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Practical management of antibiotic allergy in adults

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ABSTRACT

This review looks at the main issues around immediate hypersensitivity and the role and limitations of testing. The majority of literature on antibiotic hypersensitivity relates to β -lactam antibiotics, mainly because of the heavy usage of this class of drugs. Concerns around cross-reactivity always worry clinicians, particularly in the emergency situation. Reasonable data now exist in relation to β -lactam antibiotics and derivatives, which enable appropriate risk management to be undertaken. The available literature for other classes of antibiotics is also discussed.

INTRODUCTION

Most adverse drug reactions are not allergic in nature. Eighty per cent of drug reactions are type A category—that is, they are predictable, dose-dependent, related to known pharmacological actions, and occur in otherwise normal patients. This includes side effects, toxic effects and drug interactions. Type B reactions are not related to pharmacological actions of the drug, are unpredictable, and occur in only a small proportion of the population. Reactions in this category include drug intolerance, idiosyncratic reactions, and allergic and pseudoallergic reactions. Type B reactions comprise 10–15% of all adverse drug reactions. Drug allergies, which comprise 5–10% of all adverse drug reactions, are hypersensitivity reactions that are immunologically mediated.¹ Currently, the most widely used classification system for immunological hypersensitivity reactions continues to be the Gell and Coombs classification. In this scheme, drug allergies are divided into four main pathophysiological types: IgE-mediated immediate reactions (type 1); cytotoxic reactions (type 2); immune complex reactions (type 3); and delayed-type hypersensitivity reactions (type 4). Drug-induced reactions do not always fit nicely into one of these four categories. The greatest concern is focused on IgE-mediated reactions, and this review will concentrate mainly on this type. The extensive literature on allergic reactions to drugs is confusing, particularly with regard to the use of antibiotics. This presents clinicians with difficulty in selecting antibiotics appropriately, particularly in the acute situation when specialist advice may not be available. Published figures for allergy to antibiotics, in particular for ‘cross-reactive’ antibiotic allergy, vary widely, and a number of factors contribute to the variation in the figures, including routes of administration, duration treatment and rates of re-exposure.

Clinical history of allergic reactions to antibiotics

Choice of antibiotics may be limited by an unconfirmed or doubtful history of allergies. Clinical

histories of allergy are often vague and are often unsubstantiated by contemporary documentary evidence. Furthermore, patients may have no first-hand recollection of an allergic response if the reaction had occurred at a young age. Clinicians often accept a diagnosis of antibiotic allergy without obtaining a clear history of the nature and timing of the supposed reaction. This often means that non-specific and non-allergic reactions are erroneously labelled allergic, and drugs that could otherwise be safely tolerated are withheld. This may result in potentially denying patients optimal treatment.² Even allergists are guilty of perpetuating mythical antibiotic allergy.³

The clinical history is critical in assessing the likelihood of a true antibiotic allergy. Key features to seek out in the history of antibiotic allergy are the nature of the symptoms, timing in relation to the administration of the antibiotic and concomitant drugs (including over-the-counter drugs). A history of immediate reactions, including anaphylaxis, angioedema and urticaria, after drug administration is highly suggestive of type 1 IgE-mediated hypersensitivity. Accelerated reactions, including predominantly urticaria but also airway problems, may also occur and be IgE-mediated.

Late reactions include maculopapular rashes, Stevens–Johnson syndrome (SJS), blistering rashes, toxic epidermal necrolysis, serum sickness, drug fever, cytopenias, pneumonitis and nephritis and are more in keeping with other forms of immunological reactivity.⁴ Testing for specific IgE in these conditions is not indicated, and, in the case of suspected SJS reaction, direct patient testing is actually contraindicated. It is clear from various studies that only a small proportion of patients claiming allergy to antibiotics have histories compatible with a true allergy. Even in those who do have good histories for a type 1 IgE-mediated hypersensitivity reaction, not all have evidence on testing to support the persistent presence of specific IgE that would preclude further administration of the drug.

In most cases, antibiotics are administered to treat a suspected or confirmed infection. However, it is well established that infection itself is a potent trigger for both urticaria and angioedema. Up to 40% of episodes of acute urticaria in adulthood may be triggered by infection alone.^{5 6} Complement activation during infection will also stimulate mast cell degranulation.⁷ Often any concurrent antibiotic is blamed for the rash or swelling, and this undoubtedly explains why a significant proportion of patients with apparent allergic reactions to antibiotics do not have evidence of IgE on subsequent testing. Distinguishing between infection and drug-driven reactions is difficult on clinical grounds alone, and the timing is not always

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a reliable indicator of cause. In the acutely ill patient, it may be difficult to identify which of many drugs, administered either simultaneously or in close temporal proximity, is the most likely cause. The only recourse is to test to all drugs administered within the given timeframe. Allergy to latex has also been mistaken for drug allergy; this may be latex from gloves or other equipment, or even latex in the bungs of drug phials for intravenous administration.⁸

Methods of testing

Skin prick testing (SPT) and intradermal testing (IDT)

Guidelines on the use of SPT, IDT and patch testing have been produced by the European Network for Drug Allergy (ENDA) which outline best practice.^{9–11} Concurrent medication, particularly antihistamines, tricyclic antidepressants and topical corticosteroids, may affect the validity of skin testing and should ideally be withdrawn before testing.^{12–13} Systemic reactions may occur after both SPT and, more commonly, IDT¹⁴; in one study, up to 11% of patients being tested had systemic symptoms, with amoxicillin contributing half of these.¹⁵ Therefore drugs that may worsen systemic reactions—for example, ACE inhibitors—or interfere with treatment of systemic reactions—for example, β blockers—should, where possible, be withdrawn before testing.

Skin testing for antibiotic allergy has a low sensitivity (21–43%) depending on the particular antibiotic being tested, but a high specificity (7–99%).^{10–15} As noted below, even patients with good clinical histories may have negative tests, and those with vague histories may be positive. The literature is inconsistent in the methods used to identify allergy, and this contributes to the varying figures obtained for true allergy to drugs. Not all studies have used follow-up provocation tests to confirm the significance of skin tests. Repeat testing over time (years) may demonstrate loss of reactivity, particularly to amoxicillin, although whether this equates to loss of clinical reactivity is unknown.¹⁶ Where there is a good history of reactions in the remote past but the initial testing is negative, retesting after an interval may reveal positives in up to 28%.¹¹

Practical difficulties encountered during skin testing include patients who have dermographism—that is, whose mast cells degranulate simply to minor skin trauma. Such patients will show reactions to negative controls, and it can then be difficult to establish whether there are true-positive reactions to test agents. Anxious patients may develop similar non-specific reactions, and minimal sedation with a small dose of a benzodiazepine may be helpful. Testing with high concentrations of the drug may give rise to false positives because of irritant reactions. SPT technique is crucial to obtaining reliable and reproducible results. It is essential that both positive and negative controls are used in all cases. Obtaining a photographic record of testing for clinical notes is helpful for future reference. Where the hypersensitivity is to a metabolite of the drug that is produced in vivo, testing with the native drug may give false-negative results. Occasionally, the use of SPT and IDT may cause no signs of immediate reactions, but delayed papular reactions may occur, suggestive of delayed type 4 hypersensitivity. Patients should be encouraged to report any such reactions and ideally should return to hospital to have these inspected and recorded, preferably photographed. Follow-up patch testing may be desirable.

In vitro tests

In vitro tests for detecting specific IgEs are also used for diagnosis of immediate hypersensitivity. The literature on the use of in vitro tests for specific IgE to antibiotics is confusing. Sensitivity and

specificity figures for in vitro enzyme immunoassays (EIAs) are similar to skin testing, but comparative studies have shown that the results are not equivalent.¹⁰ The sensitivity of EIA-based tests is only moderate (~50%), although the specificity is much higher (85–100%).^{17–18} Newer flow cytometric tests based on changes in basophil activation are labour intensive and do not appear to offer significant advantages. Sensitivity (50%) and specificity (93%) appear similar to EIA-based tests.^{19–20} Again, there is not complete overlap with other testing modalities, and combination testing may be most appropriate. For the time being, the investigation of suspected antibiotic allergy will involve both in vitro and in vivo testing.

Patch testing

Patch testing may be required if delayed-type (non-immediate) hypersensitivity is suspected, and this may be combined with SPT and IDT for complex or unclear reactions.

Drug provocation (challenge testing)

ENDA has produced guidelines on the use of drug provocation testing in the investigation of adverse reactions to drugs.²¹ Severe reactions including SJS reactions and toxic epidermal necrolysis should be viewed as contraindications. The value of a challenge where the offending drug is unlikely to be needed in the future is questionable. It may be of use to prove non-reactivity in patients who are unwilling to take a drug without proof of tolerance. It can provide evidence of safety of potentially cross-reactive drugs and can confirm the nature of non-IgE reactions. It is essential that the purpose of any particular challenge is defined beforehand and that both the doctor and the patient are aware of the risks and benefits of the proposed test. The end point of the test must be identified beforehand and needs to be objective. False positives may occur if challenges are terminated too early solely on the basis of subjective symptoms. Drug provocation should ideally be carried out in a blinded manner to avoid psychological reactions in the patients and bias in the doctor. This adds to the resource implications, as additional visits are required. Graded open challenges may be used, starting with low doses and giving incremental doses at intervals until a full therapeutic dose has been administered. This is mainly used to prove safety, rather than identify reactions, and is of course unblinded. The patient must be observed for a period after the end of the administration. As above for skin testing, drugs that may complicate resuscitation in the event of a severe reaction or interfere with reactions should be withdrawn. Patients with extensive comorbidities, such as ischaemic heart disease, poorly controlled hypertension and severe lung disease, are not suitable for this type of testing unless there are pressing clinical reasons for it. In these cases, it may be necessary to carry out the testing in an intensive care/high dependency area. Crucially, testing should only be carried out if it will have a material impact on the subsequent management of the patient.

Who to test and when

Patients with a history of type I reactions merit testing only where there is likely to be a need for the use of specific antibiotics in the future. A good history would include documented anaphylactic reactions and a close temporal relationship to drug administration. When such patients are tested, the likelihood of positive reactions is increased. Where safe alternatives exist and there is no pressing need to use the antibiotic, testing is not indicated.

Resource implications

There are considerable resource implications for drug allergy testing, in view of the number of potential patients. Testing

a single patient by SPT and graded IDT takes 2 h. Appropriate dilutions of drugs need to be prepared according to published data.²² This is most appropriately carried out by trained pharmacists, rather than by clinical staff making extemporaneous dilutions in the clinic, where errors often occur.²³ Pharmacy resources are therefore required to support an effective drug allergy service. While it is desirable to offer an immediate service for testing patients, this may not be practical. In a small number of patients who may require testing, it may be possible to combine this with rush desensitisation protocols (see below).

A follow-up study of skin testing for penicillins and cephalosporins has shown that there was a subsequent decrease in the use of alternative drugs such as vancomycin and quinolones, and an increased use of penicillins and cephalosporins, without any serious adverse reactions.²⁴ This demonstrates that testing does add value by reducing the use of more toxic alternative antibiotics, and that penicillins and cephalosporins may be safely administered with a low risk of reaction after negative tests.

Allergy to β -lactam antibiotics

Allergy to penicillin

The incidence of self-reported penicillin allergy for inpatients and outpatients is up to 10%,²⁵ with a frequency of life-threatening anaphylaxis estimated at 0.01–0.05% and a death rate of 0.002–0.015%.²⁶ However, only a small proportion of patients reporting an allergy to penicillin have a history compatible with a true type 1 mediated allergy. Some 80–90% of patients will be negative on skin tests for IgE-mediated reactions.²⁷ Penicillin skin testing can accurately and safely identify patients with IgE-mediated allergy. The negative predictive value of a skin test for IgE-mediated allergy is ~99%.^{28–31} The clinical history of the reaction is useful in determining who may benefit from skin testing (figure 1). One study of 319 patients with supposed penicillin allergy divided patients into those with convincing histories, those with vague histories, and those with unacceptable histories on clinical grounds.⁵ Patients with a convincing history were felt to have an IgE-mediated reaction if they had symptoms including airway obstruction, laryngeal oedema, loss of consciousness, pruritic urticaria/angioedema, time-related diarrhoea or vomiting, and pruritic skin eruptions. Patients with a vague history had skin eruptions without pruritus, pruritus of the skin without eruption, unknown reactions told by family members, faded memory of the event, or vague breathing, gastrointestinal, central nervous system or joint symptoms. Patients who had a grossly inappropriate history or had never been exposed to penicillin were labelled as having unacceptable histories. None of the 34 patients with unacceptable histories had positive skin tests, even though the history of allergy had been accepted by 33 different primary care physicians and nine allergists. Ten of 150 (6.7%) in the vague group and 19 of 135 (14.1%) in the convincing group had positive skin tests. Similar findings have been seen in other studies.^{32–33} This shows that a history that is not compatible with immediate hypersensitivity can be dismissed without further testing. In patients with vague histories, however, care needs to be taken in dismissing these patients without further evaluation. All of these studies found a significant number of patients with convincing histories who had negative skin tests, indicating that, even in this group, testing is of value in identifying those without evidence of specific IgE who can be safely treated in the future with penicillin.

Skin testing strategies for β -lactams must include testing for reactivity to so-called minor determinants, as well as benzylpenicilloyl coupled to poly-L-lysine. In order to cover side chains,

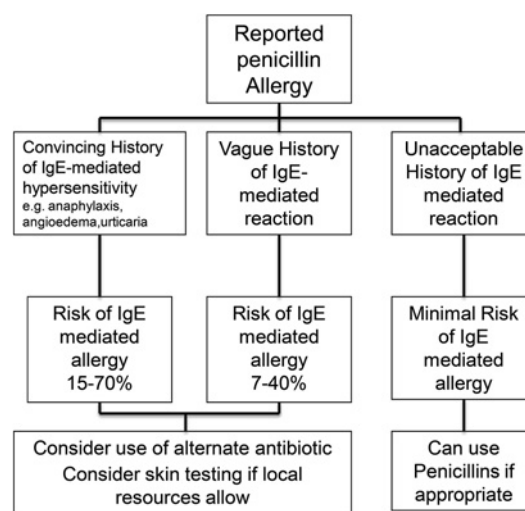


Figure 1 Algorithm for the use of penicillins in patients with reported penicillin allergy.

amoxicillin should also be tested, in addition to any specific penicillin thought to have triggered a reaction. Provided that all these agents are included, evaluation has shown sensitivity of up to 70% and a specificity of 97–100% for IgE-mediated reactions to β -lactams.¹⁰ Patients who have experienced immediate reactions to the combination of amoxycillin plus clavulanic acid should also be tested to the combination, as selective reactions to clavulanic acid have been reported.³⁴ Although in vitro assays to detect specific IgE to penicillins are available and have a high specificity (80–100%), the sensitivity is low (0–50%).^{17–35} Hence skin testing currently remains the most reliable way to identify an IgE-mediated penicillin allergy.

Allergy to cephalosporins

Data for cephalosporins are less well established than for penicillins. Immune-mediated reactions occur in 1–3% of patients receiving the drugs, but the risk of anaphylaxis appears to be low, with a reported frequency of 0.001–0.1%.^{28–36} However, deaths do occur; in a study of fatal anaphylaxis in the UK between 1992 and 1997, six of 12 fatal reactions related to antibiotic use occurred after the first dose of a cephalosporin.³⁷ In four of the six reactions, patients were known to be allergic to penicillins. It appears clear that there is an increased risk of reaction to cephalosporins in patients with penicillin allergies.³⁸ Older studies have suggested a 10–20% risk of cross-reactivity between penicillins and cephalosporins.^{39–40} However, the results are very different in studies that have analysed cross-reactivity between first-, second- and third-generation cephalosporins. The risk is higher in first-generation cephalosporins such as cephalexin, cephalothin and cefazolin, with up to a fourfold increase in reactions in penicillin-allergic patients.²⁹ Of the first-generation cephalosporins, only cephalexin is used to any extent in the UK, and this should be used with caution or not at all in patients with proven penicillin allergy, or those who have convincing histories of penicillin allergy. Newer cephalosporins such as cefuroxime, ceftazidime, ceftriaxone are unlikely to be associated with cross-reactivity because of differences in chemical structure and do not appear to pose the same level of risk.³⁹ Nevertheless, immunologist/allergist evaluation is strongly recommended where possible.⁴¹ A clinician faced with a patient with possible penicillin allergy has a number of options (figure 2). If the history of the reaction to penicillin is considered unlikely to be IgE-mediated, then the risk of cephalosporin-induced reaction

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is low and these can be given.^{39 42} If the patient has a convincing history of penicillin allergy, then the patient can receive an alternative (non- β -lactam) antibiotic, undergo skin testing, or receive a cephalosporin through rapid desensitisation. In patients who are negative on skin testing, the risks of reaction are low, and they may safely be given a cephalosporin. In patients with proven penicillin allergy, the risk of reaction to the third-generation cephalosporins is low, although first- and second-generation cephalosporins should be avoided. Expert opinion would still recommend a cautious approach and discussion with an allergist particularly to advise which cephalosporins, based on their chemical structure, are least likely to cross-react.⁴⁰ In view of the low likelihood of reactions, third-generation cephalosporins can be considered in patients with a previous history of mild reactions to penicillin (ie, not anaphylaxis) in whom the indication is strong and skin testing for penicillin allergy is impractical or treatment for drug reactions is readily available.⁴³

Skin testing for penicillin allergy can be helpful in patients with a history of reaction to cephalosporin who require a penicillin. If the skin test is negative, then they receive penicillin; if positive, then they should receive an alternative antibiotic or undergo desensitisation. Early studies suggested around half of patients who had reactions to cephalosporin would be allergic to penicillins,⁴⁴ but more recent data suggest this figure is much lower at around 15%,^{45 46} possibly in part because of the increasing use of the newer generation cephalosporins, which have less structural similarity to penicillin. Selective cephalosporin allergy has been described, and patients allergic to one cephalosporin may be able to tolerate others, especially those without similar or identical side chains. SPT may be useful for identifying cephalosporins that may be tolerated.⁴¹

Allergy to carbapenems

Initial studies suggested a very high rate of cross-reactivity between penicillins and carbapenems of nearly 50%.⁴⁷ Retrospective studies suggested lower rates of 9.5–12.2%,^{48–50} and newer prospective studies have suggested that this rate is even

lower at 0.8–0.9%.^{51–53} All carbapenem skin test-negative patients tolerated subsequent graded challenges with carbapenems. Current opinion recommends skin testing to carbapenem in patients with a penicillin allergy; if the results are negative, then a graded challenge to reach a full therapeutic dose can be safely given.⁵⁴

Allergy to monobactams

Aztreonam is the only monobactam available for clinical use. Allergic reactions to aztreonam are directed against the side chain that is not shared with other β -lactam antibiotics. Clinical trials do not show any clinical cross-reactivity between aztreonam and penicillins, and it can therefore be safely given in these patients.⁵⁴ The exception is ceftazidime, which shares the same side chain. However, reactivity to aztreonam does not appear to always cause reactions to ceftazidime.⁵⁵

Other antibiotics

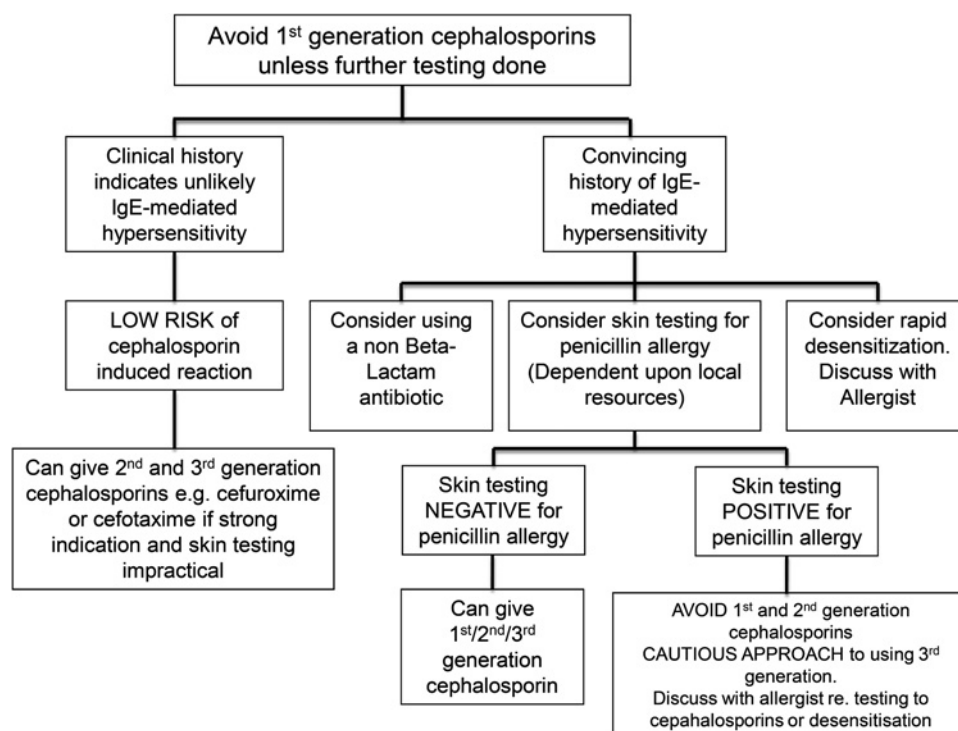
Quinolones

Most commonly described allergic reactions to quinolones are immediate, suggesting a type 1 mediated mechanism. Anaphylaxis is rare, but urticaria, angioedema and a range of non-IgE-mediated cutaneous reactions, including photosensitivity, have been described.⁵⁶ SPT is difficult, as quinolones can cause histamine release in normal individuals, although a negative skin test has a high negative predictive value for subsequent positive challenge.⁵⁷ There are no routinely available in vitro tests for quinolone-specific IgE, but research assays have demonstrated that specific IgE antibodies can occur,⁵⁸ and are often cross-reactive between quinolones, indicating that immediate hypersensitivity to one quinolone will contraindicate the use of all quinolones. Desensitisation regimens have been described.⁵⁹

Macrolides

Most adverse events relate to gastrointestinal intolerance, which is non-immunological. Allergies to macrolides are reported to be

Figure 2 Algorithm for the use of cephalosporins in patients with reported penicillin allergy.



uncommon (0.4–3%),⁶⁰ although cases of anaphylaxis have been described.^{61 62} Other non-IgE immunological cutaneous reactions may occur, including SJS, toxic epidermolysis, pustulosis and vasculitis. Skin testing for type 1 reactions is possible, although it has not been performed in enough patients for these to be validated⁶³; no in vitro tests are available. Cross-reactivity between macrolides (including tacrolimus) has been described, although it appears to be uncommon.^{64 65}

Sulfonamides

Adverse reactions to sulfa are relatively common, occurring in 3% of courses, but only 3% of these actually are true hypersensitivity.⁶⁶ The most common immune-mediated reaction is rash, but severe reactions including anaphylaxis and florid dermatological reactions, such as SJS, are well described.⁶⁷ IgE-mediated reactions are uncommon, but diagnosis is hampered by the lack of standardised SPT reagents, and sulfonamide allergy remains a clinical diagnosis. Although sulfonylurea oral hypoglycaemics, thiazide diuretics and carbonic anhydrase inhibitors have sulfa moieties, there is no evidence for immune reactions to these drugs in patients with a history of sulfonamide antibiotic reactions.⁶⁸ HIV-positive patients have a 10–50 times higher frequency of rashes and fever than non-HIV patients receiving these drugs. Drug hyposensitisation protocols can be considered where there is an absolute need. These procedures are strictly contraindicated if there is a history of desquamative or exfoliative reactions, SJS, or any similar clinical syndrome.⁶⁹

Tetracyclines

IgE-mediated reactions are very rare, although anaphylactic reactions have been described.⁷⁰ Delayed immunologically mediated hypersensitivity reactions occurring weeks after treatment are documented and can include exfoliative dermatitis, pericarditis, eosinophilic reactions and lymphadenopathy.^{71–73} Longer duration treatment, especially with minocycline, may cause autoimmune phenomena typically causing a drug-induced lupus syndrome, accompanied by the presence of autoantibodies, primarily histone antibodies.⁷⁴

Glycopeptide antibiotics: vancomycin and teicoplanin

Vancomycin is well known to cause the ‘red-man’ syndrome consisting of flushing and pruritus, occasionally accompanied by hypotension. The onset may occur within a few minutes and usually resolves over several hours after completion of the infusion, and is often mistaken for an allergic reaction. This is not IgE-mediated, but is due to direct histamine-releasing effects, and can be reduced or prevented by slowing the infusion and pretreating with potent third-generation antihistamines in high doses. This reaction is very unusual with teicoplanin because this compound does not cause histamine release, even at faster infusion rates than those of vancomycin.⁷⁵ IgE-mediated reactions have been reported in a few cases only.⁷⁶

Aminoglycosides

Topical aminoglycosides are commonly used, particularly for ear and eye infections and are well known to produce type 4 delayed hypersensitivity reactions, for which patch testing is appropriate. Anaphylaxis may occur, but is unusual, and SPT can be used, and positive results have been described.^{77 78} There is widespread cross-reactivity between aminoglycosides on patch testing, so reactivity to one generally precludes the use of others.⁷⁹

Multiple drug allergy

The existence of multiple drug allergy syndrome remains open to debate. The term ‘multiple drug allergy syndrome’ was

initially coined after a study which reported immune reactions to other antibiotic classes in 21% of 312 patients with histories of immediate reactions to penicillin compared with 1% of 349 patients without penicillin allergy.⁸⁰ There are, however, conflicting data with other studies, suggesting that there is no higher incidence.⁸¹ A reason for this proposed increased propensity is not clear, although it may relate to genetic or metabolic factors, frequent and recurrent drug exposures, or specific disease states leading to immune dysregulation. Multiple drug allergy is common in patients with chronic infective problems requiring regular antibiotic therapy such as bronchiectasis and cystic fibrosis. Patients with cystic fibrosis have an up to three times increase in acute allergic reactions to β -lactams compared with the general population.⁸² The incidence of antibiotic allergy appears to be antibiotic-dependent and increases with the number of antibiotics given.⁸³ HIV-infected patients have also shown a substantially higher frequency of drug allergies than the non-infected population.⁸⁴ Many patients given multiple antibiotics during viral infections become labelled as multi-allergic when they develop recurrent virally induced rashes. This presents problems for doctors subsequently. Testing all such patients is expensive and time consuming, and, in the UK, resources for this are not available. Management includes ensuring that minor viral infections are not treated with antibiotics, and that patients prone to infection-driven rashes are encouraged to take appropriate third-generation antihistamines to cover the period of infection.

Practical management

When faced with a patient with a possible drug allergy, the most important step is to take a detailed clinical history to assess probable causality and determine the underlying mechanisms (hypersensitivity versus pharmacological effect). However, often the clinical history is vague or lacking any supporting documentation, making this important part of the evaluation indeterminate. For hypersensitivity reactions, several options may be considered (figure 3). After severe or life-threatening reactions, the drug should not be readministered. For immune-mediated (allergic) reactions, the management option depends on the mechanism responsible for the reaction. If validated confirmatory tests are available and it is appropriate, they should be used to determine the allergic status of the patient (eg, SPT or IDT for penicillin IgE). Patients with severe non-IgE-mediated reactions such as SJS, Drug rash, eosinophilia and systemic symptoms (DRESS), erythroderma and toxic epidermolysis should not be rechallenged with the antibiotic, through SPT, IDT or drug challenge, as there is a very high risk of recurrence. If confirmatory tests are not available—and in most cases they are not—several approaches can be taken. The simplest is to avoid the drug if an alternative agent is available, bearing in mind potential cross-reactivities above. If an alternative drug does not exist, a graded challenge with the implicated agent can be performed if the previous reaction was not life-threatening and not consistent with an IgE-mediated reaction. Where there is no urgency, then the opportunity exists to carry out SPT and IDT, not only to the culprit drug but also with potential alternatives. However, if confirmatory testing for IgE-mediated reaction is positive but the medication is needed as the drug of choice, then desensitisation should be considered.

Desensitisation is possible for many drugs by continuing repeated administration of doubling doses in patients with a history of SJS or tests suggestive of an IgE-mediated reaction until a therapeutic dose is reached. Desensitisation regimens have been described for most antibiotics.²² These may be at variable

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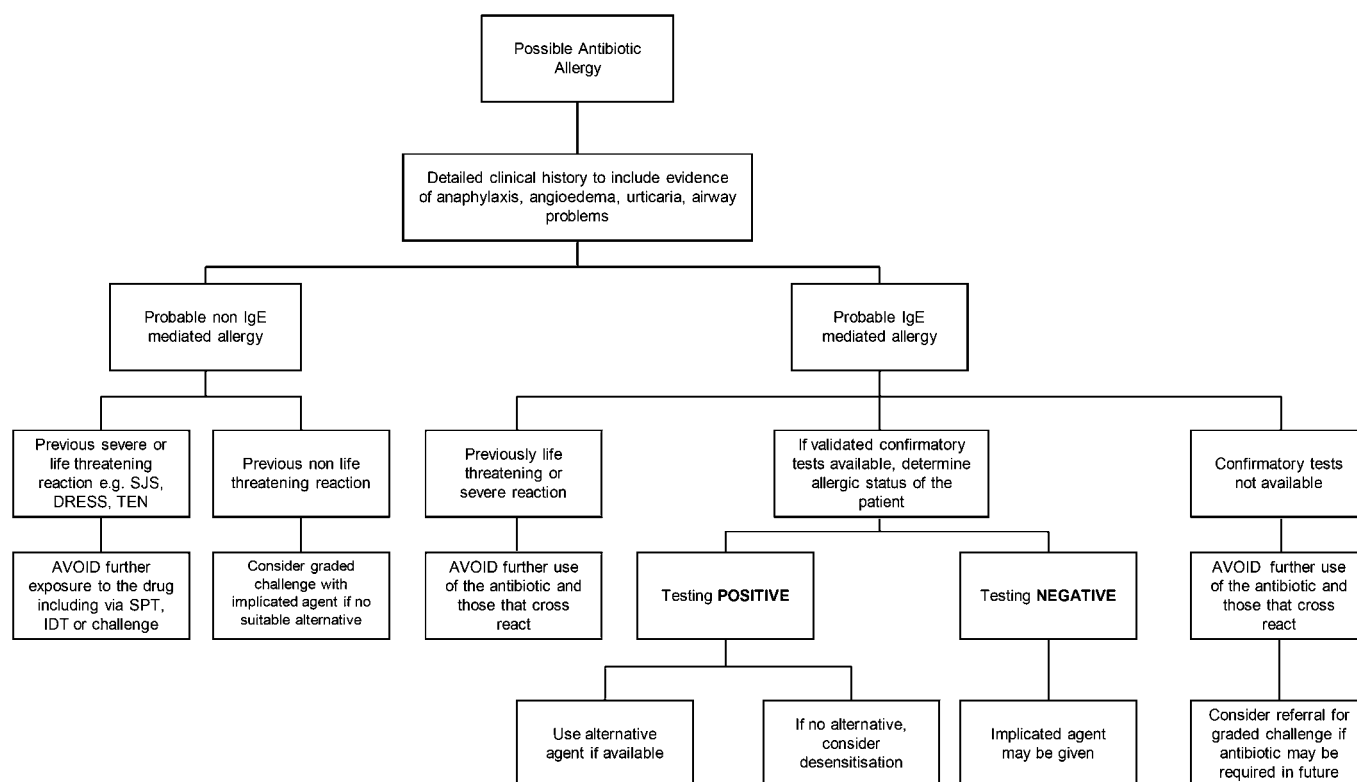


Figure 3 Management of possible antibiotic allergy.

speeds depending on clinical urgency, but are only suitable for immediate hypersensitivity reactions. The mechanism of drug desensitisation is not well understood, but may in some cases involve controlled degranulation of mast cells. However, the desensitised state is not permanent and is sustained only with a daily maintenance dose of the drug. Cessation of the maintenance dose will allow the drug hypersensitivity to return, usually within a few days, and subsequent administration will require a repeated desensitisation process. When desensitisation protocols are used, they should be carefully supervised at all times, and it is mandatory to have immediate access to full resuscitation facilities. The role of antihistamines and steroids in the prophylaxis of reactions is unknown. Published strategies exist, using high-dose steroids and antihistamines to prevent reactions to radiocontrast media. In the context of serious infection, the administration of high-dose steroids may be highly undesirable.

Take-home messages

- ▶ In assessing adverse drug reactions, a detailed clinical history and careful documentation of reactions are most important.
- ▶ In vitro tests, skin testing and challenge tests are useful in the diagnosis or exclusion of IgE-mediated antibiotic-related allergic reactions.
- ▶ Only a small proportion of those claiming to have type 1 IgE-mediated allergy will have this confirmed on testing.
- ▶ Drug challenges can be used to eliminate suspicion of a low-probability drug reaction, find a safe alternative to a proven or probable allergic reaction, or as a means of desensitisation.

CONCLUSION

The most extensive data relate to the management of reactions to β -lactam and derivative antibiotics, where there are good data regarding cross-reactivity, sensitivity, specificity and risks of testing. For other antibiotics, the information is more sparse. Appropriate management of an acute infective problem in a patient with suspected allergy will involve close liaison between the responsible consultant, medical microbiologist and immunology/allergy service. The latter need to be able to offer urgent advice on testing and desensitisation regimens for emergency use. Access to facilities for drug allergy testing is essential, but selection of appropriate patients for testing is crucial: priority must be given to those for whom the testing will make a clear and immediate difference to the clinical management. It is not practical to test all patients claiming to have allergy to penicillin, even though the majority of such patients will have no evidence of allergy on formal testing.

Competing interests None.

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