

CLINICAL MANAGEMENT OF PATIENTS WITH A SUSPICION OF DIPHTHERIA

**In case of a suspicion of cutaneous or ear-nose-throat (ENT) diphtheria,
always contact the infectious disease specialist on call**

1. Background

Since the beginning of October 2022, an increase in diphtheria cases has been reported in Europe, mainly among migrants and asylum seekers. Meanwhile, there have been more than ten reported cases in Belgium. These are mainly but not exclusively infections among asylum seekers and migrants.

2. Pathogen and transmission

Diphtheria can be caused by three different *Corynebacterium* species (*C. diphtheriae*, *C. ulcerans*, and *C. pseudotuberculosis*), with or without toxin production. Transmission can occur through droplets, contact (with an infected wound or animal), or ingestion of raw milk products. An infected person remains contagious for about 2 weeks (high infectivity), while a healthy carrier can remain contagious for a longer period (months, low infectivity).

3. How to recognize diphtheria?

- 1) Risk factors: (young) migrants from countries, often with suboptimal vaccination coverage (Afghanistan, Syria); people with incomplete vaccination against diphtheria.

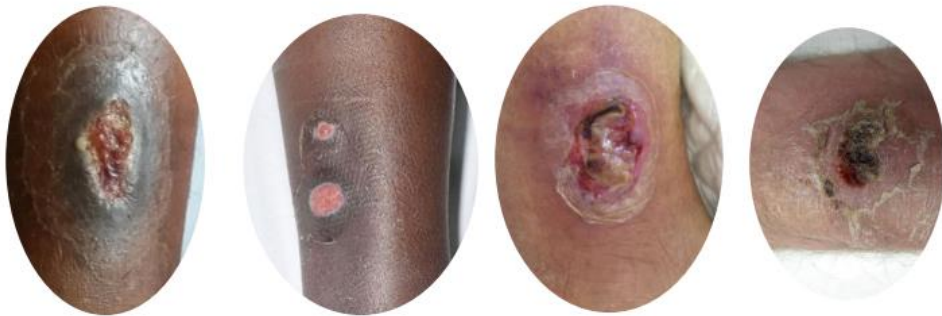
2) Clinical presentation:

- 'Pseudomembranous' angina



From: <https://en.wikipedia.org/wiki/Diphtheria>

- Ulcerative skin lesions



- Other skin lesions (papules, pustules...)



4. Diagnostic tests for diphtheria

In case of a suspicion of cutaneous or ENT diphtheria: ALWAYS contact an infectious disease specialist.

A culture is necessary for identification and diagnosis, a PCR test is necessary for identification of toxin-producing species. The Microbiology Laboratory of the UZ Brussels is the national reference center for the diagnosis of diphtheria + presence of diphtheria toxin.

- **ENT symptoms:** use a nasopharyngeal (thin swab) or swab the nasal cavity and oropharynx with a thicker swab; take a swab from the pseudomembranes if present.
- **Skin lesions:** first, clean the wound thoroughly with saline solution. Ideally, take the swab before starting antibiotics (or at the latest 24 hours after starting antibiotics).

**SWAB: Copan orange Eswab/ Copan pink Eswab
Blue swab for children**



Type	Thin swab	Thick swab
Use	Nasopharyngeal	Throat and superficial intranasal + cutaneous

*If swabs mentioned above are not available, please use an equivalent.

- Please specify the site of collection (e.g., wound on the arm/nasopharynx/oropharynx pseudomembrane...).
- PCR testing is done automatically, but mention in the clinical information that it is a suspected case of diphtheria.

5. How should diphtheria be treated?

Indication	Type	Treatment
Clinical suspicion	Cutaneous	<p>Azithromycin during 5 days</p> <p>-with food</p> <p>Adults: 500mg PO/day Children: 10mg/kg/day</p> <p>+confer vaccination</p>
Confirmed cases	Cutaneous	<p>Clarithromycine 2x500mg/day po (or if needed IV) during 10-14 days (check QTc)</p> <p>+ in case of severe presentation: <u>association with:</u> Amoxicillin 3x1g/day (IV or PO) during 14 days Or Penicillin G 6x1 million IU (IV) or PO feneticillin (Broxil) 6x500mg during 14 days</p> <p>+confer vaccination</p>
Confirmed cases (or strong suspicion)	ENT	<p>Antitoxin: confer infra</p> <p>Antibiotic treatment:</p> <p>First, call the infectious disease specialist on call</p> <p>Clarithromycin 2x500mg/day (IV) during 14 days (check QTc)</p> <p>+ in case of severe presentation, <u>association with:</u> Amoxicillin 4x1g/day (IV) during 14 days Or Penicillin G 6x1 million IU IV or PO feneticillin (Broxil) 6x500mg during 14 days</p> <p>(consider to add vancomycin for severe illness) + confer vaccination</p>
Prophylaxis in case of close contact (direct physical contact)	<p>Asymptomatic contacts</p> <p>And only if toxine positivity is confirmed in the index case</p>	<p>Azithromycin during 5 days</p> <p>-with food</p>

Diphtheria antitoxins:

Diphtheria antitoxin is an antiserum produced in horses. The antitoxin binds to the diphtheria toxin and neutralizes it.

The antitoxin is only **effective** against the penetration of the toxin into cells. Therefore, it should be administered as quickly as possible. The use of diphtheria antitoxins could reduce the mortality rate of diphtheria from 7% to 2.5%.

Hypersensitivity reactions to the antitoxin are observed in approximately 10% of patients. Before intravenous administration of the antitoxin, sensitivity testing to horse serum should be performed in selected patients (see below). Epinephrine should be available nearby due to the potential for anaphylaxis. Dosages depend on the infected site and the severity of the infection.

To obtain antitoxins in Belgium, please contact the health inspector through the infectious disease specialist:

The infectious disease specialist contacts the on-duty health inspector (Federal Health Surveillance - Federale Sanitaire Vigilantie (emergency number 0490/52.28.23)).

Second contact number: Medical On-Call Service at 0476/60.56.05 or 0477/95.16.92 (Bart Hoorelbeke - Head of Public Health Emergencies, FOD).

Antitoxins will be provided by the 'Antigifcentrum' - 'Centre Antipoison': tel. 070/245.245

Dosing and administration of antitoxins:

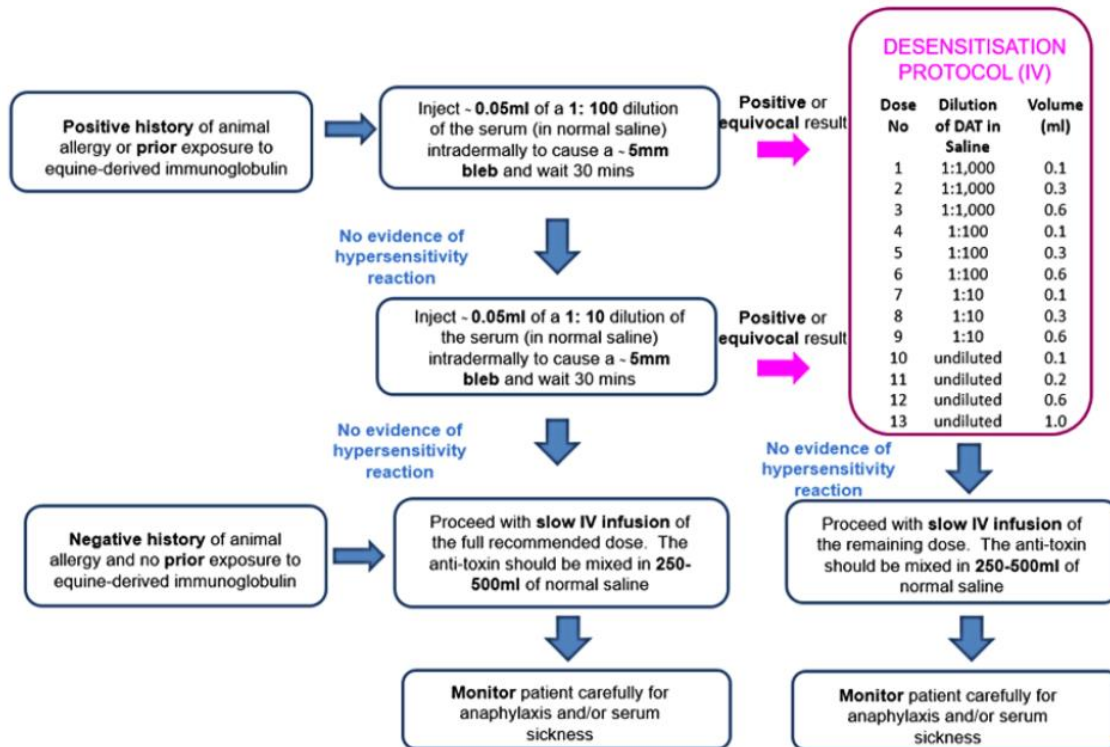
The antitoxins should be dissolved in 250-500 cc of 0.9% NaCl with 10% of the total volume remaining, and administered slowly via intravenous (IV) infusion over the first 30 minutes under supervision (CAUTION: anaphylaxis), with the remaining volume administered over 2-4 hours. **Keep an EpiPen nearby (a dilution of 1/1000 adrenalin injection).**

Prior to administration of antitoxines, ask about previous administration of immunoglobulins or antitoxins derived from horse serum (sensitization), as well as animal allergies (particularly allergies to horses). In case of a positive medical history, refer to the desensitization protocol.

In case of a history of major atopy (asthma, eczema, urticaria,...): consider administering a dose of antihistamines 15-30 min prior injection.

- **Laryngeal/pharyngeal diphtheria:** 100,000 IU of antitoxin (in cases of mild to moderate laryngeal/pharyngeal diphtheria: 70,000 IU of antitoxin can be administered); for children or underweight patients: use 250 IU/kg - 1000 IU/kg according to the severity.
- **Cutaneous diphtheria:** The risk of side effects appears to outweigh the potential benefits (exception: extensive cutaneous diphtheria (>2cm²) with membranes: 40,000 IU of antitoxin.).

Desensitisation flowchart:



From: www.gov.uk - guidance: diphtheria anti-toxin: clinical guidance (issued May 2022)

If antihistamines have been taken in the past 48-72 hours, please contact the on-duty dermatologist. In such cases, either a screening test with a positive control (histamine) and a negative control (physiological) will be conducted, or the desensitization protocol will be applied.

Keep an Epipen nearby (a dilution of 1/1000 adrenalin injection).

Dilution for the intradermal test:

- 0.1 ml serum + 0.9 ml 0.9% NaCl = 1/10 dilution
- 0.1 ml from the 1/10 dilution + 0.9 ml 0.9% NaCl = 1/100 dilution

Desensitisation test:

- According to the principles of dilution for the intradermal test
- Administer the different dilutions with 15-minute intervals

6. Vaccination against diphtheria

Indication :

- People who have not received any diphtheria vaccination in the past 10 years

Contra-indications :

- Allergy to the vaccine or any of its components
- High fever or acute infection

- Of note: suspected or confirmed cases who are not seriously ill **may** be vaccinated.

- If initially too ill for vaccination, it should still be given during the convalescent phase (a natural infection does not provide sufficient immunity against reinfection).

Which vaccines should be used?

Category	Age category	Vaccines
Children	0-6 years old	Hexyon
	6-13 years old	Tetravac
Adults	>13 years old	Triaxis of or Boostrix

+/- Imovax if needed against polio.

7. Preventive measures

- Isolation of the patient (contact + droplet isolation)
- Cover the patient's wounds
- Adequate hand hygiene

8. Notification

Clinically suspected or confirmed cases are reported by the first physician who made or suspected the diagnosis to: notif-hyg@ggc.brussels (for emergencies: 0490/52.28.23)

Notifiable data:

Details of the treating physician	Name, surname
	RIZIV/INAMI number
	Working place
	Phone number
Patient details	Name, surname
	Birth date
	Sex
	Address (or postal code)
	Collectivity?
Medical information	Presumed or definite case
	Source of contamination?
	Date of first symptoms
	Description of the signs/symptoms and photo's of skin lesions
	Vaccination history
	Presence of risk contacts (yes/no, how many)
	Sampling (type: ENT/skin) and date
	Antibiotic treatment (type and duration)
Administration of vaccination (type and date)	

9. References

1. Commission Communautaire Commune – Health academy Brussels. “Protocollen voor medisch casemanagement voor asielzoekers in een precaire situatie”. Versie: 09/11/2022
2. Hoge Gezondheidsraad. “Behandeling van infecties met *Corynebacterium ulcerans* en diphtheriae.” Via: [20190820_hgr-9503_corynebacterium_vweb.pdf \(belgium.be\)](#) (09/12/2022)
3. American Academy of Pediatrics. Red Book: 2018 Report of the Committee on Infectious Diseases, 31st ed, Kimberlin DW, Brady MT, Jackson MA, Long SS (Eds), American Academy of Pediatrics, Itasca, IL 2018. No abstract available.
4. UK Health security agency. Public health control and management of diphtheria in England. 2022 guidelines.
5. Sciensano: Diphtérie. Available from: <https://matra.sciensano.be/Fiches/Diphterie.pdf>. Accessed on June 26th, 2023.
6. CDC: Use of Diphtheria Antitoxin (DAT) for Possible Diphtheria Cases. Available from: <https://www.cdc.gov/diphtheria/downloads/protocol.pdf>. Accessed on June 26th, 2023.