

Drug allergy

Adverse drug reactions are a major cause of morbidity, complicating over 5% of therapeutic drug courses. The majority of these events are due to common predictable mechanisms linked to the way the drug works, but about 5% of all reactions are immune-mediated and constitute true allergy. Drug allergy is one of the potential causes of anaphylaxis, angioedema and urticaria and should always be considered when a patient presents with one of these conditions.

The GP curriculum and drug allergy

Drug allergy is not covered in any single curriculum statement but is relevant to several statements, particularly:

- **Curriculum statement 3.2: Patient safety: awareness** of the causes and management of drug allergy are highly relevant to patient safety given that 1.5 million prescriptions are dispensed daily and inevitably some result in a patient safety incident
- **Curriculum statement 7: Care of acutely ill patients** requires GPs to be able to recognize and manage acute adverse drug reactions, including anaphylaxis in the surgery, patient's home or elsewhere
- **Curriculum statement 5: Healthy people** require GPs to demonstrate an understanding of the concept of risk and to be able to communicate risk and also promote health on an individual basis. Prescribing practice may minimize the risk of drug allergy, which links also to 'the principles of prevention and preventive strategies'

Presentation

Drug allergy may present in the primary care consultation in the acute phase, it may be reported by the patient as a recent or previous event or it may be documented in the clinical record. The diagnosis and management of drug allergy are not easy as there are few validated tests and even those that exist may not be widely available. The challenges for primary care are the management of the acute presentation, adjustment of the patient's medication to minimize risk and identification of the patients who need referral to a specialist centre for investigation, management advice and possible desensitization if the drug needs to be continued or reinstated.

Indicators of drug allergy

A detailed history of the symptoms and their relationship to ingestion of the medication will help to indicate whether there is a possible allergic link. To be relevant, the drug should have been ingested within a few hours of the onset of the episode or else have a clear and recurrent link to a series of episodes. Drugs that have been taken regularly without adverse reactions are most unlikely to be responsible, with the single notable exception of angiotensin-converting enzyme (ACE) inhibitors. Similarly, drugs that are tolerated on subsequent occasions are unlikely to be responsible.

Terminology

The terms drug allergy and drug reaction are often used interchangeably. 'Drug reaction' encompasses all adverse events related to drug administration irrespective of aetiology. Adverse drug reactions are sometimes categorized into reactions that may affect anyone and those that only affect susceptible individuals (Table 1). Drug allergy is usually restricted to an IgE-mediated or cell-mediated adverse drug reaction. It consists of two phases: the induction of specific immune response on first exposure and elicitation of symptoms on subsequent exposure.

In the UK, adverse drug reactions are monitored by Medicines and Health Care products Regulatory Agency (MHRA) (www.mhra.gov.uk/index.htm). All serious suspected adverse reactions and any suspected adverse reactions to a new drug should be reported by the Yellow Card system. If in doubt, it is preferable to report.

Classification of allergic drug reactions

Immune-mediated drug allergies are classically divided into four types. It is interesting to note that the type of reaction may be detectable from the symptoms and signs. Clinical manifestations of each type of reaction are listed in Table 2.

Table 1. Adverse drug reactions

Non-immunological	Clinical example
Idiosyncratic—these are reactions that cannot be explained by the pharmacological actions of the drug. May be related to individual genetic factors	
Pseudo allergic or anaphylactoid—strong clinical resemblance to Type I hypersensitivity. Caused by mast cell and basophil mediator release but does not involve an IgE mechanism	Urticaria or shock after radiocontrast media. Also occurs with opioids and vancomycin.
Intolerance—lower threshold to the normal pharmacological action of the drug	Tinnitus following small dose of aspirin
Side effects due to pharmacological action	Drowsiness following antihistamine. Hypoglycaemia related to insulin.
Secondary effect of the drug	Vaginal thrush while taking antibiotic
Drug toxicity	Theophylline and anticonvulsants
Drug overdose	Deliberate or accidental
Drug–drug interactions	Reduced oral contraception owing to enzyme induction with barbiturates, phenytoin, carbamazepine, rifampicin and St John's Wort
Drug–disease interactions	Rash after ampicillin or amoxicillin in infectious mononucleosis

Table 2. Allergic drug reactions, their mechanisms and manifestations

Type of reaction*	Mechanism	Clinical manifestation
I	IgE dependent	Anaphylaxis, urticaria, angio-oedema and bronchospasm
II	Complement-mediated toxicity	Cytopenia eg anaemia, neutropenia and thrombocytopenia
III	Immune complex deposition	Vasculitis, nephritis and serum sickness
IV	Delayed type hypersensitivity (several distinct forms are now recognized involving monocytes, eosinophils, cytotoxic T cells and neutrophils. See Pichler, 2004 for details)	Contact dermatitis, maculopapular and bullous rashes

* Based on the classification of Gell and Coombs.

Examination

In adverse drug reactions, the skin is most often the affected organ, so inspection of the skin is always indicated. The cutaneous manifestations are many, including urticaria, papular, vesicular or bullous lesions, purpura and exfoliative dermatitis. Careful recording of the lesions and distribution are important because this can provide clues to the underlying mechanism. For example, urticaria is associated with IgE-mediated Type I reactions, while maculopapular lesions on fingers, toes and soles of feet are more common in Type 3 hypersensitivity reactions (e.g. serum sickness).

Photographic documentation of the patient's rash can help with diagnosis and downstream referral.

People at greater risk of drug hypersensitivity reactions

Allergic drug reactions are more common in adults than children and more common in females than males. Obviously, the most important risk factor is a history of previous

hypersensitivity reaction to the drug. A previous reaction to a chemically related drug also increases the risk as does a concomitant viral infection. Other associated characteristics are human immunodeficiency virus (HIV) infection and systemic lupus erythematosus (SLE). Patients with atopic allergy (hayfever, asthma, etc.) do not have a higher rate of sensitization to drugs; however, they appear to be at risk of serious allergic reaction once an IgE response has developed.

SLE and HIV infection are also risk factors for general (non-immune) drug reactions. Other associated factors are serious illness, polypharmacy, alcoholism and renal and liver disease (due to altered metabolism).

Testing for drug allergy

Testing for drug allergy has no place in general practice given the risk and the complexities of diagnosis. For penicillins, specific tests for IgE-related reactions (urticaria and angio-oedema) exist but there are no tests for cell-mediated responses (maculopapular rashes and vasculitis etc). Reliable skin tests can be performed for local and general anaesthetics, including muscle relaxants. Skin prick tests (SPTs) can also be undertaken on an *ad hoc* basis for many other drugs, although the reliability of these SPTs has not necessarily been validated.

Formal challenge tests

When SPT or IgE tests are not available, formal challenge tests (provocation or test dosing) may have to be performed. The drug is administered in a small amount and then increased to the therapeutic dose. The interval between doses depends on the nature of the suspected reaction, so when investigating a possible IgE reaction 30 minute intervals suffice. For a delayed hypersensitivity reaction 24–48 hours would be appropriate. Test dosing is most useful when the likelihood of true allergy is small and should not be attempted if the reported reaction was severe.

Drug discontinuation

Allergen avoidance is an essential component of long-term management of patients with drug hypersensitivity. For the majority of patients, an appropriate alternative medication can be prescribed: for example, a non-beta-lactam antibiotic is acceptable for most diseases in penicillin-allergic patients.

Drug desensitization

Drug discontinuation may be problematic in a minority of situations, e.g. patients on long-term aspirin therapy. In other settings, there may be no realistic alternative (e.g. penicillin for syphilis). In these cases, graded challenge protocols may be appropriate. Desensitization is based on the principle of administering gradually increasing doses of drugs to induce pharmacological tolerance. This requires supervision in a specialist clinic: treatment is initiated with a small dose

(e.g. 0.001% of the therapeutic dose) and this is doubled in subsequent doses until a therapeutic dose is achieved.

Either oral or parenteral routes can be used for desensitization. It is important to remember that the state of tolerance is transient and once achieved must be actively maintained by continuous drug administration. So, if a patient needs the sensitizing drug again, after a gap in administration and their SPT remains positive, desensitization would have to be repeated all over again.

Most common adverse drug reactions in general practice

Penicillin allergy and cephalosporin

When managing patients with a history of penicillin reactions, the clinician needs to be mindful of cross reactivity between penicillin and cephalosporin. For reasons that are not fully understood, the prevalence of cross reactivity has reduced from around 16% to less than 2%. This reduction may in part reflect structural changes in second and subsequent cephalosporin generations. However, even with this very low prevalence of cross reactivity, it is still important to investigate before taking a chance, given the potential risk of an anaphylactic reaction.

Ideally, if a beta-lactam is the best choice antibiotic in penicillin-allergic patients, one would want to know whether patients have had skin tests to penicillin, amoxicillin and the major and minor metabolic products of penicillin. If the SPTs are negative, then the patient can be prescribed cephalosporin with no greater risk than the general public, but a positive SPT would suggest increased risk and cephalosporins should be avoided. Ideally, this should be done well before the need arises, but this requires advance planning.

Aspirin and non-steroidal anti-inflammatory drugs

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) work by blocking cyclooxygenase and inhibiting production of inflammatory prostaglandins from arachidonic acid. Unfortunately, the unused arachidonic acid gets diverted towards production of leukotrienes and if the patient is sensitive to leukotrienes, this can lead to asthma, rhinitis and angioedema.

The problem is a class effect due to the way the drugs work rather than an allergy to aspirin, so it is best described as aspirin intolerance (or NSAID intolerance). There is no laboratory or skin test to prove or disprove NSAID sensitivity. Aspirin challenge should only be undertaken in specialist centres. Most but not all NSAID-sensitive patients can tolerate paracetamol. The new COX-2 inhibitors (e.g. etoricoxib) are safe in virtually all cases and are preferred in situations when aspirin, ibuprofen, naproxen or diclofenac would otherwise be prescribed.

ACE inhibitors

ACE inhibitors are the most common cause of drug-related angioedema, which can begin several years after the ACE inhibitor was first given. The underlying mechanism is inhibition of bradykinin breakdown (a predictable action of all ACE inhibitors). Angioedema occurs when bradykinin is generated and then cannot be inactivated. Consequently, the risk of the reaction is present continuously but the circumstances that will trigger episodes only occur sporadically. Normally, these patients will tolerate an angiotensin receptor antagonist (sartans) which do more or the less the same as ACE inhibitors as regards blood pressure and heart failure treatment.

Radiocontrast media reactions

While the acute phase of a reaction to radiocontrast media is not seen in general practice, this is not an unusual point raised by the patient when future investigations are discussed. When a patient who has previously reacted badly to injection of radiocontrast media needs further investigation involving contrast, the hospital will employ a management protocol to reduce the risk of repetition. This may include use of a non-ionic low osmolar contrast media, ensuring that the patient is well hydrated and pre-dosing with prednisone.

Although it is often said that radiocontrast reactions are more frequent in patients who are sensitive to iodine or seafood, there is no firm evidence to support this.

Neuromuscular blocking agents

Neuromuscular blockers (NMBA) are the most common cause of reactions during general anaesthesia. Other causes include latex, antibiotics, propofol, dextrans and topical cleansing agents. The value of self-reported symptoms is limited and specialist clinics will want access to the medical notes, drug, anaesthetic and nursing charts in order to identify the potential culprit agent. Skin testing is reliable for NMBAs and some antibiotics and in most, but not all, cases it is possible to find an explanation.

Local anaesthetics

Allergy to local anaesthetics is relatively uncommon. Many patients have adverse experiences at the dentist and some experience local swelling or hypotension after procedures performed under local anaesthesia or under epidural/spinal block. On closer inquiry, many of these events seem likely to be vasovagal in nature; others may reflect reactions to latex, antibiotics or cleansing agents. Spinal and epidural anaesthesia may affect the autonomic nervous system. In all cases, careful assessment is required. This is usually best done in cold blood at a specialist clinic rather than waiting until there is an urgent need to do something under local anaesthesia.

Opioids

Mast cells have surface receptors for opioids. Indeed, this is so consistent that codeine can be used as a positive control for skin testing. Some patients are undoubtedly more sensitive than others to opioids. In most cases, they will be

less affected by synthetic or semi-synthetic opioids so pethidine and alfentanil may be tolerated even if morphine and diamorphine cause rashes. As in all prescribing, the need for the drug needs to be reviewed before deciding whether there is a suitable alternative or whether specialist advice is needed.

Documentation in the clinical record

When a diagnosis of adverse event or drug allergy has been made, it is essential to document this fully in the medical record. This should specify both which drug, and drug class, is a problem and the nature of the adverse effect. The certainty of the diagnosis and suggested substitute medications should also be listed. Patients who have adverse effects due to drug toxicity, intolerance or side effects should not be labelled as 'drug allergic'. Instead, their medical record should reflect the nature of the problem and the patient should be educated that this does not represent a drug allergy. Making this distinction is important as these effects are unlikely to be reproducible on re-administration and do not represent a serious health risk. Blanket labelling of all adverse drug reactions as drug allergy and subsequent avoidance of these medications may cause inappropriate anxiety and lead to unnecessary expensive prescribing decisions.

Patient education

Advise patients that they should always inform clinicians caring for them of all drug allergies. The diagnosing clinician should provide written details of which drug(s) to avoid. Patients also need to be reminded how important their role is in avoiding the culprit drugs: they must check with pharmacists when filling prescriptions and also when buying over-the-counter medications. They should not purchase medications in which constituents are unclear.

Recommend that patients with a history of drug-induced anaphylaxis wear an engraved allergy bracelet or tag, especially those with allergy to drugs likely to be administered intravenously in an emergency situation, e.g. opioids, muscle relaxants and penicillin, or where the drug is available without a prescription. For the fashion conscious patient unenthusiastic about a metal tag, there is now a wide variety of alternative styles of engraved jewellery available from Medic Alert. There are also schemes that offer these free or at a reduced price for those patients that cannot afford the full purchase price. Self-administered adrenalin auto injectors are rarely indicated for drug allergy.

A patient leaflet about adverse reactions to drugs is available from Allergy UK [www.allergyuk.org/fs_drugs.aspx]. Useful parental information is located on the Royal College of Paediatrics and Child Health website [www.rcpch.ac.uk/allergy].

When to refer for specialist advice

Investigation of drug allergy should be conducted in specialist centres. The information required when referring a patient with suspected drug allergy is shown in Box 1. The patients for whom referral is indicated include those:

- Who have had a serious adverse reaction (e.g. anaphylaxis or requiring hospitalization)
- In whom an allergic reaction occurred when given multiple drugs, e.g. under anaesthetic
- Who fail to respond to initial management plan, e.g. symptoms persist after removal of the medication suspected to be responsible
- Where confirmation of diagnosis is required because there are no suitable alternatives

Drug allergy in children

Drug allergy is more common in young adults than infants. However, an increasing number of children are receiving a label of drug allergy, particularly allergy to antibiotics. The allergy is rarely confirmed, but the drug is discontinued and alternative treatments are prescribed as needed. The requirement for alternative prescribing could be challenged as 94% of children with a history suggestive of allergy are

able to tolerate the drug after further testing (SPT, intra-dermal testing or oral challenge). The current pragmatic approach of avoidance without investigation is safe, but further investigation may be indicated where there is an essential need for long-term treatment, and where alternative medications are less effective or much more costly.

Skin rashes are the most common adverse form of drug reaction in children. Rashes can have many causes, they can be due to the antibiotic itself and the underlying infection or an interaction between the drug and the infectious agent. The most common of the latter being the maculopapular rash in infectious mononucleosis after taking ampicillin or amoxicillin.

The two main classes of drugs to cause problems in children are beta-lactam antibiotics and NSAIDs. If a child with a doubtful history of penicillin allergy needs to be prescribed a beta lactam, then ideally he or she should be referred to a specialist indicated for skin prick testing and/or intra-dermal testing. If the history is plausible but the initial tests are negative, then an oral challenge may be performed. The frequency of cutaneous reactions to NSAIDs is estimated to range from 0.3 to 7.8% and for respiratory reactions from 0% to 28%. As the mechanism is not IgE mediated, children may report reactions to more than one NSAID. Fortunately, paracetamol is usually well tolerated and can be used in most situations. Children with intolerance to paracetamol should be offered a COX-2 inhibitor.

Box 1. Components of the referral letter for specialist advice

Description of the suspected drug reaction

- Symptoms (the order in which they appeared and their duration). As detailed as possible, e.g. was the rash maculopapular, eczematous, bullous, urticarial, etc.
- What treatment was provided?

Timing of symptoms in relation to the suspect drug administration

Use of the drug

- Use of drug previously and were there any adverse events?
- On this occasion, how long had the drug been used before symptom onset?
- When was the drug stopped and with what effect?

Other documentation that may help with problem solving

- Photograph of reaction
- Witness description (relative and paramedic)
- Hospital letter and anaesthetic chart

Indications for the medication

- Details of the problem being treated at the time of the reaction (because the illness may be the cause rather than the drug)
- If appropriate, justification of the need to continue or repeat treatment

Drugs being taken at the time of reaction

- Including regular medications, 'over-the-counter' medicines, borrowed medicine, alternative remedies and recreational drugs.

Previous history

- Other drug allergies (suspected or confirmed)
- Past medical history
- Allergies

Key points

- Most adverse drug reactions are not immunologically mediated
- Atopy is not a risk factor but may lead to more severe reactions if a drug allergy develops
- A detailed history is essential for the diagnosis of a drug-induced reaction
- Challenge tests and desensitization should only be performed by specialized clinics
- In the UK, all adverse drug reactions should be reported by the Yellow Card system to the Medicines and Health Care products Regulatory Agency (MHRA) (www.mhra.gov.uk/index.htm)

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AKT question relating to drug allergies

You speak to a 23 year-old woman on the telephone. She has developed a widespread, itchy, red rash over the last four hours. She was prescribed trimethoprim yesterday for a urinary tract infection.

Which ONE of the following features is NOT a risk factor for developing an allergic drug reaction? Select ONE option only.

- A. Atopic eczema
- B. Female
- C. Human Immunodeficiency Virus (HIV) infection
- D. Previous hypersensitivity reaction to co-trimoxazole
- E. Systemic Lupus Erythematosus (SLE)

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For more AKT questions on this subject please visit www.rcgp-innoviat.oxfordjournals.org