

EDITORIAL

How to tackle over-labelling of antibiotic allergy in children: A clear and safe procedure

Antibiotic allergies, especially β -lactams (including penicillin, amoxicillin and cephalosporins), are the most frequent drug allergies reported in the medical record. Today, around 10% of the Western population, and as many as 20% of the hospitalised patients, carry a penicillin allergy label.^{1,2} Antibiotic allergy labels are accumulated by various mechanisms and are often incorrectly self-reported or recorded. A penicillin allergy label, in particular, is associated with increased use of broad-spectrum and non- β -lactam antibiotics, which results in increased adverse events, costs and antibiotic resistance. We now understand that most of the cutaneous symptoms interpreted as drug allergy likely reflect a viral aetiology or are due to drug-virus interaction, and they usually do not represent immune-mediated antibiotic hypersensitivity.³ Even if the original reactions were immunological, immunoglobulin E (IgE)-mediated reactions to β -lactams can wane over time; approximately 80% of patients who were positive for a penicillin skin test were no longer sensitive, as measured by skin testing after a period of 10 years.^{4,5} In spite of this fact, most antibiotic allergy labels acquired in childhood are carried into adulthood. In addition, labels frequently remain despite negative testing results and/or challenge in up to 50% of patients.

β -lactams are considered first-line therapy for bacterial respiratory infections, such as acute otitis media, streptococcal infection or pneumonia, and they are mainly administered orally. Aminopenicillins are widely recognised as the most common cause of rash. However, they infrequently cause true IgE-mediated reactions. In fact, it is estimated that only about 1% of all patients in the US health care system have a true IgE-mediated hypersensitivity response to penicillin. Anaphylaxis is rare, detected in only 0.0005% when aminopenicillins are administered orally.⁴ Most patients labelled with a β -lactam allergy are not allergic (i.e. they tolerate penicillin and related drugs) when appropriately stratified for risk, tested and re-challenged. Ideally, all patients with a history of immune-mediated allergy would be referred to specialist assessment and/or skin testing followed by an oral challenge test (OCT), which for immediate penicillin allergy is particularly safe and carries over 99% negative predictive value.⁵ In a recent study on 100 children with suspected penicillin allergy and categorised as low-risk by an allergy questionnaire, no one had a true penicillin allergy resulting from skin testing and OCT procedure.⁶ In the case of adults, a systematic review of over 5000 adult participants with a reported history of penicillin allergy, 95% tolerated the dose challenges of penicillin-based antibiotics.⁷

It is important to have a clear and safe guideline to rule out or verify a suspected antibiotic allergy. In this *Journal*, Guðnadóttir et al⁸ present a retrospective study on 1440 patients aged 0.4–18 years referred from outpatient clinics with presumed allergic reaction to an antibiotic. Of all the children, 73% were less than 5 years old. The most common antibiotic involved was amoxicillin alone or with clavulanic acid (86%), the most common reaction rash (92%), and the reaction had most commonly initiated on day 4 or later after intake of the antibiotic (41%). When a direct OCT was performed without skin PRICK tests in 1440 children, 94% were tolerant to the antibiotic. Only nine (0.6%) had an immediate mild reaction within 1 h. No severe reactions occurred. If the OCT was performed in less than 6 months after the initial reaction, patients reacted significantly more often. In addition, 70% of the children (64/92) with mild reaction in the initial OCT were re-challenged 1–2 years later; 84% of the children tested had outgrown their allergy. In summary, in 99% of the children with a delayed benign cutaneous rash, the investigators were able to remove the antibiotic allergy label with a simple and safe oral challenge test without prior skin testing.

Given that 75% of the children with penicillin allergy are labelled by the age of three, and that a great majority of the penicillin allergies in the children represent delayed low-risk category, it would be crucial to tackle suspected antibiotic allergies among toddlers.⁵ To prevent unnecessary avoidance of antibiotics, particularly penicillins, risk stratification assessment of reported penicillin allergy and strategic implementation plans have been provided. The negative predictive value of penicillin skin PRICK testing has been established to be from 97% to 99%, and is easily performed even in infants. In vitro specific IgE-testing that is commercially available for penicillin, on the other hand, has been shown to have a low sensitivity in children, ranging from 0% to 25%.⁹

In evaluating and managing patients with a reported history of penicillin allergy, direct oral drug challenge without prior SPT has recently shown to be effective in carefully selected patients with low risk allergies^{5,8,10}.

- 1) delayed reaction (>1 h from exposure) with isolated benign maculopapular exanthema.
- 2) gastrointestinal symptoms only, such as nausea, vomiting or diarrhoea.
- 3) the reason for avoidance being family history of penicillin allergy.

Abbreviations: IgE, Immunoglobulin E; OCT, Oral challenge test.

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Oral challenge test is considered a gold standard for drug allergy diagnosis. Several studies have reported the possible reactions in oral drug challenge to be similar or less severe than in the original reaction.¹ A two-step graded OCT protocol for amoxicillin has been widely used in children. First, a 10% of a weight-based dose and after 30–60 min observation time the remaining 90%.^{1,5,8} If a skin PRICK test is negative, a single weight-based dose of amoxicillin has been suggested. Oral tolerance of amoxicillin is sufficient to remove all penicillin allergy labels.

When referred to a paediatrician or paediatric allergist, prompt data are needed on medications taken at the time of the reaction, previous exposure to the same antibiotic or structurally similar antibiotics, accurate documentation of the symptoms and treatment required for the reaction. A benign delayed maculopapular rash is the most common reaction that leads to penicillin allergy label. With a single- or double-dose oral challenge test, this deleterious label can be safely removed in 95%–99% of the patients.^{5,8} For an individual and a society, we should fight against an unnecessary avoidance of antibiotics, particularly penicillins.

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CONFLICTS OF INTEREST

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