BMJ Paediatrics Open

Mild to moderate hypersensitivity reactions to beta-lactams in children

Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2019-000435
Article Type:	Original article
Date Submitted by the Author:	08-Jan-2019
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Keywords:	Allergy, Paediatric Practice

TITLE PAGE

Title: Mild to moderate hypersensitivity reactions to beta-lactams in children.

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Word count for the text: 2364
Word count for the abstract:236
Number of Tables: 3

The authors declare that they have no conflicts of interest related to the manuscript contents.

All authors declare that there were no sources of funding for the research reported in the manuscript.

ABSTRACT

Objective

Beta-lactam (BL) antibiotics are the most reported drugs in hypersensitivity reactions in children. More than 90% of these children tolerate the suspected drug after diagnostic work up.

Skin tests (ST) show low sensitivity. Our aim was to assess the performance of DPT without previous ST in mild and moderate delayed reactions and to propose a new DPT protocol.

Design of the study

Charts from 213 children under 15 years of age referred for suspected BL-allergy from 2011 to 1013, were reviewed.

Prick, intradermal and patch tests were performed with major determinant penicilloyl-polylysine, minor determinant mixture, AMX, cefuroxime, penicillin G and AMX-clavulamate.

Children with negative skin tests underwent DPT. After an initial full dose of antibiotic, DPT was carried on for 3 days at home in patients reacting within the

first 3 days of treatment. If the reaction took place from day 4 on of treatment, patients took the antibiotic for 5 days.

Results

We included 108 girls and 105 boys. Mean age at the time of reaction was 3.66 ± 3.06 years. 195 patients (91,5%) reacted to one BL. 154 reactions (67.2%) were non-immediate. Mild to moderate skin manifestations were most frequently reported. AMX-clavulanate was the most frequently involved (63.4,4%). DPT confirmed the diagnosis of drug hypersensitivity in 17 (7.3%) cases. These 17 patients had negative ST.

Conclusion

In mild and moderate cases of BL hypersensitivity, diagnosis can be performed by DPT without previous ST

Key words: beta-lactam allergy, delayed hypersensitivity, amoxicillin, drug provocation test

MAIN TEXT

TITLE: Mild to moderate hypersensitivity reactions to beta-lactams in children

INTRODUCTION

Although around 10% of parents report drug hypersensitivity in their children (1, 2), after a careful evaluation, more than 90% of these children are able to tolerate the suspected drug (1, 3-5).

In the pediatric population, antibiotics, mainly beta-lactam (BL) and specially amoxicillin (AMX) (6, 7) are the most commonly involved drugs, followed by nonsteroidal anti-inflammatory drugs (1, 3). Unlike adults, children usually experience mild nonimmediate skin reactions, as maculopapular exanthema and nonimmediate urticarial rash (8). Most of these benign skin reactions are not truly allergic but related to the underlying infectious disease or due to the interaction between the antibiotic and the infectious agent (5, 9).

An accurate diagnosis of antibiotic hypersensitivity not based only on clinical history is mandatory since antibiotic allergy labels imply the use alternative antibiotics which may be more expensive, less effective and may contribute to an increase in antibiotic-resistant bacteria (10).

According to the European Network for Drug Allergy (ENDA) de diagnosis of immediate IgE-mediated reactions to beta-lactams should be based on clinical history, skin tests (ST) (skin prick test [SPT] and intradermal tests [IDT]), in vitro laboratory tests as serum specific IgE determination and drug provocation tests (DPT) (11).

For the diagnosis of non-immediate reactions there are not standardized tests available. Although the pathogenic mechanism is unknown, it is believed to be T-cell mediated (12). Late reading IDT or patch tests show very low sensitivity (4-6,8) therefore in mild skin reactions, which are the majority, performing DPT without previous skin test work up has been proposed (13). Even though considered the gold standard test for the diagnosis of drug allergy, DPT also lacks standardization and there are concerns whether the number of days of drug administration may influence its outcome and the diagnosis of delayed hypersensitivity reactions.

We have retrospectively reviewed 213 pediatric patients evaluated for beta-lactam allergy in the Complejo Hospitalario Universitario A Coruña (CHUAC) between the years 2011 to 2013. Our aim is to assess the performance of DPT, with no previous skin test evaluation, in cases of mild and moderate delayed skin reactions regarding safety and diagnosis effectiveness as well as to propose a new DPT.

METHODS

Charts from 213 children under 15 years of age referred to the Pediatric Allergy Unit of CHUAC for suspected BL allergy from 2011 to 1013, were reviewed.

Patients with severe nonimmediate reactions (drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, generalized exanthematic pustulosis and Steven-Johnson syndrome) were excluded from the study.

The study was approved by the Hospital's Ethics Committee.

Clinical data

Reactions were classified as immediate if they occurred within 1 hour after antibiotic intake and non-immediate if they occurred more than 1 hour after antibiotic intake.

Both types of reactions were graded as mild (no treatment required), moderate (patients responded readily to appropriate treatment and no hospitalization was needed) or severe (reaction required treatment in hospital, was life threatening o resulted in death).

Patients were asked to sign a written informed consent before their children were tested.

Patient involvement

Patients were not directly involved in the design of this study.

Skin tests

For immediate reactions SPT were performed with the major determinant penicilloyl-polylysine (PPL) (Diater, Madrid), minor determinant mixture (MDM) (Diater, Madrid), AMX (20mg/ml), cefuroxime (2,5mg/dl), penicillin G

(10.000UI/ml) and AMX-clavulamate (20mg/ml). Children older than 12 years also underwent ID testing at the same concentrations.

Readings were made 15 minutes after. ST were considered positive if wheal diameter was ≥ 3 mm larger than the negative control (normal saline solution), with a flare. As positive control we used histamine hydrochloride (ALK, Madrid).

Children reporting delayed reactions underwent IDT and patch tests at the concentrations above mentioned. Readings were made at 48, 72 and 96 hours.

Serum specific IgE

For immediate reactions within the previous year to clinical evaluation, serum specific IgE to the suspected drug, if available, was determined by ImmunoCAP (Uppsala, Sweden). Specific IgE levels over 0,35 kU/L was considered as positive.

Drug provocation tests

Children with mild and moderate immediate reactions whose skin tests were negative, underwent open DPT with a full dose of the drug, calculated by weight, with one hour of observation at the Hospital setting.

In cases of severe immediate reactions, doses were fractionated: 1/10, 1/2 and total dose, administered every 30 minutes, with one hour of observation.

DPT was not performed with the suspected antibiotic in case of positive ST.

Patients reporting non-immediate reactions received a full dose of the antibiotic calculated by weight and they were observed during one hour. Then daily

therapeutic doses of the antibiotic were prescribed at home. If the reported reaction took place within the first 3 days of treatment, DPT was carried on for 3 days. If the reaction took place from day 4 on of treatment, patient was asked to take the antibiotic for 5 days.

In case of a home reaction, parents were instructed to stop antibiotic and to contact us by phone as well as to visit their primary care physician.

If the patient or the family could not remember the interval between antibiotic intake and reaction, ST were performed as described above and DPT was carried on during 5 days, in case of negative ST.

DPT was considered positive if objective skin, respiratory and/or cardiovascular symptoms were observed.

In case of positive DPT with AMX, DPT with cefuroxime was performed in order to provide antimicrobial therapeutic alternatives given the high rate of tolerance to cephalosporins among patients with delayed hypersensitivity to AMX (14, 15).

Statistical analysis

A descriptive analysis was performed of all the variables under study, expressing quantitative variables as mean ± standard deviation, median and range, and qualitative variables as absolute frequencies and percentages.

The association between qualitative variables was analyzed with the Chi-square test or Fisher's exact test. Means were compared with the Mann-Whitney test or Kruskal-Wallis test based on the number of groups being compared after verifying the normality assumption by means of the Kolmogorov-Smirnov test. The

statistical analysis was performed with the SPSS 19.0 software. We defined statistical significance as a p-value of less than 0.05.

RESULTS

From January 2011 to December 2013, charts from 213 children referred with suspected hypersensitivity reactions to beta-lactam antibiotics were reviewed. There were 108 girls (50.7%) and 105 boys (49.3%). Mean age at the time of the reaction was 3.66 ± 3.06 years. Mean age at the time of the allergic workup was 6.26 ±3.9 years. Demographic characteristics are summarized in Table I.

Most children (195 patients, 91.5%) reacted to one BL. Seventeen children (8%) reacted to two different BL antibiotics and one child reacted to three different BL antibiotics. A total of 232 suspected hypersensitivity reactions to BL antibiotics were reported. One hundred and fifty-four reactions (67.2%) were non-immediate, 24 (10.5%) were reported as immediate and 51 patients (22%) could not remember the interval between antibiotic intake and reaction. AMX-clavulanate was the most frequently implicated antibiotic (63.4%), followed by AMX alone (19.4%), cefuroxime (6.9%) and cefaclor (4.7%). Mild to moderate skin manifestations were most frequently reported: maculopapular exanthema in 52.2% of cases, urticaria (UA) in 33.6%, angioedema in 13.4% and 6.5% of patients developed serum sickness-like reaction. No patient reported history of anaphylaxis. Delayed reactions took place after a mean of 3.5 ± 3.2 days of antibiotic intake.

These and other clinical characteristics are summarized in Table II.

Regarding ST, 32 children older than 12 years with non-immediate skin reactions underwent IDT. All IDT were negative. Two of the 194 children who underwent patch testing, yielded positive results. The involved antibiotic was amoxicillin in both cases. These two patients were diagnosed as allergic to amoxicillin and they tolerated cefuroxime on DPT. One patient reporting an immediate reactions, presented positive SPT with penicillin G and was diagnosed of beta-lactam allergy.

Serum specific IgE to the suspected drug was negative in patients referring immediate reactions.

DPT confirmed the diagnosis of drug hypersensitivity in 17 (7.3%) cases. All patients had delayed skin reactions. While DPT at home, 16 patients developed mild skin rashes that could be treated with antihistamines and one child developed generalized urticaria and edema of knees, wrists and ankles suggestive of serum sickness, and needed treatment with oral steroids as well.

All patients reporting immediate reactions with negative ST tolerated the suspected antibiotic on DPT. ST and DPT results are summarized in Table III.

Two patients (11,8%) with confirmed BL allergy, reported family history of drug allergy. There were non significant differences regarding family history of drug allergy between BL allergic and non allergic children (p 0.356).

Eight patients (42,1%) of BL allergic patients presented personal history of atopy. There were non significant differences regarding personal history of atopy between BL allergic and non allergic children in our population (p 0.189).

For nonimmediate hypersensitivity reactions, skin tests show very low sensitivity and are time consuming. Since 2014, we do not perform skin tests for the work up of delayed adverse reactions in our daily practice: after a carefully clinical history, patients with mild and moderate nonimmediate reactions to antibiotics undergo DPT as described previously.

DISCUSSION

Delayed skin maculopapular or urticarial rashes are frequently reported in children receiving beta-lactam antibiotics. From that moment on, the majority of those children are labeled as “allergic to beta-lactams” and they are prescribed alternative antibiotics that may be less effective and/or more expensive (10). Establishing an accurate diagnosis is associated not only with a more rationale use of antibiotics but also with lower rates of health care utilization (16).

Until recently, the diagnosis of non-immediate BL allergy was assessed by ST as IDT and patch tests, followed by DPT in those patients with negative ST results. This diagnostic work up has been reconsidered since ST are not efficient for the diagnosis of mild and moderate non-immediate reactions to beta-lactams in children, they are time-consuming and IDT are painful and difficult to perform in small children.

DPT confirmed BL hypersensitivity in 7,3% of included children our population. These 17 patients, who presented delayed hypersensitivity reactions, showed negative ST. We assumed the diagnosis of BL allergy in those patients with positive ST. Recently, Caubet and cols (17) reported that 7 out of 11 patients with positive ID tests tolerated the suspected drug on DPT, yielding a positive

predictive value for ST of 36% in that population. Vyles and cols (18) also reported that 3 children with positive ST to beta-lactams, tolerated the antibiotic on DPT. Given these observations we wonder if the 3 patients with positive ST in our study (2 with delayed reactions and 1 reporting immediate reaction) would had tolerated the suspected antibiotic on DPT.

Based on our findings, since 2014 we do not performed ST in children referred to us with nonimmediate mild to moderate skin reactions related to antibiotics. Diagnostic procedure has become simpler, less time consuming and it is safe. Up to date we have not had severe reactions during DPT at home. Considering our results and based in our experience, we conclude that non-severe antibiotic hypersensitivity may be initially studied by DPT-based protocols, as previously suggested (13,15,17,19, 20).

Even though DPT is considered the gold standard for the diagnosis of non-severe, non-immediate skin reactions, it is not standardized in children.

The duration of the DPT and the dose administered vary from one study to another. Although according to the members of the Task Force panel (12), a full single therapeutic dose should be enough to diagnose delayed hypersensitivity reactions, there are concerns whether the number of days of drug administration may influence the outcome of DTP and therefore the diagnosis. There is the possibility that short DPT protocols would not identify all allergic children with delayed skin reaction. Mill et al (15) studied 818 children with suspected AMX allergy. They performed a graded DPT with an only dose of antibiotic and found that 6% of patients reacted to it: 2% reacted within the hour after the last dose administered and 4% developed late reactions. Among those patients tolerating

AMX on DPT, 10.9% requiring subsequent full treatment with AMX developed delayed skin reactions identical to the initial reactions.

Tonson la Tour et al (21) reported high negative predictive value (96.7%) of a 2-day DPT but still, 4% of children with negative DPT reacted when retreated at home with the suspected antibiotic.

Mori et al (6) evaluated 200 children with suspected drug allergy. After ST, a 5-day DPT was performed. First dose was administered gradually, and if there were no adverse reactions, patients received daily therapeutic doses at home for 5 days. From the 17 patients (9.6%) who reacted on DPT, 14 did it on day 5. As they point out, shorter DPT would not identify 7.3% of late reactors leading to miss diagnosis.

To minimize adverse reactions as diarrhea or vomiting as well as the impact on bacterial microbiota and with the aim to diagnose the majority of true hypersensitivity reactions, we propose a different DPT protocol based on the timing of the initial reaction: for children reacting during the first 3 days of treatment, DPT lasts 3 days. In cases of later reactors (from day 3 on), DPT lasts 5 days. Based on this protocol, we found a similar prevalence of BL allergy to what has been previously reported by other authors (3-5).

Regarding risk factors for beta-lactam allergy in children Faitelson et al (22) recently found significant association between family history of drug allergy and Mill et al (16) reported the same observation. Among patients diagnosed of BL allergy by DPT included in the present study, 11,8% (2 patients) referred family history of drug allergy. We could not confirm the suggested association between family history of drug allergy and BL allergy in children.

On the other hand, although personal history of asthma and food allergy have been reported as significant risk factors for the development of AMX allergy (22) we found non-significant differences regarding personal history of atopy between BL allergic and non-allergic patients in our population.

In summary, skin tests are not useful for the diagnosis of nonimmediate hypersensitivity reactions to beta-lactams in children. In cases of mild and moderate skin manifestations, DPT without previous ST is safe, effective and less time consuming. There would be interesting to unify the different DPT protocols with the aim to achieve an accurate diagnosis minimizing the potential adverse drug reactions.

ACKNOWLEDGEMENTS

We thank our nurses, Ofelia Alba Lago, Maria Jesús Fernández Hermida and Isabel Cabana Blanco for their dedication and excellence performing skin tests and drug provocation tests.

1. What is already known on this topic:

- For diagnosis of non-immediate reactions there aren't standardized tests available. - Skin tests show low sensitivity. It has been proposed to perform only DPT for the diagnosis of non-severe hypersensitivity reactions.

- There are concerns whether the number of days of drug administration during DPT may influence its outcome.

2. What does this study add?

- We conclude that performing DPT without previous skin tests in pediatric patients with non-severe delayed drug reactions is safe and effective.

- We propose a new 3-5 day drug provocation test protocol, based on the timing of the initial reaction.

- It supports the recommendation of drug provocation test without previous skin tests for the diagnosis of non-severe beta-lactam allergy in children.

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vii. TABLES

Table I. Demographic characteristics of children with suspected hypersensitivity reactions to beta-lactam antibiotics

	Number of reactions N=232	Number of patients N = 213
Age at reaction		
Mean ± SD (years-old)	6.66 ± 3.06	
Median (range)	3 (1-14)	
Type of reaction		
Immediate	24 (10.5%)	
Delayed	154 (67.2%)	
Not determined	51 (22%)	
Age		
Mean ± SD (years-old)		6.26 ± 3.87
Median (range)		5 (1-15)
Sex		
Male, n (%)		105 (49.3%)
Female, n (%)		108 (50.7%)
Personal history of atopy		63 (29.7%)
Rhinitis, n (%)		33 (15.5%)
Asthma, n (%)		35 (16.4%)
Atopic dermatitis, n (%)		18 (8.5%)
Food allergy, n (%)		2 (0.9%)
Family history of drug allergy		13 (6.1%)
Parents		6 (2.8%)
Grandparents		6 (2.8%)
Brothers		1 (0.5%)

Symptoms	
Urticaria (UA)	78 (33.6%)
Angioedema (AE)	31 (13.4%)
Exanthema	121 (52.2%)
Serum sickness like	15 (6.5%)
Antibiotics	
Penicilin V	3 (1.3%)
Amoxicilin	45 (19.4%)
Amoxicilin/clavulanate	147 (63.4%)
Cefuroxime	16 (6.9%)
Cefaclor	11 (4.7%)
Cefixime	6 (2.6%)
Cefotaxime	1 (0.4%)

Table II. Clinical characteristics of children with suspected hypersensitivity reactions to beta-lactam antibiotics

Table III. Outcome of skin tests and drug provocation tests for the diagnosis of beta-lactam hypersensitivity

Test	Positive N (%)	Negative N (%)	Type of reported reaction
SPT (n=)	1 (0.4%)	225 (97%)	Immediate
IDT (n=)	0 (0%)	32 (13.8%)	Delayed
Patch test (n=)	2 (0.9%)	192 (82.8%)	Delayed
DPT (n=)	17 (7.3%)	93 (83.2%)	Delayed

SPT, skin prick test; IDT, intradermal tests; sIgE, serum specific IgE; DPT, drug provocation tests.

BMJ Paediatrics Open

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Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2019-000435.R1
Article Type:	Original article
Date Submitted by the Author:	28-Jan-2019
Complete List of Authors:	Vila, Leticia; Complejo Hospitalario Universitario A Coruña, Pediatrics Garcia, Vanesa; CHUAC, Allergy Martinez Azcona, Oihana; Complexo Hospitalario Universitario A Coruna, Pediatrics Pineiro, Loreley; Complexo Hospitalario Universitario A Coruna, Pediatrics Meijide, Angela; Complexo Hospitalario Universitario A Coruna, Allergy Balboa, Vanesa; Complexo Hospitalario Universitario A Coruna, Epidemiology and Biostatistics
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Word count for the text: 2463

Word count for the abstract: 239

Number of Tables: 3

Number of Figures:1

The authors declare that they have no conflicts of interest related to the manuscript contents.

All authors declare that there were no sources of funding for the research reported in the manuscript.

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Design of the study

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We included 108 girls and 105 boys. Mean age at the time of reaction was 3.66 ± 3.06 years. 195 patients (91,5%) reacted to one BL. 154 reactions (67.2%) were non-immediate. Mild to moderate skin manifestations were most frequently reported. AMX-clavulanate was the most frequently involved (63.4,4%). DPT confirmed the diagnosis of drug hypersensitivity in 17 (7.3%) cases. These 17 patients had negative ST.

Conclusion

In mild and moderate cases of BL hypersensitivity, diagnosis can be performed by DPT without previous ST

Key words: beta-lactam allergy, delayed hypersensitivity, amoxicillin, drug provocation test.

MAIN TEXT

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In the pediatric population, antibiotics, mainly beta-lactam (BL) and specially amoxicillin (AMX) (6, 7) are the most commonly involved drugs, followed by nonsteroidal anti-inflammatory drugs (1, 3). Unlike adults, children usually experience mild nonimmediate skin reactions, as maculopapular exanthema and nonimmediate urticarial rash (8). Most of these benign skin reactions are not truly allergic but related to the underlying infectious disease or due to the interaction between the antibiotic and the infectious agent (5, 9).

An accurate diagnosis of antibiotic hypersensitivity not based only on clinical history is mandatory since antibiotic allergy labels imply the use alternative antibiotics which may be more expensive, less effective and may contribute to an increase in antibiotic-resistant bacteria (10).

According to the European Network for Drug Allergy (ENDA) de diagnosis of immediate IgE-mediated reactions to beta-lactams should be based on clinical history, skin tests (ST) (skin prick test [SPT] and intradermal tests [IDT]), in vitro

laboratory tests as serum specific IgE determination and drug provocation tests (DPT) (11).

For the diagnosis of non-immediate reactions there are not standardized tests available. Although the pathogenic mechanism is unknown, it is believed to be T-cell mediated (12). Late reading IDT or patch tests show very low sensitivity (4-6,8) therefore in mild skin reactions, which are the majority, performing DPT without previous skin test work up has been proposed (13). Even though considered the gold standard test for the diagnosis of drug allergy, DPT also lacks standardization and there are concerns whether the number of days of drug administration may influence its outcome and the diagnosis of delayed hypersensitivity reactions.

We have retrospectively reviewed 213 pediatric patients evaluated for beta-lactam allergy in the Complejo Hospitalario Universitario A Coruña (CHUAC) between the years 2011 to 2013. Our aim is to assess the performance of DPT, with no previous skin test evaluation, in cases of mild and moderate delayed skin reactions regarding safety and diagnosis effectiveness as well as to propose a new DPT.

METHODS

Charts from 213 children under 15 years of age referred to the Pediatric Allergy Unit of CHUAC for suspected BL allergy from 2011 to 1013, were reviewed. Patients with severe nonimmediate reactions (drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, generalized exanthematic pustulosis and Steven-Johnson syndrome) were excluded from the study.

The study was approved by the Hospital's Ethics Committee.

Clinical data

Reactions were classified as immediate if they occurred within 1 hour after antibiotic intake and non-immediate if they occurred more than 1 hour after antibiotic intake.

Both types of reactions were graded as mild (no treatment required), moderate (patients responded readily to appropriate treatment and no hospitalization was needed) or severe (reaction required treatment in hospital, was life threatening o resulted in death).

Patients were asked to sign a written informed consent before their children were tested.

Patient involvement

Patients were not directly involved in the design of this study.

Skin tests

For immediate reactions SPT were performed with the major determinant penicilloyl-polylysine (PPL) (Diater, Madrid), minor determinant mixture (MDM) (Diater, Madrid) and the suspected drug at the following concentrations: AMX (20mg/ml), cefuroxime (2,5mg/dl), penicillin G (10.000UI/ml) and AMX-clavulamate (20mg/ml). Children older than 12 years also underwent ID testing in case of negative SPT.

Readings were made 15 minutes after. ST were considered positive if wheal diameter was ≥ 3 mm larger than the negative control (normal saline solution), with a flare. As positive control we used histamine hydrochloride (ALK, Madrid). Children reporting delayed reactions underwent SPT and if negative, IDT (if older than 12 years of age) and patch tests were performed at the concentrations above mentioned. Readings were made at 48, 72 and 96 hours.

Serum specific IgE

For immediate reactions within the previous year to clinical evaluation, serum specific IgE to the suspected drug, if available, was determined by ImmunoCAP (Uppsala, Sweden). Specific IgE levels over 0,35 kU/L was considered as positive.

Drug provocation tests

Children with mild and moderate immediate reactions whose skin tests were negative, underwent open DPT with a full dose of the drug, calculated by weight, with one hour of observation at the Hospital setting.

In cases of severe immediate reactions, doses were fractionated: 1/10, 1/2 and total dose, administered every 30 minutes, with one hour of observation.

Patients reporting non-immediate reactions received a full dose of the antibiotic calculated by weight and they were observed during one hour. Then daily therapeutic doses of the antibiotic were prescribed at home. If the reported reaction took place within the first 3 days of treatment, DPT was carried on for 3

days. If the reaction took place from day 4 on of treatment, patient was asked to take the antibiotic for 5 days.

In case of a home reaction, parents were instructed to stop antibiotic and to contact us by phone as well as to visit their primary care physician.

If the patient or the family could not remember the interval between antibiotic intake and reaction, ST were performed as described above and if negative, DPT was carried on during 5 days, in case of negative ST.

DPT was considered positive if objective skin, respiratory and/or cardiovascular symptoms were observed.

In case of positive DPT with AMX, DPT with cefuroxime was performed in order to provide antimicrobial therapeutic alternatives given the high rate of tolerance to cephalosporins among patients with delayed hypersensitivity to AMX (14, 15).

Statistical analysis

A descriptive analysis was performed of all the variables under study, expressing quantitative variables as mean ± standard deviation, median and range, and qualitative variables as absolute frequencies and percentages.

The association between qualitative variables was analyzed with the Chi-square test or Fisher's exact test. Means were compared with the Mann-Whitney test or Kruskal-Wallis test based on the number of groups being compared after verifying the normality assumption by means of the Kolmogorov-Smirnov test. The statistical analysis was performed with the SPSS 19.0 software. We defined statistical significance as a p-value of less than 0.05.

RESULTS

Clinical results

From January 2011 to December 2013, charts from 213 children referred with suspected hypersensitivity reactions to beta-lactam antibiotics were reviewed. There were 108 girls (50.7%) and 105 boys (49.3%). Mean age at the time of the reaction was 3.66 ± 3.06 years. Mean age at the time of the allergic workup was 6.26 ±3.9 years. Demographic characteristics are summarized in Table I.

Most children (195 patients, 91.5%) reacted to one BL. Seventeen children (8%) reacted to two different BL antibiotics and one child reacted to three different BL antibiotics. A total of 229 suspected hypersensitivity reactions to BL antibiotics were reported. One hundred and fifty-four reactions (67.2%) were non-immediate, 24 (10.5%) were reported as immediate and 51 patients (22%) could not remember the interval between antibiotic intake and reaction. AMX-clavulanate was the most frequently implicated antibiotic (63.4%), followed by AMX alone (19.4%), cefuroxime (6.9%) and cefaclor (4.7%). Mild to moderate skin manifestations were most frequently reported: maculopapular exanthema in 52.2% of cases, urticaria (UA) in 33.6%, angioedema in 13.4% and 6.5% of patients developed serum sickness-like reaction. No patient reported history of anaphylaxis. Delayed reactions took place after a mean of 3.5 ± 3.2 days of antibiotic intake.

These and other clinical characteristics are summarized in Table II.

Testing results

Regarding ST, 32 children older than 12 years with non-immediate skin reactions underwent IDT. All IDT were negative. Only 2 of 205 children who underwent patch testing, yielded positive results. The involved antibiotic was amoxicillin in both cases and they reported a non immediate reaction. These two patients were diagnosed as allergic to amoxicillin and they tolerated cefuroxime on DPT. One patient reporting an immediate reaction, presented positive SPT with penicillin G and was diagnosed of beta-lactam allergy. Serum specific IgE to the suspected drug was negative in patients referring immediate reactions. Diagnosis algorithm and results are showed with a flow chart in Figure 1.

DPT confirmed the diagnosis of drug hypersensitivity in 17 (7.5%) cases. All patients had delayed skin reactions. While DPT at home, 16 patients developed mild skin rashes that could be treated with antihistamines and one child developed generalized urticaria and edema of knees, wrists and ankles suggestive of serum sickness, and needed treatment with oral steroids as well.

All patients reporting immediate reactions with negative ST tolerated the suspected antibiotic on DPT. ST and DPT results are summarized in Table III.

Two patients (11,8%) with confirmed BL allergy, reported family history of drug allergy. There were non significant differences regarding family history of drug allergy between BL allergic and non allergic children (p 0.356).

Eight patients (42,1%) of BL allergic patients presented personal history of atopy. There were non significant differences regarding personal history of atopy between BL allergic and non allergic children in our population (p 0.189).

For nonimmediate hypersensitivity reactions, skin tests show very low sensitivity and are time consuming. Since 2014, we do not perform skin tests for the work up of delayed adverse reactions in our daily practice: after a carefully clinical history, patients with mild and moderate nonimmediate reactions to antibiotics undergo DPT as described previously.

DISCUSSION

Delayed skin maculopapular or urticarial rashes are frequently reported in children receiving beta-lactam antibiotics. From that moment on, the majority of those children are labeled as “allergic to beta-lactams” and they are prescribed alternative antibiotics that may be less effective and/or more expensive (10). Establishing an accurate diagnosis is associated not only with a more rationale use of antibiotics but also with lower rates of health care utilization (16).

Until recently, the diagnosis of non-immediate BL allergy was assessed by ST as IDT and patch tests, followed by DPT in those patients with negative ST results. This diagnostic work up has been reconsidered since ST are not efficient for the diagnosis of mild and moderate non-immediate reactions to beta-lactams in children, they are time-consuming and IDT are painful and difficult to perform in small children. The reasons for the low sensitivity of ST are not well understood. It could be due to the use of a drug structure or conjugate that is not well recognized by the immune system since BLs are haptens that need to bind to proteins covalently to elicit an immune response (17).

DPT confirmed BL hypersensitivity in 7,5% of cases in our population. These 17 patients, who presented delayed hypersensitivity reactions, showed negative ST. We assumed the diagnosis of BL allergy in those patients with positive ST. Recently, Caubet and cols (18) reported that 7 out of 11 patients with positive ID tests tolerated the suspected drug on DPT, yielding a positive predictive value for ST of 36% in that population. Vyles and cols (19) also reported that 3 children with positive ST to beta-lactams, tolerated the antibiotic on DPT. Given these observations we wonder if the 3 patients with positive ST in our study (2 with delayed reactions and 1 reporting immediate reaction) would had tolerated the suspected antibiotic on DPT.

Based on our findings, since 2014 we do not performed ST in children referred to us with nonimmediate mild to moderate skin reactions related to antibiotics. Diagnostic procedure has become simpler, less time consuming and it is safe. Up to date we have not had severe reactions during DPT at home. Considering our results and based in our experience, we conclude that non-severe antibiotic hypersensitivity may be initially studied by DPT-based protocols, as previously suggested (13,15,18,20,21).

Even though DPT is considered the gold standard for the diagnosis of non-severe, non-immediate skin reactions, it is not standardized in children.

The duration of the DPT and the dose administered vary from one study to another. Although according to the members of the Task Force panel (12), a full single therapeutic dose should be enough to diagnose delayed hypersensitivity reactions, there are concerns whether the number of days of drug administration may influence the outcome of DTP and therefore the diagnosis. There is the

possibility that short DPT protocols would not identify all allergic children with delayed skin reaction. Mill et al (15) studied 818 children with suspected AMX allergy. They performed a graded DPT with an only dose of antibiotic and found that 6% of patients reacted to it: 2% reacted within the hour after the last dose administered and 4% developed late reactions. Among those patients tolerating AMX on DPT, 10.9% requiring subsequent full treatment with AMX developed delayed skin reactions identical to the initial reactions.

Tonson la Tour et al (22) reported high negative predictive value (96.7%) of a 2-day DPT but still, 4% of children with negative DPT reacted when retreated at home with the suspected antibiotic.

Mori et al (6) evaluated 200 children with suspected drug allergy. After ST, a 5-day DPT was performed. First dose was administered gradually, and if there were no adverse reactions, patients received daily therapeutic doses at home for 5 days. From the 17 patients (9.6%) who reacted on DPT, 14 did it on day 5. As they point out, shorter DPT would not identify 7.3% of late reactors leading to miss diagnosis.

To minimize adverse reactions as diarrhea or vomiting as well as the impact on bacterial microbiota and with the aim to diagnose the majority of true hypersensitivity reactions, we propose a different DPT protocol based on the timing of the initial reaction: for children reacting during the first 3 days of treatment, DPT lasts 3 days. In cases of later reactors (from day 3 on), DPT lasts 5 days. Based on this protocol, we found a similar prevalence of BL allergy to what has been previously reported by other authors (3-5).

Regarding risk factors for beta-lactam allergy in children Faitelson et al (23) recently found significant association between family history of drug allergy and Mill et al (16) reported the same observation. Among patients diagnosed of BL allergy by DPT included in the present study, 11,8% (2 patients) referred family history of drug allergy. We could not confirm the suggested association between family history of drug allergy and BL allergy in children.

On the other hand, although personal history of asthma and food allergy have been reported as significant risk factors for the development of AMX allergy (23) we found non-significant differences regarding personal history of atopy between BL allergic and non-allergic patients in our population.

In summary, skin tests are not useful for the diagnosis of nonimmediate hypersensitivity reactions to beta-lactams in children. In cases of mild and moderate skin manifestations, DPT without previous ST is safe, effective and less time consuming. There would be interesting to unify the different DPT protocols with the aim to achieve an accurate diagnosis minimizing the potential adverse drug reactions.

ACKNOWLEDGEMENTS

We thank our nurses, Ofelia Alba Lago, Maria Jesús Fernández Hermida and Isabel Cabana Blanco for their dedication and excellence performing skin tests and drug provocation tests.

1. What is already known on this topic:

- For diagnosis of non-immediate reactions there aren't standardized tests available. - Skin tests show low sensitivity. It has been proposed to perform only DPT for the diagnosis of non-severe hypersensitivity reactions.

- There are concerns whether the number of days of drug administration during DPT may influence its outcome.

2. What does this study add?

- We conclude that performing DPT without previous skin tests in pediatric patients with non-severe delayed drug reactions is safe and effective.

- We propose a new 3-5 day drug provocation test protocol, based on the timing of the initial reaction.

- It supports the recommendation of drug provocation test without previous skin tests for the diagnosis of non-severe beta-lactam allergy in children.

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TABLES

Table I. Demographic characteristics of children with suspected hypersensitivity reactions to beta-lactam antibiotics

	Number of patients N = 213
Age	
Mean ± SD (years-old)	6.26 ± 3.87
Median (range)	5 (1-15)
Sex	
Female, n (%)	108 (50.7%)
Male, n (%)	105 (49.3%)
Personal history of atopy	63 (29.7%)
Rhinitis, n (%)	33 (15.5%)
Asthma, n (%)	35 (16.4%)
Atopic dermatitis, n (%)	18 (8.5%)
Food allergy, n (%)	2 (0.9%)
Family history of drug allergy	13 (6.1%)
Parents	6 (2.8%)
Grandparents	6 (2.8%)
Brothers	1 (0.5%)

Table II. Clinical characteristics of children with suspected hypersensitivity reactions to beta-lactam antibiotics

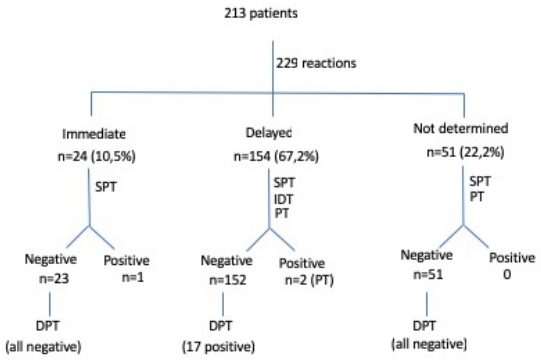
	Number of reactions N=232
Age at reaction	
Mean ± SD (years-old)	6.66 ± 3.06
Median (range)	3 (1-14)
Type of reaction	
Delayed	154 (67.2%)
Not determined	51 (22%)
Immediate	24 (10.5%)
Symptoms	
Exanthema	121 (52.2%)
Urticaria (UA)	78 (33.6%)
Angioedema (AE)	31 (13.4%)
Serum sickness like	15 (6.5%)
Antibiotics	
Amoxicilin/clavulanate	147 (63.4%)
Amoxicilin	45 (19.4%)
Cefuroxime	16 (6.9%)
Cefaclor	11 (4.7%)
Cefixime	6 (2.6%)
Penicilin V	3 (1.3%)
Cefotaxime	1 (0.4%)

Table III. Outcome of skin tests and drug provocation tests performed for the diagnosis of beta-lactam hypersensitivity.

Test	Positive n (%)	Negative n
SPT (n=229)	1 (0,4%)	228
IDT (n=32)	0	32
Patch test (n=205)	2 (0,9%)	203
DPT (n=226)	17(7,5%)	226

SPT, skin prick test; IDT, intradermal tests; DPT, drug provocation tests.

Figure 1. Diagnostic work up for suspected BL hypersensitivity



SPT: Skin prick test; IDT: intradermal test; PT: patch test; DPT: drug provocation test

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BMJ Paediatrics Open

Mild to moderate hypersensitivity reactions to beta-lactams in children, a single centre retrospective review

Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2019-000435.R2
Article Type:	Original article
Date Submitted by the Author:	08-Mar-2019
Complete List of Authors:	Vila, Leticia; Complexo Hospitalario Universitario A Coruna Garcia, Vanesa; Complexo Hospitalario Universitario A Coruna Martinez Azcona, Oihana; Complexo Hospitalario Universitario A Coruna, Pediatrics Pineiro, Loreley; Complexo Hospitalario Universitario A Coruna, Pediatrics Meijide, Angela; Complexo Hospitalario Universitario A Coruna, Allergy Balboa, Vanesa; Complexo Hospitalario Universitario A Coruna, Epidemiology and Biostatistics
Keywords:	Allergy, Paediatric Practice

TITLE PAGE

Title: Mild to moderate hypersensitivity reactions to beta-lactams in children, a single center retrospective review

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Word count for the text: 2463

Word count for the abstract: 239

Number of Tables: 3

Number of Figures:2

The authors declare that they have no conflicts of interest related to the manuscript contents.

All authors declare that there were no sources of funding for the research reported in the manuscript.

ABSTRACT

Objective

Beta-lactam (BL) antibiotics are the most reported drugs in hypersensitivity reactions in children. More than 90% of these children tolerate the suspected drug after diagnostic work up.

Skin tests (ST) show low sensitivity. Our aim was to assess the performance of drug provocation tests (DPT) without previous ST in mild and moderate delayed reactions and to propose a new DPT protocol.

Design of the study

Charts from 213 children under 15 years of age referred for suspected BL-allergy from 2011 to 1013, were reviewed.

Prick, intradermal and patch tests were performed with major determinant penicilloyl-polylysine, minor determinant mixture, AMX, cefuroxime, penicillin G and AMX-clavulamate.

Children with negative skin tests underwent DPT. After an initial full dose of antibiotic, DPT was carried on for 3 days at home in patients reacting within the

first 3 days of treatment. If the reaction took place from day 4 on of treatment, patients took the antibiotic for 5 days.

Results

We included 108 girls and 105 boys. Mean age at the time of reaction was 3.66 ± 3.06 years. 195 patients (91,5%) reacted to one BL. 154 reactions (67.2%) were non-immediate. Mild to moderate skin manifestations were most frequently reported. AMX-clavulanate was the most frequently involved (63.4,4%). DPT confirmed the diagnosis of drug hypersensitivity in 17 (7.3%) cases. These 17 patients had negative ST.

Conclusion

In mild and moderate cases of BL hypersensitivity, diagnosis can be performed by DPT without previous ST

Key words: beta-lactam allergy, delayed hypersensitivity, amoxicillin, drug provocation test.

MAIN TEXT

TITLE: Mild to moderate hypersensitivity reactions to beta-lactams in children, a single centre retrospective review.

INTRODUCTION

Although around 10% of parents report drug hypersensitivity in their children (1, 2), after a careful evaluation, more than 90% of these children are able to tolerate the suspected drug (1, 3-5).

In the pediatric population, antibiotics, mainly beta-lactam (BL) and specially amoxicillin (AMX) (6, 7) are the most commonly involved drugs, followed by nonsteroidal anti-inflammatory drugs (1, 3). Unlike adults, children usually experience mild nonimmediate skin reactions, as maculopapular exanthema and nonimmediate urticarial rash (8). Most of these benign skin reactions are not truly allergic but related to the underlying infectious disease or due to the interaction between the antibiotic and the infectious agent (5, 9).

An accurate diagnosis of antibiotic hypersensitivity not based only on clinical history is mandatory since antibiotic allergy labels imply the use alternative antibiotics which may be more expensive, less effective and may contribute to an increase in antibiotic-resistant bacteria (10).

According to the European Network for Drug Allergy (ENDA) the diagnosis of immediate IgE-mediated reactions to beta-lactams should be based on clinical history, skin tests (ST) (skin prick test [SPT] and intradermal tests [IDT]), in vitro

laboratory tests as serum specific IgE determination and drug provocation tests (DPT) (11).

For the diagnosis of non-immediate reactions there are not standardized tests available. Although the pathogenic mechanism is unknown, it is believed to be T-cell mediated (12). Late reading IDT or patch tests show very low sensitivity (4-6,8) therefore in mild skin reactions, which are the majority, performing DPT without previous skin test work up has been proposed (13). Even though considered the gold standard test for the diagnosis of drug allergy, DPT also lacks standardization and there are concerns whether the number of days of drug administration may influence its outcome and the diagnosis of delayed hypersensitivity reactions.

We have retrospectively reviewed 213 pediatric patients evaluated for beta-lactam allergy in the Complejo Hospitalario Universitario A Coruña (CHUAC) between the years 2011 to 2013. Our aim is to assess the performance of DPT, with no previous skin test evaluation, in cases of mild and moderate delayed skin reactions regarding safety and diagnosis effectiveness as well as to propose a new DPT.

METHODS

Charts from 213 children under 15 years of age referred to the Pediatric Allergy Unit of CHUAC for suspected BL allergy from 2011 to 1013, were reviewed. Patients with severe nonimmediate reactions (drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, generalized exanthematic pustulosis and Steven-Johnson syndrome) were excluded from the study.

The study was approved by the Hospital's Ethics Committee.

Clinical data

Reactions were classified as immediate if they occurred within 1 hour after antibiotic intake and non-immediate if they occurred more than 1 hour after antibiotic intake.

Both types of reactions were graded as mild (no treatment required), moderate (patients responded readily to appropriate treatment and no hospitalization was needed) or severe (reaction required treatment in hospital, was life threatening o resulted in death).

Patients were asked to sign a written informed consent before their children were tested.

Patient involvement

Patients were not directly involved in the design of this study.

Skin tests

For immediate reactions SPT were performed with the major determinant penicilloyl-polylysine (PPL) (Diater, Madrid), minor determinant mixture (MDM) (Diater, Madrid) and the suspected drug at the following concentrations: AMX (20mg/ml), cefuroxime (2,5mg/dl), penicillin G (10.000UI/ml) and AMX-clavulamate (20mg/ml). Children older than 12 years also underwent ID testing in case of negative SPT.

Readings were made 15 minutes after. ST were considered positive if wheal diameter was ≥ 3 mm larger than the negative control (normal saline solution), with a flare. As positive control we used histamine hydrochloride (ALK, Madrid). Children reporting delayed reactions underwent SPT and if negative, IDT (if older than 12 years of age) and patch tests were performed at the concentrations above mentioned. Readings were made at 48, 72 and 96 hours.

Serum specific IgE

For immediate reactions within the previous year to clinical evaluation, serum specific IgE to the suspected drug, if available, was determined by ImmunoCAP (Uppsala, Sweden). Specific IgE levels over 0,35 kU/L was considered as positive.

Drug provocation tests

Children with mild and moderate immediate reactions whose skin tests were negative, underwent open DPT with a full dose of the drug, calculated by weight, as follows: amoxicillin 50mg/kg/dose; amoxicillin-clavulanate: 50mg/kg/dose; cefuroxime: 15mg/kg/dose; cefaclor 8mg/kg/dose. They stayed for one hour of observation at the Hospital setting,

In cases of severe immediate reactions, doses were fractionated: 1/10, 1/2 and total dose, administered every 30 minutes, with one hour of observation.

Patients reporting non-immediate reactions received a full dose of the antibiotic calculated by weight and they were observed during one hour. Then daily

therapeutic doses of the antibiotic were prescribed at home. If the reported reaction took place within the first 3 days of treatment, DPT was carried on for 3 days. If the reaction took place from day 4 on of treatment, patient was asked to take the antibiotic for 5 days.

In case of a home reaction, parents were instructed to stop antibiotic and to contact us by phone as well as to visit their primary care physician.

If the patient or the family could not remember the interval between antibiotic intake and reaction, ST were performed as described above and if negative, DPT was carried on during 5 days, in case of negative ST.

DPT was considered positive if objective skin, respiratory and/or cardiovascular symptoms were observed.

In case of positive DPT with AMX, DPT with cefuroxime was performed in order to provide antimicrobial therapeutic alternatives given the high rate of tolerance to cephalosporins among patients with delayed hypersensitivity to AMX (14, 15).

Diagnosis algorithm is shown in Figure 1.

Statistical analysis

A descriptive analysis was performed of all the variables under study, expressing quantitative variables as mean ± standard deviation, median and range, and qualitative variables as absolute frequencies and percentages.

The association between qualitative variables was analyzed with the Chi-square test or Fisher's exact test. Means were compared with the Mann-Whitney test or

Kruskal-Wallis test based on the number of groups being compared after verifying the normality assumption by means of the Kolmogorov-Smirnov test. The statistical analysis was performed with the SPSS 19.0 software. We defined statistical significance as a p-value of less than 0.05.

RESULTS

Clinical results

From January 2011 to December 2013, charts from 213 children referred with suspected hypersensitivity reactions to beta-lactam antibiotics were reviewed. There were 108 girls (50.7%) and 105 boys (49.3%). Mean age at the time of the reaction was 3.66 ± 3.06 years. Mean age at the time of the allergic workup was 6.26 ±3.9 years. Demographic characteristics are summarized in Table I.

Most children (195 patients, 91.5%) reacted to one BL. Seventeen children (8%) reacted to two different BL antibiotics and one child reacted to three different BL antibiotics. A total of 229 suspected hypersensitivity reactions to BL antibiotics were reported. One hundred and fifty-four reactions (67.2%) were non-immediate, 24 (10.5%) were reported as immediate and 51 patients (22%) could not remember the interval between antibiotic intake and reaction. AMX-clavulanate was the most frequently implicated antibiotic (63.4%), followed by AMX alone (19.4%), cefuroxime (6.9%) and cefaclor (4.7%). Mild to moderate skin manifestations were most frequently reported: maculopapular exanthema in 52.2% of cases, urticaria (UA) in 33.6%, angioedema in 13.4% and 6.5% of patients developed serum sickness-like reaction. No patient reported history of

anaphylaxis. Delayed reactions took place after a mean of 3.5 ± 3.2 days of antibiotic intake.

These and other clinical characteristics are summarized in Table II.

Testing results

Regarding ST, 32 children older than 12 years with non-immediate skin reactions underwent IDT. All IDT were negative. Only 2 of 205 children who underwent patch testing, yielded positive results. The involved antibiotic was amoxicillin in both cases and they reported a non immediate reaction. These two patients were diagnosed as allergic to amoxicillin and they tolerated cefuroxime on DPT. One patient reporting an immediate reaction, presented positive SPT with penicillin G and was diagnosed of beta-lactam allergy. Serum specific IgE to the suspected drug was negative in patients referring immediate reactions. Results are showed with a flow chart in Figure 2.

DPT confirmed the diagnosis of drug hypersensitivity in 17 (7.5%) cases. All patients had delayed skin reactions. While DPT at home, 16 patients developed mild skin rashes that could be treated with antihistamines and one child developed generalized urticaria and edema of knees, wrists and ankles suggestive of serum sickness, and needed treatment with oral steroids as well.

All patients reporting immediate reactions with negative ST tolerated the suspected antibiotic on DPT. ST and DPT results are summarized in Table III.

Two patients (11,8%) with confirmed BL allergy, reported family history of drug allergy. There were non significant differences regarding family history of drug allergy between BL allergic and non allergic children (p 0.356).

Eight patients (42,1%) of BL allergic patients presented personal history of atopy. There were non significant differences regarding personal history of atopy between BL allergic and non allergic children in our population (p 0.189).

For nonimmediate hypersensitivity reactions, skin tests show very low sensitivity and are time consuming. Since 2014, we do not perform skin tests for the work up of delayed adverse reactions in our daily practice: after a carefully clinical history, patients with mild and moderate nonimmediate reactions to antibiotics undergo DPT as described previously.

DISCUSSION

Delayed skin maculopapular or urticarial rashes are frequently reported in children receiving beta-lactam antibiotics. From that moment on, the majority of those children are labeled as “allergic to beta-lactams” and they are prescribed alternative antibiotics that may be less effective and/or more expensive (10). Establishing an accurate diagnosis is associated not only with a more rationale use of antibiotics but also with lower rates of health care utilization (16).

Until recently, the diagnosis of non-immediate BL allergy was assessed by ST as IDT and patch tests, followed by DPT in those patients with negative ST results. This diagnostic work up has been reconsidered since ST are not efficient for the diagnosis of mild and moderate non-immediate reactions to

beta-lactams in children, they are time-consuming and IDT are painful and difficult to perform in small children. The reasons for the low sensitivity of ST are not well understood. It could be due to the use of a drug structure or conjugate that is not well recognized by the immune system since BLs are haptens that need to bind to proteins covalently to elicit an immune response (17).

DPT confirmed BL hypersensitivity in 7,5% of cases in our population. These 17 patients, who presented delayed hypersensitivity reactions, showed negative ST. We assumed the diagnosis of BL allergy in those patients with positive ST. Recently, Caubet et al. (18) reported that 7 out of 11 patients with positive ID tests tolerated the suspected drug on DPT, yielding a positive predictive value for ST of 36% in that population. Vyles et al. (19) also reported that 3 children with positive ST to beta-lactams, tolerated the antibiotic on DPT. Given these observations we wonder if the 3 patients with positive ST in our study (2 with delayed reactions and 1 reporting immediate reaction) would had tolerated the suspected antibiotic on DPT.

Based on our findings, since 2014 we do not performed ST in children referred to us with nonimmediate mild to moderate skin reactions related to antibiotics. Diagnostic procedure has become simpler, less time consuming and it is safe. Up to date we have not had severe reactions during DPT at home. Considering our results and based in our experience, we support previous reports proposing DPT-based protocols for the study of non-severe antibiotic hypersensitivity in children (11, 20, 21).

Even though DPT is considered the gold standard for the diagnosis of non-severe, non-immediate skin reactions, it is not standardized in children.

The duration of the DPT and the dose administered vary from one study to another. Although according to the members of the Task Force panel (12), a full single therapeutic dose should be enough to diagnose delayed hypersensitivity reactions, there are concerns whether the number of days of drug administration may influence the outcome of DTP and therefore the diagnosis. There is the possibility that short DPT protocols would not identify all allergic children with delayed skin reaction. Mill et al. (15) studied 818 children with suspected AMX allergy. They performed a graded DPT with an only dose of antibiotic and found that 6% of patients reacted to it: 2% reacted within the hour after the last dose administered and 4% developed late reactions. Among those patients tolerating AMX on DPT, 10.9% requiring subsequent full treatment with AMX developed delayed skin reactions identical to the initial reactions.

Tonson la Tour et al. (22) reported high negative predictive value (96.7%) of a 2-day DPT but still, 4% of children with negative DPT reacted when retreated at home with the suspected antibiotic.

Mori et al. (6) evaluated 200 children with suspected drug allergy. After ST, a 5-day DPT was performed. First dose was administered gradually, and if there were no adverse reactions, patients received daily therapeutic doses at home for 5 days. From the 17 patients (9.6%) who reacted on DPT, 14 did it on day 5. As they point out, shorter DPT would not identify 7.3% of late reactors leading to miss diagnosis.

To minimize adverse reactions as diarrhea or vomiting as well as the impact on bacterial microbiota and with the aim to diagnose the majority of true hypersensitivity reactions, we propose a different DPT protocol based on the

timing of the initial reaction: for children reacting during the first 3 days of treatment, DPT lasts 3 days. In cases of later reactors (from day 3 on), DPT lasts 5 days. Based on this protocol, we found a similar prevalence of BL allergy to what has been previously reported by other authors (3-5).

Regarding risk factors for beta-lactam allergy in children Faitelson et al. (23) recently found significant association between family history of drug allergy and Mill et al. (16) reported the same observation. Among patients diagnosed of BL allergy by DPT included in the present study, 11,8% (2 patients) referred family history of drug allergy. We could not confirm the suggested association between family history of drug allergy and BL allergy in children.

On the other hand, although personal history of asthma and food allergy have been reported as significant risk factors for the development of AMX allergy (23) we found non-significant differences regarding personal history of atopy between BL allergic and non-allergic patients in our population.

The main limitation of this study to be considered, is its retrospective design that as previously reported, may over-estimate the incidence of true allergy (4).

In summary, skin tests are not useful for the diagnosis of nonimmediate hypersensitivity reactions to beta-lactams in children. In cases of mild and moderate skin manifestations, DPT without previous ST is safe, effective and less time consuming. There would be interesting to unify the different DPT protocols with the aim to achieve an accurate diagnosis minimizing the potential adverse drug reactions.

ACKNOWLEDGEMENTS

We thank our nurses, Ofelia Alba Lago, Maria Jesús Fernández Hermida and Isabel Cabana Blanco for their dedication and excellence performing skin tests and drug provocation tests.

1. What is already known on this topic:

- For diagnosis of non-immediate reactions there aren't standardized tests available. - Skin tests show low sensitivity. It has been proposed to perform only DPT for the diagnosis of non-severe hypersensitivity reactions.

- There are concerns whether the number of days of drug administration during DPT may influence its outcome.

2. What does this study add?

- We conclude that performing DPT without previous skin tests in pediatric patients with non-severe delayed drug reactions is safe and effective.

- We propose a new 3-5 day drug provocation test protocol, based on the timing of the initial reaction.

- It supports the recommendation of drug provocation test without previous skin tests for the diagnosis of non-severe beta-lactam allergy in children.

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TABLES

Table I. Demographic characteristics of children with suspected hypersensitivity reactions to beta-lactam antibiotics

	Number of patients N = 213
Age	
Mean ± SD (years-old)	6.26 ± 3.87
Median (range)	5 (1-15)
Sex	
Female, n (%)	108 (50.7%)
Male, n (%)	105 (49.3%)
Personal history of atopy	63 (29.7%)
Rhinitis, n (%)	33 (15.5%)
Asthma, n (%)	35 (16.4%)
Atopic dermatitis, n (%)	18 (8.5%)
Food allergy, n (%)	2 (0.9%)
Family history of drug allergy	13 (6.1%)
Parents	6 (2.8%)
Grandparents	6 (2.8%)
Brothers	1 (0.5%)

Table II. Clinical characteristics of children with suspected hypersensitivity reactions to beta-lactam antibiotics

	Number of reactions N=232
Age at reaction	
Mean ± SD (years-old)	6.66 ± 3.06
Median (range)	3 (1-14)
Type of reaction	
Delayed	154 (67.2%)
Not determined	51 (22%)
Immediate	24 (10.5%)
Symptoms	
Exanthema	121 (52.2%)
Urticaria (UA)	78 (33.6%)
Angioedema (AE)	31 (13.4%)
Serum sickness like	15 (6.5%)
Antibiotics	
Amoxicilin/clavulanate	147 (63.4%)
Amoxicilin	45 (19.4%)
Cefuroxime	16 (6.9%)
Cefaclor	11 (4.7%)
Cefixime	6 (2.6%)
Penicilin V	3 (1.3%)
Cefotaxime	1 (0.4%)

Table III. Outcome of skin tests and drug provocation tests performed for the diagnosis of beta-lactam hypersensitivity.

Test	Positive n (%)	Negative n
SPT (n=229)	1 (0,4%)	228
IDT (n=32)	0	32
Patch test (n=205)	2 (0,9%)	203
DPT (n=226)	17(7,5%)	226

SPT, skin prick test; IDT, intradermal tests; DPT, drug provocation tests.

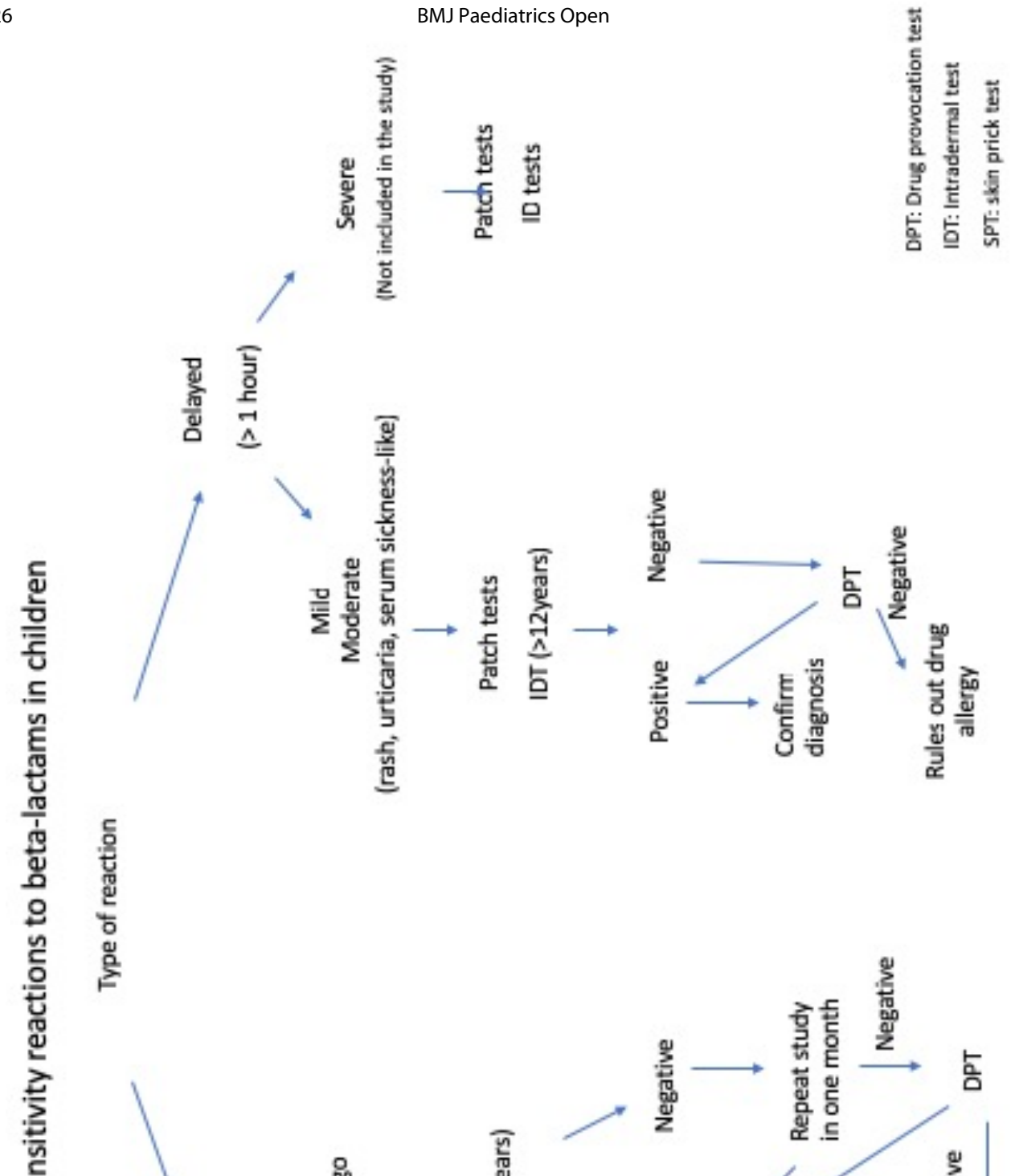
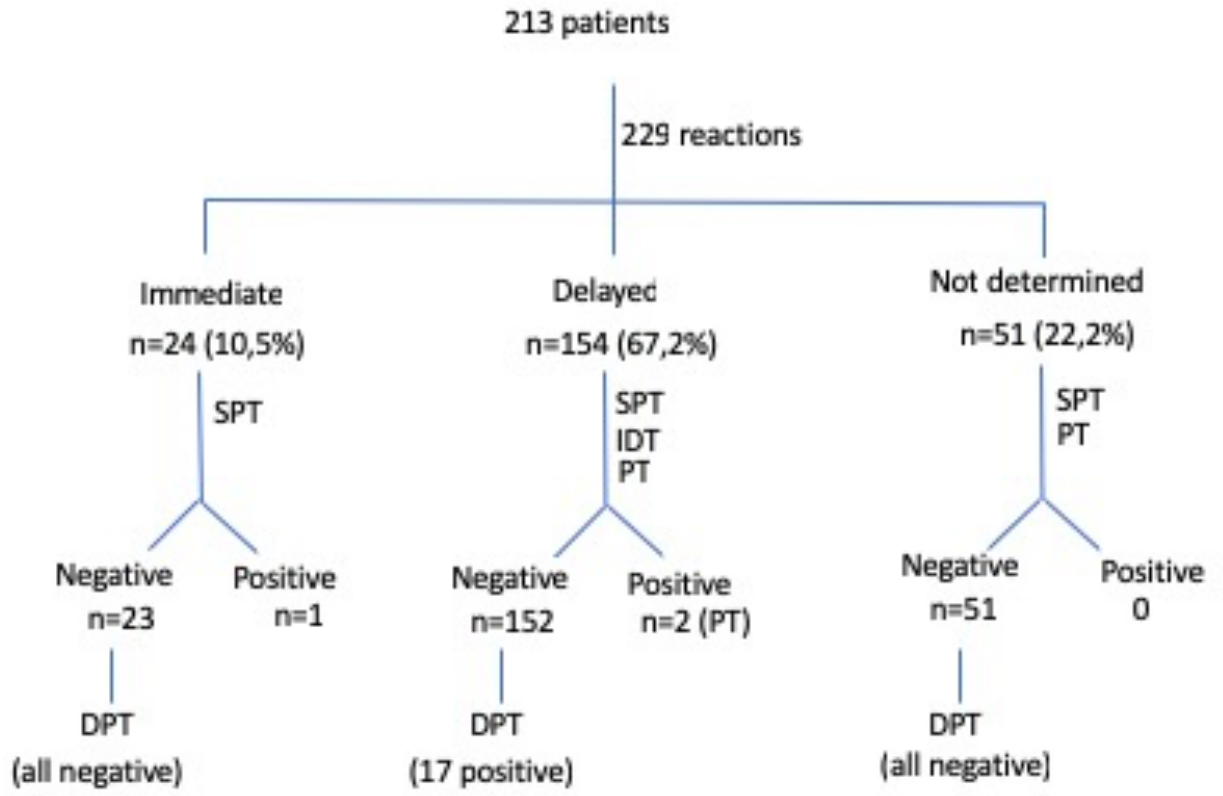


Figure 1. Diagnosis algorithm for hypersensitivity reactions to beta-lactams in children

Figure 2. Results based on diagnosis algorithm



SPT: Skin prick test; IDT: intradermal test; PT: patch test; DPT: drug provocation test