

Diphtheria

Summary

In the post-vaccine era, infection and toxicosis due to *Corynebacterium diphtheriae* are rare. In the past decade, there were less than five cases of diphtheria in the United States reported to CDC, however the disease continues to be found around the world. Respiratory diphtheria presents as a sore throat with low-grade fever and an adherent membrane of the tonsils, pharynx, or nose. Neck swelling is usually present in severe disease. Myocarditis, polyneuritis, and airway obstruction are common complications of respiratory diphtheria; death occurs in 5-10% of respiratory cases. Cutaneous diphtheria presents as infected skin lesions which lack a characteristic appearance. Consider diphtheria in patients with wounds who have recently traveled internationally. Complications and deaths are much less frequent in cutaneous diphtheria. Travel-related exposures should be considered for any suspect or confirmed report of diphtheria.

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

Agent

Corynebacterium diphtheriae is a gram-positive pleomorphic bacillus.

Transmission

Reservoir:

Humans.

Mode of transmission:

Person to person by contact with infected respiratory secretions, skin lesions or rarely fomites.

Period of communicability:

Untreated: 2-6 weeks; rare carrier may shed the organism for six months or longer.
Effective antibiotic therapy promptly terminates shedding.

Clinical Disease

Incubation period:

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

Illness:

Clinical disease ranges from localized ulcerative skin lesions to toxin-mediated membranous upper respiratory lesions (most commonly tonsillo-pharyngitis). Gray membrane adheres tightly to underlying tissue, and may involve the nose, nasopharynx, throat, tonsils, larynx, trachea, conjunctiva, ear, or less commonly other mucous membranes such as the vagina. Fever is usually low grade. There is associated tender regional (cervical) lymphadenopathy and in severe cases, marked swelling of neck. Involvement of palate or uvula suggests diphtheria, as streptococcal tonsillo-pharyngitis and infectious mononucleosis usually do not affect uvula or palate. Non-toxigenic strains may cause endocarditis or skin lesions. Myocarditis causes heart block and cardiac failure. Exposed persons may become carriers.

Laboratory Diagnosis

Specimen for culture should be collected from nose, throat, or any mucosal or cutaneous lesion. Material taken from the membrane (plaque) or just below the membrane should be submitted for culture. Notify laboratory of suspicion of diphtheria because special media are required. 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 organism. 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 not very common and only a handful of laboratories can perform this test. Antibody tests can be used to assess the probability of 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 licensed by the FDA for use in the U.S. CDC is authorized to distribute DAT to physicians as an Investigational New Drug (IND). Patients who have probable or confirmed respiratory diphtheria are eligible to receive DAT.

- Prophylactic Use:

DAT is used prophylactically only under exceptional circumstances involving known or suspected exposure to toxigenic *Corynebacterium diphtheriae*.

- Requesting DAT:

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

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. The 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.

- The dose of antitoxin depends on the site and size of the diphtheria membrane, duration of illness and degree of toxic effects (presence of soft diffuse cervical lymphadenitis suggests moderate to severe toxin absorption).
- 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.
- Appropriate antimicrobial agents in full therapeutic dosages should be started.
 - ERD will coordinate obtaining antitoxin from the CDC National Immunization Program (404-639-3158) or CDC Emergency Operations Center (770-488-7100).
 - Use of immunoglobulin (IG) instead of antitoxin is not approved.
 - Antibiotic therapy is required to eradicate the organism and stop transmission; usual treatment is with penicillin or erythromycin.
 - Unimmunized or incompletely immunized carriers should complete the series for active immunization. Carriers should also be given antibiotic therapy with either penicillin or erythromycin.

Antibiotics:

Erythromycin and penicillin are administered as a 14-day course and are required to stop toxin production and clear *C. diphtheria*

Vaccination:

Patients should be immunized during convalescence as diphtheria disease does not always confer immunity.

Cutaneous Diphtheria – Lesions should be thoroughly cleaned with soap and water and antibiotics administered for 10 days as recommended.

Surveillance

Case Definition:

Confirmed

An upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx; and any of the following:

- Isolation of *Corynebacterium diphtheriae* from the nose or throat; or
- Histopathologic diagnosis of diphtheria; or
- Epidemiologic linkage to a laboratory-confirmed case of diphtheria

Probable

In the absence of a more likely diagnosis, an upper respiratory tract illness with:

- 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.

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 fax to 505-827-0013. Investigation information should also be entered in NM-EDSS per established procedures.

Control Measures

1. Case management

1.1. Isolation:

1.1.a 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; or until completion of 14 days of appropriate antibiotic therapy.

1.1.b 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; or until completion of 14 days of appropriate antibiotic therapy.

1.2. Prophylaxis: Not applicable.

2. Contact management

2.1. Isolation: Contacts who are food handlers and adults who have contact with incompletely immunized children are excluded until nose and throat cultures are negative for *C. diphtheriae* and they have received appropriate antibiotic treatment (see 2.2 below).

2.2. Prophylaxis:

2.2.a Close contacts should have cultures of nose and throat taken and be kept under surveillance for seven days.

2.2.b A single dose of benzathine penicillin or 7-10 days of erythromycin should be given to all household contacts, regardless of immunization status.

2.2.c Contacts who cannot be kept under surveillance should receive penicillin G benzathine but not erythromycin due to better medication adherence.

3. Prevention

3.1. Immunization: Active immunization with diphtheria toxoid (combined with tetanus toxoid and acellular pertussis, DTaP) given at 2, 4 and 6 months of age, booster at 12-18 months and before school entry. Reduced diphtheria toxoid dose (Td or Tdap) is given 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. 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. A large outbreak of diphtheria occurred during 1990-1995 in states of the former Soviet Union likely due to waning immunity. Mass vaccination controlled the outbreak.

Management of Diphtheria in Child Care Centers

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

References

American Academy of Pediatrics. In: Kimberlin, DW, et al eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018.

CDC. <http://www.cdc.gov/vaccines/vpd-vac/diphtheria/>

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

See Diphtheria Fact Sheets ([English](#)) ([Spanish](#)).