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BSACI guidelines for the management of drug allergy

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Summary

These guidelines have been prepared by the Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI) and are intended for allergists and others with a special interest in allergy. As routine or validated tests are not available for the majority of drugs, considerable experience is required for the investigation of allergic drug reactions and to undertake specific drug challenge. A missed or incorrect diagnosis of drug allergy can have serious consequences. Therefore, investigation and management of drug allergy is best carried out in specialist centres with large patient numbers and adequate competence and resources to manage complex cases. The recommendations are evidence-based but where evidence was lacking consensus was reached by the panel of specialists on the committee. The document encompasses epidemiology, risk factors, clinical patterns of drug allergy, diagnosis and treatment procedures. In order to achieve a correct diagnosis we have placed particular emphasis on obtaining an accurate clinical history and on the physical examination, as these are critical to the choice of skin tests and subsequent drug provocation. After the diagnosis of drug allergy has been established, communication of results and patient education are vital components of overall patient management.

Keywords aspirin, BSACI, classification of drug allergy, drug allergy, drug allergy investigations, drug challenge, drug desensitization, drug intradermal tests, drug patch tests, drug provocation, drug skin prick, general anaesthetic, guidelines, local anaesthetic, muscle relaxants, NSAID, penicillin, specific IgE drug testing, Standards of Care Committee, tryptase

Introduction

This guideline focuses on a difficult problem faced by clinicians in everyday practice – the diagnosis and management of drug allergy. Routine and validated tests are not available for many allergic drug reactions but a body of knowledge has been developed by centres seeing large numbers of patients with adverse reactions to a number of drug classes particularly β-lactams, neuromuscular blockers, (NMBA) aspirin/non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics and opiates. Considerable experience is required to guide management, to interpret results of investigations and undertake drug challenges. For some drugs (e.g. non-β-lactam antibiotics, insulin, patent blue dye, plasma expanders) there is a paucity of published data and/or few patients have been investigated. Every case must be individually evaluated and managed. For these reasons the investigation of drug allergy is best focussed on specialist centres with adequate experience, regular exposure to a complex case mix and competence in skin testing and drug challenges. This document provides a general overview for the investigation of drug allergy and subsequent guidelines will focus on specific drug classes. During the development of these guidelines, all British Society for Allergy and Clinical Immunology (BSACI) members were consulted using a web-based system and their comments and suggestions were carefully considered by the Standards of Care Committee (SOCC). Where evidence was lacking a consensus was reached among the experts on the committee. Conflicts of interests were recorded by the BSACI. None jeopardized unbiased guideline development.

Executive summary

Grades of recommendations are defined as in Powell et al. [1]:

- Adverse drug reactions (ADRs) account for approximately 6.5% of all hospital admissions.

- Up to 15% of in-patients have a hospital stay prolonged as a result of ADR.
- ADRs affect quality of life, may lead to delayed treatment, unnecessary investigations or even death.
- Statistics of ADRs and also subsequent deaths resulting from ADRs are likely to be unreliable with widespread underreporting in both adults and children.
- Topical and particularly cutaneous routes of administration and prolonged or frequent doses are more likely to lead to sensitization.
- Atopy is not a risk factor for the majority of allergic drug reactions but may lead to a more severe reaction.
- Cutaneous reactions are among the most common of all the different patterns of ADRs.
- Some infections such as by Herpes viruses (EBV, CMV and others) as well as HIV, increase the likelihood of drug reactions and repeated use of antibiotics in diseases such as cystic fibrosis is associated with more frequent reactions.
- A detailed history is required for an accurate diagnosis of a drug-induced reaction and should include details of drug formulation, dose, an assessment of the time course and clinical pattern of the reaction. This will inform the likely immunological mechanism and direct investigation and management (*grade of recommendation = A*).
- When investigating reactions during general anaesthesia it is particularly important to review the anaesthetic chart, medical notes, drug and nursing charts (*grade of recommendation = C*).
- Skin prick test (SPT) and intradermal test provide evidence of IgE-mediated sensitization and patch tests or delayed reading of an intradermal test provide evidence for a delayed or T cell-mediated process to a specific drug. However, all skin test results must always be interpreted within the appropriate clinical context (*grade of recommendation = B*).
- If the reaction is not IgE-mediated, a negative skin test result does not exclude the drug as the cause of the reaction and further investigation should be considered (*grade of recommendation = C*).
- Skin tests may be falsely negative even if the reaction is IgE-mediated because of limitations in the availability of the relevant skin test reagents.
- Skin tests are particularly difficult to interpret for drugs known to be direct histamine releasers, e.g. opiates and some neuromuscular blocking agents (NMBA) or if the drug has been tested at a concentration causing local skin irritation.
- Skin tests should not be used to screen for drug allergy in the absence of a clinical history compatible with IgE-mediated drug allergy (*grade of recommendation = C*).
- Skin testing for immediate hypersensitivity is not indicated for type III serum sickness reactions or for T cell-mediated reactions including severe cutaneous reactions such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction/rash with eosinophilia and systemic symptoms (DRESS) (*grade of recommendation = B*).
- Skin testing for delayed-type hypersensitivity with patch tests can be helpful in T cell-mediated hypersensitivities such as DRESS syndrome and SJS/TEN. (*grade of recommendation = C*).
- Serial blood samples for serum tryptase should be taken at the time of suspected anaphylaxis, at 2 and 24 h or later (baseline sample) after onset of anaphylaxis (*grade of recommendation = C*).
- Drug challenge should only be considered after other investigations have been exhausted and the diagnosis remains in doubt. The primary aim of provocation testing should be to exclude drug sensitivity/intolerance but it can also be used to confirm diagnosis or to demonstrate tolerance to an alternative drug (*grade of recommendation = B*).
- It is not usually advisable to carry out provocation testing if the reaction has resulted in a life-threatening reaction. Drug provocation should be carried out by personnel experienced in drug challenges with adequate resuscitation facilities readily available (*grade of recommendation = C*).
- If there are no suitable alternatives, drug desensitization may be possible for one course of treatment particularly for antibiotics, aspirin, taxenes and platinum-based cancer chemotherapeutic agents (*grade of recommendation = B*).
- Prevention of future reactions is an essential part of patient management. The patient should be provided with written information about which drugs to avoid, the drugs highlighted in hospital notes and the GP informed (*grade of recommendation = B*).
- Engraved allergy-bracelets are useful when there is a risk of intravenous drug administration in an emergency, e.g. muscle relaxants, opiates or penicillin or when drugs, e.g. NSAIDs are readily available without prescription (*grade of recommendation = B*).
- Health Care Professionals should report ADRs via the Yellow Card Scheme run by the Medicines and Healthcare products Regulatory Agency (MHRA) and the Commission on Human Medicines.

Definition

The WHO has defined an ADR as 'An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product' [2]. The classification and investigation of ADRs is challenging because for many drugs the underlying mechanism is not understood.

Table 1. Investigation of drug allergy/hypersensitivity categorized by immunological mechanisms (From Gell and Coombs [5], Pichler [6] and Posadas and Pichler 2007 [149])

Reaction	Mechanism	Clinical features	Investigation
Type I	IgE-mediated, immediate reaction	Urticaria*, angio-oedema*, anaphylaxis*, bronchospasm*	Skin prick testing Intradermal testing Specific IgE testing Drug provocation
Type II	IgG/M-mediated cytotoxic reaction	Anaemia, cytopenia, thrombocytopenia	FBC/Coombs Test
Type III	IgG/M-mediated immune complexes	Vasculitis, lymphadenopathy, fever, arthropathy, rashes, serum sickness	C3, C4, ANA, ANCA, LFT, U&E, histology, CXR
Type IVa	Th1 cells activate monocyte/ macrophages via IFN-γ and TNF-α	Contact dermatitis, bullous exanthema	Patch tests
Type IVb	Th2 cells drive eosinophilic inflammation via IL-5, IL-4, IL-13, eotaxin	Maculopapular and bullous rashes, etc.	Patch tests
Type IVc	$CD4^+/CD8^+$ cytotoxic T cells kill targets via perforin, granzyme B, FasL	Contact dermatitis, maculopapular, pustular and bullous exanthemata, etc.	Patch tests
Type IVd	T cells recruit and activate neutrophils via CXCL-8, GM-CSF	Pustular xanthemata	Patch tests

*These may also be non-immunologically mediated. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; LFT, liver function test; U&E, urea and electrolytes; CXR, chest X-ray.

Pragmatically, ADRs can be classified into reactions which *may affect anyone* (type A) and reactions which *affect only susceptible individuals* (type B) [3]. In this document the term drug allergy has been applied to an ADR with an established immunological mechanism [4]. However, the mechanism at presentation may not be apparent from the clinical history and therefore the distinction into allergic and non-allergic cannot always be established without appropriate investigation. It should be noted that ADRs are different from adverse drug events (ADEs), the latter include reactions that are caused by unintentional mis-prescription or misuse of drugs. True hypersensitivity reactions are immune-mediated and are conveniently classified into Gell and Coombs categories (Table 1) [5]. More recently, type IV delayed hypersensitivity reactions have been revisited to incorporate drug-induced exanthema. This classification attempts to clinically correlate the underlying mechanism according to T cell-subtype [6]. Drug allergy requires prior exposure to the same or a cross-reacting compound (sensitization) at a dose tolerated by the majority of individuals, although patients do not always give a history of prior drug exposure [7, 8]. Symptoms occur typically during subsequent courses by a variety of mechanisms, many of which have yet to be determined.

Background and epidemiology

ADRs account for approximately 6.5% of all hospital admissions [9–11] and up to 15% of in-patients have a hospital stay prolonged as a result of ADR [12]. Between 1998 and 2005 serious ADEs increased 2.6-fold [13]. ADRs not only affect quality of life but may lead to delayed treatment, unnecessary investigations or even death. Therefore, the cost to the Health Service is substantial. Despite these data, accurate statistics remain elusive because of both under- and over-diagnosis [14] and underreporting of deaths resulting from ADRs. The United Kingdom has a yellow card system for reporting ADRs, but the statistical information from these reports is only useful qualitatively and not for estimating incidence [15]. This was illustrated by a recent study (using the Hospital Episodes Statistics database) which reported an incidence of 8.3 per 10 000 drug-induced hospital admissions [16] which is a much lower incidence than the above quoted data of 6.5%. A UK study found that 0.32% of serious ADRs were fatal [17]. A study from Norway reported that 18% of all hospital deaths over a 2-year period could be attributed to one or more drugs equating to a rate of 9.5 deaths per 1000 hospitalized patients [18]. Another study found that among 164 deaths for anaphylaxis 39% were drug-induced [19].

Most drug reactions are considered predictable, resulting from either a toxic effect (overdosage or reduced excretion), side effects (low threshold to the undesirable pharmacological effects) or because of an interaction between drugs. The remainder are considered idiosyncratic, are less common, unpredictable and less related to drug pharmacodynamics [15]. Up to 1/3 of all ADRs occurring in hospitalized patients are either allergic or clinically mimic an allergic reaction [20].

Risk factors (Tables 2 and 3)

The most important risk factor is a history of a previous reaction to the same or a related compound. Parenteral

Table 2. Risk factors for development of adverse drug reactions

Patient related	
Age	Young adults > infants/elderly
Sex	Women > men
Genetic	Atopy may predispose to more serious reactions
	Genetic polymorphism
Concomitant disease	HIV, infections with Herpes viruses (EBV, CMV and others), cystic fibrosis (because of frequent antibioic use)
Immune status	Previous drug reaction or previous positive skin test for drug
Drug related	
Drug chemistry	β-lactam compounds, NMBA, radio-contrast media, NSAIDs are the most frequently involved [46, 150].
	High MW compounds/hapten-forming drugs are more immunogenic
Route	Topical route > parenteral/oral
Dose	Frequent or prolonged doses

NSAIDs, non-steroidal anti-inflammatory drugs ; NMBA, neuromuscular blocking agent.

Table 3. Drugs to avoid in genetic diseases affecting drug metabolism

Genetic disease	Drugs to avoid
Malignant hyperpyrexia	Volatile anaesthetic agents, suxamethonium
Glucose-6-phosphate-dehydrogenase deficiency	Dapsone (and other sulphones), nitrofurantoin, methylene blue, primaquine, quinolones, sulphonamides
	Caution with: aspirin, chloroquine, menadione, quinidine, quinine
Porphyria	Amphetamines, anabolic steroids, antidepressants, some antihistamines, barbiturates, some benzodiazepines, cephalosporins, some oral contraceptives, diuretics, ergot derivatives, gold salts, hormone replacement therapy, progestogens, sulphonamides, sulphonylureas
Pseudocholinesterase deficiency	Suxamethonium
Slow acetylators	Procainamide, hydralazine, sulphasalazine
TPMT (thiopurine *S*-methyltransferase) deficiency [151]	Azathioprine (leading to marrow toxicity)

and topical routes of administration are more likely to lead to sensitization [21, 22]. A large single dose is less likely to sensitize than prolonged or frequent doses [23, 24]. Women have a 35% higher incidence of adverse cutaneous reactions and a twofold higher incidence of anaphylactic reactions following radio-contrast media [23, 25, 26]. Young adults are more likely to react than infants or the elderly [23]. Atopic predisposition does not increase the likelihood of a reaction but may contribute to a more severe allergic reaction [21, 27–29]. Proteins, high molecular weight peptides (> 1 kDa) and drugs that can haptenate serum proteins are more likely to elicit IgE-mediated reactions [23]. Genetic polymorphisms in the HLA region may predispose to drug hypersensitivity [30–32]. Viral infections such as HIV, Herpes and EBV-related mononucleosis, are associated with an increased likelihood of drug reactions [33, 34]. Conditions, such as cystic fibrosis are associated with an increased risk of reactions to antibiotics possibly because of repeated antibiotic use in these patients [35]. Aspirin and NSAIDs may exacerbate chronic urticaria [36] while ACE inhibitors can aggravate angio-oedema in susceptible individuals [37–40].

Clinical patterns of drug allergy

Table 4 shows clinical patterns of immunological and non-immunological ADRs. Table 5 lists drugs causing reactions that commonly present to the allergy clinic. Drug allergic reactions may involve one or more organs with the skin most frequently affected.

Angio-oedema and acute systemic reactions

In most cases penicillin, muscle relaxants, insulin and other hormones act via an IgE-mediated mechanism whereas opiates, ACE-inhibitors, NSAIDs, radio-contrast media and plasma expanders produce angio-oedema or anaphylaxis by non-IgE-mediated mechanisms although in some cases mast cell degranulation still occurs. Parenteral administration is most likely to induce severe reactions, including anaphylaxis [41]. Penicillin has been reported as the cause in up to 75% of fatal drug reactions [42], however, a survey of drug-induced anaphylaxis in the United Kingdom found that only 12 of 67 fatal reactions were due to antibiotics [43]. Six of the 12 followed the first dose of a cephalosporin and four of

Table 4. Clinical patterns of immunological and non-immunological adverse drug reactions

Systemic reactions	
Anaphylaxis	Antibiotics, neuromuscular blockers, general anaesthetics, radio-contrast media, recombinant proteins (e.g. omalizumab), intravenous B vitamins (e.g. thiamine) [152], allergen extracts [19, 153]
Serum sickness	Antibiotics, allopurinol, thiazides, pyrazolones, vaccines, phenytoin
SLE-like	Procainamide, hydralazine, isoniazid, minocycline, chlorpromazine, infliximab, etanercept, β-lactam antibiotics, propranolol, streptokinase, sulphonamides, NSAIDs
Scleroderma-like	Bleomycin
Microscopic polyangiitis	Amphetamines
Drug rash with eosinophilia systemic symptoms (DRESS) also called drug hypersensitivity syndrome (DHS)	Anticonvulsants (particularly carbamazepine, phenobarbitone and phenytoin), allopurinol, sulphonamides, dapsone, minocycline, gold salts, strontium ranelate [154–156]
Toxic epidermal necrolysis (TEN)	Antimicrobials: sulphonamides, nevirapine Anticonvulsant agents, NSAIDs, allopurinol, corticosteroids, moxifloxacin [154, 156]
Stevens–Johnson syndrome (SJS)	Antimicrobials: sulphonamides, nevirapine Anticonvulsant agents, allopurinol, corticosteroids, carbamazepine, modafinil, NSAIDs (especially piroxicam) highest risk early in the course of therapy, lamotrigine, phenytoin, minocycline [157]
Organ-specific reactions	
Cutaneous	
Urticaria/angio-oedema	Antibiotics, recombinant proteins (e.g. omalizumab), ACE inhibitors, anticonvulsants, NSAIDs, neuro-muscular blockers, salicylates, statins, narcotic analgesics, azole antifungals [44]
Pemphigus foliaceus	Penicillamine
Purpura	NSAID, sulphonamides, allopurinol, carbamazepine, warfarin, corticosteroids, minocycline, phenobarbitone [157]
Maculopapular rash	Ampicillin, other antibiotics and several other drugs
Contact dermatitis	Topical antibiotics, topical antihistamines, corticosteroids, excipients (e.g. parabens)
Photodermatitis	Griseofulvin, sulphonamides, tetracycline, amiodarone, isotretinoin, furosemide, all antipsychotics, barbiturates, ACE-inhibitors, nifedipine, piroxicam
Acute generalized exanthematous pustulosis (AGEP)	Antibiotics (e.g. β-lactam, macrolides, cephalosporins, tetracyclines), antimycotics (e.g. griseofulvin, nystatin, itraconazole), acetylsalicylic acid, paracetamol, allopurinol, calcium channel blockers [158]
Fixed drug eruption (FDE)	Antimicrobial agents (e.g. sulphonamide and tetracycline antibiotics), NSAIDs (e.g. ibuprofen), paracetamol, acetylsalicylic acid, sedatives (e.g. barbiturates, benzodiazepines), phenolphthalein, dapsone, hyoscine butylbromide, cytokines, chemotherapeutic agents, anticonvulsants, psychotropic agents, amide local anaesthetics [44]
Erythema multiforme (EM)	Carbamazepine, phenytoin, abacavir [157]
Nephrogenic systemic fibrosis (NSF)	Gadolinium-containing MRI contrast agents [159]
Pulmonary	
Asthma	Aspirin/NSAIDs, β-blockers, ACE inhibitors, opiates
Cough	ACE inhibitors
Interstitial pneumonitis	Bleomycin, methotrexate, cyclophosphamide, gold, penicillamine, nitrofurantoin, NSAIDs, amiodarone, ACE inhibitors, β-blockers, phenytoin, granulocyte macrophage colony stimulating factor (GM-CSF)
Pulmonary eosinophilia	NSAIDs, penicillin, minocycline, nitrofurantoin, metotrexate, sulphasalazine, amiodarone, ACE inhibitors, β-blockers, phenytoin, bleomycin, sulphonamides, iodinated radio-contrast media
Organizing pneumonia	Bleomycin, methotrexate, cyclophosphamide, amiodarone, β-blockers, carbamazepine
Hepatic	
Cholestatic hepatitis	Phenothiazines, carbamazepine, erythromycin, anti-tuberculous drugs
Hepato-cellular hepatitis	Methyldopa, halothane, isoniazide, gold, allopurinol
Renal	
Interstitial nephritis	Methicillin, NSAIDs, sulphonamides, proton pump inhibitors [57]
Membranous nephritis	Gold, penicillamine, ACE inhibitors, NSAIDs, cyclosporin, gentamicin
Haematological	
Haemolytic anaemia	Penicillin, cephalosporins, mefenamic acid, methyldopa
Thrombocytopenia	Heparin, quinine, sulphonamides, cephalosporins, thiazides, gold salts
Neutropenia	Penicillin, cephalosporins, anticonvulsants, thiouracils, gold salts
Cardiac	
Valvular disease	Ergotamine, dopamine agonists (cabergoline, pergolide)
Musculo-skeletal/neurological	
Polymyositis	Thiouracils
Myasthenia gravis	Penicillamine
Aseptic meningitis	NSAIDs, antimicrobials, vaccines

NSAIDs, non-steroidal anti-inflammatory drugs.

Table 5. Drugs causing adverse drug reactions commonly presenting to the allergy clinic

Penicillins and other β-lactams
Non-β-lactam antibiotics
Reactions during general anaesthesia due to
• Neuromuscular blockers
• Anaesthetic agents
• Latex (during general anaesthesia)
Local anaesthetics
Aspirin/NSAIDs
ACE inhibitors
Plasma expanders: gelatin, dextran
Others
• Insulin
• Heparin
• Opiates
• Vaccines
• Radio-contrast media
• Chlorhexidine
• Povidone iodine
• Corticosteroids

NSAIDs, non-steroidal anti-inflammatory drug.

these patients were previously known to react adversely to penicillins.

Cutaneous reactions

Approximately 30% of drug-induced reactions are cutaneous and occur in 2–3% of hospitalized patients [44–46]. There are many clinical patterns of skin rash, some of which can easily be confused by non-dermatologists. Therefore, a rational approach is to be aware of the underlying immune mechanisms. For example acute urticaria comprises erythematous weals with individual lesions lasting 2–12 h. Immunologically mediated urticarias resulting from type I IgE-mediated mechanisms develop early if there has been previous exposure to the causal drug but less commonly 7–14 days after starting the first treatment course. Urticaria that is not IgE-mediated, e.g. to aspirin, NSAIDs, opiates, vancomycin or quinolones can come on soon after first exposure.

Clinically, type IV T cell-mediated reactions can be similar and most commonly result from exposure to antibiotics, anticonvulsants, anti-tuberculosis drugs, ACE inhibitors and NSAIDs [47]. So-called 'toxic erythemas' resemble urticarial weals but are a form of T cell-mediated delayed hypersensitivity. Individual lesions last days rather than hours and develop 2–4 days after commencing the causative drug. Maculopapular rashes which also result from a T cell-mediated mechanism are symmetrical and may become confluent but spare the palms and the soles [48]. These eruptions can occur in patients with chronic viral infections [23] and may regress spontaneously even with continued use of the implicated drug.

Previously, erythema multiforme (EM) was regarded as forming a continuous spectrum with more severe cases involving the mucosae (Stevens–Johnson syndrome or SJS) and skin lesions forming blisters, which when extensive, formed toxic epidermal necrolysis (TEN). However, the predominant view now is that, based on the patterns of EM lesions and the extent of epidermal detachment, these are clinically separable entities. EM occurs as an eruption of circular, targetoid lesions spreading from the extremities to the face and trunk and involves the palms and soles. The initial lesions provoke a 'burning' feeling or pain but not itching. Lesions differ from urticaria and toxic erythemas in that the centres in EM are darker red. Bullous EM presents with target lesions and any blistering involves $<10\%$ of body surface area (BSA); SJS is characterized by widespread erythematous or purpuric lesions or flat atypical targets and blistering involving $<10\%$ BSA; overlap SJS/TEN presents with lesions that are like those in SJS but epidermal detachment affects between 10% and 30% BSA; TEN may present with a rash which is like that in the overlap but epidermal detachment is $>30\%$; alternatively TEN may present without 'spots' but with epidermal detachment in large sheets, affecting $>10\%$ BSA [49]. The more severe syndromes can be life-threatening and the drug must be stopped immediately. The cutaneous 'necrolysis' is due to massive apoptotic death of epidermal cells which is very hard to stop. When this condition is suspected, and before it becomes severe, it is vital to place the patient in a unit with experienced and specialized staff – usually an intensive care unit and failing that a burns unit.

Additional T cell-mediated patterns include the 'fixed drug eruption' (FDE) and 'acute generalized exanthematous pustulosis' (AGEP). In FDE red or brownish circular lesions develop at exactly the same site(s) following each exposure to the culprit drug. Sometimes these can be very extensive and can even blister, when they can be confused with SJS/TEN. However, there is generally absence of the systemic features and a much better prognosis. Common culprits include phenolphthalein-containing laxatives, NSAIDs and antibiotics including sulphonamides. For unclear reasons, drug-specific memory T cells take up residence in the affected areas of skin. In AGEP, an extensive rash of fine pustules arising on erythematous areas develops. Drug-specific T cells release large amounts of IL-8 which induces formation of neutrophil-rich sterile pustules.

Type II reactions include pemphigus and pemphigoid – auto-immune blistering diseases in which specific autoantibodies target different antigenic constituents of the intercellular attachments in the epidermis (pemphigus) or the dermo-epidermal basement membrane (pemphigoid).

A purpuric/petechial rash may be indicative of a vasculitic process (Gell and Coombs type III hypersensitivity) and further investigation including a platelet count, renal

function, C3/C4 levels, ANA and skin biopsy may be required (Table 1).

In some cases cutaneous reactions appear to result from drug administration although the same drug may be subsequently tolerated [45]. For example, a high frequency of rashes is documented in patients affected by mononucleosis treated with amoxicillin/ampicillin and cutaneous reactions occur more frequently in HIV-infected subjects treated with trimethoprim-sulfamethoxazole (reviewed in [45]). This suggests that for some drug reactions the presence of a systemic viral infection with Herpes viruses (Epstein–Barr) or HIV can act as a co-factor. It is not known whether food or exercise could also act as co-factors for an ADR in the same way as is known for viruses.

Respiratory reactions

Airway involvement in drug-induced anaphylaxis may occur as a consequence of either laryngeal oedema causing upper airway obstruction or bronchial constriction or both. ACE-inhibitor-induced angio-oedema is likely to result from reduced inactivation of bradykinin [50]. One-third of all the acquired angio-oedema treated in A/E results from ACE inhibitor use [51]. In susceptible individuals acute asthma and rhinitis can result from ingestion of aspirin/NSAIDs through cyclooxygenase-1 inhibition [47, 52]. Cough commonly occurs with ACE inhibitors and is more prevalent in women [50, 53].

Pulmonary eosinophilia is characterized by fever, rash, peripheral blood eosinophilia and pulmonary infiltrates visible on a chest radiograph as transient shadows. A number of drugs such as NSAIDs, penicillin, minocycline, nitrofurantoin and sulphasalazine may be responsible. Organizing pneumonia, alveolitis, pneumonitis and pulmonary fibrosis can all be drug-induced (Table 4) [54]. Interstitial lung disease with pleural involvement should alert the physician to the possibility of a drug-induced cause.

Other reactions

Hepatitis can be caused by many drugs, e.g. anti-tuberculous drugs, phenothiazines, carbamazepine or indomethacin. Immune-mediated hepatocellular necrosis has been described with methyldopa, halothane, allopurinol, isoniazid and gold salts [55, 56].

Interstitial nephropathy may result from β-lactam antibiotics, proton pump inhibitors [57], sulphonamides and NSAIDs.

Haemolytic anaemia can be caused by penicillin and methyldopa, *thrombocytopenia* by heparin, quinine, sulphonamides, thiazides and gold salts and *neutropenia* can result from treatment with penicillin, anticonvulsants, thiouracils and gold salts.

Drug hypersensitivity syndrome, DRESS, can result from treatment with anticonvulsants leading to a life-threatening reaction with symptoms of pyrexia, lymphadenopathy, hepatitis, nephritis, angio-oedema and eosinophilia [23, 58]. DRESS can also be caused by dapsone, minocycline, sulphasalazine, strontium ranelate and allopurinol. A recently recognized complication is re-activation of Herpes viruses (HHV6, HHV7), Epstein–Barr virus and cytomegalovirus [59, 60]. Confirmation of viral re-activation is obtained on blood by PCR for the specific viruses.

Diagnosis

History and examination

A detailed history is an essential first step towards an accurate diagnosis of a drug-induced reaction. This must include details of the drug (formulation, dose, route and timing of administration) together with the nature, time of onset and resolution of symptoms (Table 6) [61]. A thorough history is particularly important when patients are on several drugs. Adverse reactions can occur after taking a drug for years but may also occur a few days after discontinuation. The diagnosis is aided by a detailed knowledge of the reaction-pattern for each drug taken (Table 4). Medical notes, drug and nursing charts as well as photographs and eye-witness accounts should be sought in order to confirm the reaction and the implicated drug(s). When investigating reactions during general anaesthesia, it is essential to review the anaesthetic chart [62]. It is also helpful to determine whether the patient has taken the same or a similar drug subsequently. A literature search for all potentially responsible drugs may be

Table 6. Essential information required when referring a patient with suspected drug allergy

- Detailed description of reaction
  - Symptom sequence and duration
  - Treatment provided
  - Outcome
- Timing of symptoms in relation to drug administration
- Has the patient had the suspected drug before this course of treatment?
  - How long had the drug(s) been taken before onset of reaction?
  - When was/were the drug(s) stopped?
  - What was the effect?
- Witness description (patient, relative, doctor)
- Is there a photograph of the reaction?
- Illness for which suspected drug was being taken, i.e. underlying illness (this may be the cause of the symptoms, rather than the drug)
- List of all drugs taken at the time of the reaction (including regular medication, 'over the counter' and 'alternative' remedies)
- Previous history
  - Other drug reactions
  - Other allergies
  - Other illnesses

necessary. In addition to the clinical history, a careful physical examination can help to define possible mechanisms underlying the reaction and guide investigations; e.g. urticaria can be associated with IgE-mediated processes with antibiotics or can occur with NSAIDs by non-IgE-mediated mechanisms. Therefore, whether the rash is urticarial, maculopapular, purpuric, bullous or eczematous should be established.

Investigations

Immediate

Blood tryptase. Serum tryptase, a serine protease released from mast cells, is the only currently available blood test for the diagnosis of acute allergic reactions [63–65]. Release of tryptase is specific for mast cell degranulation, but does not distinguish between IgE-mediated and non-IgE-mediated/direct mast cell degranulation [63, 66]. Hence serum tryptase is elevated with mast cell activation and released in both anaphylactic and anaphylactoid reactions. When elevated, the serum tryptase is invaluable and indicates that anaphylaxis has occurred, but does not help to identify the specific cause. Serum tryptase peaks within 1–2 h of onset of the reaction, so a 5 mL blood sample (clotted) should be taken at this time point. A minimum volume of 1 mL of blood is usually adequate for analysis. In some cases of anaphylaxis caused by an injected drug, the serum tryptase level is higher immediately after the onset than at 1 h (unpublished) and therefore two blood samples should be taken, the first immediately after the patient is resuscitated, and a second within 2 h. However the level may still be raised for several hours after the onset of the reaction so blood taken up to 6 h afterwards may still be of value. It is essential to record the time each sample was taken. The separated serum should optimally be frozen but if required, samples can be stored at 4 °C for 24–48 h in clinical biochemistry and posted first class to an immunology laboratory, either as whole blood or serum. The assay is widely available through most regional immunology laboratories. A baseline tryptase is needed to interpret the results, but can be taken either >24 h after the reaction or when the patient is referred for later investigation.

In a study of 789 patients with allergic reactions during anaesthesia the positive predictive value of tryptase in the diagnosis of anaphylaxis during anaesthesia was 93% and negative predictive value 54% [67]. There are data (unpublished) to suggest that the mast cell tryptase is not always raised in anaphylaxis, and the level may depend on the clinical features. For example, if hypotension is present, serum tryptase is more likely to be raised. Therefore, a single normal mast cell tryptase does not exclude anaphylaxis and results should always be interpreted with reference to the clinical setting and severity of the reaction.

Post-mortem tryptase levels can be taken up to 72 h after death if anaphylaxis is suspected. In a study of tryptase levels in 193 post-mortem samples of which seven were known to have had anaphylactic or anaphylactoid deaths the sensitivity and specificity using a cut-off value of 10 μg/L was found to be 86% and 88%, respectively [68]. Baseline tryptase may be elevated in certain disorders including mastocytosis and patients with this condition are more susceptible to drug-induced anaphylaxis [69].

Later investigations. In many cases no further tests are required acutely. Renal function, urine microscopy, liver function, full and differential blood count, ESR, CRP, ECG and CXR may be indicated in patients according to the clinical presentation or implicated drugs (Table 1).

The presence of antinuclear antibody or low complement levels may indicate drug-induced SLE although many cases remain seronegative. A positive ANCA supports a diagnosis of vasculitis and the presence of cryoglobulins indicates an immune-complex-mediated process.

Skin tests. Skin tests provide evidence of sensitization to a specific drug but must always be interpreted within the appropriate clinical context and not used to screen for drug allergy (Tables 7 and 8) [70, 71]. For penicillin, muscle relaxants and carboplatin skin testing can provide useful information [70, 72–75]. However, for most drugs

Table 7. Skin tests

- Provide supportive evidence (with clinical history) for diagnosis (or exclusion) of IgE-mediated allergy
- Educational value, providing a visual illustration that may reinforce verbal advice to the patient
- Requires training, both for undertaking and interpretation of result

Practical aspects of SPT:

- Controls, positive (histamine) and negative (diluent), must be included
- A positive is a weal size of diameter of 3 mm or more greater than negative control surrounded by a flare
- Should be read at 10–15 min
- Patients should have been off antihistamines for 3 days
- Oral corticosteroids do not (significantly) inhibit skin prick tests
- False-positive and false-negative skin tests are likely to occur especially with drugs not known to cause IgE-mediated reactions or when the SPT concentrations are not validated
- Dermatographism may confound results
- Should not be performed in areas of severe eczema
- SPTs are more specific, safer, easier to interpret, but less sensitive than intradermal tests

SPT, skin prick test.

Table 8. Prick and intradermal skin testing

Indicated	For the identification of IgE-mediated conditions
Not indicated	For the identification of IgG/IgM-mediated immune conditions
	In SJS, TEN and DRESS but patch tests can be useful
Can be helpful (delayed intradermal reading)	In documenting DTH

SJS, Stevens–Johnson syndrome; DTH, delayed-type hypersensitivity; DRESS, drug reaction/rash with eosinophilia and systemic symptoms; TEN, toxic epidermal necrolysis.

the relevant immunogen (intermediate metabolite) is unknown and therefore the predictive value of skin testing remains undetermined. Both false-positive and false-negative results may occur. For ethical reasons the positive predictive value of skin testing for many drugs cannot be precisely evaluated as challenge testing may provoke life-threatening reactions.

When penicillin is suspected as the cause of an immediate reaction, skin testing with the major determinant penicilloyl polylysine (PPL) and the minor determinants, penilloate, penicilloate, benzyl penicillin (minor determinant mix or MDM) of penicillin, and amoxicillin provide useful information if positive [76–78]. Standardization of skin test reagents has been attempted for penicillin with PPL and MDM determinants with the re-introduction of a commercial kit. Comparison between the previous and the current commercial preparation on a database group of known penicillin sensitive patients has shown comparable results [79].

Until recently consensus, mainly derived from the United States, indicated that in the presence of a positive clinical history for β-lactam allergy and negative skin tests for PPL and MDM, patients had only a 0–6% risk of reacting with an oral challenge [77, 78, 80–83] and an approximately 6% risk of reacting upon subsequent exposure (calculated from [76–78, 81, 83, 84]). This position has been challenged by a European Drug Allergy Group position paper stating that negative skin tests for major and minor components of penicillin and for amoxicillin and ampicillin are insufficient to exclude β-lactam allergy and that provocation tests with the specific β-lactam are required [84, 85]. The absolute requirement for oral provocation in patients with positive clinical history and negative skin tests for β-lactams has been recently re-emphasized. In this study 32.9% of allergic patients had negative skin tests but were positive on provocation [86]. In a subsequent study 17.4% of patients with negative skin tests for major and minor components of penicillin were positive to a β-lactam on provocation [87]. The BSACI position is that patients with a positive history and negative skin test should undergo drug challenge with the β-lactam responsible for the original reaction. Some patients react to the side chain of the β-lactam ring and therefore, skin tests should include the specific β-lactam (e.g. cephalosporin) implicated in the reaction [88–90].

Some subjects develop positive immediate responses to several β-lactams mostly within the same family, but others develop a selective response. Penicillin may be safely administered to some patients allergic to cephalosporins but only after negative skin test results to penicillin determinants and following a negative penicillin challenge [91, 92]. Conversely, patients with a history of an immediate reaction to penicillin but negative skin tests and negative challenge to penicillin can be prescribed a second or third generation cephalosporin as $< 1\%$ have a subsequent reaction [80].

Text box 1: ***Indications for investigating patients with penicillin allergy***

1. Patients with a history of an allergic reaction when on multiple drugs, e.g. during GA
2. Patients allergic to multiple antibiotics
3. Patients with an absolute requirement for penicillin, e.g. those with central nervous system syphilis, immunodeficiency, post-splenectomy, or with cardiac valve disorders requiring prophylaxis.

Skin testing to NMBA using both SPT and intradermal tests are invaluable in the appropriate clinical context when used for the diagnosis of an allergic reaction during general anaesthesia. However, the specificity of a positive test to muscle relaxants is likely to be poor as one study screening patients pre-operatively found that 9% had either a positive skin test or specific IgE to quaternary ammonium ions [93]. Caution with interpretation is always required as anaphylaxis despite negative skin tests to NMBAs has also been reported [94, 95].

The usefulness of skin testing in the diagnosis of platinum salt hypersensitivity has been confirmed recently [96, 97]. For carboplatin the negative predictive value of skin testing appears good and in one study only 4% of patients experienced a reaction after a negative test [75].

Skin prick tests for specific Immunoglobulin E-mediated drug reactions. SPTs are useful for the diagnosis of IgE-mediated reactions with both low molecular weight [77, 98, 99] and high molecular weight agents [24, 99–102]. Tests are normally carried out at therapeutic concentrations unless the drug possesses intrinsic histamine-releasing activity (e.g. atracurium and

mivacurium) in which case a dilution of 10^{-3}–10^{-1} may be appropriate to avoid false-positive results. Rarely it may also be useful to test these drugs at therapeutic concentrations when comparison with responses in 'normal' or unexposed individuals may be needed in order to exclude a 'toxic' response [103]. In any situation where the mechanism of ADR is unknown a negative result is unreliable. The parenteral preparation should be used for skin testing. If this is not available, an oral liquid may be used or a tablet dissolved for drugs that are soluble but only available in tablet form although this is less likely to provide a reliable result [102].

Intradermal tests. Intradermal tests are more sensitive but less specific than SPTs if the same concentration is used. Intradermal testing requires considerable experience in both technique and interpretation. If the SPT is negative, intradermal tests are carried out by injecting 0.02–0.03 mL of the corresponding drug intradermally with a starting concentration of between 10^{-5} and 10^{-1} of that used for SPTs depending on the clinical situation. If the test is negative, 10-fold increasing concentrations are used sequentially until the test is positive or the highest non-irritant concentration is achieved [104]. Intradermal tests should be read at 15–20 min and require expert interpretation to differentiate true positive from irritant reactions and to understand the significance of a negative test. Water-soluble drugs are prepared from parenteral preparations by dilution in sterile 0.9% NaCl solution.

Intradermal tests are more likely to trigger systemic allergic reactions and hence should only be undertaken after SPT and by experienced staff in a hospital setting with equipment available for resuscitation [104, 105]. When investigating a previous life-threatening ADR, the risks/benefits of intradermal tests must be carefully evaluated.

All results should be compared with an appropriate negative control and ideally data from a number of control subjects should be available for both skin-prick and intradermal tests to exclude false-positive reactions caused by irritant reactions and the intrinsic histamine-releasing properties of drugs such as opiates and some muscle relaxants. Similarly, irritant concentrations of drugs should be identified by testing on healthy volunteers [106] although non-irritant doses have been identified for some drugs [104]. A delayed intradermal reaction positive at 48 h may indicate delayed-type hypersensitivity and can be used in association with patch testing to document delayed reactions to antibiotics [107, 108].

Patch tests for T cell senzitization. Patch testing involves placing potential allergens at non-irritant concentrations on the patient's back for 48 h under aluminium discs attached to hypoallergenic tape. Readings are performed at 48 and 96 h. Experience is required to differentiate true hypersensitivity reactions from false-positive irritant reactions. False negatives occur due to poor skin penetration by large drug molecules or due to a low dose of drug used [107]. A sensitivity range of between 11% and 43%, has been reported reflecting different populations selected for patch testing [109, 110]. Patient with maculopapular exanthema are the most likely to produce a positive patch test on testing. The drugs that are worth investigating are antimicrobials (especially β-lactams, clindamycin and trimethoprim), antihypertensive agents and anticonvulsants. In FDEs patch tests can also be useful but only give positive reactions if performed on the sites of lesions.

Patch testing other cutaneous reaction patterns, such as DRESS syndrome, EM, SJS, TEN and photosensitivity is not well validated, has a low sensitivity for SJS/TEN [111], but can be helpful in highly selected cases. Excipients of oral, parenteral or topical drugs are potential allergens but it is usually the active agent that is the cause. Patch tests are usually commenced with 1% of the pure drug in white soft paraffin; subsequent patches with 5% and 10% can be used if there is no response to 1%. There is very little risk of provoking SJS or TEN with patch tests although rarely a mild rash can occur which reflects some systemic absorption from the patches. If a false-negative reaction is strongly suspected after patch testing and a suitable injectable form is available then intradermal testing of an allergen can be helpful. In SJS/TEN this is a slow process as testing must start at very low drug concentrations. In non-immediate allergic reactions to penicillins, intradermal testing may be more sensitive than patch testing [107, 108]. However, wider acceptance and use of patch testing is required to collect data on the validity of this investigation in drug allergy.

Specific immunoglobulin E in sera. Testing for specific IgE in sera is only available for a limited number of drugs. These tests have unknown sensitivity and specificity as they require validation against sera from definitive cases. Serum-specific IgE is therefore useful when positive but negative results are difficult to interpret [112]. A further disadvantage is that potentially cross-reacting drugs or other co-administered drugs and reagents cannot be tested at the same time and therefore skin testing for drug allergy is preferable. We recommend that both skin tests and serum-specific IgE for unvalidated drugs should only be undertaken in expert centres where their performance characteristics can be evaluated over time in well-characterized cases.

Other in vitro tests. A number of other *in vitro* tests have been proposed for the investigation of drug allergy reactions. Among these is the cellular allergen stimulation test (CAST) for the measurement of leukotrienes after

peripheral blood leukocyte stimulation, basophil histamine release tests and a basophil activation test. Although, CAST is commercially available it has not been sufficiently evaluated to recommend as a standard investigation outside the context of prospective studies. Basophil activation markers using fluorescence activated cell sorter (FACS) analysis are currently being evaluated for certain types of drug allergic reactions but there seems to be no evidence currently of any advantage of these tests over skin testing [113, 114]. Lymphocyte transformation and lymphocyte cytotoxicity tests are not sufficiently standardized to be useful in clinical practice and are not currently available outside the research setting. However, because of the paucity of methods for *in vitro* testing we recommend that these tests are used in major drug allergy centres to allow for extensive evaluation and standardization.

Drug provocation tests. Challenge with specific drugs may be carried out after other possible investigations have been exhausted and the diagnosis remains in doubt. For each case a precise risk-benefit assessment must be established with the patient and referring clinician to determine whether the patient needs to be investigated and, in high-risk cases, consensus with peers should be sought.

The primary aim of a provocation test is to exclude drug sensitivity but it can also be used to confirm a diagnosis. In the majority of cases, it is inadvisable to carry out provocation testing if the reaction has resulted in a life-threatening reaction. Even with less serious reaction the rationale for provocation must be carefully considered [115] and the challenge then only carried out by personnel experienced in drug challenges and with adequate resuscitation facilities readily available. Provocation tests are also performed for delayed reactions and it is then necessary to give a prolonged course of the suspected drug after an initial negative challenge in the clinic. In this situation an emergency management plan should allow self-treatment of an allergic reaction.

Challenge testing is contraindicated for certain types of reactions, e.g. SJS, TEN, DRESS and EM and in patients with severe concurrent illness. For β-lactams a positive history confirmed by positive skin test is usually sufficient. If skin tests are negative, a challenge may be indicated to exclude false-negative skin tests which may occur in patients tested with penicillin and may be more likely in patients tested with amoxicillin [84, 86, 87, 116]. Skin tests are almost always unhelpful for drugs such as aspirin and NSAIDs [117] and therefore challenge with the suspected drug is needed, if there is doubt on history, or if several drugs were co-administered. Drug challenges should be designed to either implicate or exclude a drug as the cause of a reaction or to search for a suitable alternative which could potentially cross-react with the suspect drug, e.g. testing with a cephalosporin (to which skin tests are negative) in a penicillin-allergic subject [91, 118]. With local anaesthetic reactions the likelihood of a true allergic reaction is low but drug challenge is usually required as the validity of skin testing remains unproven. Provocation is also undertaken when drug avoidance is not practical either because more than one drug was involved in the original reaction or in the absence of suitable alternatives, e.g. opiates and certain antibiotics where drug provocation would be used to definitively confirm intolerance. A summary of drug provocation protocols has been reported in a retrospective study of 898 consecutive patients [119].

Written informed consent should be obtained before undertaking drug challenge. Where subjective symptoms or signs could account for the previous reaction, it may be necessary to start with a single-blind placebo challenge in order to minimize the possibility of a false-positive result [115]. The starting dose for drug challenge will vary depending on the severity of the previous reaction, the dose that caused it and whether the challenge is oral or parenteral. With some parenteral drug challenges this can be as low as 10^{-9} of the therapeutic dose and the challenge progresses in 2–10-fold increments until the therapeutic dose is reached. To minimize the risk of anaphylaxis, the oral rather than the parenteral route is preferred if possible. A negative reaction indicates that the patient is not sensitive at the time of the challenge [70, 120, 121]. However, false-negative reactions can occasionally occur due to missing co-factors such as viral infection or exercise, too low a dose being used for provocation, current or recent use of anti-allergic medications such as antihistamines, corticosteroids or anti-leukotrienes or conceivably due to desensitization by the challenge procedure [115]. Theoretically it is also possible that drug provocation leads to resensitization, although there is a lack of evidence that this occurs to penicillins [122].

A patient taking corticosteroids, antihistamines or tricyclic antidepressants may have a modified response to the challenge. β-blockers should be stopped 24 h before the drug challenge. The dose schedule for each challenge should be tailored to the individual patient depending on the nature of the previous reaction and pharmacokinetic profile of the drug. Pregnancy is generally considered a contraindication to drug provocation unless the drug is required during pregnancy or delivery.

An algorithm for the management of a suspected ADR is shown in Fig. 1.

Drug allergy in children

Epidemiology

Giving children a label of drug allergy is common and often leads to lifelong avoidance of certain drugs

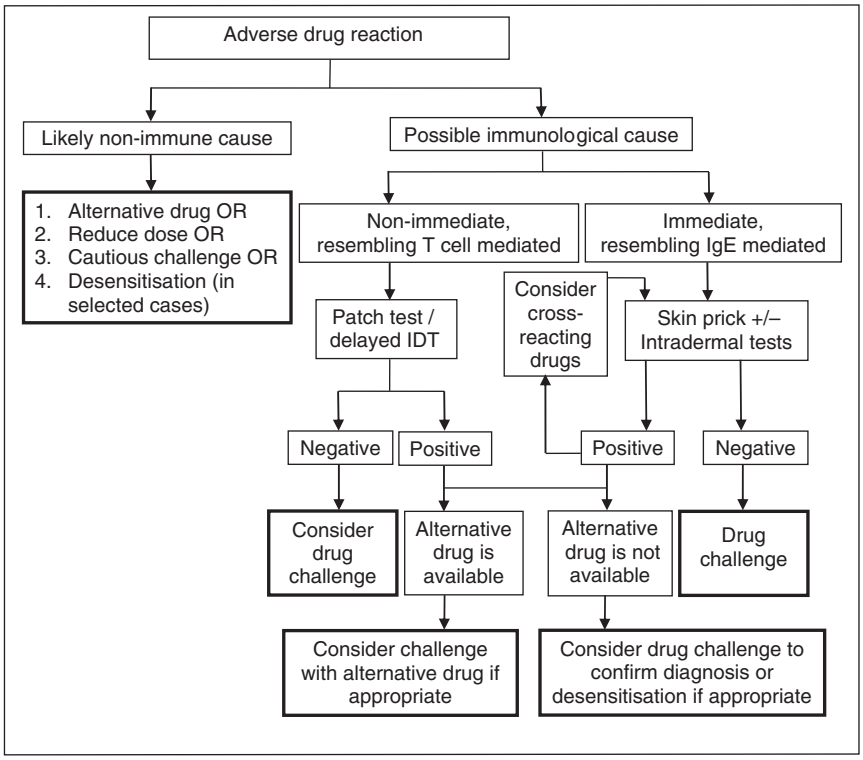

Fig. 1. Algorithm for the management of a suspected adverse drug reaction.

particularly antibiotics [123]. Undertaking investigation in children can be challenging because of the difficulty of undertaking intradermal tests. For this reason drug allergy is not usually confirmed by appropriate investigation and a pragmatic approach often taken by avoiding the suspected drug. This results in diagnostic overestimation as in the majority of studies no attempt is made to ascertain whether the reaction is allergic by skin testing and/or oral challenge. Therefore reports on the prevalence of drug hypersensitivity in children are scanty [124]. In three large cross-sectional parent surveys on drug allergy, the prevalence of self-reported drug allergy ranged between 2.8% and 7.5% [125–127]. However, in the study reporting a prevalence of 7.5% (108/1447), only 4.2% (61/1447) of cases had a clinical history suggestive of an allergic mechanism [127] but this was not investigated by skin testing.

When SPT, intradermal test or oral challenge were undertaken in children who gave a plausible history of drug allergy, 94% were able to tolerate the drug [125]. Therefore, many children can have an unnecessary lifelong label of drug allergy possibly leading to the prescription of less effective and more costly treatments [123, 128].

There is a paucity of studies reporting allergic drug reactions in children with most only providing figures for total numbers of ADRs. From a meta-analysis of 17 prospective studies the proportion of hospital admissions due to ADR was 2.1% of which 39.3% resulted from a life-threatening reaction. The incidence of ADRs in hospitalized children was 9.5%, while in the outpatient population the incidence was 1.5% [129] with severe reactions occurring in 12.3%. A retrospective cohort study over 10 years also found that a minority of ADRs in children are severe with 11% described as requiring either special care or causing harm. Mild reactions were commonly associated with antibiotics with the most severe reactions occurring with anti-neoplastic drugs and anticonvulsants [130]. From these studies it was not possible to determine the proportion of children with hypersensitivity reactions although the overall figures suggest that ADRs are a significant cause of ill-health in children accounting for substantial healthcare costs. However, clearly reliable prospective studies are required.

Cutaneous reactions

Cutaneous reactions are among the commonest of all ADRs with 2.5% of children treated with any drug and up to 12% of children treated with an antibiotic experiencing a cutaneous reaction. However, it is likely that a proportion are due to the underlying infection rather than the antibiotic itself.

The allergist should be able to recognize the different clinical patterns caused by ADRs as the majority of cutaneous reactions are not allergic in nature. SPT and

intradermal test may confirm immediate IgE-mediated reactions such as urticaria/angio-oedema and anaphylaxis and late reading of intradermal tests and patch testing confirm delayed-type hypersensitivity but considerable experience and clinical correlation is necessary in the interpretation of these tests.

Skin testing is not indicated for type III serum sickness reactions and can potentially trigger severe cutaneous reactions such as SJS, TEN and DRESS [131].

β-*lactam allergy*

Penicillins and cephalosporins are commonly prescribed in children and often responsible for IgE-mediated reactions. Allergic-type symptoms may also result as a consequence of the infectious agent or from an interaction between the infectious agent and the β-lactam, e.g. in infectious mononucleosis. If prescription of a β-lactam is necessary, a practical approach to the diagnosis of allergy requires a careful clinical history, SPT and intradermal testing. Children with negative tests should undergo oral challenge to identify the false negatives from skin testing and this is particularly important for accelerated and delayed reactions which are unlikely to be IgE-mediated [27, 132]. Children in whom the diagnosis of β-lactam allergy has been excluded previously by skin testing and/or oral challenge, have a low prevalence of subsequent adverse reactions to β-lactams and subsequent skin testing for β-lactams is unnecessary [133].

In a large prospective study over an 8-year period, children with a clinical history of immediate penicillin and/or cephalosporin allergy were skin prick/intradermal tested with PPL, MDM, benzylpenicillin, amoxicillin, ampicillin and a range of cephalosporins, and underwent *in vitro* testing. Oral challenges were also performed if the skin tests were negative. Surprisingly, 58.3% of children were found to be positive (94% positive for penicillin and 35.3% for cephalosporin) [134]. Although the results were subsequently questioned on technical grounds the study reminds us that the proportion of positive results on skin testing is determined by pre-test probability from the clinical history [135].

Structural homology particularly of the side chain is helpful in predicting cross-reactivity between penicillins and cephalosporins and most often found for first generation cephalosporins. However in each case it is important to take a careful clinical history and skin test to the implicated drug and potentially cross-react drugs [136].

Hypersensitivity to NSAIDs

Despite the relatively common use of NSAIDs in children, there are only few reports of testing for NSAID sensitivity in part due to the difficulty of undertaking oral provocation tests in children. However, evidence-based protocols for oral NSAID challenges have been reported [137].

A review of relevant studies of NSAID-induced cutaneous reactions in children reported a prevalence of 0.3–7.8% depending on whether the investigation was carried out in non-atopics or in children attending the allergy clinic or suffering from food allergy. Atopic children were found to be at risk of developing cutaneous reactions to NSAID [138]. Respiratory reactions to NSAID varied in different studies between 0% and 28% depending on the parameters (e.g. NSAID drug studied, sex of patients, etc.) of the investigation undertaken [138]. The majority of children showed a reaction to more than one NSAID. The mechanism is not IgE-mediated and SPTs are generally unhelpful [138]. Intolerance to paracetamol is rare but when present is often associated with intolerance to NSAIDs [139].

In a hospital population of Asian children, NSAID-intolerance was the second most common cause of ADR. In this study children with a diagnosis of NSAID-intolerance confirmed by modified oral provocation were found to be older (mean age 7.4 vs. 4.8 years) and more likely to be asthmatic than those who reacted to antibiotics [140].

Treatment

Acute drug reaction

Anaphylaxis must be treated promptly and appropriately and steps taken to prevent a further reaction (see Text box 2).

Referral should be made to investigate the cause of the reaction. Safe alternative medication may need to be identified quickly in order to ensure continuity of patient care and in the acute stage this is often more important than confirming the identity of the offending drug. In less severe cases where there is no alternative to the suspected drug, suppression of symptoms using corticosteroids and/or antihistamines may be considered.

Text box 2: ***Key features of acute management***

1. Stop suspected drug (e.g. IV infusion)
2. Treat the reaction
3. Identify and avoid potential cross-reacting drugs
4. Record precise details of the reaction and its treatment
5. If possible identify a safe alternative
6. If necessary – consider desensitization (rarely indicated)

Desensitization

If a drug-induced reaction is IgE-mediated and there are no suitable alternatives, it may be possible to desensitize the patient for one course of treatment. This is rarely

required but has been used for penicillin, certain other antibiotics, taxanes and platinum-based cancer chemotherapeutic agents [141–143]. Desensitization is started at a lower dose (10–1000-fold less) than that resulting in a positive intradermal reaction and increments given at regular intervals (every 20–30 min or every 60–90 min orally) until the therapeutic dose is reached [101]. Drug specific protocols should be followed where these exist. The procedure may take between 6 h to a few days depending on the starting dose, route of administration and challenge-induced symptoms requiring modification to the dosing-schedule. Oral desensitization is less likely to provoke a severe reaction [22, 141], but intravenous desensitization, e.g. for cephalosporins, may be necessary. Desensitization is not always successful and the state of desensitization is lost when the drug is discontinued. Aspirin causes non-IgE-mediated reactions involving severe bronchospasm, but oral tolerance (traditionally referred to as desensitization) is still possible if these drugs are deemed necessary or if the patient's symptoms of rhinosinusitis and nasal polyps are refractory to other treatments [144, 145]. Desensitization must be performed in a hospital setting by experienced staff with full resuscitation equipment readily available. A number of penicillin desensitization protocols have been reported [146].

Economic impact of drug allergy

The precise evaluation of the economic impact of drug allergy is complex. The studies on the cost of ADEs take into account both the direct costs of the acute treatment and delayed hospital discharge as well as the indirect costs resulting from the use of alternative more costly drugs [20]. There remains a need to collect separately prospective data on the burden of drug hypersensitivy to accurately define the potential benefits of expert evaluation in pharmacoeconomic terms.

The financial impact of ADRs on the Health Service is impressive. In one study, it was reported that patients stayed in hospital 1.9 days longer than control subjects with additional costs of $2262 per person [147]. In a more recent study carried out in the United Kingdom, admission to hospital over a 6-month period because of ADR gave a prevalence of 6.5% with median bed occupancy accounting for 4% of hospital bed capacity. The projected annual costs of such admissions were £466M with a fatality rate of 0.15% [10]. In a systematic review of studies of ADR in hospitalized patients, the cost of ADR to the NHS in England was reported to be in the order of £380M/year confirming the use of 4% of available bed capacity [26]. Therefore, expert evaluation of patients with a label of drug allergy would help to identify a significant proportion in whom allergy can be excluded and alternative more costly treatments avoided. Examples include patients with adverse reactions to local anaesthetics in whom the alternative treatment is general anaesthesia, and also exclusion of penicillin allergy in patients requiring more expensive and less effective alternatives.

Table 9. Patient education

- Make the patient aware that he/she is responsible for future avoidance of the culprit drug
- Encourage patient to wear an allergy bracelet stating the cause of the reaction
- Warn patient to avoid over-the-counter medications where precise constituents are unclear

Prevention of future reactions

This is an essential and often overlooked part of patient management. The patient should be given appropriate, written information about which drugs to avoid (see also Table 9). The drugs should be highlighted in the hospital notes and within electronic records where available, and the GP informed. Engraved allergy-bracelets such as those provided by Medic Alert (http://www.medicalert.org.uk/) are particularly useful when there is a risk of intravenous drug administration in an emergency, e.g. muscle relaxants, opiates or penicillin or when drugs, e.g. NSAIDs, are readily available without prescription. The specialist should provide the wording to be engraved. Adrenaline autoinjectors are not usually required if the cause of the reaction has been identified and the drug is easily avoided. Every allergic reaction should be reported to the MHRA using the yellow card scheme or by using the online system on http://www.yellowcard.gov.uk.

Future directions: pharmacogenomics

The application of genomic technology to the field of ADRs has started to provide clinically useful information. This could potentially facilitate identification of adverse reactions or allergic drug reactions in susceptible individuals or groups of individuals. Ethnicity has been reported as an important factor for susceptibility to ADRs to carbamazepine. In a Chinese population all patients who developed SJS after treatment with carbamazepine were found to have the HLA-B*1502 allele [148] whereas in a European population only 1/3 (4/12) had the allele. In another study the HLA-B*5701 allele was associated with hypersensitivity to abacavir in white, hispanic but not in black populations [30].

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These guidelines inform the management of drug allergy. Adherence to these guidelines does not constitute an automatic defence for negligence and conversely non-adherence is not indicative of negligence. It is anticipated that these guidelines will be reviewed 5 yearly.

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