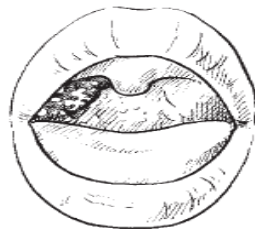


Operational protocol for clinical management of Diphtheria Bangladesh, Cox's Bazar (Version 10th Dec 2017)

Background¹: 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 tracheitis 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 Case²

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.

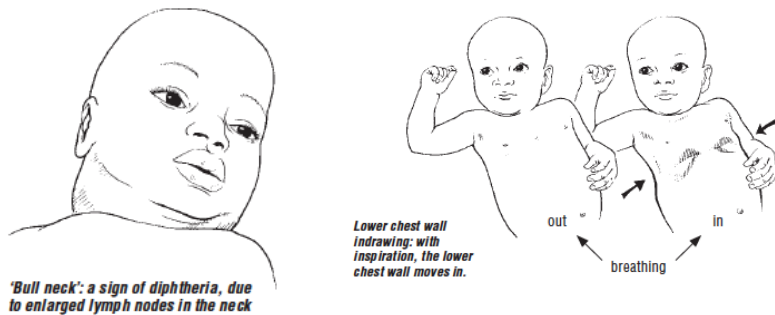
¹http://www.who.int/immunization/policy/position_papers/wer_31_diphtheria_updated_position_paper.pdf?ua=1

²http://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.



⚠ 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 contact³.

1. Apply standard precautions, droplet and contact precautions⁴, 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 precautions⁵.

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).

³http://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](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 diagnosis⁶:

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

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

Antitoxin therapy (DAT): Administer as soon as possible.

1. DAT is an equine serum product that is highly effective and the gold standard for treatment of diphtheria⁷.
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 test⁸) 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 dosing⁹.

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 |

⁷http://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>

Antibiotic treatment for probable and confirmed cases: 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 day¹¹.

*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 dose¹². 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 hours¹³. 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](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 cricothyroidotomy (as a temporizing emergency procedure until tracheostomy can be performed emergency procedure).
3. If patient develops complete airway obstruction (cyanosis, SpO₂ < 90-94, lethargy), then perform an emergent tracheostomy (if experienced surgeon is available) or needle cricothyroidotomy (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 respiratory diphtheria is not available, can consider its use for upper airway obstruction. As a trial administer nebulized adrenaline (2 ml of 1:1000 solution). If effective can repeat hourly.

Manage shock

1. A child with all 3 signs of shock (delayed CR > 3 seconds + weak and fast pulse + cold extremities or frank hypotension) needs careful resuscitation. Because shock can be due to sepsis or cardiac failure, it is imperative to look for signs of cardiac failure. In addition, also check if child has severe malnutrition. If there are no signs of cardiac failure and/or fluid overload (absence of crackles, hepatomegaly and edema), then give gentle fluid bolus. If suspect shock is due to heart failure, then

use inotropes (such as dopamine or adrenaline) and do not administer fluids. Refer to WHO IMCI Handbook for sick children.

Other supportive treatments

1. If the patient has fever (>38 °C) or pain that appears to be causing distress, give paracetamol.
2. Encourage the child to eat and drink. If the child has difficulty in swallowing, nasogastric feeding may be required. The nasogastric tube should be placed with extreme caution by an experienced clinician or, if available, an anesthetist.
3. Avoid frequent examinations and invasive procedures when possible or disturbing the child unnecessarily.

Myocarditis (may occur 2–7 weeks after the onset of illness) can present with a weak, irregular pulse and evidence of heart failure. Treat with supportive therapies according to national standards.

Neurologic paralysis (may occur 1 to 3 months after the onset of the disease) and can lead to difficulty with swallowing (paralysis of the soft palate), vision (ocular motor paralysis), breathing (paralysis of respiratory muscles) and ambulation (limb paralysis). Treat with supportive therapies according to national standards.

Care of all close contacts Contact¹⁶ⁱ:

The objective is to prevent the development of the disease among contacts who might have been infected with the *Corynebacterium diphtheriae* and provide medium and long-term protection against the disease.

1. Identify close contacts of probable cases (irrespective of age): household members (all persons who sleep in the same house/tent during the last 5 nights before onset of disease of the case) and any persons with close contact (less than one metre) for a prolonged time (over 1 hour) during the 5 days prior to onset of disease of the case (e.g. caretakers, relatives, or friends who regularly visit the home) as well as medical staff exposed to oral or respiratory secretions of a case-patient.
2. Collect contact information: names, age, mobile telephone number if possible and ways to follow up (telephone, visits).
3. Inform the contacts about the outbreak and the disease.
4. Assess diphtheria toxoid vaccination status of exposed close contacts. Vaccinate according to WHO strategy (which prioritizes children's vaccination).

- Type: Pentavalent (for 6 wks to 6 yrs) or Td (for 7 yrs and above).
- Number of doses:
 - Only one dose if documentary evidence of having completed primary vaccination schedule is available.
 - Three doses: at least 4 weeks interval between each dose

¹⁶ <https://www.cdc.gov/diphtheria/downloads/close-contacts.pdf>

- Administer antibiotics for prophylaxis.

Choose one of the following antibiotics for prevention:

IM benzathine penicillin: a single doseⁱⁱ

For children aged ≤ 5 years: administer 600 000 units

For those > 5 years: administer 1 200 000 units

Oral erythromycin

For children: 40 mg/kg/day, administered in divided dose, 10 mg per dose, every 6 hours

For adults: 1 g/day for adults, administered in divided dose, 250 mg per dose every 6 hours

Treat for total 7 days

Oral Azithromycin

Children: 10-12 mg/kg once daily, to a max of 500mg/day. Treat for total 7 days

Adults: 500mg once daily. Treat for total 7 days.

- Exclude from school or work until 48 hours of antibiotics have been completed
- Self assess for signs and symptoms of diphtheria for at least 7 days.
- If person develops any symptom of respiratory tract infection, then seek treatment at a health centre immediately.

Vaccination:

- Vaccinate according to WHO strategy. Primary prevention of disease by ensuring high population immunity through immunization.
-

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Microbiologist. National Institute for Communicable Diseases South Africa

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CDC, Atlanta
Dr. Wilson Were, WHO HQ IMCI

TRIAGE

Sore Throat
URTI
+/- Fever
+/- Malaise

Refer to Infection
Prevention and
Control measures

Some patients may
present weeks after
URTI symptoms with
new onset of cardiac
renal or neurological

Early pseudo-
membrane



Protected clinician
examines throat

pseudo-membrane OR
gross lymphadenopathy

No

URTI
Advice to return if
no improvement.
Give Paracetamol

Yes

Are there Clinical Warning Signs?

Pseudo-Membrane



Stridor
Fast Respiratory Rate
Chest in-drawing
Restlessness or lethargy
Bull neck
Delayed capillary refill
Fast Heart rate and cold extremities
Central Cyanosis

Bull Neck



Yes

No

DAT (give as soon as possible)
Antibiotics (give as soon as

Antibiotics (give as soon as possible)

Field Hospital

DAT dose
20-100,000 IU
Aqueous benzyl penicillin (penicillin G): (IM or IV)
25 000 units/kg every 6 hours. *Daily maximum dose is 4 MIU.* Treat for 14 days.
When patients are able to swallow, switch to oral
antibiotics and continue for combined total of 14
days

Laboratory sampling on a case by case basis

Isolation facility for at least 48 hours

Oral penicillin V
10-15 mg/kg/dose administered every 6 hours.
Maximum is 500 mg per dose. Treat for 14 days.
Oral erythromycin
10 mg/kg administered every 6 hours. Maximum is 500
mg per dose. Treat for 14 days.
Oral azithromycin
10 mg/kg administered once daily. Maximum is 500 mg
per day. Treat for 14 days..

Monitor for deterioration, refer to field hospital if patient worsens

Contact Tracing, Vaccination, and Prophylaxis for Contacts

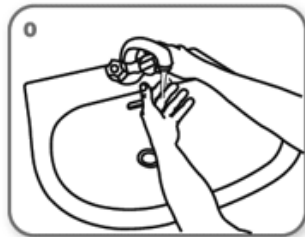
Appendix B: Differential diagnosis table

Respiratory diphtheria is a clinical diagnosis. If the patient has atypical features (i.e. lacks adherent membrane on the pharynx, tonsils or nares); must also consider alternative etiologies.

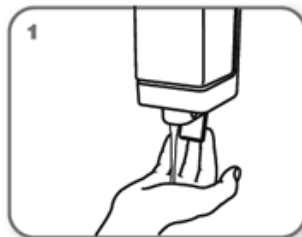
| Differential diagnosis of pharyngitis | |
|--|--|
| Group A streptococcus | Fever, no coughing, tonsillar exudate and follicles, tender jugulodigastric nodes |
| EBV | Fever pharyngitis, adenitis, hepatomegaly, splenomegaly |
| Vincent's Angina | Acute onset of painful bleeding gums, ulcers and sluffing of the gingiva |
| Oral candida | White/ yellow patches on the inner cheeks, tongue, roof of the mouth, and throat, gelatinous mass can be removed Cracking and redness at the corners of the mouth |
| Differential diagnosis of stridor | |
| Viral croup | Barking cough, respiratory distress, hoarse voice, |
| Retropharyngeal abscess | Soft tissue swelling in back of the throat, difficulty in swallowing, fever |
| Epiglottitis | Soft stridor, Septic' child, Little or no cough, Drooling of saliva, Inability to drink |
| Anaphylaxis | History of allergen exposure, Wheeze, Shock, Urticaria and oedema of lips and face |

Appendix C: Hand washing

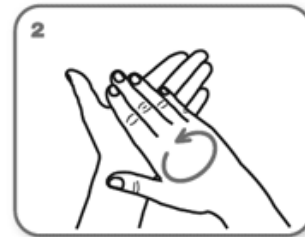
Hand hygiene must be performed before and after any contact with patients and after contact with contaminated items or surfaces. Use an alcohol-based product if hands are not visibly soiled. Wash hands with soap and water when they are visibly soiled or contaminated with proteinaceous material. The same rubbing technique can be used with alcohol-based product. This entire procedure can take should take 40-60 seconds (20-30 for alcohol-based hygiene).



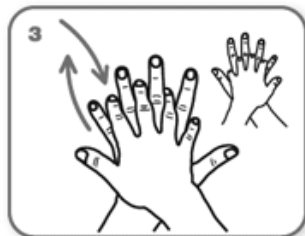
Wet hands with water



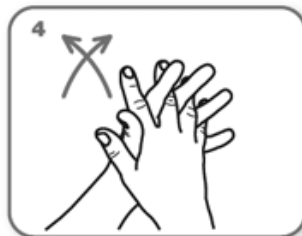
apply enough soap to cover all hand surfaces.



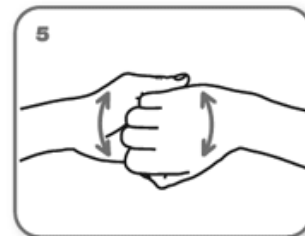
Rub hands palm to palm



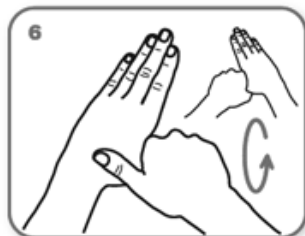
right palm over left dorsum with interlaced fingers and vice versa



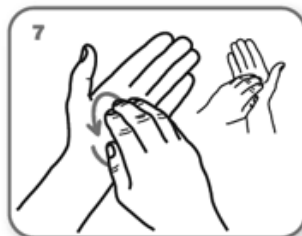
palm to palm with fingers interlaced



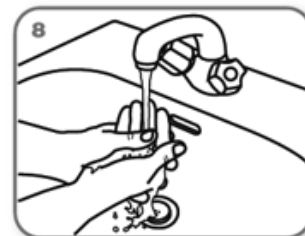
backs of fingers to opposing palms with fingers interlocked



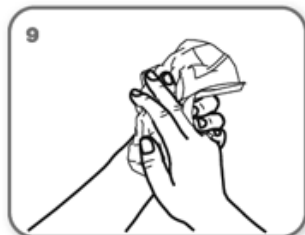
rotational rubbing of left thumb clasped in right palm and vice versa



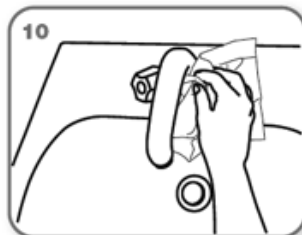
rotational rubbing, backwards and forwards with clasped fingers of right hand in left palm and vice versa.



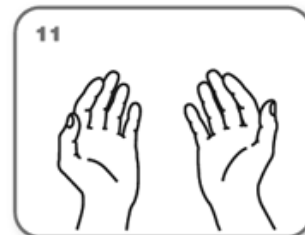
Rinse hands with water



dry thoroughly with a single use towel



use towel to turn off faucet



...and your hands are safe.

Appendix D. How to deliver diphtheria antitoxin (see package insert)

General information for family/patient: DAT is an equine serum product that is highly effective and the gold standard for treatment of diphtheria. Antitoxin is used to stop the damaging effect of the toxin and prevent the life-threatening manifestations of diphtheria infection. However, there is small risk of serious allergic reaction: < 0.6 % anaphylaxis, 4% fever, and 8.8% serum sickness.

Dose: The amount of antitoxin recommended varies with larger amounts recommended for persons with extensive local lesions and with longer interval since onset. The dose is the same for children and adults. Do not repeat dosing.

If limited availability, then use lower dose.

| Severity of diphtheria | Dosage for adults and children ⁱⁱⁱ |
|--|--|
| 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 |

Route: The IV route is the preferred route of administration of DAT, especially in severe cases. The antitoxin dose should be mixed in 250 –500 mL of normal saline and administered slowly over 2 – 4 hours, closely monitoring for anaphylaxis. The antitoxin may be given IM in mild or moderate cases.

Temperature: Antitoxin should be warmed to 32 – 34°C (90 – 95°F) before injection.

Environment: Ensure appropriate monitoring and medical interventions are available for adult and paediatric patients in case serious allergic reaction ensues.

- Monitoring devices: pulse oximeter, BP cuff, thermometer
- Emergency medicines: adrenaline (1:1000), salbutamol, antihistamine, prednisolone, crystalloid fluid, oxygen supply and delivery devices
- Emergency equipment: bag valve mask, IV giving devices, airway management

Procedure:

1. HCW uses contact and droplet precautions: gloves, long-sleeved gown, surgical mask and eye protection.
2. Monitor patient vital signs: BP, HR, RR, SpO₂, mental status, before and after administration.
3. Perform sensitization testing

Sensitization testing: use the Besredka method

- a) Inject 0.1 ml SC and wait 15 minutes. If there is no reaction then inject further 0.25 ml SC. If no reaction after 15 minutes, then inject remainder IM or IV^{iv}. This test method is simple and has been used safely in outbreak settings in South Africa.
- b) If patient demonstrates sensitivity on testing, then do not administer entire dose. Proceed with desensitization according to CDC protocol
<https://www.cdc.gov/diphtheria/downloads/skintest-guide.pdf>

4. Monitor for adverse events. If noted, then stop administration immediately.

| Adverse event | Clinical description |
|---|--|
| Anaphylaxis (rapid onset) | Onset usually within minutes. Skin: pruritus, flushing, urticaria, and angioedema. Respiratory: hoarse voice and stridor, wheeze, dyspnea, and cyanosis. Cardiac: rapid, weak pulse, hypotension, and arrhythmias. Anaphylaxis is a major medical emergency, call for help. |
| Febrile reaction (within 20-60 minutes) | When fever occurs, it is characterized by a chilly sensation, slight dyspnea and a rapid rise in temperature. Most febrile reactions are mild. Treat with antipyretics alone (i.e. paracetamol); severe reactions may require other measures (tepid water baths, etc.) to reduce the temperature. |
| Serum sickness (usually 7-10 days after initial exposure, range 5-25 d) | Symptoms are fever, maculopapular skin rashes, or urticaria in milder forms (90% of instances); arthritis, arthralgia, and lymphadenopathy also possible in more severe forms. Rarely, angioedema, glomerulonephritis, Guillain-Barré syndrome, peripheral neuritis, or myocarditis can occur. Mild cases of serum sickness frequently resolve spontaneously over a few days to 2 weeks. Medications that may be helpful include antihistamines, non-steroidal anti-inflammatory drugs, and corticosteroids. |

5. Treatment of anaphylaxis

If anaphylaxis occurs, STOP infusion.

1. Call for help.
2. Assess the airways, breathing and circulation. Start emergency treatments – If the child is not breathing, check pulse. If no pulse, start basic life support and give five rescue breaths with a bag-valve mask and 100% oxygen.
3. Give adrenaline (1:1000, 1mg/ml) IM immediately:
 - 0.15 ml of 1:1000 to children < 6 years, repeat every 5 minutes as necessary
 - 0.3 ml of 1:1000 to children 6-12 years, repeat every 5 minutes as necessary
 - 0.5ml of 1:1000 epinephrine to adolescents and adults, repeat every 5 minutes as necessary
4. Ensure stabilization of airway, breathing and circulation.
 - Get IV/IO access, give 100% oxygen, give crystalloid fluid (20 ml/kg IV) rapidly for shock, nebulized salbutamol for wheezing
5. Also give antihistamine and steroids (i.e. prednisolone 1 mg/kg).

Appendix E. How to approach airway management in patients with severe respiratory diphtheria

Scenarios: There are two scenarios you may encounter:

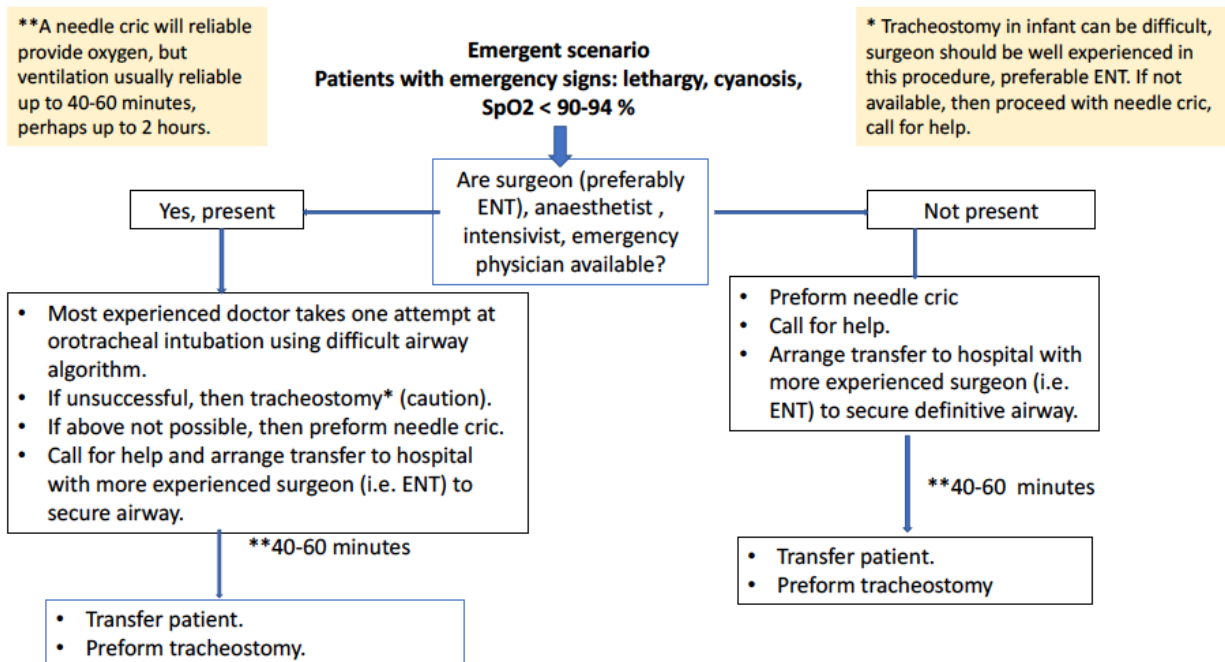
- **emergent** airway scenario;
- **urgent** airway scenario.

Emergent: If child has a low saturation, SpO₂ < 90-94%, lethargy or cyanosis, these are ominous signs (emergency signs) in patient with upper airway obstruction and the airway must be secured emergently.

Urgent: If a child with respiratory diphtheria has any signs of respiratory distress, such as inspiratory stridor, restlessness, fast respiratory rate, chest wall indrawing, accessory muscle use, this is urgent situation, proceed to secure airway as soon as possible.

In both cases, if there is an experienced doctor with difficult airway management skills and appropriate equipment, attempt an oral intubation using difficult airway algorithm.

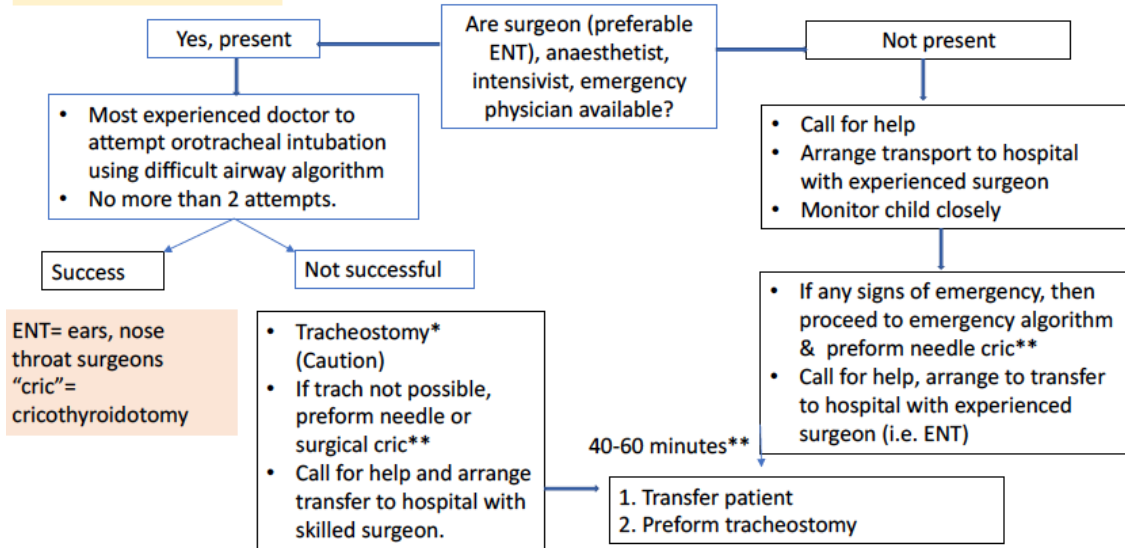
However, if experienced personnel not available, and an emergent situation develops, a needle cricothyroidotomy (needle cric) as a temporizing emergency measure can be performed by any doctor. If temporizing needle cric performed, then plan for securing airway must be in place.



****A needle cric will reliably provide oxygen, but ventilation will be reliable for average 40-60 minutes, perhaps up to 2 hours.**

**Urgent scenario
Patient with signs of any sign of respiratory distress
without emergency signs**

*** Tracheostomy in infant can be difficult, surgeon should be well experienced in this procedure, preferably ENT.**

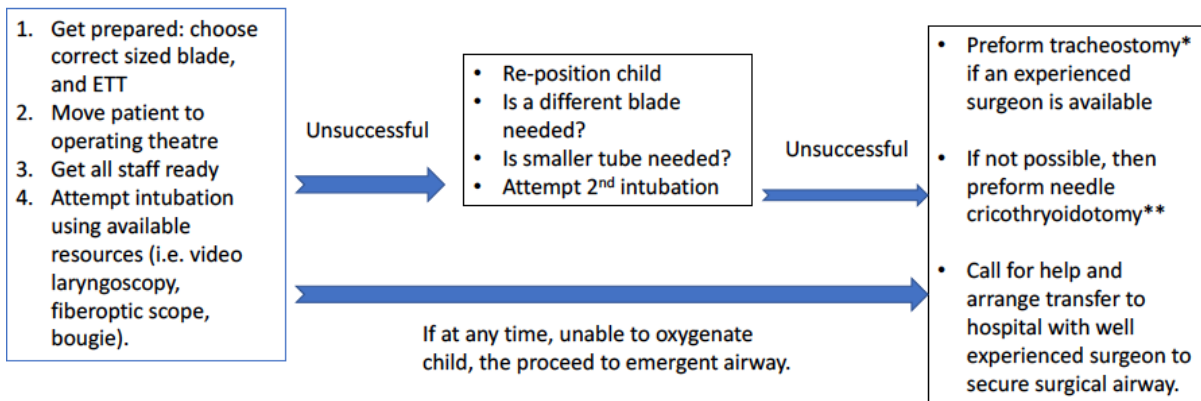


ENT= ears, nose throat surgeons
"cric"= cricothyroidotomy

****A needle cric will reliably provide oxygen, but ventilation limited, usually reliable up to 40-60 minutes, perhaps up to 2 hours.**

Difficult airway algorithm
Attempt at intubation should be done by most experienced doctor in airway management (i.e. anaesthetist, intensivist, emergency physician) only when all appropriate equipment are available (i.e. paediatric blades and tubes)

*** Tracheostomy in infant can be difficult. The surgeon should be well experienced in this procedure, preferably ENT. If not available, then proceed with needle cric, call for help.**



Basic Preparation for airway intervention

Staff: The management of upper airway obstruction due to diphtheria is best done by a multi-disciplinary team: anaesthetist (experience with paediatric, if possible), a surgeon (ears, nose throat specialist, if possible), intensivist or emergency medicine specialist. If these specialists are not available, then the most experienced doctors and nurses should be present.

Context: Perform airway management in a monitored setting, preferably the operating theatre. The patient should be placed on a continuous monitor and SpO₂, HR, RR, BP, and AVPU should be recorded frequently. Use contact precautions (HCW wear an N95, mask, gloves, eye protection, and gown).

Timing: Right timing is important. It is preferred to secure the airway pre-emptively before the child develops complete airway obstruction. Once complete airway obstruction occurs, emergent tracheostomy (if experienced surgeon present) or needle cricothyrotomy or “Needle Cric” (for non-surgeons) may be the only viable option to secure airway. Inflammation can be severe and makes recognition of abnormal anatomy difficult and may bleed during intubation. Ensure suction is working and ready.

Check equipment: ensure all equipment is available, checked and working. This includes: suction, oxygen (BVM), airways (tracheal tubes of appropriate size, oral airways, various blades); medicines (sedatives), functioning IV and crystalloid fluid. Also available should be locally available difficult airway cart: This includes: bougie, video laryngoscope (if available), fiberoptic scope (if available), needle cricothyrotomy “kit”, end-tidal CO₂ monitor. Tape to secure airway once obtained.

Sedation: In patients with an upper airway obstruction, it is preferable to maintain child’s spontaneous respiratory efforts. DO NOT administer muscle relaxants. Use only very low doses of sedative, if necessary, to ease child if crying. Oversedation can stop spontaneous breathing and if mask ventilation is difficult, then situation can become emergent (can’t oxygenate and can’t ventilate scenario).

Pre-oxygenate: for 3-5 minutes with 100% FiO₂.

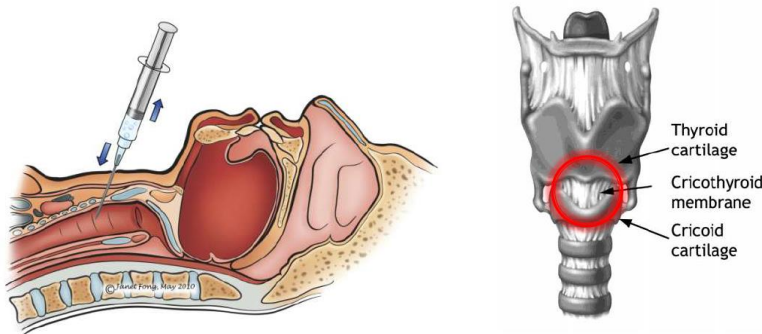
Position: Lying the child flat may worsen the obstruction. So be prepared. Do not lie child flat until ready to start procedure.

How to perform percutaneous needle cricothyroidotomy or “needle cric”

Needle cricothyroidotomy is indicated as a life-saving, last-resort procedure in children younger than 10 years who have upper airway obstruction, and the child presents or progresses to the “can’t intubate, can’t oxygenate” scenario. This procedure can be performed by a paediatrician, intensivist, anaesthetist, emergency physician, general surgeon or family physician. After inserting the needle cric, then need to arrange child to be transported quickly to hospital with surgeon that can perform tracheostomy within 60 minutes.

Preparation: Pre-assemble the “needle cric kit” and have available in the resuscitation area. The simplest equipment, appropriate for use in infants, consists of the following:

- 14G over-the-needle catheter
- To connect to BVM: a 3.0-mm ETT adapter coupled with an IV extension set (These can be obtained commercially or constructed by cutting off 6 inches of distal IV tubing and inserting a 2.5 m adapter into the opening (below)
- To connect directly to oxygen: 3- or 5-mL syringe with side port “hole” to allow exhalation, with oxygen tubing inserted inside with a “tight fit” (below)
- It is good practice to preassemble the kit, place it in a clear bag, seal the bag, and tape it in an accessible place in the resuscitation area.



How to perform procedure

1. **Prepare your adapter:** The catheter can be attached either to a 3.0 mm ETT adaptor to provide bag ventilation (if available). Or, can be attached directly to oxygen supply using a 3-way stopcock or 2-5 ml syringe as adaptor.
 - If you have three-way stopcock, then attached to oxygen tubing. The three-way stopcock will allow for inspiration of oxygen and exhalation.
 - Alternatively, use a 2-5 ml syringe with plunger removed as the “adapter”. Use scalpel to make a “hole” to serve as exhalation side port, either in the syringe (below the oxygen tubing) or in the tubing itself. Insert oxygen tubing snugly inside the syringe. Make sure the exhalation side-port is patent and below the oxygen tubing.
 - Humidified oxygen source



2. Position: Place the child in the supine position with the head extended over a towel under the shoulder. This forces the trachea anteriorly such that it is easily palpable and can be stabilized with two fingers of one hand. The key to success is strict immobilization of the trachea throughout the procedure.
3. Anatomy: "Carefully palpate the cricothyroid membrane." In reality, it is difficult to do this in an infant and is not essential. Indeed, in smaller children, it may be impossible to precisely locate the cricothyroid membrane, so the proximal trachea is utilized for access (hence the name percutaneous needle tracheostomy [PNT] vs. "needle cric"). The priority is an airway and provision of oxygen. Complications from inserting the catheter elsewhere into the trachea besides the cricothyroid membrane are addressed later.
4. Sterile technique: Clean skin and wear sterile gloves.
5. Needle insertion: Consider the trachea as one would a large vein, and cannulate it with the catheter-over-needle device directed caudally at a 30° angle. Aspirate air to ensure tracheal entry and then slide the catheter gently forward while retracting the needle.
6. Connect adaptor: The catheter can be attached either to a 3.0 mm ETT adaptor to provide bag ventilation (if available). Or, can be attached directly to oxygen supply. Both are described below:
 - Attach to BVM: Attach 3.0-mm ETT adapter to the hub of the catheter and commence bag ventilation. The provider will note exaggerated resistance to bagging. This is normal and is related to the small diameter of the catheter and the turbulence created by ventilating through it. It is not generally the result of a misplaced catheter or poor lung compliance secondary to pneumothorax. It is helpful to practice BMV through a catheter to experience the feel of this increased resistance. **The operator must allow for full expiration** through the patient's glottis (if not completely obstructed) and not through the catheter in order to prevent breath-stacking and barotrauma. This can be accomplished by watching for the chest to fall after inspiration. The required pressures are well above the limits of the pop-off valve; therefore, it must be disabled in order to permit gas flow through the catheter. A secondary source of oxygen can be put over the mouth.

- Attach to oxygen source directly (no BVM): If you have three-way stopcock, then attached to end of catheter that should already be connected to oxygen tubing. The three-way stopcock will allow for inspiration of oxygen and exhalation. Alternatively, attach the 2-5 ml syringe with exhalation side port, already connected to oxygen tubing. For inhalation, occlude exhalation side-port for one second, then allow exhalation for 3-4 seconds (look at chest wall rise and fall to determine ventilation. Always make sure the exhalation side-port is not blocked by oxygen tubing.
- 7. Transport: Transfer patient to a hospital with experienced surgeon that will be readily available to secure surgical airway. Ventilation through the small-bore catheter is limited, and after 40-60 minutes, hypercapnia may develop. Some report reasonable ventilation for up to 40-60 minutes (and in some cases, up to 2 hours.) Transfer should be done expediently, with patient on monitor, while careful bag ventilation and/or oxygen therapy.
- 8. Communication: Communicate clearly with receiving doctor so that there is not delay in securing airway promptly once child arrives.

Post intubation/tracheostomy Care:

1. After securing the airway, firmly secure tube to avoid accidental displacement, as this could be fatal.
 2. Care for child in an intensive care unit with appropriately trained staff and monitoring.
 3. The provision of humidified oxygen and ventilation will depend on available resources (i.e. manual bag ventilation, mechanical ventilation or oxygen therapy) and severity of hypoxemia. If aspiration has occurred, CPAP may be necessary.
 4. Manage secretions with careful suctioning and humidification to prevent tube obstruction from sloughed, thick pseudomembranes.
-

APPENDIX F: Specimen collection, storage and transportation

Laboratory confirmation of diphtheria is useful for diagnosis of clinically suspected cases in the early phases of a response, or when diagnosis is equivocal. Specimen of choice is a throat swab that should be collected as early as possible during the course of illness of the suspected cases. Nasopharyngeal swab is also considered as a good specimen for diphtheria diagnostics especially in infants or small children. The chances of positivity fall rapidly after 2-3 weeks of onset or by use of appropriate antibiotics. The diphtheria bacteria have fastidious growth requirements and are susceptible to drying therefore, the use of transport media is recommended to enhance positivity of laboratory tests. The prerequisites for sample collection and condition of sample storage and transportation for diphtheria is described in the table below.

Table: Prerequisites and conditions for sample collection

| Prerequisites/Conditions | Diphtheria |
|-----------------------------------|--|
| Window period from onset | 2day-4 weeks |
| Type of specimen | Throat swab or pieces of membrane or nasopharyngeal swab |
| Number | 2 |
| Transport media | Amies transport media with or without charcoal |
| Storage and transportation | 2-8 °C |

Procedures for collecting specimen:

Material required: throat swab specimen

- Wooden sticks (disposable tongue depressors)
- Gloves
- Face masks
- Disposable bag
- Tissues
- Throat swab: cotton, dacron
- Amies transport media: with or without charcoal
- Zip lock bag
- Labels
- Laboratory request form

Material required: nasopharyngeal swab specimen

- Gloves
- Face masks
- Disposable bag
- Tissues
- Paper scale
- Nasopharyngeal swab: thin flexible swab

-
- Amies Transport media with or without charcoal
 - Zip lock bag
 - Labels
 - Laboratory request form

Throat swab sample collection:

- Use any throat swab made up of cotton, polyester or Dacron
- Label the specimen tube with the unique identification code, patient's name and date of collection
- Check the expiry date on the tube and transport media
- Swab the inflamed area of tonsils, and posterior pharynx. If membrane is visible then rub the swab beneath the membrane
- Piece of membrane can also be collected on the swab
- Immediately place the throat swab sample in the Amies transport media
- Procedure to use Amies transport media:
 - immediately insert the swab till the bottom of the media
 - if capped swab then throw the cap of the tube
 - if un capped swab – then cut the shaft of the swab to fit into the tube and cap it securely
- Ship the sample to the laboratory at 2-8°C

Nasopharyngeal swab sample collection:

- Obtain a thin flexible nasopharyngeal swab made up of Dacron or nylon
- Label the specimen tube with the unique identification code, patient's name and date of collection
- Check the expiry date on the tube and transport media
- Have patient sit with head against a wall or a support as patients have a tendency to pull way during this procedure
- Explain the procedure to the parents or patient
- Measure the distance between anterior nares to the lower lobe of the ear of one side
- Mark the swab with half of the above measured distance
- Ask the patient to blow the nose forcefully to remove any mucous plug
- Position the head slightly upwards and insert the swab along the base of the nose up to the distance marked. Avoid insertion of swab in upward direction
- Do not force swab if obstruction is encountered before reaching the nasopharynx. Remove swab and try the other side
- Try to leave the swab in place for 5-10 seconds to increase sensitivity
- Immediately place the swab in Regan-Lowe transport media/Amies transport media with charcoal and tighten the cap of specimen collection container. It is recommended to wrap tape around cap to prevent any leakage
- Ship at 4°C

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