THE NATIONAL DRUG ALLERGY REPORTING GUIDELINES

2018

ACKNOWLEDGEMENTS

The *National Drug Allergy Reporting Guidelines 2018* has been developed by the Drug Allergy Documentation Workgroup (see Table 1 for composition) under the National Medication Safety Committee (NMSC) 2017-2020 term (see Table 2 for composition).

Table 1. Composition of 'Drug Allergy Documentation' Workgroup and advisors, July 2017 – June 2020

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Table 2. Composition of the National Medication Safety Committee (NMSC), July 2017 – June 2020

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INTRODUCTION

Allergic and adverse reactions to drugs are a major cause of iatrogenic injury, and can result in significant burdens on the community in terms of morbidity, mortality, and cost to the healthcare system.

Medication errors resulting from drug allergies or medically-significant adverse drug reactions are largely preventable. Prevention depends predominantly on the accuracy and reliability of documentation in patients' medical records and computerised physician order entry systems, coupled with decision support such as allergy alerts. Conversely, over-diagnosis (e.g. due to overuse of the term "allergy") and misclassification may affect treatment options and lead to the use of more expensive or less effective drugs.

The National Medication Safety Committee has therefore established a standardised and systematic approach to the diagnosis and labelling of drug allergies and medically-significant adverse drug reactions to enhance medication safety, improve patient outcomes, and allow for proper preventive measures to be instituted.

CONTENT

1. DEFINITIONS

An adverse drug reaction (ADR) is defined by the World Health Organisation as a response to a drug which is noxious and unintended, and which occurs at doses normally used for prophylaxis, diagnosis, or therapy of diseases or for the modification of physiologic function. ADRs are classified into Type A to E ADRs.

Drug hypersensitivity reactions (DHR) are the adverse effects of pharmaceutical formulations (including drugs and excipients) that clinically resemble allergic reactions, and belong to Type-B adverse drug reactions. DHRs can be defined as allergic and non-allergic.

A drug allergy is a DHR for which a definite immunological mechanism is demonstrated. Clinically, drug allergies can be classified as immediate or delayed/ non-immediate.

Refer to **Appendices 1 and 2** for examples and classification of ADRs and DHRs.

2. REPORTING OF DRUG HYPERSENSITIVITY REACTIONS AND DRUG ALLERGIES

All drug hypersensitivity reactions and drug allergies must be assessed and reported as soon as possible whenever a de novo reaction is encountered or a history of drug reaction has been reported by the patient.

When evaluating the patient, a history should be taken and a clinical examination should be performed (if applicable), and the following is to be observed:

a. The suspected drug must be reported.
    I. If more than one drug is implicated or suspected, these drugs must be reported as well.
    II. If the name of the specific drug is unknown, it is reasonable to report the drug class instead (e.g. NSAID, radiocontrast media, cephalosporin);

this report can be updated subsequently by another healthcare provider if details of the specific drug are known.

III. Allergic reactions to non-therapeutic components (e.g. preservatives, pharmaceutical stabilisers, additives) in topical medications (e.g. skin and ophthalmic products) should also be reported if these are suspected. Examples include paraben, chlorocresol, and benzalkonium chloride.

b. The clinical details of the reaction should be described as much as possible in the report (see below). It is recognised that it may not be possible to establish the full details of drug allergic reactions, especially if the history relies solely on patients' recollection and description of events.

c. The healthcare provider must establish and report the causality of the drug (see below). Reactions which are Definite, Probable, Possible or Unconfirmed must be reported. Reactions which have been assessed to be Unlikely need not be reported. These details must be entered into the patient's records and reported as per institutions' policies.

Drug allergy reporting can be performed by a doctor, dentist, pharmacist or nurse, within the scope of their clinical practice and competencies. Complex cases or cases requiring detailed clinical examination and/ or laboratory tests should be referred to a doctor with the appropriate resources for further evaluation – in the interim, the healthcare professional should report the drug allergy first but can classify this as Possible or Unconfirmed until further assessment is made.

3. ASSESSMENT OF A DRUG ALLERGY

History

This information aids the reporter and all healthcare providers, in establishing the nature and severity of the allergic reaction, as well as causality of the implicated drug.

a. The generic and proprietary name of the drug, the strength/ dose, formulation, and route of administration.

b. The indication for the drug prescribed.

c. The type of reaction and a description of relevant signs, symptoms and laboratory investigations.

    I. When a cutaneous manifestation has occurred or been reported, effort should be made in describing the morphology (e.g. urticaria, maculopapular eruption, bullous drug eruption).

    II. The presence of any systemic involvement (e.g. fever, hepatitis, interstitial nephritis) or severe manifestations (e.g. Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug-induced vasculitis) should be mentioned.

    III. Examples of signs and symptoms of common immediate and delayed drug hypersensitivity reactions are listed in **Appendix 3**.

d. The onset of the reaction, in relation to the duration and timing of administration or consumption of the drug. This may be recorded in terms of days/ weeks/ months (e.g. maculopapular eruption occurring 14 days after Allopurinol initiation) or number of doses (e.g. acute urticaria and peri-orbital angioedema after two doses of intravenous Augmentin 1.2g).

e. Any prior exposure to the drug, or another drug in same pharmacological class or with known cross-sensitivities, and whether there was any adverse reaction to these drugs.

f. Whether the reaction worsened if the drug was continued.

g. Whether the reaction improved when the drug was stopped.

Causality

Causality is established based on the temporal history and clinical/ pharmacological details of the case, as well as exclusion of any differential diagnoses. Causality can

be established as *Definite*, *Probable*, *Possible*, *Unlikely* and *Unconfirmed*. The recommended algorithms for causality assessment are the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) causality assessment system and the Naranjo algorithm. These are outlined in **Appendix 4**.

4. REMOVING OF DRUG ALLERGY STATUS

A patient's drug allergy status can be removed by doctors, pharmacists, and dentists. Drug allergy status should only be removed under the following circumstances:

a. When diagnostic tests have confirmed the absence of a drug allergy.

b. Patient's self-reported absence of a drug allergy (e.g. the patient has consumed a drug that he/ she had been previously labelled as allergic to, with no adverse reaction). A thorough history and review of available medical records should be performed to verify the patient's history.

c. The symptoms of the reaction are consistent with an adverse drug reaction rather than a true drug allergy.

The drug allergy label should be removed from the patient's records in the national drug allergy reporting platform, the patient informed, and documentation be made in the patient's notes.

If a reaction had previously been misclassified as a "drug allergy" but has now been identified as an adverse drug reaction, the healthcare provider should remove the drug allergy label from the patient's records in the national drug allergy reporting platform, and a new report of an adverse drug reaction be made instead if indicated.

If further evaluation is required, the healthcare provider should consult a specialist (see Section 5).

5. FOLLOW-UP ACTIONS

The patient should be informed of the drug allergy, counselled to stop the drug suspected of causing the drug allergy and to avoid this drug in future. The patient should be given a documentation of the suspected drug and be instructed to inform all healthcare providers of the drug allergy in future.

The symptoms of the acute reaction should be treated, if needed. Severe reactions should be referred to a specialist or hospital for inpatient treatment.

Consideration should be made to refer the patient to a specialist[1] in the following circumstances:

a. Where diagnosis is Possible or Unconfirmed drug allergy, and a specialist would be able to conduct further tests to define the culprit drug and advise on alternative medication (where needed).

b. Where multiple drugs were taken at the onset of the reaction, so as to elucidate the culprit drug.

c. A patient reports a history of multiple indeterminate or unconfirmed drug allergies, which may potentially limit therapeutic options in future (e.g. unconfirmed allergies to multiple antibiotics).

[1] A pediatric or adult allergist or dermatologist who is able to assess drug allergies and, where clinically indicated, conduct skin prick testing, drug patch testing, or drug provocation testing.

6. REPORTING OF ADVERSE DRUG REACTIONS

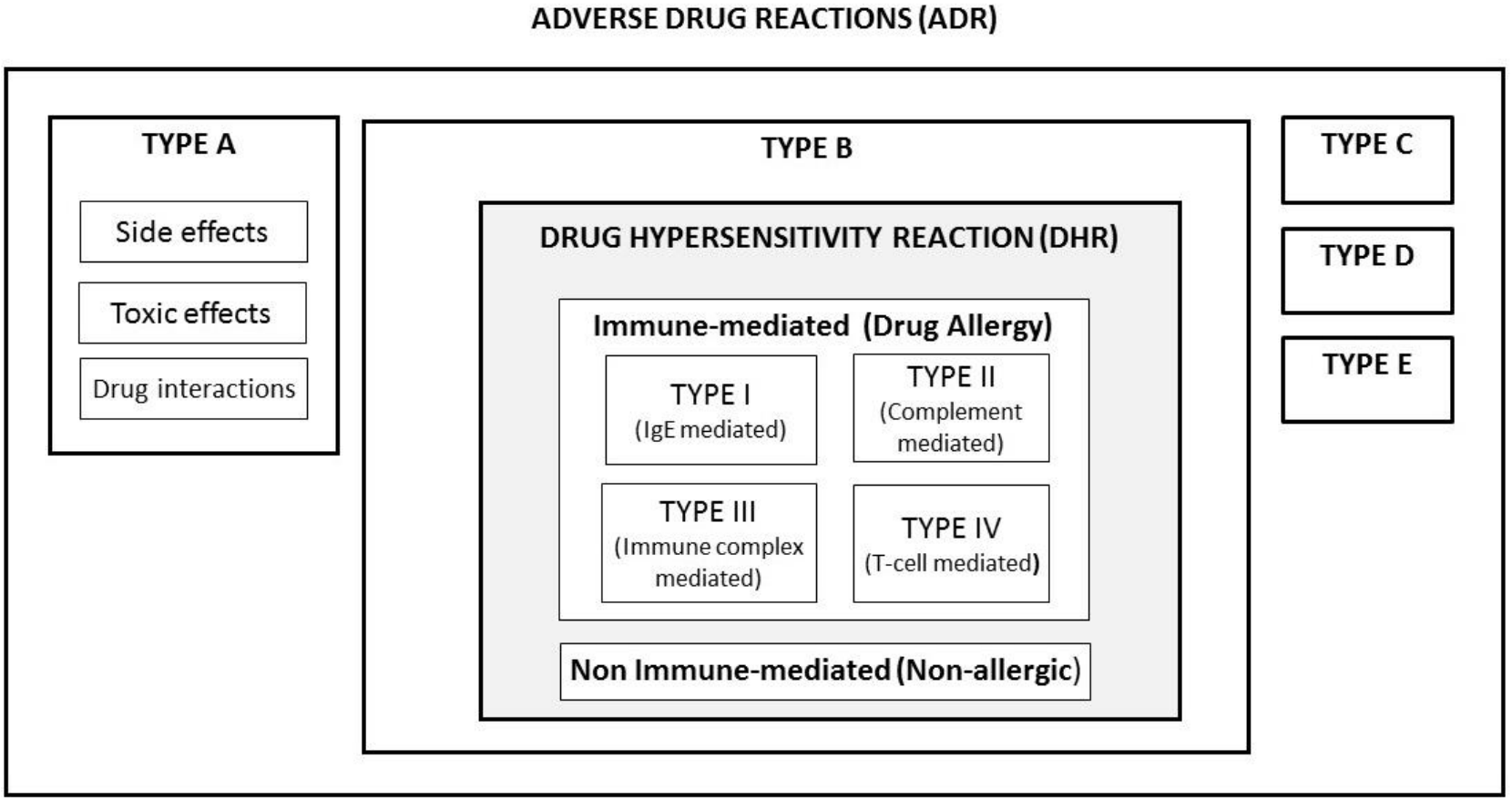
In contrast to a drug allergy, an ADR does not necessarily preclude the use of the same drug in future. These include ADRs where the reaction is dose-dependent (such as colchicine-induced diarrhoea, where the drug can be used again albeit in lower doses), or where the reaction is mild and overall benefits outweigh risks (such as cough induced by angiotensin-converting enzyme inhibitors which is tolerated by certain patients).

Hence, only ADRs which are assessed to be medically-significant should be reported. Medically-significant ADRs include ADRs which are life threatening, require additional patient monitoring or treatment, require in-patient hospitalisation, or result in significant incapacity or morbidity.

ADRs where the reaction is mild, or where the healthcare provider deems that the drug can be continued after discussing risks and benefits with the patient, need not be reported.

Adverse drug reaction reporting can be performed by a doctor, dentist, pharmacist, or nurse, within the scope of their clinical practice and competencies. Complex cases or cases requiring detailed clinical examination should be referred to a doctor with the appropriate resources for further evaluation – in the interim, the healthcare professional should report the ADR first but classify this as Possible or Unconfirmed until further assessment is made.

APPENDIX 1: OVERVIEW OF ADVERSE DRUG REACTIONS



APPENDIX 2: CLASSIFICATION OF ADVERSE DRUG REACTIONS AND DRUG HYPERSENSITIVITY REACTIONS

Reaction		Details	Examples
Adverse Drug Reaction	Type A (Augmented)	Related to the pharmacological action of the drug and are dose-dependent and predictable.	• Colchicine-induced diarrhoea. • Serotonin syndrome due to selective serotonin reuptake inhibitors (SSRIs). • Dry mouth due to anti-cholinergic agents.
	Type B (Bizarre)	Unrelated to the pharmacological action of the drug and are dose-independent and unpredictable.	• Pedal oedema due to calcium channel blockers. • Drug hypersensitivity reactions are included under Type B ADRs (see below).
	Type C (Chronic)	Related to the cumulative dose of the drug and are dose-dependent and time-dependent.	• Hypothalamic-pituitary-adrenal axis suppression due to long-term systemic corticosteroids. • Liver fibrosis due to long-term methotrexate therapy.
	Type D (Delayed)	Occur or become apparent after a certain period of drug use, and may or may not be dose-dependent.	• Carcinogenicity with long-term use of immunosuppressant.
	Type E (Withdrawal)	Occur or become apparent shortly	• Withdrawal syndrome with prolonged use of

Reaction		Details	Examples
		after withdrawal of the drug.	benzodiazepines and opioids.
Drug Hyper-sensitivity Reaction	Non-allergic drug-hypersensitivity reaction		• Angioedema induced by non-steroidal anti-inflammatory drugs or angiotensin-converting enzyme inhibitors.
	Allergic drug hypersensitivity reaction		• Drug-induced anaphylaxis (Type I/ Immediate) • Maculopapular drug eruption (Type IV/ Delayed).

APPENDIX 3: IMMEDIATE VERSUS DELAYED DRUG HYPERSENSITIVITY REACTIONS

Type of hypersensitivity reactions	Onset	Clinical features	Examples
Immediate drug hypersensitivity reactions	Onset usually occurs within one hour after drug exposure. Symptoms resolve rapidly with treatment. Previous exposure not always confirmed.	• Generalised pruritus • Ocular pruritus and tearing • Sneezing and rhinorrhea • Urticaria, angioedema • Shortness of breath, dyspnoea, wheezing, rhonchi • Abdominal pain (which is usually accompanied by the other cutaneous manifestations listed above) • Anaphylaxis	Beta-lactam antibiotics, non-steroidal anti-inflammatory drugs, biological agents, iodinated contrast media, neuromuscular blocking agents
Delayed drug hypersensitivity reactions	Onset usually 7-14 days after first drug exposure, but certain reactions (e.g. drug-induced hypersensitivity syndrome, Stevens-Johnson Syndrome, or Toxic Epidermal Necrolysis) may occur even up to 6 weeks after	• Maculopapular eruption • Fixed drug eruptions • Drug reaction with eosinophilia and systemic symptoms (DRESS)/ drug induced hypersensitivity syndrome (DIHS). This is characterised by macules/ papules with systemic features, including: ➢ Fever ➢ Lymphadenopathy ➢ Eosinophilia ➢ Hepatitis ➢ Interstitial nephritis ➢ Rarely, arthritis, cardiac or pulmonary involvement • Stevens-Johnson Syndrome (SJS); Toxic epidermal necrolysis (TEN) or SJS-TEN	Beta-lactam antibiotics; sulphur drugs; anti-epileptics; allopurinol; non-steroidal anti-inflammatory drugs, iodinated contrast media

Type of hypersensitivity reactions	Onset	Clinical features	Examples
	first drug exposure. Onset usually within 3 days of second exposure.	overlap, characterised by: ➢ Target lesions or erythema multiforme ➢ Mucosal or cutaneous erosions ➢ Vesicles, blistering, or epidermal detachment • In SJS, epidermal detachment is between 1-10% body surface area (BSA); SJS-TEN overlap 10-30% and TEN >30% BSA • Acute generalised exanthematous pustulosis (AGEP) • Drug-induced vasculitis • Bullous drug eruptions	

APPENDIX 4: CAUSALITY CATEGORIES

WHO-UMC Causality Assessment System

Causality term	Criteria
Definite	• An event or laboratory test abnormality, with plausible time relationship to drug intake. • Signs and symptoms cannot be explained by disease or other drugs. • Response to withdrawal plausible (pharmacologically, pathologically). • Rechallenge, with expected outcome, if necessary.
Probable	• An event or laboratory test abnormality, with reasonable time relationship to drug intake. • Signs and symptoms unlikely to be attributed to disease or other drugs. • Response to withdrawal clinically reasonable.
Possible	• An event or laboratory test abnormality, with reasonable time relationship to drug intake. • Could also be explained by disease or other drugs. • Information on drug withdrawal may be lacking or unclear.
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). • Disease or other drugs provide plausible explanations.
Unconfirmed	• Report suggesting an adverse reaction, but cannot be judged because information is insufficient or contradictory, or data cannot be supplemented or verified.

Adapted from the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) causality assessment system

Naranjo Algorithm

Question			
	Yes	No	Unknown
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administered?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0

The adverse drug reaction is assigned to a probability category from the total score as follows:

Category	**Priority Scoring**
Definite	>8
Probable	5 to 8
Possible	1 to 4
Unlikely	<1

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