

Asthma, Family History of Drug Allergy, and Age Predict Amoxicillin Allergy in Children



Yoram Faitelson, MD^{a,b}, Mona Boaz, PhD^{c,d}, and Ilan Dalal, MD^{b,e} *Holon, Tel Aviv, and Ariel, Israel*

What is already known about this topic? To date, physicians are unable to predict who will fail or pass oral graded challenge with amoxicillin, which is commonly used to rule out alleged amoxicillin allergy in children.

What does this article add to our knowledge? The presence of asthma, family history of drug allergy, and older age at reaction are associated with a higher risk of failing the oral challenge. Skin prick test was not helpful in diagnosing amoxicillin allergy.

How does this study impact current management guidelines? Recognizing risk factors for amoxicillin allergy in the pediatric population can assist the allergist in deciding what will be the optimal setting of an oral challenge for individual patients.

BACKGROUND: Suspected adverse reactions to amoxicillin are common, but there are no known factors that can predict amoxicillin allergy in children. In addition, methods used for the diagnosis of amoxicillin allergy are not standardized and their role in diagnosis is not clear.

OBJECTIVE: To identify predictive factors and to assess the role of skin test in the diagnosis of amoxicillin allergy in children.

METHODS: Children with a history of immediate (excluding anaphylaxis) or nonimmediate reactions to amoxicillin were tested by skin prick test, followed by oral graded challenge with amoxicillin. Clinical characteristics of the reaction before and after the challenge were recorded, and data of personal and relatives' drug allergies and atopy were collected for statistical analysis.

RESULTS: Skin prick tests followed by an oral graded challenge with amoxicillin were performed on 133 children. The skin test result was not of clinical value because it was negative in all children. Three children (2%) had an immediate reaction and 7 children (5%) had a nonimmediate reaction. Asthma (odds ratio [OR], 0.12; 95% CI, 0.017-0.869; $P = .03$), family history of drug allergy (OR, 0.12; 95% CI, 0.026-0.613; $P = .01$), older age at reaction (OR, 0.837; 95% CI, 0.699-1; $P = .05$), and

angioedema (OR, 0.22; 95% CI, 0.043-1.12; marginally significant at $P = .069$) were associated with reduced chance to pass the oral challenge.

CONCLUSIONS: Skin prick test did not contribute to the diagnosis of amoxicillin allergy. The presence of asthma, family history of drug allergy, and older age at reaction can be used as predictive factors for true amoxicillin allergy in children. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1363-7)

Key words: Amoxicillin; Children; Drug allergy; Oral challenge; Predictive factors

Antibiotics, mainly the β -lactams, are one of the most frequent drug groups prescribed for children worldwide. Approximately 5% of children and 10% of adults report a history of penicillin or beta-lactam allergy, although only a few of these patients are truly allergic.¹⁻⁴ In children, viral infection plays an important factor in the presentation of these so-called allergic reactions.⁵ Children and adults who were labeled "penicillin-allergic" without appropriate testing may not get the optimal antimicrobial coverage and are often treated with alternative broad-spectrum antibiotics (vancomycin, macrolides, cephalosporins), which have been associated with additional costs⁶ and significant morbidities, such as those caused by vancomycin-resistant *Enterococcus* and *Clostridium difficile*—associated diarrhea.⁷⁻⁹

Currently, the diagnosis of penicillin allergy is mostly assessed by using skin tests (to exclude penicillin-specific IgE sensitization), followed by an oral graded challenge (OGC)¹⁰ in those who have a negative skin test result. However, the role of skin tests in the diagnosis of amoxicillin allergy is not clear and there is no consensus about which reagents should be used for the skin tests or whether skin tests are at all needed. In some centers, skin tests include a skin prick test (SPT) followed by an intradermal test (IDT) injection with the major antigenic determinant, and various minor determinants, the most commonly used being penicillin G.^{11,12} Other centers recommend adding

^aAllergy and Immunology Unit, Edit Wolfson Medical Center, Holon, Israel

^bSackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

^cDepartment of Nutrition Sciences, Ariel University, Ariel, Israel

^dDepartment of Epidemiology & Research Unit, Edit Wolfson Medical Center, Holon, Israel

^eDepartment of Pediatrics, Edit Wolfson Medical Center, Holon, Israel

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Corresponding author: Yoram Faitelson, MD, Unit of Allergy and Immunology, Wolfson Medical Center, Ha-Lokhamim St 62, Holon, Israel. E-mail: yfaitelson@gmail.com.

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Abbreviations used

IDT- Intradermal test
NPV- Negative predictive value
OGC- Oral graded challenge
OR- Odds ratio
PPV- Positive predictive value
SPT- Skin prick test

aminopenicillins to the skin tests in patients who reacted to these drugs or may need them in the future.¹³ There is cumulative evidence supporting the safety and accuracy of performing the OGC to confirm an allergic reaction to penicillin or amoxicillin in children with only a minimal skin test including selected reagents preceding it or no skin test at all.^{4,14,15} The latter approach is supported by the fact that although the negative predictive value (NPV) of penicillin skin testing (when performed with the major determinant plus penicillin G or a full minor determinants panel) is very high, the positive predictive value (PPV) is low⁵ or not known, because data are limited due to ethical concerns of challenging skin test—positive patients with penicillin.¹⁶⁻¹⁹

Because of the weak PPV of the skin test, there is a strong need for identification of reliable risk factors that could help select the population that has a higher risk for true amoxicillin allergy. Given such risk factors, one can choose to proceed with OGC without the burden of skin testing or, in contrast, patients who have significant risk factors might need further testing before an OGC is done. In this study, we focused on finding clinical predictive factors, such as the history of the reaction and the personal or family history of atopy, that can predict true allergic reaction to amoxicillin. In addition, because SPT is time consuming and painful, especially for young children, we assessed the role of SPT in the diagnosis of amoxicillin allergy in the pediatric population and calculated its sensitivity and specificity.

METHODS

Study cohort

The study was performed at the Wolfson Medical Center, Holon, Israel. Included in the study were children who had been referred to the Allergy unit in our center from January 1, 2013, to December 31, 2015, with a suspected allergic reaction to amoxicillin or amoxicillin-clavulanate antibiotic. Patients with a history of a severe cutaneous adverse reaction (eg, Stevens-Johnson syndrome/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis) were excluded from this study. The study was approved by the Wolfson Medical Center Ethical Board (#0065-017-WOMC).

Study questionnaire

Before skin testing and oral challenge, a standardized questionnaire based on the European Network of Drug Allergy questionnaire was completed by the physician with the child guardian. The questionnaire included questions about the clinical characteristics of the reaction, comorbidities (including a history of atopy, use of medications before, after, and during the suspected reaction), family history regarding atopy and drug allergy, and management of the reaction.

TABLE I. Patient characteristics (n = 133)

Characteristic	Value
Sex, n (%)	
Male	70 (52)
Female	63 (48)
Age (y), median (min-max)	
At initial reaction	2 (0.1-17.5)
At time of challenge	4.1 (0.7-18)
Type of antibiotics, n (%)	
Amoxicillin	126 (95)
Amoxicillin-clavulanate	7 (5)
Atopy*, n (%)	
Personal	29 (22)
Asthma	9 (7)
Food allergy	8 (6)
Allergic rhinitis	8 (6)
Atopic dermatitis	6 (4.5)
Family	42 (32)
Family History of drug allergy, n (%)	35 (26)
Time to initial reaction, n (%)	
Immediate (<1 h)	6 (5)
Delayed (>1 h)	101 (75)
Unknown	26 (20)
Type of reaction, n (%)	
Skin	129 (97)
Angioedema	22 (16.5)
Gastrointestinal	2 (1.5)
Respiratory	1 (0.7)

*Atopy—Presence of asthma, food allergy, allergic rhinitis, or atopic dermatitis.

Skin testing procedure

Skin testing was performed by 1 of 2 experienced nurses. Penicillin G (at a concentration of 10,000 U/mL) and amoxicillin (at a concentration of 50 mg/mL) were used for skin prick testing as previously described. Normal (0.9%) saline and 2 mg/mL of histamine were used as negative and positive controls, respectively. Reading of test result was done by 1 of 2 experienced nurses 15 minutes after the test and was documented in the patient medical chart. The test result was considered positive if it elicited a wheal greater than 3 mm compared with the negative control. Intradermal injections of penicillin or penicillin derivative were not given in this study.

Graded drug challenge procedure

If the SPT result was negative, as it was in all of our patients, a 3-dose graded drug challenge was performed to the drug incriminated in the allergic reaction (or amoxicillin if the culprit drug could not be identified). All children received 10% of the therapeutic dose (50 mg/kg/dose, up to a maximum of 500 mg/dose of amoxicillin), then 20 minutes later 30% of the therapeutic dose, and after another 20 minutes the rest of the therapeutic dose, that is, 60% of the therapeutic dose. Children were observed for at least 1 hour after receiving their last dose. Parents were asked to continue with the drug challenge by giving 100% of the therapeutic dose as a single dose in the following 2 days after their clinic visit. Parents and patients were warned about the possibility of a delayed reaction and asked to contact the allergy clinic by email or phone if any delayed reaction was noticed. If no immediate or delayed reaction occurred, the child was considered not allergic to amoxicillin, and parents and

TABLE II. Results of SPT and OGC (n = 133)

OGC, n (%)	Passed 123 (92.5)	Failed 10 (7.5)
SPT, n (%)		
Negative	118 (96)	10 (100)
Positive	0 (0)	0 (0)
Not done	5 (4)	
Sensitivity % (95% CI)	0% (0%-31%)	
Specificity % (95% CI)	100% (97%-100%)	
NPV %	92%	
PPV %	NA	

NA, Not available.

Please note that the results for SPT sensitivity, specificity, NPV, and PPV relate to the subset of 128 patients who had SPT done.

treating physicians were informed that the child could receive amoxicillin in the future without any special precaution. If a reaction occurred during the challenge, the procedure was immediately stopped, treatment was rapidly administered according to symptoms, the patient was kept under observation until all symptoms resolved, and the patient was instructed not to use beta-lactam in the future without further evaluation by an allergist.

Statistical analysis

Data were stored on Excel spreadsheet (Microsoft Corporation, Redmond, WA) and analyzed on SPSS v22 (IBM Corp., Armonk, NY). Distributions of continuous variables were tested for normality using the Kolmogorov-Smirnov test, and all were found to have distributions significantly deviating from normal; thus, comparisons of these variables by “pass” (meaning no reaction upon the OGC) were made using the Mann-Whitney *U* test. Nominal variables were summarized using frequency tables and presented as n (%). Nominal variables were compared by “pass” using the chi-square test, or Fisher exact test as appropriate. Pass was modeled using logistic regression analysis, and odds ratios (ORs) with 95% CIs together with the sensitivity, specificity, and positive and negative predictive values of the model were calculated. All tests are 2-sided and considered significant at a *P* value of less than .05. The sensitivity, specificity, and positive and negative predictive values of the SPT were assessed and given with the 95% CIs.

RESULTS

Characteristics of study participants and clinical reactions are described in Table I. In summary, most of the reactions presented with generalized rash and were delayed (appeared more than 1 hour after the drug administration). None of the participants had cardiovascular involvement. A significant fraction of the patients had a personal or family history of atopy (asthma, food allergy, allergic rhinitis, or atopic dermatitis) and family history of drug allergy.

The results of SPT and OGC are described in Table II. Five of the participants who are not included in the data of Table II had OGC without performing SPT. Ten of the participants failed the OGC, with 7 having a delayed reaction and 3 having an immediate reaction to the challenge. Their characteristics are described in Table III. None of the reactions were severe and none of the reactions required treatment other than antihistamine. The initial reaction to amoxicillin of all the participants who failed the OGC (including those who had an immediate

reaction to the OGC) was a delayed one, whereas those who had an initial immediate reaction passed the OGC with no issues.

Sex, a presence of rash or gastrointestinal complaints, and family history of atopy were not statistically significantly different between those who passed and those who failed the oral challenge. Angioedema, asthma, history of drug allergy, and older age at initial reaction were more common in those who failed the OGC (Figure 1 and Table IV). Food allergy was also more common in those who failed the OGC but with only marginal statistical significance (*P* = .053). In the multivariate logistic regression model, asthma (OR, 0.12; 95% CI, 0.017-0.869; *P* = .03), family history of drug allergy (OR, 0.12; 95% CI, 0.026-0.613; *P* = .01), and age at initial reaction (OR, 0.83; 95% CI, 0.699-1; *P* = .05) were included to predict passing the OGC. The presence of angioedema reduced the odds of pass with marginal statistical significance (OR, 0.22; 95% CI, 0.043-1.12; *P* = .069). The model was significant (*P* = .005) and predicted 35% of the variability in this outcome. Furthermore, the model correctly classified 93% of study subjects as passing the OGC. The sensitivity of our model is 100% (95% CI, 69%-100%), specificity 64% (95% CI, 55%-73%), PPV 18.5% (95% CI, 15%-22%), and NPV 100%.

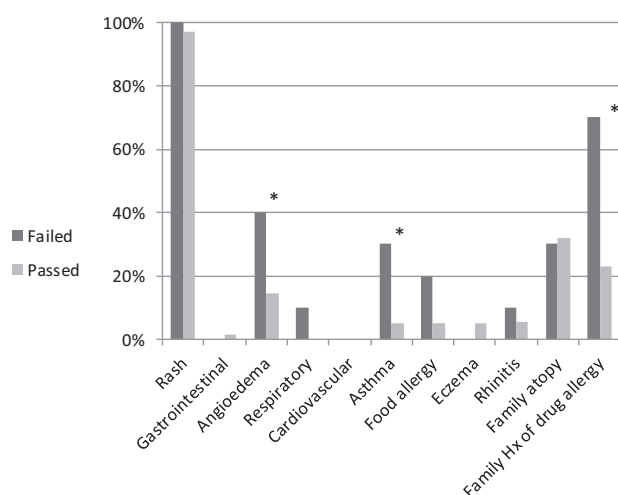
DISCUSSION

It has been shown previously that amoxicillin allergy is over-diagnosed in children and can only rarely be reproduced by OGC.³ In most cases, these so-called allergic reactions are mild and limited to the skin and related to concomitant viral infections. In contrast to other allergic phenomena, such as asthma and allergic rhinitis or eczema and food allergy, there is no clear association between atopy and drug allergy. There have been a few attempts in the past to find risk factors for drug allergy but so far without conclusive results. There are a few known genetic risk factors for beta-lactam allergy that include polymorphism in the IL-10 promoter, IL-4Rα,²⁰ and the FcεRβ genes,²¹ but there is little information about the association of clinical risk factors such as atopy, sex, or age with drug allergy. There are a few studies that suggest that women have a higher incidence of adverse drug reactions^{22,23} but this sex pattern has not been shown in the pediatric population.²⁴⁻²⁶ Different aspects of atopy, such as elevated specific IgE level, rhinitis, and eczema, were shown not to be a risk factor for beta-lactam allergy by several studies,^{5,27,28} whereas others had found that there is an association between atopic diseases and immediate reactions to beta-lactam.^{29,30} These controversies only increase the confusion and the uncertainty regarding who will fail an OGC with amoxicillin and who will pass. Because the classic approach for the diagnosis of amoxicillin allergy by SPT and intradermal injection with penicillin is controversial, time consuming, and painful, there is a need to improve the way we identify those who are more likely to be truly allergic. In this study, we investigated different risk factors that might contribute to amoxicillin allergy in children. In addition, we looked at the role of SPT in the diagnosis of amoxicillin allergy in the pediatric population. Our results confirm, as previously shown, that most children suspected to have amoxicillin allergy can receive amoxicillin without an adverse reaction. In our study, only 7% of the children reacted to the OGC with amoxicillin and none of the reactions were severe. This finding supports the conclusion from other studies that OGC with amoxicillin is safe and crucial for the diagnosis of true amoxicillin allergy.

TABLE III. Characteristics of patients who failed OGC (*italic* = immediate reaction)

Serial	Sex	Age at reaction (y)	System involved	Personal atopy	Familial drug allergy
4	F	3.5	Skin, angioedema, respiratory		Brother
7	F	1.5	Skin		Grandmother
13	M	9.5	<i>Skin, angioedema</i>		Mother
22	F	15	Skin, angioedema		
23	M	9.6	Skin	Asthma	Mother
45	M	2	Skin	Food allergy	Grandfather
47	F	2	<i>Skin, angioedema</i>	<i>Asthma, allergic rhinitis, food</i>	
96	F	8	Skin		
102	M	1.4	<i>Skin</i>	<i>Asthma</i>	Grandmother
116	F	4	Skin		Mother

F, Female; M, male.

**FIGURE 1.** Comparison of clinical characteristics between those who failed (dark bars) and those who passed (light bars) OGC. *Difference between groups is statistically significant at $P < .05$.**TABLE IV.** Comparison of patient characteristics between those who failed* and those who passed OGC (n = 133)

Characteristic	Passed oral challenge	Failed oral challenge	P value
Participants (% of total)	123 (92.5)	10 (7.5)	
Sex: male, n (%)	66 (53)	4 (40)	.4
Age at initial reaction (y), median (min-max)	1.75 (0.1-17.5)	3.75 (1.4-15)	.018
Age at time of challenge (y), median (min-max)	3.9 (0.7-18)	9 (1.9-15.1)	.08
Time to initial reaction (d)	2 (0.1-10)	1 (1-3)	.15

*All 10 participants who failed the OGC had a delayed reaction as their initial reaction.

By looking into different patient characteristics, we found that reported family history of drug allergy is associated with OGC failure. A limitation to this finding is the lack of verification of the family history of drug allergy. We considered a report by the participants regarding family history of drug allergy to be accurate because the only way to verify this information would be to

invite the family member himself for skin test and oral challenge, a procedure that was not practical. We know from the literature¹⁻⁴ that only 10% of those who report an allergic reaction to penicillin are truly allergic. We can assume that the same ratio is true for the family members in our study, a finding that might be enough to explain why family history is a positive predictive factor for drug allergy. A similar finding was described by Mill et al¹⁵ and Arikoglu et al,²⁸ supporting the idea that amoxicillin allergy tends to be more prevalent in families with a history of drug allergy.

Although the prevalence of personal atopy, in general, was similar in both groups (those who pass and those who failed the challenge), when we looked at specific clinical aspects of atopy, we found that asthma was a significant risk factor for OGC failure. To our knowledge, this is the first time that asthma was found to be associated with the risk for amoxicillin allergy in children. In addition, the presence of food allergy was also marginally significant as a risk factor, and further studies with larger cohorts are required to confirm the significance of food allergy as a risk factor for amoxicillin allergy.

In addition to personal and family atopy, we investigated the different clinical characteristics of the original reaction to amoxicillin. All the children in our study had a reaction that involved the skin but angioedema was the only clinical finding that was associated with OGC failure. Since angioedema is more common in true allergic reactions, this finding is expected as it represents those who are truly allergic to amoxicillin.

By using the significant characteristics mentioned above, we built a statistical model that shows a significantly reduced chance of passing the OGC in the presence of asthma or family history of drug allergy. The age of the child at the time of the original reaction was also meaningful, because older children had a lesser chance to pass the oral challenge (we used the age 7 years as the cutoff in our model). This finding is not surprising because younger children have more viral infections that contribute to pseudoallergic reactions in comparison to older children and adults. The PPV of our statistical model is low due to the low prevalence of amoxicillin allergy in our study cohort, but the NPV is 100%. Practically, all the children in our study who were younger than 7 years and without asthma or family history of drug allergy have passed the challenge.

Importantly, our study did not include any children with life-threatening reactions, neither immediate ones such as anaphylactic shock nor delayed-type reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis. However, life-threatening

reactions from oral amoxicillin are rare, especially in the pediatric population,³¹ meaning that our results can be generalized to the vast majority of children with an adverse reaction to amoxicillin but not to those with life-threatening reactions.

Finally, in our study, none of the children had a positive SPT result, including the 7% who failed the oral challenge. The lack of IDT is a limitation of our study because IDT is more sensitive than prick test. However, IDT has a higher rate of false-positive reactions. There are only limited data regarding the predictive values of skin tests in amoxicillin allergy in children. In one publication³² the sensitivity and specificity of prick test with IDT were 33% and 100%, respectively, for immediate reaction and 14% and 99%, respectively, for delayed reactions. According to these results, although IDT adds to the sensitivity of the test, the sensitivity remains very low and does not change our decision to continue with the oral challenge. In addition, we preferred to minimize the pain and discomfort to the participants by avoiding IDT. Considering the low sensitivity of skin tests and the high safety profile of the oral challenge in our work and others,¹⁵ it seems that skin tests do not contribute to the process of diagnosis of amoxicillin allergy in children and should be reserved for exceptional situations such as children who had an anaphylactic reaction and need amoxicillin as the drug of choice.

In summary, we identified asthma, family history of drug allergy, and older age at original reaction as clinical risk factors that can be used for screening those who have a higher chance to fail OGC with amoxicillin. Our findings also lead to the conclusion that SPT does not contribute to the diagnosis of amoxicillin allergy in the pediatric population.

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