

Skin tests and in vitro allergy tests have a poor diagnostic value for benign skin rashes due to β -lactams in children

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Key words

Antibiotic allergy, betalactams, children, diagnostic, oral challenge rash, skin test,

Abbreviations

Drug provocation test (DPT), intradermal test (IDT), lymphocyte transformation test (LTT), basophil activation test (BAT)

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To the editor,

Skin rashes are frequent in children treated by β -lactams (BL), with an estimated incidence ranging between 1% and 5% (1). In clinical practice, most of these children are labeled as “penicillin allergic” without appropriate testing, mostly due to fear of life-threatening reactions. However, an allergic reaction can be demonstrated by an oral provocation test (OPT) in less than 10% of the patients developing a rash while treated by BL (2-4). The cause is more likely to be related to the underlying infection rather than an allergic reaction to the antibiotic (3). Overdiagnosis of BL allergy constitutes a major public health problem by increasing health costs and by contributing to overall antibiotic resistance. Thus, an accurate diagnosis is considered as a major contribution to cost-effective health cares and will be based on complete allergic work-up (5). Delayed-reading intradermal tests (IDT) and lymphocyte transformation tests (LTT) have been proposed for a long time in the diagnosis of nonimmediate reactions to BL. Although several recent studies have highlighted the importance of the OPT, there are only few pediatric studies evaluating the added diagnostic value of currently available tests, i.e. IDT and LTT. Based on the gold standard, i.e. the OPT, the aim of the current study is to evaluate the diagnostic value of those tests in prospectively recruited children.

We analyzed data from 14 patients with a nonimmediate BL allergy confirmed by a positive OPT. Six patients were prospectively recruited at the emergency department of the Geneva University Hospital between 2006 and 2008 from an original study on BL allergy in children (3). Among 250 children challenged at our allergy outpatient’s clinic, eight additional patients with a positive OPT to BL were recruited prospectively. Eighty-two patients with a negative OPT from our previous

prospective study were used as negative controls (3). The inclusion and exclusion criteria are described in the supplementary Appendix E1. The study was approved by local ethics committee and informed consent was obtained before enrollment.

All the included patients underwent a complete allergic work-up including IDT to penicilloyl-polylysine (PPL), minor determinant mixture (MDM) (Diater, Spain), amoxicillin (AX) (Clamoxyl™; GlaxoSmithKline, Switzerland) at 25 mg/ml, or cefuroxim (Zinacef®; GlaxoSmithKline, Switzerland) at 3 mg/ml. Reading was performed both at 20 minutes and 48 hours (3, 5). Regardless of the results of IDT, an OPT with the incriminated BL was performed in all patients as previously reported (3). Briefly, after receiving 150% of the standard dose, the patients were observed for 2 hours in the hospital in order to exclude an immediate reaction. Then, the involved drug, at the therapeutic dose, was given at home for a further 48 hours to all the patients without immediate reactions. The parents were contacted by phone at the end of the test.

LTT were performed as previously described (6), by measuring (3) H-thymidine incorporation after 7 days of incubation with medium only, the incriminated antibiotic (i.e. amoxicillin or cefuroxim) added to the medium at concentrations ranging from 0.01 to 1 mg/mL, and phytohemagglutinin A (PHA) as a control mitogen. Stimulation Index (SI) greater than 2.5 were regarded as positive (6). In addition, basophils activation tests (BAT) were performed according to the manufacturer's instructions (Flowcast™, Buhlmann, Switzerland), by measuring the proportion of activated basophils (CCR3⁺CD63⁺) (7). Minimum of 500 basophils were analyzed. To be considered positive, the SI (% of BL stimulation divided by % of negative control) must be greater than 2 and the cut-off values for BL greater than 7%.

Characteristics of patients are shown in supplemental Table E1. The complete allergic work-up occurred at a median of 2.4 months (25-75% Interquartile Range: 2-3.1 months) after the index event. Immediate-reading IDT were positive in 7 patients (8.5%) with a negative OPT and in 7 patients (50%) with a positive OPT. The culprit antibiotics were amoxicillin (5 patients, 35.7%), amoxicillin-clavulanic acid (7 patients, 50%) and cephalosporins (2 patients, 14.3%). Patients with immediate-reading positive IDT had a higher rate of positive OPT than those without ($P<0.05$, by Fisher exact test). The overall sensitivity determined for immediate-reading IDT was 50% while the specificity was 91.5%. Delayed-reading IDT were negative in all the 96 tested patients, including the 14 patients with positive OPT.

Regarding in vitro tests, LTT were performed in 9 patients with a positive OPT and 16 negative controls selected among the 82 patients with a negative OPT from the original study. By defining a SI of 2.5 or above for positivity (6), no LTT was positive in patients with positive OPT and 2 were falsely positive in patients with a negative OPT to BL (Figure 1A). However, we found an overall higher cell proliferation in children with a confirmed allergy to amoxicillin, suggesting a potential role of T cells in the pathogenesis of nonimmediate reactions to BL (Figure 1B) ($P<0.05$, by Mann-Whitney-Wilcoxon). In addition, BAT were performed in the 14 patients with a positive OPT and 16 negative controls from the original study. According to our criteria, BATs were negative in all tested patients and controls.

Overdiagnosis of BL allergy is important and mainly due to the lack of accurate diagnostic test. Although IDT have been used since a long time to diagnose nonimmediate BL allergy, their real diagnostic value is not well defined, in previous pediatric studies (2-4, 8, 9), mainly due to the lack of using a gold standard, such as

the OPT in patients with positive IDT. In our series including a large number of prospectively recruited children with a confirmed BL allergy (positive OPT), we showed that IDT, BAT and LTT have poor diagnostic values in children suspected with a benign nonimmediate allergy to BL. None of our patients with a positive OPT had positive delayed-reading IDT. However, we found that 7 patients had positive immediate-reading IDT, leading to a low sensitivity of 50% and a specificity of 91.5%. Immediate-reading IDT have been suggested to be useful only to diagnose immediate reaction to BL. We cannot exclude that some of those positive responses may represent false positive tests, highlighting the need to standardize IDT by determining the suitable non-irritant injection volumes and the optimal size of injection papules, particularly in the pediatric population. From another point of view, our data showed that children with positive immediate-reading IDT had a higher rate of positive OPT (delayed reactions) than those with a negative test ($P < 0.05$). One may consider that performing IDT before would prevent positive response to OPT. However, our previous study showed that 88 children needed to undergo skin testing to identify only 4 patients with a mild BL hypersensitivity (3). Based on our results and data from the literature (2, 4, 8), we conclude that OPT without previous skin or in-vitro testing is an easy and safe approach that should be considered in every patients developing a benign rash during a BL treatment. This will allow lowering the number of patients falsely labeled as “penicillin allergic”.

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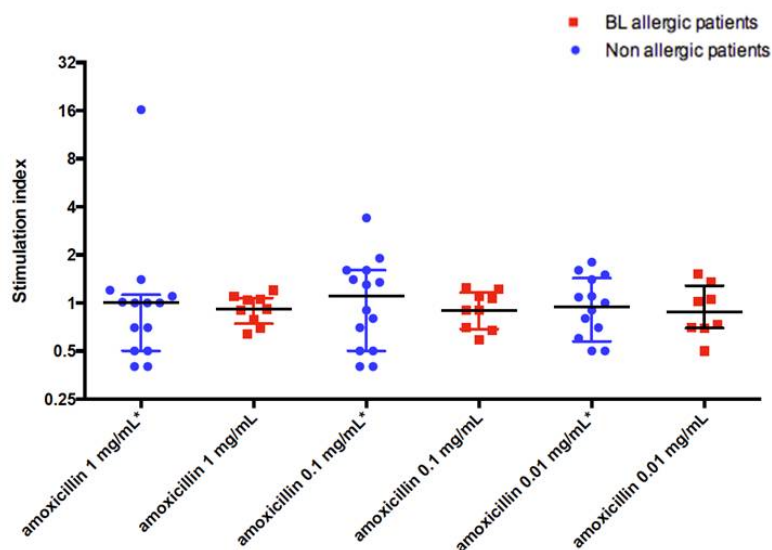
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Figure legends

Figure 1. Results of the lymphocyte transformation tests expressed by (A) Stimulation Index (SI) and (B) counts per minute (cpm)

A



*instead of amoxicillin, cefuroxime has been used in the 2 patients with a negative oral provocation test to cephalosporins

Figure 1.

B

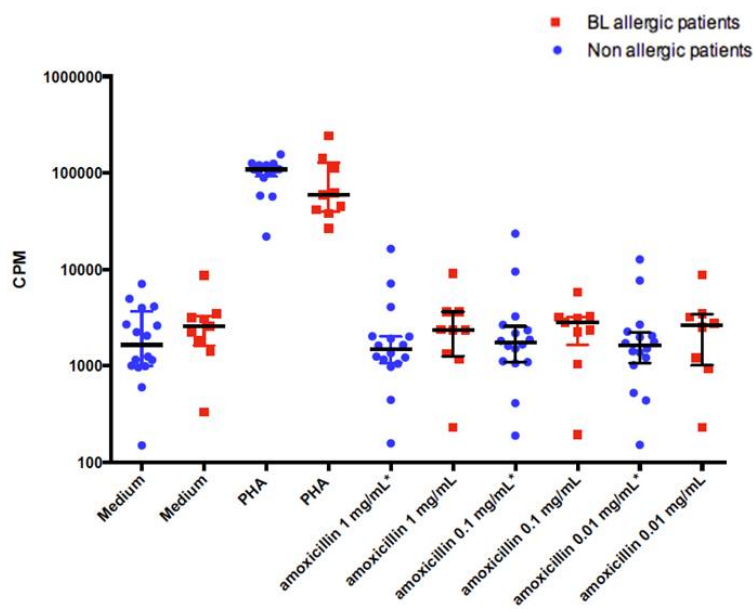


Figure 1.

APPENDIX E1

The eligibility criteria were to include patients between the ages 0 and 16 years, with a delayed urticarial or maculopapular rash during, or up to 72 hours after treatment with a β -lactam antibiotic. Only patients presenting a nonimmediate reaction, i.e. occurring by definition more than one hour after the last dose, were included. Patients with rashes clearly suggestive of childhood infectious diseases (rubella, measles, chicken pox, scarlet fever) or related to potentially severe reactions (Stevens Johnson or Lyell syndrome, Drug Rash with Eosinophilia and Systemic Symptoms, anaphylaxis with respiratory or cardiovascular involvement) were excluded.

Table E1. Characteristics of patients included in the study

Results of the oral provocation test	Negative	Positive	<i>P</i> value
Number of patients	82	14	
Sex, n (%)			
Male	40 (48.8)	8 (57.1)	NS*
Female	42 (51.2)	6 (42.9)	
Age at diagnosis (year)			
Median	1.7	4.8	NS*
(Range)	(0.5-14.5)	(1.1-12.3)	
Type of infections, n (%)			
Ear, nose, and throat	73 (89)	13 (92.9)	NS*
Others	9 (11)	1 (7.1)	
Antibiotic, n (%)			
Amoxicillin	42 (51.2)	5 (35.7)	NS*

Amoxicillin-clavulanic acid	31 (37.8)	7 (50)	
Cephalosporins	9 (11)	2 (14.3)	
Type of skin rash, n (%)			
Maculopapular	39 (47.6)	7 (50)	NS*
Urticarial	43 (52.4)	7 (50)	
Delay between the initial reaction and the allergic workup (months)			
Median	2.4	2.3	NS*
IQR**	2-3	1.8-4.9	

NS, non-significant, i.e. *P* value greater than 0.05; **IQR, interquartile range