Diphtheria
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Diphtheria

Overview [1, 2, 3, 4]

Respiratory diphtheria usually occurs as membranous nasopharyngitis or obstructive laryngotracheitis. Local infections are associated with a low-grade fever and gradual onset of manifestations over 1 to 2 days. Less commonly, diphtheria presents as cutaneous, vaginal, conjunctival, or otic infection. Cutaneous diphtheria is more common in tropical areas and among the urban homeless. Serious complications of diphtheria include severe neck swelling (bull neck) accompanying upper airway obstruction caused by extensive membrane formation, myocarditis, and peripheral neuropathies.

Diphtheria is caused by toxigenic strains of *Corynebacterium diphtheriae* and, rarely, *Corynebacterium ulcerans*. *Corynebacterium diphtheriae* is an irregularly staining, gram-positive, nonspore-forming, nonmotile, pleomorphic bacillus with 4 biotypes (mitis, intermedius, belfanti, and gravis). All biotypes of *C diphtheriae* may be either toxigenic or nontoxigenic. Toxigenic strains express an exotoxin that consists of an enzymatically active A domain and a binding B domain, which promotes the entry of A into the cell. The toxin gene, tox, is carried by a family of related corynebacteria phages. The toxin inhibits protein synthesis in all cells, including myocardial, renal, and peripheral nerve cells, resulting in myocarditis, acute tubular necrosis, and delayed peripheral nerve conduction. Nontoxigenic strains of *C diphtheriae* can cause sore throat and other invasive infections, including endocarditis.

Humans are the sole reservoir of *C diphtheriae*. The organisms are spread by respiratory droplets and/or by contact with discharges from skin lesions. In untreated people, organisms can be present in discharges from the nose and throat and from eye and skin lesions for 2 to 6 weeks after infection. Patients treated with an appropriate antimicrobial agent usually are communicable for fewer than 4 days. Transmission results from intimate contact with patients or carriers, particularly people who travel to areas where diphtheria is endemic and people who come into close contact with travelers from such areas; rarely, fomites and raw milk or milk products can serve as vehicles of transmission. Severe disease occurs more often in people who are not immunized or are immunized inadequately. Fully immunized people may be asymptomatic carriers or have mild sore throat. The incidence of respiratory diphtheria is greatest during autumn and winter, but summer epidemics can occur in warm climates in which skin infections are prevalent.

For a more complete overview of Diphtheria, refer to the following texts:

- *Control of Communicable Diseases Manual*. (CCDM), American Public Health Association. 19th ed. 2008.
- American Academy of Pediatrics. *Red Book: 2009 Report of the Committee on Infectious Diseases.* 28th ed. 2009.
- *Epidemiology and Prevention of Vaccine-Preventable Diseases*, "Pink Book", CDC. 12th ed. 2011.
- Manual for the Surveillance of Vaccine-Preventable Diseases, Centers for Disease Control and Prevention. 4th ed. 2008-2009.

Case Definition[5]

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.

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.

Information Needed for Investigation

Verify clinical diagnosis. What laboratory tests were conducted? What were the results? What are the patient's clinical symptoms?
Establish the extent of illness. Does the illness meet the case definition? Is the patient properly vaccinated? Are there others with similar symptoms?

Notification

- Contact the District Communicable Disease Coordinator, the Senior Epidemiology Specialist for the District, or the Department of Health and Senior Services Situation Room (DSR) at 800-392-0272 (24/7) immediately if an outbreak is suspected.
- Contact the Bureau of Environmental Health Services (573) 751-6095, and the Section for Child Care Regulation (573) 751-2450 if the case is associated with a childcare center.
- Contact the Section for Long Term Care Regulation (573) 526-8524, if cases are associated with a long-term care facility.
- Contact the Bureau of Health Services Regulation (573) 751-6303, if cases are associated with a hospital, hospital-based long-term care facility, or ambulatory surgical center.

*Outbreak is defined as the occurrence in a community or region, illness(es) similar in nature, clearly in excess of normal expectancy and derived from a common or a propagated source.

Control Measures[1, 2, 3, 4]

Determine the source of infection.

Immediate action on all highly suspect cases (including cutaneous) is warranted until shown not to be toxigenic *C. diphtheriae.* The following actions should be taken for any suspected toxigenic *C. diphtheria* case:

- Obtain appropriate cultures and preliminary clinical and epidemiological information, including vaccine history.
- Begin early presumptive treatment with antibiotics and antitoxin.

Whenever diphtheria is suspected strongly or proven, local public health officials should be notified promptly. Management of exposed people is based on individual circumstances, including immunization status and likelihood of adherence to follow-up and prophylaxis. The following are recommended:

- Close contacts of a person suspected to have diphtheria should be identified promptly. Contact tracing should begin in the household and usually can be limited to household members and other people with a history of direct, habitual close contact (including kissing or sexual contacts), health care staff exposed to nasopharyngeal secretions, people sharing utensils or kitchen facilities, and people caring for children.
- For close contacts, regardless of their immunization status, the following measures should be taken: (1) surveillance for 7 days for evidence of disease; (2) culture for C diphtheriae; and (3) antimicrobial prophylaxis with oral erythromycin (40–50 mg/kg per day for 10 days, maximum 2 g/day) or a single intramuscular injection of penicillin G benzathine (600 000 U for children weighing less than 30 kg and 1.2 million U for children weighing 30 kg or more and adults). The efficacy of antimicrobial prophylaxis is presumed but not proven. Follow-up cultures of pharyngeal specimens should be performed for contacts proven to be carriers after completion of therapy (see Carriers, below). If cultures are positive, an additional 10-day course of erythromycin should be given, and follow-up cultures of pharyngeal specimens should be performed.
- Asymptomatic, previously immunized close contacts should receive a booster dose of an age-appropriate diphtheria toxoid-containing vaccine (DTaP [or DT], Tdap, or Td) if they have not received a booster dose of a diphtheria toxoid-containing vaccine within 5 years (Tdap [10 through 64 years of age] is preferred over Td, if the adolescent did not previously receive pertussis booster vaccine). Children younger than 7 years of age in need of their fourth dose of DTaP (or DT) should be immunized.
- Asymptomatic close contacts who are not immunized fully (defined as having had fewer than 3 doses of diphtheria toxoid) or people whose immunization status is not known should be immunized with an age-appropriate diphtheria toxoid-containing vaccine (DTaP [or DT], Tdap, or Td).

- Contacts who cannot be kept under surveillance should receive penicillin G benzathine but not erythromycin, because adherence to an oral regimen is less likely, and a dose of DTaP, Tdap, DT, or Td vaccine, depending on the person's age and immunization history.

The use of equine diphtheria antitoxin in unimmunized close contacts is not recommended, because there is no evidence that antitoxin provides additional benefit for contacts who have received antimicrobial prophylaxis.

Treatment of patients with Diphtheria:

- Antitoxin: Because the condition of patients with diphtheria may deteriorate rapidly, a single dose of equine antitoxin should be administered on the basis of clinical diagnosis, even before culture results are available. To neutralize toxin as rapidly as possible, the preferred route of administration is intravenous. Before intravenous administration of antitoxin, tests for sensitivity to horse serum should be performed, initially with a scratch test of a 1:1000 dilution of antitoxin in saline solution followed by an intradermal test if the scratch test result is negative (see Sensitivity Tests for Reactions to Animal Sera, Red Book p 63). If the patient is sensitive to equine antitoxin, desensitization is necessary (see Desensitization to Animal Sera, Red book p 63). Allergic reactions to horse serum can be expected in 5% to 20% of patients. The site and size of the diphtheria membrane, the degree of toxic effects, and the duration of illness are guides for estimating the dose of antitoxin; the presence of soft, diffuse cervical lymphadenitis suggests moderate to severe toxin absorption. Suggested dose ranges are: pharyngeal or laryngeal disease of 48 hours' duration or less, 20 000 to 40 000 U; nasopharyngeal lesions, 40 000 to 60 000 U; extensive disease of 3 or more days' duration or diffuse swelling of the neck, 80 000 to 120 000 U. Antitoxin probably is of no value for cutaneous disease, but some experts recommend 20 000 to 40 000 U of antitoxin, because toxic sequelae have been reported. Although Immune Globulin Intravenous preparations may contain variable amounts of antibodies to diphtheria toxin, use of Immune Globulin Intravenous for therapy of cutaneous or respiratory diphtheria has not been approved or evaluated for efficacy.
  ***Antitoxin can be obtained from the CDC. During office hours, 8:00 a.m.–4:30 p.m. Eastern time, contact staff at the Meningitis and Vaccine-Preventable Diseases Branch, NCIRD, CDC, at 404-639-3158 or the DEOC at 404-639-7100 for diphtheria antitoxin at any time.*

- Antimicrobial Therapy: Erythromycin given orally or parenterally for 14 days, penicillin G given intramuscularly or intravenously for 14 days, or penicillin G procaine given intramuscularly for 14 days constitute acceptable therapy. Antimicrobial therapy is required to stop toxin production, to eradicate *C diphtheriae*, and to prevent transmission but 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.

- Immunization: Active immunization against diphtheria should be undertaken during convalescence from diphtheria; disease does not necessarily confer immunity.

- Cutaneous Diphtheria: Thorough cleansing of the lesion with soap and water and administration of an appropriate antimicrobial agent for 10 days are recommended.

- Carriers: If not immunized, carriers should receive active immunization promptly, and measures should be taken to ensure completion of the immunization schedule. If a carrier has been immunized previously but has not received a booster of diphtheria toxoid within 5 years, a booster dose of a vaccine containing diphtheria toxoid (DTaP, Tdap, DT, or Td, depending on age) should be given. Carriers should be given oral erythromycin or penicillin G for 10 to 14 days or a single intramuscular dose of penicillin G benzathine (600 000 U for children weighing less than 30 kg and 1.2 million U for children weighing 30 kg or more and adults). Two follow-up cultures should be obtained after completing antimicrobial treatment to ensure detection of relapse, which occurs in as many as 20% of patients treated with erythromycin. The first culture should be obtained 24 hours after completing treatment. If results of cultures are positive, an additional 10-day course of oral erythromycin should be given, and follow-up cultures should be performed again. Erythromycin-resistant strains have been identified, but their epidemiologic significance has not been determined. Fluoroquinolones, rifampin, clarithromycin, and azithromycin have good in vitro activity and may be better tolerated than erythromycin, but they have not been evaluated in clinical infection or in carriers.

Immunization

Universal immunization with a diphtheria toxoid-containing vaccine is the only effective control measure. For all indications, diphtheria immunization is administered intramuscularly with tetanus toxoid-containing vaccines and, when indicated, with pertussis-containing vaccines. The value of diphtheria toxoid immunization is proven by the rarity of disease in countries in which high rates of immunization with diphtheria toxoid have been achieved. No locally acquired case has been reported in the United States since 2003. Pneumococcal and meningococcal conjugate vaccines containing diphtheria toxoid or CRM197 protein, a nontoxic variant of diphtheria toxin, are not substitutes for diphtheria toxoid immunization.

Immunization of children from 2 months of age to the seventh birthday routinely consists of 5 doses of diphtheria and tetanus toxoid-containing vaccines. This typically is accomplished with DTaP vaccine. Immunization against diphtheria and tetanus for children younger than 7 years of age in whom pertussis immunization is contraindicated should be accomplished with DT instead of DTaP vaccine.

Other recommendations for diphtheria immunization, including recommendations for older children (7 through 18 years of age) and adults, can be found in the recommended childhood, adolescent and adult immunization schedules in the Pink Book.

- When children and adults require tetanus toxoid for wound management (see Tetanus section Red Book, p 655), the use of preparations containing diphtheria toxoid (DTaP, Tdap, DT, or Td vaccine as appropriate for age or specific contraindication to pertussis immunization) is preferred to tetanus toxoid and will help to maintain diphtheria and, when appropriate, pertussis immunity.
- Travelers to countries with endemic or epidemic diphtheria should have their diphtheria immunization status reviewed and updated when necessary.

Precautions and Contraindications to vaccination: Please see the Pertussis section in Red Book (p 504) and Tetanus section in Red Book (p 655).

Isolation of the Hospitalized patient: In addition to standard precautions, droplet precautions are recommended for patients and carriers with pharyngeal diphtheria until 2 cultures from both the nose and throat collected 24 hours after completing antimicrobial treatment are negative for *C diphtheriae*. Contact precautions are recommended for patients with cutaneous diphtheria until 2 cultures of skin lesions taken at least 24 hours apart and 24 hours after cessation of antimicrobial therapy are negative.

Laboratory Procedures[2]

Specimens for culture should be obtained from the nose or throat or any mucosal or cutaneous lesion. Material should be obtained from beneath the membrane, or a portion of the membrane itself should be submitted for culture. Because special medium is required for isolation (cystine-tellurite blood agar or modified Tinsdale agar), laboratory personnel should be notified that *C diphtheriae* is suspected. In remote areas, specimens collected for culture can be placed in silica gel packs or any transport medium or sterile container and transported to a reference laboratory for culture. When *C diphtheriae* is recovered, the strain should be tested for toxigenicity at a laboratory recommended by state and local authorities. All *C diphtheriae* isolates should be sent through the state public health laboratory to CDC.

Reporting Requirements

Diphtheria is a Category 2 disease and shall be reported to the local health authority or to the Department of Health and Senior Services within one (1) calendar day of first knowledge or suspicion by telephone, facsimile or other rapid communication.

- For confirmed and probable cases complete a "Disease Case Report" (CD-1), a "Record of Investigation of Diphtheria" (IMMP-5) and a "CDC Diphtheria worksheet".
- Entry of the completed CD-1 into the WebSurv database negates the need for the paper CD-1 to be forwarded to the District Health Office.
- Send the completed secondary investigation form to the District Health Office.
- All outbreaks or "suspected" outbreaks must be reported as soon as possible (by phone, fax or e-mail) to the District Communicable Disease Coordinator. This can be accomplished by completing the Missouri Outbreak Surveillance Report (CD-51).
- Within 90 days from the conclusion of an outbreak, submit the final outbreak report to the District Communicable Disease Coordinator.

References

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3. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, "Pink Book", Atkinson W, Wolfe S, Hamborsky J, eds. 12th ed. Washington DC: Public Health Foundation, 2011., 75-86. http://www.cdc.gov/vaccines/pubs/pinkbook/index.html (March 2012)
4. *Manual for the Surveillance of Vaccine-Preventable Diseases*. CDC, Atlanta, GA. 4th Ed. 2008-2009, and 5th Ed. 2011. http://www.cdc.gov/vaccines/pubs/surv-manual/index.html (March 2012)
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Other Sources of Information

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2. Immunization Action Coalition, http://www.immunize.org (March 2012)
3. eMedicine Journal, "Diphtheria" Demirci, Cem S and W Abuhammour, July 29 2008, V 3, N 7. http://emedicine.medscape.com/article/963334-overview (March 2012).
4. Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis (Tdap) Vaccine from the Advisory Committee on Immunization Practices, 2010. MMWR January 14, 2011. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6001a4.htm?s_cid=mm6001a4_w (March 2012)