80 Diphtheria

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Diphtheria is a respiratory illness with systemic manifestations that are mediated by exotoxin. In addition, skin infection occurs in some patients. After introduction of diphtheria toxoid vaccine, the incidence of the disease has decreased dramatically. In 2008, only 7,088 cases are reported globally (*Fig. 80.1*). The decrement has been impressive over the last two decades; however there was a small outburst in the years of 1994 and 1995 due the outbreak that occurred in previous USSR where 60,000–80,000 cases were reported mostly among adults who were not or incompletely vaccinated. A significant number of cases are still reported from India, Sudan, and some other developing countries. The vaccine is effective but needs to be enforced and the immunity maintained by adhering to booster vaccination especially in adolescent and adults.

Organism

Diphtheria is caused by *Corynebacterium diphtheriae* – a Gram positive, facultative aerobic, nonmotile, and nonspore-forming bacillus. It can be grown in ordinary media like blood or chocolate agar; however selective media are required to distinguish it from other bacteria. Three biotypes of diphtheria can be identified in tellurite medium: gravis, intermedius, and mitis. Gravis biotype appears as semirough grayish colonies. Intermedius biotype appears as small smooth grayish colonies with black center. Mitis biotype appears as small smooth grayish colonies. Toxigenic strains can be smooth or rough and can be of any biotype, however intermedius is found more often to be toxigenic.

Pathogenesis

Infection is acquired by inhalation of infected droplets that are produced by an infected person or asymptomatic carrier. In addition inoculation of skin or other mucus membranes like nose, conjunctivae, and genitalia by droplets or with direct contact may result in localized disease. Once the organism has reached the mucus membrane of the pharynx and tonsils, it elicits an inflammatory response and causes necrosis. This results initially in small yellowish areas of exudates over the tonsils. These lesions coalesce to form a pseudomembrane that is formed by debris and inflammatory exudates. Necrosis of the underlying mucosa results in grayish discoloration of the membrane. The membrane is usually well demarcated and mainly covers the tonsils. In some instances it extends to uvula, pharynx, larynx, and trachea. It does not extend anteriorly.

Clinical Features

Tonsillopharyngeal Diphtheria

Incubation period of the disease is 2–7 days. The onset is usually insidious with illness progressing from mild sore throat and low grade fever to signs of increasing respiratory difficulty. Lymphadenopathy is usually mild and there is no tenderness. Throat examination will reveal grayish membrane that is well demarcated and usually extends beyond the tonsils. It bleeds upon trial of scraping. If the membrane involves the larynx, the patient will have inspiratory stridor and difficulty in breathing. Occasionally the disease may take a hyperacute course, with high fever, toxicity, cardiopulmonary collapse, and encephalopathy.

Nasal Diphtheria

Five to ten percent of diphtheria will present with nasal disease. It is usually mild and lacks systemic complication of myocarditis and neuropathy. The presentation starts with nasal mucoid discharge that proceeds to be bloody due to formation of necrotic tissue. The membrane can be visualized in the nostrils and there may be evidence of irritation on the upper lip.

Laryngeal Diphtheria

It is difficult to diagnose laryngeal diphtheria unless laryngoscopy or bronchoscopy is done to evaluate the upper airways anatomy. Systemic symptoms are minimal and the main presentation is inspiratory stridor that may progress to respiratory obstruction. As with nasal diphtheria cardiac and nervous systems complications are unusual.

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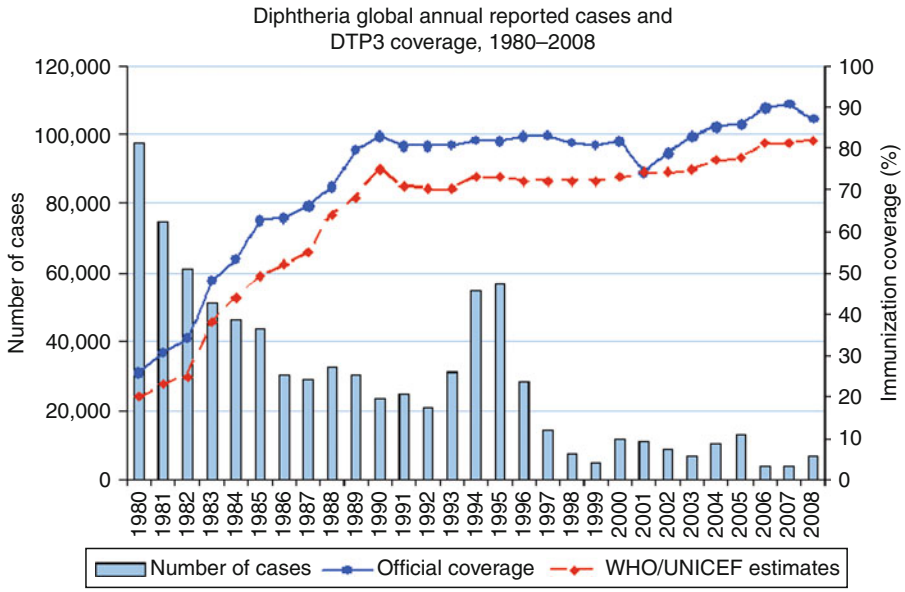

Figure 80.1
Global annual reported cases of diphtheria

Complications

Diphtheria complications are mediated by exotoxin that is produced by toxigenic strains of *C. diphtheria*. The toxin can cause damage to any organ; however CNS and heart are the most commonly involved.

Cardiac Complications

Diphtheria toxin causes myocardial degeneration with minimal inflammatory response. This degeneration also involves the conducting system. In addition to myocarditis, the affected patient usually has variable degrees of heart block and dysrhythmia. Actually the main cause of heart failure in these patients is usually dysrhythmias. Most of the toxin effects on the heart occur in the second week of illness but it can occur as early as few days and as late as 6 weeks. Early treatment will prevent or decrease the severity of heart involvement.

CNS Complications

CNS complications usually appear 4–7 weeks later. Diphtheria toxin has increased affinity to anterior horn neurons, cranial nerves neurons, as well as dorsal ganglion neurons. The most common CNS complication is bilateral motor ascending neuropathy with gradual flaccid paralysis and loss of deep tendon reflexes. Palatal and diaphragm palsies are the most common.

Cranial nerve palsies may occur. Brain stem involvement may occur with resultant blood pressure instability. There is usually no sensory impairment. Recovery is complete without any residual impairment.

Other Organ Complications

Hepatitis, nephritis, and gastritis are rare complications that have been reported in association with diphtheria. Adrenal hemorrhage also may occur with resultant adrenal failure. Hemolytic uremic syndrome has also been reported.

Diagnosis and Differential Diagnosis

Diphtheria mimics most of the upper respiratory infections like streptococcal pharyngitis, infectious mononucleosis, adenovirus infection, and Vincent's angina with faucial membrane. However the membrane in diphtheria usually extends beyond the tonsils whereas it does not in the others.

Laryngeal diphtheria has similar presentation to that of foreign body aspiration, peripharyngeal or retropharyngeal abscess, and laryngeal hemangiomas or papillomas.

In suspected cases of diphtheria, laboratory should be notified and both throat swab and nasopharyngeal aspirate be submitted. In the laboratory, specimens should be screened initially with Gram and methylene blue stains. At the same time blood agar, Loeffler's serum medium, and tellurite medium should be inoculated. Blood agar is used in order to diagnose any other or coexisting infection like streptococcal pharyngitis. Loeffler's medium is to isolate the organism in pure culture so it can be used for toxigenic evaluation or subculturing tellurite medium in case that initial inoculation was not informative. On tellurite medium *C. diphtheriae* has a characteristic appearance of black colonies surrounded by a brownish halo.

Schick test is an intradermal skin test that is used to determine the immunity status of the patient. Intradermal injection of diphtheria toxin will cause induration and erythema of >10 mm in patients who are not immune. Immune patients will not have a reaction as the toxin is neutralized with antitoxin. Some patients may show reaction secondary to hypersensitivity to the toxin or its constituents. To avoid such problem a control test with toxoid is injected into the other arm. In immune patients who are hypersensitive, a reaction will appear to both toxin and toxoid; however, it will disappear in 48–72 h. Nonimmune patients will have persistence of reaction to the toxin for more than 5 days and disappearance of reaction to toxoid in less than 5 days. Schick test is not widely used and its application in clinical practice is limited.

Treatment

Suspected cases of diphtheria should be given antitoxin and started on penicillin therapy. Antitoxin is equine derivative and therefore a test dose should be given. If there is any evidence of reaction then desensitization should be started. Penicillin can be given as procaine penicillin 25,000–50,000 units/kg/day for 14 days. Erythromycin is a good alternative for those who are allergic to penicillin.

Prevention

Isolation

Patients should be isolated for the whole duration of therapy. Two cultures from both nose and throat should be obtained 24 h apart after completion of therapy. If they are negative then isolation can be discontinued. If positive repeat the course of therapy.

Contacts

Close contacts should be cultured and given antibiotics prophylaxis with either erythromycin 40–50 mg/kg/day in four divided doses for 7 days or benzathine penicillin 600,000 units IM if the contact <30 kg in weight or 1.2 mega units IM if >30 kg in weight. Immunization status should be updated. A booster dose should be given to all contacts that have no diphtheria booster within 5 years.

Asymptomatic Carrier

Carrier patients should be treated with erythromycin 40 mg/kg/day in four divided doses for 7 days or single dose of benzathine penicillin 600,000 units IM for those below 30 kg in their weight or 1.2 mega units IM. Two throat cultures obtained 24 h apart should be obtained 2 weeks after completion of therapy. If still positive, therapy course needs to be repeated. Immunization should be updated. Those with uncertain history of immunization or who received less than four doses should be given a booster dose. In addition a booster should be given if the last vaccine dose was given 1 year or more prior to the illness.

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