Narrative Review

Antibiotic allergy: Mislabels, Misinterpretation and Mismanagement

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Abstract

Antibiotics are implicated as one of the most common medications to cause allergic reactions. Further, they account for the highest number of deaths due to drug induced anaphylaxis. Yet, antibiotic allergies are over-reported and most often, patients with a self-reported or recorded antibiotic allergy are not truly allergic when clinically evaluated, tested, and re-challenged. These antibiotic allergy "mislabels" can have devastating consequences on public health as they may result in displacement of the first-line treatment options with increased use of restricted, broad spectrum antibiotics leading to emergence of antibiotic resistance and significantly higher healthcare cost. Owing to the public health implications of inaccurate antibiotic allergy labels, this review aims to include a contextual account on classification, presentation and mechanisms of antibiotic allergy and a practical approach for investigation and management in the attempt to avoid mislabelling, misinterpretation of investigations and mismanagement of patients with antibiotic allergy.

Keywords: antibiotic allergy, hypersensitivity reactions, anaphylaxis, allergy labels, antibiotic resistance

Introduction

Antibiotics are recognised as one of the most overprescribed and misused drugs. They are implicated as the most common cause of drug induced allergy, yet, in most instances, patients are inaccurately labelled as "allergic". Evidence from around the globe suggests that most adult patients who are labelled as "allergic" to antibiotics are not truly allergic, and that most patients appear erroneously labelled when stratified for risk, tested, and re-challenged. Around 90% of adult patients with a penicillin allergy label could tolerate the culprit drug.[1-4] These mislabels have resulted in changes in care of patients with replacement of effective first-line antibiotics of choice for treatment of infections.[3-5] It has been shown that these allergy labels are rarely questioned in clinical practice and that clinicians act upon these mislabels without proper evaluation.[4-6] Inaccurate allergy labels are associated with increased use of broad-spectrum antibiotics, adverse events, antibiotic resistance, and increased healthcare cost.[1,2,4,5] A label of antibiotic allergy, whether correct or not, constitutes a major public health problem as it directly influences antibiotic prescription patterns and

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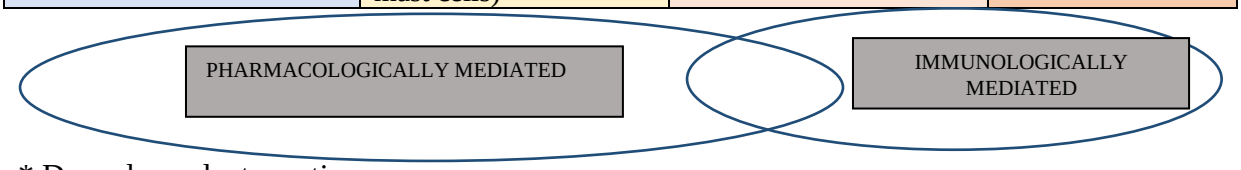
antimicrobial stewardship programmes.[4-7] The purpose of this review is to provide the basic immunological background of different types of antibiotic allergic reactions with the main aim of emphasising the importance of proper allergy evaluation before loosely labelling a patient as "allergic" in the background of rising multidrug resistant pathogens with increased use of alternative broad-spectrum antibiotics.[5-7]

Classification, mechanisms and presentation of antibiotic allergies

Antibiotics can result in adverse drug reactions (ADRs) through a variety of mechanisms of which a subset is hypersensitivity reactions (HSRs). The new classification of ADRs defines the on-target and off-target interactions of drugs with cellular components.[1-3,8,9] On-target ADRs, previously classified as type-A ADRs, are due to primary therapeutic and pharmacological actions of the drug that are predictable and are dependent upon the degree of drug exposure over time. HSRs to antibiotics are considered as off-target ADRs, previously classified as type-B ADRs, which are unpredictable and not considered to be related to the pharmacological action of the drug.[1,2,8-10] Off-target reactions can be immunologically or non-immunologically mediated. However, contrary to previous thought, some of the off-target effects may also show concentration–exposure relationships and are found to be mediated through pharmacological interactions.[8,9] These new discoveries have changed the understanding of mechanisms of off-target reactions, where some immunological as well as non-immunological off-target reactions are found to be dependent upon the dose and/or duration of drug therapy.[1,2,9-11] Hence, the mechanisms involved in some of the off-target drug reactions have overlapping immunological and pharmacological mechanisms (Figure 1).[1,2,8,9,12]

ON TARGET (more common, often >5% of those taking the drug)	**OFF TARGET** (less common, often <5% of those taking the drug)		
	Non-immunological	**Immunological**	
Predictable effects based on pharmacological action*	Interaction with off target immune receptors* (E.g. MRGPRX on mast cells)	Pure T-cell mediated (Type IV)*	Antibody mediated (type I-III)



* Dose-dependent reactions

Figure 1: Classification and mechanisms of adverse drug reactions[2,8,9,12]

Off-target reactions can be immunologically mediated HSRs or non-immunologically mediated. Immunological HSRs are mediated by adaptive immune responses, either by antibodies or T cells, and therefore elicit a memory response. On the contrary, off-target non-immunologically mediated reactions are not primarily mediated via adaptive immune mechanisms and are therefore not associated with a long-lasting memory response, but they have clinical features similar to an immunological reaction.[9-12]

Immunologically mediated reactions are conventionally classified according to "Gel and Coombs" hypersensitivity mechanisms.[12] When classified according to timing of the reaction following exposure to the allergen, reactions that usually occur within 1 hour (may occur up to 6 hours) are considered as immediate reactions, and the reactions that occur after several hours, days or weeks of treatment are classified as non-immediate.[9-12] IgE mediated type I HSRs are immediate reactions that occur within 1 hour (rarely 6 hours) of the exposure, as a result of cross-linking of allergen with the IgE on mast cells. The types II and III reactions classically present after several hours or days of exposure and are mediated via IgG antibodies. T cell mediated type IV reactions typically occur days to weeks after treatment and are classified as late reactions. [11-14]

Non-immunologically mediated reactions occur as immediate reactions due to direct mast cell activation by interaction of the drug directly with immune or non-immune receptors on mast cells, but not involving antibodies or T cells. Human G-protein-coupled receptors (MRGPRX2) are found to play an important role in activation of mast cells directly, and these reactions occur without evidence of cross linking of IgE with mast cells.[5,8,9,15] Though not immunological mediated, these reactions result in similar clinical presentation to IgE mediated reactions, hence formerly known as "pseudo-allergic" or "anaphylactoid" reactions. These reactions occur without prior sensitization contrary to IgE mediated reactions where prior sensitization is essential for a reaction to occur. It has been estimated that non-immunological reactions are accountable for two-thirds of immediate drug reactions.[8] Apart from direct mast cell activation via MRGPRX2 receptors, non-immunological reactions to drugs can occur through other mechanisms such as direct complement activation. [8,10,15]

Non-immunologically mediated off-target reactions are frequently dose and rate dependent while off-target reactions that are immunologically-mediated can be dose dependent (e.g. T-cell mediated reactions) or dose-independent (Type I IgE-mediated reactions). Non-immunologically mediated off-target reactions are not associated with memory and patients might tolerate the same antibiotic provided it is given in small doses and/or slowly. [1,2,8,9,15]

The timing and sequence of the clinical features following administration of the drug is one of the most important determinants in the evaluation of a patient with antibiotic allergy. Varying types of skin manifestations occur in different hypersensitivity reactions such as hives in immediate reactions and macular-papular rashes in late reactions, while severe cutaneous adverse reactions (SCAR) often manifest as a systemic disease with severe mucocutaneous symptoms. Table 1 describes the most common clinical features of different types of antibiotic hypersensitivity reactions with chronology and examples. Figure 2 depicts the common mucocutaneous presentations of hypersensitivity reactions.

Table 1: Mechanisms and clinical presentation of off-target adverse reactions with examples [1,2,8,9,11,12,13]

Mechanism	Presentation	Onset/ chronology	Examples
Non-immunologically mediated			
Direct mast cell de-granulation by interaction with MRGPRX2 receptors/ direct basophil activation	Flushing, itching, urticaria, angio-oedema and can present with features similar to anaphylaxis (non-immunological anaphylaxis/ anaphylactoid)	Within minutes (typically during infusion), but occur up to 1 hour. (Depends on the dose and rate of administration)	Red-man reaction with vancomycin, immediate non-immunological anaphylaxis with fluoroquinolones
Type I hypersensitivity			
Mast cell activation via IgE crosslinking with high affinity mast cell receptors, basophil activation	Itching, urticaria, angio-oedema, wheezing, features of anaphylaxis (refer Table 2)	Typically, <1 hour, but can occur up to 6 hours	Urticaria/ anaphylaxis with penicillins and cephalosporins
Type II hypersensitivity			
IgG mediated cellular cytotoxicity	Cytopenias (haemolytic anaemia, neutropenia thrombocytopenia)	Typically, within 72 hours, but up to 15 days	Neutropenia with cephalosporins, cytopenia with penicillins
Type III hypersensitivity			
Immune complex mediated serum sickness like reaction	Fever, cutaneous eruptions, lymphadenopathy, arthralgia, myalgia, vasculitis, drug fever	Days to weeks (typically 1–3 weeks)	Penicillin, amoxicillin, co-trimoxazole
Delayed type hypersensitivity (Type IV hypersensitivity)			
Type IVa Th1(IFNγ) mediated monocytic inflammation	Contact dermatitis/eczema	Days to weeks	bacitracin, ampicillin
Type IVb Th-2 (IL-4, IL-5) mediated eosinophilic inflammation	Itching, morbilliform/ maculopapular rash, peripheral eosinophilia	Days to weeks (typically in 2nd week)	amoxicillin, sulphonamides
	DRESS syndrome (SCAR)	2–6 weeks	vancomycin, rifamycin, sulphonamides, β-lactams
Type IVc CD8 T cell mediated release of IFNγ, TNFα, perforin, granzyme B, and via Fas-Ligand	Fixed drug eruptions	Days to weeks (within minutes on re-challenge)	sulphonamides, vancomycin
	SJS and TEN (SCAR)	4 days to 4 weeks	sulphonamides, anti-TB drugs, macrolides, quinolones, β-lactams
Type IVd T cell mediated (IL-8 and GM-CSF) neutrophilic inflammation	Acute generalised exanthematous pustulosis (SCAR)	<48h (typically within 24 h)	β-lactams, fluoroquinolones, clindamycin, sulphonamides

MRGPRX2=MAS-related G-protein coupled receptor member X2. Th=T-helper cell. IFN=interferon. IL=interleukin. TNF= tumor necrosis factor. DRESS= drug reaction with eosinophilia and systemic symptoms. SCAR=severe cutaneous adverse reaction SJS=Stevens-Johnson syndrome. TEN=toxic epidermal necrolysis. GM-CSF= granulocyte-macrophage colony-stimulating factor

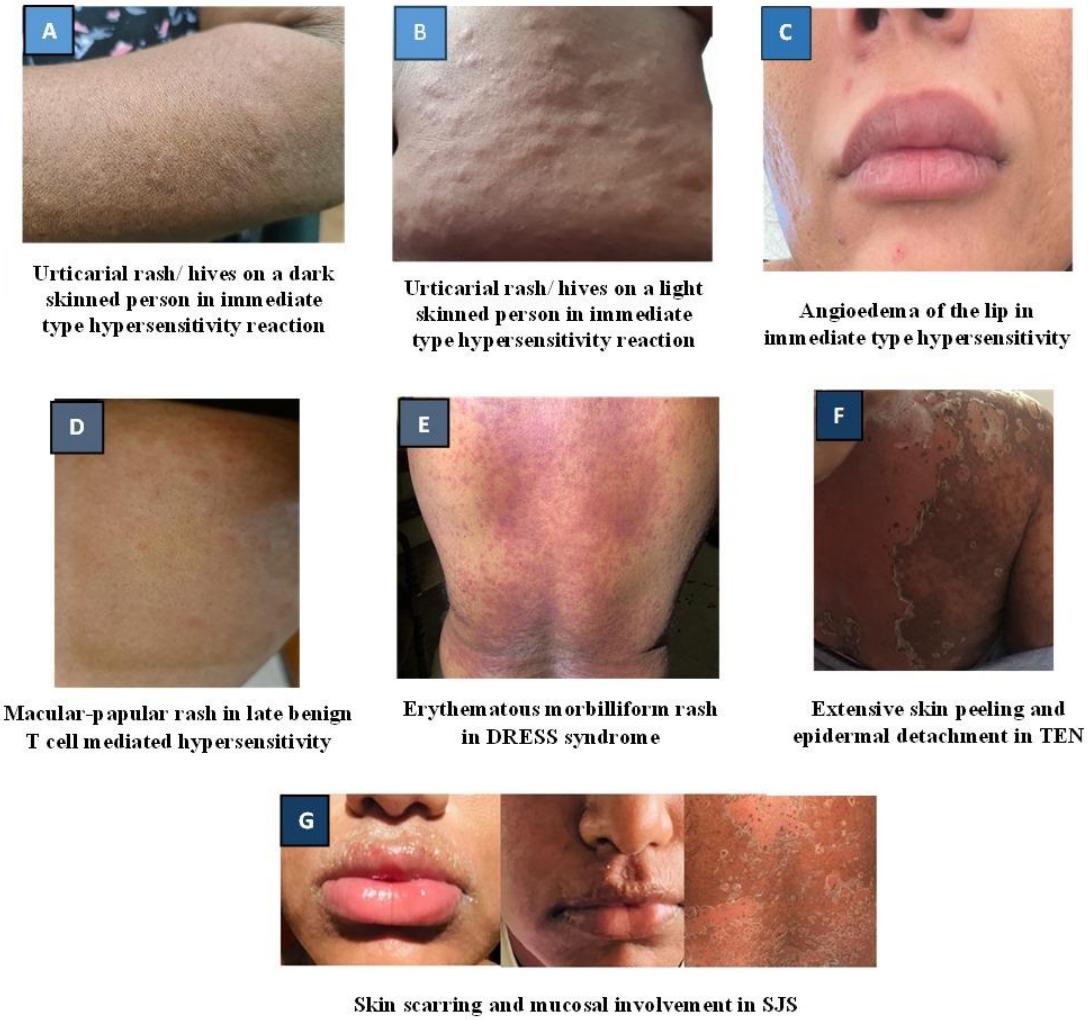


Figure 2: Mucocutaneous manifestations of hypersensitivity reactions to antibiotics

Implications of inaccurate antibiotic allergy labels

A penicillin allergy label is carried by approximately 5–15% of patients in high income countries with a higher incidence among hospitalized patients compared to patients treated as out-patients.[1,2,7,16,17] However, the data on prevalence and characteristics of antibiotic allergy in low and middle income countries is sparse. According to many studies, about 90-95% of these antibiotic allergy labels are incorrect when tested and re-challenged. In addition, the cross-reactivity between different beta-lactam antibiotics is overestimated by clinicians quite often.[1,3,4,7,17-19] Moreover, several studies have shown that the antibiotic allergies are reported and documented inadequately in a non-specific manner in patient records.[20,21] Unfortunately, many patients with an antibiotic allergy label do not undergo any form of allergy testing, let alone a proper clinical evaluation by clinicians when deciding on antibiotic treatment.[16-18] Over time, a significant number of adult and paediatric patients are labelled with multiple penicillin and non-penicillin antibiotic allergies, more frequently during inappropriate antimicrobial use. [22]

Inaccurate allergy labels have impacted adversely on patient outcomes, healthcare cost and more broadly on public health by resulting in antibiotic resistance.[1,2,4,7,16] Allergy labels have deprived patients the use of effective first-line beta-lactam antibiotics. The most effective and cost effective antibiotic treatment is omitted in patients with self-reported or unevaluated antibiotic allergies.[1,2,16-18] Treatment with 2nd line antibiotics have reduced cure rates and high adverse reactions, leading to high morbidity and mortality. Patients with an allergy label are often started on broader spectrum or reserved antibiotics, antibiotic combinations, most often in intravenous preparations, all of which result in higher cost of treatment and length of hospital stay.[1,17,18] Several studies have demonstrated the economic benefit of removing incorrect labels.[19,22-24] One of the greatest undesirable effects of allergy labels is on the development of antibiotic resistance due to increased use of alternative broad spectrum antibiotics. Many studies have shown the benefit of including allergy de-labelling protocols as a step in antibiotic stewardship programmes to improve rational prescribing and utilisation of antibiotics.[7,19,23,24]

Evaluation and management of a patient with a beta-lactam allergy label

The history is the most useful first-line tool for evaluation of an allergy to an antibiotic. It is important that adequate details of the allergy history are taken and recorded in patient records (Table 2).[7,23,24] If the history is suggestive of a true IgE mediated reaction, a risk stratification could be done as "low risk", "moderate risk" or "high risk" (Table 3), and further testing can be done by skin prick test (SPT), intra-dermal test (IDT) and graded challenge (GC). [1,2,25-31]

Skin prick tests and intradermal tests are performed to identify IgE mediated hypersensitivity reactions to beta lactams and should be performed appropriately with positive (histamine) and negative (saline) controls, major and minor determinants of penicillin metabolites and standard concentrations of other implicated beta-lactams. Since inaccurate interpretation with false positive and negative results can occur if skin prick or intradermal tests are carried out incorrectly and inappropriately, they should only be performed by a trained allergy specialist, using non-irritant concentrations of the antibiotics and results appropriately interpreted with controls. A false positive irritant skin reaction or a false negative reaction could occur if incorrect dilutions of antibiotics are used during testing.[26,32,34]

All these in-vivo tests should be performed in a setting where rare adverse reactions, such as a severe reaction, can be managed and they are contraindicated in patients who present with SCARs due to possible disastrous side effects.[34-37] The skin prick tests have a negative predictive value (NPV) of 70-95% according to the test reagents used in the panel, but if followed up with graded challenge, the NPV is increased to 100%.[24,25] In "moderate" and "high risk" patient populations, the testing protocol should include SPT, if negative followed by IDT, and if both are negative, a graded challenge.[1,2,28,31-37] In patients with a "low risk", direct challenge without preceding skin testing is advocated. This practice is specifically promoted in low risk children.[28,34-36] Rimawi et al. (2013)[24] showed the positive impact of including this testing protocol (SPT, IDT and GC) in the antimicrobial stewardship programmes to allow improved and confident prescribing of β-lactam antibiotics in patients with a label of immediate reactions to beta-lactams. De-labelling of penicillin allergy was achieved in 145 patients over a 12-month period in their hospital setting.[24]

Table 2: Clinical evaluation of an allergic reaction[31,32,33,36,37]

What were the presenting clinical features? • Features of an immediate reaction – urticaria, angioedema, flushing, itching, wheezing, chest/throat constriction • Features of anaphylaxis-respiratory compromise (e.g. dyspnoea, wheeze/bronchospasms, stridor, hypoxemia), circulatory compromise (reduced blood pressure or associated symptoms of end-organ dysfunction such as collapse/syncope, incontinence), severe gastrointestinal symptoms (e.g. severe abdominal pain, repetitive vomiting) • Features of non-immediate/late reaction - cytopenia, drug fever, morbilliform/macular-papular rash, erythematous plaques • Features of SCAR – fever, eosinophilia, deep organ involvement, blisters, ulcers, plaques or desquamation of skin and mucosa (lips, mouth, eyes, urethra, vagina)
What was the timing of the reaction after taking culprit drug? • Within minutes, hours, days or weeks of drug administration
Did the reaction occur after the first dose or after multiple continuous doses?
What was the route of administration of culprit antibiotic?
Were there any other medications administered at the same time?
Were there any other co-factors? e.g. concomitant infection, chronic urticaria, on NSAID therapy, alcohol, pregnancy
How was the reaction treated? • Need intensive care / need for adrenalin • Treated with antihistamines • Treated with steroids
Has the patient tolerated similar antibiotics since the reaction? Which antibiotics were tolerated by patient after the reaction?

There is limited availability of in-vitro blood tests for confirmation of an allergy to beta-lactam antibiotics. The specific IgE measurements for beta-lactam antibiotics can be done as a complementary test for SPT but have disadvantages such as poor sensitivity and non-availability. However, if available, beta-lactam specific IgE is preferably done before proceeding with in-vivo skin testing in patients who gave a history of a severe anaphylactic reaction to avoid rare complications associated with skin testing.[11,29]

In the local context, where specific allergy tests such as SPT and IDT are not available, patients with mild to moderate reactions can be tested with a graded oral challenge in a setting where they can be observed for reactions. However, this practice should be avoided in patients who give a history of severe allergic reactions such as anaphylaxis or SCARs. These high risk patients should be referred to an allergist or an immunologist for further evaluation.[2,27]

All patients who have convincing evidence of a true allergic reaction to antibiotic/s should be provided with a detailed record or a diagnosis card indicating the culprit antibiotic/s, type of reaction - whether immediate or delayed - with clinical features of presentation and information on how the reaction was managed. These patients should be advised to avoid exposure to the culprit antibiotic and cross reactive antibiotics.[1,2,35,36] All medical professionals should have an adequate knowledge on the management algorithms of anaphylaxis.[33,36]

Table 3
Risk stratification, testing protocol and management strategy for a patient presenting with clinical features suggestive of an IgE mediated reaction to beta-lactam antibiotics[1,2,6,27,31,33,34,35,36]

Risk category	Mild	Moderate	High
Presentation	Pruritus without rash, remote (>10 years) reaction/ unknown allergy/ symptoms that are not suggestive of allergy, family history of antibiotic allergy.	Mild urticaria (not generalized/extensive) and mild reactions with features of IgE-mediated reactions but not anaphylaxis	Anaphylaxis, recurrent reactions with beta-lactams, severe extensive urticaria/ angioedema
Action	Single dose or GC with amoxicillin (250mg/500mg)	Refer to an allergist/immunologist for allergy testing. If cannot be referred for allergy testing/not available, graded challenge can be done with amoxicillin in a monitored setting.	Refer to an allergist/ immunologist for allergy testing
Testing protocol	Single dose or GC	SPT → if negative → IDT → if negative → GC	Specific IgE if available → if negative → SPT → if negative → IDT
Management strategy	If GC negative → Remove allergy label and update medical records. Reassure and educate the patient	If SPT/IDT positive → Reinforce beta-lactam allergy label and avoid potentially cross-reactive drugs. If SPT, IDT and GC negative → Remove allergy label and update medical records. If SPT/IDT negative and GC positive, → Consider placebo-controlled challenge Update the patients' records and educate patient accordingly.	If specific IgE/SPT/IDT positive → Reinforce beta-lactam allergy label. Record if reaction was "Anaphylaxis" and mention the culprit drug in all medical records. Avoid culprit drug and all cross-reactive antibiotics. Educate patient and prescribe self-administered adrenaline if the reaction was managed as anaphylaxis.

GC= graded challenge, IDT= intra-dermal test, SPT= skin prick test

Evaluation of non-beta-lactam allergy and late hypersensitivity reactions to antibiotics

SPT and IDT are not properly standardised or validated and the non-irritant concentrations have not been established for most non-beta-lactam antibiotics to confirm an immediate hypersensitivity reaction.[38,39] For non-severe delayed reactions, drug provocation tests can be done after prescribing a 3-5-day course of antibiotic therapy. Interpretation of IDT after 48-72 hours is also suggested to elucidate the trigger in late reactions, although sensitivity is poor with some antibiotics.[38-40] Although patch testing (PT) has given a variable positivity rate in identifying culprit antibiotic in different types of mild to moderate late reactions including DRESS, due to disastrous consequences, it is generally not recommended in patients with SCARs.[41] When performed with the highest-non-irritating concentrations of the antibiotic, both PT and delayed IDT are found to be specific to identify the culprit of non-immediate hypersensitivity reactions.[41] However, it has been noted that the sensitivity of delayed IDT and PT varies with the approach, the underlying clinical phenotype and the implicated drug.[38,39,41]

Conclusion

Different pathogenesis that encompass immunological and non-immunological mechanisms lead to antibiotic allergies. Poor patient outcomes, increased healthcare costs and development of antibiotic resistance are associated with unproven, unevaluated and incompletely documented allergy labels. It has been shown that more than 90% of patients labelled as having penicillin allergy have negative allergy tests and can be safely treated with beta-lactams. Inadequate evaluation, risk assessment and poor documentation of antibiotic allergies may be a consequence of lack of familiarity of this problem among clinicians. The lack of knowledge may also have an impact on optimal antibiotic treatment of these patients. Continuous educational programmes for medical professionals on antibiotic allergies, their evaluation and management pathways need to be conducted to increase their knowledge and awareness.

Declaration

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