Diphtheria

Summary

Diphtheria is caused by toxin-producing *Corynebacterium diphtheriae* bacteria. Toxigenic diphtheria primarily manifests as a respiratory infection which can cause death in 5-10% of cases, but can also present as milder infections in non-respiratory sites (cutaneous diphtheria). People can also be infected or colonized with non-toxigenic diphtheria bacteria in a respiratory or non-respiratory site, although these are not counted as cases for surveillance purposes.

Thanks to vaccines that protect against diphtheria toxin, toxigenic respiratory diphtheria is now extremely rare in the United States, although the disease remains endemic in other parts of the world, with cutaneous diphtheria being relatively common in tropical areas.

There has been an increasing recognition of cutaneous diphtheria, with four toxigenic cases identified from 2015-2018 among travelers to areas with endemic diphtheria. (One of these travelers was identified in New Mexico.) Both respiratory and non-respiratory disease require public health follow-up, and all *C. diphtheriae* isolates should be sent to CDC for toxigenicity testing. Toxigenic cutaneous diphtheria can act as a source of transmission for respiratory diphtheria.

Travel-related exposures should be considered for any suspect or confirmed report of diphtheria.

Disease control requires maintenance of immunization coverage and prompt isolation until cases and contacts are culture negative.

See here for Surveillance Worksheet.

Agent

Corynebacterium diphtheriae is an aerobic gram-positive pleomorphic bacillus. Toxin production occurs only when the bacillus is itself infected (lysogenized) by a virus (corynebacteriophage) carrying the genetic information for the toxin (*tox* gene). All four biotypes of *C. diphtheriae* (gravis, intermedius, mitis, and belfanti) can become toxigenic and cause severe disease.

Rarely, two other *Corynebacterium* species, *C. ulcerans* and *C. pseudotuberculosis*, can also produce diphtheria toxin. Both species are zoonotic, with infections documented in pigs, cattle, dogs, and cats.

Transmission

Reservoir**:**

Humans

Mode of transmission:

- Person to person by contact with infected respiratory secretions, discharges from skin lesions, or (rarely) fomites.

Period of communicability:

- If left untreated, people can remain infectious for 2-6 weeks. Rarely, carriers may shed the organism for six months or longer. Effective antibiotic therapy promptly terminates shedding, and people are usually not infectious 48 hours after treatment is initiated.

Clinical Disease

Incubation period:

Usually 2-5 days (range: 1-10 days).

Illness:

Diphtheria infection is classified by the site of disease: respiratory (affecting the pharyngeal, tonsillar, laryngeal, or nasal areas), or non-respiratory (affecting cutaneous (skin) and non-respiratory mucus membranes). Most complications and serious outcomes are associated with diphtheria toxin, which not all diphtheria bacteria carry. Toxigenic diphtheria bacteria may be found in both respiratory and non-respiratory sites, although the highest risk of death is associated with toxigenic respiratory diphtheria.

The most common sites of respiratory diphtheria are the pharynx and/or tonsils. Illness is associated with a gradual onset of pharyngitis, with early symptoms of malaise, sore throat, loss of appetite, and low-grade fever (less than 101°F). Within 2-3 days, a bluish-white or gray membrane forms, ranging in size from a small patch on the tonsils to covering most of the soft palate. The pseudomembrane may be greyish-green or even black if bleeding has occurred, and it is firmly adhered to underlying tissue. Attempting to remove the pseudomembrane is likely to cause bleeding. Extensive membrane formation may obstruct breathing.

Some patients may develop edema (swelling) around the front of the neck and under the jaw, creating a "bull neck" appearance. Some patients recover without treatment, but death can occur within 6 to 10 days.

Cutaneous diphtheria may present as a scaling rash, or as one or more ulcers with clearly demarcated edges, with or without an overlying membrane. (These are sometimes described as "punch-out" ulcers.) Cutaneous diphtheria is relatively common in tropical areas and has also recently been observed in North American populations experiencing homelessness.

Rarely, diphtheria has been found in other (non-respiratory) mucus membranes including the conjunctiva or vulvovaginal area. Involvement of the palate or uvula suggests diphtheria may be more likely, as streptococcal tonsillo-pharyngitis (strep throat) and infectious mononucleosis usually do not affect the palate or uvula. Both toxigenic and non-toxigenic forms of diphtheria have been associated with endocarditis or myocarditis. Exposed persons may also become carriers.

Laboratory Diagnosis

Specimen for culture should be collected from the nose, throat, or any mucosal or cutaneous lesion. Material taken from the membrane (plaque) or just below the membrane (if present) should be submitted for culture. Notify the laboratory of suspicion of diphtheria. (**Note**: Some investigations for suspected diphtheria cases are prompted when *C. diphtheriae* is unexpectedly grown out on a culture plate, usually alongside other bacteria such as *Streptococcus* or *Staphylococcus* species. Labs and clinicians sometimes interpret unexpected *C. diphtheriae* as a contaminant, especially if only one out of multiple culture plates grows it out, and the patient has no compatible symptoms or exposure history.)

When *Corynebacterium diphtheriae* are recovered, the strain should be tested for toxigenicity. All isolates should be forwarded to CDC. CDC performs diphtheria confirmatory tests by polymerase chain reaction (PCR) which detects the regulatory gene for toxin production (dtxR) and the diphtheria toxin gene (tox) on nonviable organisms. PCR detection does not

demonstrate production of diphtheria toxin. A positive PCR test in the absence of a positive culture does not meet laboratory criteria for classifying a case as confirmed for diphtheria.

Serological testing is uncommon and only a handful of laboratories can perform this test. Antibody tests can be used to assess the probability of diagnosis, but should not be used to rule out or confirm diagnosis.

The Elek test is done to determine whether the organisms produce diphtheria toxin and biotyping is conducted to determine biotype (intermedius, belfanti, mitis, or gravis).

Treatment

Treatment should occur based on the clinical diagnosis and before culture confirmation.

Antitoxin:

Diphtheria Antitoxin (DAT), an equine antitoxin, is not available commercially and can only be obtained from the CDC. Patients who have probable or confirmed respiratory diphtheria are eligible to receive DAT, but providers seeking DAT for their patient must consult with and order it from CDC. (DAT neutralizes unbound toxin, and therefore is most effective the earlier it is given; clinicians should not wait for toxigenicity testing or culture results to begin administering DAT to patients with probable or confirmed respiratory diphtheria.) Antitoxin is usually not necessary for cutaneous diphtheria cases. As of spring 2023, there is a global shortage of diphtheria antitoxin, and providers who order DAT and do not use it will be asked to promptly return it to CDC. Side effects are common, with allergic reactions varying from anaphylaxis to rash occurring in 5-20% of patients.

Physicians caring for patients with suspected respiratory diphtheria can obtain DAT by contacting the CDC's Emergency Operations Center at **770-488-7100**.

Antibiotics:

Antibiotic therapy is required to eradicate the organism and stop transmission. Erythromycin (administered orally or parenterally for 14 days), aqueous penicillin G administered intravenously for 14 days, or penicillin G procaine administered intramuscularly for 14 days are acceptable antibiotic treatments. Antibiotic treatment is required to stop toxin production, clear C. *diphtheriae* infection, and prevent transmission, but is not a substitute for antitoxin. Successful treatment should be confirmed with two consecutive negative cultures taken 24 hours apart and 24 hours after completion of antibiotic therapy.

Vaccination:

Patients should be immunized or boosted during convalescence as diphtheria disease does not always confer immunity. Unimmunized or under-immunized carriers should complete the series (as age-appropriate).

Cutaneous Diphtheria – Lesions should be thoroughly cleaned with soap and water; antibiotics administered for 10 days is recommended to clear the infection. Antitoxin is usually not necessary for cutaneous diphtheria, but consult with CDC for especially severe or invasive cases.

Surveillance

Case Definition (2019):

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

Case Classification Comments:

- Cases of laboratory-confirmed, non-toxin-producing *C. diphtheriae* (respiratory or non-respiratory) should not be reported to CDC as confirmed diphtheria cases. (i.e., case status will be Not a Case when investigation is completed.)
- Negative laboratory results may be sufficient to rule out a diagnosis of diphtheria; however, clinicians should carefully consider all lab results in the context of the patient's vaccination status, antimicrobial treatment, and other risk factors.
- PCR and MALDI-TOF diagnostics for *C. diphtheriae*, when used alone, do not confirm toxin production. These tests, when used, should always be combined with a test that confirms toxin production, such as the Elek test.

Reporting:

Report all suspected or confirmed cases of diphtheria immediately to the Epidemiology and Response Division (ERD) at 505-827-0006. Information needed includes: patient's name, age, sex, race, ethnicity, home address, home phone number, occupation, and health care provider.

Case Investigation:

Complete the CDC Diphtheria Surveillance Worksheet and mail to the Epidemiology and Response Division, P.O. Box 26110, Santa Fe, New Mexico 87502-6110, or (preferably) fax to 505-827-0013. Investigation information should also be entered in NM-EDSS per established procedures.

Control Measures

1. Case management
   a. *Isolation:*
      i. For respiratory diphtheria, droplet precaution in addition to standard precautions should be instituted (Appendix 4) until two sets of cultures

from both nose and throat taken at least 24 hours apart and at least 24 hours after completion of antibiotic therapy are negative.

ii. For cutaneous diphtheria, contact isolation (Appendix 4) until two cutaneous cultures taken at least 24 hours apart and at least 24 hours after completion of antibiotic therapy are negative.

2. Contact management

a. *Contacts of Toxigenic Cases:* Contact tracing and post-exposure prophylaxis is only done for toxigenic cases. Contact tracing can usually be limited to:

i. Household members

ii. People with direct, habitual close contact

iii. Healthcare personnel exposed to nasopharyngeal secretions

iv. People sharing kitchen facilities

v. People caring for infected children

b. *Prophylaxis:* **Regardless of immunization status,** the following measures should be taken for close contacts of toxigenic cases:

1. Surveillance for evidence of disease for 7 days from last exposure to an untreated patient

2. Culture for *C. diphtheriae*

3. Antimicrobial prophylaxis with oral erythromycin (40-50 mg/kg per day for 7-10 days, maximum 1 g/day) or a single intramuscular injection of penicillin G benzathine (600,000 U for children weighing <30 kg, and 1.2 million U for children weighing ≥30 kg and for adults). (A single dose of penicillin G benzathine is preferred if a contact is likely to become lost to follow-up.)

a. Follow-up cultures of pharyngeal specimens should be performed after completion of therapy for contacts proven to be carriers. If cultures are positive, an additional 10-day course of erythromycin should be administered, and follow-up cultures of pharyngeal specimens should be performed again.

4. Use of diphtheria antitoxin in exposed contacts is not recommended, due to no evidence of additional benefit.

ii. Booster vaccination

1. Asymptomatic, previously immunized close contacts should receive an age-appropriate booster of diphtheria toxoid-containing vaccine (DTaP, Tdap, Td, or DT) if their previous dose was administered more than 5 years ago.

2. Asymptomatic close contacts who have had fewer than 3 doses of a diphtheria toxoid-containing vaccine and people whose

immunization status is unknown should receive age-appropriate diphtheria toxoid-containing vaccine (DtaP, Tdap, Td, or DT).

iii. Isolation: Contacts who are food handlers and adults who have contact with incompletely immunized children should be excluded until nose and throat cultures are negative for *C. diphtheriae* and they have received appropriate antibiotic prophylaxis.

c. *Contacts of Non-Toxigenic Cases:* Cases of non-toxigenic diphtheria do not require contact tracing or prophylaxis; however, in the period between when a *C. diphtheriae* isolate is first identified and toxigenicity test results are ready from CDC, the decision whether to begin antibiotic prophylaxis of close contacts is a judgment call, depending on factors including the clinical and epidemiologic likelihood of the case having toxigenic diphtheria, the level of exposure to close contacts, and their relative risk of disease. Persons who initiate post-exposure antibiotic prophylaxis before results are ready may discontinue if the isolate is determined to be non-toxigenic.

3. Prevention

a. Immunization: Active immunization with diphtheria toxoid (combined with tetanus toxoid and acellular pertussis, DTaP) is routinely given as five doses between the ages of 2 months and 6 years. A booster dose of Td or Tdap is recommended every 10 years to persons over 7 years old.

Circulation appears to continue in some settings even in populations with >80% childhood immunization rates. An asymptomatic carrier state exists even among immune individuals. Immunity wanes over time, and decennial booster doses are required to maintain protective antibody levels. Large populations of adults are susceptible to diphtheria in developed countries and susceptibility appears to be increasing in developing countries. Large outbreaks of diphtheria occurred during 1990-1997 in states of the former Soviet Union and in Ecuador, likely due to waning immunity and under-immunization. Mass vaccination controlled both outbreaks.

Management of Diphtheria in Healthcare Settings

For healthcare personnel who have an exposure to diphtheria, regardless of immunization status:

- Administer postexposure prophylaxis as noted above.
- Exclude from work and obtain nasal and pharyngeal swabs for diphtheria culture.
    - If nasal and pharyngeal cultures are negative for toxin-producing *C. diphtheriae*, healthcare personnel may return to work while completing postexposure antibiotic therapy.
    - If nasal or pharyngeal cultures are positive for toxin-producing *C. diphtheriae*, exclude from work and follow isolation procedures as noted above for cases.
- Implement daily monitoring for signs/symptoms of diphtheria for 7 days after the last exposure

Management of Diphtheria in Child Care Centers

A case of diphtheria in a childcare center should be managed in conjunction with ERD. Isolation criteria apply to childcare as noted above. Immunization records of children in school and daycare should be reviewed.

References

American Academy of Pediatrics. "Diphtheria." In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021 Report of the Committee on Infectious Diseases*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:304-307.

Acosta AM, Moro PL, Hariri S, Tiwari TSP. "Diphtheria." *Epidemiology and Prevention of Vaccine-Preventable Diseases.* https://www.cdc.gov/vaccines/pubs/pinkbook/dip.html.

Acosta AM, Bampoe VD. "Diphtheria." *Manual for the Surveillance of Vaccine-Preventable Diseases.* https://www.cdc.gov/vaccines/pubs/surv-manual/chpt01-dip.html.

Centers for Disease Control and Prevention. "Diphtheria." *Infection Control in Healthcare Personnel: Epidemiology and Control of Selected Infections Transmitted Among Healthcare Personnel and Patients.* https://www.cdc.gov/infectioncontrol/guidelines/healthcare-personnel/selected-infections/diphtheria.html.

Centers for Disease Control and Prevention. "Diphtheria Antitoxin (DAT)." https://www.cdc.gov/diphtheria/dat.html.

Heymann, DL, ed. Control of Communicable Diseases Manual. 19th edition. Washington, DC: American Public Health Association; 2008.

Appendix A:

Administration Information for Diphtheria Antitoxin (DAT)

The CDC Emergency Operations Center will advise the clinician on proper dosage and administration instructions. Their advice supersedes any of the information given below.

Route:

The intravenous (IV) route is the preferred route of administration, especially in severe cases. The antitoxin should be mixed in 250 – 500 mL of normal saline and administered over 2-4 hours. Antitoxin may be given intramuscularly (IM) in mild or moderate cases.

Temperature:

Antitoxin should be warmed to 32 - 34°C (90 - 95° F) before injection. Warming above the recommended temperature should be carefully avoided because the DAT proteins will denature.

Dosage:

- Perform sensitivity tests, and desensitization using a scratch test before intravenous administration. Allergic reactions to horse serum (varying from anaphylaxis to rash) can be expected in 5-20% of patients.
- The dose of antitoxin depends on the site and size of the diphtheria membrane, duration of illness and degree of toxic effects. (The presence of soft diffuse cervical lymphadenitis suggests moderate to severe toxin absorption.) Specific recommendations are available from the CDC Emergency Operations Center hotline.
- Give the entire treatment dose of antitoxin intravenously (or intramuscularly) in a single administration (except for series of injections needed for desensitization). When using the intravenous route, the antitoxin should be diluted in physiologic saline and administered slowly over several hours, closely monitoring for anaphylaxis.
- The recommended DAT treatment dosage ranges are:
  - Pharyngeal or laryngeal disease of 48 hours duration: 20,000 to 40,000 units.
  - Nasopharyngeal disease: 40,000 to 60,000 units.
  - Systemic disease of three or more days' duration, or any patient with diffuse swelling of the neck: 80,000 to 100,000 units.
  - Skin lesions only: 20,000 to 40,000 units (for cases where treatment is indicated).
- Give children the same dose as adults.
- Repeated doses of DAT after an appropriate initial dose are not recommended and may increase the risk of adverse reaction.

See Diphtheria Fact Sheets (English) (Spanish).