

APPROACH TO DRUG ALLERGY

Dr Bernard Thong

DEFINITION OF DRUG ALLERGY

An unpredictable, dose-independent adverse drug reaction which is immunologically or IgE-mediated.

BASIC PRINCIPLES

1. **Sensitisation:** Drug allergies occur only after a sufficient period of sensitization (at least 5-7 days of treatment). If it occurs immediately after one dose, a history of previous exposure to that drug or other drugs of the same class would further support a diagnosis of an allergic reaction.
2. **Delayed reactions** can occur. Reactions to anti-tuberculous drugs, allopurinol, anticonvulsants and propylthiouracil may present up to 1 month or more after the start of a course.
3. **Hypersensitivity syndromes** (commonly due to anticonvulsants and allopurinol) are potentially severe reactions with up to 25% mortality. These are associated with systemic symptoms eg. fever, lymphadenopathy, a generalised rash (usually not vasculitic) and hepatitis. These often start after 2-3 weeks of therapy.
4. **Cross-sensitivity**
Some groups of drugs cross-react. Common examples include:
 - (a) *b-lactam antibiotics* – penicillins, cephalosporins, carbapenems (immediate, type I hypersensitivity)
 - (b) *aromatic anti-convulsants* – phenytoin, phenobarbitone, carbamazepine (delayed hypersensitivity)
 - (c) *sulphonamide drugs* – patients should be advised on potential cross-reactivity although the use of another sulpha-based drug in a patient with a known allergy to a sulpha-based drug is not absolutely contraindicated eg. bactrim, sulphonylureas.
5. **Adverse reactions** that mimic drug allergy
 - (a) *side-effects* eg. erythromycin induced diarrhoea, clindamycin induced pseudomembranous colitis, non-steroidal anti-inflammatory drug (NSAID) induced gastritis.
 - (b) *idiosyncratic reactions* eg.
 - (i) NSAIDs – leukotriene synthesis → urticaria and angioedema
 - (ii) opiates, radiocontrast media, vancomycin – direct mast cell histamine release → urticaria, angioedema
 - (iii) ACE inhibitors – release of kinins → angioedema
 - (v) ampicillin rash during infectious mononucleosis.
 - (iv) carbimazole induced agranulocytosis
 - (v) isoniazid induced hepatitis.

There has been much misconception about cross-reactivities between cephalosporins and penicillins. If the reaction is a maculopapular rash, the rate of cross-reactivity is unknown – it is probably very low. It is when the reaction is urticaria or anaphylaxis that the cross-reaction is up to 10% for 1st generation cephalosporins (case reports dealt only with cephalothin and cephaloridine). For newer generation cephalosporins, the risk is much lower. Skin prick tests to the cephalosporins have been reported but the sensitivity and specificity have not been studied.

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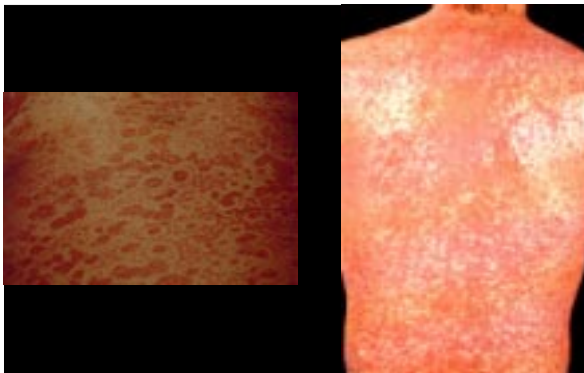


(c) *viral exanthem*

(d) *coincidental reaction* viz. a reaction that occurs at the time a drug is prescribed, but not related to that drug eg. a patient with gonococcal meningitis could have purpura, but these are due to the bacterial infection and not the penicillin used in the treatment

(e) *contact dermatitis* from topical medicaments: these may or may not be allergic.

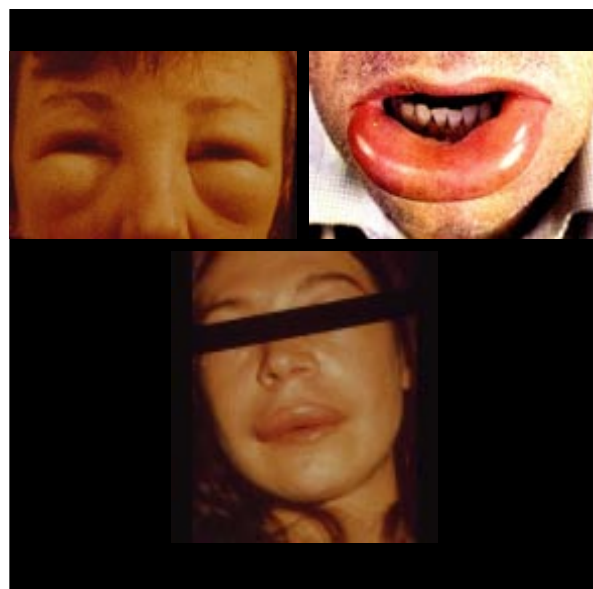
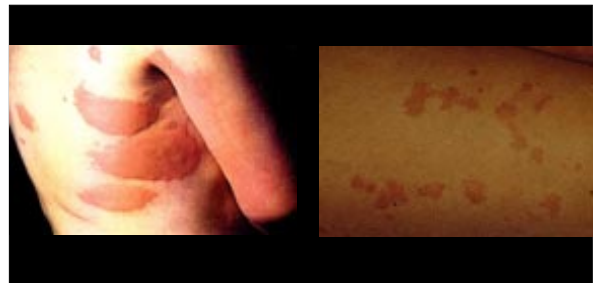
6. **“Multiple drug allergies”**: a stereotypic reaction to many drugs of different classes usually does not mean that the patient has many drug allergies. Look for an underlying skin condition eg. pustular psoriasis, eczema, recurrent idiopathic urticaria.



7. **Incorrect label of drug allergy**: if a patient is labelled as allergic to a certain medication and subsequently receives that medicine without adverse reaction, then he is not allergic to it.

8. **Desensitisation**

This is a method of making a patient tolerant to a drug that he/she previously developed an allergic reaction to, where there are no reasonable alternatives (eg. cotrimoxazole (Bactrim) in *Pneumocystis carinii* pneumonia, PCP). If the diagnosis is not verified, the allergist will determine if the suspicion of allergy is correct by history, skin test and even oral challenge before desensitization.



It is contraindicated if the allergic reaction was a dangerous reaction like SJS or TEN. However, anaphylaxis is NOT a contraindication.

Patients are given progressively larger doses of medication according to a schedule. Tolerance can be breached if doses are missed. After desensitization, the drug must be taken daily. Return of clinical sensitivity can occur within 24-48 hours of cessation of the drug.

Patients are still considered to be allergic to the drug

Two methods of desensitization are available. Rapid desensitization for IgE mediated reactions eg. anaphylaxis due to penicillin; and slow desensitization for patients with maculopapular rashes eg. cotrimoxazole desensitization for HIV patients requiring prophylaxis PCP, and allopurinol desensitization in tophaceous gout.

THE PRIMARY CARE APPROACH TO DRUG ALLERGY

1. HISTORY

a. Presenting complaint

- i. Cutaneous symptoms: onset, distribution and morphology
 - (a) wheal ("mosquito bite like reaction") suggests immediate hypersensitivity
 - (b) diffused red itchy rashes (maculopapular – suggests delayed hypersensitivity)
 - (d) blistering rash (bullous)
 - (e) purplish rash that recurs in the same spot each time drug is taken (fixed drug eruption)
 - (e) targetoid rash (erythema multiforme/ Stevens Johnson syndrome (SJS))

- (f) generalised red rash/ redness with peeling of the skin (generalised exfoliative dermatitis (GED))
- (h) peeling of the skin similar to a burn (toxic epidermal necrolysis (TEN))
- ii. Systemic symptoms
 - (a) fever
 - (b) pruritus
 - (c) lymphadenopathy
 - (d) mucosal involvement – oral, conjunctival, genital
 - (e) angioedema, syncope
 - (f) respiratory – dysphonia, nasal congestion, dyspnoea, wheeze
 - (g) gastrointestinal – abdominal pain, diarrhoea, vomiting

** A guide to the history of a previous severe reaction would be whether the patient needed hospitalisation, skin care, antibiotics and for how long.*

b. Drug History

- i. Temporal relationship of rash/systemic symptoms to drug use:
 - (a) date prescribed¹ date consumption started
 - (b) date started and stopped
 - (c) number of doses actually taken
- ii. Concomitant medications
 - (a) dates started/ stopped
 - (b) over-the-counter medications
 - (c) traditional Chinese medications, TCM (esp. pills and syrups)
 - (d) from all other sources (eg. other family physicians, polyclinics, hospitals)
- iii. Indications for medication given:
 - (a) rash/ systemic symptoms may be due to the underlying medical condition

rather than the drug eg. viral exanthem with cervical lymphadenopathy and hepatitis, cellulitis

- (b) rash/ systemic symptoms may have been precipitated by underlying condition eg. ampicillin induced maculopapular rash in infectious mononucleosis

c. Medical history

- i. Provides clue to the type of medication given (especially if patient did not bring the “culprit” drugs or has discarded the “culprit drugs”) eg.
 - (a) hyperuricemia treated with allopurinol
 - (b) headache treated with NSAID
 - (c) recent fit treated with phenytoin
- ii. Provides clue to failure of response to treatment of drug allergy eg. persistent hypotension, bradycardia from b-blockers in the treatment of anaphylaxis.

2. PHYSICAL EXAMINATION

- a. Airway (Type I hypersensitivity)
 - tachypnoea, stridor, rhonchi
- b. Breathing (Type I hypersensitivity)
 - tachypnoea, stridor, rhonchi
- c. Circulation: signs of anaphylactic shock (Type I hypersensitivity)
 - hypotension, tachycardia, flushing, generalised erythema
- d. Cutaneous
 - urticaria, angioedema
 - maculopapular rash
 - erythema multiforme
 - fixed drug eruption
 - eczema
 - cutaneous vasculitis
 - generalized exfoliative dermatitis (GED)

– toxic epidermal necrolysis (TEN)

e. Systemic

- signs of hypersensitivity syndrome
- fever
- lymphadenopathy
- hepatosplenomegaly
- signs of Steven’s Johnson syndrome (SJS)
- oral, genital mucosa
- conjunctivae

3. INVESTIGATIONS

Principle: These must be used together with the history of the reaction.

a. Skin testing

– Indication:

Prick and intradermal tests for diagnosing type I hypersensitivity reactions (urticaria, angioedema, anaphylaxis), done 6 weeks after the drug reaction.

– Advantages:

- i. most specific
- ii. convenient
- iii. least expensive

– Medical contraindications:

- i. inability to discontinue medications that interfere with skin testing eg. antihistamines
- ii. severe uncontrolled atopic dermatitis or generalized skin disorder
- iii. severe dermatographism
- iv. history of life-threatening anaphylaxis to particular antigens where alternative in-vitro tests may be safer.

– Limitations:

- i. see medical contraindications for skin testing above.

- ii. limited application (only penicillin allergy can be reliably tested)
- iii. negative results if the tests are carried out too early or too late.

– Positive test:

3 mm wheal/ 5 mm erythema in the presence of a positive histamine control and a negative saline control, implies presence of drug-specific IgE.

b. In-vitro testing

– Indication:

RAST (radioallergosorbent test) for drug specific-IgE, done 6 weeks after the reaction for diagnosing Type I hypersensitivity reactions

– Advantages:

where there are medical contraindications for skin testing

– Limitations:

- i. less sensitive compared to skin tests
- ii. limited published information on the applicability of results

– Test result:

reported as Class 0-VI (negative to positive) for drug-specific IgE levels.

c. Oral graded drug challenge

– Indication:

To exclude rather than to prove an allergic drug reaction



– Method:

- i. Giving the patient fractions of the target dose of the drug at known intervals and watching for recurrence of the suspected reaction. The challenge is supervised by an allergist and the Allergy nurse clinician and stopped when a positive reaction develops. Each challenge takes an average of 2-3 hours
- ii. Double-blind placebo-controlled drug challenge for vague or subjective reactions to drugs.

– Limitations:

- i. labour and time intensive: expensive
- ii. possible risk to patient.

– Contraindications:

Systemic drug allergy ie. anaphylaxis, mucocutaneous bullous skin disease/ SJS, drug hypersensitivity syndrome, TEN, vasculitis.

d. Basic laboratory tests

- Indication: severe drug allergy (drug hypersensitivity syndrome, SJS, TEN) to assess extent of organ involvement
- i. full blood count – for haemolytic anaemia, leukocytosis and eosinophilia
 - ii. serum creatinine – for acute renal failure
 - iii. urine microscopy – for glomerulonephritis
 - iv. liver function tests – for hepatitis/ cholestasis.

** Other tests like lymphocyte proliferation tests (for type IV hypersensitivity) are not routine techniques.*

4. MANAGEMENT

a. Immediate management

- i. Stop the culprit drug(s)
- ii. Resuscitation in type I hypersensitivity
 - (a) Airway
 - (b) Breathing
 - (c) Circulation
 - (d) Drugs (S/C EPINEPHRINE, I/V BENADRYL OR PROMETHAZINE)
- iii. Intravenous corticosteroids are not required in a type I hypersensitivity reaction but should be given in a drug hypersensitivity reaction (type IV) especially with major organ involvement eg. severe skin inflammation, hepatitis and acute renal failure.

b. Further management

- i. Oral antihistamines (chlorpheniramine 4 mg tid, hydroxyzine 25 mg tid)
- ii. For all suspected drug allergies, notify the Health Sciences Authority (HSA) Pharmacovigilance Unit
- iii. If the drug allergy is definite and the identity of the drug is definite, Medik Awas card application (passport size photograph with \$15 registration fee)
- iv. Inform patient of potentially cross-reacting drugs which should be avoided.

c. Disposition

- i. Inpatient treatment: refer to hospital emergency department if there is/are:
 - (a) angioedema or anaphylaxis
 - (b) rapid progression of a generalized maculopapular rash/ erythema multiforme to a drug hypersensitivity syndrome/ SJS/ TEN

- (c) bullous drug eruptions
 - (d) possibly more than 1 implicated drug (especially in patients with multiple medical problems on concurrent drugs where it is difficult to decide which to stop) for:
 - κ further resuscitation and/or observation
 - κ intravenous corticosteroids or venoglobulin (for TEN)
 - κ skin care
 - κ referral to an allergist (see iii).
- ii. Outpatient treatment (by the family physician)
- (a) urticaria or maculopapular rash which is not progressively worsening
 - (b) fixed drug eruption
 - (c) drug allergy without systemic symptoms
- iii. Outpatient referral (to an allergist)
- (a) uncertain whether the reaction was a drug allergy
 - (b) uncertain which drug was responsible: need for re-evaluation and testing
 - (c) treatment of a serious drug reaction
 - (d) need to use a drug the patient was previously labelled to be allergic to as there are no alternatives: desensitization.

REFERENCES

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3. Bernstein IL, Gruchalla RS, Lee RE, Nicklas RA. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999; 83 Pt 3: 665-700.