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Skin tests are important in children with β-lactam hypersensitivity, but may be reduced in number

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Abstract

There is no perfect agreement on how to perform an allergy work-up in suspected beta-lactam (BL) allergic children, since skin test (ST)-induced pain is often a limitation. The aim of the study was to assess the possibility of reducing the number of ST in children when performing a complete allergy work-up for BL hypersensitivity reactions.

A retrospective analysis of all patients referring to the Allergy Unit of the University Hospital of Montpellier (France) with positive responses in immediate- and non-immediate-reading ST to a BL over a 16-years period was performed, to determine the positive predictive value (PPV) of ST. All pediatric patients with a suspected BL hypersensitivity were skin tested with the suspected drug only, during the following 54 months.

319 patients reporting 328 BL reactions were included in the retrospective study. The PPV of ST for the reported drug was of 99.4%. Based on the results, the number of patients to include in the prospective study was estimated to be 101. In the prospective study, 229 children were included.

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We diagnosed a BL hypersensitivity in 12 children (5.2%): in 6 (50.0%) diagnosis was reached through ST (delayed reading for all) and in 6 through drug provocation test (DPT).

STs with BL should therefore be performed as a screening test, before DPT, and testing only the suspected drug may be sufficient when dealing with children.

Key words: beta-lactam allergy, children, drug allergy, skin tests

Introduction

Antibiotics are one of the most common cause of drug hypersensitivity reactions (DHRs) in children[1]. DHRs may be allergic or non-allergic, with drug allergies showing an underlying immunologic mechanism[2]. Any beta-lactam (BL) may induce a DHR, and a firm diagnosis of drug hypersensitivity should be reached to prevent useless avoidance. Most common antibiotics suspected of inducing a DHR are penicillins followed by other BLs, probably since they are the most prescribed antibiotics in children[1,3].

Even though the immune system is in evolution in children, there is no difference in the immunology of DHRs between children and adults[4,5]. The diagnosis of BL DHR is based on a complete allergy work-up: if the clinical history is compatible, skin tests (ST) should be performed. Skin tests have been well validated for BLs, and their sensitivity and negative predictive value are classified as good for immediate DHRs to this class of antibiotics[6]. If ST are negative, and in the absence of contraindications, a drug provocation test (DPT) is commonly performed, being still recognized as the *gold standard* for such diagnosis[7,8].

In recent years, some authors proposed to avoid ST in children, while older European Academy of Allergy and Clinical Immunology (EAACI) guidelines, together with other authors' recommendations,

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still underline the importance of testing several different molecules of the BL family, when evaluating patients of any age for a suspicion of DHR[6-11]. Pediatricians, though, are aware that intradermal tests (IDT) and even skin prick tests (SPT) are associated with a significant discomfort for children and parents. For this reason, sometimes, the allergy work-up is postponed and children avoid this class of antibiotics without having a true drug hypersensitivity[3,10]. In the recent EAACI Drug Allergy Interest Group pediatric Task Force on Drug Hypersensitivity in children[1], a general diagnostic algorithm for DHR evaluation in children was proposed: clinicians may perform a DPT without previously skin testing the patient, in the case of non-immediate reactions manifesting as mild cutaneous exanthemas (the most prevalent hypersensitivity manifestation in childhood), based on one study in which such children were seen at the acute phase by a doctor of the allergy unit, to ascertain the low severity of the reaction and then underwent ST and a DPT to the culprit drug[12]. In this study by Caubet et al., only patients with mild skin reactions were included, and none of them reported other allergic symptom nor a history of anaphylaxis. Between the recommendation of performing a whole panel of ST and the advice to perform none, we believe that a compromise should be found for patients assessed in a daily practice and for such reason we decided to perform the present study.

The aim of the present study was to evaluate the possibility of reducing the number of performed ST in a pediatric setting, by retrospectively evaluating the positive predictive value (PPV) of ST performed with the suspected BL only and then, if this PPV was acceptable, by prospectively testing children with a history of DHR to BL, by simply using the suspected BL only.

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Methods

Retrospective study

We run a retrospective study on all consecutive patients referring to the Allergy Unit of the University Hospital of Montpellier (France), presenting with a history of DHR to BL and with a positive reaction to SPT or IDT (immediate and delayed reading) to any BL, over a 16-year period, from July 1996 to July 2012.

Assuming that immune mechanisms of DHR to antibiotics do not differ between children and adults[4,5], we enrolled patients without considering their age, to assess the accuracy of the clinical history.

Data were expressed as numbers and percentages (for the categorical variables) and medians (with interquartile range, for the numerical ones), and we calculated the PPV of the ST for the drug reported in the clinical history.

Prospective study

For the second part of the study, we prospectively included all consecutive children evaluated at the Allergy Unit of the University Hospital of Montpellier (France) between July 2012 and December 2016, for a history of suspected BL DHR. For each child, we collected clinical characteristics, and a detailed description of the reported reaction(s), we looked for atopy, defined as the positivity to at least one SPT to a common respiratory allergen of the Montpellier area, using a previously described panel of allergens (Stallergènes SA, Antony, France)[13], and for spirometric signs of asthma. The allergy work-up was run in each patient whose clinical history seemed likely to be associated to the drug, and consisted in ST to the suspected drug only (immediate and delayed reading), followed, if

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negative, by a DPT. For patients with multiple reactions, we considered the most severe reaction (chronologically, this was typically the most recent one).

Comparisons were made using chi-square tests (or Fisher exact tests for small sample sizes) for categorical variables. All *p-values* were 2-tailed, and significance was assigned to values less than 0.05.

Drug allergy work-up

Whenever the clinical history seemed compatible with a DHR to a BL, based on the standardized ENDA (European Network for Drug Allergy) questionnaire on drug allergy[14], patients underwent a complete allergy work-up.

Skin Prick Tests and IDT were performed as recommended by the ENDA group[6]. For the first part of the study, all patients were tested with PPL, MDM (or alternatively with Penicillin G since 2007, when PPL and MDM become unavailable in France), Amoxicillin, Ampicillin and Cefuroxime (following a local protocol), and with any other BL considered as responsible of the reported reaction. Penicillins were tested at a concentration of 25 mg/ml, and cephalosporins of 2 mg/ml. For the prospective study, only the culprit drug was tested. Whenever ST were negative, in absence of contraindication, a DPT was performed, under strict hospital surveillance, following ENDA recommendations[7,8] (empirical and then data-driven protocols Messaad 2004[4]/Chiriac 2017[15]). In case of a positive ST or a positive DPT, children were skin tested for a panel of BL drugs (including amoxicillin, ampicillin and at least one cephalosporin), and underwent a DPT to find an alternative molecule. An informed consent was obtained from each patient or from both parents of the included minor. The study was considered as part of a clinical routine practice, and no supplementary authorization was needed at that time, following French legislation. All patients were

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included in the Drug Allergy and Hypersensitivity Database (DAHD®), their data being protected, anonymized and authorized for exploitation, as previously validated by the local ethics committee[15].

Results

Retrospective study

For this part of the study, we included 319 patients (98 males and 221 females) with positive ST to BL. Median age at the time of the reaction was 39 years (25^{th}-75^{th}: 24-53 years).

The 319 patients reported 328 BL reactions (7 patients reported a reaction to two different drugs and one to 3 different molecules). 212 reactions (64.6%) were immediate and 116 (35.4%) non-immediate (occurring more than one hour after the last drug intake). Suspected drugs mainly included Penicillin G, Amoxicillin, Amoxicillin/Clavulanic acid, Ampicillin, Ceftriaxone, Cefamandole, and Cefuroxime. The suspected delay of symptoms appearance, and the results of ST are shown in Table 1.

In 312 patients, SPT or IDT resulted positive for the suspected molecule. Therefore, based on the reported clinical history, the PPV of the procedure was 99.4%.

Prospective study

Considering the results of the retrospective study and other not shown data regarding the total population tested during the retrospective time-period, we needed to include a sample of at least 101 children in the prospective trial (alpha 0.05; prevalence of positive ST in the population of patients with BL DHR during childhood in the retrospective study 6.4%; proportion of patients lost to follow-up before completing the allergy work-up 10%). We included 229 children (108 boys and 121 girls) with a history suggestive of BL allergic reaction. Median age was 5 years (25^{th}-75^{th}: 1-11 years).

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21 (9.2%) children reported immediate and 208 (90.8%) non-immediate reactions. Amoxicillin was the most frequently suspected BL (204 patients, 89.1%). Clinical presentations of included patients are shown in Table 2. Among all children, 89 (38.9%) were atopic and 23 (10.0%) had asthma.

Median delay between the reported reaction and the allergy work-up was 31 months (25^{th}-75^{th} %: 6-80 months). We diagnosed BL allergy in only 12 patients (5.2%). Skin tests were positive in 6 of them (positive delayed-reading IDT in all 6 children), tested for amoxicillin alone or associated with clavulanic acid (3 and 3 children respectively) (Table 3). All 6 reported a reaction that was either non-immediate (50%) or of unknown chronology (50%). In all 6 patients having negative ST but positive DPT for the culprit drug (Amoxicillin or Amoxicillin/Clavulanic acid), adding Penicillin G, Ampicillin and Cefuroxime to the ST panel did not bring additional information, since these ST were also negative. In all patients, a DPT to Cefuroxime provided a safe alternative.

Conclusion

In children treated with BLs, skin eruptions, mostly described as maculopapular or urticarial, are frequently assumed to be a DHR, although most of these eruptions are not allergic, with viral infections being often considered as the major differential diagnosis[3,16]. It is therefore very important to complete an allergy work-up in patients reporting a history of BL DHR[16].

Older EAACI/ENDA guidelines do not differentiate between children and adults and advise to perform several ST (both SPTs and IDT) before running a DPT[6-8]. This is a limiting factor in pediatrics and sometimes parents and children refuse to complete the work-up, because they do not want to suffer from injections. Also, children are tested when they are not sick and it is sometimes difficult to make them understand the importance of performing ST that might be painful. Limiting the number of ST might be a way to convince both children and their parents to undergo a DPT if STs remain negative.

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On the other hand, in recent years, it has been suggested not to perform ST in children, in mild to moderately severe delayed reactions, but to simply prescribe a DPT[1,9,10]. Several protocols have been proposed for DPT in children reporting delayed reactions, over a 2 to 5-days period[17-19]. These protocols refer to children reporting a history of mild reactions and the Authors suggest that increasing the duration of DPT may improve its diagnostic performance without increasing the risk of severe reactions during the observation period or at home. From our personal experience, there is no advantage in the predictive value of DPT if performed over a one-day period (followed by 48 hours of surveillance at home) or over a more prolonged time[20]. Also, in these cases, it seems essential either to examine patients during the reaction and/or to be able to properly classify it as immediate or non-immediate, and mild-moderately or (potentially) severe by means of anamnesis (interview of the parents, and photographies of the reaction). Our data show that the timing of the reaction is not always correctly reported by the patients, and positive ST occur in situations where other protocols would not recommend them, and we suggest that a careful assessment through immediate and delayed-reading ST should be performed before DPT, as an extra security step.

In our prospective study, only 5.2% of all children reporting a DHR to a BL had a proven hypersensitivity to the suspected BL, which is a lower percentage if compared with previous reports[3,5,16]. This might be due to the characteristics of our pediatric population, with > 90% of patients having a non-immediate initial reaction, which rarely results to be true DHRs.

By skin testing the suspected drug only, we avoided unnecessary DPT in 2.6% of children. This percentage may seem low, but DPT is an iatrogenic intervention and it is preferable to reach diagnosis by ST.

Current knowledge suggests that direct DPT may be done, without STs, in children reporting a history of delayed benign cutaneous reaction to BLs[21]. Such approach is mainly validated in small children without a history of anaphylaxis nor of severe cutaneous reaction, when viral infections are the most important cause of non-severe skin exanthemas. Nevertheless, in our study, 9.2% and 6.1%

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of children had presented with clinical histories of immediate reactions and anaphylaxis, respectively. Mill et al.[22] performed DPT (10% followed by 90% of the therapeutic daily dose) in 818 children, with both immediate and non-immediate cutaneous reactions to BL (no anaphylactic cases were included). They only performed ST in patients reporting an immediate reaction, and skin tested them with bezylpenicillin and benzylpenicilloyl polylysine only, which is not currently recommended by the European guidelines. The Authors concluded that the procedure was safe. In our experience, however, in adults, DPT may elicit anaphylaxis at low doses, in the absence of a clinical history of anaphylaxis[15]. Therefore, we do not encourage by-passing ST, nor limiting the test to major penicillin determinants, regardless of the reported severity of the reaction. Also, differently from previous papers, we included in our study patients with a history of anaphylaxis and anaphylactic shock, while, as recommended by guidelines and by other studies, severe non-immediate reactions were excluded from the allergy work-up.

In conclusion, ST are safe and should be performed in children, to avoid exposing them directly to higher doses of the suspected drug, by DPT. Through the present study, we propose a compromise between two current attitudes (i.e., performing ST to a panel of BL *versus* by-passing ST): skin testing the suspected molecule only (considering the high PPV of the ST for the drug reported in the clinical history) could be helpful in pediatric settings, regardless the chronology of the initial reaction.

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Tables

Table 1 – Results of positive skin tests to the suspected drug in patients with a positive allergy work-up in the retrospective study.

Tested drug	Positive allergy work-up for the suspected drug	History of immediate reaction					History of non-immediate reaction				
		Total	Positive SPT	Positive IDT	Positive delayed IDT	Negative	Total	Positive SPT	Positive IDT	Positive delayed IDT	Negative
Penicillin G	13	3	1	2	0	0	10	0	2	8	0
Amoxicillin	145	95	46	41	8	0	50	0	11	37	2
Amoxicillin/Clavulanic acid	85	59	34	23	2	0	26	3	8	15	0
Ampicillin	22	7	2	4	1	0	15	0	4	11	0
Cefuroxime	9	8	8	0	0	0	1	0	1	0	0
Ceftriaxone	15	11	4	6	1	0	4	0	3	1	0
Cefamandole	11	11	1	10	0	0	0	0	0	0	0
Cefazolin	8	7	4	3	0	0	1	0	1	0	0
Cefotaxime	6	4	2	2	0	0	2	0	1	1	0
Cefatrizine	6	4	0	4	0	0	2	1	1	0	0
Piperacillin	3	1	1	0	0	0	2	1	1	0	0
Ceftazidime	2	0	0	0	0	0	2	0	2	0	0
Cefixime	1	0	0	0	0	0	1	0	1	0	0
Cefadroxil	1	1	0	1	0	0	0	0	0	0	0
Cefotiam	1	1	1	0	0	0	0	0	0	0	0
Total (No.)	328	212	104	96	12	0	116	5	36	73	2
Total (%)		64.6%	31.7%	29.3%	3.7%	0.0%	35.4%	1.5%	10.9%	22.3%	0.6%
		% of patients with a history of immediate reaction	49.0%	45.3%	5.7%	0.0%	% of patients with a history of non-immediate reaction	4.3%	31.0%	62.9%	1.7%

Legend: SPT – Skin Prick Test; IDT – Intradermal test

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Table 2 – Clinical characteristics of patients included in the prospective study (229 patients included).

Characteristics	**Number of patients No. (%)**	**Confirmed allergy No. (%)**	***p-value***
Sex			0.69
Females	121 (52.8)	7 (3.1)	
Males	108 (47.2)	5 (2.2)	
Asthma			0.23
Asthmatic	23 (10.0)	0 (0.0)	
Non-asthmatic	206 (90.0)	12 (5.2)	
Atopy			0.83
Atopic	89 (38.9)	5 (2.2)	
Non-atopic	140 (61.1)	7 (3.1)	
Tested Antibiotic			0.91
Penicillins	206 (90.0)	12 (5.2)	
Cephalosporins	19 (8.3)	0 (0.0)	
Other beta-lactams	4 (1.7)	0 (0.0)	
Chronology of the reaction			0.47
< 1 h	21 (9.2)	1(0.4)	
1-6 h	27 (11.8)	0 (0.0)	
6-24 h	43 (18.8)	1 (0.4)	
> 24 h	22 (9.6)	2 (0.9)	
Unknown	116 (50.6)	8 (3.5)	
Semiology of the reaction			*<0.001**
Anaphylaxis (without shock)	11 (4.8)	0 (0.0)	
Anaphylactic shock	3 (1.3)	2 (0.9)	
Urticaria/angioedema	77 (33.6)	2 (0.9)	
Maculo-papular exanthema	133 (58.1)	8(3.5)	
Other symptoms	5 (2.2)	0(0.0)	
Semiology of the reaction			*<0.001**
Anaphylaxis (without shock)	11 (4.8)	0 (0.0)	
Anaphylactic shock	3 (1.3)	2 (0.9)	
Other reactions	215 (93.9)	10 (4.4)	

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Table 3 – Pediatric patients with a positive allergy work-up.

	Sex	Age	Culprit Drug	Reported symptoms	Delay	ST culprit drug	DPT culprit drug	DPT symptoms	ST Penicillin G	ST Ampicillin	ST Cefuroxime	Other negative ST	Alternative negative DPT
1	F	10	Amoxicillin/Clavulanic Acid	Edema, MPE	Unknown	Positive IDT (delayed reading)	Avoided	Not applicable	Negative	Positive	Negative		Cefuroxime
2	F	7	Amoxicillin	Edema	Unknown	Positive IDT (delayed reading)	Avoided	Not applicable	Negative	Positive	Negative		Cefuroxime
3	M	7	Amoxicillin/Clavulanic Acid	MPE	> 24h	Positive IDT (delayed reading)	Avoided	Not applicable	Negative	Negative	Negative		Cefuroxime
4	F	17	Amoxicillin/Clavulanic Acid	Hypotension, MPE	> 24h	Positive IDT (delayed reading)	Avoided	Not applicable	Negative	Positive	Negative	Ceftriaxone	Ceftriaxone
5	M	14	Amoxicillin	MPE	Unknown	Positive IDT (delayed reading)	Avoided	Not applicable	Negative	Positive	Negative		Cefuroxime
6	F	9	Amoxicillin	Edema, MPE	> 24h	Positive IDT (delayed reading)	Avoided	Not applicable	Negative	Negative	Negative		Cefuroxime
7	F	15	Amoxicillin/Clavulanic Acid	MPE	Unknown	Negative	Positive	MPE	Negative	Negative	Negative		Cefuroxime
8	M	11	Amoxicillin	MPE	> 24h	Negative	Positive	MPE	Negative	Negative	Negative		Cefuroxime
9	F	15	Amoxicillin/Clavulanic Acid	Edema	Unknown	Negative	Positive	MPE	Negative	Negative	Negative		Cefuroxime
10	M	15	Amoxicillin	Malaise, bronchospasm, Urticaria	< 1h	Negative	Positive	MPE, conjunctivitis	Negative	Negative	Negative		Cefuroxime
11	M	8	Amoxicillin	MPE	Unknown	Negative	Positive	MPE	Negative	Negative	Negative		Cefuroxime
12	F	6	Amoxicillin/Clavulanic Acid	Malaise, Vomiting, MPE	Unknown	Negative	Positive	MPE	Negative	Negative	Negative		Cefuroxime

Legend: MPE –Maculopapular exanthema; IDT – Intradermal test; ST – Skin Tests; DPT – Drug Provocation Test.

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