

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.^{1,2} Hence, it is not surprising that hypersensitivity to amoxicillin is very common with an estimated incidence of 1-10%.³⁻⁷

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.⁸

They are characterized by urticaria and/or angioedema, bronchospasm, anaphylaxis, and even fatality.⁹ 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.¹⁰⁻¹³

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

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 This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest: The authors declare that they have no relevant conflicts.

Received for publication January 21, 2014; revised October 30, 2014; accepted for publication November 3, 2014.

Available online ■■

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2014.11.001>

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).¹⁴⁻¹⁶ 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.¹⁷

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 activation³ in susceptible individuals.^{4,18-25}

In children, the best-known example is ampicillin-induced exanthema in patients with Epstein Barr virus infection,²⁶ but there are other examples such as the drug-induced hypersensitivity syndrome related to the reactivation of human herpes virus 6,²⁷⁻³⁰ cytomegalovirus infection, and the human immunodeficiency virus infection.^{3,31-36} 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.¹⁷

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.³⁷

Reactions were classified as immediate if they occurred within 1 hour after antibiotic intake³⁸ or nonimmediate if they occurred more than 1 hour after the antibiotic exposure³⁹ and/or 36 hours after the antibiotic therapy initiation. Anaphylaxis was defined as a severe generalized or systemic hypersensitivity reaction.⁴⁰ 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).^{8,25}

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 recommendations⁴¹ 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-Abelló, 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,³ 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.⁴² 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

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