Fatal Respiratory Disease Due to *Corynebacterium diphtheriae*: Case Report and Review of Guidelines for Management, Investigation, and Control

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Dramatic reductions in the incidence of diphtheria and high levels of childhood vaccination in recent decades have led the United States to establish the goal of diphtheria elimination among persons ≤25 years of age by the year 2000. In 1990, an unimmunized 25-month-old child died of respiratory diphtheria in Dade County, Florida, before treatment with diphtheria antitoxin could be instituted. Twenty-three asymptomatic household contacts and other close contacts of the child were identified, cultured for *Corynebacterium diphtheriae*, given antimicrobial prophylaxis, and vaccinated with diphtheria toxoid when indicated. Three contacts (13%) had pharyngeal cultures positive for toxigenic *C. diphtheriae* of the same type as that causing infection in the deceased child, but no additional cases developed. Although the source of infection was not determined, three other close contacts had recently been to Haiti, where diphtheria is endemic. A serological survey of 396 children <5 years of age who received care at a medical center in Dade County revealed that 22% lacked protective immunity to diphtheria. Attainment of the goal of diphtheria elimination among persons ≤25 years of age—and ultimately among all persons—will depend on the maintenance of a high level of clinical awareness of the disease, the prompt institution of preventive measures among close contacts of patients with sporadic cases, and improved vaccination levels among infants, children, and adults.

In the 1920s, an average of more than 125,000 cases and 10,000 deaths due to diphtheria were reported annually in the United States. After the widespread use of diphtheria toxoid in the 1940s, the incidence of diphtheria declined steadily, with dramatic reductions in the middle to late 1970s. In the 1980s, 27 sporadic cases of respiratory diphtheria were reported to the Centers for Disease Control (CDC) (range, zero to five cases per year), including eight cases (30%) in persons <25 years of age and three fatal cases (11%). The sustained low incidence of diphtheria and the high levels of childhood vaccination in recent decades have led the United States to establish the goal of diphtheria elimination among persons ≤25 years of age by the year 2000 [1].

In spite of the extremely low risk of indigenously acquired diphtheria in the United States and other industrialized countries, importation of the organism from developing countries where diphtheria remains endemic poses a constant threat, particularly among subgroups of individuals with low vaccination levels [2–8]. Although appropriate management of diphtheria requires prompt recognition, treatment, and control measures to prevent secondary cases, few health-care providers in the United States are familiar with the disease. We report the first case of respiratory diphtheria in Dade County, Florida, since 1969 [9]; describe the ensuing epidemiological investigation; and review guidelines for case management, contact tracing, and preventive measures.

Methods

Case Investigation and Contact Tracing

After notification by hospital staff, the Dade County Public Health Unit initiated an investigation of a presumed case of diphtheria in which the patient, a 25-month-old boy, died. Clinical information was obtained by a retrospective review of medical records and by interviews with the child's family. Attempts were made to identify all close contacts who were exposed to the case-patient during his illness or within the previous week, when secondary transmission could have occurred. In addition, to determine the source of infection, attempts were made to identify any close contacts who had traveled to a diphtheria-endemic area within several months before the case-patient's illness. Close contacts were defined as household members and other persons who had intimate contact with the child (e.g., relatives and friends) as well as hospital staff directly exposed to his respiratory secretions. Hospital contacts were enumerated by infection control

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staff. Information on other close contacts was obtained through family interviews. After initial visits to the homes of close contacts to screen for signs and symptoms of diphtheria and to implement preventive measures, identified close contacts were monitored for at least 1 week by home visits, telephone contacts, and clinic visits.

Laboratory Procedures

During the first 2 weeks of the investigation, pharyngeal swabs obtained for culture of *Corynebacterium diphtheriae* were inoculated directly onto tellurite agar and Tinsdale's medium at the hospital's laboratory. Thereafter, swabs were transported on Pai slants to the Florida Department of Health and Rehabilitative Services Laboratory in Jacksonville, where they were inoculated onto tellurite agar, Tinsdale's medium, blood agar, and chocolate agar. All isolates suspected to be *C. diphtheriae* were biochemically characterized and tested for toxigenicity by the method of Elek [10] at the CDC's diphtheria reference laboratory.

Serological Survey for Antibodies to Diphtheria Toxin

Sera from a sample of children <15 years of age who had been randomly selected for a survey of human immunodeficiency virus (HIV) seroprevalence [11] and who were found to be seronegative for HIV were tested for antibodies to diphtheria toxin by toxin neutralization in VERO cells [12] at St. Christopher's Children's Hospital in Philadelphia. These children had received care at some point during the period from January through August 1990 at a community medical center that predominantly serves indigent patients in Dade County and had had blood submitted to the chemistry laboratory. For each child, information on race and age group (<5 or 5–14 years), but not on vaccination history, was available.

Case Report

Summary of the Case

On 13 January 1990, a previously healthy, 25-month-old, unimmunized boy with a 3-day history of cough and fever presented to the pediatric emergency department at a community hospital in Dade County, Florida. The child was born in the United States of parents who had immigrated from Haiti in 1981. He did not attend day care outside of his home and had no history of travel or disease exposures. At presentation he had a temperature of 39.4°C, pharyngeal erythema, wheezing, stridor, cervical swelling, and cervical lymphadenopathy. A chest radiograph showed subglottic narrowing and bilateral lung hyperinflation. Initial diagnoses were wheezing-associated acute respiratory infection and croup. Despite bronchodilator therapy in the emergency department, respiratory symptoms worsened, and on 14 January the boy required endotracheal intubation. The procedure was uncomplicated, and the epiglottis appeared normal.

By 17 January multiple complications had developed, including anuric renal failure, pneumonia with pleural effusion, transient ventricular tachycardia, and hypertrophic cardiomyopathy (demonstrated by echocardiography). On 18 January, during endotracheal tube replacement, the observation of thick gray pharyngeal and tracheal membranes that bled upon attempted removal led to a presumptive diagnosis of diphtheria. By then, the child had received cefotaxime, trimethoprim-sulfamethoxazole, and oxacillin. After collection of a pharyngeal swab for culture, treatment with intravenous penicillin was started. Diphtheria antitoxin was obtained promptly, but the child developed multiple cardiac dysrhythmias and died before it could be administered. Tonsillar, palatal, epiglottic, and laryngeal membranes were noted at autopsy. Although the culture of the pharyngeal swab obtained before the child's death was negative and postmortem histopathologic examination did not suggest diphtheritic myocarditis, the diagnosis of diphtheria was confirmed on 8 February on the basis of a postmortem epiglottic culture that yielded toxigenic *C. diphtheriae* of the mitis type.

Epidemiological Investigation

Household and other close contacts. The child had an extended family consisting of relatives and friends who lived in separate households but who typically ate meals together and slept at one another's homes. On 19 January health department staff located 11 close contacts of the child, including his parents and their seven remaining children, who lived in a two-bedroom apartment, and an adult and a child from another household. Although initially apprehensive because of language and cultural barriers, the family eventually enumerated 14 additional close contacts. Of these, 10 children (10 months to 9 years of age) and two adults from a third household were located on 5 February. All 23 contacts who were located had been exposed to the case-patient around the time of his illness. A child and an adult from the third household recently had been in Haiti for 8 months and 2 weeks, respectively, and had returned to Dade County ~6 weeks before the case-patient's illness. The remaining two contacts, including a woman who frequently traveled to Haiti, could not be located. More detailed travel and exposure histories for these two contacts could not be obtained.

For 19 of the 23 contacts located, vaccination histories were verified by vaccination cards or medical records. Five children who had not yet received three doses of diphtheria toxoid, three adults who had not received a dose within the previous 5 years, and two adults and two children whose vaccination histories were unknown were given a dose of

diphtheria toxoid. After pharyngeal swabs were obtained for culture, each of the contacts, regardless of vaccination status, was given antimicrobial prophylaxis with either one dose of intramuscular benzathine penicillin (children) or a 10-day course of oral erythromycin (adults). Except for coryza in a 10-month-old infant, all contacts remained asymptomatic.

Final culture results, reported on 2 February, indicated that three contacts (13%) were infected with toxigenic *C. diphtheriae* of the mitis type: these contacts were siblings of the case-patient and were 2, 4, and 5 years of age, respectively. Two of the three had previously received one dose each of diphtheria toxoid, and one had an unknown vaccination history. Follow-up cultures of pharyngeal swabs obtained both 1 week and 2 weeks after receipt of penicillin were negative.

Hospital contacts. Infection control staff enumerated 94 hospital employees who worked in areas where the case-patient had received care. Pharyngeal cultures were initially recommended for those who may have been exposed to his respiratory secretions. However, because the closeness of contact was not systematically ascertained and culture media were not readily available, no cultures were performed. Vaccination records indicated that eight (9%) of the 94 employees had most recently received diphtheria toxoid within the previous 5 years, 74 (79%) during the previous 6–10 years, and 12 (13%) more than 10 years earlier. Of the 86 employees in the latter two groups, 72 were given a booster dose of diphtheria toxoid at the employee health clinic and 14 were lost to follow-up. Of the 12 employees who had not received a dose within the previous 10 years, four received erythromycin prophylaxis and eight were lost to follow-up.

Neighborhood contacts. Although the family indicated that the case-patient had had no neighborhood contacts, a limited investigation was conducted because of uncertainty about the reliability of the interviews. On 6 February interviews with six other families who resided in adjacent homes confirmed the family's reports. Of cultures of pharyngeal swabs obtained from 24 persons who were at home during these visits, none were positive for *C. diphtheriae.*

Contacts of carriers. The three siblings with positive cultures had no additional close contacts. However, a preliminary report of a suspicious result of a culture for *C. diphtheriae* in their 7-year-old sibling led to his exclusion from school and to further investigation. Of five teachers and 26 students with whom he had close contact, three teachers who had not received diphtheria toxoid within the previous 5 years and one student in need of the fourth dose of diphtheria and tetanus toxoids and pertussis vaccine (DTP) were vaccinated at school. Of 26 contacts available for cultures, none were infected with *C. diphtheriae.* Final results of the initial culture and two follow-up cultures from the case-patient's 7-year-old sibling were also negative.

Table 1. Antibodies to diphtheria toxin in sera from a sample of children who attended a community medical center in Dade County, Florida, January through August 1990.

Race/ethnic group, age group (y)	No. tested	Percentage with indicated antibody level (IU/mL)	
		≥0.01*	≥0.1†
White‡			
0–4	103	79	56
5–14	73	90	73
Black§			
0–4	148	78	46
5–14	109	94	71
Haitian			
0–4	29	76	52
5–14	18	100	83
Hispanic			
0–4	116	78	52
5–14	105	96	76
All groups			
0–4	396	78	51
5–14	305	94	74

* A level of <0.01 IU/mL is generally considered nonprotective [13].
† The upper limit of antibody to diphtheria toxin that may permit breakthrough disease is generally considered to be 0.1 IU/mL [13].
‡ Hispanics are excluded.
§ Hispanics and Haitians are excluded.

Serological Survey

Levels of serum antibodies to diphtheria toxin were measured in 701 children. Of 396 children <5 years of age, 22% lacked protective immunity to diphtheria toxin (antibody level, <0.01 IU/mL) [13] (table 1). Whereas this proportion varied little by racial/ethnic group, a higher proportion of children 5–14 years of age had protective levels of diphtheria antitoxin (table 1).

Discussion

In the United States and other industrialized countries, improved control of diphtheria during the past 50 years and its near elimination in recent decades reflect the remarkable success of childhood vaccination programs. Not only does immunization against diphtheria confer individual protection; vaccination of ≥70% of a population may also provide herd immunity [14, 15]. In addition, as described by Pappenheimer, widespread immunization with diphtheria toxoid may lead to the elimination of circulating toxigenic strains of *C. diphtheriae* [2]. Diphtheria toxin is not an essential protein for the bacteriophage that carries its structural gene or for the bacterium itself [2]. However, in unimmunized populations, toxigenic strains may have a selective advantage over nontoxigenic strains because diphtheria toxin causes local

tissue destruction at the site of membrane formation, which, in turn, promotes multiplication and transmission of the bacterium [2, 16, 17]. This selective advantage of toxigenic strains is not expected in populations with high levels of immunity against diphtheria toxin. Pappenheimer's view is supported by population data on diphtherial immunity and carriage of *C. diphtheriae* in Romania from 1958 through 1972 [2] as well as by data from carriage surveys in other highly vaccinated communities [5, 7, 18–23] (table 2). Although the prevalence of circulating toxigenic *C. diphtheriae* in the United States is not known, only 13 (25%) of 52 isolates submitted to the CDC's diphtheria reference laboratory from 1981 through 1990 were toxigenic; the corresponding figure was 1,043 (56%) for 1,876 isolates submitted from 1971 through 1980 (Robert Weaver, personal communication).

In spite of what is apparently an extremely low risk of indigenously acquired diphtheria in the United States, evidence exists for subgroups of susceptible individuals. Recent surveys in 16 states and nine cities suggest that only 40%–60% of 2-year-old children, including approximately one-third of those living in Miami, have received all of the routinely recommended childhood vaccines [35–37]. Low levels of preschool vaccination are also reflected in our serological survey, in which more than 20% of preschool-aged children lacked immunity to diphtheria toxin. Moreover, our results likely underestimate community levels of susceptibility to diphtheria among preschool-aged children because those without access to medical care were not assessed. The higher level of protective immunity among children 5–14 years of age reflects state laws requiring vaccination before school entry. In other recent serological surveys, 20% to >50% of selected adolescents and adults lacked immunity to diphtheria toxin [38–42], with particularly low levels among the elderly, possibly due to lack of natural exposure during the vaccine era, low rates of vaccination, and/or waning vaccine-induced immunity [39].

As was demonstrated by diphtheria outbreaks in Sweden and Denmark in the 1980s [13, 43], epidemics may occur in unvaccinated population subgroups despite widespread childhood vaccination. As has been mentioned, importation of toxigenic *C. diphtheriae* from developing countries where diphtheria remains endemic poses a constant threat and has accounted for most cases of diphtheria in recent years in industrialized countries [2, 6–8, 20]. Although the source of infection was not documented in our investigation, the history of travel to Haiti among contacts of the case-patient and the absence of reported diphtheria in Dade County for more than 20 years suggest importation as a possibility. Because carriage of *C. diphtheriae* by untreated, asymptomatic persons lasts an average of 10 days [44, 45], some contacts may have had infections that cleared by the time pharyngeal swabs were obtained for culture. Furthermore, not all contacts were located; those who could not be found included one woman who frequently traveled to Haiti. Studies of the molecular biology of diphtheria suggest that conversion of nontoxigenic *C. diphtheriae* to a toxin-producing strain by lysogenic transfer of the gene coding for toxigenicity could have occurred [4], but no nontoxigenic strains were recovered from contacts.

Recommendations for Prevention and Control of Diphtheria

The need for rapid clinical and public health responses to diphtheria, a potentially fatal but rare disease, prompted us to review the recommendations and underlying rationale for the management of cases, the investigation of contacts, and the institution of preventive measures. On the basis of our review, we developed an algorithm to guide management and investigation of diphtheria (figure 1) should suspected or proven cases occur in the future.

Clinical Diagnosis

Because respiratory diphtheria may progress rapidly, a high index of suspicion needs to be maintained. Classical respiratory diphtheria is characterized by insidious onset, membranous pharyngitis with fever, enlarged anterior cervical lymph nodes, and edema of surrounding soft tissue, which gives rise to a "bull neck" appearance [14, 16, 47]. Although not always present, the membrane is typically gray, thick, fibrinous, and firmly adherent. Laryngeal diphtheria is characterized by gradually increasing hoarseness and stridor and most commonly occurs as an extension of pharyngeal involvement in children [14, 47].

Laboratory Diagnosis

Because the successful isolation of *C. diphtheriae* depends on rapid inoculation of special culture media, the laboratory should be notified as soon as the diagnosis is suspected. With routinely available throat or nasopharyngeal swabs, samples preferably should be obtained from the membrane (if present) or from beneath its edge. Although nasal diphtheria in the absence of pharyngeal involvement is uncommon, culturing of both nasal and pharyngeal secretions may improve the rate of isolation of *C. diphtheriae* [5, 51, 52]. Methods for the bacteriologic diagnosis of diphtheria have been described in detail elsewhere [53–55]. In brief, a confirmatory diagnosis may take several days and requires culture and isolation of the organism, biochemical typing, and toxigenicity testing. In some instances, a presumptive diagnosis may be made within <24 hours on the basis of cellular morphology on a methylene blue–stained smear of growth obtained after incubation on Loeffler or Pai medium [54, 55]. However, micro-

Table 2. Results of selected surveys of carriers of toxigenic *C. diphtheriae*, by setting and year.

Setting, year(s)	Location [reference]	No. of cases	No. of carriers/no. of persons cultured (carriage rate, %)	Comments
Household				
1986	Stockholm, Sweden [24]	5	0/NA* (. . .)	Swabs from household and other close contacts were cultured.
1985	Manchester, United Kingdom [6]	1	0/3 (. . .)	. . .
1975–1982	Ontario, Canada [25]	18	2/39 (5)	. . .
1970	London, United Kingdom [26]	1	1/4 (25)	The case-patient had a mild, recurrent sore throat for >2 y.
1969–1970	Chicago, Illinois [27]	21	7/73 (10)	Information on toxigenicity of isolates among carriers was not available.
1969	Dade County, Florida [9]	11	22/83 (27)	. . .
School				
1985	Ontario, Canada [8]	1	0/NA (. . .)	Swabs from classmates and teachers of the case-patient were cultured.
1985	Manchester, United Kingdom [6]	2	8/132 (6)	. . .
1980	Athens, Greece [19]	0	0/895 (. . .)	Swabs from a random sample of children in selected primary schools were cultured.
1975	Birmingham, United Kingdom [28]	5	0/51 (. . .)	. . .
1970	Athens, Greece [18]	0	0/818 (. . .)	Swabs from a random sample of children in selected primary schools were cultured.
1970	Elgin, Texas [29]	15	89/291 (31)	. . .
Hospital				
1984–1985	Göteborg, Sweden [22]	12	0/328 (. . .)	Swabs from hospital employees who cared for diphtheria patients were cultured.
1985	Manchester, United Kingdom [6]	1	0/NA (. . .)	Swabs from hospital employees who cared for the case-patient were cultured.
1982	Milwaukee, Wisconsin [30]	1	0/NA (. . .)	Swabs from hospital employees who cared for the case-patient were cultured.
1982	Westminster, United Kingdom [7]	1	0/81 (. . .)	Swabs from hospital contacts of the case-patient and of two hospitalized carriers were cultured.
1981	Ontario, Canada [31]	1	0/NA (. . .)	Swabs from 66 persons, including unspecified numbers of hospital employees, patients, and household contacts, were cultured.
1975	Birmingham, United Kingdom [28]	5	0/17 (. . .)	Swabs from nine patients and eight hospital employees were cultured.
Mental institution				
1972	Pontypool, United Kingdom [32]	1	36/824 (4)	Of 483 patients and 341 employees, 34 (7%) and 2 (0.6%), respectively, were infected.
1957	United Kingdom [33]	3	29/NA (NA)	Of an unspecified number of employees and 161 patients, 0 and 29 (18%), respectively, were infected.
Community				
1984–1985	Göteborg, Sweden [22]	12	0/NA (. . .)	More than 17,000 swabs for culture were obtained from an unspecified number of persons.
1982	Westminster, United Kingdom [7]	2	5/NA (NA)	More than 4,000 swabs for culture were obtained from an unspecified number of persons. Five infected persons were identified, all of whom had had direct contact with a case-patient.
1981	Hodeida, Yemen Arab Republic [34]	149	0/93 (. . .)	Swabs from children with no known exposure to diphtheria who visited an outpatient clinic were cultured.
1980	Manchester, United Kingdom [21]	1	34/24,000 (0.1)	. . .
1971	Manchester, United Kingdom [5]	9	28/>3,000 (<1)	Swabs for culture were obtained from household and school contacts and from persons with no documented exposure to a case-patient. Most carriers were school contacts.
1967	Alabama [23]	20	4/7,600 (<0.1)	Pharyngeal cultures for suspected streptococcal infections were screened for *C. diphtheriae*.

* NA indicates that data are not available.

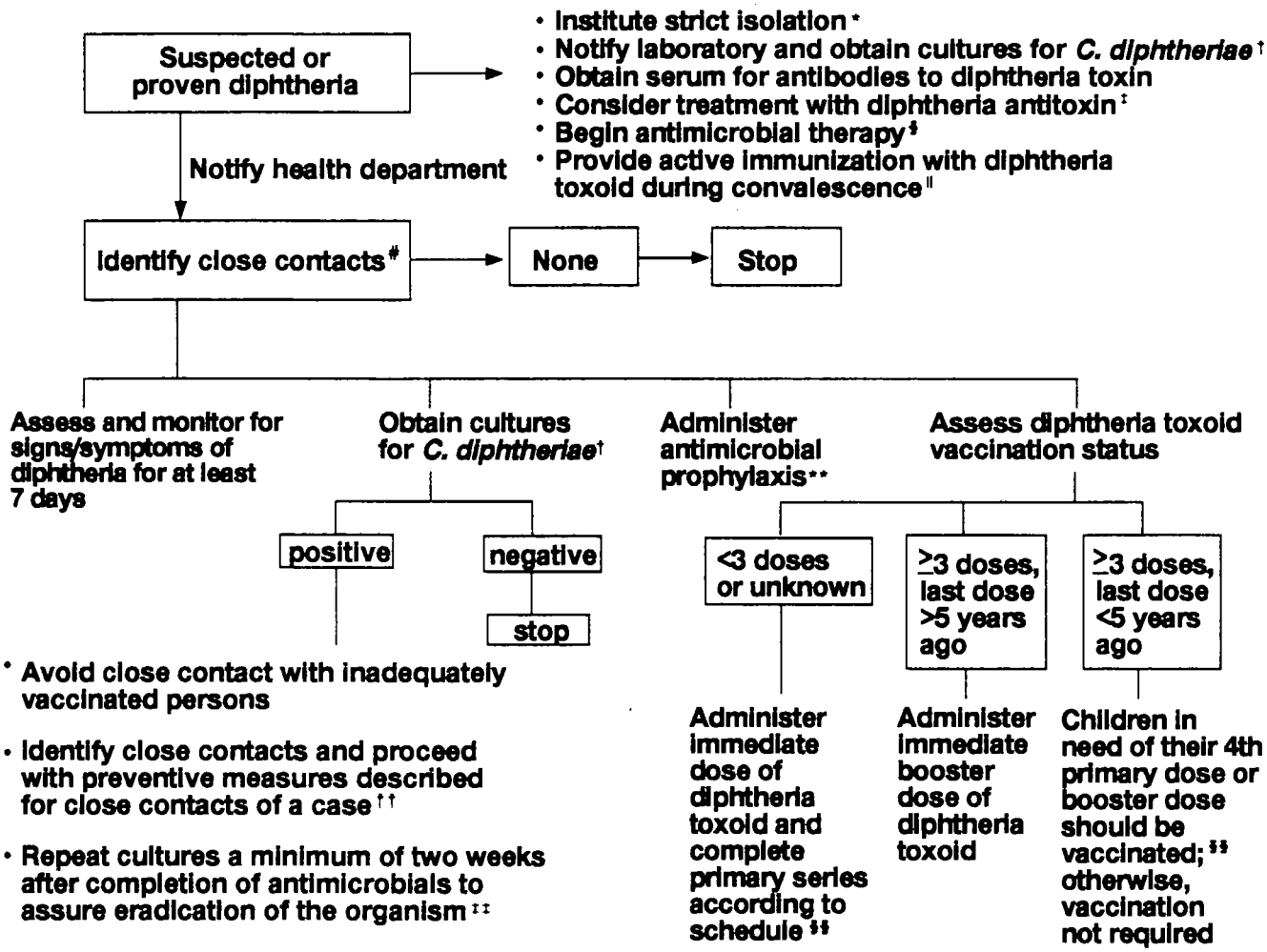

Figure 1. Respiratory diphtheria: recommendations for case management and investigation of close contacts. *Maintain isolation until elimination of the organism is demonstrated by negative cultures of two samples obtained at least 24 hours apart after completion of antimicrobial therapy [46]. †Both nasal and pharyngeal swabs should be obtained for culture. ‡Equine diphtheria antitoxin can be obtained from either the Division of Immunization, Centers for Disease Control, Atlanta (telephone 404-639-2888), or Connaught Laboratories, Swiftwater, PA. Before its administration, patients should be tested for sensitivity to horse serum and, if necessary, desensitized. The recommended dosage and route of administration depend on the extent and duration of disease. Detailed recommendations can be obtained from the package insert and other publications [14, 46–48]. §Antimicrobial therapy is not a substitute for antitoxin treatment. Intramuscular procaine penicillin G (25,000 to 50,000 units/[kg · d] for children and 1.2 million units/d for adults, in two divided doses) or parenteral erythromycin (40–50 mg/[kg · d], with a maximum of 2 g/d) has been recommended [46, 49] until the patient can swallow comfortably, at which point oral erythromycin in four divided doses [46, 49] or oral penicillin V (125–250 mg four times daily) [49] may be substituted for a recommended total treatment period of 14 days [46, 49]. ‖Vaccination is required because clinical diphtheria does not necessarily confer immunity. #Close contacts include household members and other persons with a history of direct contact with a case-patient (e.g., caretakers, relatives, or friends who regularly visit the home) as well as medical staff exposed to oral or respiratory secretions of a case-patient. **A single dose of intramuscular benzathine penicillin G (600,000 units for persons <6 years of age and 1.2 million units for persons ≥6 years of age) or a 7- to 10-day course of oral erythromycin (40 mg/[kg · d] for children and 1 g/d for adults) has been recommended [46, 50]. ††Preventive measures may be extended to close contacts of carriers but should be considered a lower priority than control measures for contacts of a case. ‡‡Persons who continue to harbor the organism after treatment with either penicillin or erythromycin should receive an additional 10-day course of oral erythromycin and should submit samples for follow-up cultures [46, 50]. §§Refer to published recommendations for the schedule for routine administration of DTP [46, 50].

scopic examination of direct-stained or fluorescent antibody-stained smears is generally considered unreliable [46, 53, 54, 56, 57].

Although not a widely available test, the measurement of antibodies to diphtheria toxin in serum collected before administration of antitoxin may support the diagnosis if the level is nonprotective (<0.01 IU/mL) [50]. This information may be particularly useful when a patient's cultures are negative as a result of prior antimicrobial therapy or for other reasons.

Management

Patients with suspected respiratory diphtheria should be placed in strict isolation and treated on clinical grounds; therapy should not be delayed until bacteriologic confirmation is available [14, 46, 48, 50]. Diphtheria antitoxin—hyperimmune antiserum produced in horses—is the mainstay of therapy. Because antitoxin neutralizes only circulating toxin that is not yet bound to tissue, prompt administration is critical. Although not a substitute for antitoxin, penicillin or erythromycin should also be administered so that the organism will be eradicated, toxin production terminated, and the likelihood of transmission decreased [14, 46, 47, 49].

Clinical attention should be directed to signs of airway obstruction, acute systemic toxicity, and toxin-mediated myocarditis and neuritis [14, 58, 59]. Myocarditis may present acutely, with congestive heart failure and circulatory collapse, or more insidiously, with progressive dyspnea, weakness, diminished heart sounds, and gallop rhythm [14, 47]. Electrocardiographic abnormalities, such as T-wave alterations and first-degree heart block, may occur in the absence of clinical signs [47, 59] and progress to severe block, atrioventricular dissociation, and other potentially fatal arrhythmias [58, 59].

Neurological complications consist primarily of motor loss involving cranial or peripheral nerves [14, 47]. Palatal and pharyngeal paralysis may occur acutely. Oculomotor and ciliary paralysis and, most commonly, lower-extremity peripheral neuritis may manifest 2–8 weeks after the onset of illness. Dysfunction varies from mild weakness to total paralysis and almost always resolves completely.

Mechanical airway obstruction and myocarditis account for most diphtheria-related deaths. The case-fatality rate for respiratory diphtheria has been nearly 10% in the United States in recent decades [60, 61] and was 18% (3/17) in the recent Swedish outbreak [43].

Identification of Secondary Cases and Carriers

Whenever the diagnosis of diphtheria is strongly suspected, local public-health officials should be notified, and measures to prevent additional cases should be instituted promptly. Infection with *C. diphtheriae* may result in asymptomatic carriage or disease of varying severity [14, 17]. In view of the short incubation period of diphtheria (1–6 days) and the delays encountered in bacteriologic diagnosis, the primary means of detecting cases is to monitor close contacts daily for at least 7 days [46, 48, 50]. Asymptomatic carriers should also be identified because they may transmit the organism [15, 26, 29, 51, 62]. In addition, finding a carrier among close contacts may support the diagnosis of diphtheria in the absence of bacteriologic confirmation. Although diphtheria toxoid protects against clinical diphtheria and complications, it has not been associated with the prevention of either infection or carriage [14, 17, 25, 29, 63, 64]. Thus, in the search for cases and carriers, nasal and pharyngeal swabs should be obtained from all close contacts, regardless of vaccination status [46, 48, 50].

Because the risk of infection is directly related to the closeness and the duration of contact and the intensity of exposure [14–16, 65, 66], the search for infected contacts should usually begin in the case-patient's household and be limited to settings in which intimate respiratory or physical contact with the case-patient may have occurred [46, 50]. Reported rates of carriage of toxigenic *C. diphtheriae* among household contacts of case-patients have ranged from 0 to 25% [6, 9, 24–27] (table 2); the carriage rate was 13% in our investigation. This variation may be due to differences in intensity of exposure, antimicrobial use, timing of cultures, and laboratory techniques. Whereas spread of diphtheria has been reported in institutions for mentally handicapped persons [32, 33], transmission in modern hospitals in the United States and other developed countries was not demonstrated in studies we reviewed [6, 7, 22, 28, 30, 31] (table 2). Investigation of casual contacts and of persons in the community without known exposure to diphtheria has generally yielded extremely low figures for carriage rates [5, 7, 21–23, 34] (table 2) and is not routinely recommended.

Antimicrobial Treatment for Contacts

A single dose of intramuscular penicillin or a 7- to 10-day course of oral erythromycin is recommended for all persons exposed to diphtheria, regardless of vaccination status, as soon as samples are obtained for culture [46, 50]. Whereas the efficacy of postexposure antimicrobial prophylaxis in preventing diphtheria is presumed but not proven, each of these drugs has been shown to eradicate *C. diphtheriae* from the respiratory tract of carriers [5, 21, 33, 64, 67–69]. Although available data suggest that erythromycin may be more effective [68, 69], intramuscular penicillin should be used if the patient's compliance is in doubt. Because neither regimen is 100% effective [67, 69] and bacteriologic relapse is possible [64], specimens from carriers should be cultured a

minimum of 2 weeks after the completion of therapy to ensure that the organism has been eradicated [64, 70].

Vaccination of Contacts

The vaccination status of all persons exposed to diphtheria should be assessed, and diphtheria toxoid should be administered according to the algorithm shown in figure 1. The rapid increase in diphtheria antitoxin expected with booster immunization [71, 72] is theoretically protective against the effects of diphtheria toxin.

Contacts of Carriers

On the basis of historical studies of diphtheria transmission, Doull and Lara estimated that the risk of developing diphtheria is sevenfold higher after household exposure to an individual with clinical diphtheria than after household exposure to a carrier (2.1% and 0.3%, respectively) [62]. Local destruction of tissue at the site of membrane formation in clinical diphtheria is thought to promote bacterial multiplication, which, in turn, enhances transmission [16, 17]. Thus, close contacts of persons with clinical diphtheria must be assigned the highest priority for preventive measures. Contacts of carriers should be given secondary priority. Moreover, prompt administration of antimicrobial prophylaxis to all persons exposed to diphtheria should reduce the likelihood of transmission by carriers. The benefits of excluding carriers from school or work may be minimal if their identification is delayed.

Routine Community-Wide Vaccination

The most important measure for preventing diphtheria is an ongoing community-wide program of active immunization that emphasizes on-time vaccination of children and booster immunization of adults. After completion of a primary series of diphtheria toxoid injections, all persons should receive a booster dose every 10 years [46, 50]. Combined diphtheria and tetanus toxoids should be given whenever the use of tetanus toxoid is indicated (e.g., for wound management) [46, 50].

Summary

Our investigation illustrates the potentially devastating consequences of the introduction of toxigenic *C. diphtheriae* into a community and emphasizes the need for a high index of suspicion regarding diphtheria, especially in inadequately vaccinated patients. Maintenance of a high level of clinical awareness of diphtheria, prompt investigation of sporadic cases with systematic identification and management of close contacts, and improvement of vaccination levels in the community are needed to prevent further morbidity and mortality due to diphtheria. In view of the continued occurrence of diphtheria in developing countries and the frequency of international travel in the current era, such measures will be necessary if the United States is to achieve its goal of eliminating diphtheria among persons ≤25 years of age by the year 2000. The ultimate goal will be to eliminate this disease among persons of all ages.

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