

Antibiotic Allergy, When to Test, Challenge or Desensitise

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Abstract

Antibiotics are widely used for treatment of bacterial infections and for prophylaxis during instrumental procedures and in certain conditions such as immunodeficiency and splenectomy.

Hypersensitivity (allergic) reactions are unpredictable and can occur in some patients even if they have taken the antibiotic in the past with no reaction. Drug allergy accounts for 11.3% of all adverse drug reactions. Drug allergy drugs can be generally classified (according to the World Allergy Organization) based on timing of symptoms into immediate (Immunoglobulin E (IgE) mediated) occurring within 1 hour and delayed (non IgE mediated) allergic reactions occurring after 1 hour. Many patients are mislabeled with drug allergy especially when the diagnosis is made based on history alone. In such cases, a referral to an allergist is important to confirm or exclude allergy through a detailed clinical history, in vitro and/or in vivo testing, as over diagnosis of drug allergy leads to the unnecessary use of broader spectrum and expensive antibiotics contributing to the emergence of multidrug resistant pathogens. Also, in cases of confirmed drug allergy it is important to establish potential cross reactivity with other drugs. Equally, patients with confirmed drug allergy, who have an absolute requirement for the drug or cross reactive drug (as in penicillin allergic females with syphilis) can undergo a process of desensitization in order to complete their treatment through induction of temporary tolerance of the drug.

Keywords: Antibiotic; Allergy; Skin testing; Challenge; Desensitization

Introduction

Hypersensitivity (allergic) reactions are unpredictable and can occur in some patients even if they have taken the antibiotic in the past with no reaction. Drug allergy accounts for 11.3% of all adverse drug reactions [1]. Many patients are mislabelled with drug allergy especially when the diagnosis is made based on history alone. Often the clinical history is not clear, for example, non-specific rash with penicillin in childhood or symptoms such as nausea and vomiting that are more likely to be related to drug side effects rather than allergy. In such cases, a referral to an allergist is important to confirm or exclude allergy, as over diagnosis of drug allergy leads to the unnecessary use of broader spectrum and expensive antibiotics contributing to the emergence of multidrug resistant pathogens [2]. Equally, under diagnosis of antibiotic allergy can have serious and sometimes fatal consequences [3]. In cases of confirmed drug allergy it is important to establish potential cross reactivity with other drugs (for example penicillins and cephalosporins).

Also, patients with confirmed drug allergy, who have an absolute requirement for the drug or cross reactive drug (as in penicillin allergic females with syphilis) can undergo a process of desensitization in order to complete their treatment through induction of temporary tolerance of the drug.

We will discuss the process of drug allergy testing and desensitization to familiarize the microbiologist and infectious disease specialist with this field of drug allergy.

Epidemiology

Drug allergy accounts for 11.3% of all adverse drug reaction [1]. Betalactams antibiotics are the most frequent drugs that cause allergic reactions [4,5]. The prevalence of beta-lactam allergy in the general population, based on patients' reports, ranges between 1%-10% [6], but only 10%-20% of patients suspected of beta-lactam allergy test positive on skin testing [7].

In a survey from the Boston Collaborative Drug Surveillance Program, the analysis of the incidence of cutaneous drug reactions in 15,438 hospitalized patients who received various antibiotics demonstrated 358 reactions reported and confirmed by a dermatologist with an overall frequency of 2.3%. The number of reactions over the number of administrations for each drug was reported as 5.1% for amoxicillin, 3.4% for cotrimoxazole, 3.3% for ampicillin, 2.1% for cephalosporins, 2% for erythromycin, 1.8% for penicillin G and 0.4% for gentamicin [8].

Types of Allergic Reactions

Hypersensitivity (or allergic) reactions to drugs can be generally classified (according to the World Allergy Organization) based on timing of symptoms into immediate (Immunoglobulin E (IgE)

mediated) and delayed (non IgE mediated) allergic reactions [9]. In most cases clinical history based on the timing of the drug reaction as well as signs and symptoms is able to establish this basic differential. In turn, this (IgE *versus* non IgE reactions) guides further testing and drug challenge (drug provocation) (Figure 1).

Immediate reactions (IgE) occur within 1 hour of exposure to the drug, whereas delayed reactions begin after 1 hour of exposure (usually between 6 hours to weeks) and are caused by other, non IgE mediated mechanisms [9].

In IgE mediated reactions (also known as Type I reactions), drug specific IgE forms upon exposure to that drug and causes mast cells and basophils to release vasoactive mediators. These cause signs and symptoms involving the skin and mucous membranes such as rash, itching and angioedema; respiratory system including chest tightness, difficulty in breathing, wheeze and stridor; gastrointestinal symptoms such as abdominal pain, diarrhoea and vomiting and cardiovascular system including tachycardia and hypotension. These should be differentiated from non-allergic symptoms such as isolated gastrointestinal upset and idiosyncratic reactions (for example, headache) as well as non IgE mediated such as maculopapular exanthema [10].

Non IgE mediated reactions (delayed reactions) generally appear after one hour and sometimes after days or weeks of treatment. Symptoms may also occur days after cessation of treatment and can pose a diagnostic challenge. These reactions are not mediated through IgE but through other immunologic mechanisms such as antibody (usually immunoglobulin G IgG)- mediated cell destruction in drug induced hemolytic anemia and thrombocytopenia (also called Type II reaction); antigen-antibody complex formation (Serum sickness, vasculitis, drug fever) (Type III reactions) and T cells activation as in Steven Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug hypersensitivity with eosinophilia and systemic symptoms (DRESS) and contact dermatitis (Type IV reactions). Penicillin is an example of an antibiotic that can cause all types of reactions.

T cell mediated reactions (Type IV reactions) occur at least 48-72 hours to weeks following exposure to the index drug. They are generally the most prevalent type of reaction. T cells are stimulated by drugs by three main processes [11] which include the drug's ability to act as a hapten, a prohaptent or to bind covalently to immune receptors (Pi concept). Haptens are small compounds (<1000 daltons) that are chemically reactive and bind to proteins or peptides and modify them covalently leading to stimulation of the innate immune system and resulting in neoantigens capable of stimulating T cells. On the other hand, Prohaptens are not chemically reactive and cannot form a covalent bond with a peptide unless converted into a hapten by being metabolized into a chemically reactive compound.

Lastly, in the Pi concept (pharmacologic interaction with immune receptors concept), although the chemically inactive drug is unable to covalently bind to proteins, it is able to reversibly interact with some of the immune receptors which under certain circumstances, can activate immune cells which then expand and cause inflammatory reactions of different types [11].

T cell mediated reactions can be tested by intradermal testing with delayed cutaneous reading and patch testing [12].

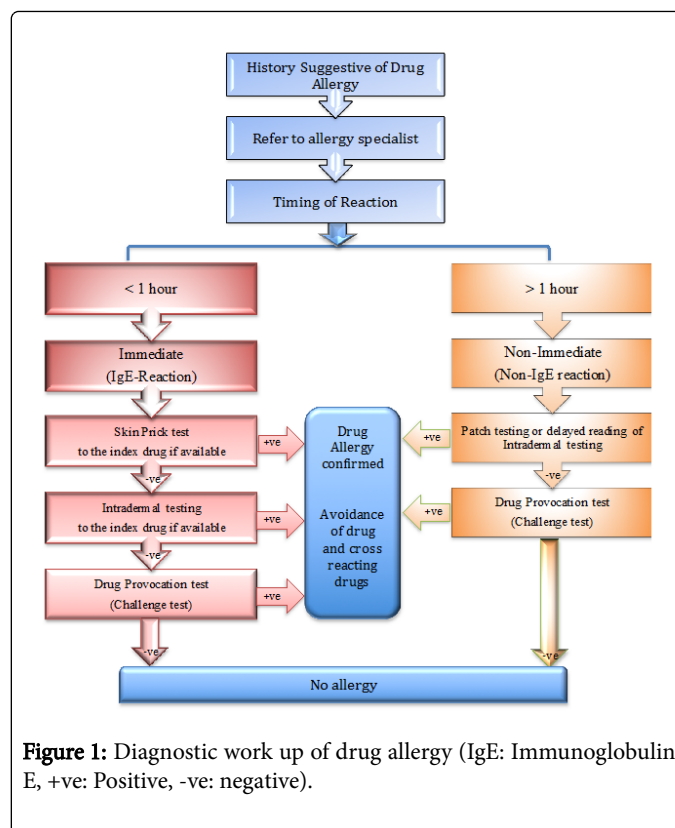


Figure 1: Diagnostic work up of drug allergy (IgE: Immunoglobulin E, +ve: Positive, -ve: negative).

Risk Factors for Drug Allergy

Risk factors for allergic drug reaction can be divided into drug related factors and host related factors. The ability of the drug to act as a hapten, a prohaptent or to bind covalently to immune receptors makes it immunogenic which explains why certain classes of drugs are more likely to cause drug allergies than others [13]. Allergic drug reactions are more likely to occur if there was a prior history of drug allergy as well as recurrent drug exposure. Cross-sensitization is another important drug factor that should be considered. Once sensitization to a drug has occurred, there is a possibility of reactivity either to drugs with chemically similar structures or to immunochemically similar metabolites.

Regarding host factors and for unclear reasons, female sex is thought to be a risk factor for allergic reactions to some drugs such as neuromuscular blockers, however, this does not apply to penicillins. Children seem to have a lower incidence of drug allergy probably because they are less likely exposed repeatedly to drugs. However, this risk increases with the frequent prescription of antibiotics in children with chronic disease such as cystic fibrosis [14]. Drug allergy in elderly hospitalized patients appears to be similar to the non-elderly, but serious reactions (anaphylaxis, SJS, TEN, DiHS) are less common [15]. Certain diseases carry risk of developing allergic reactions. These include the acquired immunodeficiency syndrome with increased rates of skin reactions to sulphonamides, abacavir and nevirapine caused by the inflammatory mediators released as a result of the Human immunodeficiency virus (HIV) [16,17]. Other diseases are Epstein-Barr virus (EBV) infection and leukemia [18]. Genetic factors appear to play in role in the predisposition of drug allergy. Certain HLA types such as HLA-B*13:01 and the dapson hypersensitivity syndrome [19],

HLA B*1502 associated with carbamazepine induced SJS/TEN in Han Chinese in Taiwan and Indians [20-22] and HLA A* 31:01 in Japanese and Europeans [23,24].

Diagnosis

It is important to start with a detailed drug and index event history. When the history is strongly suggestive of an allergic reaction to the drug in question, the diagnosis can be based on history alone and further testing can be avoided. However, when the history is poor or when multiple drugs are involved such as during general anesthesia, it is essential to establish the culprit drug through *in vitro* or proceed to *in vivo* drug testing performed by skin testing and when necessary through graded drug provocation test (DPT) also known as drug challenge.

Drug testing should be avoided if the reaction was very severe and involved bullous or exfoliative skin dermatoses such as: Steven Johnson syndrome and Toxic Epidermal Necrolysis. These patients should avoid the index drug for life.

In Vivo Testing

Skin testing

Generally, skin testing for IgE mediated reactions involves two methods, skin prick test (SPT) and intradermal test (ID). Skin prick testing detects the presence of drug specific IgE in the skin and can therefore predict only the likelihood of IgE mediated drug allergy [25]. It is not useful for identifying other types of reactions. Skin prick testing is more specific, but less sensitive than intradermal testing and should precede it. Skin prick testing is always performed before intradermal testing and severe systemic reactions can occur even at this stage [26]. Histamine and normal saline is used as positive and negative control respectively for the test. Histamine is not used intradermally. A drop of antigen is placed on the forearm and a lancet is inserted at 45° to lift the epidermis. The skin is observed for 10-15 minutes. A positive reaction is defined as a wheal and flare, with the diameter of the wheal measuring at least 3 mm more than the negative control. If SPT is negative, intradermal test is performed with a 30 gauge needle where 0.02-0.03 mL of antigen solution is injected into the dermis of the skin in order to create a small bleb. This can be marked with a pen. The skin is then observed for 15-20 minutes and any reaction rated as positive or negative. A positive reaction is defined as a wheal and flare, with the diameter of the wheal measuring at least 3 mm more than the negative control (Figure 2). Some drugs such as antihistamines can give rise to a false negative skin testing and therefore, should be stopped at least 48 hours prior to the test. In certain cases ID testing can be used for non IgE mediated drug reactions [12]. It is performed using commercially prepared, non-irritant injectable form of the drug in the same way as described above. The site is examined after 24-48 hours with a positive result as described above [12].



Figure 2: Positive skin prick test to Amoxicillin (1st upper) and Co Amoxycylav (2nd upper) defined as a wheal and flare. Negative to Cefuroxime (lower).

Patch testing is also used to evaluate non IgE mediated drug reactions. This is done using certain concentration of a drug mixed into petroleum or 0.9% saline and applied to a small area of skin covered for 48 hours. This is then removed and the area examined 48-96 hours from the start of the test [12].

Drug provocation test (DPT)

When skin testing is negative or not available, DPT is performed cautiously by a trained and experienced allergist and in a hospital setting where resuscitation facilities are available. The route of administration depends on the index drug (oral, intravenous, subcutaneous or intramuscular). Prior to the challenge, patients should stop antihistamines for at least 72 hours as these may mask early signs of an allergic reaction. Beta-blockers should not be taken for at least 24 hours before the challenge if possible as they can interfere with treatment of potential anaphylaxis. The risk of severe anaphylaxis during DPT is mitigated by reintroduction of the investigated drug at a very small dose (usually 1/100 the total dose), then increasing it incrementally every 30 minutes, provided no objective signs of allergic reaction occur, until the full therapeutic dose is received. The patient is observed for 1 hour following the last dose. Table 1 for an example of an oral challenge for amoxicillin.

Step	Time interval	Dose
1st dose of amoxicillin	30 minutes	5 mg
2nd dose of amoxicillin	30 minutes	50 mg
3rd dose of amoxicillin	30 minutes	250 mg
4th dose of amoxicillin	30 minutes	500 mg

Table 1: Example of oral challenge for amoxicillin.

Patients with positive skin tests or positive DPT to the index drug should avoid it for life. Both diagnostic methods can also be used to look for drug crossreactivity.

For example, in case of allergy to penicillin, drugs such as cephalosporins may be tolerated provided cephalosporin skin testing and challenge are negative.

In Vitro Testing

Allergen-specific IgE levels are measured by either radioallergosorbent tests (RASTs) or radioimmunoassay (RIA) commercially available as ImmunoCAP®, enzyme linked immunosorbent assay (ELISA) or fluoroenzyme immunoassay (FEIA) [27]. These tests detect the presence of serum IgE antibodies against some antibiotics including penicilloyl, amoxicilloyl, ampicilloyl and cefaclor. It is not affected by antihistamines and although the specificity is close to 100% [28,29], they lack sensitivity compared to clinical history and skin tests and a negative result cannot exclude allergy. Although most UK allergy centers perform specific IgE to penicillins, its use in clinical practice is highly varied [30].

The basophil activation test (BAT) is a method of measuring drug-induced activation of basophils using flow cytometry that measures alterations in the cell surface expression of basophil activation markers, such as CD63 or CD203 [31].

BAT is not routinely used in clinical practice at present. It has been studied in a limited number of drugs. Although it has a good specificity, the sensitivity for drug allergies is low. It is of use when skin testing and specific IgE testing results are equivocal. It is possible to examine for potential cross reactivity with related drugs [32]. For beta-lactam antibiotics, the reported sensitivity varies between 22% and 55%, and specificity between 79% and 100% [31].

The lymphocyte transformation test (LTT) has been shown to be useful in the diagnosis of T-cell mediated delayed hypersensitivity

reactions with a variety of drugs [27]. Lymphocytes isolated from peripheral blood mononuclear cells (PBMCs) of a patient with a specific delayed hypersensitivity reaction are cultured with pharmacologic concentrations of the drug in question and then stimulated after 5-7 days. Enhanced proliferative responses in the presence of a drug are considered positive for that drug-specific T-cell sensitisation.

Although a positive LTT is useful in confirming the diagnosis, a negative test does not exclude drug hypersensitivity. Positive LTT are usually drug-specific, and reaction-specific. The sensitivity of the LTT varies widely between studies, is related to both the drug and phenotype of clinical reaction and is still considered a research method [33].

Desensitization

In some cases where the patient is allergic to an antibiotic and no other alternative is available such as pregnant females with syphilis who are penicillin allergic, or when the drug in question is more effective than the alternative, a process known as desensitization can be performed.

Drug desensitization involves administration of incrementally increasing doses of the drug in order to induce temporary tolerance and hence allow the patient to take the medication safely. It is effective for as long as the patient is receiving the drug in question. Once the drug is discontinued, the patient's allergy to that drug returns. This is performed in a specialized allergy center, in a hospital setting with all resuscitation facilities available in case of anaphylaxis. Desensitization should not be performed in patients with severe exfoliative reactions such as SJS or TNE. Table 2 for indications and contraindications to performing desensitization.

Indications for Desensitisation	Contraindications to Desensitisation
Drug in question is irreplaceable (penicillin and syphilis in pregnancy, carboplatin in ovarian cancer)	Severe, life threatening immunocytotoxic reactions
Drug in question is more effective than alternatives -Antibiotics in Cystic fibrosis or HIV -Aspirin in cardiovascular disease or in aspirin exacerbated respiratory disease	Vasculitis
	Bullous skin diseases (SJS, TEN, DRESS)
	Interstitial nephritis
	Hepatitis
	Haemolytic anaemia

Table 2: Indications and contraindications to desensitization.

Desensitization can be performed by oral, intravenous, or subcutaneous routes. The oral route is the safest, and is used whenever possible. The first dose is usually 1/10 000000 to 1/10000 of the normal dose. This is doubled every 15-30 minutes until the full dose is reached (usually in 12-15 steps). Allergic reactions may occur in around 25% of patients undergoing the process of desensitization (authors

unpublished data) [34]. However, no fatal reactions have been reported so far. Desensitisations have been performed safely in pregnant women [35]. Table 3 for an example of desensitization for amoxicillin.

There is some confusion amongst the medical community as to the difference between drug challenge and drug desensitization. Table 4 where we have summarized both processes.

Summary

Majority of hospital inpatients require antibiotics during their admission [36]. It is therefore hardly surprising that antibiotics now account for the highest expenditure of all categories of medicinal products constituting 19% of the total expenditure on medicines in secondary care [37]. Antibiotic-associated adverse reactions are a significant public health care problem worldwide [2,38]. Leading to prolonged hospitalisation, antibiotic resistance, poorer health outcomes and increased cost [39]. Collaboration with allergists and antibiotic drug allergy assessment are fundamental to any successful antibiotic stewardship programme.

Keypoints

- Many patients who have been labelled with drug allergy may be able to tolerate the drug in question.

- Patients who have a requirement for the “allergen drug” or are likely to require it in the future should be referred to the drug allergy service.
- Delayed intradermal skin testing may be useful in evaluating delayed drug reactions, however, it is not diagnostic and when appropriate it should be followed by cautious drug reintroduction.
- The process of DPT for immediate, IgE mediated drug reactions differs from the process of drug reintroduction in case of delayed, non IgE mediated drug reactions.
- Patients with proven allergy and an absolute requirement for the drug may undergo desensitization process in order to achieve temporary tolerance to the drug (this is different to the challenge process).
- At present there is no evidence for efficacy of desensitization in delayed, non IgE mediated drug reactions.

Step	Time (min)	Time cumulative (min)	Solution (Concentration mg/mL)	Amount (mL)	Dose mg	Cumulative dose
1	20	0	(0.1 mg/mL)	0.1	0.01	0.01
2	20	20	(0.1 mg/mL)	0.2	0.02	0.03
3	20	40	(0.1 mg/mL)	0.4	0.04	0.07
4	20	60	(0.1 mg/mL)	0.8	0.08	0.15
5	20	80	(0.1 mg/mL)	1.6	0.16	0.31
6	20	100	(0.1 mg/mL)	3.2	0.32	0.63
7	20	120	(0.1 mg/mL)	6.4	0.64	1.27
8	20	140	(0.5 mg/ml)	2	1	2.27
9	20	160	(0.5 mg/ml)	4	2	4.27
10	20	180	(0.5 mg/ml)	8	4	8.27
11	20	200	(5 mg/ml)	1.5	7.5	15.77
12	20	220	(5 mg/ml)	3	15	30.77
13	20	240	(5 mg/ml)	6	30	60.77
14	20	260	(5 mg/ml)	12	60	120.77
15	20	280	Stock (25 mg/mL)	5	125	245.77
Switch to tablet form						
16	20	300	Tablet 250 mg	1	250	495.77
17	20	320	Tablet 250 mg	2	500	995.77
Based on Sullivan TJ. Drug Allergy. In: Middleton E Jr, et al. (Eds). Allergy: Principles and Practice, (4th edn), St. Louis: Mosby 1993.						
Stock solution=125 mg/5 mL (25 mg/mL); 5 mg/mL=1 mL of stock (25 mg/mL) add 4 mL of water; 0.5 mg/mL=1 mL of (5 mg/mL) add 9 mL of water; 0.1 mg/mL=1 mL of (0.5 mg/mL) add 4 mL of water.						

Table 3: Amoxicillin Desensitisation Premedication 1 hour before with Cetirizine 10 mg orally, Ranitidine 150 mg orally, Montelukast 10 mg orally.

Challenge	Desensitisation
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Allergy-unproven	Allergy-proven
Done to establish diagnosis	Done to produce temporary tolerance
Start with 1/100-1/10 therapeutic dose	Start with 1/1000 000 to 1/10 000 therapeutic dose
In 3-5 steps	In 12-13 steps

Table 4: The difference between drug challenge and drug desensitisation.

Disclosures:

Non to disclose by all authors

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