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Oral challenge without skin testing in children with suspected non-severe betalactam hypersensitivity

Short title: Oral challenge test to betalactam without skin allergy testing

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To the Editor,

Suspected allergy to betalactam is common in children. However, the risk of anaphylaxis and fatal anaphylaxis is low, estimated at 0.015%-0.004% and 0.0015-0.002% of treated patients, respectively (1, 2). Up to recently, a provocation challenge was recommended in children with a suspected betalactam hypersensitivity (BH) and negative skin tests. However, these tests are painful, time-consuming, require skilled team, appropriate setting and their role has been debated. In a study of Caubet et al., both skin tests and oral challenge test (OCT) were performed in 88 children with a history of mild non-immediate reactions with a betalactam antibiotic: 11 had an immediate positive intradermal test, but only 4 of them had a mild exanthema when challenged (3). In vitro and patch tests do not help for the diagnosis of these suspected drug reactions.

In that context, the pediatric task force of the European Allergy and Clinical Immunology (EAACI) drug allergy interest group published an algorithm with (OCT) as the first step of allergy work-up for those children with a history of non-severe, non-immediate drug reaction (4). Only a few studies reported on safety and no clear international recommendations have been promoted until now. Numbers of allergists still consider systematic skin tests before OCT, mainly for fear of severe reactions. Consequently, the question of systematic skin testing prior to OCT is still debated (5).

The aim of our study was to evaluate the safety and accuracy of a direct 3-days OCT without skin testing in children with a suspected non-severe, non-immediate BH.

We conducted a prospective multicenter study in all the children explored from 2016 to 2017 in 2 children's departments (Lille University Hospital and Roubaix Hospital, France) for a suspected non-severe, non-immediate BH (See Online Supplementary) (6). A 3-days OCT with the suspected antibiotic without any previous skin test, was conducted in accordance with the EAACI task force guidelines (adapted from [3], See Online Supplementary) (3, 4): the patient received 2 oral doses of the suspected antibiotic under strict hospital surveillance and then were instructed to take the full-dose antibiotic for 2 more days at home. Characteristics of the patients and outcome of the OCT were recorded. In children without any reaction during the OCT, families were contacted by phone two weeks later to check for delayed drug reaction. In case of negative OCT, they were contacted again by phone at least six months later. Reutilization of the antibiotic and following outcome were

evaluated (reaction, time of onset after administration, and treatment, if any). If no reutilization, the reasons were also analyzed.

This study was approved by the Ethic Committee of the French Pediatric Society and by the local Committee for Data and Patients Protection of the Lille University Hospital.

Means, range, and standard deviation were calculated for the continuous variable. The association between the occurrence of drug reaction and nominal parameters was performed using the Chi-square test or Fischer test depending on the sample size, and with the Mann-Whitney test for continuous parameters. A $p < 0.05$ was considered as significant.

A total of 91 children (45 boys; 50%) were included (mean age at the OCT: 6.9 years [SD: 4.2]). The characteristics of the patients are detailed in the table 1. The tested antibiotics during OCT were: amoxicillin (n=64; 70%), amoxicillin-clavulanate (n=14; 15%), cefpodoxim (n=11; 12%) and cefixim (n=2; 2%) (Figure 1).

The figure 1 shows the results of the OCT and the follow-up. In all, 13 children developed a non-severe reaction: 3 (3%) (amoxicillin, n=2) children with an immediate reaction (urticaria) during the hospitalization for the OCT and 10 (11%) (amoxicillin, n=5 ; amoxicillin-clavulanate, n=3) with a non-immediate reaction (maculopapular exanthema, n=7 ; urticaria, n=3). Four children (the 3 children with immediate reaction, one with non-immediate reaction) received oral antihistamines. Of the 10 children with a confirmed hypersensitivity to amoxicillin or amoxicillin-clavulanate, all except one tolerated an oral cephalosporin as an alternative.

Of the 78 (86%) children with a negative OCT, the index antibiotic was used in 30 (38%) at least one time during a mean follow-up of 11 months (SD: 4.3). Among them, 2 (7%) developed non-severe, non-immediate maculopapular exanthema after the reutilization.

None of the drug reactions required adrenaline injection nor hospital admission.

Among the 48 (62%) children who did not receive the index antibiotic, the practitioner and the family were reluctant to its prescription in 4 cases (8%) each and 40 (84%) did not need any antibiotic during the follow-up.

We did not find any association between the occurrence of drug reaction either during the OCT or after reutilization and patients' characteristics (Table 1).

OCT without previous skin allergy testing is safe in children with suspected non-immediate, non-severe BH. Non-immediate mild cutaneous reactions occurred in one out of 6 children, rather more than reported in previous studies (3, 7). In 88 children with a suspected BH, Caubet et al. reported drug reactions in only 6 (7%) children, immediate in one case and never more serious than the initial reaction (3). Zambonino et al. reported similar results in 783 children with suspected BH, with 62 (8%) positive OCT, irrespective to the time of onset of the initial reaction; none of the reactions were severe (7). Mill et al reported 2% of immediate and 4% of non-immediate reactions (all cutaneous mild reactions) in 818 children with a suspected hypersensitivity to amoxicillin explored with a graded OCT (8). As reported, clinicians should consider to perform a follow-up OCT few years after the initial OCT to assess the tolerance acquisition in children with non-immediate non-severe reactions (9). To date, we did not perform such follow-up OCTs.

A negative OCT to betalactam does not always predict tolerance during reutilization. We found that 10% of patients with a negative OCT will have a reaction after reutilization of the index antibiotic, in accordance with a previous pediatric study (10). Of 217 OCT performed in 203 children (antibiotics in 128 cases), 163 patients with 175 negative OCT were contacted three months later (10). Of the 91 cases with reutilization of the index antibiotic, 11 (12%) declared a new reaction (10 with antibiotics, 7.8%). The mechanisms involved in the reaction after reutilization despite a negative OCT are not clear. Resensitization, impact of cofactors and viral infections are the most reported.

In our study, 16% of children did not use the tested drug despite a negative OCT because the family or their practitioner feared an adverse reaction. This rate has been reported as high as 45% in another study (10). The impact of OCT on further prescription is raised. We have highlighted that reactions after reutilization despite a negative OCT were always mild, cutaneous, and most often non-immediate. For Misirlioglu et al., only one of the 91 children with a negative OCT to amoxicillin-clavulanate underwent an anaphylaxis after reutilization (10).

We do not identify any relevant association between characteristics of the children and the occurrence of drug reaction. A rash that lasted longer than seven days (adjusted odds ratio: 4.8; 95%CI: 1.4-16.4) and a parental history of drug allergy (adjusted odds ratio: 3.0; 95%CI: 1.3-6.8) were identified as risk factors by Mill et al. (8).

Our study has some limitations, mainly due to the small sample size. We strongly emphasize that an accurate description of the clinical manifestations (most often urticaria, maculopapular exanthema, or anaphylaxis) is essential to confirm the diagnosis, classify the reaction (benign/severe, immediate/non-immediate) and plan the diagnosis procedure, even if this classification is not always easy to apply in daily practice (11). To date, different OCT protocols have been published but the optimal protocol (dose, duration of the dose given at home after OCT) should be defined in further studies (12).

In conclusion, a 3-days OCT to betalactam without previous skin testing is safe and accurate, in selected children with non-severe, non-immediate suspected hypersensitivity. The evaluation of immediate, non-anaphylactic reaction, the optimal OCT protocol, the mechanisms involved in patients with drug reactions during reutilization after a negative OCT remain to be addressed.

Table 1. Characteristics of the 91 children with a suspected hypersensitivity to betalactam.

	Population N=91 (100%)	Patients without any drug hypersensitivity N=76 (84%)	Patients with drug hypersensitivity N=15 (16%)	p
Gender, male, n (%)	45 (50%)	39 (51%)	6 (40%)	0.42
Age at the time of the OCT, year (SD)	6.9 (4.2)	7.03 (4.3)	6.4 (3.7)	0.76
Mean duration between index drug reaction and OCT, months (SD)	34 (35.1)	35 (37.2)	31 (34.9)	0.69
Mean duration of the follow-up since OCT, months (SD)	10 (1)	10.1 (0.3)	8.9 (1.1)	0.70
History of asthma, n (%)	39 (43%)	37 (49%)	2 (13%)	0.11
History of dermatitis, n (%)	18 (20%)	17 (22%)	1 (7%)	0.29
History of rhinoconjunctivitis, n (%)	11 (12%)	10 (13%)	1 (7%)	0.68
History of food allergy, n (%)	6 (7%)	5 (7%)	1 (7%)	NC
History of sensitization to aeroallergen, n (%)	16 (18%)	13 (17%)	3 (20%)	0.72

NC: non calculable, OCT: oral challenge test

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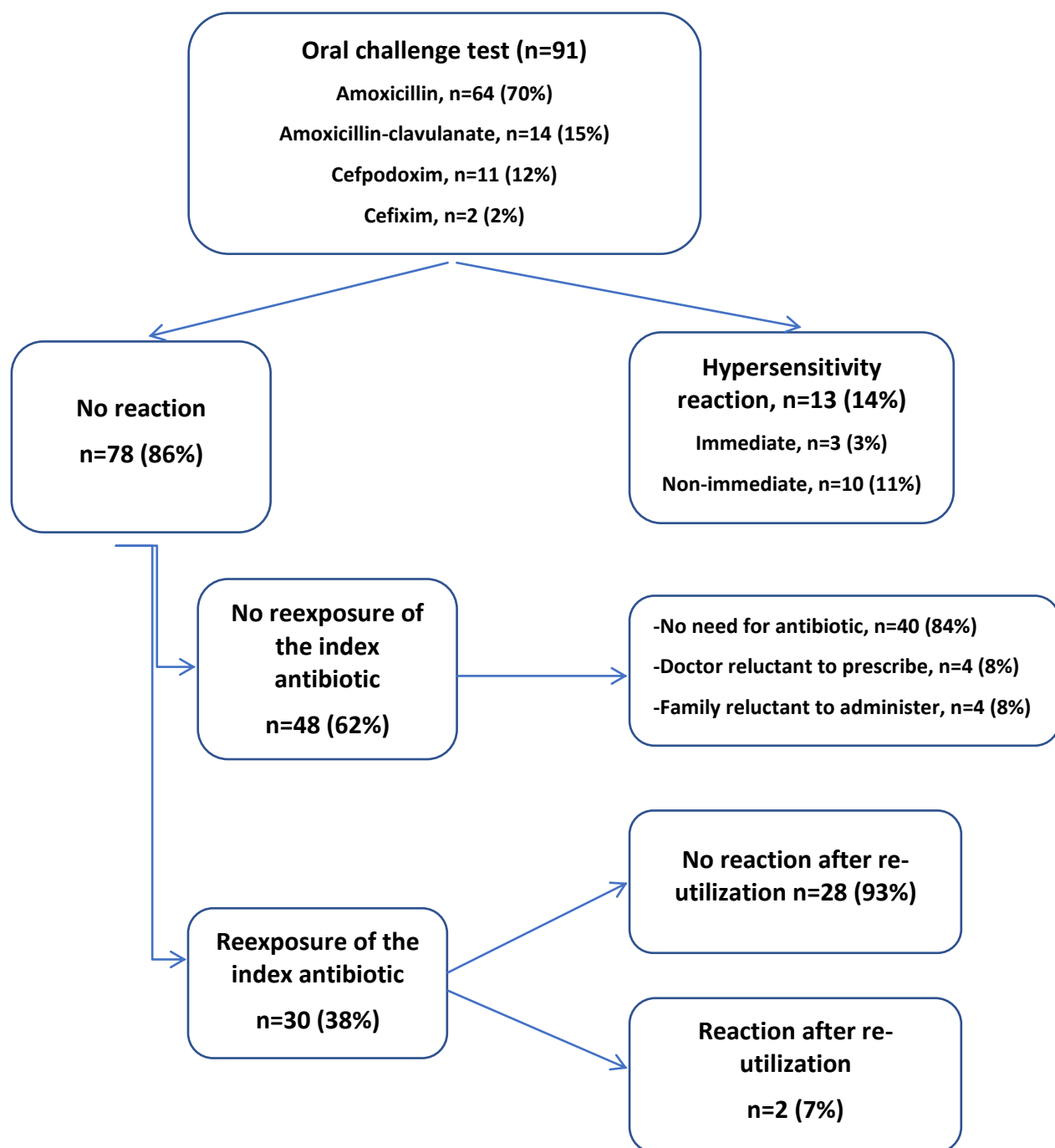


Figure 1. Flow-chart of 91 children with a suspected non-immediate, non-severe hypersensitivity to betalactam undergoing an oral challenge test and allergy follow-up.

Online Supplementary

S1. Oral challenge test (OCT)

Open 3-days-OCT were performed in children with a suspicion of non-severe, non-immediate hypersensitivity to betalactam by experienced medical teams with full resuscitation backup, in two children's hospital (Lille University hospital, Roubaix hospital). The protocol was adapted from that described by Caubet et al. (3). The patients received two oral doses of the index antibiotic, 1/10 of the therapeutic dose followed by the full dose administered at 30-minutes interval. Patients were under surveillance for at least two hours after the last drug administration. They were instructed to take the full-dose antibiotic for two more days at home and were contacted by a physician within two weeks after OCT. The test was discontinued in the event of any adverse reaction and clinical involvement as well as treatment were recorded. It was considered positive if any objective sign or symptom appeared and negative if no sign or symptom was documented during OCT or within the two weeks after.

S2.

Definition of the drug reactions (5)

Reactions occurring within the first hour were labeled as « immediate » reactions (urticaria, angiooedema, rhinitis, bronchospasm and anaphylaxis) whereas those occurring later than an hour were labeled as « non-immediate » (delayed urticaria or angiooedema, maculopapular rash).

Patients with a history of suspected life-threatening drug reaction (drug reaction with eosinophilia and systemic symptoms, hypersensitivity syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, nephritis, pneumonitis, hepatitis, vasculitis) were not included in our study.