

## Original Article

# Amoxicillin Allergy in Children: Five-Day Drug Provocation Test in the Diagnosis of Nonimmediate Reactions

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**What is already known about this topic?** A prolonged drug provocation test seems to improve the sensitivity of the allergy work-up in cases of non-immediate drug reactions in children, but a standardized protocol is lacking.

**What does this article add to our knowledge?** This is the first study that describes a 5-day drug provocation test in a large population of children with histories of amoxicillin allergy.

**How does this study impact current management guidelines?** This study shows important results both in terms of safety and sensitivity of a 5-days drug provocation test DPT in children with non-immediate reactions to amoxicillin.

**BACKGROUND:** The drug provocation test (DPT) is the gold standard to rule out drug hypersensitivity. There are standardized DPT protocols to diagnose immediate reactions to drugs, but not for nonimmediate reactions.

**OBJECTIVE:** The aim of this study was to show the sensitivity and specificity of an allergy work-up that included a 5-day DPT in children with histories of nonimmediate reactions to amoxicillin through focusing on a pediatric population with histories of immediate and nonimmediate reactions to amoxicillin.

**METHODS:** Two hundred consecutive patients with histories of amoxicillin reactions referred to the Allergy Unit of Anna Meyer Children's Hospital for suspected drug allergy from 2008 to 2011 underwent in vivo tests with the culprit drug according to European Academy of Allergy and Clinical Immunology guidelines. Moreover, most of those children, regardless of the skin tests results, were challenged with amoxicillin for a total of 5 days.

**RESULTS:** In 4 years, 200 patients were evaluated for a history of drug hypersensitivity to amoxicillin. The majority of patients (76%) had a history of mild nonimmediate reactions. All 200 patients underwent skin tests, and 9 of 200 tested positive. A total of 177 DPTs were performed with amoxicillin for 5 days in each child. Diagnosis of amoxicillin allergy was confirmed by a

DPT in 17 patients (9.6%); 14/17 had history of nonimmediate reactions; 4/14 (26.6%) reacted on day 5.

**CONCLUSION:** According to our results, a long-term DPT protocol increases the sensitivity of the allergy work-up, and it should be recommended for patients with a history of amoxicillin nonimmediate reaction. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)

**Key words:** Amoxicillin allergy; Children; Drug allergy; Diagnostic work-up; Drug provocation test; Long-term drug provocation test; Nonimmediate reactions

Amoxicillin is recommended as the first line of treatment for the most common community-acquired bacterial infections (ie, otitis media and sinus infection) and is one of the most prescribed antibiotics.<sup>1,2</sup> Hence, it is not surprising that hypersensitivity to amoxicillin is very common with an estimated incidence of 1-10%.<sup>3-7</sup>

Moreover, penicillins are more sensitizing than other antibiotics, which is another reason for the high frequency of observed reactions.

Hypersensitivity reactions to amoxicillin are classified as "immediate" or "nonimmediate" based on the time between drug intake and onset of hypersensitivity symptoms. Immediate reactions occur within 1 hour (most often within 30 minutes) of drug administration.<sup>8</sup>

They are characterized by urticaria and/or angioedema, bronchospasm, anaphylaxis, and even fatality.<sup>9</sup> In a minority of cases, they are caused by specific IgE antibodies against the beta-lactam antibiotic. The patients with IgE-mediated reactions are at the highest risk of severe, near fatal, and fatal reactions. The risk for fatal anaphylaxis with penicillin has been estimated to be approximately 1 in 100,000 and is greater in those who receive penicillin parentally than orally. However, the risk with other beta-lactam antibiotics, including amoxicillin, is poorly documented and most likely significantly lower.<sup>10-13</sup>

The nonimmediate reactions occur after more than 1 hour of the administration of the antibiotic, typically toward the end of

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**Abbreviations used***DPT- Drug provocation test**ENDA- European Network for Drug Allergy**ID- Intradermal**MDM- Mixture of minor determinant**MPE- Maculopapular exanthema**NSAIDs- Nonsteroidal anti-inflammatory drugs**PPL- Benzylpenicilloyl conjugated to poly-L-lysine**SPT- Skin prick test*

the antibiotic course, and tend to last for several days after antibiotic intake. Nonimmediate reactions are the most common reactions to beta-lactams, especially in children, and for the most part are mild, self-resolving, and limited to the skin (ie, maculopapular exanthemas [MPE] or urticaria).<sup>14-16</sup> The pathogenetic mechanism of delayed reactions to beta-lactams is poorly understood but is believed to be T-cell mediated. Currently, no standardized test is available to demonstrate a specific immunological mechanism in clinical practice.<sup>17</sup>

The vast majority of rashes that develop during an antibiotic course are either immediate or nonimmediate and are most likely driven by an infectious process that results from an interaction between the viral-induced and drug-induced immune activation<sup>3</sup> in susceptible individuals.<sup>4,18-25</sup>

In children, the best-known example is ampicillin-induced exanthema in patients with Epstein Barr virus infection,<sup>26</sup> but there are other examples such as the drug-induced hypersensitivity syndrome related to the reactivation of human herpes virus 6,<sup>27-30</sup> cytomegalovirus infection, and the human immunodeficiency virus infection.<sup>3,31-36</sup> Therefore, many reactions need to be evaluated to identify a true hypersensitivity reaction.

However, suspicions of immediate reactions are more frequently confirmed compared with nonimmediate reactions, probably due to better validated diagnostic tests, especially in the case of amoxicillin IgE-mediated reactions.

According to the European Network for Drug Allergy (ENDA), the diagnosis of immediate (ie, IgE-mediated) amoxicillin hypersensitivity reactions should be based on the patient's clinical history, skin testing (skin prick [SPT] and intradermal [ID] test), in vitro laboratory tests (namely determination of specific IgE to the beta-lactams), and a drug provocation test (DPT).

For nonimmediate MPE during amoxicillin treatment, patch tests, delayed reading ID testing, and lymphocyte transformation tests followed by a DPT with the culprit drug have been reported in the literature, but none have been standardized.<sup>17</sup>

In this article, we have retrospectively reviewed 200 patients evaluated for amoxicillin allergy in the Anna Meyer Children's Hospital between 2008 and 2011. The main aims of this study were to evaluate the proportion in which suspicions of nonimmediate hypersensitivity were confirmed by an allergy work-up and to test the validity of our diagnostic protocol that included a 5-day course of the amoxicillin DPT.

## METHODS

### Patients

Charts from all consecutive patients referred to the Allergy Unit of Anna Meyer Children's Hospital for suspected drug allergy from 2008 to 2011 were reviewed, and data (clinical evaluation, allergy

testing, and DPT outcomes) of patients referred for amoxicillin allergy were analyzed.

Patients with histories of chronic urticaria, poorly controlled asthma, and severe nonimmediate reactions (ie, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, vasculitis, acute generalized exanthematic pustulosis, Stevens-Johnson syndrome) were excluded from the study.

### Clinical data

Anamnestic data were collected using the ENDA drug allergy questionnaire before the allergy work-up.<sup>37</sup>

Reactions were classified as immediate if they occurred within 1 hour after antibiotic intake<sup>38</sup> or nonimmediate if they occurred more than 1 hour after the antibiotic exposure<sup>39</sup> and/or 36 hours after the antibiotic therapy initiation. Anaphylaxis was defined as a severe generalized or systemic hypersensitivity reaction.<sup>40</sup> Immediate and nonimmediate reactions were graded as mild (no treatment required), moderate (patients responded readily to appropriate treatment and no hospitalization was needed), or severe (reaction required treatment in hospital, was life threatening, or resulted in death).<sup>8,25</sup>

All parents were asked to sign a written informed consent before their children were tested. All children had been off antihistamines or oral corticosteroids 10 days before drug evaluation.

### Skin tests

Skin tests were performed according to ENDA recommendations<sup>41</sup> in the following sequence: (a) SPT with 20 mg/mL amoxicillin; (b) ID test (1/100-1/10 dilutions of the full-strength concentration of amoxicillin) at intervals of 20-30 minutes. The only exceptions to this protocol were that we did not test the penicillin major determinant benzylpenicilloyl conjugated to poly-L-lysine (PPL) and the mixture of minor determinants (MDM). Positive and negative controls for SPT and ID were obtained using histamine (ALK-Abellø, Milan, Italy: 10 and 1 mg/mL) and normal saline. No further skin tests were performed after a positive skin test (ie, SPT wheal >3 mm, accompanied by erythema with a negative saline control; ID > 3 mm initial wheal or increase in the diameter of the initial wheal associated with a flare after 24-48-72 hours and a negative saline control).

### Serum-specific IgE antibodies

Specific IgEs to amoxicillin, ampicillin, and penicillin G and V were measured in all children with histories of immediate reactions (ImmucapRAST, Uppsala, Sweden). According to previous studies, IgE measurement in nonimmediate reactions was not useful,<sup>3</sup> so it was not performed in these children.

### Drug provocation tests

Children whose skin tested negative or tested positive with a history of mild reactions limited to the skin (MPE and/or few hives) underwent a 5-day drug challenge. On day 1, an open challenge to amoxicillin (1/10-2/10-7/10 of the therapeutic dose [50/mg/kg/day in 2 doses] administered every 30 minutes) was performed following current guidelines until the therapeutic cumulative dose was reached or until a reaction occurred.<sup>42</sup> The DPT was considered positive if any objective skin, respiratory and/or cardiovascular, neurologic, or gastrointestinal symptoms were observed. Patients were observed for 2 hours after the last drug intake if they had a negative outcome, and 2 hours after the resolution of symptoms for any reaction. If the open challenge was negative, amoxicillin was administered the day after in 1 single dose. If this DPT was negative, daily therapeutic doses of amoxicillin were prescribed at home for 5 days. Parents were advised to stop treatment and to contact us or their primary care

physician if their children experienced any reactions. The DPT was considered positive if any objective symptoms were observed and documented with a picture by a physician or by parents during the challenge or within 48 hours after the end of the antibiotic intake. In case of reaction, patients were reevaluated in the Allergy Unit. The negative challenges were communicated by phone.

### Statistical analysis

The frequencies, percentages, and means were calculated using descriptive statistics.<sup>43</sup> The means were compared using Student's *t* test, and the frequencies were compared using a  $\chi^2$  test.

## RESULTS

From January 2008 to December 2011, 669 consecutive children (<15 years of age) with a suspected past clinical history of reactions to a drug were referred to Anna Meyer's Allergy: 57.1% beta-lactams (amoxicillin: 52% of 57%); 16.3% nonsteroidal anti-inflammatory drugs (NSAIDs); 5.4% anesthetics; 21% macrolides; and 0.1% radiocontrast media. We analyzed the data for 200 patients who reported to have a reaction to the antibiotic amoxicillin (Table I).

Seventy-six percent of patients had a history of nonimmediate reaction, 19% had a history of immediate reaction, and in 5% were undefined as the parents could not remember the latency between drug ingestion and reaction. Those with an undefined drug reaction were excluded from our subsequent DPT analysis but were equally investigated (Figure 1). Most of the patients studied reported mild to moderate skin reactions, such as MPE, urticaria, or urticaria plus angioedema (Figure 1). Only 2 cases had histories of anaphylaxis. One child had developed generalized erythema, lips angioedema, and bronchospasm (91% blood saturation) 20 minutes after the first dose; the other child developed lip and eye angioedema, generalized urticaria, vomiting, and respiratory distress immediately after the first dose. Interestingly, according to the anamnestic charts, about one fourth (55 of 200: 27.5%) of the population studied had experienced multiple drug reactions (data not confirmed) (Table I).

The children with immediate and nonimmediate reactions did not significantly differ in terms of age or sex ( $P = .7$ ).

In patients with histories of immediate reactions, serum-specific IgE was positive in 3 of 38 (7.9%) children; 2 of these patients had histories of anaphylaxis and 1 had a confirmed diagnosis of amoxicillin allergy by the DPT.

In vivo SPT and/or ID tests results are summarized in Table II.

More than 90% of patients with immediate or nonimmediate reactions (177/190) underwent the DPT with amoxicillin. Of the 190 patients, 13 were not challenged with amoxicillin: 2 were excluded because of their history of anaphylaxis and the positive skin tests, and 11 children with histories of nonimmediate reactions were also excluded because they refused to undergo the DPT.

Ninety percent of the challenges (160/177) were negative: 127 children with histories of nonimmediate reactions (one resulted positive to the skin tests) and 33 patients with histories of immediate reactions (Figure 2, Tables E1 and E2 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

Seventeen (<10%) of those children who underwent the DPT had a positive challenge (Figure 2, Tables E1 and E2 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)); 14 of those with a positive DPT had a negative skin test (2 with histories of immediate reactions and 12 with histories of nonimmediate

**TABLE I.** Demographic parameters and allergy history

|                                             |                                           |
|---------------------------------------------|-------------------------------------------|
| Age (<15 y)                                 | 8.5 ± 6.2 y (range: 1-17 y)               |
| Male:female                                 | 109 (54.5%):91 (45.5%)                    |
| History of asthma                           | (60) 30%                                  |
| History of atopic dermatitis                | (30) 15%                                  |
| Allergic rhinitis                           | (70) 35%                                  |
| Race                                        | 199 Caucasian: 1 African American boy     |
| Time between the reaction and the challenge | (120) 60% within 1 y (range: 1-18 months) |
| Multiple drug reactors*                     | 55/200 (27.5%)                            |

\*Cephalosporins, nonsteroidal anti-inflammatory drugs (NSAIDs: ibuprofen), acetaminophen, and clarithromycin.

reactions). Three out of 36 patients provoked with history of immediate reactions had a positive DPT. Those 3 patients with histories of immediate reactions reacted to the DPT with urticaria. In 2 patients, the skin manifestations occurred within 24 hours, with only 1 child developing mild urticaria within 1 hour. Among the 14 children with histories of nonimmediate reactions, 5 developed MPE, 5 developed urticaria, and 4 developed urticaria plus angioedema. All reactions were mild, and all patients were treated at home with antihistamines and/or oral corticosteroids.

According to our results and in agreement with the literature, the sensitivity of the skin test was higher for immediate reactions than for nonimmediate reactions (33.3% vs 14.3%, respectively), even though the specificity is high in both cases (100% vs 99.2%, respectively). The combination of SPT and ID tests raised the sensitivity of the skin testing. If we considered the amoxicillin allergies in the 2 children with anaphylaxis, the sensitivity of skin tests was 60% for immediate reactions.

In the nonimmediate reaction group, ID tests were positive in 6 of 152 (4%), and 3 of 6 (50%) had a positive 24-hour reading. Only 3 patients of those who were positive underwent the DPT, and of those 2 had a reaction and 1 did not react. Therefore, the sensitivity of SPT plus ID tests for the nonimmediate response was 14%, with a specificity of 99.2%. In the case of nonimmediate reactions, the sensitivity of skin tests was calculated, but the analysis was affected because some skin positive children refused to undergo the DPT. Assuming that the 3 children who refused the DPT were positive to this test based on their skin tests results, the sensitivity of skin tests in case of nonimmediate reactions would still be low (29.4%) with the same specificity.

These results may be affected by the small numbers of patients identified as sensitized after a complete allergy work-up, in agreement with the true incidence of drug allergy in the pediatric age group, particularly for nonimmediate reactions.

Given that the sensitivity of DPT is difficult to assess due to the low number of patients, if it is assumed that a positive DPT means a diagnosis of amoxicillin hypersensitivity, the sensitivity of such a test is 35.7% on day 1, 71.4% on day 2, and 100% on day 5.

Even if this probably reflects an overinterpretation of the results because the number of positive patients is too small, according to this trend, prolonging the DPT may result in more patients being identified with allergies.

## DISCUSSION

In the present study, the majority of patients referred to our hospital had histories of nonimmediate drug reactions (76%).

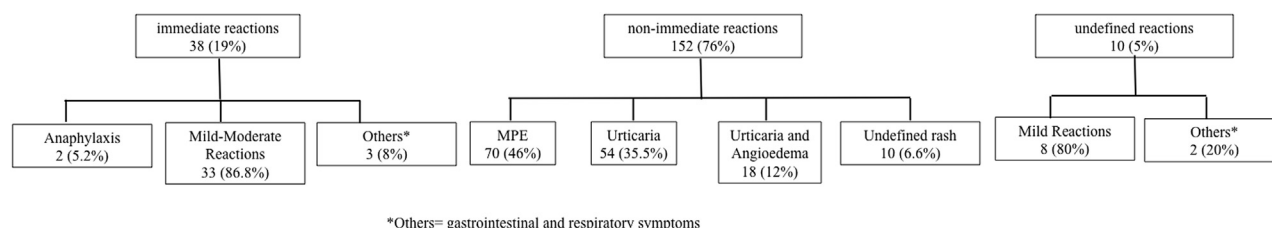


FIGURE 1. Latency periods and clinical manifestations of the 200 children.

TABLE II. Combined (ie, in vivo and in vitro) results

|                              | Positive amoxicillin<br>specific IgE | Positive amoxicillin<br>skin prick/intradermal tests | Positive DPT  |
|------------------------------|--------------------------------------|------------------------------------------------------|---------------|
| Immediate reaction (38)      | 3/38 (7.9%)                          | 3/38 (7.9%)                                          | 3/36 (8.3%)   |
| Nonimmediate reactions (152) | nd                                   | 6/152 (3.9%)                                         | 14/141 (9.9%) |
| Undefined reactions (10)     | nd                                   | 0/10                                                 | nd            |

DPT, drug provocation test; nd: not determined.

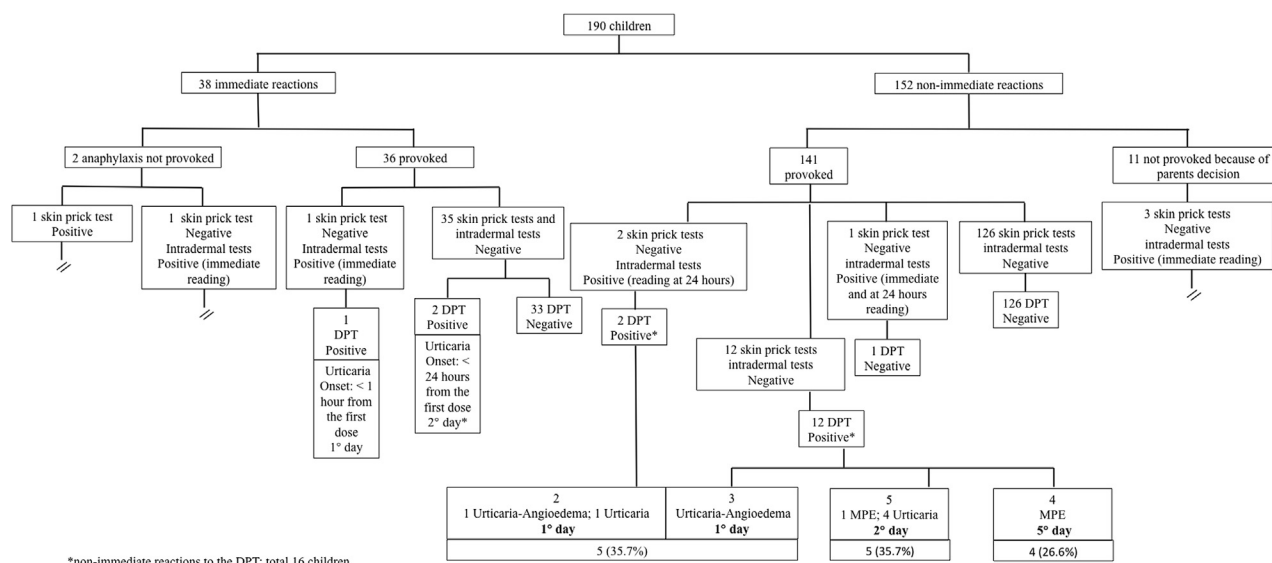


FIGURE 2. Allergy work-ups.

Moreover, a true allergy to amoxicillin was found in a very low number of children tested, as more than 90% of the tested children were not hypersensitive to amoxicillin after a complete allergy work-up, which is supported by previous research.<sup>9,15</sup>

To date, the recommended reagents to be skin tested in case of an immediate beta-lactam reaction are as follows: the PPL and the MDM and side-chain structures (ie, amoxicillin). However, with the increased use of amoxicillin, the role of side-chain structures is growing in importance, whereas the utility of PPL and MDM is decreased, although in the United States when patients are positive, it is usually to PPL or penicillin G.<sup>44-46</sup> In the present study, we used only amoxicillin for allergy evaluation. We found that skin tests had specificity (100%) and sensitivity (33.3%) for immediate reactions. Only 3 patients were DPT positive, and all of them with mild skin reactions confirming that PPL and MDM are most likely not useful in further screening of pediatric patients at risk for severe reactions. Two patients with

negative skin tests had a positive DPT. If we had tested for PPL and MDM, we hypothesize that those 2 patients would still not have been excluded, and the sensitivity of the amoxicillin allergy work-up would be higher. Although controversial, it has been shown that a significant proportion of adult patients could be missed if we focused only on amoxicillin, but there are little data to recommend this procedure in children.

In this study, two thirds of patients with histories of immediate reactions reacted after 1 hour on the first day of the DPT, which suggests that a classification into immediate and non-immediate reactions restricted to only the chronology should be reconsidered.<sup>47</sup> However, we cannot exclude that reactions were misclassified due to poor parental history. In the present study, both the combination of SPT and ID, and serum IgE tests alone had a 60% sensitivity and a 100% specificity for detecting immediate reactions as diagnosed based on history and DPT. The sensitivity and specificity of those tests diminished in detecting

nonimmediate drug reactions or any reported drug reaction (14.3% and 99.2% and 17.6% and 99.3%, respectively). This finding is in agreement with the current literature that shows that specificity tends to be high (>90%) both in immediate and nonimmediate beta-lactam reactions, whereas sensitivity is relatively low (approximately 2-10%), especially in cases of nonimmediate reactions.<sup>4,48</sup> In the case of nonimmediate beta-lactam reactions, patch and/or delayed reading ID tests have been routine in the allergy work-up for many years, but their real utility should be reconsidered based on our data and data in the literature.<sup>49</sup>

In fact, skin tests have a high negative predictive value, but a DPT is needed in many cases, especially in those patients who have tested negative *in vivo* and/or *in vitro*, and for whom diagnosis is mandatory. This finding is supported by the fact that DPT is the most sensitive test in the allergological work-up when investigating drug allergies, and specificity of DPT is high even if not 100%, particularly in nonimmediate reactions.<sup>50</sup> Moreover, the high negative predictive values of the beta-lactam antigen challenge tests of 98% and 94% have been confirmed in recent large studies that involved 256 children<sup>4</sup> and 457 patients,<sup>51</sup> respectively, and most of the reactions reported by patients were nonimmediate and not severe.

In case of immediate reactions, the DPT is performed by administering the drug at increasing doses, until the full therapeutic dose is reached.

In case of nonimmediate reactions, major limitations exist because of the lack of standardization. Many questions remain unanswered. For example, whether a full therapeutic dose should be given for a number of days similar to a therapeutic regimen, assuming that delayed appearance reactions highly depend on the cumulative dose, and whether the sensitivity of the entire diagnostic work-up will be improved if more patients react during a DPT when exposed to the suspected drug for a longer time are still under debate.<sup>50</sup>

Borch and colleagues had tested a group of 22 children with histories of nonimmediate reactions to penicillin with a full-course DPT, and they found that 50% experienced a cutaneous adverse reaction on day 6 on average.<sup>50</sup> More recently, the same group studied 405 adults by performing a 7-day DPT with penicillin. The prolonged protocol improved the diagnosis in the 11.7% (13 of 111) of those having a positive outcome on penicillin challenge.<sup>52</sup> So far, no other authors have described a prolonged DPT in children with amoxicillin reactions, where a 2-day challenge is most commonly used. For example, Caubet et al in a recent paper showed that a 2-day challenge is sufficient to diagnose an allergy in the 6 of 81 children with suspected drug allergy.<sup>3</sup>

Mendelson et al studied more than 200 children with all types of reaction histories and challenged them with a 10-day course of penicillins.<sup>53</sup>

This is the first study to include a substantial number of children with a history of nonimmediate reactions to amoxicillin who have been tested with a long-term DPT. According to our results, a 5-day DPT protocol hardly increases the sensitivity of the allergy work-up, which leads us to reach a diagnosis in the 9.6% of cases. If we had stopped the DPT on day 2, we would have been able to obtain a true diagnosis of amoxicillin allergy in the 7.3% of patients. However, we think that picking up 4 more reactors of 17 by using the 5-day challenge (vs the shorter challenge) would be important. Moreover, our protocol is not

time-consuming because patients complete the DPT at home and it is safe. In fact, the reactions after the DPT both in skin test positive and negative patients were rare and very mild, which never required hospital admission and/or were never severe.

It would be important to verify how many patients react during a subsequent course of antibiotic treatment after a negative DPT, during which, the role of viruses as triggering factors in delayed reactions would not be taken into account.

In conclusion, the DPT is important, especially in children with histories of nonimmediate reactions, and should be considered the gold standard for the diagnosis of beta-lactam hypersensitivity.<sup>39</sup>

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**TABLE E1.** SPT/ID test and DPT results in immediate-reactions

|          | DPT      |          |
|----------|----------|----------|
|          | Positive | Negative |
| SPT/ID   |          |          |
| Positive | 1        | 0        |
| Negative | 2        | 33       |

Sensitivity: 33.3%; specificity: 100%.

**TABLE E2.** SPT/ID test and DPT results in nonimmediate reactions

|          | DPT      |          |
|----------|----------|----------|
|          | Positive | Negative |
| SPT/ID   |          |          |
| Positive | 2        | 1        |
| Negative | 12       | 126      |

Sensitivity: 14.3%; specificity: 99.2%.