



PRACTICE

PRACTICE POINTER

The patient who reports a drug allergy

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What you need to know

- Non-immunological adverse drug reactions are often incorrectly labelled “drug allergy”
- Unnecessarily labelling patients “allergic” to a drug can be harmful and can deny them best treatment
- A detailed history can help clinicians decide if re-administration is safe, although specialist tests may be necessary

What should clinicians do when a patient gives a history of a “drug allergy”? If it really is an allergy—an immunological reaction—or a serious adverse drug reaction (ADR), then patients risk serious harm unless they avoid the drug. But often, patients and healthcare professionals use “drug allergy” to mean any suspected ADR. Accepting a “drug allergy” at face value can unnecessarily deprive the patient of a potentially useful treatment. It may directly cause harm: patients labelled “allergic to penicillin” are more likely to become infected with methicillin resistant *Staphylococcus aureus* or *Clostridioides difficile*, for instance.¹

In some cases it may be safe for a patient to take, perhaps in a lower dose, a drug that caused an ADR. Here we offer a guide to help patients and practitioners when the issue of “drug allergy” arises.

A scheme for assessing a patient who describes a drug allergy, based on our experience, is set out in [figure 1](#). Begin by trying to establish if the harm was caused by medication, or something else. If it was an ADR, consider whether the reaction was serious, whether it was likely to be a true allergy, and whether it might have been related to the dose.

Did the drug cause the harm?

When taking a drug history, it is better to ask: “Have you had a bad experience with any medicines or drugs?” rather than enquiring about drug allergy (see [box 1](#) for definitions). If the patient volunteers a “drug allergy,” a detailed history should help to establish what caused the harm, and whether any ADR was immunological.

Box 1: Definitions

Adverse drug reaction—any unintended harm that a patient suffers from a medicine, eg, oral thrush with a broad spectrum antibiotic

Adverse event—any unintended harm that a patient suffers, whether or not caused by a medicine

Allergy—a harmful immunological reaction from hypersensitivity to a foreign antigen, eg, anaphylaxis from peanuts

Drug allergy—a harmful immunological reaction directly or indirectly caused by a medicine, eg, toxic epidermal necrolysis from carbamazepine

Side effect—any unintended effect of a medicine on a patient, whether beneficial or harmful, eg, pink urine with rifampicin

The history will sometimes indicate that the event was likely to be a consequence of the condition that was being treated. For instance, the patient may tell you: “I took clarithromycin tablets for a cough, and then I developed chest pain.”

It can be hard to decide if an adverse event is an ADR. Some ADRs have characteristic relations to time of exposure, and characteristic clinical features. Fetal phocomelia after the mother has taken thalidomide in pregnancy is a clear example, but even this clinical picture is not absolutely specific.² Formal algorithms can help estimate the probability that a clinical event is an ADR, but they rarely give clear cut answers.³

Was the ADR serious?

Serious ADRs cause serious harm. The internationally agreed definition of a serious ADR is set out in [box 2](#). Document and report serious ADRs. With a few exceptions—such as bleeding from warfarin—avoid re-exposure to the causative drug.

Box 2: What constitutes a serious adverse drug reaction?⁴

Serious reactions are those that

- are fatal
- are life threatening
- cause hospitalisation
- result in persistent or major disability or incapacity
- require intervention to prevent permanent damage, or
- cause congenital anomalies

Patients often describe a well recognised ADR that would not be classified as serious by the formal definition. Examples include oral thrush with antibiotic treatment,³ or a throbbing headache with glyceryl trinitrate. But even these non-serious reactions can be very unpleasant for the patient, and may limit prescribing choices.

Was it a true allergic reaction?

True allergy is an immunological phenomenon. It is also uncommon: one in 10 Americans is labelled “penicillin allergic,” yet only 1 in 100 Americans is reckoned to be at risk of an acute reaction.⁵ The most feared form of drug allergy is anaphylaxis. If a patient develops swelling airways, wheeze, hypotension, tachycardia, and urticaria within minutes of an injection of benzylpenicillin, then anaphylaxis caused by a penicillin is the only likely diagnosis.⁶ The reaction is caused by mediators released when mast cells degranulate in response to specific antigen binding to IgE on the cell surface. Serum mast cell tryptase activity is very high immediately after mast cell degranulation and falls over the next several hours, so taking a blood sample to measure tryptase activity shortly after onset can help to confirm the diagnosis. As a separate phenomenon, some treatments, such as acetylcysteine used to treat paracetamol poisoning, and the antibiotic vancomycin, can provoke the non-immunological release of mediators from mast cells, which can lead to flushing, wheeze, and hypotension.

Some life threatening immune ADRs have a delayed onset, which can make them difficult to diagnose. For example, toxic epidermal necrolysis⁷ can appear after exposure to the causative drug has ceased, but can have an alternative cause, such as viral infection, that is not related to drug exposure.

Are all immune reactions serious?

Although serious immune reactions such as anaphylaxis and toxic epidermal necrolysis are a major concern, they are very rare. Non-serious drug rashes are much more common: they occur in up to 5% of patients treated with penicillins and cephalosporins. A systematic review of cutaneous reactions to drugs characterised 95% to be morbilliform drug exanthems and 5% to be urticaria.⁸ A simple classification of immune skin reactions can help guide practice (table 1).⁹

What about non-immune reactions?

Emphasis on allergy can distract attention from non-immune ADRs that are acute and life threatening and will recur on re-exposure. Examples include catastrophic haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, caused by exposure to oxidising drugs such as aspirin, primaquine, and sulfonamides; and malignant hyperpyrexia (malignant hyperthermia) provoked by anaesthetic agents. Serious ADRs such as renal or hepatic failure would generally contraindicate re-exposure to the suspected drug cause, whether or not they were immune reactions. Even if they are not serious,

it can sometimes be hard to distinguish immunological from non-immunological reactions (table 2).

The effects of drug dose

All pharmacological effects depend on dose. Even in a patient who has had anaphylaxis, the degree of systemic response depends on the dose, which is why skin prick testing is usually possible. Sometimes, the patient will have suffered a serious ADR that depends on the dose within the therapeutic range—for example, bleeding with an anticoagulant; or above the standard therapeutic range, like seizures with intravenous or intrathecal penicillin.¹⁹ Many cancer patients develop dose related neutropenia from drug therapy, but nonetheless resume treatment because the overall benefits outweigh the harms.

Making a decision

The prescriber needs to decide whether to prescribe or withhold the medicine or seek specialist advice. It is usually safest to avoid a medicine that may have caused serious harm. This is also prudent if a non-serious ADR was probably immune related, unless it was a morbilliform drug rash (table 1).

Taking a minute or two to consider the history and previous medical records of a reported drug allergy can help to assess the potential risks of re-exposure (table 3). For example, a patient who describes “penicillin allergy” in infancy, but has had repeated treatment with different penicillins as an adult, is at low risk. The additional information allows the prescriber and the patient to reach a shared prescribing decision that balances the risk of a possible ADR against the risk of sub optimal treatment.

When to refer

If a patient has suffered a suspected anaphylactic reaction, the National Institute for Health and Care Excellence (NICE) recommends referral to specialist drug allergy services.²¹ Specific allergy tests may be needed to confirm an immunological reaction. NICE also recommends referral for patients who have suffered immune mediated severe cutaneous adverse reactions such as toxic epidermal necrolysis. Family history alone is not a reason for referral. If a drug caused a serious reaction other than anaphylaxis and is needed for the patient's treatment, then seek specialist advice. The same is true of any immunological reaction other than a non-serious “drug rash.” Referral may be to a clinical pharmacologist or an allergist, or sometimes to an organ specialist for possible drug induced hepatitis or pneumonitis or after a serious cutaneous reaction.

Laboratory tests have a limited role in preventing ADRs.²² Rarely—for example with abacavir and HLA-B*5701—genetic tests carried out before the drug is prescribed can identify patients at risk of an ADR. The use of genetic testing to predict drug responses is likely to increase as pharmacogenomics precision improves.²³

The value of diagnostic tests for immunological drug reactions that occur more than six hours after exposure is disputed.²⁴

If too high a dose offers a good explanation for a serious ADR, consider restarting treatment with a lower dose, as would happen after a haemorrhagic event in a patient with a metallic heart valve prosthesis who is treated with warfarin. Rapid increases in serum concentration of drugs such as the antibiotic vancomycin or the paracetamol antidote acetylcysteine can cause mast cell degranulation with histamine release. The

resulting ADR, manifest as wheezing, flushing, and hypotension, recovers if the infusion is stopped; and does not recur if the infusion is subsequently given slowly.^{25 26}

Education into practice

- When taking a drug history, do you only ask about allergies?
- How do you code harm from drugs on patients' electronic health records?
- How do you keep up to date with new adverse drug reactions?

How patients were involved in the creation of this article

We asked five expert patients from the UK, France, and Italy for their views on an early draft of our paper, and have used their extremely helpful comments and suggestions make our article more useful for doctors and patients. Their comments led us to revise the algorithm, to adopt a cautious approach to re-exposure, and to consider the international perspective.

Additional educational resources

- National Institute for Health and Care Excellence British National Formulary. The prescribing guide for British doctors. <https://bnf.nice.org.uk/>
- Medicines and Healthcare products Regulatory Agency (MHRA) Yellow Card Scheme. UK MHRA reporting scheme, with links to downloadable infographics for patients and professionals. <https://yellowcard.mhra.gov.uk/>
- EudraVigilance—European database of suspected adverse drug reaction reports, available in 26 languages. <http://www.adrreports.eu/index.html>
- The electronic Medicines Compendium. Summaries of Product Characteristics and Patient Information Leaflets for medicines licensed in the United Kingdom. <https://www.medicines.org.uk/emc>
- Agence nationale de sécurité du médicament et des produits de santé. Information from the French pharmacovigilance agency in English. <https://www.ansm.sante.fr/Mediatheque/Publications/Information-in-English>
- Health Canada MedEffect Canada, the Canadian regulator's website, including safety updates. <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>
- New Zealand Medicines and Medical Devices Safety Authority Medsafe. The New Zealand regulator's website, with links to information for consumers and for healthcare professionals, including safety updates. <https://www.medsafe.govt.nz/>
- US National Library of Medicine DailyMed. A searchable database of medicines licensed in the USA, with links to the MedWatch voluntary reporting scheme and to MedlinePlus. <https://dailymed.nlm.nih.gov/dailymed/index.cfm>

Sources and selection criteria

We searched MEDLINE to identify any systematic reviews and meta-analyses on drug hypersensitivity. We also used NICE guidance on drug allergy and anaphylaxis and our own collection of references on adverse drug reactions.

A rash with ampicillin

A 35 year old woman presents with recurrent impetigo. You want to offer flucloxacillin but she says she is allergic to penicillin. When you ask her to tell you more about it, she says she developed a blotchy rash "like measles" when she was given ampicillin for a sore throat when she had glandular fever as a teenager. Following the algorithm in figure 1, the harm was associated with the drug, but there was no evidence that it was caused by too high a dose, and it was not serious. The association could well have been causal. A little extra knowledge about this ADR is helpful here: people with Epstein-Barr virus infections are especially prone to rashes with aminopenicillins. Most such reactions are transient,²⁷ and if they do recur, they are unlikely to be provoked by non-aminopenicillins.²⁸ You explain to your patient that she may have a mild allergic reaction to ampicillin and amoxicillin, but that it should be safe to take other penicillins. She agrees to take flucloxacillin, and to stop the treatment at once and to seek medical advice if the reaction reoccurs. You clearly document the discussion and note on her records that she developed a morbilliform rash with aminopenicillins. All goes well. Your careful analysis of the patient's history of drug allergy allowed you to define the potential cause of her adverse drug reaction and come to a shared decision with the patient to prescribe optimal treatment.

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Further details of The BMJ policy on financial interests are here: <https://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests>

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Tables

Table 1| Immunological skin reactions⁸

	IgE mediated Adverse drug reactions (ADRs)	Non-serious T cell mediated ADRs	Serious T cell mediated cutaneous ADRs (SCARs*)
Onset	In minutes to hours	In a few days	In days to weeks
Skin involvement	Urticaria ("hives"), Pale, itchy lumps	Morbilloform ("like measles") flat, red, blotchy rash	Blistering, pustules, or skin loss
Mucosal involvement	No	No	Yes: conjunctival, oral, and urogenital mucosae can all be involved
Organ involvement	Yes: in anaphylaxis	No	Yes
Is re-exposure safe?	Only if urticaria is the sole manifestation and skin prick test is negative	Rash may recur; unlikely to cause a serious ADR	Never

* SCARs include Stevens-Johnson syndrome and toxic epidermal necrolysis; drug rash with eosinophilia and systemic symptoms; and acute generalised exanthematous pustulosis

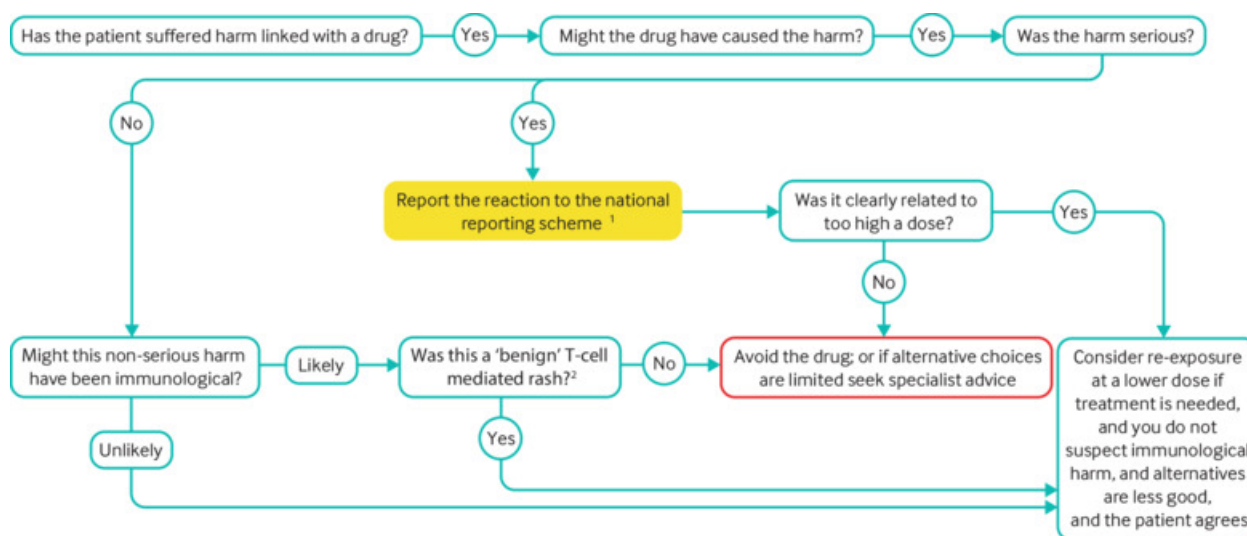
Table 2| Examples of potentially serious adverse drug reactions. Pharmacological and immunological mechanisms can sometimes cause similar clinical features

Clinical feature	Pharmacological mechanism	Immunological mechanism (allergy)
Syncope	Torsade de pointes—eg, with newer antipsychotic agents ¹⁰	Anaphylaxis—eg, to penicillins
Wheeze	Bronchoconstriction—eg, with β -blockers	Anaphylaxis—eg, to penicillins
	Aspirin exacerbated respiratory disease—with non-steroidal anti-inflammatory drugs ¹¹	
	Non-immune mast cell degranulation—eg, with hyperosmolar radio contrast media	
Abnormal liver function	Toxic liver damage—eg, with high dose paracetamol ¹²	With halothane, on re-exposure ¹³
		Cholestasis with flucloxacillin ¹⁴
Renal impairment	Renal tubular damage—eg, with aminoglycoside antibiotics	Tubulointerstitial nephritis with proton-pump inhibitors ¹⁵
	Impaired glomerular blood flow—eg, with angiotensin converting enzyme inhibitors in patients with renal artery stenosis	
Rash	Photosensitive rash—eg, with amiodarone	Drug induced urticaria ¹⁶
		Toxic epidermal necrolysis ¹⁷
		Drug induced rash, eosinophilia, and systemic symptoms ¹⁸

Table 3| Examples of adverse drug reactions where it is reasonable to consider re-exposure

Drug	Reaction	Comments
Acetylcysteine infusion	Flushing	Slow the infusion rate
Broad spectrum antibiotics	Diarrhoea	Advise the patient to cease treatment and to report to prescriber
Corticosteroid inhalers	Oral candida	Rinse mouth after dosing; use a spacer
Antihypertensives	Hypotension	Reduce dose or split dosing during the day Consider evening dosing ²⁰
Nitrates	Headache	Usually diminishes with continued treatment
Opiates	Constipation	Co-prescribe stimulant laxatives (when starting treatment)
Phenytoin	Cerebellar ataxia	Reduce the dose; keep within therapeutic range
Statins	Muscle pain	If creatine kinase activity is not elevated, discuss the benefit–harm balance with the patient
Warfarin	Bleeding	Identify source; keep within therapeutic INR range

Figure



¹ Report all serious or unusual reactions, and all reactions to 'Black Triangle' medicines (those under intensive surveillance)

² A T-cell mediated rash is typically morbilliform (it looks like measles) (See Table 2)

Fig 1 An algorithm to guide decisions when a patient reports a "drug allergy"