

Another Step Forward in the Optimization of Penicillin Allergy Delabeling Strategies in Children



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The article by Exius and coworkers¹ in this issue is the largest study published to date on the use of direct oral amoxicillin challenges in young children to evaluate current tolerance after benign cutaneous reactions attributed to amoxicillin. The study presents the outcomes of graded oral challenges in 1914 children over 7 years at three centers in Canada. Most study subjects' index adverse reactions occurred while they were treated with amoxicillin for suspected acute otitis media. Over 50% experienced an adverse reaction with first lifetime exposure to amoxicillin. Median time between the index reaction and the diagnostic challenge was 1.1 years, which reflects the typically lower time frame between the index reaction and drug hypersensitivity evaluation in children compared with adults.

The graded challenge protocol employed a weight-adjusted amoxicillin dose that was 500 mg to 1.5 g. Only 10% of the dose was administered initially, followed by 20 minutes of observation, and then the remaining 90% was given with an additional hour of observation. During the graded challenge, the researchers documented impressive safety, noting only 2.2% ($n = 42$) acute-onset benign cutaneous reactions and 3.2% ($n = 61$) delayed-onset benign cutaneous reactions. Only four children (0.21%) had a reaction after the initial 10% dose, which ranged from 50 to 150 mg. This may have reflected the only 20-minute observation before the remaining dose was administered. This challenge protocol differed from that of many other groups who routinely used a single 250-mg dose of amoxicillin, often adjusted to 125 mg for small children, with 1 hour of observation.² Surprisingly, the overall rate of confirmed hypersensitivity was not different between patients who had had the index reaction during the first exposure compared with patients who had reacted to a penicillin after multiple courses. This suggests that evaluating pediatric patients with suspected penicillin allergy whose index reaction occurred after the first exposure to a penicillin is not intrinsically safer than those who reacted after multiple exposures.

After documentation of current amoxicillin tolerance, the authors then reviewed the rate of reactions with subsequent use of therapeutic amoxicillin in 265 (29.8%) patients over a 5-year

follow-up. What was unexpected was that 39 patients (14.7%) reported a new benign cutaneous reaction. None of these were apparently retested.³ An index reaction lasting longer than 7 days and having parents who also reported drug intolerance were risk factors associated with subsequent adverse reactions. These findings highlight how young children are not just small adults; this cohort was all aged less than 10 years, and most were less than 5 years. Typically, in combined populations of children and adults receiving therapeutic courses of penicillins after negative penicillin allergy testing, the rate of new penicillin allergy reported is only about two to three times that of random individuals in the population reporting no other antibiotic allergy.⁴⁻⁷

The authors also reviewed the rate of cephalexin-associated challenge reactions in patients with positive amoxicillin challenges who consented to a cephalexin challenge. They identified that four of 32 who reacted to amoxicillin (12.5%) also reacted to cephalexin, a first-generation cephalosporin with a similar but not identical R1 side chain to amoxicillin. Three were immediate and one was delayed. All reactions were benign cutaneous reactions. This rate of reaction to cephalexin in patients with challenge-confirmed amoxicillin allergy has yet to be confirmed in adults.⁸

Critical information that is currently lacking is the population-based incidence of newly reported antibiotic allergy in children aged less than 5 years for all commonly used antibiotics, including amoxicillin. If children are noting acute onset (within 1 hour) benign rashes after their first exposure to any antibiotic, it is extremely unlikely that is reflective of an IgE-mediated process. Delayed onset rashes occurring 10 minutes after a fourth dose of an antibiotic may reflect a T cell-mediated process, but even this may be slightly early to generate new clinically significant T cell-mediated immunity. A 10-day course of amoxicillin used to treat acute otitis media in a 2-year-old appears to be enough time to lead to some form of an immune response.⁹ This study adds evidence to the idea that first exposure to an antibiotic can be associated with an immunologic response that can reoccur on subsequent doses.

An issue with this study is that the time of onset of index reaction signs and symptoms after the last dose during the course of amoxicillin is not clearly presented. More evidence is needed to differentiate potential IgE-mediated acute adverse reactions from delayed non-IgE mediated allergic reactions to penicillin antibiotics. Noting a benign rash observed 5 minutes after the fourth dose does not indicate an acute-onset adverse reaction. There is a growing international consensus, recently well-outlined by Sabato and coworkers¹⁰ in this journal, that having an urticarial eruption starting within 1 hour of the first dose and resolving within 1 day is the greatest risk factor for

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subsequently confirming a clinically significant IgE-mediated allergy to an antibiotic.

This study, like many, also raises more questions than it answers. Is a two-step challenge even necessary when only 0.21% react in the first 20 minutes?⁶ What is the optimal dose and time of observation needed to confirm current tolerance?² Because immunologically mediated hypersensitivity may wax and wane with time, is it possible to define a true reference standard to determine the sensitivity and specificity of antibiotic hypersensitivity testing? What is the population-based incidence of newly reported antibiotic-associated reactions in individuals with no previously reported antibiotic intolerance, with an active but unconfirmed antibiotic intolerance, with a historically reported antibiotic intolerance but who are challenge-negative, or in individuals with confirmed immunologically mediated antibiotic hypersensitivity? What are the clinical characteristics of children who are more likely to report antibiotic-associated rashes after infections? What are the primary mechanisms for these reactions, given that only a small minority can be attributed to an IgE-mediated or T cell-mediated process? Is it possible to treat through acute- or delayed-onset benign cutaneous antibiotic-associated reactions?

Penicillin skin testing, particularly the intradermal component, can be especially difficult to perform in young children. Therefore, routine use of penicillin skin testing can be a barrier to evaluating whether penicillin can be safely used again if needed. Because penicillin skin testing may also dramatically increase the false-positive rate² with no documented increase in safety, this study adds to the evidence that skin testing can be

avoided when evaluating almost all children with a history of benign cutaneous reactions to penicillin.

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