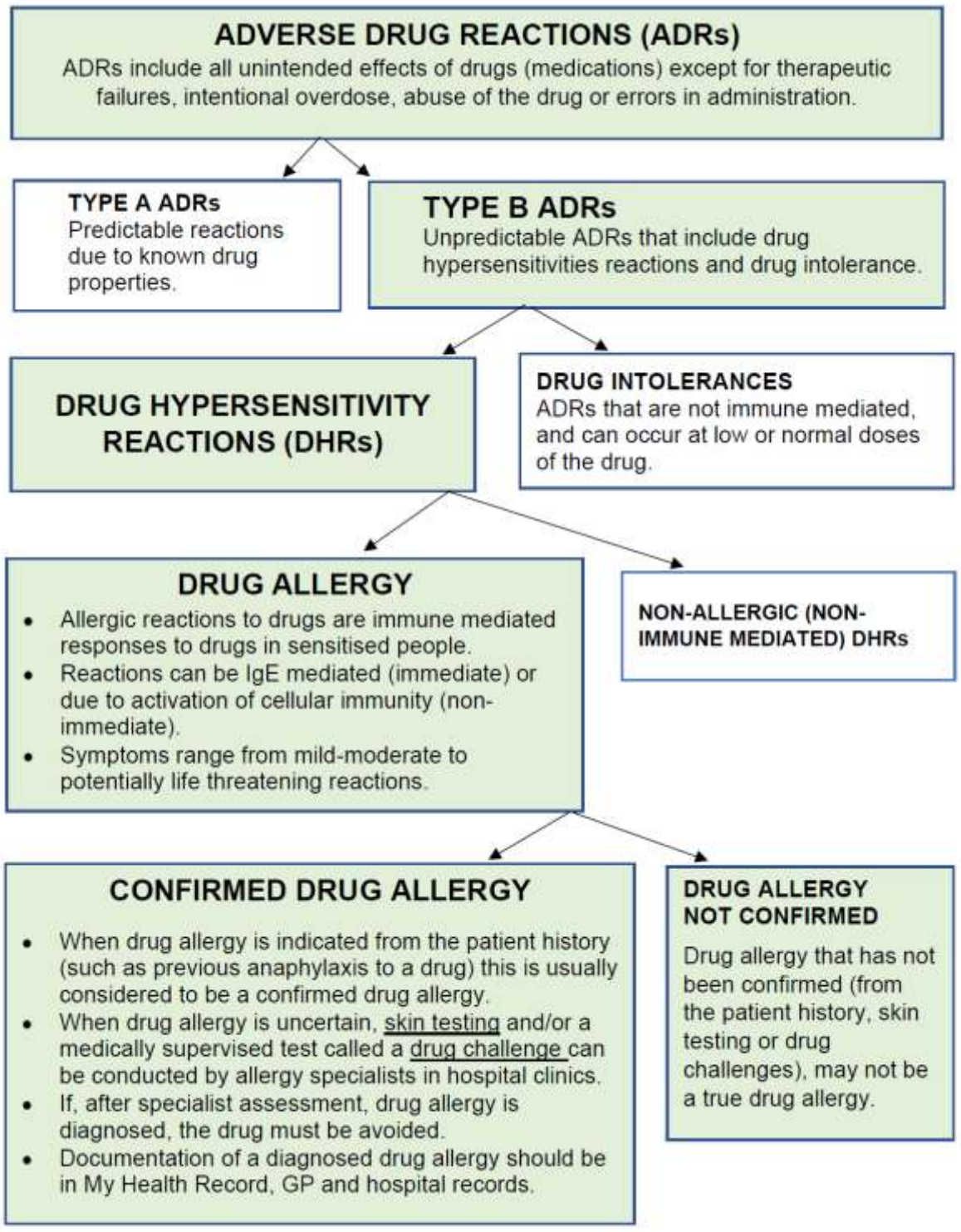
Drug (Medication) Allergy Terms

This document has been developed by the ASCIA Drug Allergy Committee to assist clinical immunology/allergy specialists and other health professionals who manage drug allergy.

It is based on expert consensus and references listed on page 9. ASCIA Drug Allergy Committee members are listed on the ASCIA website www.allergy.org.au/members/committees#dac

SUMMARY OF ADVERSE DRUG REACTIONS AND DRUG ALLERGY



TERMS ASSOCIATED WITH DRUG ALLERGY

Acute generalised exanthematous pustulosis (AGEP)	• Acute generalised exanthematous pustulosis (AGEP), also known as pustular drug eruption and toxic pustuloderma, is a rare severe cutaneous adverse skin reaction (SCAR), that is mostly related to medication administration. • AGEP appears on average five days after a medication is started.
Adverse drug reactions (ADRs)	• Adverse drug reactions (ADRs) is a general term that includes all unintended effects of a drug except for therapeutic failures, intentional overdose, abuse of the drug or errors in administration. ADRs can be classified into two types: - **Type A reactions** are predictable reactions and are based on known pharmacological properties of the drug. - **Type B reactions** are unpredictable and include drug allergy, drug intolerance and idiosyncratic reactions to drugs.
Anaphylaxis	• Anaphylaxis is a severe and immediate Immunoglobulin E (IgE) mediated allergic reaction. • Anaphylaxis can affect breathing and/or the heart and blood pressure. • Anaphylaxis is potentially life threatening and requires urgent medical attention. • Whist anaphylaxis is more likely when medication is given by intravenous (IV) or intramuscular injection (IMI), anaphylaxis to oral medications can also occur. • The most common causes of anaphylaxis are allergies to drugs (medications), foods and insect bites or stings.
Angioedema	• Angioedema is a swelling (oedema) of the structures of the skin (dermis, subcutaneous tissue), mucosa and submucosal tissues.
Benign rash	• In the context of drug allergy, a benign rash is a transient morbilliform or maculopapular rash that may be mildly pruritic and is not associated with other symptoms.
Beta-lactam antibiotics	• Beta-lactam antibiotics are antibiotics that contain a chemical structure called a beta-lactam ring. They include: - Penicillin derivatives (penams) - Cephalosporins (cephems) - Monobactams - Carbapenems - Carbacephems
Cephalosporin antibiotics	• Cephalosporins are a large group of beta-lactam antibiotics. • Some cephalosporins share side chains attached to the beta-lactam ring with penicillins, which can lead to cross reactivity. • Cephalosporins bind to and block the activity of enzymes responsible for making peptidoglycan, an important component of the bacterial cell wall. • Cephalosporins are effective against a wide range of bacteria.

Complementary and alternative medicine allergy (unproven medicines)	• While so-called complementary and alternative medicines (CAM), including herbal medicines, are often considered to be safe, ADRs including allergic reactions can occur. • It is therefore important to include questions about CAM in the patient's clinical history.
Co-reactivity	• Co-reactivity is rare and refers to if a patient reacts to structurally unrelated drugs. This has been described for T-cell mediated reactions, especially for drug reaction with eosinophilia and systemic symptoms (DRESS).
Cross-reactivity	• Cross-reactivity is an important clinical problem and may result in an ADR in some patients who are allergic to structurally related drugs. • For example, some patients who are sensitised to penicillin may also have allergic reactions to cephalosporins, due to side chain cross-reactivity and rarely due to beta-lactam ring allergy.
Cutaneous symptoms	• Cutaneous (skin) symptoms of a mild or moderate allergic reaction to a drug can include urticaria (hives) and angioedema. • Rashes due to infections can be mistaken as an allergic reaction to a drug. • Non-immediate severe cutaneous adverse reactions (SCAR) are life threatening and are described on page 6.
De-labelling	• Drug allergy de-labelling is the process of removing a drug allergy diagnosis from the patient medical record, after assessment. • Assessment is achieved by allergy testing or subsequent safe exposure to the drug. • The patient should receive a written and dated confirmation if their drug allergy diagnosis 'label' is removed. • It is important that the updated drug allergy status is recorded in all medical records for each patient.
Drug-induced liver injury (DILI)	• Drug-induced liver injury is a drug allergy and a leading cause of acute liver failure. • Antibiotics are the most common cause for DILI worldwide. • DILI can clinically present with hepatocellular, cholestatic or mixed liver dysfunction.
Drug allergy	• Drug allergies are immune mediated ADRs. • In drug allergies, IgE or other antibodies or activated T cells are directed against the drug and its metabolite, which can be bound to serum proteins (haptens). • Allergic reactions to pain killers, anti-inflammatories and antibiotics are the most common drug allergies. • Symptoms range from mild rashes through to potentially life-threatening anaphylaxis and SCAR. • Failure to accurately diagnose drug allergy, particularly to antibiotics, may result in the unnecessary use of less effective medications, which is associated with negative patient outcomes.

Drug challenge (provocation test)	• Drug challenges are medically supervised tests using protocols in which a drug is administered (parenteral or oral), while the patient is being monitored for adverse effects at each stage. • Drug challenges are also known as provocation tests and are considered to be the gold standard for drug allergy assessment. • Location of challenges depends on the pre-existing risk profile of the patient and should be performed in a suitably equipped hospital or clinic, which can manage severe reactions. • If a true drug allergy is diagnosed after a drug challenge, the drug must be avoided. Documentation of a diagnosed drug allergy should be in My Health Record, GP and hospital records. People with a diagnosed drug allergy should carry or wear medical identification jewellery or a card listing their drug allergies.
Drug desensitisation	• Drug desensitisation is a medically supervised treatment, using protocols for rapid administration of incremental does (parenteral or oral), of allergenic drugs. • The aim is to induce temporary immune drug tolerance, by which effector cells are rendered less reactive to allergic immune responses.
Drug hypersensitivity reactions (DHRs)	• Drug hypersensitivity reactions (DHRs) are unpredictable adverse effects of drugs that are allergic (immune mediated) or non-allergic (non-immune mediated). • DHRs can be classified as immediate and non-immediate, based on the timing when the reaction occurs. • Immediate allergic DHRs develop as a result of IgE production by antigen-specific B lymphocytes after sensitisation, and occur typically within one hour, or up to six hours following exposure. • Most non-immediate allergic DHRs are mediated through the actions of T lymphocytes, and typically occur after six hours following exposure. • DHRs can be life-threatening, may require or prolong hospitalisation, and may require changes in therapy.
Drug idiosyncrasy	• Idiosyncratic reactions to drugs are abnormal and unexpected ADRs. • These reactions can be allergic or non-allergic and are often reproducible on re-administration of the drug.
Drug intolerance	• Drug intolerance is an undesirable pharmacologic effect that may occur at low or usual doses of the drug. • Immune mechanisms are not thought to be involved, and a scientific explanation has not yet been established.
Drug reaction with eosinophilia and systemic symptoms (DRESS)	• Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a severe idiosyncratic drug reaction. • DRESS typically occurs two to eight weeks following exposure to the drug. • DRESS has been linked to infection with human herpes virus 6 (HHV 6).
Drug tolerance	• Drug tolerance is defined as a state in which a patient will tolerate a drug without an adverse reaction. • Desensitisation can induce temporary, but not permanent drug tolerance.

Eosinophilia	• Eosinophilia is a condition in which the eosinophil count in the peripheral blood exceeds the laboratory reference range. • In drug allergy, eosinophilia is often accompanied by a skin rash. • Eosinophilia and skin rashes are common, whereas systemic DRESS is rare.
Exanthema	• Exanthema describes a skin eruption, which can be caused by a range of reasons, including toxins, drugs, infections and autoimmune disease. • Viral exanthem is a widespread rash usually occurring in children.
Extrapyramidal symptoms (EPS)	• Extrapyramidal symptoms (EPS) are various movement disorders (including acute dystonic reactions, pseudoparkinsonism and akathisia) which can result from taking dopamine antagonists. These are usually antipsychotic (neuroleptic) drugs, that are often used to control psychosis. • EPS can also be symptoms of metabolic diseases.
Fixed drug eruption (FDE)	• A fixed drug eruption (FDE) is an allergic reaction to a medication that usually recurs at the same site/s each time a particular drug is taken. • The number of involved sites may increase over time.
Generalised bullous fixed drug eruption (GBFDE)	• Generalised bullous fixed drug eruption (GBFDE) is a bullous type of fixed drug eruption (FDE), characterised by sharply defined bullae at the same site following administration of offending drug. • Unlike FDE, GBFDE requires aggressive treatment.
Human Leucocyte Antigen (HLA)	• Certain non-immediate drug allergies are associated with the carriage of defined HLA (e.g. ADR to abacavir with HLA B*57:01).
Immunoglobulin E (IgE)	• Immunoglobulin E (IgE) is one of the five subclasses of antibody related to allergic reactions present in the blood, usually in very low concentrations and bound to the surface of cells such as mast cells. • Cross linking of bound IgE on the surface of mast cells leads to the release of allergic mediators, including histamine. This can trigger mild, moderate or severe (anaphylaxis) allergic reactions. • These reactions are known as IgE-mediated allergies. • Allergen specific IgE can be measured using skin testing or blood tests.
Maculopapular rash	• Maculopapular rash is a skin rash with a combination of macular (flat, red areas) and papules (raised bumps).
Multiple drug intolerance syndrome	• Multiple drug intolerance syndrome occurs in patients with intolerance to three or more neither structurally nor pharmacologically related drugs, with no confirmation of allergy after evaluation, and can possibly be driven by patient anxiety.
Non-IgE mediated allergy	• In non-IgE -mediated allergic reactions a patient may have similar clinical symptoms to IgE-mediated reactions, ranging from mild or moderate to severe allergic reactions, including anaphylaxis. • These reactions do not involve IgE antibodies against the allergens.

Non-steroidal anti-inflammatory drug (NSAID) allergy (intolerance)	• Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) can cause reactions in some people. Symptoms include flushing, itchy rashes, blocked/runny nose and sometimes severe asthma, usually within an hour of taking a tablet. • Aspirin allergy (more correctly referred to as aspirin intolerance) is more common in people with nasal polyps and asthma (AERD or Samter's Triad). • Aspirin-induced respiratory disease (AERD) is characterised by aspirin or non-steroidal anti-inflammatory drug (NSAID) induced respiratory reactions in a patient with underlying asthma and/or rhinitis or sinusitis.
Penicillin antibiotic allergy	• Penicillin antibiotics were among the first medications to be effective against many bacterial infections. They are still widely used today, despite some bacteria developing resistance following extensive use. • Approximately 10% of people report that they are allergic to penicillin, however, up to 90% of this group have an unconfirmed allergy and may not actually be allergic to penicillin. • Penicillin allergy de-labelling is the process of removing an unconfirmed allergy diagnosis from the patient medical record. This may be achieved by allergy testing or subsequent safe exposure to the drug.
Perioperative allergic reactions	• Allergic reactions, including anaphylaxis, can occur during surgical and interventional procedures involving anaesthetics and antibiotics. • Allergic reactions to antiseptics, latex and anaesthetic drugs given during operations are rare, but can be serious. • Allergic reactions to chlorhexidine antiseptics are increasing in frequency and may be due to common usage of chlorhexidine-containing products.
Pharmacologic interaction with immune receptors (P-i) concept	• The p-i concept (pharmacologic interaction with immune receptors) is a recently proposed drug hypersensitivity classification in which a drug binds noncovalently to an immune receptor, such as a T cell receptor. This may lead to an immune response via interaction with a major histocompatibility complex molecule.
Pharmacovigilance (drug safety)	• Pharmacovigilance (also known as drug safety), is the pharmacological science relating to the collection, detection, assessment, monitoring and prevention of adverse effects with pharmaceutical products.
Pseudoallergic (anaphylactoid) reactions	• Pseudoallergic (anaphylactoid) reactions are immediate systemic reactions that mimic anaphylaxis, but are caused by non IgE-mediated reactions with the release of mediators from mast cells and basophils. • This term is rarely used and is incorrect as the anaphylaxis that results has the same characteristics as an IgE-mediated reaction.
Severe cutaneous adverse reaction (SCAR)	• Non-immediate severe cutaneous adverse reactions (SCAR) are rashes that are associated with fever, flu-like and other systemic symptoms. • SCAR are potentially life-threatening, and require urgent specialist care. • SCAR often involve mucosal surfaces as well as the skin and include: - Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) - Drug reaction with eosinophilia and systemic symptoms (DRESS) - Acute generalised exanthematous pustulosis (AGEP) - Generalised bullous fixed drug eruptions (GBFDE)

Skin tests • **Skin prick tests (SPT)** • **Intradermal tests (IDT)**	• A skin prick test (SPT) introduces a tiny amount of allergen into the skin, via a prick into the skin. • Intradermal skin testing (IDT) injects a defined amount of allergen into the dermal layer of the skin. • IDT is more sensitive than SPT as it delivers a larger amount of allergen but can carry a risk of anaphylaxis in highly sensitised individuals. • SPT and IDT elicit a localised allergic response in the form of a wheal (bump) and flare (redness) at the site of testing. • IDT can also elicit a delayed inflammatory reaction in the skin in non-immediate drug reactions. • When drug allergy is uncertain, SPT or IDT or a medically supervised drug challenge can be conducted by clinical immunology/allergy specialists.
Stevens–Johnson syndrome (SJS)	• Stevens–Johnson syndrome (SJS) is a life-threatening skin condition, in which cell death causes the epidermis to separate from the dermis. • SJS is thought to be a hypersensitivity complex that affects the skin and the mucous membranes. • The most well-known causes of SJS are certain medications, but it can also be due to infections, or more rarely, cancers.
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)	• Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) is also known as Baboon syndrome because of its resemblance to the distinctive red buttocks displayed by female baboons, • SDRIFE is a systemic contact dermatitis with well-demarcated patches of erythema distributed symmetrically on the buttocks. • The cause of SDRIFE may be drug-related, induced by systemic administration of drugs, including hydroxyzine, penicillin and iodinated radio contrast media.
Toxic epidermal necrolysis (TEN)	• Toxic epidermal necrolysis (TEN) is a type of severe skin reaction. • Symptoms include fever and flu-like symptoms, followed by blister and peel.
Tryptase	• Tryptase is a proteinase that is abundant in human mast cells and basophils. • Serum Tryptase is used as a marker for mast cell activation and rises in anaphylaxis particularly when caused by drugs and stings.
Urticaria (hives)	• Urticaria (also known as hives or welts) is a raised, itchy rash that appears on the skin. • Urticaria can be limited to one part of the body or spread across large areas of the body.

ACRONYMS AND ABBREVIATIONS ASSOCIATED WITH DRUG ALLERGY

ADR	Adverse drug reaction
AERD	Aspirin-exacerbated respiratory disease
AGEP	Acute generalized exanthematous pustulosis
AMP	Ampicillin
AX	Amoxicillin
BAT	Basophil activation test
BP	Benzyl penicillin
COX-1	Cyclooxygenase 1
COX-2	Cyclooxygenase 2
DMARDS	Disease modifying anti-rheumatic drugs
DRESS	Drug rash with eosinophilia and systemic symptoms
DHR	Drug hypersensitivity reactions
DIHS	Drug-induced hypersensitivity syndrome
DILI	Drug-induced liver injury
DPT	Drug provocation (challenge) test
DRESS	Drug reaction with eosinophilia and systemic symptoms
FDE	Fixed drug eruption
GBFDE	Generalised bullous fixed drug eruption
HHV 6	Human herpes virus 6
HLA	Human leukocyte antigen
HSS	Hypersensitivity syndrome
iDILI	Idiosyncratic drug-induced liver injury
IDT	Intradermal test
IgE	Immunoglobulin E
LTT	Lymphocyte transformation test
MDH	Multiple drug hypersensitivity
MDM	Minor determinant mixture
MHC	Major histocompatibility complex (HLA in humans)
NMBA	Neuromuscular blocking agent
NSAIDs	Non-steroidal anti-inflammatory drugs
OPC	Oral provocation challenge
RCM	Radio contrast media
SCAR	Severe cutaneous adverse reaction
SDRIFE	Symmetrical drug-related intertriginous and flexural exanthema
SJS	Stevens-Johnson syndrome
SPT	Skin prick test
TEN	Toxic epidermal necrolysis

REFERENCES

International Consensus (ICON) on Drug Allergy 2014

European Academy of Allergy and Clinical Immunology (EAACI), the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the World Allergy Organization (WAO).

Demoly, P., Adkinson, N.F., Brockow, K., …. Thong, B.Y-H. (2014) Allergy. European Journal of Allergy and Clinical Immunology, Vol 69, pp 420-437.
https://onlinelibrary.wiley.com/doi/pdf/10.1111/all.12350

Drug Allergy: An Updated Practice Parameter 2010

American Academy of Allergy, Asthma and Immunology (AAAAI), and the American College of Allergy, Asthma and Immunology (ACAAI).

Solensky, R., and Khan, D.A. editors, (2010) Annals of Allergy, Asthma & Immunology, Vol 105, pp273e78
https://www.aAAAAI.org/AAAAAI/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/drug-allergy-updated-practice-param.pdf

World Allergy Organisation (WAO) 2014

Thong, B., and Vervolet, D., https://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/drug-allergies

Drug Allergy: Diagnosis and Management of Drug Allergy in Adults, Children and Young People (2014)

National Institute for Health and Care Excellence UK, Clinical Guidelines, No. 183.
https://www.ncbi.nlm.nih.gov/books/NBK274156/