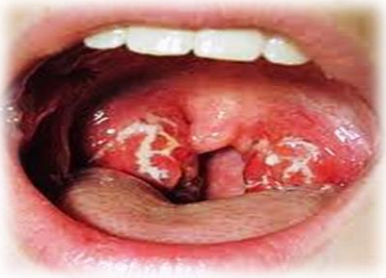
World Health Organization

Operational protocol for clinical management of Diphtheria
Bangladesh, Cox's Bazar (Version 10th Dec 2017)

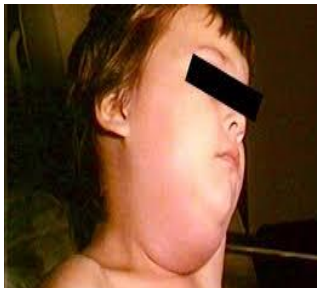
Background[1]: Diphtheria is a bacterial infection caused by toxigenic strains of *Corynebacterium diphtheria (C. diphtheria)* and most often causes infection of the upper respiratory tract. It leads to the clinical syndromes of pharyngitis, naso-pharyngitis, tonsillitis, laryngitis (or any combination of these) associated with a firmly adherent pseudo-membrane over the tonsils, pharynx, larynx and/or nares. In severe cases, infection can spread into trachea causing tracheiitis and/or severe cervical adenopathy leading to life-threatening airway obstruction. Death can occur from asphyxiation or aspiration of sloughed pseudo-membrane. *C.diphtheriae* can also cause skin and wound infections. Diphtheria is most commonly spread from person to person, usually through respiratory droplets, like from coughing or sneezing or by direct contact with either respiratory secretions or infected skin lesions. Respiratory diphtheria usually occurs after an incubation period of 2-5 days.

Probable Case[2]

A person with an illness characterized by laryngitis or pharyngitis or tonsillitis, and an adherent membrane of the tonsils, pharynx and/or nose OR gross lymphadenopathy



Pharyngeal membrane of diphtheria. Note: the membrane extends beyond the tonsils and covers the adjacent pharyngeal wall.



Summary of initial clinical management of all probable cases

1. Place patient immediately in isolation room (or area) and apply standard, droplet and contact precautions when caring for the patient.
2. Administer diphtheria antitoxin (DAT) as soon as possible.
3. Administer antibiotics (penicillin, erythromycin or azithromycin) as soon as possible.
4. Monitor closely and provide supportive therapy for severe complications (i.e. airway management, cardiac, neurologic and renal failure)
5. Vaccinate with an age appropriate diphtheria toxoid-containing vaccine.

[1]http://www.who.int/immunization/policy/position_papers/wer_31_diphtheria_updated_position_paper.pdf?ua=1

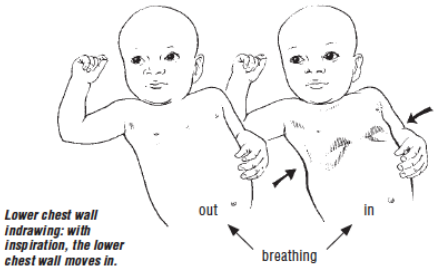
[2]http://apps.who.int/iris/bitstream/10665/68334/1/WHO_V-B_03.01_eng.pdf?ua=1

Clinical presentations

Symptoms: Initial symptoms include malaise, sore throat and nasal discharge resembling **viral upper respiratory illness (URTI)**. Symptoms can then progress to bloody nasal discharge, hoarse voice, cough, and/or pain with swallowing. In children, this may cause drooling or pooling of secretions. In severe cases, patients may develop noisy breathing (inspiratory stridor) and shortness of breath. Fever may or may not be present. Skin can become infected with the diphtheria bacteria (cutaneous diphtheria); clinically wounds have a grey covering over it. (See differential diagnosis table in **Appendix A).**

Throat and nares examination: Conduct a careful examination. Be careful not to cause distress in children as this may worsen the clinical situation. On inspection, child may also have an obviously swollen neck, referred to as **"bull neck"** due to swollen cervical lymph nodes, soft tissue edema and mucosal edema. Look at the nares and throat to visualize the typical gray-white adherent membrane overlying the inflamed, edematous mucosa. The grey membrane may be localized asymmetrically (i.e. affecting nares, tonsils, pharynx) or may extend to affect the larynx and trachea. When this membrane is agitated with a swab it does not "come off" and may cause profuse bleeding if dislodged.

'Bull neck': a sign of diphtheria, due to enlarged lymph nodes in the neck



Lower chest wall indrawing: with inspiration, the lower chest wall moves in.

⚠ **Look for presence danger signs (impending airway or circulatory failure)**: **If any present, call for help for urgent supportive treatment.**

- Any sign of respiratory distress such as inspiratory stridor, fast breathing, chest indrawing, accessory muscle use, or restlessness are warning signs of impending airway obstruction and the need to secure the airway.
- The presence of lethargy, cyanosis or SpO_2 < 90% is ominous in child with upper airway obstruction (implies overt airway obstruction) and emergent need to secure airway.
- Any sign of shock such as capillary refill > 3 seconds, presence of cold extremities, fast pulse rate, or low blood pressure, is also an emergency that needs urgent attention.

.

Look for other serious complications: Within 1-12 weeks, after the initial pharyngeal phase, some patients may develop myocarditis (congestive heart failure, conduction abnormalities, and arrhythmias), debilitating neurologic dysfunction (neuropathy of cranial and peripheral nerves, and/or motor weakness/paralysis), or renal failure.

Infection Prevention and Control

Transmission of *C. diphtheriae* occurs from person to person through respiratory droplets (i.e. from coughing or sneezing) and close physical contact[3].

1. Apply standard precautions, droplet and contact precautions[4], at all times.
2. At triage, immediately place patients with symptoms of URTI to a separate area until examined, and if a probable case cohorted with patients with same diagnosis. Keep the isolation area segregated from other patient-care areas.
3. Maintain one metre between patients, when possible. Keep patient care areas well ventilated.
4. The disease is usually not contagious after completing 48 hours of effective antibiotic therapy. May consider discharge at this time if patient is improving.
5. After discharge, restrict contact with others until completion of antibiotic therapy (ie remain at home, do not attend school or work until treatment course is complete).

How to implement droplet and contact precautions[5].

Patient:

- Place patient in separate, isolation area away from other patient care areas.
- Avoid patient movement or transport out of isolation area.
- If movement is necessary out of isolation area, have patient use a medical-surgical mask.

Health care worker (HCW):

- Hand hygiene **(See Appendix B)**
- HCW wears medical-surgical mask, gloves, eye protection (face shield or goggle), and long sleeved-gown when within one metre of patient or when entering room.
- Removes PPE after leaving room
- Uses disposable or dedicated patient equipment when possible. If not possible, then cleans and disinfects between use if sharing between patients.
- Refrains from touching his/her eyes, nose or mouth with contaminated gloved or ungloved hands.
- Avoids contaminating surfaces not involved with direct patient care (i.e. door knobs, light switches, mobile phones).

[3] http://www.who.int/immunization/policy/position_papers/wer_31_diphtheria_updated_position_paper.pdf?ua=1

[4] http://www.nicd.ac.za/assets/files/Guidelines_diphtheria_20160322_v2_3(1).pdf

[5] http://apps.who.int/iris/bitstream/10665/112656/1/9789241507134_eng.pdf

Laboratory diagnosis[6]:

During outbreak, routine sampling of throat samples is not recommended. However, collection of samples should be considered in the following situations:

a) when diagnosis is unclear (i.e. swollen neck without adherent pseudo-membrane);
b) or if suspect antimicrobial resistance.

Material for culture should be obtained by swabbing the edges of the mucosal lesions, placed in appropriate transport media (Amies or Stuart media in ice packs; or dry swabs in silica gel satchets) and followed by prompt inoculation onto blood agar and tellurite-containing media, e.g. Tinsdale media.

Suspected colonies may be tested for toxin production using the modified Elek immunoprecipitation test for detection of toxin; this standard assay takes 24–48 hours. A positive culture with toxin-producing *C. diphtheriae* confirms the etiologic diagnosis.

See **Appendix F** for sample collection protocols

[6]http://www.who.int/immunization/policy/position_papers/wer_31_diphtheria_updated_position_paper.pdf?ua=1

<u>Antitoxin therapy (DAT):</u> Administer as soon as possible.

1. DAT is an equine serum product that is highly effective and the gold standard for treatment of diphtheria[7].
2. DAT should be administered **immediately** to probable cases with respiratory diphtheria (sore throat, low grade fever and presence of adherent membrane on tonsils, pharynx or nose) based on clinical diagnosis. Do not wait for laboratory diagnosis.
3. Diphtheria toxin that has already entered the host cells is unaffected by DAT. Therefore, to reduce complications and mortality DAT should be administered as soon as possible after disease onset (see Appendix D)
4. Due to small risk for a serious allergic reaction to the horse serum (0.6 % anaphylaxis), perform a **sensitization test (**i.e. Besredka test[8]**)** for all candidate patients.
5. DAT should be administered in a closely monitored setting with appropriate medical interventions available, if needed.
6. Pregnant women should not receive DAT.
7. The amount of antitoxin recommended varies with larger amounts recommended for persons with extensive pseudomembrane, neck swelling, systemic signs and with longer interval since onset. The dose is the same for children and adults. Do not repeat dosing[9].

If limited availability, then use lower dose range.

Severity of diphtheria	**Dosage for adults and children [8]**
Laryngeal or pharyngeal of 2 days duration	20,000-40,000 IU
Nasopharyngeal disease	40,000-60,000 IU
Extensive disease of 3 or more days of duration or any patient with diffuse swelling of the neck (respiratory distress, hemodynamic instability)	80,000-100,000 IU

[7] http://www.who.int/immunization/policy/position_papers/wer_31_diphtheria_updated_position_paper.pdf?ua=1

[8] https://medicalguidelines.msf.org/viewport/CG/english/diphtheria-16689456.html

[9] https://www.cdc.gov/diphtheria/downloads/protocol.pdf

<u>Antibiotic treatment for probable and confirmed cases:</u> Antibiotics should be administered as soon as possible.

1. For patients who cannot swallow or are critically ill, use IV or IM preparations.
2. For severely ill patients unable to take oral therapy, use IV/IM formulation at the onset. Once patient improves clinically, stepdown to oral antimicrobials
3. For less sick patients, oral therapy can be used at the onset.
4. Check for penicillin allergy (risk of anaphylaxis from penicillin is very rare).

For severely ill patients, choose one of the following:

Procaine benzyl penicillin (penicillin G): administer IM All persons: 50 mg/kg once daily (maximum 1.2 grams a day)[10]. Treat for total 14 days. * Powder for injection: 1 g (=1 million IU); 3 g (=3 million IU) in vial.
Aqueous benzyl penicillin (penicillin G): administer IM or slow IV All persons: 100,000 units/kg/day administer in divided dose of 25 000 IU/kg every 6 hours. Maximum dose is 4 MIU or 2.4 grams per day[11]. *Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial
IV Erythromycin All persons: 40-50 mg/kg/day (maximum, 2 gm/day). Administer in divided dose, 10-15 mg/kg every 6 hour, maximum 500 mg per dose[12]. Treat for total 14 days.

For patients who can swallow and are less ill, use oral preparation. Choose one:

Oral phenoxymethylpenicillin V All persons: 50 mg/kg/day, administer in divided dose 10-15 mg/kg/dose administered every 6 hours[13]. Maximum is 500 mg per dose. Treat for 14 days.
Oral erythromycin All persons: 40-50 mg/kg/day (maximum, 2 gm/day). Administer in divided dose, 10-15 mg/kg every 6 hour, maximum 500 mg per dose. Treat for total 14 days.
Oral azithromycin For children: 10-12 mg/kg once daily (max. 500 mg/day). Treat for total of 14 days. For adults: 500 mg once daily. Treat for total of 14 days. Note: There is no data to support the exact duration required for azithromycin

[10] http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf?ua=1

[11] https://medicalguidelines.msf.org/viewport/CG/english/diphtheria-16689456.html

[12] https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/dip.pdf

[13] http://www.nicd.ac.za/assets/files/Guidelines_diphtheria_20160322_v2_3(1).pdf

Admission criteria/patient disposition (see appendix A)

Patients with a diagnosis of probable or confirmed Diphtheria and with severe symptoms will require admission to a facility capable of dealing with the respiratory and systemic complications as well as isolation for first 48 hours. This includes national hospital's and Type 2 or Type 3 Field hospitals (facilities with inpatient and surgical capacity, and the ability to provide high level nursing care, experienced medical and/or infectious disease doctors, along with anaesthetic and surgical specialists).

Patients with probable diphtheria but mild symptoms require at least 48 hours isolation but can be discharged within 48 hours of treatment commencing if clinically well enough. Isolation via cohort versus individual isolation needs to be managed at a facility level, but cross infection to those without diphtheria may occur in mixed wards, and a flow within a facility will need to be designed to allow early discharge of the well, and admission to a lower level isolation after 48 hours for those who have medical reasons to remain in the clinic or hospital, but with less risk of infecting others after 2 days of treatment.

Co-location of severe and mild patients should be considered, and criteria and methods for referral established, given the risk of some mild cases worsening. All cases in the initial phase of admission (48 hours) require 2-4 hourly review and close observation, particularly in the very young.

Supportive therapy for patients with complications[14] [15]

Monitor the patient closely

1. The patient's condition, especially respiratory status, should be assessed often, at least every 2-4 hours, for any signs of respiratory distress from the development of airway obstruction or aspiration. This includes vital signs and pulse oximetry.
2. Also monitor cardiac function with ECG for conduction abnormalities and arrhythmias (if possible).

⚠ If patient shows any sign of inspiratory stridor, fast respiratory rate, chest indrawing, restlessness, lethargy, or cyanosis, then call for help and proceed with airway management.

Oxygen therapy can mask airway obstruction, use with caution:

1. Avoid using oxygen routinely. Signs of respiratory distress (such as fast respiratory rate, severe lower chest wall indrawing and restlessness) are signs of requiring airway support and proceed to secure airway. Desaturation in isolated upper airway obstruction is a sensitive sign for impending airway compromise and deterioration. If there is desaturation ($SpO_2 < 90\%$), this is a sign that the airway is obstructing and you need to act to secure the airway. Use oxygen while you are in the process of securing the airway.

[14] http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/

[15] http://www.who.int/maternal_child_adolescent/documents/paediatric-emergency-triage-update/en/

2. Administer oxygen if there is incipient airway obstruction and securing airway is deemed necessary and soon to be performed or if SpO2 < 90%.

> ⚠Avoid pharyngeal irritating interventions such as routine use of nasogastric tubes and nasopharyngeal catheters. Even placement of a nasal cannula may disturb child and precipitate obstruction of the airway.

If signs of airway compromise, proceed to secure airway (see Appendix D). Securing airway is a life-saving intervention. Call for help immediately.

1. Securing airway is life-saving intervention. Consult senior doctor, with extensive experience with difficult airway management immediately. This includes an anesthetist, intensivist, surgeon (preferably, an ears, nose, throat (ENT) surgeon). Tracheostomy in infants carries significant risks, so should be done with great caution by skilled surgeons.
2. If there are signs of incipient (impending) complete airway obstruction (signs of respiratory distress such as inspiratory stridor, fast respiratory rate, restlessness, chest wall in-drawing, accessory muscle use, desaturation), then secure airway immediately. If skilled personnel are available, take patient to operating theatre. A graded approach is recommended, with orotracheal approach preferred (when possible), always using a difficult airway algorithm. If airway not secured with orotracheal approach, then proceed to tracheostomy (if experienced surgeon available) or needle cricoithyroidotomy (as a temporalizing emergency procedure until tracheostomy can be performed emergency procedure).
3. If patient develops complete airway obstruction (cyanosis, SpO_2 < 90-94, lethargy), then perform an emergent tracheostomy (if experienced surgeon is available) or needle cricoidthyroidotomy (temporizing emergency procedure). Under such circumstances, orotracheal intubation may not be possible and may dislodge the membrane and fail to relieve the obstruction, and should only be performed by skilled personnel. If attempted, be prepared also to perform emergent airway procedure.
4. Administration of nebulized adrenaline is used in many causes of upper airway obstruction as a temporizing measure. Though specific data on efficacy in acute