NIGERIA CENTRE FOR DISEASE CONTROL AND PREVENTION

PROTOCOL FOR DIPHTHERIA ANTITOXIN (DAT) USE

December 2022

Version_01

1.0 BACKGROUND

Diphtheria is a clinical syndrome caused by an exotoxin produced by the bacterium Corynebacterium diphtheriae; non-toxin-producing strains of C. diphtheriae are not associated with the syndrome but can cause localized inflammation. Most commonly, toxigenic infection results in respiratory or cutaneous disease. Diphtheria is transmitted from person-to-person by respiratory droplets or contact with discharges from skin lesions. The severe local and systemic manifestations of respiratory diphtheria result after diphtheria toxin binds to a wide range of 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 pseudo-membrane (a firmly adherent leather-like exudate that looks like a membrane) formation in the nose, and/or pharynx and/or larynx, which can progress to life-threatening airway obstruction. Systemic effects may occur from the absorption of diphtheria toxin and include myocarditis, polyneuritis, and, rarely, renal failure.

DAT was first produced in the 1890s and is still being produced using serum from horses that are hyperimmunized with diphtheria toxoid. The evidence for the efficacy of equine-based DAT for the treatment of respiratory diphtheria 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.

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 based on 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.

2.0 OBJECTIVE

The purpose of this protocol is to provide access to diphtheria antitoxin (DAT) for the treatment of suspected/confirmed diphtheria cases and for prophylactic use under ***exceptional*** circumstances in exposed contacts in the affected areas with outbreaks.

3.0 PRODUCT INFORMATION

The DAT is a sterile, transparent (clear) serum solution supplied in 10 mL ampoules containing 10,000 International Units (IU) per vial. The composition of DAT is based on the manufacturer's information. DAT must be stored in the refrigerator at 2 - 8°C **(DO NOT FREEZE).**

4.0 OUTBREAK INTERVENTION DESCRIPTION

States with possible diphtheria outbreaks needing to request DAT should contact the National Diphtheria EOC at NCDC. The National Incident manager for the EOC will release DAT if the population meets eligibility criteria based on the discussion with the states and according to available data. In the states, hospital facilities identified for the administration of DAT, will identify a site investigator under the period of the intervention during the outbreak.

5.0 LOCAL GOVERNMENT AREA AND STATE TEAM RESPONSIBILITY

It is a requirement that cases of suspected diphtheria (e.g., cases for whom DAT is requested) and known contacts be reported to Local Government Area (LGA) Disease Surveillance Notification Officer (DSNO) and state DSNO/State Epidemiologist (SE).

6.0 PATIENT ELIGIBILITY FOR DAT

Patients who are suspected or confirmed diphtheria based on the available case definition or classification of cases in the outbreak are eligible to receive DAT.

7.0 DAT TREATMENT PROCEDURES

7.1 Informed Consent/Parental Permission

Written informed consent for ethical reasons by the parent should be obtained before the intervention with DAT is initiated. Since it is an outbreak situation or an emergency, the state government can stand in for its population. Hence parental consent will not be needed directly for the intervention to be initiated.

7.2 Precautionary measures

DAT is an equine serum product and precautionary measures are recommended for all patients. Patients with the following history may be at increased risk of developing serious anaphylactic reactions upon receipt of DAT administered subcutaneously (SC), intramuscularly (IM), or intravenously (IV).

7.3 All cases should have the following:

- An appropriate history taken for factors suggesting an increased risk.
- Careful monitoring during DAT administration for evidence of hypotension and bronchoconstriction.

Health Care Workers (HCW) who administer DAT should be trained to treat anaphylactic reactions.

8.0 DAT ADMINISTRATION

8.1 General information for family/patient

DAT is an equine serum product that is highly effective and the gold standard for treatment of diphtheria. Antitoxin is used to stop the damaging effect of the toxin and prevent the life-threatening manifestations of diphtheria infection. However, there is small risk of serious allergic reaction: < 0.6 % anaphylaxis, 4% fever, and 8.8% serum sickness.

8.2 Route

The IV route is the preferred route of administration of DAT, especially in severe cases. The antitoxin dose should be mixed in 250 –500 mL of normal saline and administered slowly over 2 – 4 hours, closely monitoring for anaphylaxis. The antitoxin may be given IM in mild or moderate cases.

8.3 Temperature

Antitoxin should be warmed to **32 – 34°C** before injection. Warming above the recommended temperature should be carefully avoided because the DAT proteins will denature.

8.4 Dosage

The amount of antitoxin recommended varies with larger amounts recommended for persons with extensive local lesions and with longer interval since onset. The dose is the same for children and adults. Do not repeat dosing. ***If limited availability, then use lower dose.***

Dosage for diphtheria antitoxin

Dose	Indication
20,000 to 40,000 IU	Pharyngeal or laryngeal disease of 48 hours duration or less
40,000 to 60,00 IU	Nasopharyngeal lesions
80,000 to 120,000 IU	Extensive disease of three or more days' duration or diffuse swelling of the neck

Note:

i. Give the entire treatment dose of antitoxin IV (or IM) in a single administration.
ii. Give children the same dose as adults.
iii. Repeated doses of DAT after an appropriate initial dose are not recommended and may increase the risk of adverse reactions.

8.5 Environment

Ensure appropriate monitoring and medical interventions are available for adult and pediatric patients in case serious allergic reaction ensues.

- Monitoring devices: pulse oximeter, BP cuff, thermometer
- Emergency medicines: adrenaline (1:1000), salbutamol, antihistamine,
- prednisolone, crystalloid fluid, oxygen supply and delivery devices
- Emergency equipment: bag valve mask, IV giving devices, airway management

8.6 Procedure:

1. HCW uses contact and droplet precautions: gloves, long-sleeved gown, surgical mask and eye protection.
2. Monitor patient vital signs: BP, HR, RR, SpO_2, mental status, before and after administration.
3. Perform sensitization testing.

8.7 Sensitization testing:

Use the Besredka method

a. Inject 0.1 ml SC and wait 15 minutes. If there is no reaction then inject further 0.25 ml SC. If no reaction after 15 minutes, then inject remainder IM or IV. This test method is simple and has been used safely in outbreak settings in South Africa.

b. If patient demonstrates sensitivity on testing, then do not administer entire dose. Proceed with desensitization according to CDC protocol.
https://www.cdc.gov/diphtheria/downloads/skintest-guide.pdf

9.0 POSSIBLE ADVERSE REACTIONS FOLLOWING ADMINISTRATION OF DAT

9.1 Clinical Description 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. **Anaphylaxis** (rapid onset): Onset usually within minutes.
   - **Skin:** pruritus, flushing, urticaria, and angioedema.
   - **Respiratory:** hoarse voice and stridor, wheeze, dyspnea, and cyanosis.
   - **Cardiac**: rapid, weak pulse, hypotension, and arrhythmias.

   Anaphylaxis is a major medical emergency, call for help.
2. **Febrile reaction** (within 20-60 minutes): When fever occurs, it is characterized by a chilly sensation, slight dyspnea and a rapid rise in temperature. Most febrile reactions are mild. Treat with antipyretics alone (i.e. paracetamol); severe reactions may require other measures (tepid water baths, etc.) to reduce the temperature.
3. **Serum sickness** (usually 7-10 days after initial exposure, range from 5-25 days): Symptoms are fever, maculopapular skin rashes, or urticaria in milder forms (90% of instances); arthritis, arthralgia, and lymphadenopathy also possible in more severe forms. Rarely, angioedema, glomerulonephritis, Guillain-Barré syndrome, peripheral neuritis, or myocarditis can occur. 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.

9.2 Treatment of Anaphylaxis

If anaphylaxis occurs, STOP infusion immediately.

1. Call for help.
2. Assess the airways, breathing and circulation. Start emergency treatments – If the child is not breathing, check pulse. If no pulse, start basic life support and give five rescue breaths with a bag-valve mask and 100% oxygen.
3. Give adrenaline (1:1000, 1mg/ml) IM immediately:
   a. 0.15 ml of 1:1000 to children < 6 years, repeat every 5 minutes as necessary
   b. 0.3 ml of 1:1000 to children 6-12 years, repeat every 5 minutes as necessary
   c. 0.5ml of 1:1000 epinephrine to adolescents and adults, repeat every 5 minutes as necessary
4. Ensure stabilization of airway, breathing and circulation.
   a. Get IV/IO access, give 100% oxygen, give crystalloid fluid (20 ml/kg IV) rapidly for shock, nebulized salbutamol for wheezing.
5. Also give antihistamine and steroids (i.e., prednisolone1mg/kg).

9.3 Monitoring and Reporting of Adverse Events

Adverse events (AE) are any untoward medical occurrence with the use of DAT in humans, whether or not considered related to DAT. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of DAT, without any judgment about causality. It can be classified as either mild or serious.

NAFDAC has a monitoring system for AE in place. The system provides a form (pharmacovigilance form) which is used is used in reporting A. The form exists as hard copy (yellow form; see Annex 1) and e-form (https://primaryreporting.who-umc.org/NG). All AEs should be reported using the pharmacovigilance form.

9.4 Case Monitoring

Since DAT is an investigational product, it is the responsibility of HCW to perform case evaluation and monitoring, recording, and reporting requested information to NCDC and NAFDAC, such as any occurrence of serious adverse events (SAEs) during and following DAT.

9.5 Recording and Reporting Adverse Events

The HCWs must report all adverse events by means of the Diphtheria Antitoxin Treatment and AE Form (pharmacovigilance form). These may include adverse events that the patient reports spontaneously, those the HCW observes, and those the HCW elicits in response to open-ended questions. Serious adverse event must be reported within 24 hours of occurrence or as soon as possible by contacting the DSN. All serious adverse events reported will be reviewed by the National EOC based on the report from the state team, to assess and determine causality to DAT.

10.0 ACCESSING DAT FROM NATIONAL STOCKPILE

At the national level, NCDC is responsible for managing the national stockpile for DAT. When the need for it arises such as during outbreaks, states will request for DAT through the National EOC at NCDC. Such requisition must be backed by data (CIF data, lab data, AE data). team, to assess and determine causality to DAT. Health facilities in the states will then request for DAT from the state. The state will be responsible for account for all DAT supplied to the state.

11.0 MANAGEMENT OF EXPIRED AND DAMAGED PRODUCTS

This section describes the procedures involved in the handling and disposal of expired and damaged products. It's intended to cover all activities for the identification, segregation, handling and disposal of expired and damaged products in care of NCDC

11.1 Responsibility

The Store Officers (SO)/State Logistic Officer and NCDC logistic officer will implement this section of the SOP.

11.2 Identification, Verification and Segregation of Expired and Damaged Products

The designated SOs/SLOs should conduct physical stock inspections within the last week of every month. On identification of a short-expiring, expired or damaged product(s), separation from the integral products should be done and with the approval of the NCDC logistic officer, the identified products should be physically transferred to "Reject area" of the warehouse. The reject area is a segregated area of the warehouse which is used in holding and storing rejected, expired, damaged products. The bin cards at the "Reject area" should be updated to include the recently added products. The NCDC logistic officer should fill in a request for stock adjustment

ensuring that all relevant information corresponding to the product(s) are included, and forward same to his/her supervising officer for approval. With the approval of the supervising officer, the NCDC logistic officer should verify and remove the quantities of expired/damaged products from the bin cards of usable products accordingly. The approved request for stock adjustment should be forwarded to Head of Finance (HF) and in the cases of program stock, the supervising officer. The HF and accounts Department should use the approved stock adjustment request received to prepare stock adjustment journals. The LoMIS should be updated to reflect all the changes.

Note: *supervising officer at NCDC should coordinate the identification and production of a list of slow-moving products using the Logistic Management Information System (LoMIS) to reduce their procurement frequency*

11.3 Destruction of Expired/Damaged Products

The designated SOs/SLOs should compile a list of expired/damaged products including all relevant details as weight, pack sizes, value, etc. and forward to the NCDC supervising officer for approval. The NCDC supervising officer should assign a designated SO/SLO to verify that the listed products require destruction and approve the list. The approved list should be forwarded to NCDC supervising officer in the case of program stocks. The NCDC supervising officer should liaise with NAFDAC and other stakeholders to schedule a date for the destruction exercise. After destruction, a "Destruction Certificate" should be obtained from NAFDAC.

Annex 1: Pharmacovigilance form

NATIONAL PHARMACOVIGILANCE CENTRE (NPC) NIGERIA

National Agency for Food and Drug Administration & Control (NAFDAC), Headquarters Office
Plot 2032 Olusegun Obasanjo Way
Wuse Zone 7 Abuja

Tel: 08086899571 or 07098211221

FORM FOR REPORTING OF SUSPECTED ADVERSE DRUG REACTIONS

IN STRICT CONFIDENCE

1. * PATIENT'S DETAILS

Full Name or Initials: _____ Patient Record No: _____

AGE/DATE OF BIRTH: _____ SEX: M ☐ F ☐ WEIGHT (kg): _____

HOSPITAL/Treatment Centre _____

2. * ADVERSE DRUG REACTION (ADR)

A. DESCRIPTION

DATE Reaction Started	DATE Reaction Stopped

C. OUTCOME OF REACTION
TICK AS APPROPRIATE

☐ Recovered fully ☐ Recovered with disability (Specify) _____

☐ Congenital Abnormality (Specify) _____ ☐ Life Threatening (Specify) _____

☐ Death ☐ Others (specify) _____

B. Was Patient Admitted Due to ADR Yes ☐ No ☐

If Already Hospitalized, Was it Prolonged Due to ADR Yes ☐ No ☐

Duration of Admission (days) _____

Treatment of Reaction: _____

3. * SUSPECTED DRUG (Including Biologicals Traditional/Herbal Medicines & Cosmetics)

A. DRUG DETAILS (State name and other details if available / attach product label / Sample (if available)

Brand Name: _____ Generic Name: _____ Batch No: _____

NAFDAC No: _____ Expiry Date: _____

Name & Address of Manufacturer: _____

B. Indications for Use	Dosage	Route of Administration	Date Started	Date Stopped

4. * CONCOMITANT MEDICINES (All medicines taken within the last 3months including herbal and self medication)

Brand or Generic Name	Dosage	Route	Date Started	Date Stopped	Reason for Use

5. * SOURCE OF REPORT:

Name of Reporter: _____

Address: _____

Profession: _____

Signature: _____ Date: _____ Tel No/E-mail: _____

* : MANDATORY FIELDS

FORMS ARE AVAILABLE AT www.nafdac.gov.ng AND CAN BE SENT TO npcadr@nafdac.gov.ng