Diphtheria Quicksheet

January 2025

Background

Diphtheria is caused by gram-positive *Corynebacterium diphtheriae* bacteria that produce diphtheria toxin (toxigenic strains). Important sites of infection are the respiratory mucosa (respiratory diphtheria) and the skin (cutaneous diphtheria). The last U.S. case of confirmed respiratory diphtheria was in 1997. A small number of cutaneous cases associated with international travel have been reported since then.

Diphtheria is endemic in countries throughout Africa, Latin America, Asia, the Middle East, and parts of Europe where toxoid-containing vaccines are not in widespread use, or where there have been historic gaps in vaccination. See WHO's webpage with a list of cases reported by country.

Rarely, other mucosa—the eye, ear, or genitals—may be infected. Both respiratory and non-respiratory disease caused by diphtheria toxin- producing *Corynebacteria* require immediate public health follow-up. Non-toxigenic infections are much more common than toxigenic infections. Non-toxigenic infections are typically less severe and are not vaccine-preventable, as vaccines target diphtheria toxin rather than the bacteria.

Mode of transmission

Person-to-person through inhalation of respiratory droplets and/or by contact with open skin lesions.

Incubation period

2-5 days (range, 1-10 days).

Communicability

In people with untreated diphtheria, *C. diphtheriae* can be present in nose, throat, eye, and skin lesion discharges for 2-6 weeks. Chronic carriers may shed *C. diphtheriae* for 6 months or more. Effective antibiotic therapy typically terminates shedding within 48 hours.

Alternate diagnoses

Health departments may receive inquiries about patients with exudative pharyngitis and what appears to be an adherent pharyngeal membrane. Given the rarity of respiratory diphtheria, alternate diagnoses should also be considered, especially in patients who have been immunized and who have not recently traveled to diphtheria- endemic countries. More common causes of membranous pharyngitis include Group A β- hemolytic *Streptococcus*, *Staphylococcus aureus, Arcanobacter hemolyticum, Candida albicans, Borellia vincenti* (Vincent's angina), *H. influenzae* (acute epiglottitis), Epstein Barr virus, cytomegalovirus, adenovirus, herpes simplex, and Toxoplasma. In addition, some anti-neoplastic agents, such as methotrexate, may induce a pharyngeal membrane.

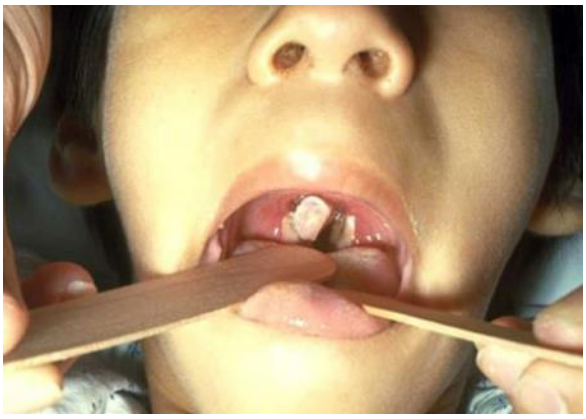
Symptoms

Respiratory diphtheria usually presents as membranous nasopharyngitis or obstructive laryngotracheitis. Initial symptoms include a sore throat, difficulty swallowing, malaise, and low-grade fever. The hallmark of respiratory diphtheria is the presence of a tough, grayish-white pseudomembrane over the tonsils (see figure 1, left), the pharynx, or larynx. The pseudomembrane is strongly adherent and attempts to dislodge it usually result in bleeding.

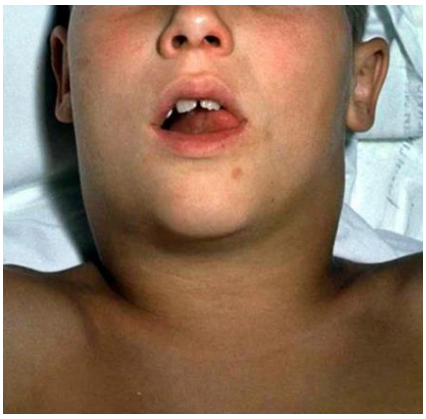
The membrane may progressively extend into the larynx and trachea and cause airway obstruction, which, if left untreated, can be fatal. Swelling of the cervical lymph nodes and soft tissue can lead to a "bull neck" appearance in moderate to severe disease (see figure 1, right). Absorption of diphtheria toxin from the site of infection can cause systemic complications, including damage to the myocardium, nervous system, and kidneys. See CDC webpage for a list of considerations when respiratory diphtheria is suspected.

Figure 1. Images of symptoms

Pseudomembrane over the tonsils



"Bull neck" appearance



From Red Book 2024-2027.

Case definition clinical criteria

- Upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx ***OR***
- Infection of a non-respiratory anatomical site (e.g., skin, wound, conjunctiva, ear, genital mucosa).

Laboratory criteria

Confirmatory laboratory evidence:

- Isolation of *C. diphtheriae* from any site ***AND***
- Confirmation of toxin-production by Elek test or by another validated test capable of confirming toxin production.

Supportive laboratory evidence:

- Histopathologic diagnosis

Epidemiologic linkage requires direct contact with a laboratory-confirmed case of diphtheria.

Case classification

Confirmed:

- An upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx ***AND*** any of the following:
  - isolation of toxin-producing *Corynebacterium diphtheriae* from the nose or throat ***OR***
  - epidemiologic linkage to a laboratory- confirmed case of diphtheria

OR

- An infection at a non-respiratory anatomical site (e.g., skin, wound, conjunctiva, ear, genital mucosa) ***WITH***
  - isolation of toxin- producing *C. diphtheriae* from that site.

Suspect:

- In the absence of a more likely diagnosis, an upper respiratory tract illness with each of the following:
  - an adherent membrane of the nose, pharynx, tonsils, or larynx ***AND***
  - absence of laboratory confirmation ***AND***
  - lack of epidemiologic linkage to a laboratory-confirmed case of diphtheria

  OR
- Histopathologic diagnosis.

Suspected non-respiratory diphtheria

Diphtheria in non-respiratory sites became reportable in 2019. In the years 2019–2020, there were 3 cases of non-respiratory diphtheria (2 cutaneous infections and 1 bloodstream infection) reported in the United States. Health departments may receive inquiries about non-respiratory (usually wound/cutaneous) cultures growing *C. diphtheriae*. These specimens are very unlikely to be toxigenic; however, testing should be performed to rule out toxin production (see page 5). Toxin-producing *C. diphtheriae* infections in non-respiratory sites may serve as reservoirs for respiratory and non-respiratory diphtheria in susceptible contacts but are unlikely to cause systemic disease in the case-patient. **Antitoxin is not generally indicated for non-respiratory diphtheria.**

Cutaneous diphtheria, is usually mild, typically consisting of sores or shallow ulcers. Antibiotic treatment as above is recommended.

Conjunctival infection may be mild, resembling a viral conjunctivitis, but the more typical infection is that of membranous conjunctivitis. Infiltration of the conjunctival surface leads to extreme edema and erythema of the eyelids with increasing stiffness of the lids. Membrane formation occurs over the conjunctivae, which ultimately becomes necrotic.

Treatment

Diphtheria antitoxin (DAT)

DAT should be administered promptly to patients with suspected respiratory diphtheria, without waiting for results of toxin testing. DAT can only be obtained through the CDC. If respiratory diphtheria is suspected and a request for DAT is being considered, an infectious disease consult can be helpful in determining whether the level of suspicion is high enough to consult CDC for DAT. If you wish to consult CDC, **please contact CDPH first.** To contact CDPH during office hours, contact the Immunization Branch at VPDReport@cdph.ca.gov or 510-620- 3737. Outside of office hours, contact the CDPH Duty Officer. For more information, please see CDC's DAT webpage.

Antibiotic treatment for 14 days is also indicated:

- Until the patient can swallow comfortably, administer:
  - IM procaine penicillin G (units/dose q 12 hours: 300,000 if weight ≤10 kg, 600,000 units if >10 kg), or
  - IV erythromycin (10 mg/kg/dose, q 6 hours, up to maximum of 500 mg/dose).
- Once swallowing comfortably, may substitute oral doses every 6 hours:
  - erythromycin (10 mg/kg/dose, up to maximum of 500 mg/dose), or
  - penicillin V (250 mg per dose).

For toxigenic cases, elimination of the organism should be documented 24 hours after completion of treatment by two consecutive negative cultures taken 24 hours apart. If cultures remain positive after treatment, a second antibiotic course should be given, and follow-up cultures performed. Because

disease does not necessarily confer immunity, DTaP or Tdap should be administered during convalescence per ACIP recommendations.

Infection control for confirmed or suspected diphtheria cases

Appropriate infection control precautions should be instituted until proven that the patient is not infected with toxin-producing *C. diphtheriae*. For respiratory diphtheria, droplet precautions, in addition to standard precautions, are indicated until elimination of the bacteria is documented 24 hours after the completion of antimicrobial therapy by 2 consecutive negative culture sets of both nose and throat collected 24 hours apart. For cutaneous diphtheria, contact precautions are indicated until there are two negative cultures of skin lesions taken at least 24 hours apart and 24 hours after cessation of antimicrobial therapy.

Close contact management

Contact tracing and post-exposure prophylaxis (PEP) for **confirmed toxigenic** diphtheria cases is usually limited to household members and other people with a history of direct, habitual close contact (including sexual contacts), healthcare workers exposed to nasopharyngeal secretions, people sharing utensils or kitchen facilities, and people taking care of children.

Decisions regarding whether to undertake contact tracing and PEP for suspected diphtheria cases while confirmatory lab testing is pending should be made on a case-by-case basis. For suspected cases in whom *C. diphtheriae* has been detected in a blood or skin culture, if the person has:

- No exudative pharyngitis, and
- No history of travel to or contact with travelers from countries endemic for diphtheria, then public heath personnel may defer contact tracing and management, including chemoprophylaxis.
- Additional reassurance is provided if the patient received one or more doses of diphtheria toxoid (e.g., DTaP, DT, Td, Tdap) in the last 10 years.

Management of close contacts includes:

- Surveillance for 7 days for evidence of disease from last exposure to an untreated patient
- Nose and throat cultures for *C. diphtheriae*
- Immunization, as appropriate (complete primary series if <3 doses; booster if last dose >5 years ago)
- Antibiotics:

Antibiotic options for close contacts	**Dose**
Penicillin G benzathine, IM, one dose	Children weighing <30 kilos should receive 600,000 units, and children and adults weighing ≥30 kilos should receive 1.2 million units.
Erythromycin, oral, 7 -10 days	Children: 40-50 mg/kg per day in divided doses, maximum 1g/day Adults: 1 g per day in divided doses

- Persons who cannot be relied upon to complete a multiday oral antibiotic course or who cannot be kept under surveillance should receive penicillin G and a dose of DTaP or Tdap as appropriate for their age and according to the CDC algorithm on page 6.
- Follow-up cultures of nasal or oropharyngeal specimens should be performed after completion of therapy for contacts proven to be carriers. If cultures are positive, an additional 10-day course

erythromycin should be administered, and follow-up cultures of pharyngeal specimens should be repeated after completion of therapy.

Laboratory testing

If respiratory diphtheria is strongly suspected, treatment with antitoxin should occur whether or not laboratory testing has been completed. The diagnosis should be confirmed with laboratory testing.

Specimen collection: For respiratory diphtheria, swab the underside of the pharyngeal membrane with a cotton or synthetic swab, or submit a portion of the membrane**.** For cutaneous diphtheria, swab the lesion.

Clinical laboratory testing: *C. diphtheriae* can be isolated from culture of nasal or throat swabs, membrane tissue, and/or swabs or tissue from other sites. Isolation of *C. diphtheriae* requires culture media containing tellurite. Clinical laboratory testing can identify *C. diphtheriae* but cannot determine whether *C. diphtheriae* is toxigenic. CDPH Microbial Diseases Laboratory (MDL) cannot culture primary specimens. *Public health laboratory testing*: Please send samples from all isolates of *C. diphtheriae* (regardless of suspected or known toxigenicity) to CDPH MDL for potential additional toxigenicity testing at CDC.

- CDPH MDL accepts bacterial isolates of *C. diphtheriae,* as well as isolates of *C. pseudotuberculosis* and *C. ulcerans* from any specimen site to forward to CDC for toxin testing.
- If specimens need to be shipped to CDC for primary culture, it is best for the submitter to ship directly to CDC (although MDL can assist, as needed) due to the short time frames for submitting primary specimens for culture to be performed at CDC. Please see this website for details: CDC Test Order 10168.
- Swabs for culture: Place all swabs in transport media such as Amies and store refrigerated within 30 minutes. Ship to CDC overnight with refrigerated of frozen ice packs (specimen must arrive at CDC between 2-8°C and should be shipped within 24-72 hours of collection.
- Dry swabs are acceptable for PCR only (not culture). Swabs for PCR should be placed in a dry, sterile tube and frozen within 30 minutes of collection. Swabs for PCR should be shipped frozen on dry ice to CDC.
- Store pieces of membrane or other tissue in sterile saline (not formalin), store refrigerated within 30 minutes, and ship overnight to CDC with refrigerated or frozen ice packs within 24-48 hours of collection.

Please contact MDL at (510) 412-3700 or MDL.Submissions@cdph.ca.gov for further information.

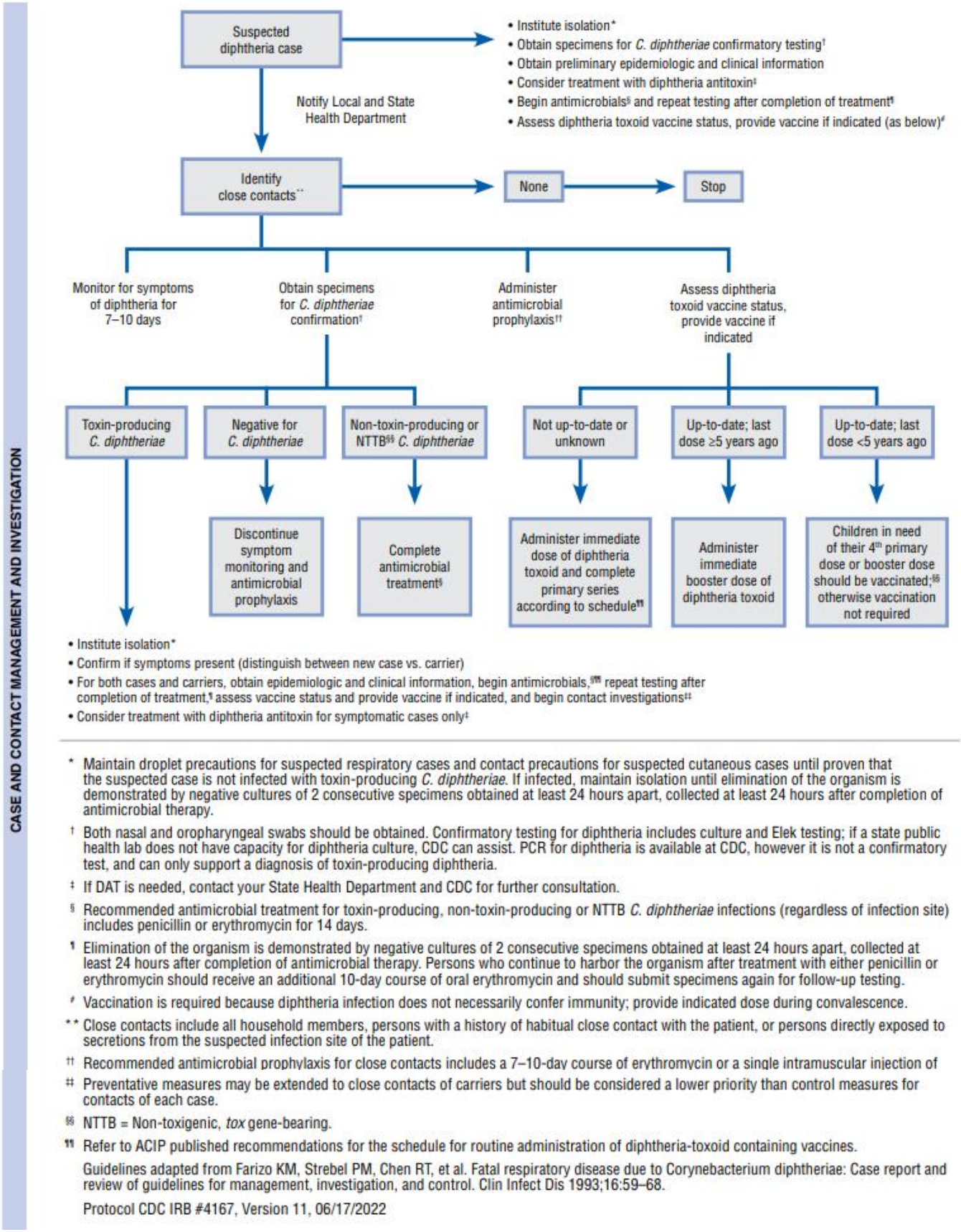
Laboratory detection of *C. diphtheriae*

With the advent of technologies such as MALDI- TOF mass spectrometry, *C. diphtheriae* strains are being detected more frequently. These bacteria are unlikely to be toxigenic, but all specimens positive for *C. diphtheriae* should be submitted to CDPH MDL for toxin testing per laboratory testing guidance above.

Non-toxigenic strains of *C. diphtheriae* have been detected in:

- healthy individuals;
- persons with pharyngitis (unclear if causal or colonizing);
- persons with skin and soft tissue infections, including in persons experiencing homelessness (skin infections may be polymicrobial); and
- persons with invasive disease, including endocarditis.

Figure 2. Case and Contact Management Diagram from CDC



* Maintain droplet precautions for suspected respiratory cases and contact precautions for suspected cutaneous cases until proven that the suspected case is not infected with toxin-producing *C. diphtheriae*. If infected, maintain isolation until elimination of the organism is demonstrated by negative cultures of 2 consecutive specimens obtained at least 24 hours apart, collected at least 24 hours after completion of antimicrobial therapy.

† Both nasal and oropharyngeal swabs should be obtained. Confirmatory testing for diphtheria includes culture and Elek testing; if a state public health lab does not have capacity for diphtheria culture, CDC can assist. PCR for diphtheria is available at CDC, however it is not a confirmatory test, and can only support a diagnosis of toxin-producing diphtheria.

‡ If DAT is needed, contact your State Health Department and CDC for further consultation.

§ Recommended antimicrobial treatment for toxin-producing, non-toxin-producing or NTTB *C. diphtheriae* infections (regardless of infection site) includes penicillin or erythromycin for 14 days.

¶ Elimination of the organism is demonstrated by negative cultures of 2 consecutive specimens obtained at least 24 hours apart, collected at least 24 hours after completion of antimicrobial therapy. Persons who continue to harbor the organism after treatment with either penicillin or erythromycin should receive an additional 10-day course of oral erythromycin and should submit specimens again for follow-up testing.

Vaccination is required because diphtheria infection does not necessarily confer immunity; provide indicated dose during convalescence.

** Close contacts include all household members, persons with a history of habitual close contact with the patient, or persons directly exposed to secretions from the suspected infection site of the patient.

†† Recommended antimicrobial prophylaxis for close contacts includes a 7–10-day course of erythromycin or a single intramuscular injection of

‡‡ Preventative measures may be extended to close contacts of carriers but should be considered a lower priority than control measures for contacts of each case.

§§ NTTB = Non-toxigenic, *tox* gene-bearing.

¶¶ Refer to ACIP published recommendations for the schedule for routine administration of diphtheria-toxoid containing vaccines.

Guidelines adapted from Farizo KM, Strebel PM, Chen RT, et al. Fatal respiratory disease due to Corynebacterium diphtheriae: Case report and review of guidelines for management, investigation, and control. Clin Infect Dis 1993;16:59–68.

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