Diphtheria Guide for Health Care Professionals

This information requires knowledgeable interpretation and is intended primarily for use by health care workers and facilities/organizations providing health care including pharmacies, hospitals, long-term care homes, community-based health care service providers and pre-hospital emergency services.

Public Health Division

Ministry of Health and Long-Term Care

May 2015

Ontario

A Quick Response Guide to Diphtheria

Diphtheria – The Treatment of Diphtheria is Guided by Clinical Diagnosis

The diagnosis of diphtheria is made by the isolation of toxigenic *Corynebacterium diphtheriae* from an appropriate clinical specimen. Although rare, other toxigenic *Corynebacterium* species (*Corynebacterium ulcerans or Corynebacterium pseudotuberculosis*) may cause clinical diphtheria. A comprehensive case history should be obtained to support the diagnosis pending laboratory confirmation. Immediate medical treatment is required to treat diphtheria; do not await laboratory confirmation.

Clinical Description

Diphtheria is an acute bacterial disease primarily involving the upper respiratory tract, cutaneous, or other mucous membranes (e.g., conjunctivae, vagina).The onset of disease is insidious and symptoms may initially be nonspecific with a moderate fever; however, symptoms may become severe with signs of toxicity, requiring treatment with Diphtheria Antitoxin (DAT).

Laboratory Diagnosis and Specimen Collection

Clinical specimens must be obtained prior to medical treatment and the administration of DAT. Clinical specimens should be transported to Public Health Ontario Laboratories for testing. **DAT should not be withheld pending laboratory results** if there are strong clinical indications for diphtheria.

Place a Request for Diphtheria Antitoxin

Ministry of Health and Long-Term Care (MOHLTC) staff will arrange for the shipment of DAT. Information on ordering DAT is on page 6. Vaccine storage and handling practices should be in place at all times to ensure DAT is maintained within a temperature range of +2 °C to +8 °C.

Notify your Local Public Health Unit

Individuals who have or may have diphtheria shall be reported as soon as possible to the Medical Officer of Health by persons required to do so under the *Health Protection and Promotion Act*, R.S.O. 1990.

Complete and Submit Follow-Up Patient Information to the Ministry of Health and Long-Term Care

After administering DAT, complete and submit Form C (available at http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/index-eng.php) to Immunization Policy and Programs, MOHLTC at vaccine.program@ontario.ca. This information will be provided to Health Canada's Special Access Programme.

The full document, *Diphtheria Guide for Health Care Professionals* is available at: http://www.health.gov.on.ca/en/pro/publications/disease/diptheria.aspx.

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Diphtheria

Diphtheria is an acute toxin-mediated disease caused by *Corynebacterium diphtheriae.* There are four biotypes of *Corynebacterium diphtheriae* (*gravis, mitis, belfanti* and *intermedius*). Strains may be toxigenic or non-toxigenic. Invasive infection generally occurs with toxigenic strains. Although rare, other toxigenic *Corynebacterium* species (*Corynebacterium ulcerans or Corynebacterium pseudotuberculosis*) may cause clinical diphtheria.

Clinical Description

Diphtheria is an acute bacterial disease primarily involving the upper respiratory tract, cutaneous, or other mucous membranes (e.g., conjunctivae, vagina).

Respiratory diphtheria can be classified based on clinical manifestation. Anterior nasal diphtheria may appear as mild or chronic unilateral mucopurulent to serosanguinous nasal discharge and excoriations. Onset of symptoms often cannot be distinguished from those of a common cold.

Pharyngeal and tonsillar diphtheria initially presents with low-grade fever, sore throat, difficulty swallowing, malaise and anorexia. The characteristic lesion is an asymmetrical adherent greyish white membrane with surrounding inflammation visible on the tonsils and oropharynx within two to three days of illness. Neck swelling and enlarged cervical lymph nodes may give the appearance of a “bull neck”. Pharyngeal membranes may extend into the trachea resulting in upper airway obstruction and subsequent acute respiratory distress; asphyxia can occur in young children. Systemic complications from dissemination of diphtheria toxin can result in myocarditis and central nervous system effects.

Laryngeal diphtheria can be confined to this site or an extension of pharyngeal diphtheria, characterized by fever, hoarseness, stridor and a barking cough that can progress to airway obstruction, coma and death. Case-fatality ratio for respiratory diphtheria is 5% to 10%.

Cutaneous diphtheria is localized to the area of infection and rarely associated with systemic complications. Disease is often associated with homeless persons and is presumed to be responsible for high levels of natural immunity in this population. Lesions may vary from scaly rash to ulcers with demarcated edges.

Modes of Transmission

Transmission is most often person-to-person spread from the respiratory tract. Both cases and carriers can be a source of infection. Rarely, transmission may occur from skin lesions or articles soiled with discharges from lesions of infected persons (fomites).

Laboratory Diagnosis

Clinical illness or systemic manifestations compatible with diphtheria in a person with an upper respiratory tract infection or infection at another site (e.g., wound, cutaneous) and at least one of the following constitutes confirmed case diphtheria:

- Isolation of *Corynebacterium diphtheriae* with confirmation of toxin from an appropriate clinical specimen (e.g., throat, nasal, nasopharyngeal or cutaneous sites, exudate of membrane)

- Isolation of other toxigenic Corynebacterium species (*Corynebacterium ulcerans or Corynebacterium pseudotuberculosis)* from an appropriate clinical specimen

  (e.g., throat, nasal, nasopharyngeal or cutaneous sites, exudate of membrane)
- Histopathologic diagnosis of diphtheria
- Epidemiological link to a laboratory-confirmed case (contact within two weeks prior to onset of symptoms)

Refer to Appendix A for detailed information on specimen collection and transportation.

Incubation Period

Usually two to five days, occasionally longer; range from one to ten days.

Antitoxin Use and Clinical Management

DAT should not be withheld pending laboratory results if there are strong clinical indications for diphtheria.

DAT is an equine immunoglobulin preparation that neutralizes the toxin from the bacterium *Corynebacterium diphtheriae*, and is administered as per the product insert (See Appendix B). DAT is the only class of drugs known to treat diphtheria, and can be accessed through the MOHLTC. Health care practitioners are strongly advised to consult the product insert **before** an order is placed for DAT. The product insert contains information required to determine the amount of DAT to be ordered and administered. Instructions outlined in the product insert provided by the manufacturer should be followed carefully. In addition, **DAT is a biological agent and should be stored and handled similarly to vaccines; ensure DAT is maintained within a temperature range of +2 °C to +8 °C.** Exposing DAT to temperatures above or below this range may impact its effectiveness and may result in wastage. DAT replacement is costly and supplies are limited.

Medical care including antibiotic treatment combined with rapid administration of DAT is crucial to the management of diphtheria.

Process for Ordering Diphtheria Antitoxin

Before placing an order for DAT, it is essential that you read the following sections within this guide: i) Clinical Description; ii) Modes of Transmission; iii) Laboratory Diagnosis;

iv) Incubation Period; and v) Antitoxin Use and Clinical Management.

Step 1 – Place a Request for Diphtheria Antitoxin

A limited supply of DAT is kept on-site at the Ontario Government Pharmaceutical and Medical Supply Service (OGPMSS). MOHLTC staff will arrange for the shipment of DAT, and will inform OGPMSS of the authorization. The practitioner's information (e.g., name, phone number, hospital/clinic name and delivery address) will be provided to OGPMSS to prepare for the delivery of DAT.

Contact the MOHLTC to place a request for DAT:

During business hours (Monday to Friday: 8:30am - 5:00pm): Contact the Public Health Division, MOHLTC at 416 327-7392 and request to speak with a staff member from the Immunization Policy and Programs Section.

After-Hours, Weekends and Holidays: Contact the Spills Action Centre at 416 325-3000 or

1 800 268-6060 and request to speak with the Public Health Division on-call person.

Information to be provided to MOHLTC staff includes but is not limited to:

- name of attending health care practitioner
- contact telephone number for attending health care practitioner
- amount of DAT required
- hospital/clinic name
- unit name
- delivery address
- name of receiving personnel
- name of the Public Health Unit the hospital/clinic (delivery address) is located

Step 2 – Notify your Local Public Health Unit

Diphtheria is a reportable disease in Ontario under the *Health Protection and Promotion Act*, R.S.O. 1990, and must be reported as soon as possible to the local Medical Officer of Health by telephone. The disease should be reported even if it is only suspected and has not yet been confirmed.

Step 3 – Complete and Submit Form C to the Ministry of Health and Long-Term Care

As per the reporting requirements outlined by Health Canada's Special Access Programme, once DAT has been administered, the administering practitioner is required to complete and submit Form C to the MOHLTC. This information will be provided to Health Canada's Special Access Programme. To access Form C, please visit: http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/index-eng.php.

Information collected on Form C includes but is not limited to:

- practitioner's name
- hospital/clinic name
- date
- patient's initials
- patient's date of birth
- patient's sex
- indication for use
- route of administration
- dosage form
- current dosage
- date administered
- stop treatment date
- treatment response
- adverse reactions

Should you have any questions or comments, please contact the Public Health Division, MOHLTC during business hours at 416 327-7392 and request to speak with a staff member from the Immunization Policy and Programs Section.

Process for Returning Unused Diphtheria Antitoxin

Step 1 – Contact Public Health Division of the Ministry of Health and Long-Term Care

In the event that DAT is not administered, contact the Public Health Division, MOHLTC at 416 327-7392 and request to speak with a staff member from the Immunization Policy and Programs Section.

Please have the Temperature Log Book available for discussion as you may be requested to fax the Temperature Log Book to 416 327-7438.

A staff member from the Immunization Policy and Programs section will provide instructions regarding the process for returning DAT to OGPMSS including obtaining a Return Authorization Number (RAN).

Step 2 – Contact the Ontario Government Pharmaceutical and Medical Supply Service

Contact OGPMSS to obtain a RAN and to provide details on the location of the DAT.

Reference List

The information provided is subject to change. The information was collated from the following sources:

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Heymann, D.L. (2008). *Control of Communicable Diseases Manual* (19th ed.). Washington, D.C: American Public Health Association.

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Ministry of Health and Long-Term Care. (2014). *Appendix B: Provincial Case Definitions for Reportable Diseases: Diphtheria.* Retrieved from http://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/docs/infdispro.aspx#d.

Murray P.R. (2003). *Manual of Clinical Microbiology* (8th ed.). Washington, D.C.: ASM Press.

Public Health Agency of Canada (1998). *Canada communicable disease report: Guidelines for the control of diphtheria in Canada.* Retrieved from http://www.collectionscanada.gc.ca/webarchives/20071124030257/http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/98vol24/24s3/index.html.

Public Health Agency of Canada. (2014). *Canadian Immunization Guide: Diphtheria Toxoid*. Retrieved from http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-dip-eng.php.

Vins Bioproducts Limited (2013). *Diphtheria antitoxin*. Retrieved from http://www.vinsbio.in/diphtheria.html.

Vitek, C.R., & Wharton, M. (2004). Diphtheria toxoid. In S.A. Plotkin & W.A. Orenstein (Eds.), *Vaccines* (pp 139 - 156). Philadelphia, PA: Saunders Elsevier.

Appendix A: Suitable Specimen Collection and Transportation

The diagnosis of diphtheria is made by the isolation of toxigenic *Corynebacterium diphtheriae* from an appropriate clinical specimen. Although rare, other toxigenic *Corynebacterium* species (*Corynebacterium ulcerans or Corynebacterium pseudotuberculosis*) may cause clinical diphtheria.

Obtain swabs for culture from inflamed areas of the throat, nose and nasopharynx in symptomatic patients. If present, membranous material should also be submitted. For detection of asymptomatic carriers, nasopharyngeal and throat swabs (tonsillar fossae, posterior pharynx and uvula) should be collected. Two or more specimens will increase the chance of detection of the organism.

Swabs should be placed in Amies charcoal transport medium, with all specimens transported to Public Health Ontario Laboratories as soon as possible. Notify Public Health Ontario Laboratories prior to specimen submission (please see www.publichealthontario.ca for laboratory submission and contact information).

Specimens should be collected prior to medical treatment and the administration of DAT.

Appendix B: Product Insert for Diphtheria Antitoxin

For the Medical Profession

DIPHTHERIA ANTITOXIN B.P.

Diphtheria antitoxin is prepared by hyperimmunising Equines with diphtheria toxin/toxoid. Plasma obtained from hyperimmunised Equines which is rich in antibodies to diphtheria toxin is enzyme refined, purified and concentrated. The antitoxin has specific capacity of neutralizing toxin secreted by *Corynebacterium diphtheriae*, the causative organism of diphtheria.

Use in prophylaxis - The use of diphtheria antitoxin is not recommended for prophylaxis as its protective effect is of short duration (1 to 2 weeks only) and furthermore, it may cause sensitization to horse sera. Instead, the contacts of diphtheria patients should receive a dose (0.5 mL) of adsorbed diphtheria vaccine (Diphtheria vaccine, adsorbed PTAP), or adsorbed diphtheria - tetanus vaccine, (D-T vaccine adsorbed PTAP, which protects against both diphtheria and tetanus) and followed after 1 to 2 months with the second dose. Prophylaxis with diphtheria vaccine gives protection for many years and is practically free from reaction.

Use in treatment - A dose of 10,000 to 30,000 I.U. of diphtheria antitoxin may be injected intramuscularly in mild to moderately severe cases of diphtheria and upto a maximum of 100,000 I.U. in severe cases after testing serum sensitivity (see below for reactions to horse serum). I.V. route is the preferred route of administration in severe cases. In that case Diphtheria Antitoxin is mixed in 250 to 500 mL of normal saline and administered over 2-4 hours. In addition, antibiotics & corticosteroids may be administered. It is advised that after recovery from diphtheria, patients should be actively immunised for long term protection by the use of two doses at an interval of 1 to 2 months with adsorbed diphtheria vaccine or with adsorbed diphtheria - tetanus vaccine.

Reactions to Horse serum - Injection of diphtheria antitoxin in horse-serum-sensitive individuals can produce immediate reaction of acute anaphylaxis which could sometimes be fatal unless immediately countered by injecting 1 mL of 1:1000 adrenaline intramuscularly. Every care should be taken to prevent this reaction. Before injection of diphtheria antitoxin, it is necessary to enquire from the

patient (1) whether he/she has had injections of any serum before, (2) whether there is personal or family history of allergy i.e. asthma, eczema or drug allergy. The sensitivity of the patient to serum is tested by injecting subcutaneously 0.1 mL of diphtheria antitoxin diluted 1:10 and the patient is observed for 30 minutes for local and general reactions. If the test dose shows either local reaction such as wheal and flare or general anaphylactic reaction such as pallor, sweating, nausea, vomiting, urticaria or fall of blood pressure these should be treated with 1 mL of 1:1000 adrenaline (which should always be kept handy) before injecting the main dose of diphtheria antitoxin. Half the dose of adrenaline may be repeated 15 minutes later if necessary.

In allergic individuals Diphtheria antitoxin is to be injected 15 to 30 min. after administration of antihistamines such as injectable pheniramine maleate and injectable hydrocortisone intramuscularly. One mL of adrenaline (1:1000) may be injected intramuscularly at the same time as the antiserum. Administration of hydrocortisone or adrenaline may be repeated if necessary.

In some cases symptoms such as itching, urticaria rash, pains in joints and muscles, fever, enlargement of lymph glands appear 7-12 days after the injection of diphtheria antitoxin. These should be treated with antihistamines and corticosteroids. Usually these symptoms of serum sickness last a few days and the patients recover without any complications.

Storage - Diphtheria antitoxin should be stored between 2°C & 8°C. DO NOT FREEZE. Store protected from light.

Packing - Diphtheria antitoxin 10,000 I.U. in 10 mL vials

Manufactured by:

ViNS BIOPRODUCTS LIMITED
Survey No: 117, Thimmapur (V) - 509 325
Kothur (Mandal), Mahaboobnagar (Dist.),
Andhra Pradesh, India.

Code: 130202061 A.W.No: 14/AAW/PI/00.01 DT: 28.04.2014

Important Telephone Numbers

Health Canada

Special Access Programme

- 613 941-2108

Ministry of Health and Long-Term Care

Public Health Division

- 416 327-7392
- After Hours: 416 325-3000 or 1 800 268-6060

Ontario Government Pharmaceutical and Medical Supply Service

Customer Service

- 416 327-0837

Public Health Ontario Laboratories

Customer Service

- 416 235-6556
- 1 877 604-4567 (Toll-Free)
- After Hours: 416 235-6556 (Main line will provide emergency number)