Chapter 1: Diphtheria

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I. Disease description

Diphtheria is an uncommon disease caused by the bacterium *Corynebacterium diphtheriae* and has two main forms, respiratory and cutaneous. Respiratory diphtheria is typically caused by toxin-producing (toxigenic) strains of *C. diphtheriae*; cutaneous disease can be caused by either toxigenic or nontoxigenic strains. In the respiratory form of the disease, a membrane is formed; this membrane is usually visible on the throat or tonsils. Respiratory diphtheria begins 2–5 days after infection with *C. diphtheriae*. Initial symptoms of illness include a sore throat and low-grade fever; swelling of the neck ("bull-neck") from inflammation can develop and is a sign of severe disease. Persons may die from asphyxiation when the membrane obstructs breathing. Other complications of respiratory diphtheria are caused by remote effects of the diphtheria toxin, including myocarditis (inflammation of the heart) and nerve paralysis. The respiratory form of diphtheria usually lasts several days, and complications can persist for months.

Membranous pharyngitis from nontoxigenic *C. diphtheriae* is also reportable, the disease is usually mild with no systemic complications; nontoxigenic *C. diphtheriae* may also cause bloodstream infections.[1] Isolation of *C. diphtheriae* from the throat does not necessarily indicate a pathogenic role in the illness. Although the frequency at which this occurs is unknown, a small percentage of the population may carry nontoxigenic or toxigenic strains of *C. diphtheriae* without disease symptoms. Rarely, other *Corynebacterium* species (*C. ulcerans* or *C. pseudotuberculosis*) may produce diphtheria toxin and lead to classic respiratory diphtheria.[2,3]

In recent outbreaks, the majority of cases of diphtheria have occurred among adolescents and adults, instead of children.

Cutaneous diphtheria, caused by either toxigenic or nontoxigenic strains, is usually mild, typically consisting of nondistinctive sores or shallow ulcers and only rarely involving toxic complications (1%–2% of infections with toxigenic strains). Since 1980, cutaneous diphtheria has not been a nationally reportable disease.

II. Background

Diphtheria remains endemic in many parts of the world, including countries of the Caribbean, Latin America and Eastern Europe. In the 1990s, a large epidemic of diphtheria in the former Soviet Union, where diphtheria had previously been well controlled, renewed interest in the factors associated with persistent circulation of toxigenic *C. diphtheriae*.[4,5] During the past decade, many developing countries (e.g., Algeria and Thailand) have achieved marked reduction in diphtheria incidence with high childhood immunization coverage.[6,7] However, sporadic

cases and outbreaks still occur among population subgroups.[4, 6] A feature of these outbreaks is that the majority of cases have occurred among adolescents and adults instead of children. Many of these adolescents and adults did not routinely or recently receive diphtheria toxoid booster vaccinations. Rarely, outbreaks occur in well-vaccinated populations with intense exposure to toxigenic *C. diphtheriae*, but disease is usually mild, with fewer complications and no fatalities.[7]

Persons traveling to the U.S. from countries where diphtheria is endemic may import the disease.

Diphtheria was one of the most common causes of death among children in the pre-vaccine era. Since the introduction and widespread use of diphtheria toxoid vaccine (formalin-inactivated diphtheria toxin) in the United States beginning in the 1920s and 1930s, diphtheria has been well controlled in the United States. In the 1970s, diphtheria remained endemic in the Southwest, the Northern Plains, and the Pacific Northwest.[8] The last major outbreak was in Seattle, Washington in the 1970s.[8] In recent years, some cases in the United States have been related to importation.[9] From 1980 to 2001, 53 cases of diphtheria were reported to the Centers for Disease Control and Prevention's (CDC) National Notifiable Diseases Surveillance System. The majority of cases (77%) were among persons ≥ 15 years of age. Four of the five fatal cases occurred among unvaccinated children and the fifth fatal case was in a 75-year-old man.[9,10] Although few cases of respiratory diphtheria have been reported in the United States in recent years, enhanced surveillance in a previously endemic area—a Northern Plains Indian community—has revealed ongoing circulation of toxigenic *C. diphtheriae*.[11] Similarly, despite the near-elimination of diphtheria cases, endemic circulation of toxigenic *C. diphtheriae* strains has also persisted in some communities in Canada.[12]

III. Importance of rapid case identification

Prompt recognition and reporting of the disease is important to assure early, appropriate treatment with diphtheria antitoxin; to obtain necessary laboratory specimens before antibiotic or antitoxin treatment; to identify and evaluate contacts; and to provide necessary antimicrobial prophylaxis to prevent further spread. The outcome of diphtheria infection improves with early, appropriate treatment.

IV. Importance of surveillance

Because immunity to diphtheria wanes with time after vaccination and because many adults either have not had a primary vaccination series or do not receive the recommended tetanus-diphtheria toxoid (Td) boosters every 10 years, half of U.S. adults are estimated to have levels of diphtheria toxin antibodies below the level considered to be the lower limit of protection (0.01 international units/ml). In 1996, endemic transmission of *C. diphtheriae* was documented in a Northern Plains state. Persons traveling to the U.S. from countries where diphtheria is endemic may import the disease. Therefore, continued awareness of diphtheria is needed and enhanced surveillance is particularly important in areas in which diphtheria was endemic in the 1970s.[11]

Usually asymptomatic carriers (persons infected with the *C. diphtheriae* bacteria in the nose and/or throat who do not have disease symptoms) are contacts of each diphtheria case-patient. Carriers often augment the spread of the bacteria to other people. Surveillance, prompt investigation, and treatment of cases and contacts help halt the spread of disease.

Information obtained through surveillance is used to assess progress towards the year 2010 disease elimination goals. This information is used to characterize infected persons or areas so that additional intervention efforts can be focused to reduce disease incidence.

V. Disease reduction goals

A Healthy People 2010 goal is the elimination of indigenous diphtheria among persons < 35 years of age in the United States.[13]

VI. Case definition

The following case definition for diphtheria was revised in 1995 by the Council of State and Territorial Epidemiologists (CSTE) and published in 1997.[14]

Clinical description

An upper-respiratory tract illness characterized by sore throat, low-grade fever, and an adherent membrane of the tonsil(s), pharynx, and/or nose.

Laboratory criteria for diagnosis

- Isolation of *C. diphtheriae* from a clinical specimen
- Histopathologic diagnosis of diphtheria

Case classification

Probable: A clinically compatible case that is not laboratory confirmed and is not epidemiologically linked to a laboratory-confirmed case.

Confirmed: A clinically compatible case that is either laboratory confirmed or epidemiologically linked to a laboratory-confirmed case.

Comment: Cutaneous diphtheria should not be reported. Respiratory disease caused by nontoxigenic *C. diphtheriae* should be reported as diphtheria. All diphtheriae isolates, regardless of association with disease, should be sent to the Diphtheria Laboratory, National Center for Infectious Diseases, CDC. Rarely, respiratory diphtheria may result from infection with other *Corynebacterium* species (*C. ulcerans* or *C. pseudotuberculosis*). These isolates should also be forwarded to the CDC.

An epidemiologically linked case is one in which the patient has had contact with one or more persons who have or had the disease, and transmission of the agent by the usual modes of transmission is plausible. A case may be considered epidemiologically linked to a laboratory-confirmed case if at least one case in the chain of transmission is laboratory confirmed.

VII. Laboratory testing

Diagnostic tests used to confirm infection include isolation of *C. diphtheriae* on culture and toxigenicity testing. Although no other tests for diagnosing diphtheria are commercially available, CDC can perform a polymerase chain reaction (PCR) test on clinical specimens to confirm infection with a toxigenic strain. The PCR test can detect non-viable *C. diphtheriae* organisms from specimens taken after antibiotic therapy has been initiated. Contact your state health department to report a suspected case and to arrange laboratory testing.

Although PCR for the diphtheria toxin gene and its regulatory element, as performed by the CDC Diphtheria Laboratory, provides supportive evidence for the diagnosis, data are not yet sufficient for PCR to be accepted as a criterion for laboratory confirmation. At present, a case that is PCR positive without the isolation of the organism or histopathologic diagnosis and without epidemiologic linkage to a laboratory-confirmed case should be classified as a probable case.

For additional information on laboratory testing for confirmation of diphtheria see Chapter 19, "Laboratory Support for the Surveillance of Vaccine-preventable Diseases."

Note: Other pathogens can cause a membrane of the throat and tonsils, including *Streptococcus* spp.; Epstein-Barr virus and cytomegalovirus, both of which cause infectious mononucleosis syndrome; *Candida*; and anaerobic organisms (Vincent's angina). The patient's health-care provider should be encouraged to perform appropriate laboratory tests to rule out these conditions.

The laboratory should be alerted to the suspicion of diphtheria since isolation of *C. diphtheriae* requires special culture media containing tellurite.

Isolation of C. diphtheriae by culture

The bacteriological culture is essential for confirming diphtheria. A clinical specimen for culture should be obtained as soon as possible when diphtheria (involving any site) is suspected, even if treatment with antibiotics has already begun. Specimens should be taken from the nose and throat and from the membrane. For more information on collection of clinical specimens, see **Appendix 1**. If possible, swabs also should be taken from beneath the membrane. The laboratory should be alerted to the suspicion of diphtheria because isolation of *C. diphtheriae* requires special culture media containing tellurite. Isolation of *C. diphtheriae* from close contacts may confirm the diagnosis of the case, even if the patient's culture is negative.

All suspected cases and their close contacts should have specimens taken from the nose and throat (i.e., both a nasopharyngeal and a pharyngeal swab) for culture.

Biotype and toxigenicity testing

After *C. diphtheriae* has been isolated, the biotype (substrain) should be determined. The four biotypes are intermedius, belfanti, mitis, and gravis. Also, toxigenicity testing using the Elek test should be performed to determine if the *C. diphtheriae* isolate produces toxin. These tests are not readily available in many clinical microbiology laboratories; isolates should be sent to a reference laboratory proficient in performing the tests.

Polymerase chain reaction (PCR) testing

Additional clinical specimens for PCR testing at CDC should be collected at the time when specimens are being collected for culture. Because isolation of *C. diphtheriae* is not always possible (many patients have already received several days of antibiotics by the time a diphtheria diagnosis is considered), PCR can provide additional supportive evidence for the diagnosis of diphtheria. The PCR assay allows for detection of the regulatory gene for toxin production (*dtxR*) and the diphtheria toxin gene (*tox*).[15] Clinical specimens (swabs, pieces of membrane, biopsy tissue) can be transported to CDC with cold packs in a sterile empty container or in silica gel sachets. For detailed information on specimen collection and shipping, and to arrange for PCR testing, the state health department may contact the CDC Diphtheria Laboratory at 404-639-1730 or 404-639-1231.

Serologic testing

Measurement of the patient's serum antibodies to diphtheria toxin before administration of antitoxin may help in assessing the probability of the diagnosis of diphtheria. The state health department or CDC can provide information on laboratories that offer this test (few laboratories have the capability to accurately test antibody levels). If antibody levels are low, diphtheria cannot be ruled out accurately, but if levels are high, *C. diphtheriae* is less likely to produce serious illness.

Submission of C. diphtheriae isolates

All isolates of *C. diphtheriae*, from any body site (respiratory or cutaneous), whether toxigenic or nontoxigenic, should be sent to the CDC Diphtheria Laboratory for reference testing. Clinical specimens should also be sent to the CDC Diphtheria Laboratory for PCR testing. To arrange specimen shipping, contact the state health department.

VIII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[16] These regulations and laws list the diseases that are to be reported and describe those persons or groups who are responsible for reporting, such as health-care providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Contact the state health department for reporting requirements in your state.

Reporting to CDC

At the direction of the state health department, suspected cases should be reported promptly by telephone to CDC, so that diphtheria antitoxin can be obtained for the patient. Diphtheria antitoxin is no longer available commercially in the United States; it is only available from the CDC as an investigational agent.[17] (See Section X, "Treatment," for contact information.) A provisional report should then be sent to the state health department and forwarded by the state health department to the National Notifiable Disease Surveillance System (NNDSS) via the National Electronic Telecommunications System for Surveillance (NETSS) or National Electronic Disease Surveillance System (NEDSS), when available. Reporting should not be delayed because of incomplete information or lack of confirmation.

Additional epidemiologic and clinical data are needed because diphtheria antitoxin is available only as an investigational agent in the U.S.

Cutaneous diphtheria is no longer reportable, and cases should not be reported to NNDSS. Respiratory disease caused by nontoxigenic *C. diphtheriae* should be reported as diphtheria. All diphtheriae isolates, regardless of association with disease, should be sent to the Diphtheria Laboratory, National Center for Infectious Diseases, CDC. Rarely, respiratory diphtheria may result from infection with other *Corynebacterium* species (e.g., *C. ulcerans* or *C. pseudodiphtheriticum*). Such cases should also be reported and the isolates forwarded to the CDC laboratory (Phone: 404-639-1730 or 404-639-1231).

The following data elements are epidemiologically important and should be collected in the course of a case investigation. Additional information may be collected at the direction of the state health department.

Information to collect

- Demographic information
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth
  - Length of time in U.S.
- Reporting Source
  - County
  - Earliest date reported
- Clinical
  - Hospitalizations: dates and duration of stay
  - Date of illness onset
  - Site of infection (e.g., nose, throat, larynx)
  - Symptoms (e.g., fever, sore throat)
  - Signs (e.g., neck edema, stridor, tachycardia)

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Information to collect (con't.)

  - Complications (e.g., myocarditis, neuritis)
  - Outcome (case survived or died)
    - Date of death
    - Postmortem examination results
    - Death certificate diagnoses

- Treatment
  - Date of administration of antitoxin
  - Number of units of antitoxin given
  - Antibiotics given
  - Antibiotic dosage given
  - Duration of therapy

- Laboratory
  - Culture
  - Biotype and toxigenicity test
  - PCR
  - Molecular typing

- Vaccine Information
  - Dates and types of diphtheria vaccination
  - Number of doses of diphtheria toxoid received
  - Manufacturer name
  - Vaccine lot number
  - If not vaccinated, reason

- Epidemiological
  - Contact with a probable or confirmed case
  - Contact with immigrants or travelers to endemic areas
  - Number of contacts cultured
  - Results of contact cultures
  - Travel history: 6 weeks prior to illness onset or date of presentation

IX. Vaccination

Primary diphtheria immunization with diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) is recommended for all persons at least 6 weeks old but less than 7 years of age and without a history of contraindications. DTaP is the preferred vaccine for all doses in the vaccination series (including completion of the series in children who have received one or more doses of whole-cell DTP). The primary vaccination with DTaP series consists of a three-dose series, administered at ages 2, 4, and 6 months, with a minimum interval of 4 weeks between the first three doses. The fourth (first booster) dose is recommended at 15–18 months of age to maintain adequate immunity during preschool years. The fourth dose should be administered ≥ 6 months after the third. If the interval between the third and fourth doses is ≥ 6 months and the child is unlikely to return for a visit at the recommended age, the fourth dose of DTaP may be

administered as early as age 12 months. The fifth (second booster) dose is recommended for children aged 4–6 years to confer continued protection against disease during the early years of schooling. A fifth dose is not necessary if the fourth dose in the series is administered on or after the fourth birthday.[18] Routine tetanus booster immunization with Td, the adult formulation of tetanus and diphtheria toxoids, is recommended for all persons ≥ 7 years of age every 10 years. Because diphtheria disease does not always confer immunity, diphtheria toxoid vaccination should be undertaken during convalescence.

Health-care providers should ensure that travelers to all countries with endemic or epidemic diphtheria are up to date with diphtheria vaccination. Information on diphtheria endemic and epidemic areas is summarized in a recent *Morbidity and Mortality Weekly Report (MMWR)*[19], and updates can be found on the CDC Internet website for travelers at http://www.cdc.gov/travel. From November 2000 through much of 2002, the discontinuation of tetanus toxoid production by one of the nation's two manufacturers led to a shortage of tetanus toxoid-containing vaccines.[20-23] Vaccination with tetanus and diphtheria toxoids was deferred for some individuals during this period. Vaccine providers should carefully review the vaccine history of all travelers to areas with endemic and epidemic diphtheria to assure that they are optimally protected according to the recommendations of the Advisory Committee on Immunization Practices (ACIP).[24]

X. Treatment

Diphtheria antitoxin

The mainstay of therapy is administration of diphtheria antitoxin; this should be given when diphtheria is suspected, without waiting for laboratory confirmation. The recommended dosage and route of administration depend on the extent and duration of disease. Detailed recommendations can be obtained from the state health department and CDC. Diphtheria antitoxin is currently available for treatment of clinical cases of respiratory diphtheria in the United States only through CDC.[17] If diphtheria is suspected, the responsible health-care provider should contact the state health department. The health-care provider should then contact CDC to obtain authorization for release of antitoxin and assistance with arrangements for its transport.

Consultation is available at all times through the CDC operator at 404-639-2888 or 2889. During office hours, 8:00 a.m. – 4:30 p.m. ET, contact staff at the Bacterial Vaccine-Preventable Diseases Branch, NIP, at 404-639-8257.

Antibiotics

Suspected diphtheria case-patients should also receive antibiotics to eradicate carriage of *C. diphtheriae*.[25] Erythromycin or penicillin is recommended to be administered for a 14-day treatment course.

Contacting CDC

Consultation is available at all times through the CDC operator at 404-639-2888 or 404-639-2889. During office hours, 8:00 a.m.–4:30 p.m. Eastern Time, contact staff at the Bacterial Vaccine-Preventable Diseases Branch, NIP, at 404-639-8257.

XI. Enhancing surveillance

Because diphtheria has occurred only rarely in the United States in recent years, many clinicians may not consider the diagnosis; even if diphtheria is suspected, appropriate laboratory confirmation may not be obtained because isolation of the organism requires selective media.

Many laboratories are not proficient in the necessary laboratory procedures, and the widespread practice of empiric treatment with antibiotics may further decrease the probability the organism will be isolated.

Clinicians are reminded to consider the diagnosis of respiratory diphtheria in patients with membranous pharyngitis. Local health departments should assure the availability of laboratory capacity for isolation, and at the state level, reference capacity for biotyping and toxigenicity testing should be available.

In areas that were endemic for *C. diphtheriae* in the 1970s, public health officials should consider recommending routine screening of clinical specimens obtained from patients with pharyngitis or ear drainage for *C. diphtheriae* in high-risk populations. High-risk populations are defined based on the epidemiology of diphtheria in the area. For consultation and assistance in deciding which populations may be at increased risk for *C. diphtheriae* infection, contact the state health department. See Chapter 16, "Enhancing Surveillance," for additional recommendations for enhancing surveillance of vaccine-preventable diseases.

XII. Case investigation

Guidelines for investigating a suspected case and for managing contacts are published and are included in **Appendix 2**, Figure 1.[25] Management of contacts of suspected cases should include screening for possible respiratory or cutaneous diphtheria, obtaining nasopharyngeal cultures for *C. diphtheriae*, administering prophylactic antibiotics, assessing diphtheria vaccination status, and administering any necessary vaccinations. The CDC Diphtheria Worksheet may be used for guidelines in conducting a case investigation (see **Appendix 3**).

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