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.

Drug allergy is an immunologically mediated reaction that is specific to a particular drug and reoccurs on subsequent exposure to that drug. Many different immunological mechanisms may be involved, including IgE, basophil, eosinophil, cytotoxic/complement, immune complexes 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 are 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 the choice of diagnostic technique.

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 anaemia, 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.

Diagnosing Drug Allergy: A Rational Approach

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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**:1,5

- **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 expert laboratories.
  - 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**:1,5

- **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.

- **T-cell proliferation tests**
  - Only in expert laboratories.
  - 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.

- **Drug provocation tests**: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.
Alpha Laboratories provides two options for the Basophil Activation Test (BAT), both from BÜHLMANN Laboratories.

The Flow2 CAST® system represents a significant step forward in \textit{in vitro} allergy testing, allowing the simple detection of Basophil Activation on whole blood samples. It uses a dual labelling system to identify basophils, negating the requirement for lengthy and labour intensive leukocyte isolation steps.

Using a flow cytometer, basophils are identified in the sample by a specific marker (CCR3) and then the level of CD63 is analysed on this sub-population to give a read out of the response to a purified allergen which is added to the sample.

In the CAST-2000® ELISA, leukocytes isolated from patient blood are simultaneously primed with Interleukin 3 (IL-3) and stimulated with allergens. The ELISA measures de novo synthesis of the allergic sulfidoleukotriene mediators (LTC4, LTD4 and LTE4) as a quantitative read-out of the patient’s response to the allergen.

References: