Use of Diphtheria Antitoxin (DAT) for Suspected Diphtheria Cases

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Sponsored by:

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1.0 OBJECTIVE
The purpose of this IND is to provide a treatment plan for the use of an unlicensed diphtheria antitoxin (DAT) for treatment of acute cases of diphtheria and, under exceptional circumstances, to provide passive, transient protection against diphtheria in an exposed contact.

No licensed diphtheria antitoxin is available in the United States.

2.0 BACKGROUND
Diphtheria is a clinical syndrome caused by a polypeptide exotoxin produced by the bacterial pathogen Corynebacterium diphtheriae; non-toxin-producing strains of C. diphtheriae are not associated with the syndrome but can cause localized inflammation. The severe local and systemic manifestations of diphtheria result after diphtheria toxin binds to a wide range of mammalian cells, including epithelial, nerve and muscle cells. The toxin interferes with enzymes necessary for protein synthesis, leading to cell damage and death. Local effects include severe inflammation and pseudomembrane (a firmly adherent exudate that looks like a membrane) formation in the pharynx or larynx, which can progress to airway obstruction. Systemic effects include myocarditis, polyneuritis, and, rarely, renal failure.

There are four biotypes of C. diphtheriae: gravis, mitis, belfanti and intermedius. All four biotypes are capable of producing an identical exotoxin. No difference in pathogenicity has been demonstrated among the three biotypes. Rare human cases of infection with toxin-producing Corynebacterium ulcerans cause identical clinical outcomes (1). Severe clinical manifestations result from absorption of toxin (either local or systemic) produced by infection with C. diphtheriae at an epithelial site (usually pharynx, occasionally nasal lining, or skin). The onset of disease is insidious. Following an incubation period of 1-5 days, low-grade fever begins and a pharyngeal pseudomembrane develops over 2-3 days, along with lymphadenopathy and diffuse systemic toxicity, resulting in a rapid, thready pulse, weakness, and irritability. Although the systemic effects of diphtheria can occur in the first week of illness, they usually occur later (1-2 weeks after onset for myocarditis, 2-8 weeks for neuritis).

The hallmark of suspected diphtheria is a febrile, membranous pharyngitis of insidious onset. In a minority of instances, diphtheria can result from an isolated diphtherial infection in the larynx, nasal lining, or skin. Other diseases that can occasionally produce a similar membranous pharyngitis include streptococcal pharyngitis and infectious mononucleosis. Patients who have been treated with immunosuppressive drugs can present with a membrane that mimics diphtheria. Isolated diphtherial laryngitis can usually be differentiated from Haemophilus influenzae type b epiglottitis, spasmodic croup, or the presence of a foreign body by the gradual onset of diphtherial disease. Differentiation of isolated diphtherial laryngitis from viral laryngotracheitis or bacterial tracheitis can be difficult on the basis of symptoms alone.

Diphtheria antitoxin (DAT) was first produced in the 1890s and is still produced using serum from horses hyperimmunized with diphtheria toxoid. The evidence for efficacy of DAT is based on observations and studies done several decades ago. Mortality rates for clinical diphtheria frequently exceeded 50% in the pre-antitoxin era. Almost as soon as antitoxin was available, clinical experience showed dramatic declines in mortality in groups of patients treated with antitoxin compared to historical control groups or groups treated at hospitals not using antitoxin. In one controlled trial in which patients at a hospital were allocated to antitoxin treatment or no antitoxin treatment on an alternating day schedule, mortality in treated patients was 3.3% compared to 12.2% in untreated patients (2). It was also shown that early treatment is critical, with the degree of protection from DAT inversely related to the duration of clinical illness preceding its administration. Mortality increased progressively within the interval from onset of illness to treatment, with a sharp increase from 4% mortality in those treated with antitoxin within 24-48 hours to 16.1% in those treated on the third day of illness (3). Mortality rates continued to increase with
more prolonged intervals, reaching 29.9\% in those treated 7 or more days after onset. Current thinking is that toxin fixes to susceptible cells early in disease and fixed toxin is not neutralized by antitoxin (4).

The management of a patient with suspected diphtheria includes:

(i) Administration of diphtheria antitoxin as soon as possible after testing for hypersensitivity to horse serum; early administration of appropriate antitoxin is critical for survival (5).
(ii) Establishing the diagnosis through appropriate bacterial cultures;
(iii) Administration of antibiotics; and
(iv) Appropriate supportive care including special attention to maintaining an adequate airway in the presence of laryngeal or extensive pharyngeal membranes and to careful monitoring for cardiac rhythm disturbances or other manifestations of myocarditis.

Diphtheria is currently a rare disease in the United States; 0-5 cases a year have been reported annually since 1990. There is evidence that toxigenic strains of diphtheria continue to circulate in at least limited areas of the United States (6). In 2003, a case of respiratory diphtheria was imported from a country that is endemic for the disease. Access to diphtheria antitoxin is essential to ensure effective treatment of all cases of diphtheria.

3.0 PRODUCT INFORMATION
A U.S. licensed DAT product manufactured by Connaught was available until 1996 after which it was no longer manufactured in the U.S. In 1997, a DAT product manufactured by Pasteur Merieux and licensed in France and other European countries, was made available in the U.S. through an IND program (BB IND 6937). Pasteur Merieux stopped manufacturing DAT in 2002. CDC has been unable to identify a manufacturer that plans to license a DAT product in the U.S. and thus has sought alternative, international sources. A DAT product manufactured by the Instituto Butantan in São Paulo, Brazil is available for use in the United States under this IND program. This product is similar to the previously licensed DAT.

4.0 CLINICAL DESIGN
This is a program to allow DAT treatment for patients with suspected diphtheria infection. Physicians requesting diphtheria antitoxin should contact the CDC’s Emergency Operations Center (EOC) at 770-488-7100. Decisions to release DAT will be made by the CDC diphtheria duty officer or his/her designee in discussion with the treating physician. The decision to administer DAT (once dispensed) to a patient will be made by the treating physician.

5.0 ELIGIBILITY

Therapeutic use

Patients who have probable or confirmed respiratory diphtheria are eligible to receive DAT. The Council of State and Territorial Epidemiologists approved of the following case definition for clinical respiratory diphtheria: an upper respiratory tract illness characterized by sore throat, a low grade fever, and an adherent membrane of the tonsil(s), pharynx, larynx, and/or nose. A confirmed case is either a clinical case from which \textit{C. diphtheriae} is isolated from respiratory specimens (nasal or throat swab, membrane tissue) or a clinical case that is epidemiologically linked to a laboratory-confirmed diphtheria case. A probable case is a clinically compatible case that is not laboratory confirmed and is not epidemiologically linked to a laboratory confirmed case.

A patient’s eligibility for treatment will be determined through discussion between the CDC diphtheria duty officer and the treating physician. The diphtheria duty officer will always release DAT if, following
the discussion, it is still the decision of the treating physician to request and administer DAT. The final
decision to administer DAT to a case-patient lies with the treating physician. The treating physician may
decide against using DAT after it is released.

DAT should be released and administered without delay to:

A. All cases of respiratory diphtheria with laboratory-confirmed toxigenic *Corynebacterium diphtheriae*.

B. Probable cases. Diphtheria should be strongly suspected in a probable case-patient who is toxic in
appearance and
- is without another clearly established diagnosis and/or
- has rapidly worsening illness and/or
- has history of recent travel to a country where diphtheria is endemic or epidemic and/or
- was exposed to travelers from countries with endemic or epidemic diphtheria and/or
- has history of recent contact with dairy animals and/or
- was never vaccinated or is not up-to-date with diphtheria toxoid vaccination

For probable cases which are considered to have a low probability for diphtheria, the duty officer will
encourage the requesting physician to aggressively consider other diagnoses. However the final decision
to request and administer DAT to a patient lies with the requesting physician.

C. Case-patients who have isolated or localized lesions in the nose, eye, skin, or other anatomical
sites from which is obtained, and in whom there are signs of systemic toxicity (fever, tachycardia, and
weakness). DAT treatment is not routinely indicated for treatment of diphtheria skin infection; toxigenic
sequelae are rare when the infection is limited to the skin and when the case-patient is up to date on
vaccination with diphtheria toxoid.

**Prophylactic use**

DAT is used prophylactically only under exceptional circumstances. Eligibility for prophylactic use of
DAT will be limited to the following situations:

- An individual who has had known exposure to toxigenic *C. diphtheriae* (or possibly other toxigenic
  *Corynebacteria*).
- An individual who is not up-to-date for vaccination against diphtheria and who has suspected or
  known exposure to toxigenic *Corynebacteria*.
- An individual who cannot be kept under surveillance for the development of clinical symptoms or
  is not available for follow-up of results of culturing for the diphtheria organism after exposure to a
  known or suspected infection with toxigenic *Corynebacteria*.

Each request for use of DAT for prophylactic use will require detailed discussion of all possible options
with the diphtheria duty officer.

Under the rare circumstances when these conditions are met, the recommended dose of DAT is 10,000
units (after appropriate sensitivity testing). These patients also should be given prophylactic antibiotics
and appropriate up-date vaccination with diphtheria toxoid.
6.0 TREATMENT PROCEDURES

Informed Consent/Parental Permission

Written informed consent in compliance with 21 CFR 50 will be obtained before any program-related procedures are initiated. Consent via the enclosed consent form (Appendix I) must be obtained from the patient before DAT is given to the patient, if the patient is able to give consent. If the patient is unable to give consent, consent must be obtained from the next-of-kin or legal guardian/representative. The treating physician or designee will provide information on DAT in lay terms to the patient. Questions about the nature of the program, the means by which the program is to be conducted, and the risks to the patient will be solicited.

A single informed consent form will be used to obtain consent from adults or parental permission for minors. Waiver of assent for older children (7–17 years of age) has been requested from the CDC IRB for all patients under this protocol. Parental permission will be sought in accordance with 21 CFR 50.55(c) for all minors aged 17 years and younger (permission of only one parent is required). Please see Appendix I. The ultimate responsibility for decision making for this product for all minors should lie with the parent or guardian.

If a patient is unable to respond and make wishes known about DAT treatment, and no next-of-kin or legal guardian/representative is available, and the patient’s illness is life-threatening, per 21 CFR 50.23 “Exception from General Requirements”, informed consent may be deemed not feasible and the treating physician can make the determination to administer DAT. Per 21 CFR 50.23, the patient’s treating physician, acting as site investigator, and a physician who is not otherwise participating in this treating protocol, will document the following on the consent form and will return a copy of the consent form to CDC. CDC will also report to CDC IRB as required and according to CDC IRB’s policy and procedures.

1. Patient is confronted by a life-threatening situation necessitating the use of DAT.
2. Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally-effective consent from, the patient.
3. Time is not sufficient to obtain consent from the patient’s legal representative.
4. There is no alternative method of approved or generally recognized therapy available that provides an equal or greater likelihood of saving the life of the patient.

If immediate use of DAT is, in the treating physician’s opinion, required to preserve the life of the patient, and time is not sufficient to obtain the independent determination required above in advance of administering DAT to the patient, the determinations of the treating physician shall be made and, within 5 working days after the use DAT, be reviewed and evaluated in writing by a physician who is not participating in this treatment protocol.
Precautionary measures
DAT is an equine serum product and precautionary measures are recommended (described below) for all patients. A history of hypersensitivity reactions to equine proteins or positive skin testing in a patient indicates that additional special precautions should be taken in giving DAT or other equine material to these patients.

All patients should have the following:
- An appropriate history taken for factors suggesting increased risk (see below)
- Sensitivity testing to DAT*
- Careful monitoring during sensitivity testing and DAT administration for evidence of hypotension and bronchoconstriction

Patients with a history suggesting increased risk should have the following:
- Initial sensitivity testing with a reduced dose*
- Very careful monitoring during sensitivity testing and DAT administration for evidence of hypotension and bronchoconstriction

*Patients with positive sensitivity testing to DAT or with a history of hypersensitivity reactions to equine proteins (even with a negative or equivocal sensitivity test) should have “desensitization” performed (see below).

Personnel who test for sensitivity to or administer DAT should be trained to treat anaphylactic reactions. The necessary medications, equipment, and staff competent to maintain the patency of the airway and to treat cardiovascular collapse must be immediately available.

History suggesting increased risk from DAT administration
Patients with the following history may be at increased risk of developing serious anaphylactic reactions upon receipt of equine origin serum administered subcutaneously, intramuscularly, or intravenously:
- Asthma, allergic rhinitis, or urticaria
- Asthma, allergic rhinitis, or urticaria or other symptoms of distress when in proximity to horses
- Previous injection of serum of equine origin
These patients must be desensitized (see below) before administering DAT even with a negative or equivocal sensitivity testing.

Tests for Sensitivity to DAT
A test for sensitivity to DAT should be carried out each time DAT is administered. Sensitivity to DAT may be assessed by two methods (7): the scratch, prick, or puncture skin test is followed by an intradermal test if the skin test is negative. This order is recommended as the skin test is thought to be safe while the intradermal test has been reported to cause fatal anaphylactic reactions. Personnel who perform skin tests for sensitivity to DAT should be trained to recognize and treat acute anaphylaxis. The necessary medications, equipment, and staff competent to maintain the patency of the airway and to treat cardiovascular collapse must be immediately available.

A. Scratch, prick, or puncture skin test
After cleaning a skin site on the volar surface of the patient’s forearm with alcohol and air drying, make a superficial scratch, prick, or puncture using a sterile needle or other sterile sharp instrument, breaking the skin but not drawing blood. Apply one drop of a 1:100 dilution of the serum in normal saline to the site. Positive (histamine) and negative (physiologic saline) control tests should also be applied to similar scratch, prick, or puncture sites. A positive scratch test is a wheal with surrounding
erythema at least 3 mm larger than the negative control test, read at 15-20 minutes. The histamine control must be positive for valid interpretation; a positive response consists of a wheal at the scratch site surrounded by an erythematous area. If the scratch test is negative, an intradermal (ID) test is performed.

B. Intradermal (ID) test
Administer a dose of 0.02 ml of 1:1,000 saline-diluted serum intradermally; this quantity should raise a small ID wheal. If the test is negative, repeat it using a 1:100 dilution. In persons with a negative history for animal allergy and negative history for prior exposure to animal serum, the stronger (1:100) dilution of serum may be used in the ID test without prior testing with the lower dilution (1:1,000). Positive (histamine) and negative (physiologic saline) intradermal control tests should be applied. Interpretation of the ID test is done as with the scratch test.

A positive skin test indicates the probability of sensitivity with some correlation between the severity of the reaction on skin testing and the likelihood and severity of reaction to the DAT. However, a negative skin test does not preclude the possibility of an adverse reaction. In addition, antihistamines (and possibly other drugs such as tricyclic antidepressants) administered previously can interfere with the results of skin testing for periods of one day or longer depending on the antihistamine. DAT should be administered cautiously even in patients with negative skin tests.

Desensitization
Patients with positive sensitivity testing to DAT or with a history of hypersensitivity reactions to equine proteins (even with a negative or equivocal sensitivity test) should undergo desensitization. Tables 1 & 2 (appended) serve as guides for desensitization. Table 1 gives an intravenous (IV) regimen and Table 2 gives an intramuscular (IM) regimen (7). The IV route is considered safer because it offers better control.

The personnel performing desensitization need to have the expertise to treat anaphylaxis and the necessary equipment and medications available. Some physicians recommend concurrent treatment with an oral or IM antihistamine with or without IV administration of a corticosteroid such as hydrocortisone or methylprednisolone. The protection from anaphylaxis afforded by giving DAT according to the desensitization treatment schedule requires that no interruption occur in the sequence of administration of doses; if an interruption occurs the protection is lost.

Administration
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
A. Perform sensitivity tests, and desensitization if necessary.
B. 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.

C. The recommended DAT treatment dosage ranges (8) are:
   - Pharyngeal or laryngeal disease of 2 days duration: 20,000 to 40,000 units
   - Nasopharyngeal disease: 40,000 to 60,000 units
   - Systemic disease of 3 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 (for cases where treatment is indicated)

D. Give children the same dose as adults.

E. Repeated doses of DAT after an appropriate initial dose are not recommended and may increase the risk of adverse reaction.

F. Appropriate antimicrobial agents in full therapeutic dosages should be started.

Any person with clinical symptoms of diphtheria should receive DAT as soon as it can be made available, without waiting for bacteriologic confirmation of the diagnosis. Supportive treatment should be continued until all local and general symptoms are controlled.

Prophylactic regimen
Patients and contacts should be reported urgently to local and/or state health department personnel. All asymptomatic, unimmunized contacts of patients with diphtheria should receive prophylactic antimicrobial therapy after specimens for cultures are obtained. Specimens for culture should be obtained again after treatment. Immunization with diphtheria toxoid should be given, if necessary, and surveillance for illness continued for seven days. This is the standard of care for contacts of a diphtheria case.

Prophylactic treatment with DAT can be considered but is recommended only in exceptional circumstances. For example, a contact who has had known exposure to a case and would not have access to medical personnel (unavoidable travel to a developing country) might be considered for DAT. Such exceptional circumstances should be discussed in detail with the CDC diphtheria epidemiologist on duty. If it is concluded that a close contact may benefit from receiving DAT, DAT can be administered in addition to antimicrobial prophylaxis and immunization with diphtheria toxoid. Before administering DAT:

   A. Perform appropriate sensitivity tests.
   B. If sensitivity testing is negative, give 10,000 units intramuscularly. The dose depends on the length of time since exposure, the extent of the exposure and the medical condition of the individual.
   C. If sensitivity testing is positive, proceed with desensitization schedule outlined above.

Possible adverse reactions following administration of DAT
Anaphylactic Reaction: Although onset and severity are highly variable, anaphylaxis usually begins in susceptible patients within minutes after exposure to DAT; in general the more rapid the onset, the more severe the reaction. The major manifestations are 1) cutaneous, including pruritus, flushing, urticaria, and angioedema; 2) respiratory, including hoarse voice and stridor, wheeze, dyspnea, and cyanosis; and 3) cardiovascular, including a rapid, weak pulse, hypotension, and arrhythmias. Anaphylaxis is a major medical emergency.

In the event of an anaphylactic reaction, treatment will depend on the nature and severity of the reaction. Parenterally administered epinephrine is the primary drug for all types of reactions. Antihistamines should also be given. Additional medications, depending on the severity of the reaction may include corticosteroids, alpha-adrenergic blocking agents, aminophylline, and beta-2 agonists (7).
Febrile Reaction:
When fever occurs, it usually develops twenty minutes to one hour after the injection of serum or antitoxin. It is characterized by a chilly sensation, slight dyspnea and a rapid rise in temperature. Most febrile reactions are mild and can be treated with antipyretics alone; severe reactions may require other measures (tepid water baths, etc) to reduce the temperature.

Serum Sickness:
The symptoms of serum sickness are fever, maculopapular skin rashes, or urticaria in milder forms (90% of instances) with arthritis, arthralgia, and lymphadenopathy also possible in more severe forms. Rarely, angioedema, glomerulonephritis, Guillain-Barré syndrome, peripheral neuritis, or myocardiitis can occur. The onset of symptoms is usually 7 to 10 days (range 5 –24 days) after initial exposure to the foreign protein (DAT). Onset can be as short as several hours to 3 days after re-administration of serum in persons who have received a dose of animal serum in the past; these individuals are also more likely to develop serum sickness. Mild cases of serum sickness frequently resolve spontaneously over a few days to 2 weeks. Medications that may be helpful include antihistamines, non-steroidal anti-inflammatory drugs, and corticosteroids (7).

Febrile reactions and serum sickness are not IgE mediated and therefore are not predicted by skin testing. The frequency of anaphylaxis and serum sickness is partially dependent on the frequency of previous administration of animal serums in the population; this frequency is now low. Recent data on the frequency of adverse reactions to horse serum products is extremely limited due to their infrequent use. In a review of 1,433 diphtheria cases treated with antitoxin between 1940 and 1950, the frequency of adverse reactions was as follows: anaphylaxis, 0.6% (without any fatalities); febrile reactions, 4.0%; and serum sickness, 8.8% (6).

7.0 LABORATORY TESTING
Although the decision to administer DAT in a suspected case of diphtheria must frequently be made in the absence of confirmatory laboratory evidence, it is essential to obtain the specimens to confirm the diagnosis early in the course of illness, and if possible, before the administration of antibiotics. The recommended specimens include the following:

A. Throat, membrane (swabs or fragments), and nasal swab specimens for diphtheria culture. These are plated on special media. The laboratory must be notified to look for C. diphtheriae so that the appropriate, special medium is available, and laboratory personnel must have the necessary expertise to process cultures for C. diphtheriae. In patients who have not yet had specimens collected for culture, or who have had cultures processed that were negative for C. diphtheriae, the diphtheria duty officer at CDC may recommend that existing or new specimens be sent directly to the CDC Diphtheria Laboratory for culture and polymerase chain reaction (PCR) testing. Testing by PCR has the capability of identifying C. diphtheriae toxin from swabs or from membrane specimens when cultures are negative. Tissue and swabs for culture and PCR should be maintained in transport medium or in a sterile container kept moist with sterile, non-bacterial static saline until they reach the laboratory. Specimens for culture and PCR should not be placed in formaldehyde.

All Corynebacterium strains isolated and suspected of being toxin producers should be forwarded to the CDC Diphtheria Laboratory (telephone 404 639-1231) for confirmation and toxigenicity testing.

B. A serum specimen can be obtained from the patient before antitoxin administration and tested for diphtheria antibodies. A low titer level (<0.01 IU/ml) indicates susceptibility but does not confirm
the diagnosis. A high titer (>0.1 IU/ml) suggests that a diagnosis is less likely to be diphtheria.

C. If the patient has signed the consent for measurement of anti-diphtheria antibody levels before and after administration of DAT, a blood sample (5 mL) will be collected at the following time points (for a total of 30 mL):
- Prior to DAT infusion
- One-hour post DAT infusion
- 1 DAY post DAT infusion
- 3 DAYS post DAT infusion
- 7 DAYS post DAT infusion
- 28 DAYS post DAT infusion or at time of hospital discharge (whichever is earlier)

Information to accompany the serum samples includes patient initials, sex, age, weight, date and time of DAT administration and dose of DAT administered.

**Rationale for blood draws:**
Diphtheria antitoxin (DAT) is obtained from horse serum and there is a risk for an allergic reaction to horse proteins. A laboratory in the United States, called MassBiologics of the University of Massachusetts Medical School, is working to develop a human antitoxin to treat diphtheria as an alternative to equine diphtheria antitoxin. In order to establish comparability and determine the optimal dose of human monoclonal antibodies required to treat diphtheria, it would be most helpful to determine the amount of diphtheria antitoxin antibodies in the blood of persons treated with DAT during illness and convalescence; this information is currently not available.

Participation is voluntary and non-participation will not affect receiving treatment by the patient.

**8.0 LOCAL AND STATE HEALTH DEPARTMENT NOTIFICATION**
It is a requirement that cases of suspected diphtheria (e.g., cases for whom DAT is requested) be reported to local and state health departments. A physician who requests and administers DAT will notify the local and state health departments. The CDC duty officer will also notify the state health department of any DAT that is released. Public health officials will assist in identifying contacts at risk of infection, will often obtain cultures, and will facilitate antibiotic prophylaxis of contacts when necessary to prevent spread to other members of the community.

**9.0 DATA COLLECTION AND STORAGE**
A requirement for release of DAT under IND is that CDC will obtain and store information relating to the patient’s illness (including patient identifiers). Data obtained will be shared with the state health departments for public health investigation. In the event of serious adverse reactions, complete medical records may be requested for evaluation by the principal investigator from the treating physician. Serious adverse reactions will be reported to CDC IRB and FDA. Stored data will be analyzed as needed by CDC staff to prepare annual summary reports for renewal or continuation of the program with the CDC IRB and FDA. The data containing personal identifiers will be stored in locked file cabinets. This information will be kept strictly confidential. All forms should be returned directly to the CDC Drug Service.

CDC Drug Service, Mailstop D-09
1600 Clifton Rd.
Atlanta, GA 30329-4027
Phone: 404-639-3670
Fax: 404-639-3717
### Table 1. Desensitization to DAT - Intravenous route (7)

<table>
<thead>
<tr>
<th>Dose number *</th>
<th>Dilution of DAT in normal saline</th>
<th>Amount of injection (cc)</th>
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<tbody>
<tr>
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<td>1:1,000</td>
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<td>2</td>
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* Administer at 15 minute intervals.

### Table 2. Desensitization to DAT - Intradermal, subcutaneous and intramuscular route (7)

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<th>Route of administration</th>
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* Administer at 15-minute intervals.
10.0 REFERENCES


6. CDC. Unpublished data.
