Frequently asked questions for healthcare professionals on: Diphtheria

What is diphtheria?
Diphtheria is a contagious and potentially life-threatening bacterial disease. It is caused by infection with toxin producing strains of *Corynebacterium diphtheriae* (and rarely *Corynebacterium ulcerans* or *Corynebacterium pseudotuberculosis*), which are gram-positive, non-sporulating, bacilli. It occurs primarily in two forms; respiratory (the commonest) or cutaneous (prevalent in the tropics). The toxin is also absorbed and can produce a variety of systemic effects involving the kidneys, heart and the nervous system causing significant damage. It is the later effects of diphtheria toxin on the heart and nervous system that produce the most severe complications.

How is infection acquired?
Diphtheria spreads from person to person very easily by contact with large respiratory droplets or hand-to-mouth contact with secretions from an infected person’s mouth, nose, throat or skin, or from an asymptomatic carrier of the bacteria. Diphtheria can also spread by contaminated objects or food (such as contaminated milk). Humans are the only natural hosts of *C. diphtheriae*.

What are the clinical features of diphtheria?
The clinical features and systemic complications of diphtheria (e.g. myocarditis and peripheral neuritis) are toxin mediated and not due to invasion of the organism. The nose and throat (tonsils or pharynx) are the most common sites of infection. Toxin is produced locally by the toxin-producing strains of *C. diphtheriae* causing tissue necrosis and exudate formation triggering an inflammatory reaction. Local symptoms and signs of inflammation may then develop. Classically there is the presence of a tough grey to white adherent membrane (pseudomembrane) on the tonsils, pharynx, and/or nasal cavity. It adheres to the tissues and bleeds on removal. The membrane develops typically on the tonsil(s) and spreads locally resulting in a potential for suffocation if the membrane spreads if it is dislodged e.g. during sampling for a throat culture (swabs must be performed with extreme care and with equipment for intubation readily available).

Diphtheria may be mild or severe. Some people may be asymptomatic carriers. The classic pseudomembrane is not always present especially in previously vaccinated individuals. In severe cases the membrane spreads rapidly over the uvula, palate, oropharynx, nasopharynx. The extent of the membrane correlates with the severity of the local and systemic symptoms. The respiratory form of diphtheria has an incubation period of 2 to 5 days although this can be longer.
The onset of disease is gradual. Symptoms include local and more generalized ones. Generalized symptoms and signs may include fever, chills, listlessness, nausea, vomiting, pallor, fast heart rate and low blood pressure. Some patients do not show symptoms until the infection has progressed further. In rare instances, *C. diphtheriae* may become invasive and cause endocarditis, arthritis and bacteraemia.

Cutaneous diphtheria is prevalent in the tropics. It often presents as a secondary infection of a pre-existing skin disease e.g. impetigo. Lesions occur more commonly on exposed skin starting as small vesicles and developing into ulcers. The toxin can be absorbed systemically but systemic complications are less common than from respiratory infections with *C. diphtheriae*.

**Symptoms and signs of diphtheria may be divided into two groups:**

- **Local**
- **Systemic**

1. **Local:** these are as a result of a non-invasive infection of the respiratory tract and may include:
   - Sore throat (may range from mild to severe)
   - Problems swallowing
   - Bloody watery drainage from the nose – nasal diphtheria
   - Drooling (suggesting airway blockage is about to occur)
   - Hoarseness – laryngeal diphtheria
   - Croup-like (barking) cough
   - Stridor
   - Difficulty breathing or tachypnoea (rapid breathing) due to obstruction by the membrane
   - Enlarged lymph nodes in the neck (10% of cases)
   - “Bull neck” appearance due to severe cervical lymphadenopathy and oedema of the anterior cervical tissues

2. **Systemic:** these occur due to secondary to dissemination of the *C. diphtheriae* toxin through the blood stream to other organs such as the heart, kidneys, nervous system potentially life-threatening complications.
   - Myocarditis (inflammation of the heart muscle) is the most common
   - Demyelinating peripheral neuritis which may result in temporary paralysis following an acute illness
   - Muscle weakness
   - Profound exhaustion
   - Cardiac failure often resulting in death

**What is the treatment for diphtheria?**

Diphtheria is a medical emergency. A delay in treatment can result in death or long-term cardiac complications. Empirical treatment should generally be started immediately in a patient in whom a clinical suspicion of diphtheria is very high, even before test results are available. Patients with diphtheria should be hospitalized until fully recovered. Severe cases e.g. those with respiratory obstruction may require intubation or a tracheostomy and must be admitted to an intensive care unit (ICU) for care. Patients should be given diphtheria antitoxin to neutralize the diphtheria toxin. Since the antitoxin does
not neutralize toxin that is already bound to tissues, delaying its administration is associated with an increase in risk of mortality. Therefore a decision to administer diphtheria antitoxin is based on clinical diagnosis, and should not await laboratory confirmation. Unfortunately there is currently no diphtheria antitoxin available in South Africa for treatment of cases. Antibiotics have not been demonstrated to affect healing of local infection. However antibiotics are used to eradicate *C. diphtheriae* from the nasopharynx and prevent its transmission to others:

- Erythromycin (orally or IM) for 14 days OR
- Benzylpenicillin G intramuscularly for 14 days
- Azithromycin and clarithromycin can also be used as alternatives for treatment.

Supportive care also includes:
- Cardiac monitoring – an increase in heart rate may cause cardiac arrest
- IV fluids
- Bed rest
- Management of systemic complications as required

**How do we make a definitive diagnosis of diphtheria?**
The need to initiate antitoxin therapy as soon as possible means that the diagnosis of diphtheria needs to be presumptive and made on clinical grounds initially. Diagnosis is first suspected clinically after a thorough physical examination. 

Confirmation of the diagnosis of diphtheria depends upon isolation of a *toxin-producing* strain of *C. diphtheriae*. Non-toxigenic *C.diphtheriae* may be isolated from throat swabs, blood cultures and/or other sites but these strains do not cause clinical diphtheria and do not require the same public health response.

**Method of collection of specimens:**

**Throat swabs**

- The pharynx should be clearly visible and well illuminated
- Depress the tongue with an applicator and swab the throat without touching the tongue or inside the cheeks
- Rub vigorously over any membrane, white spots, or inflamed areas; slight pressure with rotating movement must be applied to the swab
- If any membrane is present, lift the edge and swab beneath it to reach the deeply located organisms
- Transport the swab immediately to the laboratory for culture

**Nasopharyngeal specimens**

- Insert the swab into the nose through one nostril beyond the anterior nares
- Gently introduce the swab along the floor of the nasal cavity, under the middle turbinate, until the pharyngeal wall is reached
- Force must not be used to overcome any obstruction
- Transport to the laboratory immediately
Skin lesions
- Lesions should be cleansed with sterile normal saline and crusted material removed
- Press the swab firmly into the lesion
- Transport to the laboratory without delay

Culture for *C. diphtheriae* is not routinely performed on all throat swabs and it is therefore essential that the laboratory is informed when diphtheria is suspected. The procedure for processing of throat swabs for *C. diphtheriae* includes:

1. **Microscopy**
   - *C. diphtheriae* is a gram-positive, non-sporulating bacillus. The organism is highly pleomorphic and appears in palisades or as individual cells lying at sharp angles to another in V and L formations (“Chinese lettering”). It is commonly seen as club-shaped swellings and beaded forms. The methylene blue stain (Albert’s stain) often stains the organisms irregularly, giving them a beaded appearance. Albert staining of smears made directly from clinical specimens is not reliable for diagnostic purposes, since metachromatic granules are found in other bacteria as well. Furthermore, *C. diphtheriae* must be a toxigenic strain to be diagnostic of diphtheria.

2. **Culture**
   - Should be performed on Blood agar and a Hoyle’s tellurite plate.
   - Examine all agar plates at 24 and 48 hour for colonies typical of *C. diphtheriae*. Then subculture colonies that are catalase positive and exhibit typical morphology on gram stain to blood agar to provide growth for identification procedures.

   **Gram’s stain**: pleomorphic gram-positive rods that occur in angular arrangements (commonly referred to as palisades or Chinese letters); possibly coccobacillary forms, most notably in older cultures.

   **Albert’s stain (methylene blue)**: pleomorphic beaded rods from the Loeffler slope whose ends may be swollen, producing a club shape; angular arrangements; brownish-black metachromatic granules or bars apparent.

   **Colony morphology**:
   - **Tellurite medium**: Colonies appear greyish black on tellurite containing media e.g. Hoyles and have a garlic-like odour. Black colonies on Hoyle’s tellurite agar can be due to other organisms capable of reducing tellurite to tellurium. Other *Corynebacterium* spp., staphylococci, and some streptococci possess this ability.

**NOTE**: *C. diphtheriae* and *C. ulcerans* will also grow on standard blood agar and other primary culture media e.g.: chocolate agar. However the laboratory diagnosis of diphtheria can be missed if only standard processing is performed as the colonies of *C. diphtheriae* are not distinct on standard agar media used for routine throat or wound cultures. In addition, corynebacteria in mixed culture with other throat or skin will often be ignored as “normal flora” if a diagnosis of suspected diphtheria has not been communicated.

Four biotypes of diphtheria can be determined by biochemical testing: *gravis, mitis, intermedius* and *belfanti*
Procedures for presumptive identification:
The minimal laboratory criteria required to presumptively report an isolate as *C. diphtheriae* are as follows:

- catalase positive
- urea: negative for *C. diphtheriae*, positive for *C. ulcerans*
- nitrate positive (except the biotype var belfanti)
- carbohydrate fermentation – maltose and glucose positive

3. Tests for toxigenicity
- Identification of an isolate as *C. diphtheriae* does not mean that patient has diphtheria. The diagnosis of diphtheria depends on showing that the isolate produces diphtheria toxin.
- Toxin detection can be done by either in vivo or in vitro testing.
- In vitro methods are reliable, less expensive, and free from the need to use animals and therefore the in vivo methods are rarely done.
- The Elek test is the in vitro diphtheria toxin detection procedure first described by Elek. It is an immunodiffusion test where organisms are streaked on media of low iron content to optimize toxin production.
- The Elek test requires that reagents and antiserum be carefully controlled and titrated and for this reason, and because of the difficulty of the test, it should be performed only in certain reference laboratories. In South Africa the current reference laboratory for the Elek test is Greenpoint NHLS in the Western Cape Province.

References for laboratory procedures:
2. NHLS SOP MIC0381: available on Q-pulse.

What is the differential diagnosis of diphtheria?
The differential diagnosis includes:
- **Infectious mononucleosis** – the tonsillar exudate of infectious mononucleosis is creamy in color. It does not extend beyond the tonsil and does not produce bleeding when removed.
- **Streptococcal tonsillitis** – is usually associated with more severe local symptoms and a higher fever.
- **Acute epiglottitis** – is more acute in onset. It is not associated with membrane formation.

Is diphtheria common in South Africa?
The true burden of illness in South Africa is unknown but the incidence of clinical diphtheria has been reduced by widespread childhood immunization. However, some people are not adequately vaccinated, and immunity due to vaccination wanes.
How is diphtheria prevented?
Diphtheria can be prevented by active immunization with formalin detoxified diphtheria toxin (toxoid). Immunity wanes over time and 20-80% of adults have a very low antibody titres. In South Africa (SA), the Expanded Programme on Immunisation (EPI) schedule includes 6 doses of diphtheria vaccine. The primary series of vaccination is given in 3 doses at 6, 10, 14 weeks of age using diphtheria toxoid given as DTaP-IPV/Hib (Diphtheria, Tetanus, acellular Pertussis, inactivated Polio Vaccine and *Haemophilus Influenzae* type b combined). The fourth dose (first booster) is given at 18 months using DTaP-IPV/Hib (Diphtheria, Tetanus, acellular Pertussis, inactivated Polio Vaccine and *Haemophilus Influenzae* type b combined). As from 1 February 2008, two additional booster doses have been introduced by the SA-EPI programme. Diftavax® (Td) vaccine (containing Tetanus and a reduced strength dose of diphtheria toxoid) is now administered at 6 and 12 years of age, respectively. Td vaccine has replaced DT vaccine, which was previously administered at 5 years of age. Td can be used as a booster in individuals ≥ 6 years of age. Antitoxin levels decline following vaccination and boosters are recommended at 10 year intervals to ensure protective levels.

Who is at risk of acquiring diphtheria?
Persons, especially children who are not immunized or who did not receive adequate immunization are the most at risk. Diphtheria is most common in areas where people live in crowded conditions with poor sanitation.

What is the recommended public health response in SA to a case of diphtheria?
Diphtheria is a notifiable condition in South Africa. All suspected cases should be reported to infection control nurses and district and provincial communicable disease control staff urgently. Antibiotic treatment using penicillin or erythromycin should be given to cases for 14 days and elimination of the organism confirmed on follow-up cultures. Diphtheria anti-toxin treatment is only effective if given very early in the course of illness and is not available in SA. Cases should be isolated with droplet and contact precautions until 2 negative throat and nasal swabs are obtained >24 hours after completion of treatment and taken 24 hours apart.

Follow up of close contacts is essential. Throat and nasal swabs should be obtained from those who have had close contact with the case in the previous 7 days. Post-exposure chemo-prophylaxis should also be provided with benzylpenicillin or erythromycin (newer macrolides may also be effective). Those with positive cultures will require full treatment and follow up cultures as per symptomatic cases. The aim of chemoprophylaxis is both to eliminate asymptomatic carriage and to treat incubating disease. Booster immunisation should also be provided to those who have not received a booster in the previous 12 months. Contacts should be monitored for symptoms for at least 7 days.