

Diphtheria in Children

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Abstract

Diphtheria, an acute, communicable, and life-threatening disease has been on the verge of decline owing to rigorous vaccination in most parts of the world. However, certain crops of epidemics pop up, mostly in underdeveloped countries. There has been a paradigm shift in the epidemiology with more and more adults being afflicted with Diphtheria. Adults have also been known to develop more complications commonly associated with Diphtheria. Though on the decline, this disease is still associated with significant morbidity and mortality. In this article, we discuss in detail Diphtheria and review a few studies adding to our known literature about the disease.

Keywords: Diphtheria; *Corynebacterium*; Pseudomembrane; Diphtheria Toxin.

INTRODUCTION

Diphtheria, as we know, is an acute contagious disease caused by *Klebs-Löffler bacillus*, more commonly referred to as *Coryne bacterium diphtheriae*. *C. Diphtheriae* is an aerobic, non-capsulated, usually nonmotile, and characteristically pleomorphic gram positive bacillus. The disease can also be caused less commonly by the other toxigenic strain, *Corynebacterium ulcerans*. The

family of *Corynebacteriaceae* comprises more than 100 species of Gram positive, aerobic bacteria that have a rod like structure exhibiting a club shaped morphology. Three species, *C. diphtheriae*, *C. ulcerans*, and *C. pseudo tuberculosis*, produce and release the diphtheria toxin (DT) through horizontal gene transfer carried by tox encoding bacteriophage incorporated into specific sites of the *C. diphtheriae* chromosome by site specific recombination. This bacterium was preserved by its eponymous name, the *Klebs-Löffler bacillus* as it was first identified and described by Klebs in 1883 and was successfully cultured thereafter by Löffler in 1884.

Diphtheria is known to be highly transmissible and potentially life threatening. Before the era of immunization, diphtheria was one of the main causes of death amongst the pediatric population around the globe. It is a toxin mediated infection that results in a clinical disease respiratory and cutaneous or an asymptomatic carrier state is also known to exist. Although effective vaccines

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have been made available through the years, this particular disease has the potential to show reemergence in countries where recommended vaccination programs are not carried on well and an increasing percentage of adults are known to fall prey to diphtheria, as compared to children in the pre-vaccination period. This thus emphasizes the need to continue rigorous disease control programs worldwide to prevent further diphtheria associated morbidity and mortality.

EPIDEMIOLOGY

Humans are the only known reservoir for *C. Diphtheriae*, seen both in mucus membrane and skin with the existence of a carrier state. In a region endemic to diphtheria, about 3-5% of asymptomatic individuals are known to be carriers. Cutaneous diphtheria, in comparison with mucosal infection, is known to cause more and prolonged bacterial shedding and greater transmission of disease to the skin of close contacts and to the pharynx. Animal contact is known to be the predominant risk factor associated with the spread of *C. ulcerans* spp. causing mostly respiratory and even systemic infection.

Since the inception of vaccines containing diphtheria toxoid alone or combined Diphtheria Pertussis-Tetanus (DPT) vaccines, the incidence of diphtheria has reduced considerably and certain developed countries have also managed to virtually eliminate the disease over the past three decades. Even in developing countries, with increasing immunization coverage, the incidence of Diphtheria has also been showing a declining pattern as per a study by Vitek and Winger.¹ Information regarding the incidence of diphtheria in some developing countries is unavailable, where it stands for nearly 80-90% of the global load of diphtheria cases. In addition to a decrease in the incidence of Diphtheria, KhuriBulos et al, 1988; Galazka and Robertson, 1995; Eskola et al, 1998, in their study, have noticed a change in the epidemiological profile of the disease.

In 2009, a diphtheria epidemic occurred in Barbaruah, a rural district of the Dibrugarh District in the Indian state of Assam. Between 27 May and 20 July, there were 13 established cases of Diphtheria were reported. The index case reported was that of a 45 year old female. In the next 45 days, 5 additional cases occurred, three of whom succumbed to the disease, having a similar clinical presentation. Patients presented with complaints of fever (11 cases), sore throat (11 cases), and the tonsillar membrane was noticed (11 cases). None

of them received anti-diphtheria serum (ADS) due to its unavailability. Of the 13 confirmed cases, male and female cases were reported to be 8 and 5, respectively. The case-fatality rate of this Diphtheria outbreak was reported to be 30.8% (4/13). One of the patients developed a known neurological complication of palatal palsy and polyneuritis. The age groups of patients were: (1/13) in the 5-9-year-old group accounting for 7.7%, 23.1% (3/13) in the 10-14-year-old group, and 69.2% (9/13) in the 15-45-year-old group. There were no confirmed cases of Diphtheria recorded in this epidemic among children under the age of five.

S. Bhagat *et al.* found that between January 2012 and December 2014, the National Centre for Disease Control (NCDC) in Delhi, India, received 941 throats and/or nasal swab samples from cases clinically suspected of being *C. diphtheriae* from various government hospitals in Delhi and the the National Capital Region (NCR). Of all these above samples received, 218 (23.2%) were tested positive by culture for *C. diphtheriae*. In 2012, 2013, and 2014, the percentage of diphtheria cases that were positive was 26.1, 30.6, and 17%, respectively. During the research period, Haryana (35 percent) had the largest number of Diphtheria patients in India, followed by Uttar Pradesh (30 percent), Delhi (17 percent), and Rajasthan (15 percent), and other states (3 percent). The age group 1-5 years had the highest number of cases, with the disease's seasonal distribution revealing that the months of September and October had the highest number of cases.³

C. diphtheriae is categorized into four biovars or biotypes based on biochemical responses and colony morphology: *gravis*, *mitis*, *intermedius*, and *belfanti*. *Belfanti* is a toxigenic strain, but the other biotypes are called for the illness severity with which they are frequently associated: *gravis*, *mitis*, and *intermedius* biotypes, which stand for serious, mild, and intermediate disease severity, respectively.⁴

TRANSMISSION

Diphtheria strikes immediate and near contact with people via infectious respiratory secretions (direct or via airborne droplets) or exudates from the lesions on the skin and even though fomites (eg, contaminated milk). Transmission through an infected food handler is also suspected but not well established. Infection may happen at any time of year, although it is more common in the winter. The infectious period, in an untreated patient, begins with the onset of symptoms and continues for

nearly two to six weeks, whereas communicability, if treated with appropriate antibiotics, usually lasts less than four days. Asymptomatic carriers maintain and spread the organism in endemic populations as humans are the only known reservoir. A Carrier state is not prevented by immunity, whether natural or passive acquired through vaccination. The immunized population, however, is less frequently affected and has less severe diseases.

CLINICAL MANIFESTATIONS

The signs and symptoms that come with being infected by *C. diphtheriae* depend on the anatomical site of the lesion, the immunity that the host holds, and the production and systemic distribution of the toxin. Respiratory Diphtheria can be seen to affect any part of the respiratory tree. Tonsillopharyngitis affects up to 70% of people. When compared to respiratory diphtheria, the laryngeal, nasal, and tracheobronchial regions are equally well known, but they are less usually afflicted. The incubation period may vary from two to five days. Sore throat, generalized weakness, and low grade fever are also common. Tonsillopharyngeal diphtheria is usually a mild form of pharyngeal infection that progresses to isolated spots of grey and white exudates, leading to the characteristic formation of a coalescing pseudomembrane, which is tightly adherent to the underlying tissue (resulting in bleeding if dislodged), is well demarcated, and is classically grey in color (basically made of necrotic fibrin, leukocytes, erythrocytes, epithelial cells, and organisms) and can extend from the nasal passages to the tracheobronchial tree. The traditional bull neck look is caused by malignant diphtheria, which manifests as severe "membranous pharyngitis" with significant swelling of the tonsils, uvula, cervical lymph nodes, submandibular area, and anterior neck. Respiratory stridor may develop, leading to respiratory failure and possibly death. Nasal diphtheria is a mild disease with a serosanguinous/seropurulent nasal discharge causing irritation of the external nares and upper lip. Cough and hoarseness of voice are the usual presentations of laryngeal diphtheria. A tracheobronchial infection is usually secondary to a downward spread. Systemic manifestations seen are due to the production and dissemination of the diphtheria toxin. Cutaneous diphtheria can be associated with primary chronic, nonhealing ulcers with a dirty grey membrane or with colonization and infection of preexisting dermatoses. Systemic toxicity is an uncommon complication caused by both toxigenic and nontoxigenic strains of *C.*

diphtheriae. It triggers a rapid antibody response, implying immunity.⁵

COMPLICATIONS

C. diphtheriae is known to cause various complications. Myocarditis may occur by the second week with ECG changes such as ST-T wave changes, QTc prolongation, and/or first-degree heart block in two-thirds of cases, often seen occurring when local respiratory symptoms are improving.⁶ Complex heart blockages, arrhythmias, heart failure, and circulatory collapse are all symptoms of severe, life threatening myocarditis, which is the leading cause of death.⁷ Other complications associated with Diphtheria may be neurological and may manifest as that of local neuropathies in the second week with paralysis of the soft palate and posterior pharyngeal wall. Cranial neuropathies usually affecting oculomotor and ciliary nerves, followed by facial or laryngeal paralysis in the third week of infection are also seen. Peripheral neuritis develops over weeks to months. Lastly, renal complications like oliguria and proteinuria may also ensue.

Charles Henry Washington et al. reported a case of a 9-year-old male child referred on the fifth day of illness to Chiang Mai University Hospital (CMUH), Thailand in 2014, diagnosed outside with pharyngitis not responding to OTC antibiotics with progressive worsening of symptoms. The Gram stain on the throat swab revealed Gram-positive bacilli, and a throat swab culture revealed *Coryne* bacterium diphtheriae growth, as well as a positive Elek test for toxigenic *Coryne* bacterium strain identification. On day 3 of hospitalization, the patient developed severe myocarditis treated with IVIG and subsequently developed a third-degree heart block requiring a temporary transvenous pacemaker inserted via the right internal jugular vein. However, the patient succumbed over the next few days with the diagnosis being progressive fulminant myocarditis secondary to diphtheria.⁸

DIAGNOSIS

The usual presentation of diphtheria is pharyngitis associated with low grade fever and/or cervical lymphadenopathy, associated with adherent pharyngeal, palatal or nasal pseudomembrane, and slowly may progress to systemic toxicity, hoarseness of voice, stridor, paralysis of the palate, and/or serosanguinous nasal discharge (particularly unilateral).⁹ On Gram's stain, gram-positive rods in a typical "Chinese character" distribution are identified with black colonies

with halos on Tindale's media, and multi-colored granules on Löffler's media to make a presumptive diagnosis of Diphtheria.¹⁰ Toxin detection can be done by the Elek test. Isolation of *C. diphtheriae* from respiratory tract secretions or skin lesions is a laboratory diagnosis that leads to a clear diagnosis of this illness is present. It is frequently necessary to use specialized culture mediums (Löffler's or Tindale's).

If samples sent for culture from a patient with suspected diphtheria are negative because antibiotic therapy was initiated before the samples were collected, a probable diagnosis of diphtheria can be established if *C. diphtheriae* is isolated from any of the patient's immediate contacts, and the patient has a minimal anti-DT antibody titer (0.1 IU) in serum samples obtained before the Diphtheria Anti-Toxin (DAT) is administered, though this parameter is not a key diagnostic indicator.

DIFFERENTIAL DIAGNOSIS

Infections that may present as Diphtheria are group A streptococcal tonsillopharyngitis, infectious mononucleosis, epiglottitis, viral pharyngitis, *Corynebacterium ulcerans* and severe oral candidiasis, oral syphilis and *Borrelia vincentii* infection (Vincent angina/ trench mouth).

TREATMENT

Treatment of diphtheria basically depends on the neutralization of toxins. The antitoxin dosage is determined by the intensity and location of the illness. 20,000 to 40,000 units for pharyngeal/laryngeal infection that has been present for at least 48 hours, 40,000 to 60,000 units for nasopharyngeal disease, and 80,000 to 120,000 units for illness lasting more than three days or generalized neck edema ("bull-neck").¹¹ To effectively inactivate toxins, this is injected intravenously over 60 minutes. Serum sickness and hypersensitivity can occur.

The cornerstone of Diphtheria treatment is the immediate treatment with Diphtheria Antitoxin (DAT), which comprises antibodies derived from the serum of horses immunized against the toxin released by *Corynebacteriae* species and thus neutralizes circulating DT while also limiting clinical progression. In severe and acute cases, intubation or even a tracheostomy may be required. DAT is ineffective against DT that has attached to bodily tissues, and therefore it should be provided as soon as possible once the diagnosis of Diphtheria is suspected clinically and

is established, probably even before bacteriological confirmation, ideally by IV infusion, particularly in cases when the infection is severe. DAT may trigger anaphylaxis in people allergic to it, such as people who have asthma, urticaria, or allergic rhinitis who have previously been administered with a dosage of horse serum. A prick test using diluted DAT to detect the development of any skin response, such as erythema/urticaria and irritation, within 15–20 minutes can avoid possible hypersensitivity reactions.

In his research, Shaun A Truelove discovered that giving diphtheria antitoxin after infection reduced mortality by about 76 percent. Antitoxin, on the other hand, only neutralizes circulating toxins and not intracellular toxins, therefore its efficacy is dependent on rapid delivery in the event of symptom development. It was estimated that the chances of mortality increases daily, from 4.2 percent (95 percent CrI, 2.5 percent 7.1 percent) if given to the patient within 24–48 hours to 24 percent if administered on day 5 or later, nearly increasing two times with each day of delay.¹²

Antibiotics for bacterial eradication

Erythromycin (40 to 50 mg/kg per day, up to a maximum of 2 grams per day intravenously) or procaine penicillin G (25,000 to 50,000 units per kg per day for children and 1.2 million units per day given intramuscularly in two divided doses) until the patient can swallow. Change to oral penicillin V (125 to 250 mg QID) or Erythromycin (25–30 mg/kg/day for a total of 14 days).

Isolation and follow-up

Respiratory droplet isolation for respiratory disease and contact precautions for cutaneous disease. Isolation is continued until no growth is detected in two successive cultures obtained at least 1 day apart. As natural infection does not induce immunity, the patient should be immunized with diphtheria toxoid during the convalescence period.

Symptomatic and Supportive Care

Bed rest, fluids, nasogastric feeding, diuretics, digoxin, and tracheostomy to relieve respiratory obstruction may be warranted.

Prophylaxis of contacts

Close observation and chemoprophylaxis with oral Erythromycin (40 mg/kg/day for seven days) should be done for immediate contacts, who should also be cultured for growth of Diphtheria bacteriae. Benzathine penicillin (60,000–120,000

units IM) can also be used for chemoprophylaxis. Fully immunized asymptomatic contacts merit a booster dose of diphtheria toxoid. Unimmunized contacts should be immunized as per age.

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