CHAPTER 24
DRUG ALLERGIES

24.1 DRUG ALLERGIES
T88.7

DESCRIPTION
Drug allergy is an immune-mediated reaction to the drug. Reactions are idiosyncratic and, unlike side effects, cannot be predicted by physiological action of the pharmaceutical agent. Common drugs involved include penicillin, sulphonamides, non-steroidal anti-inflammatory drugs, anticonvulsants, and chemotherapeutic agents.

CLASSIFICATION
Drug hypersensitivity reactions are simply classified as:
» immediate (≤ 1 hour after exposure): anaphylaxis, urticaria, angioedema; or
» delayed (≥ 6 hours): often involving rash with or without systemic symptoms.

DIAGNOSIS
Drug allergies are diagnosed clinically, based on symptoms and signs, and their timing relative to drug exposure, as well as exclusion of other potential causes.

In the acute setting, laboratory tests help to confirm the diagnosis and to determine the extent of systemic involvement (e.g. eosinophil counts, liver or renal function tests).

Tryptase measurement
An elevated serum tryptase concentration can help to confirm the diagnosis of anaphylaxis in cases where this is in doubt, but normal measurements do not necessarily exclude it. Serial tryptase measurements are the most helpful, with sampling at 1–2 hours, 4–6 hours, and 24 hours after the start of the reaction.

No serum biomarkers are currently available to identify delayed hypersensitivity reactions.

Specific diagnostic testing to identify the causative drug
Do tests to confirm the causative drug only if the benefit to the patient outweighs the risk, and only in consultation with a specialist.
» Skin tests: Includes subcutaneous skin prick tests, intradermal tests, and patch tests:

- > Should be performed in specialised units. Safety equipment is required as significant reactions can occur.
- > Have variable sensitivity and specificity depending on the drug.

» Serum specific IgE against the suspected drug:
- > Available for a few drugs only.
- > The majority have low sensitivity but high specificity.

» Cellular antigen stimulation tests for selected drugs:
- > Useful for non-IgE mediated reactions.
- > Either measures basophil activation markers (via flow cytometry) or sulpholeukotrienes (via ELISA).

Drug provocation testing

» Is the gold standard to identify the causative drug and is often required for a number of drugs due to the limited diagnostic accuracy of *in vitro* and *in vivo* testing.

» Perform only in specialised units. Safety equipment must be available as they can provoke significant reactions.

24.2 IMMEDIATE HYPERSENSITIVITY REACTIONS

24.2.1 DRUG RELATED ANAPHYLAXIS

T88.6

See Chapter 1: Emergencies and Trauma, section 1.1.3: Anaphylaxis/ anaphylactic reactions.

24.2.2 DRUG RELATED URTICARIA

L50.9

See Chapter 5: Dermatology, section 5.3.7: Urticaria.

24.2.3 DRUG RELATED ANGIOEDEMA

T78.3

DESCRIPTION

Local swelling of skin and/or mucosal tissue. May occur in isolation or together with urticaria or anaphylaxis. It must be distinguished from recurrent non-pruritic angioedema which has a hereditary component and does not respond to the treatment below. Complement C4 and C1 esterase inhibitor levels are used to help to distinguish the two entities.

GENERAL AND SUPPORTIVE MEASURES

» Stop potentially causative drug(s).

» Monitor the airway closely and intubate early if necessary.

MEDICINE TREATMENT

If symptoms and signs of anaphylaxis: treat as for anaphylaxis, see Chapter 1: Emergencies and Trauma, section 1.1.3: Anaphylaxis /anaphylactic reactions.

If angioedema in isolation:

- Chlorphenamine, oral, 0.1 mg/kg/dose 6 hourly.

AND

- Prednisone, oral, 1–2 mg/kg daily for 1 week.

OR

If unable to take orally and ≥ 2 years:

- Promethazine, IM, 0.5 mg/kg immediately, followed by above oral therapy.

LoE III[1]

REFERRAL

» All cases after stabilisation for confirmation of diagnosis and long-term management.
» Recurrent non-pruritic angioedema.

24.3 DELAYED HYPERSENSITIVITY REACTIONS

See Chapter 5: Dermatology, sections 5.2.1: Erythema multiforme, 5.2.2: Stevens-Johnson syndrome, and 5.3.1: Drug reactions.

DESCRIPTION

Broad spectrum of clinical manifestations involving different organs, including liver, kidneys and skin. Cutaneous reactions are most prevalent and range from maculopapular or morbilliform rashes (most common presentation), to life-threatening cutaneous reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Common drugs associated are antiretrovirals (efavirenz or nevirapine), anticonvulsants, anti-tuberculous therapy, penicillins and co-trimoxazole.

GENERAL AND SUPPORTIVE MEASURES

Stop the suspected causative medicine(s) immediately. Use an alternative class of agent if required.
If there are compelling reasons to continue with the suspected medicine, seek expert advice.

Severe cutaneous reactions will usually require admission and intensive supportive therapies. See Chapter 5: Dermatology, sections 5.2.1: Erythema Multiforme and 5.2.2: Stevens-Johnson syndrome.

MEDICINE TREATMENT

Mild reactions without systemic or mucosal involvement may be treated symptomatically:

- Chlorphenamine, oral, 0.1 mg/kg/dose 6 hourly.

If child is asthmatic, see Chapter 15: Respiratory System, section 15.4: Conditions with predominant wheeze.

REFERRAL

» SJS/TEN for management in a specialist centre with experience or a unit familiar with managing burns.

24.4 SPECIFIC ALLERGIES

24.4.1 ALLERGIES TO PENICILLINS

Z88.0

DESCRIPTION

Patients may present with immediate (e.g. anaphylaxis, bronchospasm, angioedema) or delayed reactions (most commonly maculopapular rash without systemic involvement; rarely SJS/TEN or other systemic reactions).

GENERAL AND SUPPORTIVE MEASURES

Stop penicillin.

MEDICINE TREATMENT

If an antibiotic is still required, treat with a suitable alternative antibiotic class according to the condition.

Milder infections

E.g. upper respiratory tract infections:

- Azithromycin, oral, 10 mg/kg/day for 3 days.

OR

E.g. impetigo, mild cellulitis:

- Clindamycin, oral, 6 mg/kg/dose 6 hourly for 3 days.

Severe infections e.g. osteomyelitis, pneumonia:

- Third generation cephalosporin, provided there is no history of immediate hypersensitivity (see below, cross-reactivity of other β-lactams).

Alternative antibiotics for gram-positive infections:

- Clindamycin, oral, 6 mg/kg/dose 6 hourly.

OR

- Vancomycin, IV, 15 mg/kg 8 hourly.

Urinary tract infection

- Neonates: Ciprofloxacin, oral, 6 mg/kg/dose 12 hourly.
- Infants: Ciprofloxacin, oral, 6 mg/kg/dose 8 hourly.
- > 1 year of age: Ciprofloxacin, oral, 10 mg/kg/dose 12 hourly.

Prophylaxis in rheumatic heart disease or post splenectomy, consider**:**

- Macrolide, e.g.
  - < 11 years: Azithromycin, oral, 10 mg/kg/day, 3 times weekly.
  - ≥ 11 years: Azithromycin, oral 250 mg daily.

LoEIII[2]

Cross-reactivity of other β-lactams in patients with penicillin allergy

The risk of cross-reactivity to cephalosporins in penicillin allergic patients is low. Consequently, only avoid oral cephalosporins in patients with a history of anaphylaxis to penicillin.

In hospitalised patients, and in those with mild reactions such as rash to aminopenicillin, cephalosporins should not be avoided if indicated for infection. If concerned, discuss with expert and/or consider a test dose.

Risk of cross-reactivity is very low with carbapenems, and these agents can be used without allergy assessment in penicillin allergic patients.

If no alternative antibiotic is available, consider desensitisation after consultation with a specialist. Desensitisation to be done by a specialist, in a tertiary facility.

REFERRAL

» In cases where desensitisation is considered.
» Consult a specialist for alternative antibiotics in all patients with severe, immediate reactions.

24.4.2 ALLERGIES TO SULPHONAMIDES

Z88.2

DESCRIPTION

The commonest sulphonamide allergies are related to co-trimoxazole, especially when used in HIV-infected patients for *P. jirovecii* treatment and/or prophylaxis.

Patients may present with:

» a morbilliform or maculopapular rash only, usually within a few days of starting treatment (most common presentation),
» a rash with fever, which may progress to,
» a drug-induced rash with eosinophilia and systemic symptoms (DRESS) usually with hepatitis (usually within 1–2 weeks of treatment commencement),

» SJS/TEN, or
» an immediate hypersensitivity reaction (rare).

GENERAL AND SUPPORTIVE MEASURES

Stop the sulphonamide-containing drug. Severe cutaneous drug reactions with or without organ involvement require admission and specialist review to optimise supportive management. See Chapter 5: Dermatology, section 5.2.2: SJS/TEN.

MEDICINE TREATMENT

Options for HIV-infected patients requiring treatment for *P. jirovecii* pneumonia with a history of a mild reaction, e.g. rash to prior co-trimoxazole exposure.

P. jirovecii pneumonia treatment:

» There is no clear alternative recommendation to co-trimoxazole in this setting and thus a general alternative recommendation cannot be made. In these cases, management will need to be carefully considered with a specialist.

P. jirovecii pneumonia prophylaxis:

- Dapsone, oral, 2 mg/kg daily.
  - Maximum dose: 100 mg (1 tablet) daily.
  - **Note**: Dapsone is a sulphone, not a sulphonamide; but there are cases of cross-reactivity with sulphonamide allergy, however, reactions are usually mild. Avoid dapsone if there is a history of anaphylaxis, SJS/TEN, or rash with systemic involvement.

If no alternative antibiotic is available, consider desensitisation after consultation with a specialist. Desensitisation to be done by a specialist in a tertiary facility.

REFERRAL

» In cases where desensitisation is considered. Consult a specialist.
» For alternative antibiotics in all patients with severe immediate reactions.

References

[1] Promethazine: South African Medicines Formulary. 11th Edition. Division of Clinical Pharmacology. University of Cape Town. 2014.
[2] Azithromycin: Gerber MA, Baltimore RS, Eaton, CB, Gewitz M, Rowley AH, Shulman ST, Taubert KA. Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis. Circulation. 2009; 119:1541-1551.