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Diphtheria is a potentially lethal infection caused by toxin-producing strains of *Corynebacterium diphtheria*, a Gram-positive bacillus. Humans are the only known reservoir, with spread via respiratory droplets or direct contact with skin lesions. Although now rare in developed countries, this vaccine-preventable disease remains an important problem in countries with poor or failing health systems with about a 10% mortality rate. Pathogenesis—diphtheria develops when toxigenic bacteria lodge in the upper airway or on the skin of a susceptible individual. An intense inflammatory reaction develops, leading to a characteristic greyish-coloured pseudomembrane that is adherent to underlying tissues. Systemic effects are caused by release of diphtheria toxin, carried by a lysogenic corynebacteriophage, a single molecule of factor A of which can kill a eukaryotic cell. Clinical features—after an incubation period of 2–6 days the disease presents acutely in several ways, classified by the location of the pseudomembrane: (1) anterior nasal—usually relatively mild; (2) tonsillar (faucial)—the commonest form, with malaise, fever, sore throat, painful dysphagia and tender cervical lymphadenopathy; (3) tracheolaryngeal—with particular risk of airway obstruction; (4) malignant—with rapid onset, circulatory shock, cyanosis, gross cervical lymphadenopathy ('bull neck'), and very poor prognosis; (5) cutaneous—usually mild but chronic; morphological features can be extremely variable. Later complications include (1) myocarditis—seen in 10% of cases; and (2) segmental demyelinating neuropathy—most often palatal paralysis, and more sinister paralyzes of pharyngeal, laryngeal, respiratory, and limb muscles. Diagnosis—infection may be confirmed by bacterial culture, with detection of toxin production by one of several laboratory techniques, or of the toxin-producing gene by polymerase

chain reaction. Treatment and prognosis—aside from supportive care, this involves (1) antitoxin—20 000 to 100 000 units, depending on disease severity; preferably given within 48 h of the onset of symptoms; (2) antibiotics—benzylpenicillin (or penicillin V), or erythromycin in those allergic to penicillin; (3) maintaining the airway—lifesaving procedures such as tracheostomy may be required. Recovery is usually complete if the patient survives. Prevention—diphtheria is completely preventable by vaccination, but immunity is not lifelong and may wane in adult life if booster doses are not given regularly. Similarly, infection does not necessarily confer complete protection and the disease may recur in previously infected individuals.

Introduction Diphtheria is an acute and potentially highly lethal infection of the upper respiratory tract caused by toxigenic strains of *Corynebacterium diphtheriae* and *C. ulcerans*. Today diphtheria has been virtually eliminated from most developed countries by mass immunization, yet it remains a threat in countries with poor vaccine coverage. During the 1990s there was a huge epidemic in parts of the former Soviet Union. Smaller outbreaks have been reported in several other countries.

Historical perspective Since ancient times diphtheria has been one of the most feared childhood diseases, characterized by devastating outbreaks. Diphtheria was recognized as an infectious disease by Bretonneau in 1819. The causative bacillus was described by Löffler in 1884 and a soluble toxin was identified by Roux and Yersin in 1889. In 1890, Fränkel developed an attenuated vaccine and von Behring produced an antitoxin, the first therapeutic antiserum that was first used clinically by Roux in 1894. Before the introduction of antitoxin, mortality in some epidemics had exceeded 50%. In 1913, von Behring produced a successful vaccine and the Schick (skin) test was used to detect immunity. In the United

section 8 Infectious diseases 960 Kingdom there was an average of 50 000 cases and 4000 deaths each year from 1915 to 1942 and it was the leading cause of death among children aged 4 to 10 years. During the Second World War, more than a million cases were reported, including 50 000 deaths. In the United States of America, W. Barry Woods Jr declared in 1961 that: 'Were it possible merely to apply what is now known about diphtheria to every part of the world, this devastating malady could be wiped from the face of the earth'. However, even in that country, epidemic outbreaks continued in major cities (e.g. the 1970 San Antonio epidemic involving 201 cases with three deaths mainly in the unimmunized poor nonwhite population aged less than 15 years). In the United Kingdom, mass vaccination had reduced diphtheria to approximately 8–10 notified cases each year. In 2016 there were 7100 cases reported to WHO, with the most cases reported from India.

Pathogenesis *C. diphtheriae* are slender pleomorphic Gram-positive rods or clubs. There are four biotypes: *gravis*, *intermedius*, *belfanti*, and *mitis*, any of which can cause diphtheria if they produce exotoxin. Early manifestations of diphtheria, including pseudomembrane formation, result from an inflammatory reaction to the multiplying toxigenic *C. diphtheriae*. Fluid and leucocytes move from dilated blood vessels to surround necrotic epithelial cells. The fluid clots to enmesh dead cells, leucocytes, diphtheria bacilli, cellular debris, and occasionally small blood vessels. The resulting pseudomembrane is therefore adherent to underlying tissues and bleeds when pulled away. *C. diphtheriae* does not usually pass beyond the pseudomembrane site; it is the toxin that causes the later complications of diphtheria. Diphtheria toxin is a 535-amino acid residue 62-kDa exotoxin consisting of three domains, A (enzymatic), B (binding), and T (translocation). Domain B binds on the cell surface to heparin-binding epidermal growth factor (EGF)-like growth factor precursor and CD9 complex, allowing the lethal factor A to pass through the endosome membrane into the cytosol where it catalyses the NAD⁺-dependent ADP-ribosylation of eukaryotic elongation factor 2 preventing protein synthesis leading to cell death, facilitated by apoptosis.

Delivery of a single molecule of factor A to the cytosol of a eukaryotic cell will kill it. Employing this mechanism, recombinant diphtheria toxin with its B domain truncated and fused with the human interleukin (IL)-2 receptor is marketed as denileukin diftitox (DT388-IL2) for the treatment of cutaneous T-cell lymphoma, chronic lymphocytic leukaemia, and non-Hodgkin's lymphoma. The structural gene of the toxin (TOX) is carried by a lysogenic corynebacteriophage. However, TOX gene expression is regulated by the bacterial chromosome and requires low extracellular iron concentrations. Locally the toxin causes tissue necrosis and, when absorbed into the bloodstream, systemic complications. In addition to bacterial exotoxin, cell wall components such as the O- and K- antigens are important in disease pathogenesis. Pathological changes may be seen in all human cells, but the most profound changes are seen in the myocardium, peripheral nerves, and kidneys. Common cardiac changes include fatty degeneration of cardiac muscle (myocarditis) and infiltration of the interstitium with leucocytes, which may involve the conduction fibres. Although the heart can recover completely from these effects, severe fibrosis and scarring may lead to death in late convalescence. Mural endocarditis may cause embolism leading to cerebral infarction and hemiplegia. Valvular endocarditis is extremely uncommon. Neuritic changes may be seen in the nerves to the heart during the late paralytic stage of the disease. Diphtheria toxin also causes demyelination and degeneration of both sensory and motor nerves. It affects the nerves to the eye, palate, pharynx, larynx, heart, and limb muscles. It is unclear whether the toxin crosses the blood-brain barrier to cause central lesions.

Epidemiology Humans are the only known reservoir for *C. diphtheriae*. In most cases transmission to susceptible individuals results in transient pharyngeal carriage rather than disease. Spread is via respiratory droplets or direct contact with skin lesions. Cutaneous diphtheria is more contagious than respiratory diphtheria and chronic skin infections are the main reservoir in environments of poverty and overcrowding. Patients may become carriers of the infection and continue to harbour the organism for weeks or months. The organism can survive for up to 5 weeks in dust or on fomites. Today diphtheria remains an important health problem in countries with poor vaccine coverage. In these areas, children generally meet *C. diphtheriae* early, sometimes becoming a carrier, and young children may have severe or fatal attacks of diphtheria. *C. diphtheriae* tends to die out in highly immunized populations, and children may grow to adult life without encountering the bacillus. Recent serological studies in several countries indicate that up to 50% of adults are susceptible to diphtheria, and their immunity decreases significantly with increasing age. This potential risk is becoming increasingly important with the growth in international travel. Immunity to systemic disease depends on the presence of IgG antitoxin antibodies. Type-specific protection against carriage and mild forms of local disease is induced by antibodies to the variable K-antigens of the bacterial cell wall. Infection does not always confer protective immunity and outbreaks of mild disease have been reported even in highly vaccinated populations. In endemic countries protective immunity is boosted naturally through circulating strains of toxigenic *C. diphtheriae*. Diphtheria is a devastating but preventable disease. Experience suggests that declining immunity in adults poses the risk of outbreaks, but is probably not sufficient in itself to sustain a large diphtheria epidemic unless there are large numbers of susceptible children and adolescents. In the newly independent states of the former Soviet Union (NIS), economic hardship, large urban migration, and low vaccination coverage due to failing health systems probably contributed to the massive outbreak of the 1990s. This started in Russia but spread to all the NIS, leading to more than 150 000 cases and 5000 deaths between 1990 and 1998 and more than 2700 cases subsequently. Widespread immunization campaigns have largely controlled the epidemic, but the risk of diphtheria remains in all countries of the former Soviet Union (e.g. there were outbreaks in Western Siberia in 2003).

and the southern Urals in 2004) and rare cases of diphtheria continue to be reported in tourists and travellers to the NIS. Since 2002 *C. ulcerans* infections have been more commonly reported than *C. diphtheria* in the United Kingdom and France. The patients usually contracted the infection from raw milk or animals or close contact with companion animals and pets (cow, goat, cat, and dog). The

8.6.1 Diphtheria 961 increasing incidence of the diseases has resulted in the expansion of the notification criteria of the E-CDC and US-CDC for diphtheria to include infection caused by *C. diphtheria* and *C. ulcerans*. This increase in the number of clinical cases of diphtheria also emphasized the need to maintain vaccination coverage in the population above the 95% as recommended by the World Health Organization. In May 2010, a diphtheria outbreak was reported from Cite Soleil district, Port-au-Prince, Haiti, in one of the settlements housing people displaced by the January 2010 earthquake. In 2017 an outbreak of diphtheria was reported in an Amerindian tribe in Venezuela, a country that had last reported a case 25 years earlier. Clinical features Early features Diphtheria has an incubation period of 2–6 days and presents acutely in a variety of forms, classified according to the location of the pseudomembrane. Anterior nasal This is usually unilateral and relatively mild unless it coexists with other forms. It is relatively common in infancy. There is a nasal discharge, initially watery, then purulent and blood-stained. The nostril may be sore or crusted and a thin pseudomembrane can sometimes be seen within the nostril itself. Tonsillar (faucial) This is the most common form of diphtheria. Malaise, sore throat, and moderate fever develop gradually. At the onset of symptoms only a small, yellow-grey spot of pseudomembrane may be present on one or both tonsils and is easily mistaken for other types of tonsillitis; it is associated with marked fetor. The surrounding areas are dull and inflamed. Over the next few days the pseudomembrane enlarges and may extend to cover the uvula, soft palate, oropharynx, nasopharynx, or larynx (Fig. 8.6.1.1). There is tender cervical lymphadenopathy, nausea, vomiting, and painful dysphagia. The pseudomembrane becomes greenish-black and eventually sloughs off. Tracheolaryngeal Some 85% of tracheolaryngeal presentations are secondary to faucial diphtheria, but occasionally there may be no pharyngeal pseudomembrane. Initial symptoms include moderate fever, hoarseness, and a nonproductive cough. Over the next day or two, as the pseudomembrane and associated oedema spread, the patient becomes increasingly dyspnoeic with severe chest recession, cyanosis, and eventual asphyxiation unless the obstruction is relieved. Tracheostomy brings instant relief if the obstruction is confined to the larynx and upper trachea. In a minority of cases the pseudomembrane also involves the bronchi and bronchioles and tracheostomy has little effect. Malignant The onset is rapid, with high fever, tachycardia, hypotension, and cyanosis. Pseudomembrane spreads from the tonsils to cover much of the nasopharynx. It has a thick edge and as this advances the earlier parts become necrotic and foul-smelling. There is gross cervical lymphadenopathy. Individual lymph nodes are difficult to feel because of surrounding oedema; this is the characteristic 'bull neck' of malignant diphtheria (Fig. 8.6.1.2). The patient may bleed from the mouth, nose, or skin (Figs. 8.6.1.3, 8.6.1.4). Cardiac involvement with heart block occurs within a few days. Acute renal failure may ensue. Survival is unlikely. Cutaneous diphtheria In contrast to respiratory forms, cutaneous diphtheria is usually chronic but mild. The morphological features of individual lesions can be extremely variable as *C. diphtheriae* can colonize any pre-existing skin lesion (such as impetigo, scabies, surgical wounds, or Fig. 8.6.1.1 Severe diphtheria in Vietnamese children. Typical faucial pharyngeal pseudomembrane. Copyright Bridget Wills. Fig. 8.6.1.2 Malignant diphtheria with typical bull neck. Copyright Rachel Kneen.

section 8 Infectious diseases 962 insect bites) without altering their picture. However, the ulcerative form is the most frequent and typical (Fig. 8.6.1.5). Initially vesicular or pustular, and filled with straw-coloured fluid, it soon breaks down to leave a punched-out ulcer several millimetres to a few centimetres across. Common sites are the lower legs, feet, and hands. During the first 1–2 weeks, it is painful and may be covered with a dark pseudomembrane which separates, revealing a haemorrhagic base, sometimes with a serous or serosanguinous exudate. The surrounding tissue is oedematous and pink or purple in colour. Spontaneous healing to leave a depressed scar usually takes 2–3 months, and sometimes much longer. Systemic complications such as myocarditis are rare. Occasionally, the affected limb becomes paralysed. Other sites A mild conjunctivitis may accompany faucial diphtheria. Occasionally, pseudomembrane forms in the lower conjunctiva and spreads over the cornea causing considerable damage. Dysphagia may indicate that pseudomembrane has spread from the tonsils to the oesophagus. Other parts of the gastrointestinal tract are not usually affected, but melaena with colicky abdominal pain is described. Diphtheria may spread by fingers from the throat to vulva or penis causing localized sores. *C. diphtheriae* occasionally invades the vagina and cervix, allowing the absorption of toxin. Endocarditis is rare, but at least one reported case recovered following antimicrobial treatment. Diphtheria caused by other corynebacteria *C. ulcerans* produces two toxins, one of which seems to be the same as diphtheria toxin. It may cause membranous tonsillitis, but toxic manifestations are rare. *C. ulcerans* has been spread to humans in cows' milk. *C. pseudodiphtheriticum* is commonly present in the flora of the upper respiratory tract. It is nontoxigenic, but can cause exudative pharyngitis with a pseudomembrane identical to that produced by *C. diphtheriae*. More commonly it causes endocarditis in patients with anatomical abnormalities or infections of the lungs, trachea, or bronchi in immunosuppressed patients or those with pre-existing respiratory disease. Later complications Patients surviving acute diphtheria may develop one or more later complications. These result from delayed effects of the toxin following haematogenous spread. The risk and severity of complications correlates directly with the extent of the pseudomembrane and the delay in administration of antitoxin. Cardiovascular Approximately 10% of patients with diphtheria will develop myocarditis, usually those with clinically severe infection. There is a much greater frequency of cardiac involvement in laryngeal and malignant diphtheria than in faucial diphtheria, and where antitoxin administration was delayed more than 48 h after onset of symptoms. Cardiac toxicity usually appears after the first week of illness, but in malignant diphtheria can occur after just a few days. Patients complain of upper abdominal pain and may vomit. They become very lethargic and tired. Examination reveals a rapid, thready pulse with hypotension. At this stage profound shock may lead to death. In less severe cases, congestive cardiac failure may develop with a displaced apex beat, gallop rhythm, and murmurs audible over all areas of the Fig. 8.6.1.4 Malignant diphtheria with serosanguinous oral discharge. Copyright Tran Tinh Hien. Fig. 8.6.1.5 Cutaneous diphtheria. Courtesy of the late Dr B. E. Juel-Jensen. Fig. 8.6.1.3 Malignant diphtheria with serosanguinous nasal discharge. Copyright Rachel Kneen.

8.6.1 Diphtheria 963 heart. Profound bradycardia may result from heart block. There is hepatomegaly and oliguria. Electrocardiography (ECG) is the best way to demonstrate cardiac involvement (Fig. 8.6.1.6). The most common abnormalities are T-wave inversion with ST-segment changes in one or more chest leads and prolonged QTc and PR intervals. There may be right or left axis deviation, bundle branch block, or heart block. Very occasionally, atrial fibrillation or tachyarrhythmias are seen. Many more bursts of arrhythmias can be demonstrated if 24-h ECG monitoring is performed. Numerous ectopic beats have been recorded in patients who lacked other

manifestations of cardiac involvement. Although most patients surviving myocarditis recover completely, the presence of left bundle branch block at discharge is associated with poor long-term outcome. Neurological Diphtheria toxin causes a segmental demyelinating neuropathy. Neurological complications usually appear weeks after the onset of the disease, when the patient appears to be recovering, and may show a temporal progression. Palatal paralysis is relatively common and may be seen from the third week onwards. The patient develops a nasal voice and regurgitates fluids through the nose. This usually resolves within a week or so. From the third to the fifth week there may be blurred vision from paralysis of accommodation, or a transient squint from external rectus paralysis. From about the sixth or seventh week more sinister paralyses may develop involving pharyngeal, laryngeal, respiratory, and limb muscles (Fig. 8.6.1.7). The nerves to the heart may be affected causing tachycardia and dysrhythmias. In severe cases patients may become profoundly hypotonic over a few hours and can die from respiratory arrest. However, if intensive care facilities and skilled staff are available, complete recovery over the following weeks or months should ensue.

Differential diagnosis Clinical diagnosis is difficult where diphtheria is rare. The differential diagnosis includes infectious mononucleosis, streptococcal or viral tonsillitis, peritonsillar abscess, Vincent's angina, oral thrush, anthrax (Chapter 8.6.20, Fig. 8.6.20.2), Lassa fever (Chapter 8.5.17), and leukaemia and other blood dyscrasias. The bull neck of malignant diphtheria may be mistaken for mumps. In adults, secondary syphilis can sometimes cause a glairy (resembling egg white) exudate on the tonsils, and may be accompanied by rash and laryngitis.

Clinical investigation Bacterial culture of *C. diphtheriae* is the mainstay of investigation. Material for culture should be obtained preferably from the edges of the mucosal lesions and inoculated onto appropriate selective media. Suspected colonies may be tested for toxin production by gel precipitation (Elek's test), guinea pig inoculation, or enzyme immunoassay. Direct smears of infected areas of the throat are often used for diagnostic purposes, but are only of value in experienced hands. More reliably the diphtheria toxin gene may be detected directly in clinical specimens using polymerase chain reaction techniques.

Criteria for diagnosis In areas where diphtheria is relatively common and during outbreaks, the disease should be suspected in any patient with exudate in the throat. Treatment must not be delayed until the disease is confirmed, except in cases of suspected cutaneous diphtheria without associated respiratory symptoms.

Fig. 8.6.1.6 Fifteen-year-old girl with cardiac and neurological complications (paralysis of muscles innervated by cranial nerves IX, X, and XII). Copyright D. A. Warrell. Fig. 8.6.1.7 Generalized muscle weakness. Copyright Rachel Kneen.

section 8 Infectious diseases 964 Other corynebacterial skin infections *C. diphtheriae* and some other corynebacteria are associated with cutaneous 'desert sores'. Erythrasma is caused by *C. minutissimum* and, in HIV-immunosuppressed patients, *C. striatum* can cause exuberant ulceration (Fig. 8.6.1.8). Treatment Antitoxin is the mainstay of treatment, but to be maximally effective it must be given before the toxin has reached tissues such as the heart and kidneys, preferably within 48 h of the onset of symptoms, implying that it must be given empirically before bacteriological confirmation. Dosage depends on the site of primary infection, the extent of pseudomembrane, and the delay between the onset of symptoms and antitoxin administration. Between 20 000 and 40 000 units are given for faucial diphtheria of less than 48 h duration or for cutaneous infection, 40 000 to 80 000 units for faucial diphtheria in excess of 48 h duration or for laryngeal infection, and 80 000 to 100 000 units for malignant diphtheria. For doses over 40 000 units, a portion is given intramuscularly followed by the bulk of the dose intravenously after an interval of 30 min to 2 h. Anaphylaxis can occur following antitoxin administration, and adrenaline

(epinephrine) should always be available. Antibiotics are given to eradicate the organism and prevent further toxin production. Benzylpenicillin 150 000 to 250 000 units/kg per day (90–150 mg/kg per day) is given intravenously in four to six divided doses in children aged 1 month to 12 years. In adults the dosage is 12 million to 20 million units/day (7.2–12 g/ day) in four to six divided doses. Oral penicillin V is substituted when the patient is able to swallow. Erythromycin may be used for penicillin-sensitive individuals, but it may not be as effective in eradicating carriage. Antibiotic therapy should continue for 10–14 days. Facilities for urgent tracheostomy should always be available in case of respiratory obstruction. Indications include increasingly laboured breathing and agitation. This procedure will be lifesaving in many cases. Most tracheostomies can be closed after just a few days. Steroids may be used in conjunction with tracheostomy to reduce airway swelling, but there have been no controlled trials to support their use. Steroids are of no benefit in preventing myocarditis or neuritis. Patients with signs or symptoms of cardiac involvement need to be managed in intensive care units. Oxygen should be given. Temporary cardiac pacing is useful in patients with heart block, but is of doubtful value in cases of malignant diphtheria. An isoprenaline infusion may buy valuable time while the patient is transferred to a centre with facilities for pacing. Digoxin has been used in congestive cardiac failure. It has been suggested that carnitine may prevent some cases of myocarditis. There is no specific treatment for neuritis. The severest cases will need mechanical ventilation and intragastric or intravenous feeding. With skilled nursing care full recovery can be expected. Patients recovering from clinical disease should complete active immunization during convalescence. Prevention Diphtheria toxoid is highly effective in conferring protection against clinical disease. Circulating antitoxin levels of less than 0.01 IU/ml are considered nonprotective, while levels of 0.01 IU/ml may confer some protection. Levels of 0.1 IU/ml or more are considered fully protective, and levels above 1.0 IU/ml are associated with long-term protective immunity. The potency of (a) (b) (c) Fig. 8.6.1.8 *Corynebacterium striatum* infection on the thigh of an African patient with HIV-immunosuppression (a) clinical appearance of exuberant ulcerative lesion, (b) and (c) histopathological appearances of a biopsy of the lesion showing *Corynebacteria* (Gram-positive short rods, banded forms that look like diplococci and clubbed forms). (a) Courtesy of C. P. Conlon, Oxford. (b) and (c) Courtesy of Kevin Hollowood, Oxford.

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