

EDITORIAL

Provocation Challenges to Evaluate Amoxicillin Allergy in Children

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Although β -lactam antibiotics are the most common cause of drug allergy, most patients who are labeled as being allergic to penicillin are not, either because they were never sensitized or because they have lost their allergy over time.¹ Although 6% of children are labeled as being allergic to penicillin, only 4% to 9% of those so labeled are currently allergic.² It is impor-



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tant to identify those who are not allergic, because children mislabeled as penicillin allergic have more medical visits, receive more antibiotic prescriptions, and have longer hospitalizations with more antibiotic-related complications.^{3,4}

Penicillin is metabolized primarily to its major penicilloyl determinant and also to minor penilloate and penicilloate determinants.¹ In patients with suspected penicillin allergy, the current standard of care is to perform immediate-type skin tests with penicillin and the penicilloyl determinant and, if negative, to perform an oral provocation challenge with amoxicillin under observation.⁵ The amoxicillin challenge identifies the very small percentage of penicillin-allergic patients who would have reacted only to the minor determinants or who are sensitized only to the amoxicillin side chain.⁶ Using this approach, Solensky and Macy⁵ reported that among a population of 1482 patients suspected to have penicillin allergy, 1431 (96.6%) had negative results on skin tests and oral challenges, 30 (2.0%) had positive skin test results and did not receive the oral challenge, 15 (1.0%) had objective positive acute oral challenge results (most had urticaria treated with oral antihistamines, but 2 had more serious reactions requiring epinephrine), and 6 (0.4%) had reactions beginning more than 24 hours after challenge (4 with presumed delayed-type hypersensitivity rashes and 2 with gastrointestinal symptoms).

In this issue of *JAMA Pediatrics*, Mill et al⁷ take a different approach to evaluating children who developed rashes while receiving amoxicillin. Instead of performing skin tests first and administering the oral challenge only to those with negative skin test results, they administered oral amoxicillin challenges in all children and then performed skin tests only in those with positive challenge results. Of 818 children assessed, 770 (94.1%) tolerated the challenge without any reaction, 17 (2.1%) developed immediate reactions (all hives only), and 31 (3.8%) developed nonimmediate reactions (maculopapular rashes and serum sickness-like reaction).

For the 17 children who developed immediate reactions, skin tests were performed 2 or 3 months later with penicillin and the penicilloyl determinant; the skin test result was positive in only 1 patient, implying poor predictive values and lead-

ing the authors to conclude that penicillin skin tests "are not useful for the diagnosis of immediate reactors."⁷ The positive predictive value of penicillin skin testing is unknown owing to prudent reluctance to challenge history-positive, skin test-positive patients with penicillin, but based on the small numbers of these patients who have received penicillin, 33% to 100% develop immediate reactions and such patients should not receive penicillin.^{1,8} In the study by Solensky and Macy,⁵ skin tests with these same reagents had a 99% negative predictive value. However, in the study by Mill and colleagues, only those children with positive immediate challenge results underwent skin testing and therefore predictive values cannot be calculated; perhaps the children in this study who had negative skin test results but still developed hives on oral challenge were sensitized only to the minor determinants or to the amoxicillin side chain. Alternatively, perhaps the reactions were not IgE mediated but instead involved direct mast cell degranulation or non-mast cell mechanisms.

Mill and colleagues also followed up a subset of those with no immediate or delayed reaction to the challenge over time to determine whether they received amoxicillin in the future and, if so, whether they had any reaction. Forty-nine such children tolerated subsequent full treatment courses of amoxicillin, but 6 developed late-onset rashes to these subsequent exposures. Thus, a single-dose challenge, while sufficient to exclude an IgE-mediated reaction, may not be sufficient to exclude a possible late-onset reaction on subsequent exposure to a full course of antibiotics.

In the study by Mill and colleagues, most of the children are described as having their historical ("alleged") reaction to amoxicillin required for study entry with their first exposure.⁷ This argues strongly against these prior reactions being immune mediated because such reactions require prior exposure. Many are also described as developing persistent rashes that began after several days. Thus, many of the children who underwent amoxicillin challenge in this study had a very low likelihood of having an IgE-mediated reaction to amoxicillin. Although it was not the authors' intent to exclude them, none of the children who received the challenge had a history of anaphylaxis and they acknowledge that the results should "not be generalized to all cases of suspected amoxicillin allergy but rather might only be generalized to pediatric cases presenting with cutaneous, nonanaphylactic reactions."⁷

Is performing oral amoxicillin challenges on children with a history of developing rashes while taking this medication safe without prior skin testing? The risk associated with such challenges is largely confined to the child with IgE-mediated al-

lergy having an anaphylactic reaction to the challenge. This risk depends on a number of factors including prior exposure, the nature and timing of the suspected reaction, and how long ago the reaction occurred.¹ A child without prior exposure and a distant history of a rash that was nonurticarial or began days into a course of penicillin is at low risk for a reaction, and an oral provocation challenge without prior skin testing may be reasonable. However, a child with prior exposure and a more recent history of an urticarial or anaphylactic reaction that occurred shortly after the first dose of a new course of antibiotics is at high risk and penicillin skin testing should be performed prior to an oral challenge.¹

Given the morbidity and costs associated with being mislabeled as penicillin allergic,^{3,4} it is absolutely appropriate for children so labeled to be evaluated so that the majority who are not allergic can be “delabeled.”² Mill and colleagues conclude that challenges “provide an accurate and safe confirmatory test for skin-related reactions to amoxicillin.”⁷ The chance

of an anaphylactic reaction to an oral provocation challenge is small but not 0, and anaphylaxis by definition is a potentially life-threatening event. As described earlier, while all of the immediate reactions to the amoxicillin challenge in the study by Mill and colleagues were hives only,⁷ rare patients have been reported who required epinephrine to treat systemic reactions to such oral challenges.⁵ This emphasizes the importance of such challenges being performed in a medical setting with personnel and equipment able to recognize and treat anaphylaxis. The study by Mill and colleagues suggests that some children with a history of possible penicillin allergy may be able to undergo an oral amoxicillin challenge without prior skin testing; however, for other children, skin testing prior to challenge is appropriate. The study was conducted in an allergy clinic by board-certified allergists and, given the complexities of determining the risk of reactions and deciding whether skin tests should be performed prior to oral challenge, this is the most appropriate setting for these evaluations to occur.

ARTICLE INFORMATION

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