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Hypersensitivity to beta-lactam antibiotics: a three-year study

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Key words
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Summary
Background. *Beta-lactams antibiotics (BL) are the most frequent elicitors of allergic drug reactions. The aim of our study was to characterize the patients referred with suspected hypersensitivity (HS) to BL.* ***Methods.*** *Over a three-year period (2011-2013), a total of 234 adult and paediatric patients (pts) with suspected HS to BL were investigated according to the European Network for Drug Allergy guidelines.* ***Results.*** *HS to BL was confirmed in 43 pts (18%), without differences between adult and paediatric pts; anaphylaxis was reported by 20 pts. Diagnosis was ascertained by: serum-specific IgE antibodies in 5 pts (12%), skin prick tests in 5 (12%), intradermal tests in 25 (58%), 3 with delayed reading, and the remaining 8 (18%) by drug provocation tests. Penicillins / derivatives were the culprit drugs in 39 pts, mainly amoxicillin, and cephalosporins in 4.* ***Conclusions.*** *In most of these patients with suspected HS to BL, allergological work-up was negative and HS was excluded. One fourth of confirmed cases had a plausible non-IgE mediated mechanism.*

Introduction

Hypersensitivity to beta-lactams antibiotics (BL) continues to be the most commonly reported cause of adverse drug reactions mediated by specific immunological mechanisms, being the reactions classified as immediate or non-immediate. Immediate reactions usually appear within the first hour after BL administration, and are mediated by specific IgE-antibodies; the remaining reactions, not immediate, usually occur within 24 hours after drug intake (1). The symptoms can range from urticaria to anaphylaxis (2) (most in immediate reactions), to maculopapular exanthema and delayed urticaria (non-immediate reactions). T cells are implicated in all types of hypersensitivity reactions to BL, indirectly by regulating IgE production or directly as effector cells. A Th1 pattern is observed in both CD4(+) and CD8(+) peripheral T cells in non-immediate reactions, whereas a Th2 pattern is expressed in CD4(+) T cells in immediate reactions (3).

IgE responses to benzylpenicillin (BP), the first antibiotic producing the benzyl penicilloyl structure, are characterized by an acute release of inflammatory mediators, resulting in urticaria, angioedema and eventually anaphylactic shock. BP has been progressively replaced by other compounds, as amoxicillin (AX) and, to a lesser extent, cephalosporins, carbapenems, monobactams or the related betalactamase-inhibitor clavulanic acid, which are responsible for IgE selective responses and cross-reactivity reactions (4).

BL (penicillins, cephalosporins, carbapenems, monobactams and beta-lactamase inhibitors) are the most widely used antibiotic drugs worldwide and constitute the most commonly reported cause of drug allergy, with a prevalence rate of 0.7 to 10% in adults and children (5-8). In large-scale studies, 80 to 90% of patients with a history of penicillin allergy were considered not to be allergic, but recent data suggest that this number may even be as high as 95% (9,10). Potential reasons that can explain the dissociation between patients labelled as allergic and those with confirmed allergy include

misdiagnosed reaction, reaction due to underlying disease, levels of specific IgE that wane over time and outgrown allergy to BL (10). Patients labelled as penicillin-allergic are more prone to receive broader spectrum antibiotics, with more adverse effects, if not less effective alternative drugs, with consequent increase of bacterial resistance. Furthermore, alternative drugs are usually more expensive with the consequent increase in medical costs (11).
According to the ENDA / EAACI (*European Network of Drug Allergy / European Academy of Allergy and Clinical Immunology*), the evaluation of BL hypersensitivity includes a detailed clinical history, *in vitro* quantification of specific IgE-antibodies, skin tests, and drug provocation test (DPT) (12,13).
The aim of this study was to describe the work-up activity developed at our Immunoallergy outpatients' hospital of a large group of patients with suspected hypersensitivity to BL.

Materials and methods

Patients

The authors included in this evaluation a group of consecutive patients, adults and children, who were referred to our drug allergy center of CUF Descobertas Hospital (Lisbon, Portugal) with suspected hypersensitivity to BL, over a three-year period (from January 2011 to December 2013). Clinical data with detailed description of symptoms and circumstances of the reaction was collected in clinical files and a proper questionnaire adapted from ENDA (14) was filled in. All patients were fully informed about the procedures (risks and possible adverse reactions) and all of them signed an informed consent according to the Helsinki Declaration. The diagnostic procedures followed the ENDA/EAACI recommendations (12,13).

In vitro tests

Serum-specific IgE antibodies (*ImmunoCAP®, Thermo Fisher Scientific, Uppsala, Sweden*) for penicillin G/V, AX and ampicillin were used. Assays were performed at least 4 weeks interval after the clinical reaction and a *cut-off* value ≥ 0.35 kU/L was considered for positivity.

In vivo tests

Skin prick tests (SPT) were the first step of the *in vivo* investigation, and only if negative, intradermal tests (IDT) were carried out. Skin tests were accomplished using solutions, daily prepared, of benzylpenicilloyl octa-L-lysine (PPL) (5×10^{-5} mM) and sodium benzylpenilloate - minor determinant (MD) (2×10^{-5} mM) (*DAP® Penicillin, Diater, Madrid, Spain*), penicillin G (25.000 IU/mL), AX (25 mg/mL) and clavulanic acid (CLV) (2.5 mg/mL), and cefuroxime (2.5 mg/mL) (12). Histamine (10 mg/mL) was used as a positive control for SPT and 0.9% saline solution as a negative control.
To all patients that reported symptoms compatible with severe reactions, IDT were carried out beginning with more diluted solutions (PPL diluted 1/100, MD diluted 1/1000, Penicillin G 2.500 IU/mL, AX 2.5 mg/mL and cefuroxime 0.25 mg/mL), which were gradually increased until the appearance of a positive skin response or until reaching the maximum concentration described above.
First readings were taken after 15 and 20 minutes for SPT and IDT, respectively. Both tests were performed on the volar forearm. In SPT a mean wheal larger than 3 mm, accompanied by erythema, with a negative response to negative control was considered positive. IDT were done by the injection of 0.02-0.05 mL of the hapten solution, raising a small wheal that was marked initially. In IDT an increase in mean diameter greater than 3 mm of the wheal area marked initially was considered positive. All patients, particularly in case of high suspicion of non-immediate reactions, were advised of the possibility of having a late reaction within an interval of 24-48 hours, and a delayed reading has been taken. Other drugs (penicillin derivatives / cephalosporins) were tested according to the suspicion.

Drug provocation tests (DPT)

After skin tests, the patients underwent oral challenges with the culprit drug, whether previous investigation (SPT and IDT) was unequivocally negative. By contrast, in the patients where SPT or IDT have been positive a DPT with alternative BL drug has been conducted. DPT was always fulfilled in posterior appointment to allow delayed readings of the skin tests. The therapeutic dose of selected drug was administered stepwise, increasing each 20 to 30 minutes, or as a single dose, according to clinical history documented. The patients were retained in the hospital for at least 2 hours after the last dose and were informed about the possibility of delayed reactions after hospital discharge. Depending on the likelihood of the reaction during the time of the procedure, some patients were given further doses to fulfilled 24 to 72 hours of oral challenge. If necessary, the oral challenge was prolonged until 5 to 7 days. The telephone number of medical staff, and appropriate medication in case of late allergic reaction including antihistamine and corticosteroid drugs, were provided on hospital discharge, and were available during the follow-up period.
All tests were performed under strict medical surveillance, by professionals with experience in recognition and management of acute reactions. Epinephrine and other appropriate medication and resuscitation equipment have been always available during carrying out of the tests.

Results

A total of 234 patients with clinical suspicion of hypersensitivity reactions to BL were evaluated over the three years (**table 1**

and **figure 1**). The mean age was 36 [standard deviation (SD) ± 16.2] years old (2-75 years), and 68% where female. Thirty seven (16%) had less than 18 years old, with a mean age of 7.8 (SD ± 3.7), and 54% were boys. In 161 patients (69%) penicillins / derivatives were the culprit drug, AX alone in 49 patients (21%), and in association with CLV in 75 patients (32%). Cephalosporins were involved in 26 patients (11%). Reactions with more than one BL were reported by 11 patients. Atopy, personal history of allergic disease and family history of BL allergy is presented in **table 1**.

***Table 1** - Clinical characteristics of study population comparing with confirmed cases.*

	HS to BL	Total population
n (%)	43 (18)	234
Age (yrs, mean, SD)	37 (16.6)	36 (16.2)
Under 18 yrs (n, %)	7 (16)	37 (16)
Sex (female, %)	24 (56)	160 (68)
Atopy (n, %)	8 (19)	74 (32)
Personal history of allergic disease	23 (53)	154 (66)
Personal history of asthma	7 (16)	53 (23)
Family history of BL allergy	2 (5)	15 (6)
Clinical manifestations (n, %)		
Mucocutaneous	43 (100)	190 (81)
Respiratory	10 (23)	20 (9)
Gastrointestinal	7 (16)	16 (7)
Cardiovascular	3 (7)	10 (4)
Loss of consciousness	6 (14)	12 (5)
Swollen glottis	6 (14)	8 (3)
Anaphylaxis	20 (47)	30 (13)
Not specified	1 (2)	8 (3)
Drug involved (n, %)		
Benzylpenicillin	3 (7)	29 (12)
Ampicillin	1 (2)	3 (1)
Flucloxacillin	1 (2)	5 (2)
Amoxicillin	13 (30)	49 (21)
Amoxicillin-clavulanic acid	21 (49)	75 (32)
Cephalosporins	4 (9)	26 (11)
Unrecalled	2 (5)	54 (23)

BL, beta-lactam antibiotics; HS, hypersensitivity.

Hypersensitivity to BL was confirmed in 43 patients (18.4%), being 7 younger than 18 years old (18.9%) and 36 adults (18.3%). Only 19% of these patients were atopic (sensitized to at least one common aeroallergen). The majority (53%) had personal history of allergic disease, and 16% had asthma as co-morbidity. Only 5% had family history of BL allergy. Considering the confirmed cases, all patients had mucocutaneous symptoms, which were the only manifestation in 53% of them. Severe reactions (anaphylaxis) occurred in 20 patients (47%) with swollen glottis and loss of consciousness in 6 patients. Regarding medical approach of allergic reactions, we found that 50% of the patients who developed anaphylaxis were properly treated with epinephrine.

***Table 2** - Results of positive skin tests.*

BL drug	SPT	IDT		Total
		Immediate	Delayed	
PPL	3	6	-	9
Penicillin	1	5	1	7
AX	3	14	2	19
Cefazoline	-	3	-	3

AX, amoxicillin; BL, beta-lactam antibiotics; IDT, intradermal tests; PPL, benzylpenicilloyl octa-L-lysine; SPT, skin prick tests.

The hypersensitivity was ascertained by means of serum-specific IgE antibodies in 5 patients (12%), by SPT in 5 (12%), by IDT in 25 (58%) and the remaining 8 (18%) by DPT. The results of skin tests are described in **table 2**. Ten children with negative specific IgE antibodies and nonimmediate reactions were excused from skin tests and performed DPT with the culprit drug, which were negative.

Regarding the serum-specific IgE antibodies, the negative predictive value (NPV) was 82.4% and the sensitivity was 18.6%. Whereas, for the skin tests the NPV was 97.4% and the sensitivity was 85.7%.

Analyzing the five patients diagnosed by *in vitro* tests, positive results were obtained to AX in 4 patients [three with generalized urticaria (AX-IgE 1.87, 1.92 and 3.01 kU/L) and one with anaphylaxis with loss of consciousness (AX-IgE > 100kU/L)]. The other patient was positive to ampicillin (26,9 kU/L).

It is important to notice that although with negative skin tests by immediate reading, three patients presented delayed reading of IDT (**table 3**), one to penicillin and two to amoxicillin. Two of these have been referred with suspected allergy to BL presenting with generalized urticaria and the other with severe anaphylaxis with loss of consciousness.

Four patients experienced systemic reaction during skin testing (**table 3**), one child had anaphylaxis during IDT with amoxicil-

Table 3 *- Clinical characteristics of patients with delayed readings and systemic reactions with skin tests.*

Age of reaction	Culprit drug	Reaction	Timing	sIgE	SPT (+)	IDT (+)	Systemic reactions during ST
23	AX-CLV	Angioedema (face and lips)	IR	(-)	AX	NP	Pruritus and erythema of the upper limb after SPT
23	AX	Urticaria and angioedema (hands and legs)	IR	(-)	PPL, Penicil-lin, AX	NP	Pruritus and erythema of the upper limb after SPT
3	AX-CLV	Anaphylaxis (generalized urticaria, angioedema lips and tongue and dyspnea)	IR	(-)	(-)	AX 2,5 mg/mL (imme-diate reading)	Anaphylaxis 15 min after IDT (urticaria, prostration, rhinoconjunctivitis, cough, bronchospasm)
38	AX-CLV	Anaphylaxis (angioedema of face, swollen glottis, loss of consciousness)	NIR	(-)	(-)	AX 25 mg/mL (delayed reading, 10 h)	Pruritus and facial rash 1h after IDT
36	AX-CLV	Generalized urticaria	NIR	(-)	(-)	AX 25 mg/mL (delayed reading, 6 h)	no
46	Fluclox-acillin	Generalized erythema	NIR	(-)	(-)	Penicillin 25.000 IU/mL (delayed reading, 24 h)	no

AX, amoxicillin; AX-CLV, amoxicillin-clavulanic acid; IDT, intradermal tests; IR, immediate reaction; NIR, non-immediate reaction; NP, not performed; sIgE, specific IgE antibodies; SPT, skin prick tests; ST, skin testing; (+), positive; (-), negative.

Figure 1 *- Investigation allergological work-up performed.*

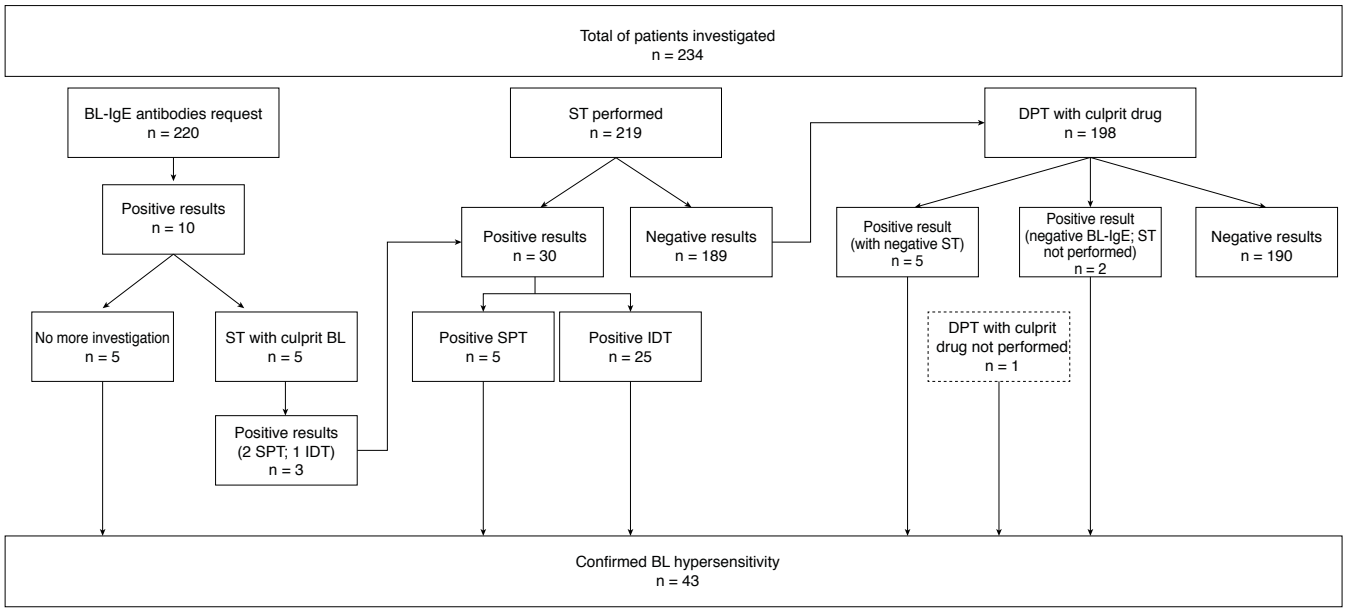

***Table 4** - Clinical characteristics of patients diagnosed by drug provocation test.*

Age (interval reaction-study) (yrs)	Type of reaction (time); day of intake	Reaction	Culprit drug	sIgE	ST	DPT(+)	Reaction during DPT	Time	DPT(-)	Conclusion
27 (10)	IR; 1	Anaphylaxis (urticaria, angioedema, loss of consciousness)	AX-CLV	-	-	AX	Anaphylaxis (pruritus, cough, bronchospasm, urticaria, angioedema, conjunctivitis, throat tightness) (250 mg)	30 min	0	HS non-IgE-mediated AX
						CFX	Facial and palmar pruritus, auricular angioedema	20 min		HS non-IgE mediated CFX
6 (5)	NIR; 4	Anaphylaxis (exanthema, vomiting)	AX	-	NP	AX	Vomiting	3h	CFX	HS non-IgE-mediated AX
44 (3)	NIR; 1	Exanthema (pelvic)	AX-CLV	-	-	AX	Exanthema (pelvic)	12h	CFX	HS non-IgE-mediated AX
2 (1)	NIR; 8	Exanthema (generalized)	AX-CLV	NP	NP	AX	Urticaria, angioedema	15 min	CFX	HS non-IgE-mediated AX
31 (1)	IR; 3	Anaphylaxis (urticaria, dyspnea)	AX-CLV	-	-	AX	Anaphylaxis (urticaria, cervical edema, throat tightness, cough (100 mg)	20 min	CFX	HS non-IgE-mediated AX
36 (3)	NIR; 2	Fixed drug eruption	AX-CLV	-	-	AX	Fixed drug eruption	day 5	CFX	HS non-IgE-mediated AX
33 (1)	IR; 1	Anaphylaxis (pruritus, urticaria, angioedema, laryngeal stridor)	AX-CLV	-	-				AX	Suspicion of HS to CLV (DPT with CLV not performed)
10 (9)	NIR; 8	Urticaria, angioedema	AX-CLV	-	-	AX-CLV	Nausea, abdominal pain, diarrhea	2h	AX	HS to CLV

AX, amoxicillin; AX-CLV, amoxicillin-clavulanic acid; CFX, cefuroxime; DPT, drug provocation test; HS, hypersensitivity; IR, immediate reaction; NIR, non-immediate reaction; NP, not performed; sIgE, specific IgE; ST, skin testing; +, positive; -, negative.

Table 5 *- Clinical characteristics of confirmed cases which involved cephalosporins.*

Age of reaction	Culprit drug	Reaction	Route	Timing	IDT +	DPT (-)
11	Cefatrizine; AX-CLV	Urticaria and angioedema (face and neck)	oral	IR	AX 25 mg/ml	CFX
40	Cefazoline	Anaphylaxis (urticaria, generalized angioedema, swollen glottis, hypotension)	i.v.	IR	Cefazoline 0,25 mg/ml	CFX
42	Cefazoline	Anaphylaxis (generalized urticaria, hypotension)	i.v.	IR	Cefazoline 2,5 mg/ml	AX
36	Cefazoline	Anaphylaxis (tachycardia, hypotension, bronchospasm, swollen glottis, angioedema lips)	i.v.	IR	Cefazoline 2,5 mg/ml	AX; CFX

AX-CLV, amoxicillin-clavulanic acid; CFX, cefuroxime; DPT, drug provocation test; IDT, intradermal tests; IR, immediate reaction.

lin (2.5 mg/mL), that resolved with intramuscular epinephrine; three adults had urticaria (face and upper limb), with resolution without need of epinephrine: one during IDT with amoxicillin (25 mg/mL), one during SPT with amoxicillin and the other during SPT with PPL, penicillin and amoxicillin.

Regarding DPT, 8 patients (6 with negative results in skin testing) revealed to be allergic when challenged with the culprit drug (**table 4**): 7 to AX and 1 to CLV (who had a negative oral challenge with AX).

Considering the 4 patients who was found to be allergic to cephalosporins (**table 5**), 1 reacted with cefatrizine and with AX-CLV, and had positive IDT with amoxicillin (injectable formulation of cefatrizine is not available in Portugal); and 3 patients reported intra-operative anaphylaxis with cefazoline and had positive IDT only with cefazoline.

The remaining 31 patients with confirmed hypersensitivity to other BL had negative DPT to the alternative BL antibiotic (cefuroxime, second generation cephalosporin).

Discussion

In this study, we evaluated a large group of patients including children and adults with suspected hypersensitivity to BL over a 3-year period time, and realized that only 18% of them were truly BL allergic. The diagnosis was based up on a positive serum-specific IgE determination (12%), skin tests (70%) or DPT (18%).

Overall, our results confirm that clinical history by itself is insufficient to label the patient as "penicillin allergic", since it will lead to over-diagnosis when solely used. Moreover, the occurrence of reactions in a distant past made it difficult for the patient to recall the symptoms, and some patients can outgrow penicillin allergy over time. Time interval until evaluation is critical. Patients with clear anaphylactic reactions did not always have positive skin tests or specific IgE, and that results could be in part caused by the time interval between drug exposure and the time of evaluation (15). In our study, 30 patients had reported anaphylactic reactions and only 20 of those were diagnosed as being BL allergic. In these patients, an extensive allergologic work-up was carried out to study other causes than could explain the anaphylactic reaction, either others drugs namely non-BL, general anesthetics or non-steroids anti-inflammatory drugs, either food allergy.

The work-up for the diagnosis of BL hypersensitivity included performing skin tests with major and minor determinants of BP, penicillin and other related-compounds and cephalosporins. AX was the most relevant, showing positive results in 19 patients. In spite of being considered time-consuming, skin testing followed by DPT continue to be the most accurate strategy to investigate these patients. These allergological tests should always be performed in hospital setting, by experienced medical staff. Even though the immediate reactions are considerably more common, delayed reactions should be kept in mind, and the patients must be advised that it can occur and must be registered. Furthermore, as reported in our study, skin testing can be responsible for systemic reactions, which should be promptly recognized and treated. We had 9.3% (4 patients) with systemic reactions in the positive tested patients (one with anaphylaxis during IDT), which represented 1.7% of systemic reactions in all tested patients. Comparable results were published by Co Minh *et al.* in a study performed over 8 years, where 14.7% (147 patients) had positive skin tests results and 8.8% of those (13 patients) showed a systemic reaction during skin tests, which represented 1.3% of all tested patients; among

those with systemic reactions, 5 reacted with SPT and 10 had clinical history of anaphylaxis (16).

In our study, considering the four patients who had systemic reactions during skin tests, in all the culprit drug was AX, in three associated with CLV. Two developed cutaneous symptoms during SPT, being the clinical history urticaria and angioedema, and the other two had reported anaphylactic reactions with drug intake and reacted with IDT (table 3). One was a 3-year-old child who developed an immediate anaphylactic reaction after IDT with 10-fold diluted solution of AX; the other was a woman who developed facial rash after 1 hour, along with positive delayed reading of IDT with AX.

There were two patients with negative allergological investigation tests, who had tolerated DPT with AX alone but had reacted with AX-CLV. Considering the period of time of the present study, CLV extract (*DAP® Clavulanic, Diater, Madrid, Spain*) was not still available in our country. However, DPT remains the gold standard for confirming or ruling out the hypersensitivity diagnosis. In some cases of nonimmediate reactors, the DPT must be prolonged, and a 5-day or even a 7-day challenge with the culprit BL may yield more positive reactions than the accepted 1-day or 2-day challenge (17,18). Therefore, the interpretation of skin testing should always be made with caution.

We found that in 18% of patients DPT has been paramount for the diagnosis validation, since this couldn't have been achieved without it. Similar results were found by Bousquet *et al.* (19), that included 1218 patients in whom BL allergy was confirmed in 21.1% by skin tests (178; 69.3%) or by DPT (79; 30.7%). In this study, 17.4% of the patients with negative skin tests to major and minor penicillin determinants were positive for a BL antibiotic. According to these authors, if all skin tests are negative, skin tests with other determinants and provocation tests under strict surveillance are mandatory.

Studies performed in a large series of patients with cutaneous symptoms showed that 19% were diagnosed as being allergic to BL (6,10). We found similar results, over a 3-year period time, since 18% of our patients were allergic to BL. In a previous Portuguese study, also performed in a drug allergy center, Silva R *et al.* (20) studied 67 patients with suspected BL hypersensitivity reactions and found a higher percentage (27%) of confirmed cases. Campina S *et al.* (21) studied 110 patients with suspected BL hypersensitivity, also referred to an allergy specialized center, and found an even higher percentage (44%) of confirmed cases. This study includes an adult population, and this may justify the higher percentage of confirmed diagnosis. In a large paediatric French study, over 20-year (22), 1431 children were studied with suspected BL hypersensitivity, but after work-up only 15.9% were diagnosed allergic to BL. In another large paediatric study, performed in Spain (8), 783 children were studied with suspected BL hypersensitivity, and after work-up an even lesser percentage (7.9%) were diagnosed allergic to BL.

The sensitivity of skin tests, previously around 95%, has been decreasing in publications from last decade (12,23). According to a study performed by Torres *et al.* (23), which included 290 patients, skin tests were positive in only 70.3% of them. The lower sensitivity of skin test explains why some cases of BL allergy, will fail to be diagnosed if DPT is not performed. In our study, five patients with negative skin test results reacted with culprit drug, resulting in 85.7% of sensitivity for the skin tests. We stress out that two women with negative skin tests had anaphylaxis during DPT with AX (immediately after 100 mg and 250 mg, respectively).

In skin test-negative patients, five of 189 reacted to the culprit drug, which represents a NPV of 97.4%. Comparing with the study performed by Goldberg and Confino-Cohen (24) they found that four out of 94 skin test-negative patients reacted to penicillin V or amoxicillin challenge, achieving a NPV of 95.7%. In skin test-positive patients, as defending by other authors (1,12,15,25), the diagnosis was confirmed, and DPT was not performed. The authors feel that on the basis of the current literature and standard of care, to demonstrate the positive predictive value of these skin tests is unnecessary and potentially dangerous.

Regarding *in vitro* tests, commonly used as the first approach in these patients, the specificity of BL-specific IgE antibodies ranges from 83.3 to 100% and the sensitivity from 12.5 to 45%, depending on the clinical manifestations (15). In our study, we found a sensitivity of 18.6% and a NPV of 82.4%.

As a result of our allergological investigation, we demonstrated that the majority of patients who were labelled as "allergic" can safely be treated with BL, and those whose BL hypersensitivity has been confirmed, a second generation cephalosporin can be used. Accurate diagnosis has an enormous economic and biological impact. These patients have no longer need to be prescribed with more expensive or less effective antibiotics. Studies have been published showing clear cost-implications associated with BL allergy, namely prolonged intravenous antibiotics instead of oral formulations, increased length of stay and total cost of hospital admission and a worrying growing of bacterial resistance resulting from the use of non-penicillin-based alternatives. Moreover, their potential toxicities and reduced efficacy must be considered (26). Owing to the possibility of cross-reactivity, patients with confirmed BL hypersensitivity were advised to avoid first generation cephalosporins (15,27,28).

Conclusions

Hypersensitivity to BL can be responsible for distinct reactions, ranging from mild symptoms to systemic and severe reactions. Clinical history might frequently lead to misdiagnosis, being the investigation negative and suspicion of hypersensitivity ruled out in most of the cases. The confirmed cases are mainly due to IgE-mediated reactions. However, one fourth of confirmed cases seem to have non-IgE mediated reaction.

We evaluated a large number of patients, under the same protocol. All patients were properly investigated with standardized *in vitro* and *in vivo* tests. Despite time-consuming, skin testing seems to be the more accurate approach to confirm BL hypersensitivity. Our results show that we should be aware for the possibility of systemic reactions either during skin tests or DPT. Most patients have positive results to several BL, within the same group, but others can have selective reactions. In our country, the oral formulation of penicillin is not available. For that reason, we did not perform DPT with this drug. Considering this, it is difficult to convince patients to undergo DPT which requires parenteral administration. This can be seen as a limitation, because due to this circumstance we might have missed selective hypersensitivity reactions.

Considering all the implications of a proper diagnostic approach, including systemic reactions during skin tests and DPT, all these patients should be evaluated in specialized centers. Accurate diagnosis of hypersensitivity to BL is crucial not only to improve patient safety, when they need to be treated with antibiotics, but also to avoid increased rates of bacterial resistance and to reduce medical costs. For these reasons, the study of all suspected cases of BL hypersensitivity is highly important and cost-effective.

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