic.

## Period of Communicability

- Transmission may occur as long as virulent bacilli are present in discharges.
- The time is variable but is usually less than two weeks, occasionally however it may be more than four weeks without antibiotics. Appropriate antibiotic therapy

quickly terminates the bacterial shedding. The disease is usually not highly contagious after 48 hours of antibiotic therapy.

- Rarely chronic carriers may shed organisms for six months or longer.

## Susceptibility & resistance

- Infants born of immune mothers have some passive immunity until about six months of age.

- Lifelong immunity is usually, *but not always*, acquired after disease or subclinical infection.

- A primary course of diphtheria toxoid vaccination provides long lasting, but not lifelong immunity. Vaccinated individuals may become colonised by C. diphtheriae in the nasopharynx while still being protected from clinical disease.

## Clinical Features

Diphtheria is primarily an infection that involves the upper respiratory tract, (tonsils, pharynx, nasal cavity and larynx).

1. The onset is usually insidious.

   Early symptoms include:

   - Fever

   - Sore throat

   - Non-specific constitutional symptoms, (headache, anorexia, malaise, lethargy, myalgias)

2. Progressively severe upper respiratory tract symptoms then develop:

   - The characteristic lesion of diphtehria is an **adherent greyish-white membrane** that first occurs on the tonsils, but may then spread up onto the palate and pharynx.

     Attempts to remove the membrane result in mucosal bleeding.

     **In severe cases it may continue to spread throughout the respiratory tree and result in respiratory obstruction and death.**

   - In severe cases pharyngeal disease may result in neck swelling due to gross lymphadenopathy, resulting in a characteristic “bull neck appearance”.

- Laryngeal diphtheria can present as a slowly progressive croup type picture which can result in death if the airway obstruction from airway obstruction.

3. Severe systemic stmptoms:

   Systemic absorption of the toxin may result in:

   **Cardiomyopathy**, (which may result in death)

   - **Myocarditis, leading to arrhythmias, conduction delays and heart failure and death.**

   **Neuropathy** or later neurological complications.

   - Cranial nerve lesions
   - Peripheral neuropathy

   Neuropathies usually resolve with supportive management.

*Uncommon manifestations include:*

- Non-toxigenic strains of C. diphtheriae rarely cause local disease but may cause an infective endocarditis.
- Cutaneous diphtheria presents with lesions of variable appearance but which may resemble impetigo.

## Investigations

*Blood tests:*

1. FBE
   - Leukocytosis is seen.
2. CRP
3. U&Es/ glucose
4. Blood cultures:
   - Positive blood cultures carry a worse prognosis.
5. Troponin I levels:
   - These may correlate with the severity of myocarditis.

6. Antibody levels: [3]

- Circulating levels of antitoxin are closely related to protection from diphtheria.
- Antitoxin levels of <0.01 IU are poorly protective, 0.01 to 0.1 IU are usually protective, and titres of >0.1 IU are associated with more certain and prolonged protection.

*Microbiology:*

- Take **throat and nasal** swabs for gram stain, microscopy, culture and sensitivity testing.
- Special media are required for culture, (Loeffler or tellurite) and if diphtheria is suspected then the lab should be informed of this.

*PCR:*

- There is a PCR test for detection of DNA sequences encoding the A subunit of the tox + strain.

*ECG:*

Look for evidence of:

- Myocardial injury, (ST changes)
- Conductions delays
- Arrhythmias

*Imaging:*

Soft tissue neck x-rays

- This may assist in evaluating any airway obstruction.

CXR:

- To look for lung involvement

CT scan neck:

- This will determine the degree of airway obstruction or local extension.

Echocardiography:

- To look for evidence of myocarditis or endocarditis.

## Management

1. Airway

    - Intubation or tracheotomy may be required as the first priority if the airway is compromised.

2. **Antitoxin:**

    - The mainstay of treatment is diphtheria antitoxin that neutralizes circulating toxin **prior to its entry into the cells.**

    - **Antitoxin should be given as soon as the diagnosis is suspected, and without waiting for laboratory confirmation, in order to neutralize toxin before it enters the cells.**

    - Diphtheria antitoxin is a horse-derived hyperimmune antiserum. Its use can therefore be associated with acute allergic reactions, and hence it is best given in a hospital setting under expert guidance.

    - The exact dose and route (IM or IV) of antitoxin will depend on how unwell the patient is. **Specialist advice must guide this.**

    - Patients must be tested for hypersensitivity prior to administration. Co-administration of antitoxin with corticosteroid, adrenaline, and antihistamine cover may be recommended for patients with hypersensitivity to antitoxin.

    - **Supplies of antitoxin can be obtained from CSL.**

3. Antibiotics:

    - Antibiotics will hasten recovery and help prevent the spread of organisms to others.

    - Parenteral antibiotic treatment is can be either **erythromycin or penicillin.**

    - These can be substituted for by equivalent oral formulations once the patient can swallow comfortably. These should be continued to complete a total of 14 days of treatment.

4. Isolation:

- Suspected cases should be isolated and universal precautions taken to limit the number of possible contacts.

*Contacts:*

- The Health Department, will investigate and follow-up possible contacts.
- Household and other close contacts will need to be traced, and treated with antibiotics and vaccination where appropriate.
- Contacts of proven cases should be given oral penicillin or erythromycin.

*Vaccination:*

- Diphtheria vaccination is part of the Australian Standard Vaccination Schedule.
- **See latest edition of the Austrlaian Immunization handbook for full vaccination details.**

*Notification:*

- Diphtheria (Group A disease) must be notified immediately by telephone (**1300651160**) or fax followed by online or written notification within five days.

*School exclusion:*

School exclusion is relevant for both cases *and* contacts:

- Cases should be excluded until a medical certificate of recovery is received following at least two negative throat swabs. The first should be 24 hours or more after finishing a course of antibiotics and the second 48 hours later.
- Contacts should be excluded until cleared to return by the Department of Human Services.

*References*


1. The Bluebook Website, January 2008

2. Antibiotic Therapeutic Guidelines, 13th ed 2006

3. Australian Immunization Handbook 9th ed 2008


Dr J.Hayes
September 2008