**Review article**

**Drug Allergy**

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**Introduction**

Adverse reactions to pharmaceutical and diagnostic products constitute a major hazard in the practice of medicine and are responsible for substantial morbidity and cost. Adverse drug reactions can be divided into predictable and unpredictable reactions. Predictable reactions including drug toxicity, drug interactions, and adverse effects are dose dependent, can be related to known pharmacologic actions of the drug and occur in patients without any unique susceptibility. In contrast, unpredictable reactions are dose independent, often not related to the pharmacologic actions of the drug and occur in susceptible patients. These include idiosyncratic reactions, allergic (hypersensitivity) reactions, and pseudoallergic reactions. Pseudoallergic reactions resemble allergic reactions but are distinguished by the fact that an immunologic mechanism is not involved.1 In this review, we will concentrate on drug allergy, its underlying immunological abnormalities, clinical manifestations, diagnosis and management.

**Definition and Epidemiology:**

**Definition:** Drug allergy is an unpredictable immunologically mediated response to a pharmaceutical and/or formulation (excipient) agent in a sensitized person with heterogeneous mechanisms and clinical presentations. It can occur at doses significantly below the therapeutic range. Drug allergy should be differentiated from drug idiosyncracy which is an abnormal and unexpected drug effect that is unrelated to its intended pharmacologic action, reproducible on re-administration and is usually related to underlying abnormalities of metabolism, excretion or bioavailability.2

**Epidemiology:** Giving an individual a label of drug allergy is common especially in children and often leads to lifelong avoidance of certain drugs particularly antibiotics. Allergic reactions are thought to account for less than 10% of all adverse drug reactions. However, the overall incidence of allergic drug reactions is difficult to estimate accurately due to the wide spectrum of disorders they encompass and a lack of accurate diagnostic tests. Additionally, most studies on incidence of allergic drug reactions include only adult subjects. There are limited epidemiological data for specific types of hypersensitivity disorders in pediatric patients. Diagnosis of drug allergy in children can be challenging because of the difficulty of undertaking intradermal or provocation tests. For this reason drug allergy is not usually confirmed by appropriate investigation and a pragmatic approach is often taken by avoiding the suspected drug.3

The overall incidence of adverse drug reactions in the general as well as pediatric populations is estimated to be 6.7%. Only 6-10% of adverse drug reactions can be attributed to an allergic or immunologic mechanism.4 The most common culprit drugs among new drug hypersensitivity reactions were antibiotics (32%), radio contrast media (26%) and anti-neoplastic drugs (17%). The estimated incidence of drug hypersensitivity reactions was 0.18 % among hospital admissions.5

**Risk factors for developing drug allergy**

The risk factors for the development of drug allergy are poorly understood and most of the limited data come from studies on penicillin allergy in adult subjects. The presence of atopy is not a risk factor for drug allergy,5 although patients with asthma may be more prone to having severe reactions (as is the case with food allergies).6,8 The parental route of administration and repeated courses of the same or cross-reacting antibiotic appear to favor the development of immediate-type drug allergy.9 Genetic susceptibility has been described for several types of drug allergy.10, 11 Patients with ‘multiple drug allergy syndrome’ have an inherent predilection to develop hypersensitivity reactions to more than one non cross-reacting medication.12,13

**Pathogenesis and immunological classification of drug allergy**

**Haptenation:** Most medications, due to their relatively small size, are unable to elicit an immune response independently. Drugs must first covalently bind to larger carrier molecules such as tissue or serum proteins to act as complete multivalent antigens. This process is called haptenation and the drugs act as haptons. The elicited immune response
may be humoral (with the production of specific antibodies), cellular (with the generation of specific T cells), or both. Most drugs are not reactive in their native state and must be converted (either enzymatically or via spontaneous degradation) to reactive intermediates in order to bind to proteins. Frequently, the identity of the intermediates is not known, making it impossible to develop accurate diagnostic tests for drug allergy.\textsuperscript{14}

**Pi-concept:** The pi concept (pharmacological interaction with immune receptors) is a recently described mechanism of drug allergy and it is an exception to the hapten hypothesis described above, since it requires neither haptenation nor formation of reactive intermediates. In this scheme, a drug binds noncovalently to a T cell receptor, which leads to an immune response via interaction with a major histocompatibility complex (MHC) receptor. No sensitization is required, since there is direct stimulation of memory and effector T cells, analogous to the concept of superantigens. It is not clear what proportion of allergic reactions to drugs, such as antibiotics, occur via the pi mechanism vs the hapten mechanism.\textsuperscript{15}

**Immunological classification of drug allergy:** According to the Gell and Coombs system of hypersensitivity, drug allergy is comprised of immediate-type reactions mediated by drug-specific IgE antibodies (type I), cytotoxic reactions mediated by drug-specific IgG or IgM antibodies (type II), immune complex reactions (type III), and delayed-type hypersensitivity reactions mediated by cellular immune mechanisms (type IV).\textsuperscript{16} Type IV reactions can be subdivided into 4 categories involving activation and recruitment of monocytes (type IVa), eosinophils (type IVb), CD4\(^+\) or CD8\(^+\) T cells (type IVc), and neutrophils (type IVd) (table 1).\textsuperscript{14}

**Clinical manifestations of drug allergy**

Drug-induced allergic reactions can affect numerous organ systems and manifest in a variety of reactions, including various drug-induced allergic syndromes. Most of the cases present with cutaneous manifestations (about 70\%) rather than systemic manifestations or anaphylaxis.\textsuperscript{17}

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<td><strong>Type IVa</strong></td>
<td>Th1 cells activate monocyte/macrophages via IFN-γ and TNF-α</td>
<td>Contact dermatitis, bullous exanthema</td>
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<tr>
<td><strong>Type IVb</strong></td>
<td>Th2 cells drive eosinophilic inflammation via IL-5, IL-4, IL-13, eotaxin</td>
<td>Maculopapular and bullous rashes, etc</td>
<td>Patch tests</td>
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<td><strong>Type IVc</strong></td>
<td>CD41/CD81 cytotoxic T cells kill targets via perforin, granzyme B, FasL</td>
<td>Contact dermatitis, maculopapular, pustular and bullous exanthema,, etc.</td>
<td>Patch tests</td>
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<td><strong>Type IVd</strong></td>
<td>T cells recruit and activate neutrophils via CXCL-8, GM-CSF</td>
<td>Pustular xanthemata</td>
<td>Patch tests</td>
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ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; LFT, liver function tests; U&E, urea and electrolytes; CXR, chest X-ray. IFN-γ: gamma interferon; TNF-α: Tumor necrosis factor alpha; IL: interleukin; CXCL-1: Chemokine (C-X-C motif) ligand 1; GM-CSF: granulocyte monocyte colony stimulating factor; CBC: Complete blood count; ANCA: Anti neutrophil cytoplasmic antibody; Th1: T helper 1 lymphocyte; FasL: Fas ligand (quoted from Mirakian et al, 2009)\textsuperscript{17}
Drug allergy

Angio-oedema and acute systemic reactions
Angio-oedema and acute systemic reactions can occur via IgE-mediated mechanism as in cases of penicillin, muscle relaxants, insulin and other hormones, while opiates, ACE-inhibitors, NSAIDs, radio-contrast media and plasma expanders produce angio-oedema or anaphylaxis by non-IgE-mediated mechanisms. Parenteral administration is most likely to induce severe reactions including anaphylaxis. Penicillin has been reported as the cause in up to 75% of fatal drug reactions. However, a survey of drug-induced anaphylaxis in the United Kingdom found that only 12 of 67 fatal reactions were due to antibiotics.

Cutaneous reactions
There are many clinical patterns of skin rash with different underlying immune mechanisms. Because certain drug eruptions are associated with specific immunologic reactions, it is important to characterize the type of eruption in order to be able to determine the possible cause, further diagnostic tests and management decisions.

Type I IgE mediated reactions: Acute urticaria comprises erythematous wheals with individual lesions lasting 2–12 hours. Immunologically mediated urticaria 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 (figure 1).

Type IV T cell-mediated reactions: 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. So-called ‘toxic erythemas’ resemble urticarial wheals 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 (figure 2). Delayed hypersensitivity responses may also be systemic, involving lymphoid organs and other tissues throughout the body. Sensitized T cells produce a wide array of proinflammatory cytokines that can ultimately lead to lymphocytic infiltrates, disseminated granulomata, and fibrosis. It has been suggested that there is a marked clinicopathological similarity between some late-onset drug reactions and graft versus host reactions that are initiated and maintained by T cells.

Allergic contact dermatitis after exposure to medications containing active drugs, additives, or lipid vehicles in ointments is the most frequent form of drug-mediated delayed hypersensitivity. Morphologically, it usually cannot be distinguished from contact irritant dermatitis. Almost any drug applied locally is a potential sensitizer, but fewer than 40 allergens produce most cases of contact dermatitis. Among the drugs involved, the most universally accepted offenders are topical formulations of bacitracin, neomycin, glucocorticosteroids, local anesthetics, and antihistamines. Potent excipient topical sensitizers include the parabens, formaldehyde, ethylenediamine, lanolin and thimerosal (figure 3).

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 (figure 4). 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 (figure 5).
Toxic erythema: Acute morbilliform erythematous eruption that may occur due to drugs. Spontaneous resolution occurs over 1–2 weeks, followed by desquamation (quoted from Kane et al, 2009).22

Figure 3. Allergic contact dermatitis: Sharply demarcated linear erythematous plaque with early vesiculation on the abdomen of a child exposed to adhesive tape (quoted from Elston and Johnston, 2007).27

Erythema multiforme (EM), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN): 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 less than 10% of body surface area (BSA) (figure 6). SJS is characterized by widespread erythematous or purpuric lesions or flat atypical targets and blistering involving less than 10% of BSA in addition to mucous membranes involvement (figure 7). Overlap SJS/TEN presents with lesions that are like those in SJS but epidermal detachment affects between 10% and 30% of BSA. TEN may present with a rash which is like that in the overlap but epidermal detachment is more than 30%; alternatively TEN may present without ‘spots’ but with epidermal detachment in large sheets, affecting more than 30% BSA. The more severe syndromes can be life-threatening and the drug must be stopped immediately.28

Type II reactions: They 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) (figure 8).17

Type III hypersensitivity reactions (hypersensitivity vasculitis): A purpuric/petechial rash may be indicative of a vasculitic process. Many agents, hematopoietic growth factors, cytokines and interferons are suspected of causing widespread vascular inflammation of skin and visceral organs. Frequently, the vascular changes occur during or at the endstage of drug-induced syndromes of serum sickness or drug fever. Drugs such as hydralazine, antithyroid medications, minocycline, and penicillamine are often associated with antinuclear cytoplasmic antibody or peri-antinuclear cytoplasmic antibody–positive vasculitis-like disease. A Henoch-Schönlein purpura syndrome with cutaneous vasculitis and glomerulonephritis may be induced by carbidopa/levodopa. Further investigations including platelet count, renal function, C3/C4 levels, ANA and skin biopsy may be required (figure 9).21

In some cases, cutaneous reactions appear to result from drug administration in the presence of certain viral infections although the same drug may be subsequently tolerated. This suggests that for some drug reactions the presence of a systemic viral infection like Herpes viruses (Epstein–Barr) or HIV can act as a cofactor.29

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.30 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, interstitial lung disease and pulmonary fibrosis can all be drug-induced.31
Figure 4. Fixed drug eruption: Hyperpigmented plaques of old lesions with superimposed erythema of new active lesions. Figure 5. Acute generalized exanthematous pustulosis: Numerous confluent pustules superimposed on the erythematous edematous confluent plaques (quoted from Kane et al, 2009)\textsuperscript{22}.

Figure 6. Erythema multiforme Polycyclic target lesions with alternating rings of erythema and dusky desquamation on the arm. Figure 7. Steven-Johnson syndrome: Debilitating mucosal involvement with hemorrhagic ulcerations and crusting requiring hospital admission (quoted from Kane et al, 2009)\textsuperscript{22}.

Figure 8. Bullous Pemphigoid: Itchy bullae that occur as autoimmune response to different antigens, mainly in the old age and tend to concentrate in flexural areas (quoted from Elston and Johnston, 2007)\textsuperscript{27}.

Figure 9. Hypersensitivity Vasculitis over the leg after the intake of an oral NSAID (quoted from Elston and Johnston, 2007)\textsuperscript{27}.
Other reactions

Immune-mediated hepatocellular necrosis has been described with methyldopa, halothane, allopurinol, isoniazid and gold salts.\textsuperscript{32} Haemolytic anaemia can be caused by penicillin and methyldopa.\textsuperscript{17} The drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a drug-induced, multiorgan inflammatory response that can be life-threatening with symptoms of pyrexia, lymphadenopathy, hepatitis, nephritis, angio-oedema and eosinophilia. It was first described in conjunction with anticonvulsants, but later on, it was ascribed to a variety of other drugs like dapsone, minocycline, sulphasalazine, strontium ranelate and allopurinol. The reaction usually develops 2 to 8 weeks after therapy is started; symptoms can worsen after the drug is discontinued and symptoms can persist for weeks or even months after the drug has been discontinued.\textsuperscript{33}

Diagnosis:

History and examination

**History taking:** A detailed history is an essential first step towards an accurate diagnosis of a drug-induced reaction. The history helps guide the clinician in the choice of diagnostic tests and whether it might be safe to reintroduce the medication. The history must include details of the drug (formulation, dose, route and timing of administration) together with the nature and time of onset and resolution of symptoms.\textsuperscript{34} A thorough history is particularly important when patients are on several drugs. The diagnosis is aided by a detailed knowledge of the reaction-pattern for each drug taken. 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).\textsuperscript{17}

A sample of clinically important questions that should be answered while evaluating a patient with suspected drug allergy include: Which systems (e.g., cutaneous, respiratory, and gastrointestinal) were involved in the reaction, and what were the characteristics? Was the patient taking concurrent medications at the time of the reaction? What was the therapeutic management required secondary to the reaction? Had the patient taken the same or a cross-reacting medication before the reaction? Has the patient experienced symptoms similar to the reaction in the absence of drug treatment? Does the patient have an underlying condition that favors reactions to certain medications?\textsuperscript{21}

**Clinical examination:** In addition to the clinical history, a careful physical examination can help to define possible mechanisms underlying the reaction and guide investigations. Physical examination should include all systems that could possibly account for the clinical presentation. Cutaneous manifestations are the most common presentation for drug allergic reactions. Although drug allergic reactions may present with noncutaneous physical findings, these findings are generally nonspecific and are not nearly as helpful in diagnosis and management decisions as the cutaneous findings.\textsuperscript{35}

**Investigations**

**Laboratory evaluation:** Routine laboratory evaluation appropriate to the clinical setting might be useful for the evaluation of a patient with a suspected drug reaction, depending on the history and physical examination findings. Most patients with drug-induced allergic reactions do not have eosinophilia, and therefore the absence of eosinophilia clearly does not exclude a drug-induced allergic cause.\textsuperscript{21} **Autoantibodies** might be helpful in the evaluation of drug induced vasculitis (e.g., antinuclear cytoplasmic antibody) and drug-induced lupus erythematosus (DILE). In the case of systemic DILE, antihistone antibody levels are frequently positive, whereas in patients with cutaneous DILE, anti-Ro/SSA, anti-La/SSB, or both levels are frequently positive.\textsuperscript{36}

Diagnosis of anaphylaxis might be made by detecting an increase in serum total tryptase levels above baseline values or in serum mature tryptase (also known as b-tryptase) levels, which peak 0.5 to 2 hours after drug administration and then decrease with a half-life of about 2 hours.\textsuperscript{37} Additional methods for detecting systemic mast cell mediator release include obtaining 24-hour urine collections for major urinary metabolites of histamine or prostaglandin D2.\textsuperscript{21}

**Skin prick tests for specific Immunoglobulin E-mediated drug reactions:** Demonstration of the presence of drug-specific IgE is usually taken as sufficient evidence that the patient is at significant risk of having a type I reaction if the drug is administered. This is helpful in the case of high-molecular-weight agents. In the case of small-molecular-weight drugs, validated and reliable skin test reagents are only available for penicillin. The negative predictive value of penicillin skin testing (with penilloyl polylysine, penicillin G, and penicilloate and/or penilloate) for serious immediate-type reactions approaches 100%. However, insufficient knowledge about drug degradation products, metabolites, or both and how
they are conjugated with body proteins has been an impediment to developing either skin or in vitro assays for assessing immune responses to most other small molecular-weight drug chemicals.\(^{35}\)

Skin prick tests for drug allergy 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. The parental 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.\(^{38}\)

**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.\(^{39}\)

Intradermal tests require expert interpretation to differentiate true positive from irritant reactions and to understand the significance of a negative test. 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.\(^{40}\)

**Patch tests for T cell sensitization:** Patch testing involves placing potential allergens at non-irritant concentrations on the patient’s back for 48 hours under aluminum discs attached to hypoallergenic tape. Readings are performed at 48 and 96 hours. 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.\(^{41}\) A sensitivity range of between 11% and 43%, has been reported reflecting different populations selected for patch testing.\(^{42}\)

Drug patch testing might be useful for certain types of cutaneous drug reactions, including maculopapular exanathemas, acute generalized exanathematous pustulosis, and fixed drug eruptions, but generally is not helpful for SJS or urticarial eruptions.\(^{35}\)

**Specific IgE in vitro assays** (e.g. RASTs, ImmunoCAP, and Immulite): Specific IgE assays are available, although most are not adequately validated with unclear specificity and sensitivity and lack positive controls. In addition, in vitro assays for IgE to drugs are hampered because of difficulties with binding of drug allergens to solid-phase matrices.\(^{21}\) Thus, although a positive in vitro test result for penicillin specific IgE can be highly predictive of penicillin allergy, a negative in vitro test result does not adequately exclude penicillin allergy.\(^{35}\)

**Basophil activation test:** The basophil activation test evaluates the expression of CD63 or CD203C on basophils after stimulation with an allergen. There are very limited data using this method to evaluate patients with possible drug allergies to b-lactam antibiotics, NSAIDs, and muscle relaxants, and further confirmatory studies, especially with commercially available tests, are needed before its general acceptance as a diagnostic tool.\(^{43}\)

**Skin biopsy:** In complex cases in which multiple drugs are involved without a clear-cut temporal relationship, a skin biopsy might be useful. However, there are no absolute histologic criteria for the diagnosis of drug-induced eruptions and a skin biopsy might not definitively exclude alternative causes.\(^{35}\)

**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. 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 and the challenge then only carried out by personnel experienced in drug challenges and with adequate resuscitation facilities readily available.\(^{44}\) 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. Challenge testing is contraindicated for certain types of reactions, e.g. SJS, TEN, DRESS and EM and in patients with severe concurrent illness.\(^{37}\)

A summary of drug provocation protocols has been reported in a retrospective study of 898 consecutive patients. Written informed consent should be obtained before undertaking drug
challenge. 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.\textsuperscript{45}

A negative reaction indicates that the patient is not sensitive at the time of the challenge.\textsuperscript{46} 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. B-blockers should be stopped 24 hours before the drug challenge.\textsuperscript{44}

Differential diagnosis of drug allergy
Drug-induced allergic reactions can present in numerous ways, affecting single organs or with multiorgan involvement. However, each clinical presentation is not unique or specific to drug induced allergic reactions, and therefore other conditions might need to be considered based on the presentation (table 2). For example, a morbilliform eruption occurring in a child receiving amoxicillin for an upper respiratory tract infection might indeed be due to a viral exanthema and not a drug-induced allergic reaction. In addition, patients with multiple drug allergies might actually have an underlying chronic disease and are inappropriately labeled with multiple drug allergies. This frequently occurs in patients with underlying chronic urticaria or anxiety disorders but can also occur with other conditions, such as asthma, vocal cord dysfunction, idiopathic anaphylaxis or rarely even mastocytosis.\textsuperscript{21}

Management of drug allergy
Acute drug reaction
Anaphylaxis must be treated promptly and appropriately and steps should be taken to prevent a further reaction. 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. Cross reacting drugs should be identified and avoided. In less severe cases where there is no alternative to the suspected drug, suppression of symptoms using corticosteroids and/or antihistamines may be considered.\textsuperscript{17} Corticosteroids may also be required for immune complex reactions, drug-induced hematologic diseases, early stages of erythema multiforme major/ Stevens-Johnson syndrome, and contact sensitivities.\textsuperscript{35}

Table 2. Conditions to consider in the differential diagnosis of drug allergy\textsuperscript{21}

<table>
<thead>
<tr>
<th>IgE-mediated drug allergy</th>
<th>Non-IgE mediated reactions</th>
</tr>
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<tbody>
<tr>
<td>(urticaria, angioedema, anaphylaxis, bronchospasm)</td>
<td>(exanthema, DRESS, SJS, TEN):</td>
</tr>
<tr>
<td>- Carcinoid syndrome</td>
<td>- Acute graft-versus-host disease</td>
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<tr>
<td>- Insect bites/stings</td>
<td>- Kawasaki disease</td>
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<tr>
<td>- Mastocytosis</td>
<td>- Still’s disease</td>
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<tr>
<td>- Asthma</td>
<td>- Psoriasis</td>
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<tr>
<td>- Food allergy</td>
<td>- Insect bites/stings</td>
</tr>
<tr>
<td>- Scombroid fish poisoning</td>
<td>- Viral infection</td>
</tr>
<tr>
<td>- Latex allergy</td>
<td>- Streptococcal infection</td>
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</table>
| - Infection (EBV, hepatitis A, B, C, gastrointestinal parasites)                                         | IgE: immunoglobulin E; EBV: Epstein-Barr virus; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; DRESS: Drug rash with eosinophilia and systemic symptoms (quoted from Khan and Solensky, 2010)\textsuperscript{21}

Temporary induction of drug tolerance:
Definition: Induction of drug tolerance procedures modifies a patient’s response to a drug to temporarily allow treatment with it safely. They are indicated only in situations where an alternate non–cross-reacting medication cannot be used. Induction of drug tolerance can involve IgE immune mechanisms (desensitization), non-IgE immune mechanisms, pharmacologic mechanisms, and undefined mechanisms.\textsuperscript{35} This is rarely required but has been used for penicillin, certain other antibiotics, taxanes and platinum-based cancer chemotherapeutic agents.\textsuperscript{17}

Procedure: Induction of tolerance 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. The procedure may take between 6 hours to a few days depending on the starting dose, route of administration and challenge-induced symptoms requiring modification to the dosing-schedule. Oral route is less likely to provoke a severe reaction, but intravenous desensitization, e.g. for cephalosporins, may be necessary. The procedure must be performed in a hospital setting by experienced staff with full resuscitation equipment readily available.\textsuperscript{17} A number of penicillin desensitization protocols have been reported.\textsuperscript{48}
Graded Challenge

**Definition:** Graded challenge, or test dosing, is defined as a procedure to determine whether a patient will have an adverse reaction to a particular drug by administering lower than therapeutic doses over a period of time with observation for reactions. The rationale for starting with a lower dose is based on the concept that a smaller dose of allergen will result in a less severe and more easily treated reaction. Unlike induction of drug tolerance procedures, a graded challenge does not modify a patient’s immunologic or nonimmunologic response to a given drug. Although it is not possible to be absolutely certain that a patient is not allergic to a drug because valid diagnostic tests are not available for most drugs, graded challenges are intended for patients who, after a full evaluation, are unlikely to be allergic to the given drug. Furthermore, the benefit of treatment with the drug should outweigh the risk of performing the graded challenge.

**Procedure:** The starting dose for graded challenge is generally higher than for induction of drug tolerance procedures, and the number of steps in the procedure might be 2 or several. The time intervals between doses are dependent on the type of previous reaction, and the entire procedure can take hours or days to complete. After a successful graded challenge and therapeutic course of the drug, future courses of the drug can be started without another challenge. A typical starting dose for a graded challenge is 1/100 th of the final treatment dose. This is in contrast to the starting dose for an IgE immune induction of drug tolerance, in which case the starting dose is often 1/10,000 th of the final dose. The choice of whether to introduce a clinically indicated drug through a graded challenge or through induction of drug tolerance mainly depends on the likelihood that the patient is allergic at the time of the procedure.

**Contraindications:** Graded challenge or induction of drug tolerance should almost never be performed if the reaction history is consistent with a severe non–IgE-mediated reaction, such as SJS, TEN, DRESS, hepatitis, or hemolytic anemia.

**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. The drugs should be highlighted in the hospital notes and within electronic records where available, and the GP informed. Engraved allergy-bracelets 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. Adrenaline auto injectors are not usually required if the cause of the reaction has been identified and the drug is easily avoided.

In Summary, drug allergy is a common clinical problem; assessment by an allergist is important for appropriate diagnosis and management of the condition. Diagnosis relies on a careful history and physical examination and, in some instances; skin testing and graded challenges may be required. The mainstay of treatment for drug allergy is avoidance of the offending drug. When available, alternative medications with unrelated chemical structures should be substituted. If there is no suitable alternative, induction of drug tolerance procedures may be considered to induce temporary tolerance to the drug.

**REFERENCES**


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