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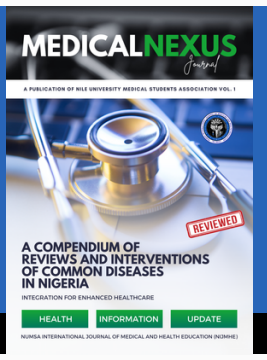

Diphtheria: A Review for Medical Student

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Abstract

Diphtheria is a highly contagious and potentially fatal infection caused by Corynebacterium diphtheriae, primarily transmitted through respiratory droplets and, less commonly, contaminated fomites or skin contact. Despite the availability of an effective vaccine, diphtheria persists as a global health challenge, especially in regions with poor vaccination coverage and disrupted healthcare systems. This review highlights the epidemiology, aetiology, pathophysiology, clinical presentation, diagnosis, and management of diphtheria, with a particular focus on recent outbreaks in Nigeria and other conflict-affected regions. The diphtheria toxin plays a central role in disease progression, causing local airway obstruction and systemic complications such as myocarditis, neuritis, and renal failure. Treatment relies on the prompt administration of diphtheria antitoxin, antibiotic therapy, and supportive care. Prevention through immunization remains the cornerstone of control, yet challenges such as vaccine hesitancy, inadequate healthcare access, and limited availability of antitoxin complicate eradication efforts. Strengthening vaccination programs, enhancing surveillance, and addressing systemic barriers are essential for reducing the burden of diphtheria and preventing future outbreaks.

Keywords: : *Diphtheria, Corynebacterium diphtheriae, diphtheria toxin; respiratory infection, myocarditis; neuritis; vaccination*

INTRODUCTION

Diphtheria is a serious, contagious disease caused by toxin-producing strains of the bacteria Corynebacterium diphtheriae. This bacteria primarily spreads through respiratory droplets when an infected person coughs, sneezes, or talks. Diphtheria can also spread through contact with objects contaminated by the bacteria, such as utensils or tissues. Importantly, not everyone who contracts the bacteria shows symptoms; some can be asymptomatic carriers who continue to spread the infection for weeks without knowing it.

Before the introduction of the diphtheria vaccine in the 1930s, the disease was widespread and a leading cause of childhood mortality worldwide. The diphtheria toxin can cause damage to the respiratory tract, but its effects can extend throughout the body, leading to complications like myocarditis (inflammation of the heart muscle), neuritis (nerve damage), and kidney failure. Early symptoms of diphtheria include fever, sore throat, and swelling of the neck glands, often referred to as "bull neck." The infection can also cause a thick, gray pseudomembrane to form in the throat, which can obstruct the airway.

Vaccination is the most effective way to prevent diphtheria. The vaccine contains a diphtheria toxoid (an inactivated form of the toxin), which stimulates the immune system to produce protective antibodies. Despite the availability of a safe and effective vaccine, recent outbreaks have occurred in regions where vaccination rates have declined, highlighting the ongoing need for immunization programs.

EPIDEMIOLOGY

Diphtheria was once a significant cause of illness and death in children before vaccines were developed. The widespread introduction of the diphtheria vaccine has greatly reduced the number of cases globally, particularly in high-income countries. However, the disease continues to pose a threat in parts of the world with inadequate vaccination coverage.

GLOBAL PERSPECTIVE

According to the World Health Organization (WHO), diphtheria continues to occur sporadically in various parts of the world, particularly in regions with low vaccine coverage or disruptions in healthcare systems. Outbreaks have been documented in parts of Southeast Asia, Eastern Europe, and Africa.

The most significant diphtheria outbreak in recent decades occurred in the Newly Independent States (NIS) of the former Soviet Union from 1990 to 1995, following the dissolution of the Soviet Union. This epidemic caused more than 157,000 cases and 5,000 deaths, primarily affecting older adults who had not received booster vaccinations. The epidemic was largely attributed to interruptions in vaccination programs and economic instability during this period.

Smaller outbreaks have been reported in various parts of the world:

- **India**: Diphtheria remains endemic in some areas, particularly in rural and underserved regions where vaccination rates are lower. In 2017, India reported more than 3,000 cases, underscoring the ongoing public health threat in the region.
- **Yemen**: In 2017, Yemen experienced a significant diphtheria outbreak amid the country's ongoing civil war. As of 2020, over 3,000 cases were reported, with more than 180 deaths. The conflict severely hampered vaccination efforts, leading to the spread of the disease.
- **United States:** While diphtheria is rare in the U.S. due to high vaccination coverage, isolated cases have been reported in recent years, primarily linked to international travel or unvaccinated individuals.

EPIDEMIOLOGY IN NIGERIA

Nigeria has experienced periodic outbreaks of diphtheria, with a notable increase in cases since June 2023. Between June and August 2023, Nigeria reported 5,898 suspected cases from 59 Local Government Areas (LGAs) across 11 states, with Kano state being the epicenter of the outbreak. The majority of cases have been linked to unvaccinated or partially vaccinated individuals, highlighting gaps in vaccine coverage.

The WHO has classified Nigeria’s diphtheria outbreak as a high-risk event at the national level, though the risk to neighboring countries remains low. Public health measures, including mass vaccination campaigns, enhanced surveillance, and case management, are ongoing efforts coordinated by the Nigeria Centre for Disease Control (NCDC) in collaboration with WHO and other international partners.

AETIOLOGY

Diphtheria is caused by the bacterium Corynebacterium diphtheriae, which can infect the respiratory tract, skin, or other body tissues. The bacteria release a potent exotoxin, which is responsible for the serious complications of the disease. This toxin inhibits protein synthesis in cells, leading to cell death and tissue damage.

MODES OF TRANSMISSION

- **Respiratory Droplets**: The primary mode of transmission is through airborne droplets expelled when an infected person coughs, sneezes, or talks.
- **Fomites**: Diphtheria can also be spread through contact with objects contaminated by respiratory secretions, such as shared utensils, tissues, or cups.
- **Cutaneous Diphtheria**: Skin infections can occur, especially in tropical climates or in people with poor hygiene. Cutaneous diphtheria is transmitted through contact with infected skin lesions or open wounds.

CARRIERS AND DISEASE SPREAD

Even individuals who do not show symptoms of diphtheria can carry the bacteria and transmit the infection to others. Asymptomatic carriers can continue to shed the bacteria for up to six weeks, making early identification and isolation of carriers crucial in outbreak settings.

PATHOPHYSIOLOGY

The virulence of Corynebacterium diphtheriae lies in its ability to produce a powerful exotoxin. Once the bacteria colonize the respiratory tract, they adhere to the mucosal lining and release the diphtheria toxin. This toxin consists of two fragments:

- **Fragment B**: Binds to the surface of susceptible host cells and facilitates the entry of the toxin into the cell.
- **Fragment A**: Once inside the cell, this fragment inhibits elongation factor 2 (eEF2), which is crucial for protein synthesis. This inhibition results in the disruption of protein production, leading to cell death and tissue necrosis.

In the respiratory form of diphtheria, the local effects of the toxin lead to the formation of a thick, gray pseudomembrane in the throat and nasal passages, which can obstruct the airway and cause difficulty breathing. The systemic spread of the toxin can result in damage to distant organs, including the heart, kidneys, and nervous system.

COMPLICATIONS FROM TOXIN SPREAD

- **Myocarditis**: The toxin can damage heart muscle cells, leading to arrhythmias and heart block, which may cause circulatory collapse.
- **Neuritis**: The toxin can cause nerve damage, particularly affecting cranial nerves and peripheral nerves, leading to muscle weakness, paralysis, or difficulty swallowing.
- **Kidney Damage**: The toxin can also affect renal function, leading to acute kidney injury.

TRANSMISSION

Diphtheria is primarily spread through respiratory droplets, but transmission can also occur via direct contact with infected skin lesions or fomites. In cutaneous diphtheria, contact with open wounds or sores can spread the bacteria to the skin or respiratory tract of others. Given the highly contagious nature of the disease, individuals exposed to diphtheria patients or carriers are at risk, particularly in close-contact settings or areas with low vaccination coverage.

The WHO has introduced updated terminology for pathogens that spread through the air, including diphtheria, using the term "infectious respiratory particles" (IRPs) to encompass a wide range of airborne transmission modes. This terminology highlights the importance of understanding the different ways respiratory pathogens like diphtheria can spread.

DIAGNOSIS

The diagnosis of diphtheria is based on both clinical symptoms and confirmatory laboratory tests. Given the potentially rapid progression of the disease, early diagnosis and treatment are critical.

CLINICAL FEATURES

- Pseudomembrane Formation: The formation of a thick, grayish membrane in the throat, tonsils, or nasal passages is a hallmark of diphtheria.
- Bull Neck: Swollen lymph nodes and tissue inflammation can cause significant swelling of the neck.
- Other Symptoms: These include sore throat, fever, nasal discharge, difficulty swallowing, and respiratory distress.

LABORATORY DIAGNOSIS

- **Throat Swab and Culture:** A sample from the throat or nasal passages is cultured to confirm the presence of Corynebacterium diphtheriae. However, culture results may take several days, so treatment should begin before confirmation if clinical suspicion is high.
- **Elek Test**: This immunoprecipitation test determines whether the isolated strain produces diphtheria toxin, distinguishing between toxigenic and non-toxigenic strains.
- **PCR (Polymerase Chain Reaction)**: PCR testing can rapidly detect the tox gene responsible for toxin production, providing faster confirmation than culture or Elek testing.

In severe cases, additional diagnostic tests like blood work and electrocardiograms (ECGs) may be required to assess for complications such as myocarditis.

TREATMENT

The treatment of diphtheria focuses on three key goals: neutralizing the toxin, eradicating the bacteria, and managing complications. Diphtheria can be life-threatening, especially in unvaccinated individuals, so early, aggressive treatment is essential.

- **Diphtheria Antitoxin:** The administration of diphtheria antitoxin is the most critical aspect of treatment. It neutralizes circulating toxins but cannot reverse the damage already done by the toxin. The antitoxin should be given as early as possible and is typically administered intravenously or intramuscularly. The dosage depends on the severity of the disease, with higher doses required for severe cases involving myocarditis or extensive pseudomembrane formation.

- **Antibiotics:** Antibiotics such as penicillin or erythromycin are used alongside the antitoxin to eradicate Corynebacterium diphtheriae and prevent its spread. The typical duration of antibiotic therapy is 14 days. Prophylactic antibiotics may also be given to close contacts of diphtheria patients to reduce the risk of transmission.

- **Supportive Care:** In severe cases, the pseudomembrane can obstruct the airway, necessitating urgent interventions such as intubation or a tracheostomy. Patients with myocarditis or nerve involvement may require close monitoring in an intensive care unit. Management of fluid balance, electrolyte disturbances, and cardiac function is essential. Bed rest and adequate hydration are important components of supportive care, especially as diphtheria often causes systemic toxicity and fatigue.

COMPLICATIONS

Diphtheria can cause a variety of complications, many of which are life-threatening. The diphtheria toxin's effects on the heart, nervous system, and kidneys are particularly dangerous.

- **Cardiac Complications**: Myocarditis, an inflammation of the heart muscle, is one of the most serious complications of diphtheria. It can cause arrhythmias, heart block, or even heart failure. Electrocardiograms (ECGs) in diphtheria patients often show a prolonged P-R interval and ST/T wave changes, which are early indicators of myocardial involvement.

- **Neurological Complications**: Neurological complications include paralysis of the cranial nerves, which may lead to difficulty swallowing, muscle weakness, and regurgitation of food and liquids. In severe cases, diphtheria can cause peripheral neuropathy, affecting the nerves in the extremities. Rarely, encephalitis (inflammation of the brain) may occur, particularly in children.

- **Respiratory Obstruction**: The pseudomembrane formed by the diphtheria infection can obstruct the upper airway, causing breathing difficulties. If untreated, this can lead to suffocation or require emergency interventions such as tracheostomy or intubation.

- **Septicemia and Toxic Shock Syndrome**: If the bacteria or their toxins enter the bloodstream, diphtheria can cause septicemia, leading to a widespread infection. Toxic shock syndrome (TSS) can also occur as the immune system reacts to the toxins, resulting in multi-organ failure and death.

CURRENT CHALLENGES

Global and Local Challenges

Diphtheria continues to present challenges to global public health, particularly in areas with unstable healthcare systems or conflict zones where vaccination efforts are disrupted. For instance:

- In Nigeria, the ongoing outbreak, which began in May 2022, has led to over 13,000 suspected cases and more than 600 deaths as of October 2023. The hardest-hit states include Kano, Yobe, Katsina, and Bauchi, with children aged 1-14 being disproportionately affected. Contributing factors include population growth, climate-related water shortages, and gaps in vaccine coverage.
- Yemen and Other Conflict Zones: Countries experiencing conflict, such as Yemen, face similar challenges, with diphtheria

outbreaks exacerbated by the breakdown of healthcare systems and poor living conditions.

Healthcare Access and Vaccine Distribution

Healthcare access is a critical issue in controlling diphtheria outbreaks. In regions with poor infrastructure, such as northern Nigeria, logistical challenges, security concerns, and a shortage of healthcare personnel have hindered efforts to reach affected communities. The limited availability of diphtheria antitoxin (DAT) and intravenous antibiotics further complicates treatment efforts.

Efforts by the Nigerian Centre for Disease Control (NCDC), in collaboration with WHO, Médecins Sans Frontières (MSF), and other partners, aim to increase vaccine coverage and treatment access. The deployment of National Rapid Response Teams and the use of digital reporting platforms have improved case detection, but security challenges and migration continue to hamper these efforts.

CONCLUSION

The resurgence of diphtheria in Nigeria and other regions underscores the importance of maintaining high vaccination coverage to prevent outbreaks of vaccine-preventable diseases. The current outbreak in Nigeria highlights the vulnerability of populations with low immunization rates, where more than 60% of confirmed cases involve unvaccinated individuals.

Diphtheria's complications, including myocarditis, neuritis, and respiratory obstruction, can be fatal if not treated promptly. Public health measures, such as mass vaccination campaigns, enhanced surveillance, and education, are essential to controlling the disease. However, ongoing challenges, including conflicts, migration, and resource shortages require sustained international cooperation and investment.
Looking forward, improving healthcare infrastructure, expanding vaccination programs, and addressing the underlying social and environmental factors contributing to disease spread will be key to preventing future diphtheria outbreaks.

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