Clinical management of diphtheria

Guideline

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World Health Organization

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Sections

1. Summary of the guideline

Clinical question: What is the role of antibiotics and diphtheria antitoxin (DAT) in the treatment of diphtheria?

Context: This clinical practice guideline has been rapidly developed recognizing the global increase in diphtheria outbreaks. Outbreaks of diphtheria in Nigeria, Guinea and neighbouring countries in 2023 have highlighted the urgent need for evidence-based clinical practice guidelines for the treatment of diphtheria. Given the sporadic nature of outbreaks, many clinicians in the affected regions have never managed acute diphtheria and its related complications. The diphtheria case definition is provided in the WHO document: Diphtheria: Vaccine Preventable Diseases Surveillance Standards*(1)*.

Scope: This guideline focuses on the clinical management of respiratory diphtheria and does not provide advice on vaccination.

See WHO Laboratory manual for the diagnosis of diphtheria and other related infections *(2)*.

New recommendations:

- In patients with suspected or confirmed diphtheria, WHO recommends using macrolide antibiotics (azithromycin, erythromycin) in preference to penicillin antibiotics [Strong recommendation, low certainty evidence].

- In patients with suspected or confirmed diphtheria, WHO recommends not to perform routine sensitivity testing prior to administration of diphtheria antitoxin (DAT) [Strong recommendation, moderate certainty evidence].

- In patients with suspected or confirmed symptomatic diphtheria, WHO suggests an escalating dosing regimen for diphtheria antitoxin (DAT) which is based on disease severity and time since symptom onset, in comparison with a fixed dose for all patients [conditional recommendation, very low certainty evidence].

Characteristic of diphtheria disease	Dose of diphtheria antitoxin (IU)
• Laryngitis **or** pharyngitis **and** • Duration < 48 hours	20 000
• Nasopharyngeal disease (extensive pseudomembrane) **and** • duration < 48 hours	40 000
One or more of: • Diffuse swelling of the neck • Any disease ≥ 48 hours • Severe disease (respiratory distress, shock)	80 000

About this guideline: This guideline was developed according to standards and methods for trustworthy guidelines. These guidelines are based on the synthesis of the available evidence on the health effects of interventions, and the grading of the certainty of that evidence using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. The synthesized and graded evidence on the health effects of interventions, as well as any evidence on contextual factors, is used to develop an evidence-to-decision (EtD) framework for each recommendation *(3)*. The judgement on the different factors in the EtD framework (including the certainty of evidence) facilitates the determination of the strength and direction of each recommendation *(4)*.

Expert input is important for the interpretation of the evidence, and the development of guidance may rely on expert opinion, particularly in areas where the evidence is currently weak, scarce or absent. For example, the DAT dosing recommendations presented in the guidelines are based on a consideration of the evidence gained from observational data as well as the technical knowledge and experience of the Guideline Development Group (GDG). Details of contributors are available online here.

Update and access: The living guideline is written, disseminated, and updated on an online platform (MAGICapp, https://app.magicapp.org/#/guideline/7759), with a user-friendly format and easy-to-navigate structure that accommodates dynamically updated evidence and recommendations, focusing on what is new while keeping existing recommendations updated within the guideline. This format should also facilitate adaptation, which is strongly encouraged by WHO, to contextualize recommendations from a health care system perspective to maximize country impact.

A planned update is already ongoing to address clinical questions related to the prevention of infection in close contacts of people with diphtheria.

Broader context:
The guideline closely aligns with the WHO Health Emergencies Programme goal of strengthening preparation, preparedness, response and resilience in response to health emergencies, particularly the ability of member states to provide safe and scalable care *(5)*.

2. Abbreviations

AMR	antimicrobial resistance
AST	antibiotic sensitivity testing
DAT	diphtheria antitoxin
DOI	declaration of interest
DST	drug sensitivity testing
ETD	evidence to decision
GDG	guideline development group
SAE	serious adverse event
WHO	World Health Organization

3. Introduction

What triggered this guideline?

Despite the implementation of diphtheria vaccination early last century there has continued to be outbreaks of diphtheria in regions where vaccine coverage is not optimal. Vaccine coverage has been negatively impacted by the COVID-19 pandemic, population displacement, and structural disruption of health systems. There is now a prolonged outbreak of diphtheria in multiple countries in West Africa and sporadic outbreaks in all WHO regions. Although diphtheria is both preventable and treatable, successful treatment depends on rapid recognition of the clinical syndrome as well as rapid implementation of the appropriate treatment, which includes the timely administration of the appropriate antibiotics and DAT. Access to DAT has been a challenge due to limited global supply and rapid distribution systems.

The WHO Clinical management of diphtheria guideline aims to provide, in a single reference, the latest evidence-based recommendations to support clinicians in their efforts to provide acute treatment for diphtheria. This guideline responds to direct requests from clinicians and health ministries of affected countries. Currently, clinicians in countries affected by the outbreak have limited or no clinical experience managing patients with diphtheria and limited access to antimicrobial susceptibility testing.

What are the guideline's objectives?

- To provide evidence-based and context-sensitive recommendations on the appropriate choice(s) for diphtheria clinical management including the use of diphtheria antitoxin (DAT) and antibiotics.
- To support the adaptation by WHO Member States of these evidence-based guidelines into national diphtheria policies for the clinical management of diphtheria.
- To inform the clinical research agenda by identifying knowledge gaps which limit our capacity to produce evidence-based recommendations.

Who is this guideline for?

The primary audience for the guideline is clinicians treating patients with diphtheria. The guideline is also intended for use by health managers at facility or jurisdiction level to develop local tools or protocols to assist clinicians in managing patients with diphtheria and orient procurement and allocation of recommended treatments. Furthermore, the guideline is intended to guide researchers and research funders to address the highlighted evidence gaps and uncertainties.

4. Clinical characterization

Clinical characterization

Respiratory diphtheria is caused by strains of *Corynebacterium diphtheriae*, which have affinity for the upper respiratory tract (nose and throat) and produce a toxin which causes local disease and, in severe cases, airway compromise and systemic complications. Diphtheria occurs when the bacterial toxin inflames the epithelial mucosal, causing an exudate which can have a characteristic greyish-white “pseudomembrane” in the pharynx, nasopharynx, tonsils, or larynx (or a combination of these). The fibrinous pseudomembrane can lead to respiratory obstruction. The toxin disrupts protein synthesis and causes cell death leading to the breakdown of the epithelium, and subsequent spread to local lymph nodes can cause a swollen neck. Spread of the toxin in the blood can affect the myocardium (heart), kidneys, and nervous system. *C. diphtheriae* can also cause skin and wound infections. Cutaneous disease is not further discussed in this guideline.

The severity of diphtheria is described in previous WHO operational guidance.

- Mild disease: localized laryngeal or pharyngeal disease of 2 days duration;
- Severe/extensive disease: duration of 3 or more days, or diffuse neck swelling (the so called “bull neck”), or respiratory distress, or hemodynamic instability”*(6)(7)*.

A recent systematic review suggests the case fatality ratio in unvaccinated individuals infected with toxin-producing strains is 29% *(8)*. Case fatality ratios in resource-limited settings are highly variable but, in some outbreaks, can be as high as 50% *(9)(10)*.

Transmission: Diphtheria spreads from person to person mostly through the air, and less frequently by direct contact. The incubation period is usually from 2 to 5 days.

Current treatments include:

- neutralization of unbound toxin with DAT;
- antibiotics to prevent further bacterial growth;
- monitoring and supportive care to prevent and treat complications, e.g. airway obstruction, myocarditis. In patients with imminent airway obstruction, urgent airway intervention may be lifesaving. The possible options include basic airway manouevres, endotracheal intubation, cricothyroidotomy (needle or surgical approach), and tracheostomy. The risks and benefits of each approach will depend on the experience of the treating medical personnel.

5. Recommendation for antibiotics treatment

Antibiotics are used to prevent further bacterial growth and toxin production reducing the risk from further organ damage, and to reduce bacterial transmission to others. Historically, penicillins have been used (including benzylpenicillin, procaine penicillin and penicillin V), but macrolides have also been employed (for example, erythromycin or azithromycin). Antimicrobial resistance prevalence amongst strains of *C. diphtheriae* occurs to both classes, and is variable by region and over time. Local resistance patterns can therefore only be known by bacterial susceptibility testing. Recent studies have demonstrated increased resistance to penicillin over the macrolide class of antibiotics *(11)*. Antibiotics are also used to prevent the development of diphtheria in close contacts of infectious patients; WHO recommendations on this topic are under development.

Strong recommendation for

In patients with suspected or confirmed diphtheria, WHO recommends using macrolide antibiotics (azithromycin, erythromycin) in preference to penicillin antibiotics [Strong recommendation, low certainty evidence].

Remarks:

- Antibiotics should be administered alongside DAT and should not be delayed.
- Recent evidence suggests that there is increasing resistance to penicillins and less resistance to macrolide antibiotics. Local antimicrobial susceptibility testing is vital to ensure the ongoing appropriate use of antibiotics. Advice on laboratory testing in outbreaks is available here.
- The choice of macrolide will depend on availability and feasibility.

Practical info

Macrolide antibiotics include azithromycin and erythromycin. Parenteral administration of macrolide antibiotics is possible; however, it is typically indicated for where oral administration is not possible, such as when patient is unable to swallow oral medications. The choice of macrolide will be based on availability and feasibility. Dosing recommendation are as follows:

- **Azithromycin:** administer orally or intravenously once a day.
  - For children: 10 – 12 mg/kg once daily (maximum 500 mg per day).
  - For adults: 500 mg once daily.
- **Erythromycin**: administer orally or intravenously every six hours.
  - Dose (children and adults): 10 – 15 mg/kg every 6 hours, maximum 500 mg per dose or 2 grams a day.

Penicillin antibiotics

We are providing practical information on penicillin for the scenario where macrolide antibiotics are not available and susceptibility testing demonstrates sensitivity to penicillin. Penicillin can be given orally or parentally (intravenous or intramuscular). Parenteral administration is used primarily to achieve adequate tissue concentrations, especially in patients with severe disease.

- **Procaine benzyl penicillin (penicillin G)**: administer by intramuscular injection**.**
  - Dose (children and adults): 50 mg/kg once daily. Maximum is 1.2 g per day.
- **Aqueous benzyl penicillin (penicillin G)**: administer by intramuscular injection or slow intravenous infusion.
  - Dose (children and adults): 100 000 units/kg per day in divided dose of 25 000 IU/kg every 6 hours. Maximum is 4 MIU or 2.4 g per day.
- **Phenoxymethylpenicillin V:** administer orally.
  - Dose (children and adults): 50 mg/kg per day in divided doses administered every 6 hours (each dose 10 – 15 mg/kg. Maximum 500 mg per dose).

In a diphtheria outbreak it is important that antibiotic stewardship and monitoring are implemented particularly in relation to any changes in antibiotic resistance, which can be determined by antibiotic sensitivity testing.

Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

In patients with suspected or confirmed diphtheria, the GDG deemed the use of antibiotics to be the standard of care over no antibiotics. The use of macrolides, compared with penicillins, probably does not affect mortality or rate of serious side-effects, but erythromycin may increase the rate of gastrointestinal side-effects. The treatment effect of macrolide antibiotics, compared with penicillin antibiotics, is very uncertain for the outcomes of rate of myocarditis, hospitalization, need for airway intervention, new cases of diphtheria, or treatment failure. However, the point estimate of treatment failure favurs macrolides over pencillins.

The treatment burden of penicillins is substantially greater than that of azithromycin, including the need for more frequent doses of penicillins generally, and the need for intravenous administration of benzylpenicillin specifically. Though the risk of antibiotic resistance was uncertain and dependent on local resistance patterns the panel noted that current data suggests that the risk of penicillin resistance is higher than macrolide resistance, therefore suggesting potential benefits of macrolide therapy.

In the circumstances where antitoxin is unavailable and unlikely to be accessible in a short period, there is a speculative benefit of dual antibiotic treatment. In such cases, where bacteriological susceptibility is unknown, clinicians might choose, pending susceptibility data, to treat concurrently with both macrolide and beta-lactam antibiotics.

Certainty of the Evidence

Low

The evidence summary for the prioritized outcomes were largely informed by one randomized clinical trial (n=86) which compared penicillin (benzylpenicillin followed by penicillin V) with erythromycin for the treatment of diphtheria.

Certainty of evidence was rated as: moderate for mortality (rated down for imprecision), very low for myocarditis (rated down for imprecision and risk of bias), very low for hospitalization and airway intervention (rated down for imprecision and indirectness), very low for new cases of diphtheria (rated down for imprecision and indirectness) and very low for treatment failure (rated down for risk of bias, imprecision, and indirectness). The certainty of evidence was rated as: moderate for serious side-effects (rated down for risk of bias), low for gastrointestinal side-effects (rated down for risk of bias, imprecision), high for burden of treatment, and very low for antibiotic resistance.

Values and preferences

No substantial variability expected

Patients place a high value on receiving fewer doses and oral drug treatment, rather than multiple doses and parenteral drug administration, and to a lesser extent on the speculative possibility of greater effectiveness with macrolide treatment. The panel felt that considerations of antimicrobial resistance were as or more important than individual patient considerations.

Resources

Important issues, or potential issues not investigated

The resources required to routinely use penicillin antibiotic treatment, with frequent intramuscular or intravenous dosing, are substantially greater than with a daily, oral treatment such as azithromycin.

The availability and reliability of microbiological susceptibility testing for isolates to guide therapy will not always be available in a timely fashion , particularly in outbreak settings. Therefore, clinicians should administer the antibiotic with the lowest probability of resistance.

Equity

Important issues, or potential issues not investigated

The GDG discussed at length the availability of both pencillin and macrolide antibiotics, and how there were no significant equity-related concerns as to accessibility of the two treatments in most settings. Treatment burden being higher with penicillins led considerations for preference of macrolides, which has equity implications for accessing health care resources.

The GDG discussed data on diphtheria resistance to beta-lactam and/or macrolide antibiotics, and the possibility of widespread use of macrolides in worsening antimicrobial resistance, and worsening health equity longer term. The agreed

values and preferences statement heavily weighed on the considerations of the GDG, where antibiotic resistance was seen as, or more important than, individual patient considerations. The GDG made a strong recommendation for the use of macrolides, given the feasibility of implementation and the likely limited impact of macrolide usage in diphtheria outbreaks on wider resistance patterns.

Acceptability

Important issues, or potential issues not investigated

The GDG remarked that intravenous dosing may be appropriate for patients who are severely ill and admitted to hospital, or who may be unable to tolerate orally administered medications. In addition, some panelists commented on the potential for concomitant use of penicillin and macrolide antibiotics for severely ill patients when susceptibility patterns are unknown, and particularly during the early phases of outbreaks when DAT may be unavailable.

There are known gastrointestinal side-effects of macrolides, which may impact acceptability of the recommendation, but these are not serious *(12)*.

The acceptability of implementation was a primary consideration in making recommending administration of macrolides, specifically oral azithromycin rather than intravenous or intramuscular penicillin.

The current WHO AWaRe antibiotic book does not list diphtheria as an indication for azithromycin, and this was noted *(13)*.

Feasibility

Important issues, or potential issues not investigated

The feasibility of implementing macrolide antibiotics, compared with penicillin antibiotics, is very high. For patients who are severely ill, feasibility considerations are less relevant, as intravenous routes of administration may be preferred and are available for either antibiotic. Treatment of severely ill patients largely focused on the potentially high burden of resistance to beta-lactam antibiotics.

In a diphtheria outbreak it is important that antibiotic stewardship and monitoring are implemented particularly in relation to any changes in antibiotic resistance, which can be determined by antibiotic sensitivity testing.

Justification

When moving from the evidence to a recommendation the GDG emphasized the relative treatment burden of penicillins and macrolides. The GDG discussed the known and variable epidemiology of antibiotic resistance in *Corynebacterium diphtheriae*, in addition to no compelling adverse clinical consequences of macrolide use.

Typically, WHO does not make strong recommendations with low certainty evidence. One exception is when low evidence suggests equivalence or benefit of a therapy (in this case macrolides equivalent or superior to penicillins) and there is high certainty evidence of less harm with that therapy. In this case, we have high certainty evidence of the higher burdens associated with penicillin parenteral therapy multiple times a day.

The GDG made a strong recommendation for the use of macrolides, given the feasibility of implementation and the likely limited impact of macrolide usage in diphtheria outbreaks on wider resistance patterns.

Clinical question/ PICO

Population: Persons with suspected or confirmed diphtheria
Intervention: Macrolide antibiotic
Comparator: Penicillin antibiotic

Summary

Full summary of the evidence synthesis is available here. *(14)*

Outcome Timeframe	**Study results and measurements**	**Comparator** Penicillin	**Intervention** Macrolide	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Mortality 10 days	Relative risk 1 Based on data from 86 participants in 1 studies. [1] (Randomized controlled)	10 per 1000 Difference:	10 per 1000 **0 fewer per 1000** CI 95%	Moderate Due to serious imprecision. [2]	The choice of antibiotic probably does not affect mortality.
Myocarditis	Based on data from 86 participants in 1 studies. [3] (Randomized controlled)	68 per 1000 Difference:	0 per 1000 **68 fewer per 1000** (CI 95% 166 fewer — 29 more)	Very low Due to serious imprecision, Due to serious risk of bias [4]	We are very uncertain if the choice of antibiotic affects the rate of myocarditis.
Treatment failure as inferred from non-clearance of colonisation at day 8 (higher value suggests more treatment failure) [5]	Relative risk Based on data from 238 participants in 1 studies.	160 per 1000 Difference:	80 per 1000 **80 fewer per 1000** (CI 95% 173 fewer — 8 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [6]	We are uncertain if choice of antibiotic affects the rate of treatment failure.
Serious side effects	Based on data from 86 participants in 1 studies. [7] (Randomized controlled)	0 per 100 Difference:	0 per 100 **0 fewer per 100** CI 95%	Moderate Due to serious risk of bias [8]	The choice of antibiotic probably does not affect the rate of serious side effects.
Gastrointestinal side effects	Relative risk Based on data from 86 participants in 1 studies. [9]	23 per 1000 Difference:	191 per 1000 **167 more per 1000** (CI 95% 18 more — 318 more)	Low	Erythromycin may increase the rate of gastrointestinal side effects.
Hospitalization + airway intervention as inferred from time to membrane clearance [10]	Measured by: Time to membrane clearance Lower better Based on data from 86 participants in 1 studies. (Randomized controlled)	3 days (Median)	3 days (Median) CI 95%	Very low Due to very serious indirectness, Due to serious imprecision [11]	We are very uncertain if the choice of antibiotic affects the rate of hospitalization or need for airway intervention.

Outcome Timeframe	**Study results and measurements**	**Comparator** Penicillin	**Intervention** Macrolide	**Certainty of the Evidence** (Quality of evidence)	**Summary**
New cases of diphtheria as inferred from time to bacteriological clearance by culture	Measured by: Time to bacteriological clearance by culture Lower better Based on data from 86 participants in 1 studies. (Randomized controlled)	2 days (Median)	2 days (Median) CI 95%	Very low Due to serious imprecision, Due to very serious indirectness [12]	We are very uncertain if the choice of antibiotic affects the rate of new cases of diphtheria.

1. Primary study[15]. **Baseline/comparator:** No studies available.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
3. Primary study[15]. **Baseline/comparator:** Primary study[15].
4. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting. **Imprecision: serious.** Only data from one study.
5. undefined
6. **Risk of Bias: serious.** Selective outcome reporting. **Indirectness: serious.** Direct comparisons not available. **Imprecision: serious.** Only data from one study.
7. Primary study[15]. **Baseline/comparator:** Control arm of reference used for intervention[15].
8. **Risk of Bias: serious.** Selective outcome reporting.
9. Primary study[15]. **Baseline/comparator:** Control arm of reference used for intervention[15].
10. undefined
11. **Indirectness: very serious.** Direct comparisons not available. **Imprecision: serious.** Only data from one study.
12. **Indirectness: very serious.** Direct comparisons not available. **Imprecision: serious.** Only data from one study.

6. Recommendations for diphtheria antitoxin (DAT)

Diphtheria antitoxin (DAT) is the standard of care for treatment of diphtheria cases. DAT has a significant impact on mortality,and has been used since the late 19th century. The relative mortality reduction based on systematic review is 76% (RR 0.24 [95% CI 0.22–0.28]), and it is more effective when administered earlier *(8)*.

There is a global shortage of DAT due to the limited number of manufacturers and their capacity.

6.1 Mechanism of action of diphtheria antitoxin (DAT)

DAT targets the diphtheria toxin released from the pathogen. Diphtheria toxin binds to cells through the heparin-binding epidermal growth factor-like growth factor precursor (pro-HB-EGF). After binding, the toxin is internalized by endocytosis during which it is processed into constituent subunits. The active subunit A is released from the endosome and inhibits ADP-ribosylating elongation factor 2 (EF-2), which terminates protein synthesis thereby eliciting cell death.*(16)* DAT is most effective in neutralizing extracellular toxin, and once toxin is internalized DAT is ineffective in preventing its intracellular consequences.

Antibody concentrations, and anti-toxin neutralizing activity by cytotoxicity assays, have been assayed in serum from four patients receiving diphtheria antitoxin for suspected diphtheria (but who did not have diphtheria).*(17)* The minimum effective dose of DAT has not been formally determined in humans, and doses employed in the management of diphtheria assume that duration of disease and/or severity roughly indicate the amount of circulating toxin.

6.2 Diphtheria antitoxin sensitivity testing: rationale

DAT is derived from the serum of horses exposed to diphtheria toxoid. Due to the potential for immediate allergic reactions to infusions of DAT, some manufacturers have recommended sensitivity testing, an incremental exposure of the patient to small doses of DAT during a period of observation. If no adverse events are noted, the full dose is given. If there is evidence of a reaction to DAT, desensitization using progressive administration of escalating doses can be performed in an effort to enable allergic patients to receive treatment.

In many outbreaks, sensitivity testing has not been performed. Reasons have included: perceived poor predictive value of the procedure for adverse reactions to the full DAT dose; the significant potential delay in life saving treatment where resources and severely limited; the relative safety to medically manage DAT reactions, where the risk of not giving antitoxin is significant.*(18)* The need for DAT sensitivity testing was reviewed in this guideline and a recommendation provided.

6.3 Recommendation on DAT sensitivity testing

Strong recommendation against

In patients with suspected or confirmed diphtheria, WHO recommends not to perform routine sensitivity testing prior to administration of diphtheria antitoxin [Strong recommendation, moderate certainty evidence].

Remarks:

- Due to the risk of allergic reaction, ensure sufficient trained staff and equipment are available and the patient is cared for in an area where they can be monitored closely.

Practical info

WHO recommends not to perform routine sensitivity testing prior to administration of diphtheria antitoxin.

In the 2017-18 diphtheria outbreak in Bangladesh in a crowded camp of Rohingya migrants, patients were administered antihistamines and weight-based corticosteroids 30 minutes prior to DAT infusion.*(18)* Oral chlorphenamine and intravenous hydrocortisone were used. We found no diphtheria-specific literature comparing prophylactic strategies. Implementers of this guideline might consider indirect evidence from snakebites given equine-derived antitoxin. The largest RCT for snakebite (n = 1,007) found rates of adverse events to the antitoxin in those treated with either steroid, or antihistamine, or both, were similar to placebo.*(20)*

In case serious allergic reaction occurs, ensure sufficient trained staff and equipment are available and the patient is being cared for in area where they can be monitored closely. This includes:

- Monitoring equipment: pulse oximeter, blood pressure monitoring, thermometer.
- Emergency medicines: adrenaline (1:1000), salbutamol, intravenous antihistamine (e.g. chlorphenamine), corticosteroid (e.g. prednisolone, hydrocortisone), intravenous fluid (Ringer's lactate or 0.9% w/v saline), oxygen supply and delivery devices.
- Emergency equipment: age appropriate equipment for airway management and suction, oxygenation (bag valve mask and oxygen), and cardiovascular support (intravenous cannulae and giving sets).

Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

In patients with suspected or confirmed diphtheria who will receive diphtheria antitoxin therapy (DAT), giving DAT without routine sensitivity testing probably reduces mortality compared with performing allergy testing and desensitization. This benefit results because routine sensitivity testing will lead to an appreciable number of patients who will not receive DAT due to a test result suggestive of allergy, and because desensitization is either not available or not usually successful. When routine sensitivity testing is not employed, patients will receive DAT and therefore the benefit of reduced mortality. This is true even for the vast majority of those who experience allergy in whom reactions are clinically manageable, allowing complete DAT administration.

Certainty of the Evidence

Moderate

The evidence on routine sensitivity testing before DAT is from single-arm interventions reporting rates of adverse events related to antitoxin use. The decision analysis undertaken by the methods incorporated evidence from 14 single-arm studies, and provided moderate certainty evidence that routine sensitivity testing increases mortality.

Values and preferences

No substantial variability expected

Patients place a high value on avoiding death, and a lower value on avoiding severe adverse events resulting from treatment.

Resources

No important issues with the recommended alternative

Not performing routine sensitivity testing on all patients recommended to receive DAT is resource-saving, both in terms of the time and the materials required for sensitivity testing and desensitization.

Equity

No important issues with the recommended alternative

The GDG provided insight that not routinely performing sensitivity testing for all patients recommended to receive DAT may increase accessibility and timeliness to receive DAT.

Acceptability

Important issues, or potential issues not investigated

The GDG commented on the available data on time-to-DAT for improved outcomes for severely ill patients, and the impact that routine sensitivity testing may have on delays to administering DAT.

The GDG also commented on the available protocols in place to routinely administer antihistamines and/or corticosteroids prior to DAT administration. The GDG does not provide specific recommendations for these, but strategies used in one outbreak are summarized in "Practical info".

Feasibility

Important issues, or potential issues not investigated

The GDG commented on the complexity of performing routine sensitivity testing, particularly in outbreak settings with large numbers of patients and varied providers.

Justification

When moving from the evidence to a strong recommendation against performing routine sensitivity testing in patients recommended to receive DAT, the GDG emphasized the moderate certainty evidence in the mortality benefit. Although there remains concerns about the possibility of a systemic allergic response during the administration of DAT, the GDG recommended to not routinely perform sensitivity testing, given the high value placed on avoiding death.

Clinical question/ PICO

Population: Persons with suspected or confirmed diphtheria for whom diphtheria antitoxin is indicated

Intervention: Sensitivity testing performed prior to administration of diphtheria antitoxin

Comparator: Sensitivity testing not performed prior to administration of diphtheria antitoxin

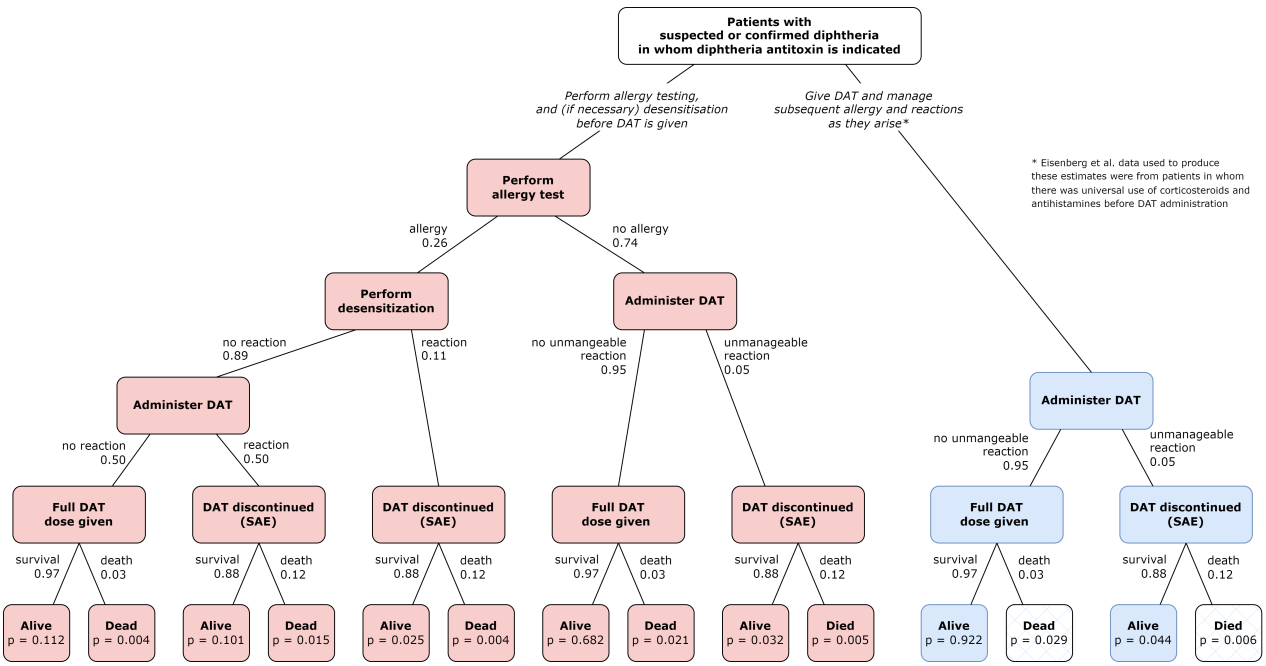
Summary

Full summary of the evidence synthesis is available here. *(14)*

A decision tree was created from assumptions based on Eisenberg *et al*.*(18)*

Mortality was modeled at 12.5% without diphtheria antitoxin (DAT), and 3% with DAT, by applying the relative risk ratio of 0.24.*(8)* Key assumptions were that: 1) incomplete administration of diphtheria antitoxin had no clinical benefit; 2) complete administration of DAT is attained in 95% of cases where given with concurrent antihistamine and corticosteroid administration; 3) Serious adverse events (SAE) associated with DAT occur at 3% (anaphylaxis); 4) Serious adverse events associated with DAT administration have trivial (zero) mortality.*(18)*

Figure: Outcome probabilities based on alternative strategies



Red boxes (left side of diagram) represent the probability tree where allergy testing and (where necessary) desensitisation is performed before DAT is administered.

Blue boxes (right side of diagram) represent the probability tree where DAT is given, and allergies are treated as they arise (with no allergy testing, and no desensitisation).

Outcome Timeframe	**Study results and measurements**	**Comparator** No sensitivity testing	**Intervention** Sensitivity testing	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Mortality	Relative risk 0.74 (Observational (non-randomized))	47 per 1000 Difference:	35 per 1000 **12 fewer per 1000** CI 95%	Moderate	Giving DAT without allergy testing probably reduces mortality compared with performing allergy testing and desensitization.

6.4 Recommendation on DAT dose

Conditional recommendation for

In patients with suspected or confirmed symptomatic diphtheria, WHO suggests administration of a single dose of diphtheria antitoxin with choice of dose based on disease severity and time since symptom onset, in comparison with a fixed dose for all patients [Conditional recommendation, very low certainty evidence].

Characteristic of diphtheria disease	Dose of diphtheria antitoxin (IU)
• Laryngitis **or** pharyngitis **and** • Duration < 48 hours	20 000
• Nasopharyngeal disease (extensive pseudomembrane) **and** • Duration < 48 hours	40 000
One or more of: • Diffuse swelling of the neck • Any disease ≥ 48 hours • Severe disease (respiratory distress, shock)	80 000

Remarks:

- DAT must be administered as soon as possible as early administration of DAT is associated with improved clinical outcomes. *(8)* Early treatment may reduce overall DAT usage by avoiding the higher doses required once disease has progressed.

Practical info

Pre-medication

Steroids and antihistamines have been used in some outbreak settings, the largest of which reported very low rates of adverse events (3% with no deaths). However, indirect evidence from antitoxin administration in other diseases treated (snake bite), did

not find significant difference in reduction of adverse events when antihistamines were given.*(20)* Pre-medication should not delay administration of DAT, and where they are considered standard, doses for antihistamines can be used.

DAT should be administered in a monitored setting.

In rare cases, a serious allergic reaction may occur. Clinical settings should have trained staff, equipment, emergency medicines, equipment and protocols available to manage anaphylaxis or other serious adverse events. This includes:

- Monitoring equipment: pulse oximeter, blood pressure monitoring, thermometer.
- Emergency medicines: adrenaline (1:1000), salbutamol, intravenous antihistamine (e.g. chlorphenamine), corticosteroid (e.g. prednisolone, hydrocortisone), intravenous fluid (Ringer's lactate or 0.9% w/v saline), oxygen supply and delivery devices.
- Emergency equipment: age-appropriate equipment for airway management and suction, oxygenation (bag valve mask and oxygen), and cardiovascular support (intravenous cannulae and giving sets).

See posters for more details:

- **WHO/Diph/DAT/Poster_A/2024.1:**

https://iris.who.int/bitstream/handle/10665/375883/WHO-Diph-DAT-Poster_A-2024.1-eng.pdf

- **WHO/Diph/DAT/Poster_B/2024.1:**

https://iris.who.int/bitstream/handle/10665/375884/WHO-Diph-DAT-Poster_B-2024.1-eng.pdf

- **WHO/Diph/DAT/Poster_C/2024.1:**

https://iris.who.int/bitstream/handle/10665/375885/WHO-Diph-DAT-Poster_C-2024.1-eng.pdf

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

There is very low certainty on the impact of different diphtheria antitoxin dosing regimens on mortality. However, the current standard of care – escalating dosing regimens – is well established in clinical practice globally. The main adverse consequence of excess dosing of DAT is consumption of a scarce resource. Dose-related adverse clinical events are not well-described. The benefit of escalating DAT dosing reflects theoretical assumptions of higher circulating amounts of diphtheria toxin in severe or late disease. The GDG felt that recommending a change in practice would require compelling evidence of the benefits of such a change; that evidence does not exist.

Certainty of the Evidence

Very low

The evidence summary for DAT dosing is from a series of observational case series and one quasi-randomized clinical trial. Overall, the certainty of the evidence for the outcome of mortality is deemed as very low, down-rated for risk of bias, imprecision, and inconsistency.

Values and preferences

Substantial variability is expected or uncertain

Where the optimal dose of diphtheria antitoxin is uncertain, patients place a high value on receiving a dose that is sufficient, but might reduce the total number of patients who could be treated. The GDG acknowledges the substantial variability in these values and preferences that are likely to exist.

Resources

Important issues, or potential issues not investigated

DAT availability is a worldwide concern, and every effort must be made to ensure that manufacturing and distribution capacity for DAT matches global needs. The GDG discussed the increased resources required to provide varied dosing regimens, with higher doses provided to patients with more severe disease, or those who present later in their illness. However, given the importance patients will place in the possible benefits of improving the outcomes of very unwell patients, as articulated in the values and preferences statement, the GDG recommends a varied dosing regimen.

The GDG also discussed the importance of providing early dosing to patients so as to avoid deterioration and requiring higher doses later, incorporating evidence on positive association of time-to-DAT with clinical outcomes.

The administration of a second dose in patients with progressive disease was not discussed.

Equity

Important issues, or potential issues not investigated

Equity in this situation demands a dose regimen that the majority of patients would choose given the extreme uncertainty. The panel, in keeping with the values and preference statement, believes the choice would be to maximize the likelihood that those most at risk of adverse outcomes receive a sufficient dose.

The WHO strongly advocates for increasing the supply of DAT so that all patients who require this therapy have access to it. This will require an increase in production of DAT which could be facilitated by increasing the numbers of suppliers with WHO pre-qualification.

Acceptability

No important issues with the recommended alternative

The current standard of care – varied dosing regimens – is acceptable across care settings. The increased dose comes with increased volume of administration, which may require some added clinical monitoring, particularly in small children.

Feasibility

No important issues with the recommended alternative

Varied dosing regimens are the current standard of care, and their administration is feasible across care settings. A conditional recommendation allows for flexibility for practitioners who might therefore incorporate alternative dose regimens based on their clinical judgement.

Justification

When moving from the evidence to a conditional recommendation for varied dosing of DAT compared with fixed dosing regimens in patients with suspected or confirmed symptomatic diphtheria, the GDG emphasized the very low certainty evidence of a mortality benefit, compared with fixed dosing regimens. Although there remain concerns about the possibility of excess dosing of DAT in periods of scarcity, a varied dose regimen is the current standard of care and reflects the values and preferences statement.

Clinical question/ PICO

Population: Persons with suspected or confirmed diphtheria for whom diphtheria antitoxin is indicated
Intervention: Escalating doses of diphtheria antitoxin
Comparator: Fixed dose diphtheria antitoxin

Outcome Timeframe	**Study results and measurements**	**Comparator** Low dose	**Intervention** Higher dose	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Mortality (quasi-randomized trial)	Relative risk 0.92 (CI 95% 0.38 — 2.24) Based on data from 50 participants in 1 studies. [1] (Observational (non-randomized))	27 per 100 Difference:	29 per 100 **2 fewer per 100** (CI 95% 27 fewer — 23 more)	Very low Due to very serious risk of bias and serious imprecision [2]	We are very uncertain which diphtheria antitoxin dosing regimen most effectively reduces mortality
Mortality (observational)	Based on data from 1,631 participants in 5 studies. [3] (Observational (non-randomized))	No comparative data available Low mortality (1%) in studies which have given modest DAT doses (Eisenberg)		Very low Due to serious risk of bias and serious inconsistency [4]	We are very uncertain which diphtheria antitoxin dosing regimen most effectively reduces mortality

1. Primary study. 22/26 [85%] had severe disease in low dose arm; 20/24 [83%] had severe disease in the higher dose arm. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [19],
2. **Risk of Bias: very serious. Imprecision: serious.**
3. Systematic review **Supporting references:** [21], [22], [23], [18], [24], [10],
4. **Risk of Bias: serious. Inconsistency: serious.**

7. Methods: how this guideline was created

These emergency guidelines have been developed in accordance with the *WHO Handbook for guideline development*).*(4)*

General approach

The production of the guideline has included the following steps:

1. Identification of guideline scope and priority questions
2. Evidence identification and synthesis
3. Consideration of the evidence by the GDG
4. Formulation of recommendations
5. Review of draft guidelines (internal and external)
6. Approval by the WHO Guideline Review Committee

Step 1: Identification of guideline scope and priority questions

Important questions were identified through clinical networks responding to current and recent outbreaks of diphtheria (notably Nigeria 2023 and Bangladesh 2018). Existing guidance from WHO was reviewed by the technical team. *(6)* The WHO Steering Committee and the Guideline Review Committee reviewed and revised this list, and determined the priority and scope of the initial guideline.

Step 2: Evidence identification and synthesis

Questions were codified using a PICO framework (identifying the population, intervention, comparator and outcomes of interest), and refined by the methodologist, technical team and clinical chair. Outcomes of interest were focused on those most believed to be most important to patients, agreed by the GDG.

Systematic review was undertaken according to a pre-defined protocol and search strategy as per the attached appendix.

Evidence certainty was assessed using GRADE methodology *(4)*.

Step 3: Consideration of the evidence by the GDG

GDG members were selected for global geographical representation, gender balance, and appropriate technical and clinical expertise. The technical unit collected and managed written statements of declarations of interests (DOI). There were no relevant conflicts of interest. Additionally, during the first meeting, the WHO Secretariat described the DOI process and GDG members were asked to verbally update any other DOI; no verbal conflicts were declared. Web searches did not identify any additional interests that would likely affect members' independence.

The GDG members are listed online here, and were convened in online meetings on 28 November 2023 and 11 December 2023.

Step 4: Formulation of recommendations

Deliberations on the direction and strength of recommendations were facilitated by the methodologist and clinical chair. *A priori* voting rules informed procedures if the GDG failed to reach consensus by discussion; The chair was not eligible to vote in this setting. For the current recommendations, voting was not necessary.

The following factors informed the formulation of recommendations:

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE summary of findings tables including effect estimates and confidence intervals or narrative summaries);
- quality/certainty of the evidence;
- values and preferences of patients;
- resources and other considerations (including considerations of feasibility, applicability, equity).

When possible, we used research evidence to inform discussion around these key factors. If not available, discussion of these factors was informed by expert opinion of both external and GDG members.

Benefits and harms
The guideline used recently prioritized patient-important outcomes from other WHO guidelines which related to those with severe and critical illness.*(?)*

Values and preferences

There was insufficient information to provide the GDG with an evidence-based description of patient experiences or values and preferences regarding treatment decisions for diphtheria treatment. The GDG therefore relied on their own judgments of what well-informed patients would value after balancing the benefits, harms, and burdens of treatment. In addition to individual patient perspectives, the GDG considered a population perspective in which feasibility, acceptability, equity and cost were important considerations.

Specific deliberations on values and preferences and associated feasibility and resource-related considerations are presented for each recommendation.

Step 5: Review of draft guidelines (internal and external)

An external review group reviewed the final guideline document to identify, correct and clarify errors, contextual issues, and implications for implementation.

The guideline was then reviewed and approved by the WHO Guideline Review Committee.

8. How to access and use the guideline

This guideline from WHO will be updated periodically.

How to access the guideline:

- WHO website in PDF format. This is a full read out of the MAGICapp content for those without reliable web access. It can also be downloaded directly from MAGICapp (see cogwheel on top right).
- MAGICapp online in multilayered formats: (https://app.magicapp.org/#/guideline/7759). This is the fullest version of the guideline, as detailed below.

How to navigate this guideline

The guideline is written, disseminated, and updated in MAGICapp, with a format and structure that ensures user-friendliness and ease of navigation. It accommodates dynamic updating of evidence and recommendations that can focus on what is new while keeping existing recommendations, as appropriate, within the guideline.

The online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting information pertinent to applying the recommendations in practice. End-users will also need to understand what is meant by strong and conditional recommendations (displayed immediately below) and certainty of evidence (the extent to which the estimates of effect from research represent true effects from treatment).

For each recommendation additional information is available through the following tabs:

- ***Research evidence:*** Readers can find details about the research evidence underpinning the recommendations as GRADE summary of findings tables and narrative evidence summaries
- **Evidence to decision*:*** The absolute benefits and harms are summarized, along with other factors such as the values and preferences of patients, practical issues around delivering the treatment as well as considerations concerning resources, applicability, feasibility, equity and human rights. These latter factors are particularly important for those adapting the guidelines for the national or local context.
- ***Justification:*** Explanation of how the GDG considered and integrated evidence to decision factors when creating the recommendations, focusing on controversial and challenging issues.
- ***Practical information:*** For example, dosing, duration and administration of drugs, or how to apply tests to identify patients in practice.
- ***Decision aids:*** Tools for shared decision-making in clinical encounters.

Additional clinical training, tools, and resources are also available:

- WHO OpenWHO.org training course on Clinical care of diphtheria (https://openwho.org/)
- WHO Facility Estimator tool to support estimation of required medicines and equipment for treatment areas (https://partnersplatform.who.int/essentialitemsestimator).

This guideline from WHO is also used to inform the activities of the WHO Prequalification of Medicinal Products.

9. Uncertainties, emerging evidence and future research

There is a need for high-quality clinical trials in all aspects of the clinical management of diphtheria.

- Determination of the minimal clinically effective dose of DAT according to disease severity.
- Scaling up capacity for routine antimicrobial susceptibility testing and surveillance for resistance across regions, particularly during outbreaks.
- Investigation of third-line antibiotic therapies or combination therapies for increasing resistance across diphtheria isolates.
- The initiation of randomized controlled trials to investigate novel therapies for diphtheria that may reduce the reliance on DAT.
- Efficacy of premedication with DAT administration.

In addition standardized clinical data collection to better describe disease characterization, evolution and impacts of treatments including adverse event.

10. Authorship, contributions and acknowledgements

WHO would like to thank the collaborative efforts of all those involved to make this process rapid, efficient, trustworthy and transparent.

WHO Steering Committee

The committee includes representatives from WHO departments at regional offices and headquarters, including specialty technical input.

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The WHO Steering Committee is fully responsible for decisions on guidance production and convening the GDG.

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