



REVIEW ARTICLE

Shedding Misconceptions: The importance and impact of Drug allergy de-labelling

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ABSTRACT

Correctly labelling antibiotic allergies has become essential to global antimicrobial stewardship due to rise in multi-drug resistant organisms.

Drug hypersensitivity reactions are often misunderstood, leading to misconceptions that can both hinder effective medical treatment and contribute to patient anxiety. It leads to avoidance of drugs with label of allergy and prescription of other broad spectrum antibiotics which can be contributing to antimicrobial resistance, economic burden to the patient and the healthcare system. By the process of de-labelling, we can be championing for antimicrobial stewardship.

De-labelling often involves a structured approach, including a detailed medical history, assessment of the initial allergic reaction, and consideration of potential testing, such as skin tests or supervised drug challenges. It is a collaborative effort, requiring expertise from allergists in combination with the patient's healthcare team, leading to improved patient care and reduced constraints on medication choices.

Informed consent and shared decision-making with patients are essential when deciding which medications to delabel first and weighing the advantages/disadvantages of testing against the temporary use of substitute antibiotics.

If these evaluations show that a patient can safely tolerate a drug they were previously labelled allergic to, the allergy label is removed, or de-labelled, it can pave the way forward to use it in future if required.

Recent initiatives have focused on patients with beta lactam allergy and high risk populations that may require these antibiotics as first line treatment, as they are believed to be the most likely to benefit from the removal of false antibiotic allergy labels. An overview of current risk stratification techniques along with a summary of how various delabeling programs have applied these ideas to their delabeling algorithms is given in this review.

Keywords: Drug allergy, antimicrobial resistance, Delabelling.

Introduction

Given the rising prevalence of multi-drug resistant organisms, it is essential to delabel incorrect antibiotic allergies as part of global antimicrobial stewardship efforts. Often, patients have both allergic and non-allergic adverse drug reactions inaccurately labeled as 'drug allergies.' These incorrect labels can have significant implications for future treatment. For instance, patients may be wrongly labeled with multiple antibiotic allergies, severely limiting their options for future antibiotic prescriptions, including acute infections, pre-operative or pre-procedural antimicrobial prophylaxis, or long-term suppressive therapy

There are many reports on drug allergies where the incidence of drug allergy label is more in self-reported surveys as compared to the actual incidence proven by history, appropriate test/challenge when indicated. A survey to assess adverse drug reactions in children showed that as many as 46% of children were labelled as having a drug allergy reaction by parents and close to 31% by medical professionals. Upon proper diagnostic work-up showed drug hypersensitivity only in 5%.¹

The prevalence of drug allergy labels in the Asia Pacific region is close to 9% in the general population where antibiotics, non steroidal anti-inflammatory drugs and radiocontrast media are the most drugs with label of drug allergies² A retrospective review of medical records in a tertiary care pulmonary unit showed prevalence of 5.6% drug allergy reports with unverified drug allergy labels to antibiotics and NSAIDs.³

Indian data also showed similar prevalence for drug hypersensitivity in 2-5% upon proper history and evaluation for the same.⁴

It is important to understand the approach to drug hypersensitivity reactions as it forms the basis for structured approach to de-labelling.

Adverse drug reactions are broadly classified into

1. Type A reactions
2. Type B reactions

Type A reactions are dose dependent and predictable. Few examples include

Overdose (e.g. hepatic necrosis from acetaminophen)

Side effects (e.g. tremor from salbutamol)

Secondary effects (e.g. C.difficileinfection from clindamycin)

Drug-drug interactions (e.g. macrolide causing supratherapeutic INR in patient on coumadin)

Type B reactions are dose independent and unpredictable. Some examples include

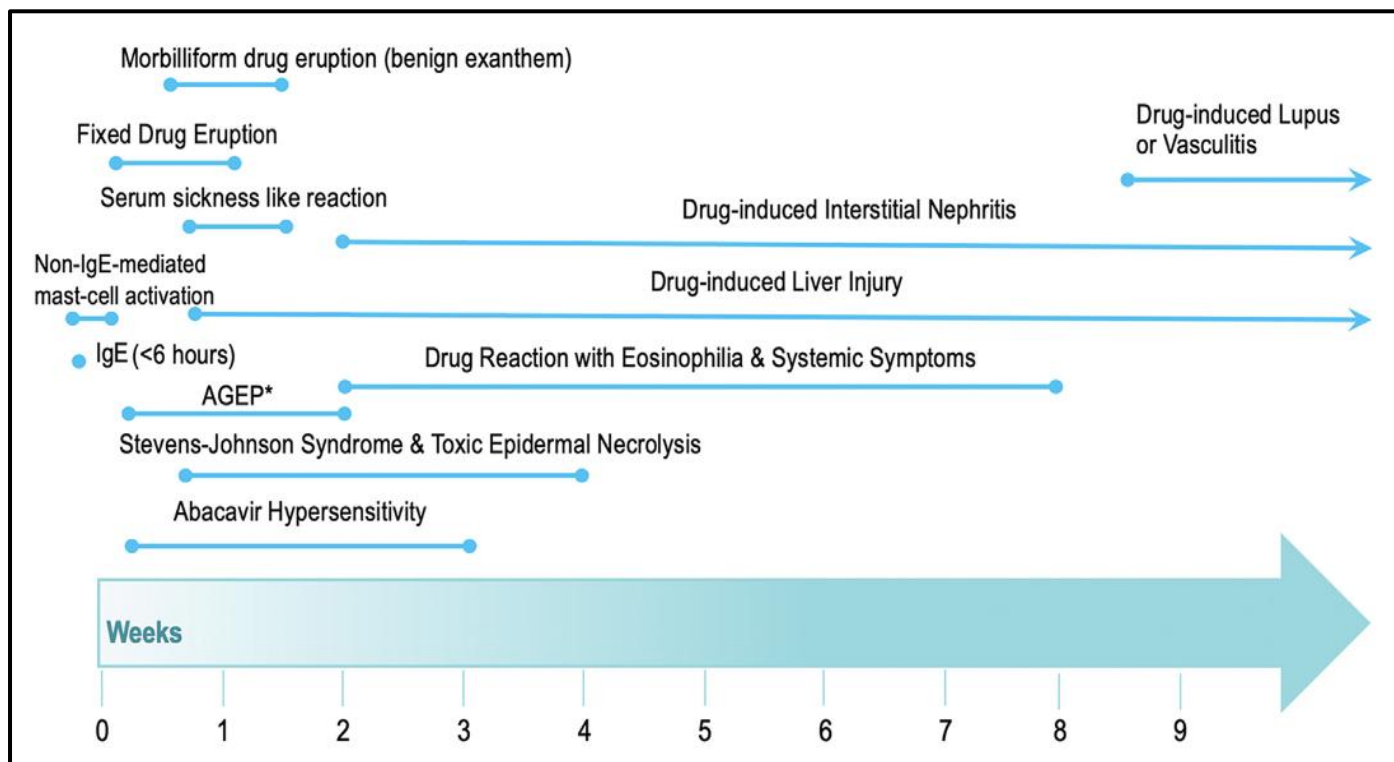
Intolerance (e.g. tinnitus with aspirin)

Idiosyncratic (e.g. hemolysis in G6PD deficiency)

Pseudoallergic (e.g. vancomycin rapid intravenous infusion causing red man syndrome)

Drug Allergy/Hypersensitivity reactions^{5,11}

Drug hypersensitivity reactions can have a varied presentation in clinical presentation ranging between few hours to few weeks after the administration of the index drug.⁶



Common misconceptions on drug hypersensitivity reactions are many. It is important to educate patients and peers regarding the same.

1. Adverse Drug Reactions (ADRs) are All Allergies:

- Not all ADRs are allergic in nature. Some are side effects or toxic reactions at normal doses and do not involve the immune system. True drug allergies involve an immune response.

2. Intolerance Equals Allergy:

- Many individuals mistake drug intolerance, such as gastrointestinal upset from antibiotics, for an allergy. Intolerance doesn't involve an immune-mediated allergic reaction.

3. Once Allergic, Always Allergic:

- People often believe that a drug allergy is a lifelong condition. While this may be true in some cases, many drug allergies can be outgrown or may not be true allergies at all.

4. Allergic to One, Allergic to All:

- There's a misconception that being allergic to one drug within a class (like penicillin) means allergic to all related drugs. Cross-reactivity is not guaranteed, and testing can often identify safe alternatives.

5. Minor Reactions Predict Major Reactions:

- A mild past reaction doesn't necessarily predict a severe future reaction. Each allergic response is unique, and the severity of reactions is unpredictable without proper medical evaluation.

6. Skin Tests Determine All Drug Allergies:

- Some drug allergies, such as penicillin, can be tested with skin tests, but for many others, there are no validated skin or blood tests available.

7. Only Immediate Reactions are Allergic:

- Drug allergies can manifest hours to days after exposure, not solely as immediate reactions. Delayed-type hypersensitivities also represent important allergic responses.

The current major world allergy organisations place emphasis on delabelling to improve access to medications labelled allergic in the past.

What is delabelling of drug allergy?

A. DEFINITION OF DRUG ALLERGY DELABELLING
Drug allergy delabelling refers to the process of removing an incorrect drug allergy label from a patient's medical record after a thorough

evaluation. It usually involves structured allergy assessments, which may include a detailed patient history, clinical examinations, skin tests, in vitro tests, or drug provocation tests. If these evaluations show that a patient can safely tolerate a drug they were previously labelled allergic to, the allergy label is removed, or delabelled.

Many patients carry an inaccurate label of beta-lactam allergy, leading to the use of alternative antibiotics. However, this practice can result in broader antibiotic spectra, increased risks, and higher costs. To champion effective antimicrobial stewardship, it is imperative to correct these labels.¹⁴

B. IMPORTANCE OF ACCURATE ALLERGY DOCUMENTATION

Accurate allergy documentation in healthcare is crucial for several reasons:^{12,13}

1. Patient Safety: Accurately documented drug allergies ensure that patients avoid medications that could cause harmful allergic reactions.

2. Quality of Care: Correct documentation helps healthcare providers to make well-informed clinical decisions, thereby improving the overall quality of care.

3. Avoidance of Ineffective Treatments: When drug allergies are accurately recorded, clinicians can avoid prescribing alternative medications that may be less effective, more expensive, or have more adverse effects.

4. Decreased Risk of Antimicrobial Resistance: In cases of incorrectly labelled penicillin allergies, accurate delabelling can reduce unnecessary use of broad-spectrum antibiotics, helping combat antimicrobial resistance.

C. PREVALENCE OF INCORRECT DRUG ALLERGY LABELS AND THEIR IMPACT ON HEALTHCARE

Incorrect drug allergy labels are a common issue in healthcare, with a significant impact on patient care and healthcare systems.¹⁰

Adverse drug reactions (ADRs) are often confused with allergic reactions, which can lead to mislabelling. ADRs can include a wide range of unwanted effects, varying from mild to severe. Drug intolerance, for instance, may cause symptoms like gastrointestinal discomfort but does not involve the immune system. On the other hand, a true allergic reaction is an immune response where the body mistakenly identifies a drug as a harmful substance, triggering symptoms such as hives, respiratory distress, or anaphylaxis. Distinguishing between non-allergic ADRs and true allergies is critical but can be challenging without proper evaluation

D. COMMONLY MISLABELLED DRUGS AND THEIR PRESUMED ALLERGIES

Certain drugs are more frequently associated with being incorrectly labelled as allergens. For example, penicillin and related antibiotics are among the most misreported drug allergies. Patients might report a penicillin allergy based on a childhood reaction, which may have been a rash commonly associated with a viral infection rather than the antibiotic itself. Another example is the mislabelling of opioid allergies, where side effects such as nausea or itching may be incorrectly documented as allergic reactions.

The Delabelling Process

A. ASSESSMENT AND IDENTIFICATION OF CANDIDATES FOR DELABELLING:

Patients potentially eligible for delabelling include those with a history of drug allergy that is vague, non-specific, or based on a reaction that occurred in childhood which they may have outgrown after risk stratification. Additionally, those with allergies to antibiotics, such as penicillins, are often considered for delabelling due to the high rates of reported allergies and the benefits of these drugs.

The following patients can be defined as low or minimal risk for direct oral provocation test for a penicillin challenge, who have had label of drug allergy to penicillin.

- 5 to 18 years
 - history of a benign cutaneous only reaction more than 1 year ago
- >18 years as a history of a benign cutaneous only reaction more than 10 years ago⁷
- Benign rash occurring more than 1 year ago, any other benign somatic symptoms, or an unknown history^{8,9}

B. DIAGNOSTIC METHODS TO CONFIRM OR RULE OUT DRUG ALLERGIES:

1. Skin testing: In the case of some drug allergies, such as penicillin, skin testing can be used to verify the presence or absence of an IgE-mediated allergic reaction.

2. In vitro testing: This includes methods like the enzyme-linked immunosorbent assay (ELISA) to detect specific IgE antibodies to drugs, although its availability may vary and are not validated in many countries across the globe.

3. Drug provocation testing (challenge testing): This is considered the gold standard for allergy testing to include/exclude the diagnosis and involves the administration of the incremental doses of the drug in a controlled setting to observe for a potential reaction.

As the specificity of both methods of skin prick, intradermal test followed by a direct oral provocation test as compared to direct amoxicillin drug challenge in low risk stratified patients was found to be similar. In resource limited settings in a country like India, where there is minimal clinical pathways established for delabelling and emerging evidence for collaboration between HCP/allied professionals with locally adapted strategies, we can use direct penicillin challenge for de-labelling patient with minimal/no risk for possible reactions for future reactions with label of penicillin allergy.^{7,8}

Implementing Drug Allergy Delabelling in Clinical Practice

A. Education and training for healthcare professionals:

Medical staff must be educated about the importance of accurate allergy history-taking, the benefits of delabelling, and how to properly refer patients for assessment.

B. PATIENT EDUCATION AND INVOLVEMENT:

Patients should be informed about what delabelling entails, the potential benefits, and the risks associated with diagnostic testing. Understanding the process and participating actively can reduce anxiety and promote cooperation.

C. THE USE OF ELECTRONIC HEALTH RECORDS AND ALERT SYSTEMS TO FACILITATE DELABELLING:

Electronic health records (EHRs) with improved allergy documentation and clinical decision support systems can identify candidates for delabelling and alert healthcare providers to outdated or unverified allergy labels.

D. PROTOCOLS FOR FOLLOW-UP AND MONITORING AFTER DELABELLING:

After delabelling, patients should be monitored to ensure that they do not experience subsequent reactions when exposed to the drug. Follow-up can also provide information on the long-term safety and effectiveness of the delabelling process.

Outcomes and benefits of delabelling programs

The benefits of successful delabelling programs include a reduced reliance on broad-spectrum antibiotics, which can decrease rates of antibiotic resistance. Additionally, patients have access to safer, more effective, and often less expensive medications. Hospitals also benefit from reduced rates of nosocomial infections, such as *Clostridioides difficile*, and improved antimicrobial stewardship.^{6,7,8}

Research continues to refine delabelling protocols and address limitations in current diagnostic tests. Studies are investigating the long-term outcomes of delabelled patients, the optimization of testing methodologies, education interventions to promote delabelling, and the use of electronic health records to identify candidates for delabelling.

The Future of Drug Allergy Practice

As we have advances in diagnostic testing and precision medicine rapidly evolving, promising improved identification of true drug allergies augmented by techniques such as component-resolved diagnostics and basophil activation tests, clinicians may soon have more tools at their disposal to assess drug hypersensitivity with greater specificity.

The integration of genetic information holds vast potential in predicting drug allergies, where pharmacogenomics can play a crucial role. Identifying genetic variants that predispose individuals to adverse reactions could lead to a proactive approach in managing drug allergies, minimizing the risk of reactions through tailored drug selection. Developing personalized treatments and prophylactic measures may reduce adverse reactions and improve drug tolerability.

Conclusion

The significance of drug allergy delabelling is multifaceted. Firstly, it reduces the risk of patients being unnecessarily exposed to alternative drugs, which may be less effective or have a higher risk for adverse effects. Delabelling also minimizes the misuse of broad-spectrum antibiotics, which contributes to the growing issue of antibiotic resistance.

Accurate allergy documentation is crucial for proper patient care. It ensures patients receive the most effective medications without delay and prevents unnecessary avoidance of certain drugs. This article emphasizes the need for continued research, education, and policy development in drug allergy practice.

Drug allergy delabelling represents a significant advancement in personalized medicine, transforming the lives of patients by safely clarifying true allergies and expanding treatment options. As our understanding of the mechanisms underlying drug allergies improves, it would be prudent to establish more precise diagnostic methods and management protocols. Developing comprehensive policies that support drug allergy delabelling initiatives is necessary to achieve the systemic change required for these improvements to be realized on a large scale.

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