

Diphtheria

Diphtheria	3
General	3
Transmission	5
Clinical aspects	6
Diagnosis	6
Differential diagnosis	7
Treatment	7
Prevention	7

Diphtheria

Summary

- Caused by the gram-positive bacillus *Corynebacterium diphtheriae*
- Infection leads to respiratory or cutaneous disease or an asymptomatic carrier state
- The pseudomembranes in combination with neck swelling can cause life threatening croup
- Diagnosis in most low-resource settings is clinical
- Treatment with erythromycin or penicillin
- Antitoxin and airway protection in severe cases
- Worldwide vaccination lead to a significant decrease in diphtheria cases

General

Diphtheria is an infectious diseases caused by the gram-positive bacillus *Corynebacterium diphtheriae*. Symptoms range from mild to severe. Whereas in the 1980s about 100,000 cases were reported worldwide, in 2015 this number had dropped to 4,500 cases with >80 percent vaccination rates worldwide. Regions mostly affected are sub-Saharan Africa, the Indian subcontinent and Indonesia where mostly children are affected. In 2015, 2,100 deaths were reported, down from 8,000 in 1990. The disease has become rare in high-income countries thanks to widespread vaccination but re-emergence is a threat when vaccination rates decrease. Diphtheria death rate in those diagnosed varies from 5% to 10%.

There are four types of *C. diphtheria*: *gravis*, *intermedius*, *mitis* and *belfanti*. All four can cause Diphtheria, although *mitis* strains cause less severe disease. Symptoms are caused by bacterium's toxin. In rare occasions toxigenic strains of other *Corynebacterium* species (*C. ulcerans*, *C. haemolyticum*, *C. pseudotuberculosis*) evoke respiratory symptoms.

The name comes from the Greek word “diphthera” which means “leather” referring to the appearance of the pseudomembrane in the throat.

History of Diphtheria (Source: Wikipedia, <https://en.wikipedia.org/wiki/Diphtheria>)

The disease was first described in the 5th century BC by Hippocrates

In 1613, Spain experienced an epidemic of diphtheria. The year is known as El Año de los

Garrotillos (The Year of Strangulations) in the history of Spain.

Before 1826, diphtheria was known by different names across the world. In England, it was known as Boulogne sore throat, as it spread from France. In 1826, Pierre Bretonneau gave the disease the name diphthérite (from Greek diphthera “leather”) describing the appearance of pseudomembrane in the throat.

In 1878, Queen Victoria’s daughter Princess Alice and her family became infected with diphtheria, causing two deaths, Princess Marie of Hesse and by Rhine and Princess Alice herself.

In 1883, Edwin Klebs identified the bacterium causing diphtheria <https://en.wikipedia.org/wiki/Diphtheria> - cite_note-34 and named it Klebs-Loeffler bacterium. The club shape of this bacterium helped Edwin to differentiate it from other bacteria. Over the period of time, it was called Microsporon diphtheriticum, Bacillus diphtheriae, and Mycobacterium diphtheriae. Current nomenclature is Corynebacterium diphtheriae. Friedrich Loeffler was the first person to cultivate C. diphtheriae in 1884. He used Koch’s postulates to prove association between C. diphtheriae and diphtheria. He also showed that the bacillus produces an exotoxin.

Joseph P. O’Dwyer introduced the O’Dwyer tube for laryngeal intubation in patients with an obstructed larynx in 1885. It soon replaced tracheostomy as the emergency diphtheric intubation method.

In 1888, Emile Roux and Alexandre Yersin showed that a substance produced by C. diphtheriae caused symptoms of diphtheria in animals.

In 1890, Shibasaburo Kitasato and Emil von Behring immunized guinea pigs with heat-treated diphtheria toxin. They also immunized goats and horses in the same way and showed that an “antitoxin” made from serum of immunized animals could cure the disease in non-immunized animals. Behring used this antitoxin (now known to consist of antibodies that neutralize the toxin produced by C. diphtheriae) for human trials in 1891, but they were unsuccessful. Successful treatment of human patients with horse-derived antitoxin began in 1894, after production and quantification of antitoxin had been optimized. Von Behring won the first Nobel Prize in medicine in 1901 for his work on diphtheria.

In 1895, H. K. Mulford Company of Philadelphia started production and testing of diphtheria antitoxin in the United States Park and Biggs described the method for producing serum from horses for use in diphtheria treatment.

In 1897, Paul Ehrlich developed a standardized unit of measure for diphtheria antitoxin. This was the first ever standardization of a biological product, and played an important role in future developmental work on sera and vaccines.

In 1901, 10 of 11 inoculated St. Louis children died from contaminated diphtheria antitoxin. The horse from which the antitoxin was derived died of tetanus. This incident, coupled with a tetanus

outbreak in Camden, New Jersey, played an important part in initiating federal regulation of biologic products.

In the 1920s, each year an estimated 100,000 to 200,000 diphtheria cases and 13,000 to 15,000 deaths occurred in the United States. Children represented a large majority of these cases and fatalities. One of the most infamous outbreaks of diphtheria was in Nome, Alaska; the “Great Race of Mercy” to deliver diphtheria antitoxin is now celebrated by the Iditarod Trail Sled Dog Race. In 1926, Alexander Thomas Glenny increased the effectiveness of diphtheria toxoid (a modified version of the toxin used for vaccination) by treating it with aluminium salts. Vaccination with toxoid was not widely used until the early 1930s.

In 1943, diphtheria outbreaks accompanied war and disruption in Europe. The 1 million cases in Europe resulted in 50,000 deaths.

In 1974, the World Health Organization included DPT vaccine in their Expanded Programme on Immunization for developing countries

About a million cases a year are believed to have occurred before the 1980s

Transmission

Diphtheria is airborne and spreads between people by coughing and sneezing. In rare occasions, direct contact with diphtheria skin lesions can transmit the bacteria. Indirect transmission is possible when an infected person touches an object on which the bacteria can remain viable. Asymptomatic carriers exist and they can still spread the infection to others. Immunity from past infection or vaccination does not prevent carriage of the bacterium.

Diphtheria toxin

C. diphtheria produces an exotoxin when it is infected with a bacteriophage that integrates the toxin-encoding gene (*tox+*) into the bacteria. Diphtheria toxin is composed of two peptide chains: fragment A and fragment B. Fragment B facilitates toxin entry into host cells by binding the heparin-binding EGF-like growth factor on the cell membrane. Once inside the cell's endosome, a trypsin-like protease splits the toxin in the A and B fragments. The low pH in the endosome causes fragment B to create pores in the endosome membrane through which fragment A can enter the cytoplasm. Fragment A catalyses ADP-ribosylation of elongation factor EF-2, a protein that moves tRNA from the A-site to the P-site of the ribosome during the translation step in protein synthesis. The final result is a disturbed protein synthesis leading to cell death.

Clinical aspects

The incubation period is usually two to five days and the disease starts with a gradual onset of sore throat with pharyngeal erythema and fever. In more severe cases diphtheria destroys the respiratory tract tissues with dead tissues forming a thick, grey, friable and tightly adhering coating in the throat. This is called a pseudomembrane which is composed of necrotic fibrin, white- and red blood cells, epithelial cells and bacteria. The pseudomembrane may expand from the nose to the tonsils, the throat up to the bronchial tree. This can lead to dysphagia and can obstruct the airways provoking hoarseness, stridor and sometimes suffocation when membranes are aspirated. This can be exacerbated with extreme neck swelling (“bull neck”) due to enlarged lymph nodes causing external pressure on the airways. This clinical picture is referred to as “diphtheritic croup” or “true croup” (= laryngotracheobronchitis caused by diphtheria). Children who have smaller airways are more vulnerable to the complications of diphtheritic croup. Nowadays, croup is mostly related to viral infections causing milder respiratory symptoms.

Diphtheria can be complicated by myocarditis (in two-thirds of severe cases) and nerve inflammation (in up to 75 percent of severe diphtheria). Paralysis of the soft palate and posterior pharyngeal wall can occur, as well as cranial nerve paralysis. Cardiac and neurological symptoms often arise from the moment respiratory symptoms are improving. A peripheral polyneuropathy can develop weeks or months after the acute illness.

Cutaneous diphtheria presents as chronic, non-healing ulcers with a grey membrane. The infection is often preceded by local trauma. Epidemics of cutaneous diphtheria have occurred in populations living in poor hygienic conditions. The ulcers can serve as a reservoir from which the infection spreads to others.

Diagnosis

Diagnosis is often made considering the setting and clinical manifestations in a non-vaccinated person. Positive cultures confirm the diagnosis, but the need for special culture media (Löffler’s or Tindale’s media), the need for appropriate transport media and the necessity of quick inoculation, make the confirmation challenging, even in high-resource settings. Toxin detection with PCR is possible and confirms that the strain is toxicogenic.

A probable case is a clinically compatible case that is not laboratory-confirmed nor epidemiologically linked to a confirmed case. A confirmed case is a clinically compatible case that is laboratory confirmed or epidemiologically linked to a laboratory-confirmed case. It is important that the antitoxin

and antibiotics are administered prior to confirmation when diphtheritic croup is suspected. Cases of diphtheria should be reported to the World Health Organization (WHO).

Differential diagnosis

Several diseases can give a clinical picture that can resemble pharyngitis with pseudomembranes: infectious mononucleosis, group A streptococcal tonsillopharyngitis, epiglottitis, viral pharyngitis, Vincent's angina (= acute necrotizing ulcerative gingivitis), oral candidiasis, pertussis (100-day cough).

Treatment

When diphtheria is suspected, prompt initiation of antibiotics is needed since severe untreated diphtheria has a mortality rate of 40% to 50%. Erythromycin (500 mg 4 times daily, 14 days) and penicillin G (300,000 IU IM daily for patients < 10 kg and 600,000 IU IM daily for patients > 10 kg) followed by penicillin V (250 mg 4 times daily, oral) for a total of 14 days are the antibiotics of choice. In severe diphtheria with pseudomembranes or cardiac involvement, diphtheria antitoxin is indicated. These antibodies are produced in horses that have been challenged with diphtheria toxin. The antitoxin does not neutralize toxin that is already bound to tissues, hence a delay in administration increases mortality rates. In about 10 percent of patients receiving antitoxin hypersensitivity or serum sickness arises.

In case of (threatening) respiratory failure airway protection with intubation is necessary. This procedure can be difficult if there is extensive throat oedema and mucosal friability. There is a risk of dislodging the pseudomembranes into the bronchi. In rare occasions a tracheotomy is needed. After recovery, vaccination is still needed since pharyngeal infections do not protect against future infections. Skin infections are an exception since they evoke a strong antibody response.

Prevention

An effective vaccine exists with different available formulations. In childhood, three or four doses are given along with tetanus and pertussis in a penta-, sexta- or heptavalent vaccine. A booster vaccination, together with tetanus, is recommended every ten years.

Close contacts can be given prophylaxis with a single dose of penicillin G benzathine (1.200.000 IU IM) or oral erythromycin 500 mg 4 times daily for 1 week.