Ministry of Health

Diphtheria Guide for Health Care Professionals

February 2024

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.

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 (MOH) staff will arrange for the shipment of DAT. Information on ordering DAT is on page 5. 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. Once open the DAT vial should be used immediately. Do not freeze the product.

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

After administering DAT, complete and submit Form C to the MOH at vacpro@ontario.ca. This information will be provided to Health Canada's Special Access Programme.

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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; the incubation period ranges 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 (Appendix B). **DAT is the only class of drugs known to treat diphtheria and can be accessed through the Ministry of Health (MOH)**.

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. Once open the DAT vial should be used immediately. Do not freeze the product. 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). MOH staff will arrange for the shipment of DAT and will inform OGPMSS of the authorization.

Contact the MOH to place a request for DAT:

- During business hours (Monday to Friday: 8:30am - 5:00pm) contact the Office of the Chief Medical Officer of Health, Public Health: 416-327-7392
- After-Hours, Weekends and Holidays: Contact the ministry's Health Care Provider

Hotline at 1 866 212-2272 and request to speak to the on-call person.

Information to be provided to MOH 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

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 MOH. This information will be provided to Health Canada's Special Access Programme.

To access Form C, please visit https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs.html

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 **Office of the Chief Medical Officer of Health, Public Health** at the MOH during business hours at: 416 327-7392.

Process for Returning Unused Diphtheria Antitoxin

Step 1 – Contact the Ministry of Health

In the event that DAT is not administered, contact the MOH at: 416 327-7392.

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

A MOH staff member 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

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Appendix A: 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.

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

Appendix B: Product Insert for Diphtheria Antitoxin

PACKAGE INSERT SAMPLE TEXT - HEALTH PROFESSIONALS

Diphtheria Antitoxin (DAT)
1,000 UI/mL equine-derived immunoglobulin against the diphtheria toxin

DOSAGE FORM
Injectable solution

Each mL of DAT neutralizes at least 1,000 IU of diphtheria toxin out of at least a total of a 10,000 IU in a 10 mL vial.

Each carton contains 5 vials with 10 mL of diphtheria antitoxin.

Diphtheria antitoxin is supplied in 10 mL vial containing an injectable solution of the specific and purified $F(ab')_2$ equine-derived immunoglobulin fractions. Each vial neutralizes at least 10,000 IU of toxin produced by *Corynebacterium diphtheriae* (serum neutralization in guinea pigs).

Diphtheria antitoxin is produced from the plasma of horses hyperimmunized with diphtheria anatoxin.

ROUTE OF ADMINISTRATION: INTRAVENOUS.

ADULT AND PEDIATRIC USE.

COMPOSITION 1,000 IU/mL
Each 10 mL vial contains:
- $F(ab')_2$ equine-derived immunoglobulin fractions neutralizing at least 10,000 IU of the diphtheria toxin (serum neutralization in guinea pigs):
- phenol ---------- 35 mg (maximum);
- saline solution at 0.85%---------- q.s. 10 mL.

TECHNICAL INFORMATION FOR HEALTHCARE PROFESSIONALS

1. INDICATIONS
This product is indicated for the treatment of patients with diphtheria. Diphtheria antitoxin is the only effective drug that neutralizes the toxin secreted by the diphtheria bacillus (*Corynebacterium diphtheriae*). The antibodies (specific immunoglobulins) contained in the antitoxin specifically bind to the toxin that is not yet fixed to the tissues and neutralize it. In these conditions, the earlier the administration of the antitoxin, the better its therapeutic response, therefore, treatment should be started as soon as possible.

2. EFFICACY RESULTS
There are no controlled clinical trials assessing the efficacy of DAT originating from horse plasma, however, its ability to neutralize the toxic activities of the toxins has been demonstrated in laboratory animal models and in the systematic use in patients.

3. PHARMACOLOGICAL CHARACTERISTICS

Diphtheria antitoxin is an isotonic solution of equine-derived specific immunoglobulins (IgG), purified by enzymatic, non-pyrogenic digestion. The immunoglobulins derive from the plasma of healthy horses, hyperimmunized with diphtheria anatoxin. The neutralizing biological activity of the antitoxin against the diphtheria toxin is assessed by the protection obtained in guinea pigs, after subcutaneous inoculation of mixtures of different volumes of antitoxin with a fixed amount of the reference diphtheria toxin. The neutralizing power of DAT should be of at least 1,000 International Units (IU) per mL of product.

Equine plasma enzymatically digested by pepsin reduces IgG molecular weight from 160 kDa to 90 kDa or 100 kDa, eliminating the Fc fraction from the immunoglobulin molecule that is responsible for the activation of the classical complement pathway. Thus, a purer molecule that is less reactive to hypersensitivity events observed in patients is obtained. The neutralizing activity of the antigen-binding site of pepsin-treated immunoglobulin molecules remains unchanged and there is a significant reduction in the probability of spontaneous formation of protein aggregates, which is also responsible for undesirable allergic reactions. Despite the highly purified degree of the antitoxin, there is still a small potential for allergic reactions in hypersensitive individuals. Among the undesirable reactions, anaphylaxis can occur by mast cell degranulation or complement system activation, although lethal anaphylactic shock is very rare.

Once attached to the tissues, the diphtheria toxin is not neutralized by DAT.

Diphtheria antitoxin neutralizes circulating diphtheria toxin but does not eliminate *C. diphtheriae* from the bloodstream.

4. CONTRAINDICATIONS

There are practically no contraindications but in patients with an allergic history or sensitivity to equine-derived immunoglobulins, DAT should be administered alongside strict medical observation.

NOTES:

- Diphtheria antitoxin is not contraindicated in pregnancy but the physician should be informed about this condition;
- Prior feeding and/or drinking do not contraindicate the use of the DAT, but greater care is required due to the risk of vomiting aspiration.

5. WARNINGS AND PRECAUTIONS FOR USE

Diphtheria antitoxin should be administered intravenously and under medical supervision.

Store DAT refrigerated 2-8°C. DO NOT FREEZE.

Once open the DAT vial should be used immediately.

NOTES:

- Success of diphtheria treatment with DAT is directly related to the earliest possible administration of the correct doses after the onset of symptoms thus requiring prompt diagnosis;
- The recommended doses are the same for children, adults and the elderly. Patients with a history of allergy or sensitivity to equine-derived immunoglobulins are considered risk groups;
- Treatment discontinuation should only occur if recommended by a physician.

6. DRUG INTERACTIONS

No concomitant medication is contraindicated to be administered with DAT but physicians should be informed about any medications used by patients.

7. DRUG STORAGE AND HANDLING

Diphtheria antitoxin should be stored and transported at 2-8°C. Do not store in a freezer. Freezing is strictly contraindicated. Once open, the drug should be used immediately.

SHELF-LIFE:

Shelf life of DAT is of 36 months from date of manufacture provided it has been stored refrigerated at 2-8°C as indicated on the package. These instructions have to be strictly followed.

Batch number and date of manufacture and date of expiry: see packaging.

Do not take this medicine after the expiry date. Store in original packaging.

The product is a clear to slightly opalescent liquid, which is colorless to pale yellow. Do not use the DAT if turbidity or precipitates are present.

Inspect the appearance of the drug before using it.

Store medicines out of the reach of children.

8. DOSAGE AND ADMINISTRATION

Diphtheria antitoxin should be administered intravenously, in a single application, under medical supervision and at the doses prescribed according to clinical form or severity:

MILD FORM (nose, skin, tonsils): 40,000 IU

MODERATE FORM (larynx, tonsils or mixed): 60,000 to 80,000 IU

SEVERE OR LATE FORM (4 days after disease onset): 80,000 to 100,000 IU

Administer DAT by slow intravenous infusion. The antitoxin dose should be diluted in 100 mL of normal saline solution or as required. Note, however, for the risk of volume overload in children and patients with heart failure. Doses of DAT should not be fractionated. The frequency of reactions to DAT appears to be lower when the diluted product is administered.

SPECIAL RECOMMENDATIONS:

- Diphtheria antitoxin is effective only for the treatment of diphtheria;
- Antibiotic therapy should also be introduced and administered to eliminate *C. diphtheriae* and thereby interrupt the production of diphtheria toxin;
- Treatment discontinuation should only occur if recommended by a physician.
- Administer the same dose of DAT for the treatment of diphtheria in adults and children.

9. ADVERSE REACTIONS

Very common reactions (occur in 10% of patients taking this drug):

Immediate and early reactions may occur during the infusion and for two hours thereafter, and up to 24 hours after administration of the DAT. They are often mild reactions. In addition to releasing histamine, animal-derived proteins can lead to the formation of protein or immunocomplex aggregates that activate the complement system. This, in turn, can lead to the formation of anaphylatoxins and trigger the release of mast cell and basophil chemical mediators. The most common signs and symptoms are pruritus, urticaria, flushing, angioedema, morbilliform rash, tachycardia, rhinorrhea, sneezing, coughing, nausea, abdominal cramps and diarrhea.

Common reactions (occur in 1-10% of patients taking this drug):
Late reaction, also known as Serum Sickness, can occur 5 to 24 days after the use of animal-derived immunoglobulins. The reaction is initially characterized by fever, urticaria, different size and irregularly distributed. Joint involvement can occur, at times severe and usually involving large joints, presenting with swelling with no redness, spontaneous and pressure-related pain and difficulty in motion. Lymph node infarction produces generalized adenopathy of different intensity, resulting in palpable, mobile and painful nodes. They usually heal with no sequelae. Vasculitis and nephritis rarely occur.

Uncommon reactions (occur in 0.1-1% of the patients taking this drug):
Pyrogenic reaction, described with decreasing frequency, occurs during the use of the antitoxin and can lead to high temperature (up to 39ºC), accompanied by chills and sweating. In such cases, the infusion should be discontinued and antipyretic medication administered. After symptom remission, DAT infusion should be resumed. If symptoms recur, discard the antitoxin solution and prepare a new antitoxin solution.

Rare reactions (occur in 0.01-0.1% of the patients taking this drug):
Immediate reactions can rarely progress to severe conditions in which case pallor, dyspnea, glottis edema, respiratory failure with hypoxemia, severe tachycardia, bradycardia, hypotension, which may progress to shock and syncope, loss of consciousness and persistent circulatory collapse are observed.

Very rare reactions (occur in less than 0.01% of the patients taking this drug): Not described in the literature.

PREVENTION OF REACTIONS:
- Ask the patient about previous use of animal-derived immunoglobulin (tetanus, diphtheria, rabies or antivenom) and for any allergic history;
- Absence of allergy history does not rule out the possibility of adverse reactions. There is no consensus on pre-medication with histamine receptor blockers to prevent or reduce allergic manifestations. Thus, the administration of antihistamines (H_1 and H_2) and corticosteroids 15 minutes before the recommended DAT dose is at the discretion of the physician;
- Sensitivity testing should not be performed as it is unable to detect patient sensitivity and may trigger reactions on its own. In addition, the time spent on performing sensitivity testing delays the administration of DAT.

TREATMENT OF EARLY REACTIONS:
Once the reaction is diagnosed, temporarily stop DAT administration and start treatment. In case of generalized hives, asthma-like attacks, glottis edema and shock an intramuscular (IM), dose of 0.01 mg/kg (0.01 mL/kg) up to a maximum dose of 0.5 mL of an aqueous solution of adrenaline (1:1,000, millesimal, 1 mg/mL) should be immediately administered on the anterolateral thigh (vastus lateralis). If there is no response, the same dose can be repeated at 5-15 minutes intervals. Corticosteroids and antihistamines play a secondary role in controlling these reactions and may also be used. Patients that continue to present bronchospasms, administer β2 inhaled agonists, such as fenoterol. Resume DAT administration after the remission of hypersensitivity manifestations.
In the event of severe early reactions (rare), which usually progress with hypotension, shock and/or acute respiratory failure, the patient should be placed in the supine position if hypotensive or in shock (if patient tolerates the position and is not in respiratory failure), or left lateral position if the patient is vomiting. Volume replacement with a saline IV solution (20 mL/kg) should be initiated and supplied according to the response. Orotracheal intubation may be eventually needed in cases of severe respiratory failure.

NOTE:
- Once an early severe reaction is controlled, DAT administration should be resumed.

In case of adverse events notify the Adverse Event Reporting System - VIGIMED, available at http://portal.anvisa.gov.br/vigimed or the State or Municipal Health Surveillance.

10. OVERDOSE
There is no information on cases and/or consequences of DAT overdose.

If you need further information in case of poisoning call 0800 722 6001.

DISCLAIMERS:

MS Registry Number: 1.2234.0011

Qualified Pharmacist:
Alina Souza Gandufe
CRF-SP No. 39,825

Registered and Manufactured by:

INSTITUTO BUTANTAN
Av. Dr. Vital Brasil, 1500, Butantã
CEP 05503-900 - São Paulo/SP
CNPJ: 61.821.344/0001-56
Made in Brazil

Customer Service: 0800 701 2850
e-mail: sac@butantan.gov.br

Prescription use.

Not for retail.

This package insert was approved by ANVISA on XX/XX/2019.

Diphtheria Antitoxin

Important Telephone Numbers

1. **Health Canada - Special Access Programme**

   Telephone: 613-941-2108

2. **Ministry of Health - Vaccine Policy and Programs Branch/Health Protection Policy and Partnerships Branch**

   Monday to Friday, 8:30 a.m. to 6 p.m. EST

   Telephone: 416-327-7392

   After Hours: 1-866-212-2272

3. **Ontario Government Pharmaceutical and Medical Supply Service**

   Telephone: 416-327-0837

4. **Public Health Ontario Laboratories**

   Monday to Friday, 7:30 a.m. to 7 p.m. EST;

   Saturday, 8 a.m. to 3:45 p.m. EST

   Telephone: 416-235-6556

   Toll-Free: 1-877-604-4567

   After Hours Duty Officer: 416-605-3113