

AN APPROACH TO ANTIBIOTIC ALLERGIES

Chapter

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Many patients experience adverse reactions to drugs, but most of these are predictable, dose-dependent and do not involve the immune system. These include side effects, drug interactions and toxic effects due to overdosing. Some patients may also be very sensitive to the normal pharmacological effect of a drug or have a genetic or enzyme deficiency affecting the metabolism of certain drugs.

Drug allergy is an immunologically mediated reaction that is specific to a particular drug and re-occurs on subsequent exposure to that drug. Many different immunological mechanisms may be involved, including IgE-mediated, basophil-mediated, eosinophilic, cytotoxic/complement-mediated, immune complex-mediated and T-cell mediated reactions. These immunologic drug reactions may necessitate changes in therapy or may be life-threatening, therefore a definitive diagnosis and the identification of safe alternatives is usually required.

A generally accepted classification of immunologic drug reactions (drug allergy) is based upon the timing of the appearance of symptoms. This can help guide the clinician in choosing the appropriate diagnostic tests.

IMMEDIATE REACTIONS

- Occur within one to six hours after drug administration, but typically within the first hour after administration.
- IgE-mediated reactions account for many immediate reactions.
- Basophil-mediated reactions and other non-IgE dependant reactions have also been described in this context.
- On re-exposure, patients may experience the potential risk of life-threatening anaphylaxis.
- Symptoms include: pruritus, flushing, urticaria, angioedema, wheezing, laryngeal oedema, abdominal distress with emesis or diarrhoea and hypotension.

NON-IMMEDIATE OR DELAYED-TYPE REACTIONS

- Occur any time later than one hour after drug administration, but typically after 24 hours.
- T-cell, basophilic, eosinophilic, cytotoxic, complement or immune-complex mediated reactions may be involved.
- Delayed type reactions often appear after multiple doses of treatment, typically after days or weeks of administration.
- T-cell mediated reactions mainly present as maculopapular rashes, pustular rashes or Stevens-Johnson syndrome (SJS)/Toxic Epidermal Necrolysis (TEN).
- Basophil-mediated reactions often present as delayed urticaria.

- Eosinophilic reactions may present with maculopapular rashes or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- Cytotoxic/complement-mediated reactions may present as auto-immune haemolytic anaemia, thrombocytopaenia and interstitial nephritis.
- Immune complex-mediated reactions may present as serum sickness or vasculitis.

Note that this classification tends to over-simplify and there may be considerable overlap between immediate and non-immediate reactions. Several other factors such as the route of administration and drug metabolites should also be considered as part of the working classification. Some IgE-mediated reactions may only appear after one hour, especially if the drug is administered orally, when taken with food or with enteric coated drugs. When patients are primarily sensitised to a drug, initial symptoms may appear only later on in the first course of treatment.

DIAGNOSTIC TESTING FOR DRUG ALLERGIES

The starting point in diagnosing a drug allergy is to obtain a detailed history of the event, including the onset of symptoms and signs and their timing in relation to drug exposure.

When taking a history, try to answer the following questions:

- Is it a drug allergy or another type of adverse drug reaction?
- Is it an immediate or delayed reaction?
- What mechanism of allergy is probably involved?
- What is the eliciting drug? (Important when patients are taking multiple drugs – some drugs are more allergenic than others.)

The aim is to establish or disprove a causal relationship between the drug and the patient's reaction. If clinical suspicion is high with negative tests, challenge with the drug in a controlled environment. Always correlate the laboratory results with the clinical picture.

TESTING FOR DRUG ALLERGY

The allergy workup should ideally be carried out approximately four weeks after resolution of symptoms. The patient should discontinue systemic corticosteroids two weeks prior to testing and antihistamines three days prior to testing.

When requesting laboratory tests, use a step-wise diagnostic approach and be guided by:

- Clinical suspicion obtained from the patient's history, symptoms and signs.
- The cost of testing and need for specialist facilities, e.g. in vivo drug testing and drug challenges.

ALLERGY TESTS

IN VITRO (LABORATORY) TESTS	
Drug-specific IgE (ImmunoCap/RAST tests)	<ul style="list-style-type: none"> • Limited availability of allergens, e.g. penicillin V, penicillin G, ampicillin and amoxicillin • Lacks sensitivity, but may have good specificity (~90%) <ul style="list-style-type: none"> – < 5% of all drug hypersensitivity is IgE-mediated – < 20% of penicillin allergy is IgE-mediated • Negative tests should always be followed up with additional testing in patients with a convincing history of drug allergy

Cellular allergen stimulating tests (CAST)/Basophil activation tests (BAT)	<ul style="list-style-type: none"> • Only in specialised centres, but can be used as part of a routine diagnostic algorithm • Can be used as first-line testing for drug allergy • Specificity of BAT for drug allergy is generally high (~93%); sensitivity depends on the drug tested, but usually exceeds 50% • BAT should ideally be used in combination with other tests for optimal sensitivity • Negative tests should always be followed up with additional testing in patients with a convincing history of drug allergy
T-cell proliferation tests (MELISA/ Delayed-type CAST tests)	<ul style="list-style-type: none"> • Only in expert laboratories • Modified lymphocyte proliferation assays, flow-cytometry and cytokine assays available • Should only be used for patients with a history consistent with a delayed, T-cell mediated response (e.g. maculopapular rash) • Should be used in combination with other tests, as tests may lack sensitivity

COMMERCIAL ALLERGENS AVAILABLE FOR CELLULAR TESTING OF ANTIBIOTICS

<ul style="list-style-type: none"> • Penicillin G • Penicillin V • Benzylpenicilloyn-Polylysine (Penicillin) • Minor Determinant Mix (Penicillin) • Amoxicillin • Ampicillin • Clavulanic acid • Clindamycin • Cefamandole • Cefazolin • Cefuroxime • Cefaclor • Ceftriaxone 	<ul style="list-style-type: none"> • Cephalosporin C • Ciprofloxacin • Clarithromycin • Clindamycin • Doxycycline • Erythromycin • Levofloxacin • Moxifloxacin • Rifampicin • Sulfamethoxazole • Trimethoprim • Tetracycline
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The list of commercial allergens will expand in future as new allergens become available. If a commercial allergen is not available, dilutions of actual drugs can also be used. The medication in question should be provided in addition to the patient's blood specimens. Ampoules or capsules are preferable to tablets where possible, due to the potential interfering effects of binding agents and preservatives.

OTHER LABORATORY TESTS

- Mast cell tryptase
 - Used to confirm anaphylaxis and indicates the involvement of mast cells, whatever the cause of degranulation.
 - Especially valuable for drug reactions under anaesthesia.
 - Take a serum specimen within two to four hours after allergic reaction. An additional determination is needed after 24 hours to exclude increased baseline levels of tryptase (e.g. mastocytosis) and to aid in the diagnosis of anaphylaxis. An increase of four times above the baseline is significant, regardless of the test cut-off value.
- Pharmacogenomics
 - HLA-B*5701 for true immunologically mediated abacavir hypersensitivity.

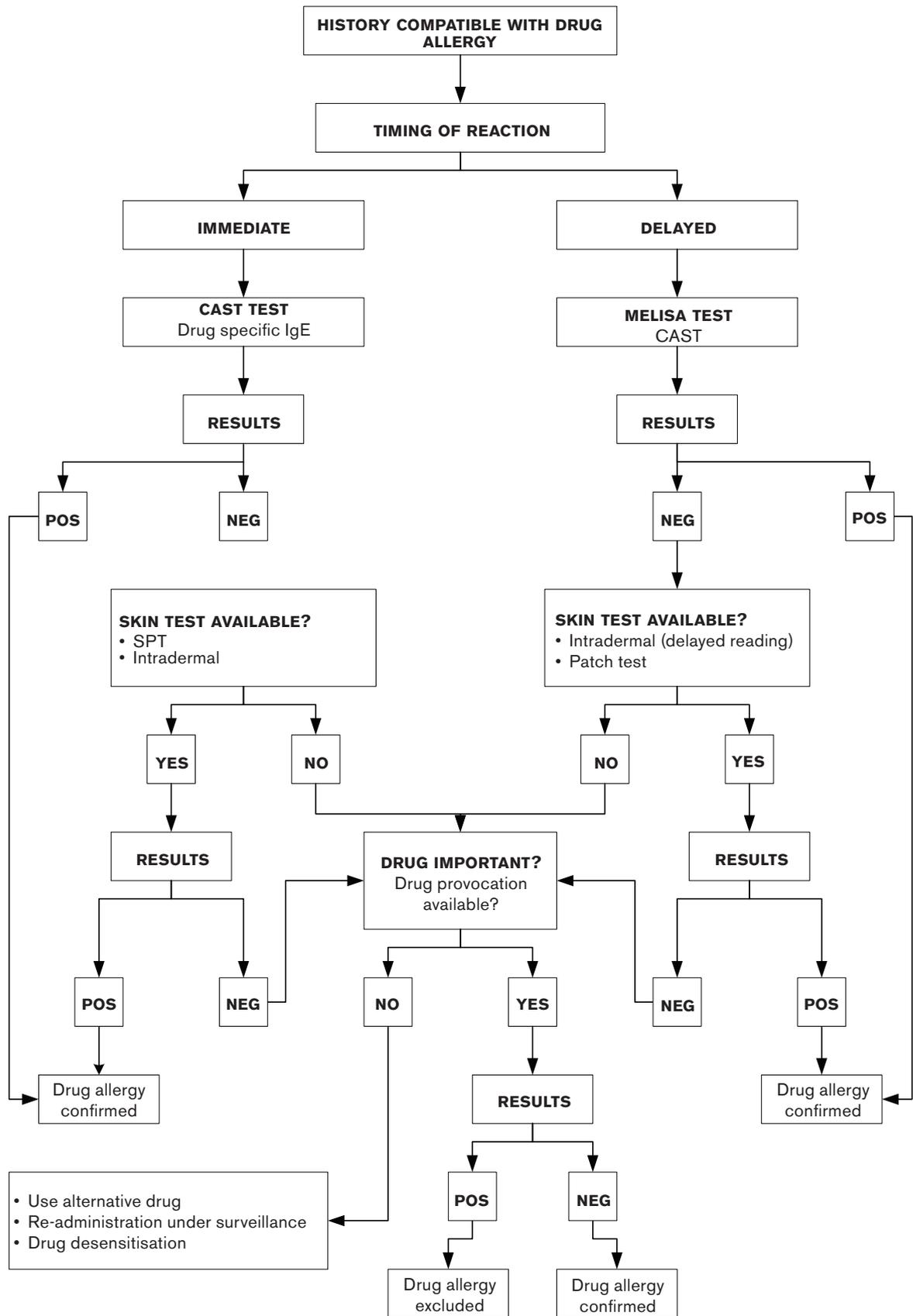
IN VIVO TESTS (CLINIC-BASED/PATIENT-BASED TESTS)

- Skin tests
 - Skin prick tests using more than one dilution of the drug is recommended for immediate drug hypersensitivity reactions.
 - Intradermal tests using more than dilution of the drug may be undertaken when skin prick tests are negative.
 - Intradermal tests with delayed reading (24–48 hours) and patch tests may be used to diagnose delayed drug reactions.
 - Testing of both major and minor penicillin determinants should be performed if penicillin allergy is suspected.
- Drug provocation tests
 - Should be performed in specialist allergy centres under the highest safety conditions.
 - Should only be performed then other available drug allergy tests have been performed and are negative.
 - The oral route of administration is preferred, where possible.
 - Absolute contraindications are severe, life threatening cutaneous reactions (e.g. SJS, TEN, vasculitis) or systemic reactions (e.g. DRESS).
 - A risk-benefit analysis should be performed before performing a drug provocation test in a patient with a history of anaphylaxis to the tested drug, severe concurrent illness or pregnancy.

METHOD FOR PERFORMING A DRUG PROVOCATION TEST

- The starting challenge dose is typically between 1/10 000 and 1/1000 of the therapeutic dose.
- Ten-fold increasing doses are administered every 30–60 minutes until the full therapeutic dose is reached.
- If subjective symptoms appear, the clinician can proceed more slowly by using three-fold increases.
- Once the full therapeutic dose has been achieved without incident, continuous therapy should begin immediately with appropriate monitoring.

A SUGGESTED ALGORITHM TO AID IN THE DIAGNOSIS OF DRUG ALLERGY



PENICILLIN ALLERGY

- Penicillin is the most commonly reported medication allergy. Penicillin allergies are self-reported by approximately 5–10% of patients, however 85–90% of these patients are found not to have positive skin tests and are able to tolerate penicillins.
- The incidence of anaphylaxis secondary to penicillin varies between one and four episodes per 10 000 administrations.
- Reactions can be immediate or delayed.

TIME ELAPSED SINCE THE REACTION

- Penicillin-specific IgE antibodies decreases over time.
- Approximately 50% of patients with IgE-mediated penicillin allergy have lost the sensitivity five years after their last reaction.
- Approximately 80% of patients with IgE-mediated penicillin allergy have lost the sensitivity after 10 years.

PATHOGENESIS

Allergic reactions to the core ring structure that is common to all penicillins, or much less commonly, to an epitope which includes the R-group side chains.

- **Core beta-lactam structures**
 - Penicillins spontaneously degrade to reactive intermediates under physiologic conditions and these act as haptens which covalently bind to tissue and serum proteins. These may elicit various immune responses, including the production of specific IgE antibodies.
 - 95% of penicillin degrades to the penicilloyl moiety, the 'major antigenic determinant'.
 - The remainder is degraded to penicilloate, the 'minor antigenic determinant'.
- **Side chain specific reactions**
 - Formation of IgE antibodies which can recognise the R-group side chains and not the core ring structure.
 - Individuals develop immediate-type reactions to amoxicillin or ampicillin but are able to tolerate penicillin, and are said to be selectively allergic to the aminopenicillins.

Note: Patients who reacted to the combination of amoxicillin-clavulanate may be allergic to clavulanate.

DIAGNOSTIC TESTING

- In vivo testing – skin-prick testing, intradermal tests for immediate type reactions; patch tests for delayed type reactions.
- Skin testing helps clarify the current level of risk for anaphylaxis by using the major (penicilloyl-polylysine) (PPL) and minor penicillin determinants (MDM) where the diagnostic sensitivity is 99% for IgE-mediated reactions to penicillin. If penicilloyl-polylysine and penicillin G are used for skin testing, the sensitivity is 85%.
- In vitro testing – penicillin V IgE, penicillin G IgE, CASTs, MELISA, delayed type CASTs.

USE OF CEPHALOSPORINS, CARBAPENEMS AND MONOBACTAMS IN PENICILLIN ALLERGIC PATIENTS

- A beta-lactam structure is also found in cephalosporins, carbapenems, and monobactams.
- The aminopenicillins amoxicillin and ampicillin, each have R-group side chains that are identical to the side chains of certain cephalosporins. The R-group side chains are believed to be most important in predicting cross-reactivity between aminopenicillins and cephalosporins.

- Penicillin G has the same side chain as cefamandole, cefaloram, cephalothin and cephaloridine.
- Ampicillin has the same side chain as Cefaclor®, cephalixin, cephradine and Loracarbef®.
- Amoxicillin has the same side chain as cephadroxil, cefprozil and cefatrizine.
- Aztreonam has the same side chain as ceftazidime.
- Approximately 2% of patients with skin-test proven sensitivity to penicillin can be expected to react to cephalosporins.

THE ADMINISTRATION OF CEPHALOSPORINS TO PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY CAN BE DIVIDED INTO SCENARIOS WHERE PENICILLIN SKIN TESTING IS AND IS NOT AVAILABLE

WHERE PENICILLIN SKIN TESTING IS NOT AVAILABLE

- This is the typical scenario in South Africa.
- Do alternative in vitro testing to attempt beta lactam allergy diagnosis including penicillin V IgE, penicillin G IgE, CASTs against most penicillins, the major and minor determinants, cephalosporins, MELISA, delayed type CASTs.
- Determine the likelihood of a serious IgE-mediated reaction to a cephalosporin based on the clinical history and time elapsed since the penicillin reaction (greater risk for reacting to a cephalosporin if the reaction to penicillin occurred within the past 10 years).
 - These patients may be given a cephalosporin (with a dissimilar side chain) via graded challenge provided all the in vitro tests are negative. If the in vitro test(s) are positive, consider desensitisation.
 - Graded challenge – Give 1/100th or 1/10th of the full dose. Ten-fold increasing doses are administered every 30–60 minutes until full therapeutic dose is reached.

WHERE PENICILLIN SKIN TESTING IS AVAILABLE

Penicillin skin testing with standardised major determinant and minor determinant mix antigens (PPL and MDM) are the gold standard in diagnosing penicillin allergy and has a diagnostic sensitivity of ~99%. These will be available soon at a few select allergy clinics in South Africa. A few centres do in-house penicillin skin-prick testing, but the sensitivity and predictive values of these non-standardised tests are suboptimal.

- If penicillin skin testing with PPL and MDM is negative, patients may safely receive cephalosporins.
- If penicillin skin testing is positive, ~2% of these patients can react to cephalosporins. Some of these reactions could be severe. The options are then:
 - Administer an unrelated antibiotic (neither a penicillin nor a cephalosporin)
 - Administer a cephalosporin using a graded challenge
 - Administer a cephalosporin using a rapid desensitisation procedure

PATIENTS SELECTIVELY ALLERGIC TO AMOXICILLIN OR AMPICILLIN

- Avoid cephalosporins with identical R-group side chains or only give cephalosporins to patients after desensitisation.

CARBAPENEM ALLERGY

Imipenem, meropenem, doripenem, and ertapenem share a common beta-lactam ring with penicillins. Studies have demonstrated that 99% of patients with positive skin tests to penicillin will tolerate a carbapenem and IgE-mediated allergic cross-reactivity between the drugs has therefore been mostly ruled out.

- Perform in vitro testing to attempt the diagnosis of a penicillin allergy, including penicillin V IgE, penicillin G IgE, CASTs against most penicillins, the major and minor determinants, cephalosporins, MELISA, delayed type CASTs.
- Non-standardised carbapenem CAST tests are available.
- If penicillin skin testing with PPL and MDM is unavailable and in vitro tests are all negative, carbapenems may be administered via graded challenge.
- If penicillin skin testing with PPL and MDM is available and is negative, patients may safely receive carbapenems.
- If penicillin skin testing is positive, carbapenems may be administered via a two or three-step graded challenge.

MONOBACTAM (AZTREONAM) ALLERGY

- Have a monocyclic beta-lactam structure.
- There is no immunologic cross-reactivity between penicillin and aztreonam.
- Patients with a history of penicillin allergy may safely receive aztreonam.

SULPHONAMIDE ALLERGY

Specific mention of blisters, peeling of skin, mucous membranes, emergency department visit, 'anaphylaxis' or 'nearly died', in association with prior sulphonamide reactions, must be taken very seriously.

- Sulphonamide-containing antibiotics are the second most frequent cause of allergic drug reactions after the beta-lactams (penicillins and cephalosporins).
- Incidence of reactions to cotrimoxazole (trimethoprim-sulfamethoxazole/TMP-SMX) is approximately 34 per 1 000 patients exposed.
- There are two distinct groups of sulphonamides that differ in chemical structure as well as clinical use:
 - Antimicrobial sulphonamides. This group includes sulfamethoxazole (in TMP-SMX) and other less commonly used antimicrobials.
 - Non-antimicrobial sulphonamides
- Cross-reactivity
 - There is minimal evidence of cross-reactivity between sulphonamide antimicrobials and non-antimicrobials, but information is based upon observational studies.
 - The imprecise term 'sulpha drugs' has led to the ongoing confusion of cross-reaction within the sulphonamide group of drugs.

TYPES OF HYPERSENSITIVITY REACTIONS TO SULPHONAMIDES

- Isolated cutaneous reactions:
 - Isolated skin reaction that rapidly subsides on withdrawal of the drug
- Morbilliform rash with fever and systemic symptoms:
 - May progress to multisystem involvement – mild or overt
 - Appears one to two weeks after administration of the drug, with fever typically appearing first

- Disappears after one week of discontinuation of the drug, may rapidly reappear on re-exposure
- Type I hypersensitivity or anaphylaxis:
 - Immediate-type hypersensitivity reactions
 - Not common
 - Symptoms include urticaria, angioedema, bronchospasm, laryngeal angioedema, and hypotension
- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN):
 - Strong association with antimicrobial sulphonamides, not with the non-antimicrobial sulphonamides
- Erythema multiforme
- Serum sickness:
 - 10–14 days after initiation of treatment
 - Self-limiting after discontinuation
- Haemolytic anaemia in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

DIAGNOSIS

A variety of immunologic testing techniques are available, although none is 100% sensitive.

SJS and TEN is a clinical diagnosis supported by histology – in vivo testing contraindicated in these conditions.

FUTURE MANAGEMENT

TMP-SMX ALLERGY IN A PATIENT WHO REQUIRES TMP-SMX

- Desensitisation is advised.
- Re-exposure to the offending drug or a sulphonamide in the same group is contraindicated if a patient describes symptoms consistent with an exfoliative dermatitis or diffuse erythroderma.

AVOID ALL SULPHONAMIDES AND SULFONES IN PATIENTS WITH PAST SJS OR TEN

Desensitisation protocols are available for use in patients with the more common presentation of rash and fever.

- If patients need a sulphonamide from a different group to which they reacted:
 - Simply give the drug normally – in a patient who does not have multiple drug allergies and whose past reaction to the sulphonamide was limited to morbilliform rash, or rash and fever.
 - Administration of one or more test doses of the desired drug – for patients with other drug allergies.

QUINOLONE ALLERGY

- Quinolones are a group of broad-spectrum synthetic antibiotics with structural similarity suggesting frequent cross-reactivity.
- Some of the more frequently used quinolones are ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, gemifloxacin and norfloxacin.
- The prevalence of quinolone allergy is uncertain, but is reported to be approximately 4% of antibiotic allergy reactions.

- At Ampath we have seen an increase in positive tests for quinolones, especially levofloxacin, which probably reflects an increase in use rather than an increase of incidence/days of treatment.
- Quinolone allergy may cause anaphylactic or anaphylactoid reactions, pruritis, urticaria or angio-oedema.
- Delayed cutaneous reactions, including maculopapular rashes, fixed drug eruptions and erythema multiforme and Stevens-Johnson syndrome have also been described.
- Strict avoidance of all quinolones is advisable in patients with a quinolone allergy. Non-standardised tests to quinolones can also be performed by the laboratory.
- Management is primarily based on avoidance, but desensitisation protocols have been described. Desensitisation should only be attempted for vital indications when no alternative drug is available.

MACROLIDE ALLERGY

- Macrolides are characterised by a basic structure made up of a lactonic cycle with two osidic chains. They are classified according to the number of carbon atoms in the cycle: 14-membered (erythromycin, roxithromycin, clarithromycin), 15-membered (azithromycin) and 16-membered (spiramycin).
- Macrolides are generally well tolerated and are considered to be the safest antibiotics in use from an allergy perspective.
- Adverse reactions are much more common than allergic reactions.
- Anaphylaxis has been described, especially to erythromycin.
- Cutaneous reactions occur more commonly, including urticaria, angio-oedema, maculopapular rashes, Stevens-Johnson syndrome (azithromycin) and fixed drug eruptions (erythromycin, clarithromycin).
- Management is based on avoidance of the single causal macrolide, as cross-reactivity is not common. If doubt exists, we suggest that the patient be tested with the macrolide of choice before administering an alternative.

DESENSITISATION

- Desensitisation is the cautious administration of small and increasing doses of a medication under medical supervision to patients who are most likely allergic to the drug in question.
- Appropriate when there are no acceptable alternatives.
- Used mostly in patients with IgE-mediated, type I hypersensitivity reactions.
- Desensitisation can be performed by oral, intravenous, or subcutaneous routes.
- The oral route is preferred.

PENICILLIN DESENSITISATION

- Starting dose in most patients is 1/10 000th of the normal therapeutic concentration.
- Double the dose every 15 minutes until the recommended dose is reached.
- The drug needs to be continually present in the bloodstream in order for the patient to remain desensitised.

- If symptoms appear, dosing should not be increased until the symptoms have been treated and resolved:
 - Antihistamines for pruritus or urticaria, inhaled bronchodilators for chest tightness or wheezing, epinephrine for systemic reactions.
 - Protocol is then resumed with the step before the one that caused the reaction.

OPTIONS FOR CONTINUING TREATMENT

There are three options for providing continued treatment in patients with a confirmed drug allergy:

- Administration of an unrelated medication
- Administration of a related medication
- When skin tests are negative, graded challenges should ideally be performed
- Desensitisation to the culprit drug

LONG-TERM MANAGEMENT

- Education about avoidance
- Provide the patient with a list of possible cross-reactive drugs
- Always wear a Medic Alert bracelet/card
- Consider carrying an EpiPen® (adrenaline auto-injector), depending on the type and severity of the reaction
- Limit antibiotic use
- In drug allergy prone patients, new drugs should be started at lower than normal doses when possible, and occasionally under medical supervision.