REVIEW ARTICLE

DIPHTHERIA: THE STRANGLING ANGEL OF (OLDER) CHILDREN

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Abstract

Diphtheria, a dreaded disease of childhood which had undergone a dramatic decline in incidence and mortality in the twentieth century as a result of immunisation and effective treatment, has recently been enjoying a minor resurgence especially amongst older children and adolescents, mainly due to waning immunity. Caused by toxigenic Corynebacteria, it is spread by droplet infection from acute cases as well as asymptomatic carriers. The clinical manifestations result from the local infection especially in the upper airways as well as the potent exotoxin which can have long term effect on the heart and nervous system. Management of diphtheria requires administration of antibiotics and anti-toxin as well as effective supportive care for the airway management, myocarditis and neuropathy. Universal immunisation with the five doses of Diphtheria, Pertussis, Tetanus toxoid (DPT) vaccine needs to be augmented by Tetanus, diphtheria, acellular Pertussis (TdaP) at the of 10-12 years for controlling the rising incidence of diphtheria, especially in India.

Introduction

Vaccine preventable diseases surveillance programme revealed that 533 microbiologically proven diphtheria cases were diagnosed in Kerala in the year 2016. (1) This was a startling finding since Kerala recorded a vaccine coverage of over 85%, well over the level required to prevent diphtheria epidemics. What caused this spurt in the incidence of this preventable disease? The oft-quoted reasons for persistence of diphtheria in a community are inadequate vaccine coverage and, waning immunity as the age increases.

Often called as 'strangling angel of children', diphtheria has been known from ancient times contributing significantly to childhood morbidity and mortality, till the discovery of anti-toxin and initiation of widespread immunisation programmes in 20th century. The introduction of anti-toxin for treatment and then development of an effective vaccine for prevention had a dramatic impact in the incidence and mortality of diphtheria. However, diphtheria has not been eliminated. The widespread vaccination coverage protects young children, historically the most susceptible population, from diphtheria. The waning immunity, due to inadequate coverage with booster vaccination, has led to the epidemiologic shift in the vulnerable age group to adolescents and young adults. This review aims to revisit the diphtheria infection and analyse the factors behind the resurgence of the it in recent years.

Etiology

Diphtheria is caused by gram positive, aerobic, non-capsulated bacteria *"Corynebacterium diphtheriae"*. Less commonly, toxigenic strains of *Corynebacterium ulcerans* also cause the disease. The bacteria become toxigenic by lysogenic conversion on acquiring Corynebacteriphage. The differentiation between *C. diphtheriae* and *C. ulcerans* is done by the urease activity: *C. diphtheria* has urease activity, while *C. ulcerans* doesn't. (2) Exotoxin produced by *Corynebacteria* is lethal to human beings, causing death with a dose of 130 µg/kg body weight. However, it has to be remembered that diphtheria may be caused by both toxin producing and non-producing strains. Myocarditis and neuritis are the only manifestations limited to toxigenic strains of *Corynebacteria*.

Epidemiology

The only natural reservoir of diphtheria is asymptomatic human carriers, who are instrumental in transmission of diphtheria as much as the clinical cases. Active immunisation reduces the number of clinical case of diphtheria without drastically affecting the carrier state. However, vaccine coverage of over 70% can prevent epidemics of diphtheria in a community. (3) Transmission of C. diphtheria occurs more commonly through droplet infection and less commonly through skin lesions and fomites. Apart from a single case report of two siblings affected, C ulcerans is not known to have any person to person transmission. Development of anti-toxin, antimicrobials, effective supportive care and widespread immunisation coverage has helped in significantly reducing the burden of diphtheria. Throughout the second half of 20th century, the incidence of diphtheria continued to fall drastically all around the world. However, in 1990s, soon after the fall of USSR, the erstwhile territories of USSR, which had only recently acquired 'independence', suffered from a huge epidemic of diphtheria with 150,000 cases diagnosed over a period of 7 years with 4000 fatalities. (4) The epidemic started showing a waning trend only after the implementation of a mass immunisation programme from 1993. Apart from this upward blip, the incidence of diphtheria continued to fall till the first few years of 21st century. However, over the past decade, further progress has stalled and over 5000 cases of diphtheria are reported every year from around the world. (5) South East Asia, particularly India, contributes maximum diphtheria cases.

In the pre-vaccine era, children less than 5 years of age were the principal victims of the infection. Diphtheria vaccination changed the epidemiology of diphtheria. Initially, with the increasing coverage of under five children with primary vaccination schedule caused an upward shift in the average age of children getting affected by diphtheria from preschool age to school going children, because these older children had never received diphtheria vaccination. As the children who received diphtheria vaccination grew older, a further upward shift in the susceptible age group was noted with the infection most commonly affecting adolescents and young adults. (5) As per World Health Organization (WHO) data from 2000 to 2016, over 82% of diphtheria cases occurred in children above 5 years and over 40% occurred in individuals over 15 years of age. (5) This second shift is due to the waning immunity as the child grows older and is the reason why regular booster doses are recommended. In fact the United States Advisory Committee on Immunisation

Practices recommends booster doses with Td (Tetanus, diphtheria) every ten years for adults also. (5)

As already mentioned, India has the maximum number of diphtheria cases in the world. From 2011 to 2015, India had a total of 18,350 cases of diphtheria. Indonesia and Madagascar were the other two countries with most diphtheria cases in the same period. (6) In the year 2016, a total of 7097 cases were reported, out of which 3380 cases were from India. (7) However, it has to be remembered that over 40% of cases reported in India are from individuals over 15 years. (5) Only about 20% cases are reported from children under the age of 5 years. This reflects the upward shift in the susceptible population as the immunisation coverage in the community increases.

Pathogenesis

Corynebacteria enter into the body through the airway via droplet infection mainly and through skin lesions and fomites rarely. Both asymptomatic carriers and active cases can cause transmission of the infection. After entry, they colonise and remain localised to the upper airway and start producing exotoxin after a period of 2-4 days. Diphtheria toxin is a single polypeptide with 535 amino acids and having 2 subunits. The A subunit is the enzymatically active component while B subunit is required for binding with the receptor. Major mechanism of toxin mediated cell injury is through the inhibition of protein synthesis. (8) However, an independent mechanism involving DNA fragmentation leading cytolysis also cause cellular injury. (9) The inability to invade mucosa confines the bacteria to the upper respiratory mucosa where they proliferate, cause toxin mediate tissue necrosis and induces severe inflammatory response. This causes formation of an easily removable patchy exudate early in the disease followed by the formation of a closely adherent pseudomembrane formed of fibrinous exudate, inflammatory cells, epithelial cells and colonies of bacteria. The pseudomembrane is white in the beginning but soon becomes dirty grey with green or black spots. The pseudomembrane and oedematous tissue can cause severe airway compromise. As the disease progresses, sloughing of the membrane with profuse bleeding, secondary infection (classically with Streptococcus pyogenes) and bronchopneumonia may all develop. Though the bacteria remain localised to the upper airway, the toxin is distributed throughout the body by blood and lymph and can affect almost all the organs. The most important tissues affected are myocardium, nervous system, liver and kidneys leading to myocarditis, peripheral neuropathy, necrosis with hyaline degeneration and acute tubular necrosis respectively. These toxin mediated manifestations are important causes of mortality in settings where effective airway management is possible.

Clinical Features

The clinical features of diphtheria depend on many factors such as the immune status of the patient, site of infection, production of the exotoxin and the extent of its distribution in the body. The incubation period of the disease is 1 to 6 days. Anatomical site of the infection can be used to classify diphtheria (Table 1).

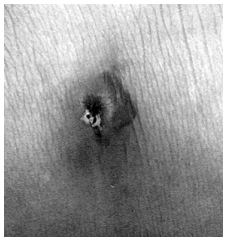
Table 1. Classification of diphtheria based on anatomic location

Common	Pharyngeal / Tonsillar
	Laryngeal / Laryngeotracheal
	Nasal
	Cutaneous
Rare	Conjuctival
	Aural
	Vulvovaginal
Atypical	Meningitis
	Hepatitis
	Endocarditis
	Osteomyelitis
	Septic arthritis

Pharyngeal diphtheria is the most common type of diphtheria and begins with non-specific symptoms like fever, malaise, loss of appetite and pharyngitis. The membrane formation takes 2-3 days and once formed it can vary in extent with limited involvement to extensive involvement from the soft palate to as down as the trachea in the most severe cases. Cervical lymphadenopathy is common and in association with the soft tissue edema of the neck which may be severe may lead to the appearance of 'bull neck'. Toxin production and extent of membrane determine the severity of the disease. Circulatory and respiratory collapse leading to stupor, coma and death within 7 to 10 days may happen in the most severe cases. In less severe cases, recovery may start from the second week of the illness. The convalescence is prolonged and may be complicated by the development of complications such as myocarditis and neuritis. Laryngeal diphtheria is often the result of downward extension of pharyngeal diphtheria and can be rapidly fatal due to airway compromise. Isolated laryngeal diphtheria is a very rare occurrence.

Nasal diphtheria is a less common and less severe form of the disease which is often indistinguishable from a common cold. Diagnosis is often delayed due to the mild nature of the disease. The sequalae due to elaboration of toxin is rare in nasal diphtheria because toxin is only slowly and inefficiently absorbed from the nose. Most commonly, nasal diphtheria affects infants. Cutaneous diphtheria is a rare occurrence seen more commonly in tropical areas (Fig 1). Though highly contagious, they are generally not complicated by toxin production and systemic involvement. (10)

Fig 1. Cutaneous diphtheria lesion



Complications

Complications of diphtheria occur due to the production of diphtheria toxin. The toxin may affect any system and lead to the short term as well as the prolonged complications of diphtheria (Table 2).

Table 2. Toxin mediated complications of diphtheria

Common	Myocarditis and arrhythmias
	Neurological sequelae
Rare	Gastritis
	Nephritis
	Hemolytic Uremic Syndrome

Most of the complications develop after the second week of infection and accounts for the protracted recovery period from the disease. Regular monitoring of patients even after recovery from the acute infection is needed for timely diagnosis and management of these complications.

Myocarditis is an important complication of diphtheria, commonly occurring in the second week of the disease and contributing to the mortality of diphtheria. It is characterized by tachycardia, muffled S1, murmurs, arrhythmias and left ventricular dysfunction. However, since it can occur as early as the first week or as late as the sixth week, each patient should be monitored for myocardial involvement from the diagnosis till at least 6th week of illness. With advances in airway management, the mortality due to airway compromise has been coming down. (11)

Descending paralysis of varying extent is another important complication diphtheria and may be seen in up to 75% of all patients with diphtheria, usually with onset during the third week of the illness. The onset of neurological sequelae may have a variable latent period and often correlate well with the severity of respiratory symptoms. The neurological involvement is usually bilateral, motor more than sensory and usually resolves spontaneously, requiring only supportive management in the interim period. Palatal paralysis is the most common neurological involvement. Peripheral neuropathy involving the limbs, loss of deep tendon reflexes, paralysis of diaphragm and elevated cerebrospinal fluid protein may also be seen and can mimic Guillain-Barré syndrome. (12,13)

Diagnosis

Diagnosis of Diphtheria is clinical and must be made early as the delayed initiation of treatment is an important cause of mortality. Being a non-fastidious organism, Corynebacterium may be grown in selective media containing inhibitory factors for other organisms. Löffler slant, tellurite plate and blood agar should all be inoculated with a sample taken from just beneath the membrane to demonstrate the characteristic black colonies of Corynebacterium. Fig 2 shows a typical appearance of Corynebacterium culture in a tellurite plate and Fig 3 and 4 depict the microscopic appearance with gram stain and Albert stain respectively. The diagnostic tests must always be accompanied by tests for toxigenicity. Elek test was classically used to assess toxigenicity. Nowadays toxigenicity is tested by the newer and more sensitive tests such as enzyme immunoassay and PCR specific to the toxin producing gene (tox). Immune status of the patient should also be assessed in each patient. Shick test was classically used for this, but has been replaced by ELISA. Anti-toxin level above 0.01 IU/mL is said to be protective.

Fig 2. Black coloured colonies of *Corynebacterium diphtheria* on Hoyle's tellurite agar

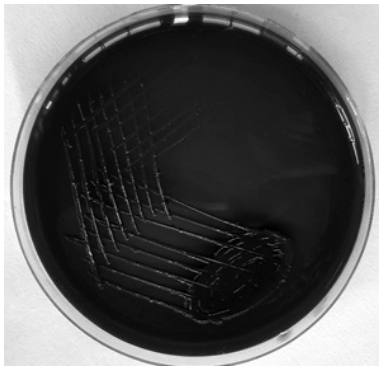


Fig 3. Gram stain showing gram positive rod shaped *Corynebacterium diphtheria* bacilli in Chinese letter pattern

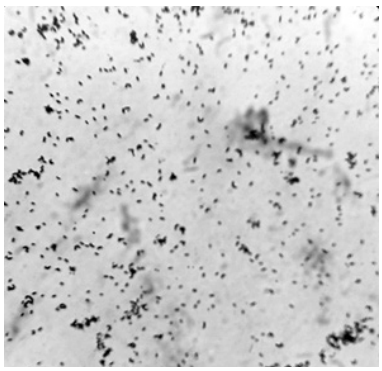
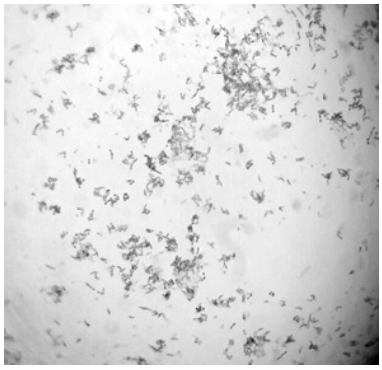


Fig 4. Albert stain showing rod shaped *Corynebacterium diphtheria* bacilli with metachromatic granules



Treatment

Management of diphtheria has three aspects:

Table 3. Factors leading to adverse outcome

Clinical parameters	Delayed diagnosis and initiation of treatment
	Virulence of the infecting organism
	Site of infection- laryngeal infection has the worst prognosis
Lab parameters	Amegakaryocytic thrombocytopenia
	Leukocytosis (>25,000 cells/mm3)
Development of complications	Airway compromise
	Cardiac involvement (myocarditis or arrhythmia)
	Neurological involvement (phrenic nerve involvement or vasomotor centre involvement)

administration of antibiotics and anti-toxin and supportive care. Equine anti-toxin can neutralise the circulating toxin but is ineffective in the intracellular milieu. Anti-toxin should be administered as single dose intravenously to avoid the risk of development of sensitisation with repeated administration. The administration should be preceded by sensitivity testing. Anti-toxin may be needed in sensitive individuals also and can be given in gradually increasing doses administered at 15-minute intervals. The anti-toxin dosage is empirical and range from 20,000 U to 120,000 U depending on the duration and severity of the disease.

Antibiotics are not a substitute for anti-toxins. However, they are to be given in all cases of diphtheria to eradicate the infection and minimise transmission. 100,000-150,000 U/kg/d aqueous penicillin G given in four divided doses or 40-50 mg/kg/d erythromycin given in four divided doses for a total of 14 days are the most commonly employed regimens. Procaine penicillin may also be administered intramuscularly as an alternative regimen. Single dose of intramuscular benzathine penicillin may be administered for treating carriers.

Effective supportive measures are integral to the successful management of diphtheria. Bed rest for a period of 2-3 weeks (longer for patients with myocarditis), hydration and high calorie diet should be prescribed to all patients. Airway management is essential. Certain patients may even need tracheostomy to bypass the obstruction or for management of neuropathy and respiratory paralysis. Serial electrocardiograms (ECGs) should be performed up to 6 weeks to detect myocarditis early.

It must be remembered that all the contacts should be screened for diphtheria by culture of nasal and throat swab. Immunisation does not prevent infection with non-toxigenic strains of C diphtheriae and carrier state. All close contacts of an index case of diphtheria require chemoprophylaxis with appropriate antimicrobials irrespective of their immunisation status. The antimicrobials used are single dose of Benzathine Penicillin G (600,000 U for children weighing <30 Kg and 1.2 Million U for those weighing above 30 Kg) or a seven days' course of erythromycin (40-50 mg/kg/day divided into 4 doses). The asymptomatic individuals who grow diphtheria must be managed like the index case with isolation, antibiotics and supportive care. The contacts as well as the index case must be given a booster vaccination if the last dose of the diphtheria vaccine they had received was more than 5 years ago.

Prognosis

The factors leading to adverse outcome are enumerated in Table 3.

Prevention

The effective reduction of the disease burden of diphtheria, can be attributed to the widespread coverage with immunisation against the disease. The coverage with DTP vaccination against diphtheria with 3 doses of Diphtheria, Tetanus, whole cell Pertussis (DTwP) vaccine in India has been found to be over 78%. (14) However, only about 41% of these children receive a booster dose between 18-23 months. (15) This is not optimal and public health measures need to be boosted up to increase coverage of DTP vaccination. The consequences of this reduced coverage of primary as well as booster immunisation are two-fold. One, there is always a subset of children who have no immunity against diphtheria. Two, the waning immunity as the age advances due to lack of booster doses lead to a larger proportion of adolescents and adults who have suboptimal immunity against the infection.

Currently, five vaccines are available against diphtheria (Table 4). DTwP vaccine is recommended by both National Immunisation Programme (NIP) as well as Indian Academy of Pediatrics (IAP). DTwP contains 20-30Lf Diphtheria Toxoid per dose along with tetanus toxoid and whole cell pertussis. The recommended schedule for DTwP vaccination is at 6,10 and 14 weeks of age followed by two boosters at 18 months and 5 years. Schedule for catch-up vaccination is 0,1, 6 months. Due to increased risk of side effects, DTwP is not recommended for children above 7 years. After three doses of primary immunisation the effective seroprotection reaches over 95%. However, over 6-12 years, the efficacy reduces. DT (Diphtheria, Tetanus) is the vaccination used for immunising children less than 7 years in whom pertussis is contraindicated for whatever reason, most common being hypersensitivity or encephalopathy following previous dose.

As the incidence of diphtheria reduced drastically, the increased side effects, especially due to the whole cell component of DTwP vaccine became a chief concern especially in developed nations which eventually led

to the development of vaccines containing acellular components of pertussis, known as DTaP (Diphtheria, Tetanus, acellular Pertussis). These vaccines have the advantage of having less side effects vis a vis DTwP as well as easily reproducible production processes. The side effects reduce by as much as two thirds on using acellular pertussis vaccine. (15) Most of the commercially available DTaP vaccines contain 15 Lf of diphtheria toxoid. The schedule of DTaP is the same as that of DTwP.

The other vaccines available against diphtheria are used for immunisation of children above 7 years as well as adults. TdaP and Td are the two vaccines commonly used for immunising children above 7 years. These vaccines contain 2 Lf of diphtheria toxoid. IAP recommends a single dose of TdaP at the age of 10-12 years for children who have received a full course of DTwP vaccination earlier in the childhood. The recommended catch-up schedule is TdaP at 0 months followed by Td at 1 months and 6 months. The aim of immunising these older population is to protect them against active disease as well as reducing the reservoir of the disease in the environment.

In view of the high case fatality rate and the high incidence of severe complications, it is imperative that high levels of immunity are maintained in the community through primary as well as booster immunisation to prevent a resurgence of diphtheria. A high degree of suspicion and early initiation of appropriate management as well as close monitoring for development of complications are key factors in successful management of individual cases.

Table 4. Diphtheria vaccines

Name of vaccine	Quantity of diphtheria toxoid in Lf
DTwP	20-30
DTaP	15 (in most preparations)
TdaP	2
DT	20-30
Td	2

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