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Exanthems and drug reactions

Background

Drug reactions are a common cause of rashes and can vary from brief, mildly annoying, self limiting rashes to severe conditions involving multiple organ systems.

Objective

This article outlines an approach to exanthems that may be related to drug reactions and details appropriate management.

Discussion

Rashes related to drug reactions are both nonallergic and allergic. Nonallergic rashes are usually predictable and may be avoidable. Allergic rashes include morbilliform erythema, urticaria and angioedema, erythema multiforme and vasculitic rashes. The vast majority of cases are rapidly resolving and self limiting once the offending agent is removed. Early recognition and supportive measures are the keys to care in the majority of cases. However, an awareness of serious drug reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis), which are potentially life threatening conditions and require immediate specialist assessment and treatment in hospital, is important.

Keywords: drug toxicity; drug eruptions; exanthema



'Well, Mr Jones, I think we should put you on this tablet to fix this problem. Now, the things you need to look out for are any rashes...'

How often in general practice do you hear yourself offering this advice? Why do almost all drugs list rash as a side effect? How do they occur and what can you do to recognise and manage them?

The skin is the largest organ of the body and, from a diagnostic viewpoint, we can see it change to various stimuli. Medications are commonly used and are integral to the general practitioner's armamentarium for treating most ills. However, it is also important to note that increasing access to medications by consumers through other health professionals (eg. naturopaths) and the self prescribed use of over-the-counter, complementary and alternative medicines should be remembered in the history taking of a patient presenting with rash.

Exact incidences of rash vary from compound to compound, but it is likely that 1–10% of medication reports are for rash.¹ This may be an underestimation of overall incidence, as most commonly used drugs have adverse skin reaction rates of more than 1%.²

Drug reaction rashes range from mild, short lived localised rashes of mild nuisance value to severe life threatening occurrences that are fulminant and include multiple organ systems in their progression.

What causes the rash?

Broadly, the drug reaction causing the rash can be thought of as nonallergic or allergic in origin.

Nonallergic rashes

There are several mechanisms to nonallergic rashes:

- idiosyncratic
- associated with a property of the drug (eg. silver grey pigmented deposition rash caused by minocycline or striae caused by corticosteroid use)
- toxic reaction of the drug (eg. mouth ulcers due to cytotoxic use)
- exacerbation of pre-existing or latent skin disease (eg. psoriatic worsening with beta blockers or angiotensin converting enzyme inhibitors [ACEIs])



- as part of their therapeutic action (eg. dapsone and rifampicin cause erythematous granulomas as they stimulate the body's immune attack on mycobacteria infections, such as in leprosy). Most of these skin reactions are reported before a drug is released on the market and should be known to GPs. Therefore, as these nonallergic rashes are predictable, patients should be warned of the side effects of both prescribed and nonprescribed medications.

Allergic rashes

Allergic rashes are unpredictable and are due to an individual's immune response to a particular drug, its metabolites or the complexes it makes within the body.

The reaction may be immediate or slow, depending on past exposures, and may require only small quantities of the drug to have a profound effect. There may also be a familial component.³

Types of allergic rashes

- Urticaria and angioedema
- Erythema multiforme
- Morbilliform erythema
- Vasculitic.

Rarely, the most severe presentations can occur due to allergic processes with bullous skin eruptions, erythroderma, toxic epidermolysis and Stevens-Johnson syndrome.

Other allergic manifestations may present with rashes, such as anaphylaxis, and need to be treated promptly (see *Resources*).⁴

What do they look like?

Drug reaction rashes may present as:

- exanthematous
- urticarial
- blistering
- vasculitic, or
- pustular.

Exanthematous rashes

Exanthematous rashes are the most common, accounting for about 95% of drug reaction rashes.⁵ Many are mild, but they can also be generalised.

The rash is either morbilliform or macropapular in nature, and is usually red and nearly always itchy (*Figure 1*).

The rash usually starts about 1 week after commencing the medication, initially appearing on the trunk and spreading peripherally. It may affect the face, palms of the hands and soles of the feet. The rash may become confluent red and radiate heat. Many patients find the itch difficult, and excoriation and full thickness skin loss can occur.

Common causative agents of exanthematous rashes are listed in *Table 1*.

Exanthematous rash from particular drugs

Specific mention needs to be made regarding the use of certain



Figure 1. Exanthematous rash

Table 1. Drugs causing exanthems¹⁰

Most common	Less common
Penicillins	Cephalosporins (note ~10% cross reaction with penicillin allergy)
Sulphonamides	Thiazides
Phenytoin	Nonsteroidal anti-inflammatory drugs (NSAIDs)
Carbamazepine	Phenothiazines
Gold	Quinidine
Gentamicin	Atropine

drugs. For instance, using amoxicillin in patients with infectious mononucleosis increases the risk of rash from ~3% to ~60%⁶ and sulfonamides used in HIV positive individuals have similar problems with rash.²

Exanthematous rashes spontaneously resolve with the cessation of the precipitant, usually 2–3 weeks later.

Rechallenge usually provokes a further episode of rash and may occur more quickly than previously. Rechallenge is usually best avoided, but can occur in unplanned ways (eg. the prescriber being unaware of any previous reactions), or less commonly in planned ways when there is uncertainty about the causative drug and the drug is potentially therapeutically important.

Urticaria

In urticaria, lesions are red-pink with a haphazard distribution and size. They may become large and confluent and have a surrounding pale or red halo. Lesions fluctuate and are itchy. Blistering can also appear (*Figure 2*).

Erythema multiforme

These lesions appear to be target-like and appear most commonly on the palms of the hands, forearms, feet, and lower limbs; they are rare



Figure 2. Urticaria



Figure 3. Erythema multiforme

on the trunk. Lesions are usually 1–3 cm in diameter and may occur on the lips and mouth (Figure 3).

The most serious potential drug reactions relating to the skin are Stevens-Johnson syndrome and toxic epidermal necrolysis (skin bullae and detachment with minimal trauma). These are potentially life threatening conditions and require immediate specialist assessment and treatment in hospital.

Features of Stevens-Johnson syndrome are:

- fever and marked constitutional symptoms
- widespread rash and purpura
- mucosal membrane involvement
- skin breakdown
- internal organ involvement – pulmonary, gastrointestinal, central nervous system and renal
- fluid imbalance and sepsis.

Clinical features of Stevens-Johnson syndrome are shown in Figure 4a, b.

Rashes from complementary and alternative medicines

It is important to also consider complementary and alternative medications that can cause a range of skin reactions. The most common causes of skin reactions noted in an adverse drug reactions reporting system in Sweden were purple coneflower (*Echinacea purpurea*), purple coneflower and siberian ginseng (*Eleutherococcus senticosus*), malabar nut (*Alhatoda vasica*), ginkgo leaf (*Ginkgo biloba*), and tea tree oil (*Melaleuca alternifolia*). However, a wide range of substances were reported to be the cause of rashes of varying types.⁷

Diagnosis

A diagnosis is usually clinical in nature. Rarely the diagnosis may be confirmed via histological features, particularly in the case of a fixed drug reaction.

A thorough clinical history of the rash, preceding illnesses, previous rashes, the evolution of the rash, systemic symptoms and the timeline of recent medications (prescribed and nonprescribed) and other drugs is essential.

Typically the rash starts about 1 week after commencement of the drug. However, it may be also be immediate or take several weeks into treatment before appearing.⁸ Potential warning symptoms are listed in Table 2.

Eosinophilia and other organ involvement may be found if a blood test is ordered, particularly in more severe cases.

Treatment

If the rash appears to be drug related in origin – cease the medication where possible. Seek specialist advice if it is imperative that the medication is continued.

Supportive symptom relief measures are the mainstay of therapy

Antihistamines, either nonsedating or sedating, are helpful. Both sedating and nonsedating antihistamines have similar efficacy,⁹ so the choice of which to use depends on whether the side effect of sedation will be helpful (eg. at night).

Simple skin cooling techniques (cool compresses or bathes) and cool ambient temperatures may relieve the associated itch.

Moisturising emollients, such as sorbolene (kept in the refrigerator), may provide good relief and reduce the dry, flaky scale that can occur with skin healing.



Figure 4. Clinical features of Stevens-Johnson syndrome

Table 2. Features warning of a potential severe drug reaction¹⁰

Systemic

- Fever +/- internal organ involvement (pharyngitis, malaise, cough, arthralgia, meningism)
- Lymphadenopathy

Skin

- Generalised rash worsening
- Facial oedema or swelling
- Mucous membrane involvement, especially if erosive or eyes
- Skin tenderness, blistering or skin loss
- Purpura



Topical steroids for a period of 1–2 weeks can assist in more severe cases, however this is not routine. In very severe cases there may be a role for a short course of oral steroids.¹⁰

Reporting reactions

Reporting drug reactions is necessary to allow monitoring of medication safety. Reporting can be made through the Australian Adverse Drug Reaction Reporting System, which is part of the Therapeutic Goods Administration (see *Resources*). In serious reactions, it is important to ensure that the patient carries a medical alert and is aware of the need to report the reaction to their GP or other health professional before taking other medications.

Summary

Drug reaction rashes are here to stay. Fortunately the vast majority of cases are rapidly resolving and self limiting once the offending agent is removed. Early recognition and supportive measures are the keys to care in the majority of cases.

Resources

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- The Australian Society of Clinical Immunology and Allergy: www.allergy.org.au/content/view/10/3
- Dermnet: <http://dermnetnz.org>
- Therapeutic Good Administration: www.tga.gov.au/hp/problem-medicine.htm

Further reading

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