Introduction:

Many patients experience adverse reactions to drugs, but most of these are predictable, dose dependent and don’t 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.

Immediate reactions:

- Occur within 1-6 hours after drug administration, but typically occur within the first hour after administration.
- IgE-mediated reactions account for many immediate reactions.
- Basophil-mediated reactions and other non-IgE dependent 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 1 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, days or weeks after 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 autoimmune haemolytic anemia, thrombocytopenia and interstitial nephritis.
- Immune complex mediated reactions may present as serum sickness or vasculitis.

How do I diagnose a drug allergy?

The starting point in the diagnosis of drug allergy is obtaining 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 and 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 in patients 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.

**Allergy tests:**

The allergy workup should ideally be carried out approximately 4 weeks after the resolution of symptoms. The patient should discontinue systemic corticosteroids 2 weeks prior to testing and antihistamines 3 days prior to testing to allow any testing modality to be used.

The tests requested should depend on:

- Clinical suspicion obtained from patient history.
- Keep resources in mind: test menus available, cost of testing and access to specialist facilities, e.g. in vivo drug testing and drug challenges.
- Try and use a step-wise diagnostic approach.

Diagnostic tests (accessibility will vary in different countries and settings):

1. **In vitro (laboratory) tests:**
   - Drug-specific IgE
     - Limited availability of allergens
     - Lacks sensitivity, but may have good specificity (90%)
     - Negative tests should always be followed up with additional testing in patients with a convincing history of drug allergy
   - Basophil activation tests (BAT)
     - 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 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.
   - T-cell proliferation tests
     - Only in expert laboratories.
     - Often still only a research tool.
     - Modified lymphocyte proliferation assays, flow-cytometry and cytokine assays available.
     - Should only be used for second/ third-line testing in 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.
   - Mast cell tryptase
     - Used to confirm anaphylaxis and indicates the involvement of mast cells, whatever the cause of degranulation.

2. **In vivo (clinic / patient based) tests:**
   - Skin tests
     - Skin prick tests using more than 1 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.
     - Sensitivities of skin prick tests vary, but are generally good for β-lactam antibiotics, neuromuscular blocking agents and heparins. Testing to both major and minor penicillin determinants should be performed if penicillin allergy is suspected.
• Drug provocation tests\textsuperscript{7,8}:
  ◦ Should be performed in specialist allergy centres under the highest safety conditions.
  ◦ The oral route is preferred where possible.
  ◦ Absolute contra-indications 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.

Approach to drug allergy diagnosis:

As drug allergy diagnosis may be quite complicated, it is essential to follow a rational approach utilising available resources. Figure 1 shows an example of an approach followed in private practice in South Africa. This could be adapted to suit local resources and test menus.

Concluding remarks:

It is essential to correlate all test results with your clinical history. No single drug allergy test is sensitive enough to rule out drug allergy in a patient with a convincing history of drug allergy. A combination of drug allergy tests provide the highest sensitivity.

Once a diagnosis of drug allergy has been confirmed, it is important to identify a safe alternative to the drug in question. If no alternative can be found and the drug is essential, drug desensitization should be considered.

References:


*Drug provocation contra-indicated in patients with a history of severe reactions e.g. SJS, TEN, DRESS or vasculitis.