

## Review on the Pathology of Diphtheria

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### ABSTRACT :-

Diphtheria is a vaccine-preventable, bacterial communicable disease caused by toxin-producing strains of *Corynebacterium diphtheriae*. Transmission is person-to-person via respiratory droplets or by close contact with a skin lesion or discharge. The incubation period is usually 1 to 5 days, and the disease is characterized by the presence of a firmly adherent, tough pseudo-membrane over the mucous membrane of the upper respiratory tract or in skin ulcers. Symptoms and manifestations include sore throat of variable severity, difficulty in swallowing, and mild fever; life-threatening airway obstruction; and toxin-related systemic complications (including myocarditis and polyneuropathy of cranial and peripheral nerves). Early diagnosis and treatment with diphtheria antitoxin and antibiotics prevent complications and death. Fatality rate ranges between 5% and 10%, even if properly treated, and can exceed 50% among untreated patients. For prevention, a primary series of combined diphtheria-tetanus-pertussis vaccines are recommended for all infants, with booster vaccinations being administered to older children and adults

**Topic:** lung, *Corynebacterium diphtheriae*; Cutaneous diphtheria; Cutaneous ulcers; Diphtheria, Adult ,outbreak, critical vaccination threshold, reproductive number, systematic review

### I. INTRODUCTION :-

*Corynebacterium diphtheria* is the causative agent of diphtheria. *Corynebacterium diphtheria* is an unencapsulated, immobile gram-positive rod resembling a club. A predisposing factor for this disease is lack of vaccination in childhood. It mainly affects the respiratory system, the skin system or manifests itself in the asymptomatic state of the carrier. The only host of this organism is humans and it is found in the upper respiratory tract. The pathogens are transmitted through droplets suspended in the air.[1] Based on colony morphology and biochemical reactions, *C. diphtheriae* is divided into four biovars or biotypes: Gravis, Mitis, Intermedius and Belfanti. Among these, Belfanti is described as extremely poisonous.[2] Diphtheria has a high mortality rate (5-17%) in the unvaccinated population, even among those who receive appropriate care and treatment.[3] A trivalent diphtheria-tetanus-pertussis (DPT) vaccine is available and may protect against diphtheria in children. Booster doses of Toxoid (inactivated toxin) are recommended for adults[4] Diphtheria is an acute infectious disease caused by toxin-producing strains of *Corynebacterium diphtheriae*, a gram-positive bacillus. Two other zoonotic species of *Corynebacteria*, *Corynebacterium ulcerans* and *Corynebacterium pseudotuberculosis*, can also produce diphtheria toxin.[5] In 1990, a widespread diphtheria epidemic occurred in the former Union of Soviet Socialist Republics (USSR). This epidemic was characterized by a high incidence of adult infections and the spread of the disease.

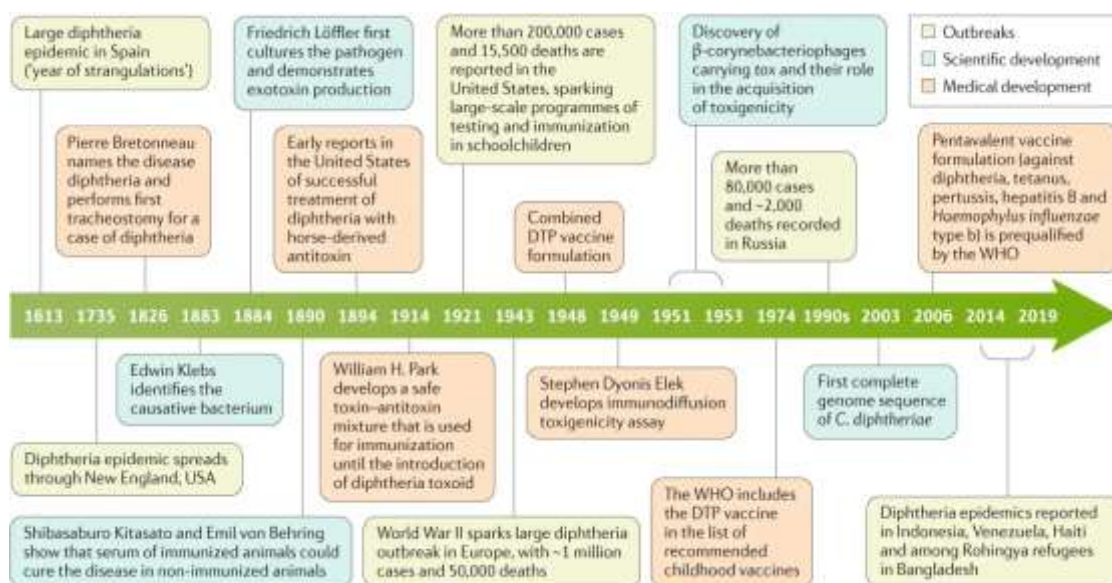


Fig. 1: Milestones in the history of diphtheria

Major milestones in the history of diphtheria, highlighting major epidemics and scientific and medical developments. Major scientific breakthroughs include the discovery of the  $\beta$ -Corynebacteriophage carrying the toxin gene99 and the complete sequencing of the Corynebacterium diphtheriae genome234. DPT, diphtheria, tetanus and whooping cough.

### History And Physical :-

Diphtheria initially manifests itself through non-specific flu-like symptoms such as fever, sore throat and swollen cervical lymph nodes. In general, the average incubation period is 2 to 5 days (range 1 to 10 days). In most cases, the patient's medical history indicates travel from an endemic area where there is no record of vaccination. In these cases, the healthcare professional should know the main characteristics of the disease, namely: a thick, gray, adherent pseudomembrane on the tonsils and throat. Respiratory tract involvement is a common feature of this disease. It begins with mild erythema, which then develops into a confluent pseudomembrane. The pseudomembrane consists of red blood cells, white blood cells, remnants of dead cells and organisms. This pseudomembrane often bleeds when you try to scrape it off an adjacent surface. Common symptoms of diphtheria include mild fever, sore throat, malaise, swollen cervical lymph nodes, headache and difficulty swallowing. In a study by Pancharoen C et al. Pimples, followed by fever and upper respiratory tract infections were

the most common symptoms of diphtheria. In addition, systemic damage occurs when the toxin enters the lymphatic and blood systems after local tissue destruction.[6]

### Epidemiology of diphtheria :-

Widespread vaccination has significantly reduced the global incidence of diphtheria; However, the disease remains endemic in many countries, although precise documentation of its incidence in these countries is limited. The implementation of the DTP vaccination program in several countries has reduced the number of diphtheria cases in children. For example, in the first 13 years of the mass vaccination period (1919–1931), the number of registered diphtheria cases among the Dutch fell by 82.4%. Timely vaccination against has significant public health implications.[7] A study of the timeliness of scheduled vaccine doses in urban Indigenous Australian children found that 72% of children received their first dose of DTP vaccine (at 2 months of age) on time, but only 59% of children received the first dose of DTP vaccine. DTP vaccine (at 2 months of age). 2 months) as expected, but only 59% received the third dose (DTP-3 at 6 months) as expected15. In endemic areas, the incidence of diphtheria in hospitals remains high (27.3%)16 and the overall mortality rate of cases is between 20 and 31.[8]

The 2023 diphtheria outbreak in Nigeria is a cause for concern. As of February 2023, 216 cases and 40 deaths have been reported in four

states. The outbreak is said to have started in Kano State in late December, but cases have also been reported in Lagos, Osun and other states, Yobe says. Reports included Kano with 172 of 216 cases (91.0%), Katsina with 9 cases (4.8%) and Lagos with 8 cases (4.8%).2%). Of the suspected cases reported, 111 cases were confirmed, accounting for 42.1% of the total.[9] Of these confirmed cases, 8 were laboratory confirmed and 103 were considered clinically consistent with the disease. In addition, 18 cases (7.1%) were rejected as unrelated, 40 cases (15.3%) were awaiting classification, and 84 cases (33.2%) had unknown status. It should be noted that the majority of confirmed cases (91.9%) occurred in the age group of 2 to 14 years. Unfortunately, a total of 22 deaths were reported among confirmed cases, giving a case fatality rate (CFR) of 19.8%. Of note, only 12 of the 111 confirmed cases (10.8%) received full vaccination with diphtheria toxin vaccine. All confirmed cases were reported from nine local government areas (LGAs) of Kano State, with four deaths among the confirmed cases, giving a fatality rate of 7.4%. [10]

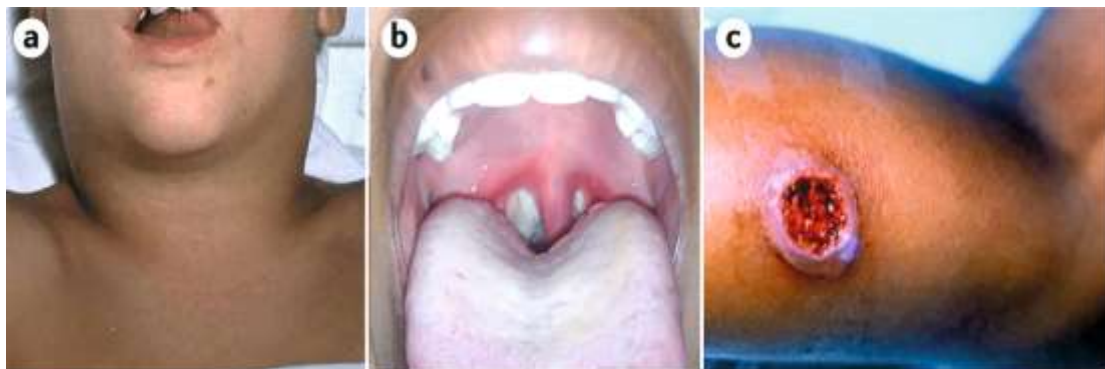
#### **Clinical Features :-**

The incubation period of diphtheria is 2 to 5 days, with a range of 1 to 10 days. The disease can affect almost all mucous membranes. In untreated individuals, microorganisms may appear in secretions and lesions 2 to 6 weeks after

infection. For clinical purposes, diphtheria should be classified according to its anatomical localization: respiratory diseases (throat, tonsils, larynx, nose) and non-respiratory diseases (skin and other mucous membranes).[11]

#### **Diagnosis :-**

The time between infection with *C. diphtheriae* and the onset of symptoms can be 1 to 10 days (usually 2 to 5 days)<sup>5</sup>. People infected with *C. diphtheriae* remain contagious for up to four weeks, even if they do not show symptoms<sup>15</sup>. The disease is transmitted through direct contact with skin lesions, direct contact, or inhalation of air secretions from the mouth or respiratory tract. The infection can also be transmitted through contact with contaminated objects. Lack of vaccination, weakened immune system, history of atopic dermatitis (eczema), congestion and/or unsanitary living conditions, and travel to areas where the disease is endemic are pragmatic risk factors for diphtheria<sup>12</sup>. Early diagnosis of diphtheria is based on typical clinical symptoms (Figure 4), allowing initial treatment to be initiated quickly. The clinical diagnosis of diphtheria is generally based on the presence of pseudomembranous pharyngitis. Other common symptoms of acute diphtheria are swollen lymph nodes in the neck (bull neck), inflammation of the heart muscle and inflammation of the nerves.<sup>13</sup>



a. Characteristic bull neck caused by enlarged lymph nodes. B. Thick pseudomembrane in the posterior pharynx. The pseudomembrane is a layer of bacteria and debris from necrosis of the surrounding tissues due to diphtheria toxin. C. Cutaneous lesion caused by *Corynebacterium diphtheriae*.

#### **Complications :-**

#### **Treatment And Management :-**

The most common complications are myocarditis and neuritis. Death occurs in 5 to 10% of cases. Serious complications include pseudomembrane formation in the upper

respiratory tract, leading to airway obstruction and requiring immediate mechanical ventilation and intubation.

**Cardiac complications:-**

Presents as myocard it is accompanied by arrhythmia with 1st,2nd or 3rddegree heart block and circulatory collapse. ECG changes noted in these patients were P-R interval prolongation and ST/T wave changes.[14]

**Neurological complications :-**

Neurological complications of diphtheria include nerve weakness or paralysis, especially involving the cranial nerves and also affecting the nerves of the limbs, leading to muscle weakness in the extremities. limbs Involvement of the pharyngeal muscles and soft palate leads to reflux of food and liquid through the nose. In rare cases, encephalitis as a complication of diphtheria is observed in children.

The two most important treatments for diphtheria are antitoxins and antibiotics. In addition to these two factors, the patient must be evaluated for any respiratory and cardiovascular instability. When a patient is suspected of having diphtheria, antitoxin must be administered immediately on clinical grounds without waiting for confirmatory testing. Suspected cases must be kept in quarantine and appropriate droplet prevention measures implemented. Additionally, the patient should be assessed for respiratory distress and the correct airway should be secured if necessary.Cardiac monitoring is also an essential part of early care.[15]

**Antitoxin therapy (DAT) :-** Use as soon as possible

1. DAT is a highly effective equine serum product and the gold standard for the treatment of diphtheria.
2. DAT should be given immediately in cases of probable respiratory diphtheria (sore throat, low-grade fever, and adhesions on the tonsils, pharynx, or nose) based on clinical diagnosis. Don't wait for a lab diagnosis.
3. Diphtheria toxin that has entered host cells is not affected by DAT. Therefore, to reduce complications and mortality, DAT should be administered as soon as possible after disease onset (see Appendix D)
4. Due to the low risk of serious allergic reactions to horse serum ( 0.6% anaphylactic shock), should be carried out for sensitivity testing (I.D. Besredka test) for all candidate patients.
5. DAT must be administered in a closely monitored environment and with appropriate medical interventions available if necessary.
- 6.Pregnant women should not use DAT.
7. The recommended amount of antitoxin varies with higher recommended amounts for those with pseudomembranous extension, neck swelling, systemic signs, and a longer interval from onset. Dosage for children and adults is the same. Do not repeat dosage.[16]

**If limited availability, then use lower dose range.**

Severity of diphtheria	Dosage for adults and children
Laryngeal or pharyngeal of 2 days duration	20,000-40,000 IU
Nasopharyngeal disease	40,000-60,000 IU
Extensive disease of 3 or more days of duration or any patient with diffuse swelling of the neck (respiratory distress, hemodynamic instability)	80,000-100,000 IU

**Antibiotic Treatment :-**

The antibiotic of choice for diphtheria is erythromycin or penicillin G. Antibiotics should be started as soon as possible to kill the bacteria. This helps limit the release of toxins into the system, speeds up the patient's recovery period, and

prevents the spread of infection to close contacts. Additionally, in cases of antibiotic resistance, linezolid or vancomycin can be used.

### **Vaccination :-**

Diphtheria vaccine is available in a toxified form. Anatoxin is a denatured protein (a bacterial toxin) that has an intact receptor binding site and is capable of producing antibodies. Typically, the diphtheria vaccine is given in combination with other tetanus and pertussis vaccines. Some forms of diphtheria conjugate vaccine are:

- DTaP: includes vaccines against diphtheria, tetanus and pertussis.
- Tdap: Includes tetanus, diphtheria, and pertussis vaccinations.
- DT: This involves diphtheria and tetanus vaccination.
- TD: This involves vaccination against tetanus and diphtheria.

Diphtheria vaccination prevents toxin-related symptoms but does not prevent colonization with invasive NTCDs and *Corynebacter* spp. in the host, this may pose significant health risks to unvaccinated individuals and does not provide protection against asymptomatic transmission of *C. diphtheria*. [17]

### **Consultation :-**

- Infectious disease centers: Infectious disease centers should be notified immediately when there is a suspected case.
- Cardiovascular: In case of cardiac complications, a cardiologist should be consulted to assess the severity of the disease and take necessary measures in case of arrhythmia and heart block.
- Intensive care unit: Patients with severe illness and sepsis should be admitted to the intensive care unit and managed appropriately. [18]

### **Outlook:-**

#### **Strengthening of surveillance and diagnosis**

Diphtheria surveillance is important not only to control the disease burden but also to identify modes of transmission, detect outbreaks and develop appropriate management policies, including vaccination. Diphtheria continues to be one of the major infectious diseases in countries with inadequate implementation of DPT vaccination programs and is a threat to public health in developed countries due to its emergence of NTCD and species other than *C. diphtheria*. NTCD gravis biotype is increasingly isolated frequently in association with endocarditis and pharyngitis. The involvement of infectious disease experts in this case is equally important. Nurses are

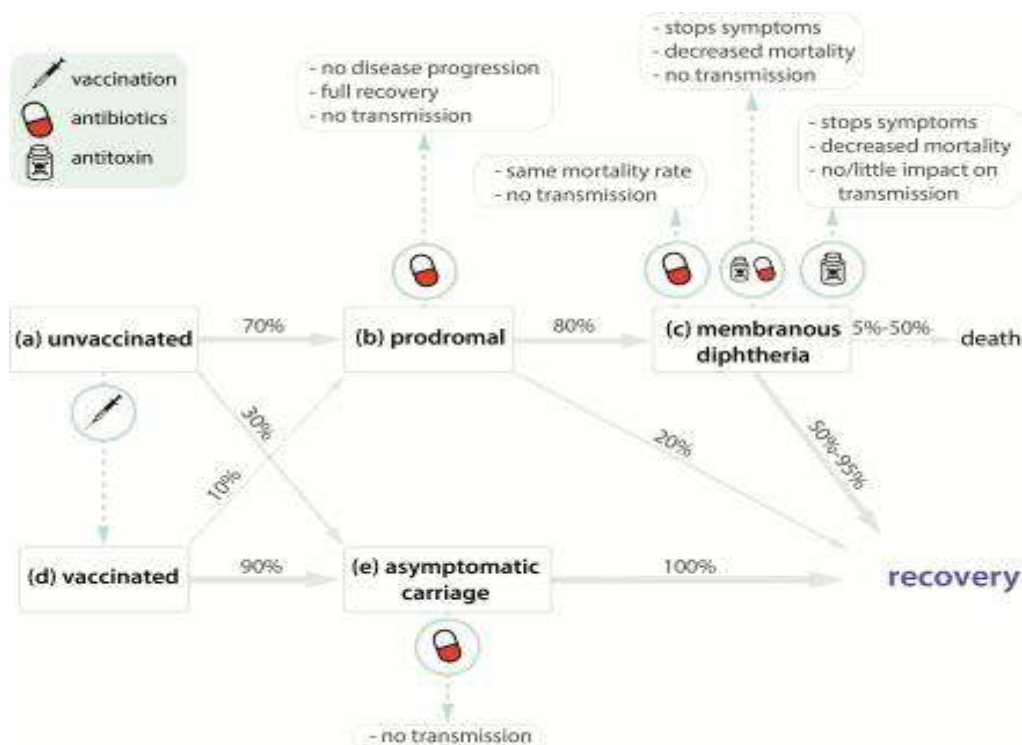
also essential members of the interpreter team because they will monitor the patient's vital signs. Radiologists and pathologists also play an important role in helping providers make an accurate diagnosis. [19] Preventive medicine professionals can significantly reduce diphtheria outbreaks by raising awareness of the situation through vaccination programs. Early intervention by a cardiologist and neurologist in case may have helped control the complication if it was observed during the course of the disease. Public health experts and international organizations must be informed and informed of any suspected outbreak. The outcome of diphtheria depends on early diagnosis and treatment. A well-trained healthcare team can help achieve this goal and prevent any disease-related morbidity and mortality. However, to improve outcomes, prompt consultation with a multidisciplinary team of specialists is recommended. [20]

### **II. CONCLUSION :-**

This study identified several risk factors for diphtheria. We found moderate to low quality evidence that inadequate vaccination, exposure to people with skin lesions, and low knowledge about diphtheria increase the risk of disease. Exposure to a case of diphtheria Most factors identified in this review are difficult to change. Therefore, to achieve significant reductions in diphtheria incidence, countries will need sustained efforts to strengthen laboratory capacity, improve vaccination coverage, and increase public knowledge. people about this disease as well as prevention methods, with the support of medical staff. Although these interventions have been advocated in the past, the current resurgence of diphtheria makes their implementation more important than ever.

### **III. RESULT :-**

Diphtheria is caused by infection with the toxigenic bacteria *Corynebacter diphtheriae* or, more rarely, *Corynebacteria Ulcerans*, with the disease resulting from exotoxins produced by the bacilli. Of the two common forms of diphtheria (respiratory and cutaneous), respiratory diphtheria carries a significantly higher risk of death and is the only form that is reportable to the World Health Organization (WHO). Respiratory tract infections often progress from prodromal symptoms to inflammation of the pharynx, tonsils, larynx, or larynx.



Natural history of diphtheria with prevention and treatment interventions. Of the unvaccinated individuals who become infected with toxigenic *Corynebacterium diphtheriae* (a), 70% develop prodromal symptoms (b), whereas 30% become asymptomatic carriers (e). Eighty percent of individuals with nonspecific symptoms develop membranous diphtheria (c) whereas 20% recover. Of those with membranous diphtheria, 5%–50% of individuals die of complications, and 50%–95% recover. Vaccinated individuals can be colonized; however, the toxoid vaccine provides protection against symptoms. Thus, 90% of fully vaccinated individuals become asymptomatic carriers (e), whereas only 10% develop prodromal symptoms (b). Vaccinated individuals who develop nonspecific symptoms have lower risk of severe disease and death compared with unvaccinated individuals and are more likely to recover directly from prodromal symptoms, although they can develop severe complications (c) and die.

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