ABSTRACT

Diphtheria is an acute localized infection of the throat associated with systemic manifestations caused by the toxin producing *Corynebacterium diphtheriae*. Diphtheria continues to remain a serious public health problem in children largely related to lack of effective immunisation. The grey, brown, and dirty pseudo membrane is pathognomonic of this disease. The exotoxin produced by the pathogen is responsible for systemic effects. Severity of infection is determined by site of infection, immunization status of the patient, and extent of systemic involvement. Airway obstruction, myocarditis, acute kidney injury, thrombocytopenia and neuropathy are some of the serious complications associated with this disease. Of these, myocarditis is the most dreaded complication and carries a very high mortality. Diphtheria is a clinical diagnosis and specific antitoxin is the mainstay of therapy and should be administered as early as possible. Antibiotics are used to eradicate residual organisms, stop toxin production and decrease infectivity. The indications for PICU transfer include severe pharyngo tonsillar disease, delayed presentation to hospital (> 5 days), delayed antitoxin therapy, signs of airway obstruction and/or myocarditis. Extremes of ages, severe disease, unimmunized children, myocarditis and delayed administration of antitoxin are all poor prognostic factors.

**Key words:** diphtheria, children, intensive care, myocarditis, antitoxin
Introduction

Diphtheria is an acute localized infection of the throat associated with systemic manifestations caused by the toxin producing Corynebacterium diphtheriae. The pseudo membrane in the throat is pathognomonic of this disease. The ability of C.diphtheriae to produce exotoxin results from the acquisition of a lysogenic bacteriophage which encodes for the toxin gene and facilitates production of the toxin.

The four biotypes of diphtheria (mitis, gravis, belfanti, and intermedius) can be differentiated by their colony characteristics, degree of haemolysis and fermentation reactions. The other non-toxin producing strains cause milder disease in humans. In the pre-vaccine era, diphtheria called the "strangling angel of children“ was the leading cause of death among them.

Diphtheria was first recognized as a specific disease by Brettoneau in 1826 and named “la diphthérite” owing to its leather-like exudate in the oropharynx (Greek: leather = dipthera). Edwin Klebs discovered the organism in 1884, followed a year later by Fredrick Loeffler who first cultured the bacterium. In 1889, Emile Roux and Yersin purified the diphtheria toxin. A year later, Von Behring demonstrated the use of serum therapy in diphtheria which won him the first Nobel Prize in the year 1901.

Epidemiology

C. diphtheriae is an exclusive inhabitant of human mucous membranes and skin. The spread of the disease occurs via respiratory droplets, direct contact with respiratory secretions or infected skin lesions. Asymptomatic respiratory tract carriage plays an important role in transmission.

With effective vaccine, the incidence of diphtheria has steadily declined throughout the United States and Western Europe. However, resurgence and epidemic outbreaks have been reported from different parts of the world mainly in adolescents and adults, rather than in children. Some of the factors attributed to this resurgence were waning immunity in adults, lack of natural exposure to toxigenic C diphtheriae, large population of under immunized adults, decreased childhood immunization rates, population migration, and overcrowding. This possibly resulted in an epidemiologic shift towards more adolescents and adults getting the disease.

The scenario in developing economies is different; diphtheria continues to remain a serious public health problem in children largely related to lack of effective immunisation. In 2015 an outbreak of respiratory diphtheria with a case fatality of 27% was reported from two health districts in the province of KwaZulu-Natal in South Africa. More recently, Corynebacterium ulcerans from cats and dogs is emerging as an important causative agent for diphtheria.

Pathogenesis

Corynebacteria are aerobic, non-encapsulated, non-spore-forming, non-motile, pleomorphic, Gram-positive bacilli. The upper respiratory tract mucosa is the most common site of infection, other sites being, buccal mucosa, upper and lower lips, hard and soft palate, tongue and nasal cavity. Nasal infection presents with whitish membrane on the nasal septum. Fauclial diphtheria is characterised by the pathognomonic grey, brown dirty pseudo membrane which is a dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes. The organisms multiply locally but exotoxin produced is absorbed into the blood and is responsible for systemic manifestations like acute tubular necrosis, thrombocytopenia, cardiomypathy, and polyneuropathy or myelopathy. Severity of infection is determined by the site of infection, immunization status of the patient, and the extent of dissemination of exotoxin. The exotoxin inhibits cellular protein synthesis by...
inactivating protein synthesis elongation factor 2 (EF2). An alternative cytotoxic pathway consisting of direct toxin mediated chromosomal DNA damage has also been proposed.\textsuperscript{9}

**Clinical presentation**

*C. diphtheriae* causes localized mucosal infection and exotoxinemia. Tonsils or pharynx is the primary site of infection followed by nose and larynx. The local signs and symptoms of inflammation follow an incubation period of 2-5 days. Sore throat is the universal symptom in tonsillar and pharyngeal diphtheria. Dysphagia, hoarseness, malaise, or headache may be reported. Fever is usually low grade or absent unlike streptococcal sore throat which are characterised by high grade fever. The membrane can be unilateral or bilateral extending up to uvula, soft palate, posterior oropharynx, glottis, and larynx. The concurrent soft-tissue oedema and enlarged cervical lymph nodes gives rise to the characteristic ‘bull-neck’ appearance.\textsuperscript{10}

Nasal diphtheria presents as serosanguinous, purulent, and erosive rhinitis with shallow ulceration of the external nares and upper lip. A membrane severity scoring has been proposed to grade the extent of pseudo-membrane at time of presentation; ‘0’ membrane cleared before presentation; ‘1’ only nose or incomplete coverage of tonsils; ‘2’ confluent coverage of tonsils; ‘3’ as above plus palate and/or pharyngeal wall; ‘4’ as above, plus nasal and/or larynx.\textsuperscript{11} Severe disease is associated with extensive local spread, profound prostration, bull-neck, airway compromise and systemic complications. Untreated patients, shed the bacterium in nasal and oropharyngeal secretions for two to six weeks after inoculation.

**Complications:**

**Airway obstruction**

Upper airway obstruction presenting as stridor is the commonest complication seen in nearly three fourths of patients, reasons being manifold; laryngeal membrane and edema, extensive pharyngotonsillar disease, oedema of soft tissues in submental and anterior cervical areas, necrosis or bleeding into the airways.

**Myocarditis**

It is the most dreaded complication of diphtheria as it is associated with very high mortality. Diphtheric myocarditis is a late first week complication and seen in about two thirds of patients, with respiratory symptoms. Incompletely immunized state, severity of the local disease and delayed antitoxin therapy are associated with high risk of myocarditis.\textsuperscript{11,12} The combination of bull neck and pseudo-membrane admission score of > 2 was found to be the best predictor for development of diphtheritic myocarditis. The toxin has a predilection for the conduction system of the heart and causes acute inflammation of sinoatrial and atrioventricular nodes. Carnitine a co transporter of long chain fatty acids is depleted, resulting in fatty acid accumulation. Disproportionate tachycardia may be the first sign of toxin-induced myocarditis. The other manifestations include conduction disturbances, arrhythmias, congestive heart failure and circulatory collapse. ECG changes of complete heart block and ischemia, were associated with high mortality compared.\textsuperscript{11}

**Neuropathy**

Peripheral neuropathy, is a late complication and develops anywhere from 10 days to 3 months after the onset of oropharyngeal disease. Like myocarditis, the incidence of polyneuropathy is also directly proportional to the severity of local disease and exotoxinemia. Bulbar symptoms in the form of nasal or hoarse voice along with dysphagia and palatal palsy begin 3–6 weeks after initial infection and progress to polyneuropathy at around 8 weeks.\textsuperscript{13} The bulbar symptoms vary from mild to severe but are seen in almost all patients with diphtheritic polyneuropathy.\textsuperscript{13,14} Dysphagia may be accompanied by excessive salivation, nasal regurgitation and aspiration into the airways, necessitating nasogastric feeding. Numbness of the tongue and face and dysphonia may also be
seen. The polyneuropathy is predominantly motor but can be associated with paraesthesia, hypoesthesia, and hyperesthesia. Sensory ataxia may be seen in few patients. Autonomic neuropathy manifests as tachycardia, arrhythmias, hypertension or hypotension; these are difficult to distinguish from diphtheritic myocarditis. There is an inverse relationship between latency and recovery of motor symptoms, longer latency is associated with early recovery. Respiratory muscles are first to recover, followed by palatal and limb muscles.  

**Acute kidney injury**

Renal tubules are susceptible to the toxin mediated injury, leading to acute tubular necrosis. Elevated serum creatinine at admission is predictive of a fatal outcome.  

**Diagnosis**

Diphtheria is a clinical diagnosis and requires a high degree of suspicion especially in an unimmunised child.  

**Clinical criteria**

Any patient with at least one of the following:

- Respiratory diphtheria: An upper respiratory tract illness with fever and one of the following two: croup or an adherent membrane in at least one of the following three locations: tonsil, pharynx or nose.
- Nasal diphtheria: Uni- or bi-lateral nasal discharge initially clear and becoming bloody.
- Cutaneous diphtheria: Skin lesion.
- Diphtheria of other sites: Lesion of conjunctiva or mucous membranes.
- Laboratory criteria: Isolation of toxin-producing *C. diphtheriae* or *C. ulcerans* from a clinical specimen.
- Epidemiological criteria: An epidemiological link by human-to-human transmission.

**Case classification**

A: possible case: Any person meeting the clinical criteria for respiratory diphtheria.

B: probable case: Any person meeting the clinical criteria for diphtheria and with an epidemiological link.

C: confirmed case: Any person meeting the clinical and the laboratory criteria.

**Differential diagnosis**

Other causes of membranous tonsillopharyngitis like infectious mononucleosis, Group A streptococcal tonsillo-pharyngitis, oral candidiasis, Vincent’s angina, and agranulocytosis must be considered in the differential diagnosis of respiratory diphtheria. Presence of high grade fever, tonsillar exudates, tender anterior cervical adenopathy, white plaques on the buccal mucosa, painful and bleeding gums, and atypical lymphocytosis suggests alternative diagnosis.

**Laboratory Diagnosis**

A throat or nasopharyngeal swab for Albert staining is the first diagnostic test for respiratory diphtheria. The organism is gram positive, club shaped and pleomorphic bacilli with terminal swelling (Chinese letter pattern) on the Albert’s stain. The diphtheroid which are normal throat commensals can also stain positive on Albert’s stain. The tests for toxigenecity are required to differentiate both.
Specimens must be transported immediately and rapidly inoculated into blood agar and selective tellurite media. The latter inhibits the growth of normal oral flora; however, *C. diphtheriae* reduce the tellurite salts, producing characteristic black colonies.

**Test for Toxigenicity:** The *Elek test* uses the principle of immunoprecipitation based on the detection of characteristic precipitin lines formed when the exotoxin meets the diffusing antitoxin. 16 7 mm is taken as the best antitoxin to inoculum distance.17 The tests for toxigenicity is most important and should be done without delay.

Recently, real time PCR with rapid turnaround time has been used for the detection of the diphtheria toxin structural gene (*tox*).18 A negative toxPCR test on isolates excludes the diagnosis. Another toxin assay method which includes rapid phenotypic enzyme immunoassay (EIA) using equine polyclonal antitoxin is simple, rapid, accurate, and specific phenotypic method for the detection of toxigenicity.19

**Management**

**Emergency Room Management**

The initial part of management should always focus on stabilisation of the Airway, Breathing and Circulation. Airway compromise should be anticipated and treated promptly in children with extensive local disease and bull neck. Intubation is risky as it can cause dislodgement of pseudo membrane and other friable local tissue and bleeding.20 Tracheostomy on the other hand provides a better conduit for tracheal toileting and is easier to maintain compared to endotracheal tube.20

Strict hemodynamic monitoring including continuous 24-h electrocardiographic monitoring is necessary for early detection and progression of myocarditis.

**Indications for transfer to PICU**

Patients with diphtheria require strict isolation. The indication for PICU transfer includes severe pharyngo tonsillar disease, delayed presentation to the hospital (> 5 days), delayed antitoxin therapy, signs of airway obstruction and/or myocarditis.

**Intensive Care Needs**

1. Airway maintenance and care
2. Hemodynamic monitoring for shock, and arrhythmias
3. Fluid and electrolyte balance
4. Bleeding diathesis due to thrombocytopenia
5. Respiratory muscle weakness and need for ventilation
6. Disseminated intravascular coagulation and multiorgan failure
7. Acute kidney injury and need for renal replacement therapy

**Specific therapy**

The goals of specific therapy are: neutralization of circulating toxin, eradication of residual bacteria, and establishment of active immunity to diphtheria toxin.
Antitoxin

Specific antitoxin is the mainstay of therapy and should be administered as early as possible based on clinical diagnosis. Since antitoxin neutralizes only unbound toxin, its efficacy diminishes if therapy is delayed. The dose of antitoxin is determined by site and size of the membrane and duration of illness. Both intravenous and intramuscular route can be used; the former is given as an infusion over 30-60 minutes. Equine diphtheritic antitoxin requires a test dose of 50-100 units prior to full dose. Antitoxin is not useful for cutaneous diphtheria. The recommended treatment dosages are as follows:

- Pharyngeal or laryngeal disease of 2 days duration: 20,000 – 40,000 units
- Nasopharyngeal disease: 40,000 – 60,000 units
- Extensive disease of 3 days or more or any patient with diffuse swelling of the neck: 80,000 – 120,000 units

Antibiotics:

Eradication of residual organisms to halt toxin production and reduce infectivity (prevent transmission to others) is done with antibiotics. The drug of choice includes penicillin or erythromycin for 14 days. The dosage regime is:

- Penicillin G:40,000 IU/Kg 4-6 hourly IM/IV till toxicity subsides; followed by procaine penicillin 25 – 50,000 IU/Kg IM once daily for a total duration of 14 days.
- Erythromycin: 40-50 mg/kg/day in four divided doses for 14 days is an effective drug for elimination of carriers. Patients treated with appropriate antimicrobials usually become non-infective in less than four days.

Other Supportive therapy:

Carnitine: Carnitine replacement has been studied as a therapeutic option keeping in mind that carnitine depletion occurs in diphtheritic myocarditis. In a case controlled study from Brazil, patients who received carnitine showed a significant reduction in the incidence of myocarditis, and mortality as compared to the controls.21 Despite this the current evidence does not support the role of carnitine in Diphtheric myocarditis.

Cardiac Pacing: Conduction system disturbances in patients with diphtheria myocarditis are markers of severe myocardial damage and poorly responsive to ventricular pacing.12 Though the study from Vietnam, had reported a 27% survival rate in patients who underwent cardiac pacing,22 insertion of a pacemaker in critically ill children and adolescents can be potentially risky and life-threatening procedure. Also it has been shown that improving electrical activity (pacemaker)failed to translate into good mechanical activity (cardiac output) due to severely damaged myocardium. Pacemaker insertion can be associated with complications like infection, thrombus and myocardial perforation.23 The role of immunosuppressive therapies such as steroids and immunoglobulin is inconclusive.24,25

Isolation

Patients with suspected diphtheria should be strictly isolated until complete treatment and two cultures obtained at least 24 hours apart are negative. Patients, whose initial cultures are negative, should also be isolated till completion of antibiotic course.

Contact prophylaxis

All close contacts including household members, healthcare providers, exposed to oral or respiratory secretions, require prophylaxis and toxoid immunization if immunization status is
incomplete. After cultures have been obtained, contacts should be treated with a single dose of Benzathine penicillin (600,000 units intramuscularly [IM] for individuals <6 years of age and 1.2 million units IM for individuals ≥6 years of age) or oral erythromycin (500 mg four times daily for 7 to 10 days.26 All traceable contacts of these patients should be advised throat swab cultures and must be closely watched for symptoms.

**Prognosis**

The case fatality rate of diphtheria with treatment is 5–10%.10 Mortality is higher in extremes of ages, severe disease, unimmunized children and delayed administration of antitoxin. Diphtheritic myocarditis is associated with a mortality rate of 60-70%; cardiogenic shock, ventricular arrhythmias, acute kidney injury are poor prognostic markers. Children with bull neck, mucosal, skin, or nasal bleeding, severe airway obstruction requiring a tracheotomy, or a pseudomembrane score of >2 are at risk of death.11

**Protection**

Clinical disease does not provide natural immunity. The only effective control measure against diphtheria is universal immunization with diphtheria toxoid. Immunization does not prevent respiratory or cutaneous carriage of toxigenic *C diphtheriae*, but decreases the severity of local disease, systemic complications, transmission, and provides herd immunity. Serum antitoxin concentration of 0.01 IU/mL is considered protective.

**Conflict of Interest:** None  
**Source of Funding:** None

**References:**