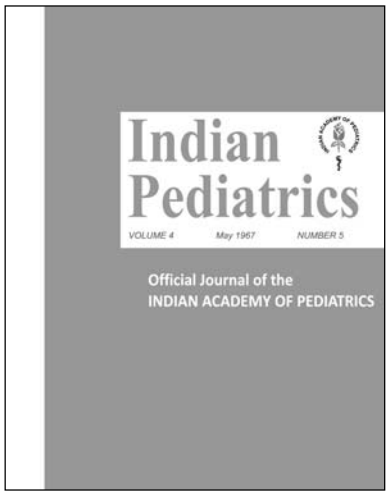
Diphtheria Revisited

Surendra B Mathur and *Sharmila B Mukherjee
From the Department of Pediatrics, Lady Hardinge Medical College and Associated Hospitals, New Delhi, India.
**theshormi@gmail.com*

The forty-paged May 1967 issue of *Indian Pediatrics* published four observational studies (growth in the first year of life, clinical and bacteriological study of diphtheria, cephalic index changes during the first ten months of life and therapeutic efficacy of Tin in hymenolepiasis), besides case reports and other regular features. We selected a study on Diphtheria for this section as it exemplified the scientific curiosity that existed in those days, and meticulousness of protocol planning in order to solve a diagnostic dilemma. This is followed by a brief discussion of the change in epidemiology, clinical profile, diagnostic tests and treatment protocols over the last five decades.



The Past

The study by Pohowalla, *et al*. [1] aimed to evaluate the clinical and bacteriological profile of children presenting with white patches in their mouths. At that time, on one hand, many cases of diphtheria were being missed in the early stages resulting in fatalities, while on the other, oropharyngeal moniliasis and follicular tonsillitis were being misdiagnosed and treated as diphtheria. The study population comprised of 116 children diagnosed clinically as diphtheria at MGM Medical College, Indore over nine months. Two throat swabs were collected from each patient before treatment was started. One was used to prepare smears with Albert-, methylene blue- and Gram-stain, while the other was directly plated on Loeffler's medium and cornmeal agar followed by sub-culture on potassium tellurite medium and blood agar. This was followed by a detailed bacteriological routine that included colony morphology and various biochemical tests that enabled differentiation of diphtheria from moniliasis and pyogenic follicular tonsillitis. Thirty nine (33.6%) cases were culture positive for diphtheria (37 *gravis*, 1 *intermedius* and 1 *mitis*). The remaining 63 (55.8%) isolated pyogenic organisms (*Streptococcus hemolyticus,* Staphylococcus, *E. Coli,* Pseudomonas, Aerobacter and others); 8 combinations of diphtheria and pyogenic organisms (also including pneumococcus), and 9 combinations of monilia (various types of candida) and pyogenic organisms. Clinically all cases of proven diphtheria were above 6 months of age. Fever was the most common presentation, and ten children developed obstructive breathing necessitating tracheostomy. The case fatality was 8.6% (10/116), out of which four had required tracheostomy and two developed myocarditis. As bacteriological evidence was found in only one-third of the cases of suspected diphtheria, the authors concluded that majority of children with oropharyngeal white patches were due to either bacteria other than *C. diphtheria* or mycotic organisms. Authors recommended that when a bacteriological diagnosis could not be established in suspected diphtheria, a combination of either penicillin or erythromycin with nystatin be used.

Historical background and past knowledge: Since the Biblical ages, Diphtheria has historically been identified as a childhood disease marked by sore throat, membrane in the oral cavity or pharynx, and death through suffocation. In the mid-sixties, it was recognized that making a correct and early diagnosis was the cornerstone of effective management. Though the number of cases of diphtheria had started to decline, this trend was mainly observed in developed countries.

In 1980, nearly 97000 cases of Diphtheria were reported globally, which decreased to 21000 by 1992 [2]. Most of these (80–90%) were from the developing countries. By the 1990's, it appeared that diphtheria was under control. However resurgence occurred with the collapse of the Soviet Union that evolved into an epidemic extending into Europe. By 1996, 140,000 cases (mostly adults) were reported (29–95% culture positive), with a case fatality rate of 3–23% [3]. This was attributed to a

reduction in vaccination coverage during childhood, use of vaccines with low dose formulation, waning adult immunity, large-scale population movements, disruptions in health services, and inadequate supplies of vaccine and antitoxin.

Diagnosis of diphtheria remains primarily clinical, supported by careful visualization of the pseudomembrane. Confirmatory laboratory diagnosis is by isolation of the diphtheria bacillus in Tellurite-containing culture media. Toxigenicity tests detect the potent exotoxin, which is a phage-encoded protein. *In vivo* virulence testing in guinea pigs was replaced by the Elek test, first described in 1949 and later modified in the early 1990s.

The mainstay of treatment of diphtheria is antitoxins, which work by neutralizing the free toxins. A single dose of 20,000-100,000 units should be administered as soon as a clinical diagnosis is made. Antibiotics abort toxin production, treat localized infection and prevent transmission to susceptible contacts. The antibiotics of choice are penicillin or erythromycin for 14 days after which two negative cultures from nose and throat should be obtained. Subsequently, the immunization protocol should be completed as per individual status. All close contacts must be identified, immunization status ascertained, given diphtheria booster appropriate for age, monitored for 7 days and treated if disease develops. Asymptomatic unimmunized contacts should receive erythromycin for 7 days or a single intramuscular dose of Benzathine penicillin if surveillance is not feasible. Immunization should be completed according to schedule.

THE PRESENT

Though diphtheria is on the verge of being eliminated in a few developed countries, 4530 cases were reported worldwide in 2015. Unfortunately 2365 (52.2%) of these were from India [2]. The World Health Organization Vaccine Preventable Diseases Monitoring System has also reported periodic resurgence in India. A waxing and waning pattern has been evident over the last three decades. The number of cases have been 39231 in 1980, 1326 in 1997, 8465 in 2004, 2525 in 2012 and 6094 in 2014 [2]. Though there are multiple causes, dismal vaccination coverage stands out. According to successive National Family Health Survey reports, the coverage of 3 primary doses of DPT vaccine has been significantly lower than the desired goal of >90%; 51.7% in 1993, 55% in 1999, 55.3% in 2006 and 78.4% in 2016 [4]. After the advent of widespread vaccination against diphtheria, circulation of toxigenic strains have reduced, resulting in decline in immunity in older age groups and increased susceptibility. This age shift has been demonstrated in studies from West Bengal, Southern India, and Delhi [5-7]. Reasons for high case fatality include inconsistent and restricted availability of antitoxin and delay in diagnosis [8]. Improvements in respiratory care and support have resulted in the main cause of death shifting from obstructive respiration to myocarditis [9,10].

The diagnosis of diphtheria still remains mainly clinical, supported by microbiological demonstration of corynebacterium by Albert stain, and confirmation by positive culture. Recently, polymerase chain reaction has made establishment of toxigenicity possible within a few hours. In situations where children have already received antibiotics, a low (<0.1 IU) level of diphtheria antibody titer in serum (signifying non protection) and isolation of *C. diphtheria* from close contacts can facilitate diagnosis.

At an individual level, each one of us can play an important role in the journey towards elimination of diphtheria in India. The immunization status of each child we encounter in our daily practice should be actively enquired about, and primary and catch-up immunization should be promoted. A high level of clinical suspicion towards diphtheria should be maintained and early treatment should be initiated. We should not overlook treatment of carriers and close contacts.

REFERENCES

1. Pohowalla JN, Upadhyaya LN, Chhaparwal BC, Gupta JC, Bhoraskar SN. Clinical and bacteriological study of diphtheria in children. Indian Pediatr. 1967;4:208-20.
2. World Health Organization. Reported cases of selected vaccine preventable diseases. Available from: *http://www.who.int/immunization/monitoring_surveillance/data/en*. Accessed March 28, 2017.
3. Vitek CR, Wharton M. Diphtheria in the former Soviet Union: Reemergence of a pandemic disease. Emerg Infect Dis. 1998;4:539-50.
4. International Institute for Population Sciences. National Family Health Survey, India. Available from: *http://rchiips.org/NFHS/index.shtml*. Accessed March 28, 2017.
5. Ray SR, Gupta SD, Saha I. A report of diphtheria surveillance from a rural medical college hospital. J Indian Med Assoc. 1998;96;236-8.
6. Havaldar PV. Diphtheria in eighties: experience in a south Indian district hospital. J Indian Med Assoc. 1992;90:155-6.
7. Singhal T, Lodha R, Kapil A, Jain Y, Kabra SK. Diphtheria – down but not out. Indian Pediatr. 2000;37:728-38.
8. Dandinarasaiah M, Vikram BK, Krishnamurthy N, Chetan AC, Jain A. Diphtheria re-emergence: Problems faced by developing countries. Indian J Otolaryngol Head Neck Surg. 2013;65:314-8.
9. Jayashree M, Shruthi N, Singhi S. Predictors of outcome in patients with diphtheria receiving intensive care. Indian Pediatr. 2006;43:155-60.
10. Jain A, Samdani S, Meena V, Sharma MP. Diphtheria: It is still prevalent!!!. Int J Pediatr Otorhinolaryngol. 2016;86:68-71.