

Diphtheria

Organism: *Corynebacterium diphtheriae* is an aerobic gram-positive pleomorphic bacillus that can cause diphtheria, a rare disease in the United States. Toxin production (toxigenicity) occurs when the bacillus becomes infected by specific viruses carrying the genetic information for the toxin. Diphtheria toxin causes the local and systemic manifestations of diphtheria. Humans are the only known reservoir of *C. diphtheriae*.

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

Clinical features: Sites of infection are primarily respiratory mucosa (respiratory diphtheria) and the skin (cutaneous diphtheria). Rarely, extra-respiratory mucosal sites (e.g., eye, ear, genitals) may be affected.

- **Respiratory:** The hallmark of respiratory diphtheria is a pseudomembrane that appears within 2–3 days of illness over the mucous lining of the tonsils, pharynx, larynx, or nares that can extend into the trachea. Fatal airway obstruction can result if the pseudomembrane extends into the larynx or trachea or if a piece of it becomes dislodged.
- **Cutaneous diphtheria** may present as a scaling rash or as ulcers with clearly demarcated edges and membrane, but any chronic skin lesion may harbor *C. diphtheriae* along with other organisms. The systemic complications from cutaneous diphtheria with toxigenic strains appear to be less than from other sites.

Prompt recognition and reporting of the disease are essential to ensure early, appropriate treatment with diphtheria antitoxin (DAT) and antibiotics when indicated.

Key questions to consider when assessing suspected respiratory diphtheria cases

Symptoms of respiratory diphtheria?	Difficulty swallowing? Sore throat? Changes in voice? Fatigue? Severity of illness – outpatient vs inpatient?
On examination?	Exudative pharyngitis/laryngitis or pseudomembrane present? Lymphadenopathy (swollen glands) in neck? Stridor or wheezing? Fever?
Diphtheria toxoid vaccination history?	Unvaccinated or partially vaccinated (not up to date)?
Possible exposures and risk factors?	Travel to areas with endemic disease the prior 1-3 weeks? Contact with animals (dogs, cats, horses)? Ingestion of unpasteurized dairy products? On immunosuppressants?
Laboratory testing to confirm <i>C. diphtheriae</i> ?	Culture + biochemical tests (API Coryne)? Culture + MALDI-TOF?
Other tests to assess differential diagnoses?	Rapid strep (group A <i>Streptococcus</i>)? Monospot (EBV)? KOH prep (<i>Candida</i>)? HIV?

Infectious period: Usually 2 weeks or less, rarely up to 4 weeks. Effective antibiotic therapy promptly terminates shedding, usually within 4 days. A rare chronic carrier may shed the organisms for 6 months or more. Humans are the only known reservoir.

Transmission route: Transmission is most often person-to-person spread via respiratory droplets and direct contact with either respiratory secretions or exudates from infected skin lesions. Fomites can play a role in transmission, and epidemics have been caused by contaminated milk.

Diagnostic Testing: Lab specimens for culture testing should be obtained from the nares and oropharynx or any mucosal or cutaneous lesion. If possible, the material should be obtained from beneath the membrane (if present) or a portion of the membrane itself. Specimens are more likely to be culture-positive if obtained before the patient receives antibiotic treatment.

Swabs should be placed in general microbiology transport media such as Amies or Stuarts.

Any *C. diphtheria* isolate should be submitted to the state public health laboratory for toxigenicity testing by the Elek test at CDC Pertussis and Diphtheria Laboratory. CDC is currently the only laboratory in the United States that performs the Elek test.

Medical Management:

Diagnosis of respiratory diphtheria is usually based on clinical presentation since it is imperative to begin presumptive therapy quickly. After making the provisional clinical diagnosis, obtain appropriate clinical specimens, and start antitoxin and antibiotic treatment. Respiratory support and airway maintenance may be needed.

Even though the disease is usually not contagious 48 hours after antibiotic treatment begins, maintain droplet precautions until the diphtheria patient has completed the antibiotic course and is culture-negative. Document the organism's elimination by obtaining two consecutive negative cultures 24 hours apart once antibiotic therapy is complete.

Treatment of cutaneous diphtheria with antibiotics is usually sufficient, and antitoxin is typically not needed.

Diphtheria antitoxin (DAT) <https://www.cdc.gov/diphtheria/dat.html>

Alaska physicians caring for a patient with suspected respiratory diphtheria can obtain DAT only after consultation with the AK-SOE and a CDC diphtheria duty officer. To initiate the consultation, please contact AK-SOE at 907-269-8000 or 1-800-478-0084 after hours and ask to speak to an Epi Team member. AK-SOE

will then coordinate a meeting with the CDC diphtheria duty officer by contacting the CDC's Emergency Operations Center at 770-488-7100 anytime, 24/7.

The CDC diphtheria duty officer will discuss the protocol for DAT release with the treating clinician. Afterward, if the clinician decides DAT is indicated, it will be dispatched from the AK-SOE Depot, where limited stock is available. DAT is made available by CDC as an investigational new drug (IND). The Food and Drug Administration has not licensed DAT for use in the United States.

Cover Letter to Clinicians for DAT Release

<https://www.cdc.gov/diphtheria/downloads/dat-cvr-letter.pdf>

Use of Diphtheria Antitoxin (DAT) Protocol for Suspected Diphtheria Cases (Appendix A) <https://www.cdc.gov/diphtheria/downloads/protocol.pdf>

A test for sensitivity to DAT should be carried out before each time DAT administration. Histatrol® (histamine phosphate) is needed for use as a control in testing for sensitivity before DAT administration.

<https://www.cdc.gov/diphtheria/downloads/skintest-guide.pdf>

See appendix B for additional forms and worksheets if DAT is administered.

- Antibiotics:** The recommended antibiotics for respiratory and cutaneous diphtheria are erythromycin or penicillin.
- Erythromycin administered orally or parenterally for 14 days, penicillin G administered intramuscularly or intravenously for 14 days, or penicillin G procaine administered intramuscularly for 14 days constitute acceptable therapy.

Antimicrobial therapy is required to stop toxin production, eradicate *C* diphtheriae, and prevent transmission, but it is not a substitute for antitoxin, which is the primary therapy. Elimination of the organism should be documented 24 hours after completion of treatment by 2 consecutive negative cultures from specimens taken 24 hours apart.

Information Needed for the Investigation

Determine the Extent of Illness

- Investigate all suspected respiratory and non-respiratory diphtheria cases. This investigation should include:
 - Obtaining nasal and throat cultures. Any *C. diphtheria* isolate(s) should be submitted to the state public health laboratory for toxigenicity testing by the Elek test at the CDC Pertussis and Diphtheria Laboratory.
 - Collecting preliminary epidemiologic and clinical information, including any recent travel history or daycare involvement.
 - Identify close contacts

- Notify the Epi team of any suspect cases.

Contact and Control Measures

- If the strain is shown to be non-toxigenic, AK-SOE can discontinue the investigation of contacts. Otherwise:
- Identify close contact of diphtheria patients. Document using the CDC Close Contact Form <https://www.cdc.gov/diphtheria/downloads/appendix-4-close-contact-form.pdf>
Persons include:
 1. All household members
 2. Persons with a history of habitual close contact with the patient
 3. Persons directly exposed to secretions from the suspected infection site of the patient
- Management of close contacts should include monitoring for respiratory and cutaneous diphtheria for 7 to 10 days from the last exposure to the diphtheria patient.
- Obtain nasal and throat culture specimens for laboratory diagnostic testing.
- Close contacts should also receive erythromycin.
- Close contacts should receive a diphtheria toxoid booster, appropriate for age if they are not up to date with diphtheria vaccination.
- Close contacts who are food workers or school children should be excluded from work/school until proven not to be carriers.
- Close contacts who are health care personnel should be excluded from work pending culture results:
 1. If nasal and throat cultures are negative for toxin-producing *C. diphtheria*, HCP may return to work while complete post-exposure antibiotic therapy
 2. If nasal or throat cultures are positive for toxin-producing *C. diphtheria*, HCP should return to work when postexposure antibiotic therapy is completed and there has been two consecutive pairs of nasal and throat cultures, obtained 24 hours apart, are negative for toxin-producing *C. diphtheria*.

Hospital Considerations

- Patients with pharyngeal diphtheria should be placed in “droplet precautions” until off antimicrobial treatment and culture negative.
- Patients with cutaneous diphtheria should be placed in “contact precautions” until off antimicrobial treatment and culture negative.

Reporting Requirements

- CDC Case Definition is used for case definition.
- Complete the [CDC Diphtheria Worksheet](#). Enter all the data elements into NBS for all probable and confirmed cases.
- FTR: write up all confirmed, presumptive, and probable cases.

References

- CDC Diphtheria webpage for clinicians <http://www.cdc.gov/diphtheria/clinicians.html>
- Control of Communicable Diseases Manual, 20th Edition
- Red Book, 2012 Report of the Committee on Infectious Diseases, 29th Edition

- Siegel JD, Rhinehart E, Jackson M, Chiarello L, and the Healthcare Infection Control Practices Advisory Committee. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings. Available at <http://www.cdc.gov/hicpac/pdf/isolation/isolation2007.pdf>
- CDC Infection Control and Healthcare Personnel: Epidemiology and Control of Selected Infectious Transmitted Among Healthcare Personnel and Patients, Update November 5, 2021. Available at <https://www.cdc.gov/infectioncontrol/guidelines/healthcare-personnel/selected-infections/index.html>

Appendix A - [Use of Diphtheria Antitoxin \(DAT\) Protocol for Suspected Diphtheria Cases](#)

Appendix B – [Additional DAT Form and Worksheets](#)

[Informed Consent/Parent Permission for Use of DAT for Suspected Diphtheria Cases](#)

[DAT Treatment and Adverse Effects Form](#)

[Investigator Statement Form \(FDA 1572\)](#)

[DAT Product Accountability and Disposition Form](#)

[CDC IRB Central Memo](#)

[4167 IRB Continuation](#)

[Instructions for Serum Samples for MassBiologics](#)

[Informed Consent/Parental Permission Form for Additional Blood Draws for Suspected Diphtheria Cases](#)

[Assent for Additional Blood Draws for Suspected Diphtheria Cases Aged 12-17 Years Old](#)

[Assent for Additional Blood Draws for Suspected Diphtheria Cases Aged 7-11 Years Old](#)