

Diphtheria: An Emerging Disease

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Abstract

Diphtheria is caused by a toxigenic bacterium *Corynebacterium diphtheriae* which remains as one of the important causes of illness and death among children. Globally, epidemic waves of diphtheria have killed thousands of children in early 1920s, i.e., before the vaccine era. There are four main biotypes of *C. diphtheriae* available namely *C.d. Gravis*, *C.d. Intermedius*, *C.d. Mitis*, and *C.d. Belfanti*. Globally, the *C.d. Intermedius* is most often associated with exotoxin production, although all three strains are capable of producing exotoxin. Diphtheria patients are usually prescribed for diphtheria antitoxin and antibiotics such as erythromycin/penicillin. Keeping all the pathogenic information in context, here in the present review we have accumulated all the recent updates on diphtheria and also presented a timely discussion on diagnosis and vaccination procedure, which might assist future therapeutics.

Keywords: Diphtheria; *C. diphtheriae*; Pseudomembrane; Antitoxin; Penicillin

Epidemiology

Diphtheria is caused by a toxigenic bacterium *Corynebacterium diphtheriae* which remains as one of the important causes of illness and death among children. This disease is defined as a respiratory illness that comprised of pharyngitis, tonsillitis/laryngitis, cervical lymphadenopathy and an adherent tonsillar or nasopharyngeal pseudomembrane. Multiplication of *C. diphtheriae* cells destroy healthy tissues in the bronchial tract, resulting in thickening of the tissues that leads to acute respiratory failure. The other common complications include endocarditis of either native or prosthetic valves, disseminated intravascular coagulation, renal, endocrine failure and paralysis of lower limbs. There are four main biotypes of *C. diphtheriae*: *Gravis*, *Intermedius*, *Mitis*, and *Belfanti*. Globally, the *Intermedius* is most often associated with exotoxin production, although all three strains are capable of producing exotoxin.

Globally, epidemic waves of diphtheria have killed thousands of children in early 1920s, i.e., before the vaccine era. From the beginning of the 1980s, many developed countries progressed towards the elimination of diphtheria by implementing the vaccine program. In 1990s, re-emergence of diphtheria has witnessed large scale morbidity and mortality in the Russian Federation and the Newly Independent States of the former Soviet Union. Recent outbreaks of respiratory and cutaneous diphtheria in several countries showed the existence of this disease and pose a global threat [1-6]. Human displacement compounds the problem further with increased incidence of diphtheria in Latvia [7] and New Zealand [5].

Historically, toxigenic *C. diphtheriae* has been associated with diphtheria in children. Non-toxicogenic *C. diphtheriae* recently gained importance as it causes severe pharyngitis and tonsillitis, endocarditis,

septic arthritis, polyneuropathy and osteomyelitis. Recent changes in the epidemiology of diphtheria include emergence of other toxin-producing species such as *C. ulcerans* and *C. pseudotuberculosis* associated with respiratory and cutaneous infections [8,9]. In Western countries, the clinical presentation is different from endemic countries i.e., without the typical diphtheria symptoms. Zoonotic infections caused by *C. ulcerans* were reported to be about 60% in England during 2007-2013 with respiratory diphtheria and the absence of a pharyngeal membrane [10]. Most of the patients in this study were not immunized. Circulation of *Corynebacterium* spp. appears to continue in some settings, even in populations with more than 80% childhood immunization rates. An asymptomatic carrier state can exist even among immune individuals.

Virulence

Diphtheria toxin (DT) is the major virulence factor in *C. diphtheriae*. This exotoxin carries A and B subunits, encoded in the *tox* gene of the β -corynebacteriophage, which is integrated into the bacterial chromosome [11]. This mobile temperate bacteriophage may transform non-toxicogenic strains/closely associated species into toxicogenic strains. The lethal dose of DT for humans is about 0.1 μ g per kg of body weight.

Diagnosis and Treatment

Diagnosis of diphtheria is often based on the appearance of typical throat infection with confirmation by microbiological culture. For confirmation, throat swabs from suspected cases will be tested by culture methods. Generally, treatment has been made without anticipating the culture results. Until now, there are no rapid diagnostic tests for the detection *C. diphtheriae*. Early diagnosis will help in the implementation of control measures and clear guidelines are needed to assist clinicians in managing clinical diphtheria. Several other exiting methods in the detection of pathogenic bacteria such as

matrix assisted laser desorption ionization-time of flight mass spectrometry will enhance the confirmation of diphtheria in a very short duration. Polymerase chain reaction (PCR) or the real-time PCR has been used for the detection of toxin encoding genes (*toxA* and *toxB*).

Diphtheria patients should be treated with diphtheria antitoxin and antibiotics such as erythromycin/penicillin. Since this disease spreads through the air and personal contacts, patients should be kept in isolated ward/place. Penicillin is widely recommended as the first-line drug for the prophylaxis against and treatment of *C. diphtheriae*. Penicillin-resistant cutaneous *C. diphtheriae* has been reported [12]. Epidemic *C. diphtheriae* strains from Brazil and Algeria has shown reduced susceptibility to penicillin G [2,13]. Emergence of penicillin resistance *C. diphtheriae* has been reported from UK and India [12]. Antibiotic-induced biofilm formation might also be a factor to the variable success of antimicrobial therapy for *C. diphtheriae* infections [14]. Diphtheria can be effectively treated with antitoxin (DAT, 20000-100000 Units) made from horses. Diphtheria antitoxin reduces the progression of the disease by binding DT that has not yet attached to the body's cells. But the antitoxin does not neutralize the toxin if it bound to tissues. DAT may cause adverse event, i.e., anaphylaxis.

Vaccination

Diphtheria toxoid vaccine is available in combination with tetanus toxoid or with tetanus and pertussis antigens (DTP). More recently, this pentavalent vaccine has been supplemented with hepatitis B surface antigen and *Haemophilus influenzae* type B. For pediatric use, these combination vaccines are used in a 3-dose vaccination series starting from 6 weeks of age with a minimum interval of 4 weeks between doses, then a booster dose at age 15–18 months [15]. In diphtheria endemic countries, about 31% of the <10 years age group who had received three doses of DTP vaccine were found to be infected by diphtheria [16].

There is an urgent need for improving childhood immunisation coverage in low and middle-income countries. Implementation of seroepidemiology and use of bio-markers are not only helping in understanding of the ongoing infection status and in monitoring the effectiveness of vaccination programs. Vaccine-acquired immunity tends to wane with ageing, hence, booster doses are recommended to fully protect adolescents [17]. Maternal immunization has been debated as it helps not only for the pregnant woman, but also for the developing fetus and young infant [18]. Antibody levels for diphtheria decline with aging and hence it is important that vaccine administration should be emphasized for the protection of young adult and elderly people also, not limited to children [19-22]. Moreover, the benefits of adolescent immunization are more than the risks [23].

Molecular studies

Genomic studies have shown several recombination events in toxin gene and pilus gene clusters that have driven diversification of *C. diphtheriae* strains [10]. The currently circulating non-toxigenic *C. diphtheriae* strains therefore represent a potential source for the emergence of toxigenic *C. diphtheriae* in the United Kingdom [24]. Whole genome sequence of *C. diphtheriae* provided evidence of the recent acquisition of additional pathogenicity factors such as iron-uptake systems, adhesions and fimbrial proteins [25]. Recent outbreaks associated *C. diphtheriae* strains were found to belong new sequence types [9,6].

Integrated surveillance is needed to outline current trends in the epidemiological profiles of diphtheria. Strengthening of routine immunization with DPT vaccine as well as diagnostic capacity is important. The investigation should also focus on the levels of immunity in children, adolescents and adults [26].

Conclusion

Epidemic waves of diphtheria killed thousands of children in early 1920s. However, when diphtheria anti-toxin was available, the mortality and morbidity came down sharply. Diphtheria toxoid vaccine changed the situation. Now-a-days clinicians see cases of diphtheria rarely and hence may overlook and miss the diagnosis. With the upsurge of cases in adults, this disease should be kept in mind as a differential diagnosis whenever the clinician sees a case of sore throat.

References

1. Besa NC, Coldiron ME, Bakri A, Raji A, Nsuami MJ, et al. (2014) Diphtheria outbreak with high mortality in northeastern Nigeria. *Epidemiol Infect* 142: 797-802.
2. Santos LS, Sant'anna LO, Ramos JN, Ladeira EM, Stavracakis-Peixoto R, et al. (2015) Diphtheria outbreak in Maranhão, Brazil: microbiological, clinical and epidemiological aspects. *Epidemiol Infect* 143: 791-798.
3. Garib Z, Danovaro-Holliday MC, Tavares Y, Leal I, Pedreira C (2015) Diphtheria in the Dominican Republic: reduction of cases following a large outbreak. *Rev Panam Salud Publica* 38: 292-299.
4. Sein C, Tiwari T, Macneil A, Wannemuehler K, Soulaphy C, et al. (2016) Diphtheria outbreak in Lao People's Democratic Republic, 2012-2013. *Vaccine* 34: 4321-4326.
5. Reynolds GE, Saunders H, Matson A, O'Kane F, Roberts SA, et al. (2016) Public health action following an outbreak of toxigenic cutaneous diphtheria in an Auckland refugee resettlement centre. *Commun Dis Intell Q Rep* 40: E475-E481.
6. du Plessis M, Wolter N, Allam M, de Gouveia L, Moosa F, et al. (2017) Molecular characterization of *Corynebacterium diphtheriae* outbreak isolates, South Africa, March-June 2015. *Emerg Infect Dis* 23: 1308-1315.
7. Kantsons I, Lucenko I, Perevosikovs J (2016) More than 20 years after re-emerging in the 1990s, diphtheria remains a public health problem in Latvia. *Euro Surveill* 21: pii: 30414.
8. Hacker E, Antunes CA, Mattos-Guaraldi AL, Burkovski A, Tauch A (2016) *Corynebacterium ulcerans*, an emerging human pathogen. *Future Microbiol* 11: 1191-1208.
9. Rajamani Sekar SK, Veeraraghavan B, Anandan S, Devanga Ragupathi NK, Sangal L, et al. (2017) Strengthening the laboratory diagnosis of pathogenic *Corynebacterium* species in the vaccine era. *Lett Appl Microbiol* 65: 354-365.
10. Sangal V, Hoskisson PA (2016) Evolution, epidemiology and diversity of *Corynebacterium diphtheriae*: New perspectives on an old foe. *Infect Genet Evol* 43: 364-70.
11. Canchaya C, Fournous G, Brussow H (2004) The impact of prophages on bacterial chromosomes. *Mol Microbiol* 53: 9-18.
12. FitzGerald RP, Rosser AJ, Perera DN (2015) Non-toxigenic penicillin-resistant cutaneous *C. diphtheriae* infection: a case report and review of the literature. *J Infect Public Health* 8: 98-100.
13. Benamrouche N, Hasnaoui S, Badell E, Guettou B, Lazri M, et al. (2016) Microbiological and molecular characterization of *Corynebacterium diphtheriae* isolated in Algeria between 1992 and 2015. *Clin Microbiol Infect* 22: 1005.e1-1005.e7.
14. Gomes DL, Peixoto RS, Barbosa EA, Napoleão F, Sabbadini PS, et al. (2013) SubMICs of penicillin and erythromycin enhance biofilm formation and hydrophobicity of *Corynebacterium diphtheriae* strains. *J Med Microbiol* 62: 754-760.

15. World Health Organization (2017) Diphtheria vaccine: WHO position paper. *Wkly Epidemiol Rec* 92: 417-435.
16. Sangal L, Joshi S, Anandan S, Balaji V, Johnson J, et al. (2017) Resurgence of diphtheria in North Kerala, India, 2016: Laboratory supported case-based surveillance outcomes. *Front Public Health* 5: 218.
17. Capua T, Katz JA, Bocchini JA Jr (2013) Update on adolescent immunizations: selected review of US recommendations and literature. *Curr Opin Pediatr* 25: 397-406.
18. Perrett KP, Nolan TM (2017) Immunization During Pregnancy: Impact on the Infant. *Paediatr Drugs* 19: 313-324.
19. Wanlapakorn N, Yoocharoen P, Tharmaphornpilas P, Theamboonlers A, Poovorawan Y (2014) Diphtheria outbreak in Thailand, 2012; seroprevalence of diphtheria antibodies among Thai adults and its implications for immunization programs. *Southeast Asian J Trop Med Public Health* 45: 1132-1141.
20. Bernstein HH, Bocchini JA Jr, Committee on infectious diseases (2017) The need to optimize adolescent immunization. *Pediatrics* 139: pii: e20164186.
21. Burke M, Rowe T (2018) Vaccinations in older adults. *Clin Geriatr Med* 34: 131-143.
22. Bhatnagar P, Gupta S, Kumar R, Haldar P, Sethi R, et al. (2016) Estimation of child vaccination coverage at state and national levels in India. *Bull World Health Organ* 94: 728-734.
23. Vernon N, Jhaveri P (2014) Adverse effects of adolescent immunizations. *J Am Osteopath Assoc* 114: S13-17.
24. De Zoysa A, Efstratiou A, Hawkey PM (2005) Molecular characterisation of diphtheria toxin repressor (dtxR) genes present in non-toxigenic *Corynebacterium diphtheriae* isolated in the UK. *J Clin Microbiol* 43: 223-228.
25. Mokrousov I (2009) *Corynebacterium diphtheriae*: genome diversity, population structure and genotyping perspectives. *Infect Genet Evol* 9: 1-15.
26. Both L, Collins S, de Zoysa A, White J, Mandal S, et al. (2015) Molecular and epidemiological review of toxigenic diphtheria infections in England between 2007 and 2013. *J Clin Microbiol* 53: 567-572.