Allergol Immunopathol (Madr). 2010;38(6):300–306

Allergologia et immunopathologia

www.elsevier.es/ai

ORIGINAL ARTICLE

Drug provocation tests to betalactam antibiotics: experience in a paediatric setting

M. Chambel[a,*], P. Martins[a,b], I. Silva[a], S. Palma-Carlos[a], A.M. Romeira[a,c], P. Leiria Pinto[a,c]

[a]*Immunoallergy Department, Dona Estefânia Hospital, Lisbon Central Hospital, Lisbon, Portugal*
[b]*Pathophysiology Department, CEDOC/FEDER, Faculty of Medical Sciences, New University of Lisbon, Lisbon, Portugal*
[c]*Paediatric Department, Faculty of Medical Sciences, New University of Lisbon, Lisbon, Portugal*

Received 26 September 2009; accepted 26 January 2010
Available online 15 May 2010

KEYWORDS
Betalactam;
Children;
Drug allergy;
Penicillin

Abstract
Background: Few studies have been performed in children with suspected betalactam allergy. We aimed to assess the role of the drug provocation test (DPT) with betalactams in a paediatric setting and to study the association between allergy to betalactam antibiotics and other allergic diseases.
Methods: We included all the patients under 15 years old who were consecutively referred to the Immunoallergy Department, Dona Estefânia Hospital, Portugal (January 2002 to April 2008) for a compatible history of allergic reaction to betalactam. All were submitted to a DPT. Children were proposed to perform skin tests (ST) to betalactam antibiotics followed by DPT. If they decline ST, a DPT with the culprit drug was performed.
Results: We studied 161 children, 60% were boys, with a median age of 5 years old at the time of the DPT. Thirty-three patients (20.5%) had an immediate reaction and 33 (20.5%) a non-immediate reaction. The severity of the reported reactions was low in most cases. Skin tests to betalactams were performed in 47 children and were positive in 8. DPT was positive in only one (3.4%) of the patients skin tested and in 11 (13.4%) of those not skin tested. The severity of the DPT reaction was low. Asthma and food allergy were associated with a positive DPT in the later group.
Conclusions: DPT seems a safe procedure even in the absence of ST in non-severe cases. This could be a practical option in infants and pre-school children, where ST are painful and difficult to perform. Additional caution should be taken in children with asthma and food allergy.

*Corresponding author.
E-mail address: chambel.marta@gmail.com (M. Chambel).

0301-0546/$ - see front matter © 2009 SEICAP. Published by Elsevier España, S.L. All rights reserved.
doi:10.1016/j.aller.2010.01.005

Introduction

Allergy to betalactam antibiotics is the most common cause of adverse drug reactions mediated by specific immunological mechanisms. Less than 10% of patients treated with betalactam antibiotics report an adverse drug reaction suggestive of having an immunological mechanism.[1,2] In children, the prevalence of allergic adverse reactions to betalactam seems to be significantly lower than in adults, as in paediatric age infectious diseases are responsible for the clinical picture.[3,4]

In clinical practice, patients who have experienced a drug reaction are frequently categorised as being allergic to the culprit drug without any further investigation. This leads to frequent over-diagnosis of drug allergy. In fact, only 10–20% of patients reporting a history of penicillin allergy are truly allergic when correctly assessed.[5] Over-diagnosis of penicillin allergy in the paediatric population is a cause of concern, with the accompanying increases in health costs.[6]

According to the European Network for Drug Allergy (ENDA), the diagnosis of betalactam antibiotics allergy should be based on the clinical history, skin testing (prick and intradermal tests), in vitro laboratory tests (namely determination of specific IgE to the betalactam) and drug provocation tests.[7,8] Skin prick tests are the safest and easiest tests for immediate drug reactions but are only moderately sensitive. Intradermal tests are more sensitive but carry a higher risk to serious adverse reactions. These could be difficult to perform on children under 6 years old because of patient fear, as the tests are more invasive and painful.[9]

Few studies have been performed in children with suspected betalactam allergy. In these studies, allergy to this class of antibiotics was diagnosed by skin tests in 4.9–40% of children.[10]

In this study we aimed to assess the role of the drug provocation test with betalactam in a paediatric setting. We also sought to study the association between allergy to betalactam antibiotics and other allergic diseases, as this is not clear in the literature.

Methods

We included all consecutive patients under 15 years of age who, over a six-year period (January 2002 to April 2008), were referred to the Immunoallergy Department of the Dona Estefânia Hospital, Portugal, due to a compatible past clinical history of allergic reaction to betalactamic antibiotics. All of them were submitted to a drug provocation test (DPT). It was proposed that children be first skin tested to betalactam antibiotics (Penicilloyl-Polylysine – PPL, Minor Determinant Mixture – MDM, penicillin, amoxicillin, amoxicillin with clavulanic acid and cefuroxime) followed by a DPT in the following weeks. Those children with a mild reaction, non-collaborant (intensive crying, motor agitation because of fear), were proposed to perform a DPT with the culprit drug or with an alternative drug without previous skin testing. Specific IgE to amoxicillin, penicillin G and V was performed independently of the chronology of the reaction (Immulite® 2000, Siemens Healthcare Diagnostics, Deerfield, USA).

Data collection

Clinical data were registered before the investigation and included questions derived from the ENDA drug allergy questionnaire.[11] Demographic parameters, clinical presentation, score of the reaction, chronology of the reaction, allergy clinical history, airborne allergen skin prick test results, time delay from the adverse drug reaction to final diagnosis, implicated antibiotic, drug provocation test antibiotic, betalactam skin tests and drug provocation test results were all analysed. Asthma was considered according to consensus definitions.[12] IgE-mediated food allergy was established on the basis of standardised criteria.[13] Reactions were classified as immediate reactions, which occurred within one hour after antibiotic administration, or non-immediate reactions, which became apparent one hour after the antibiotic exposure.[14] The Ring and Messmer classification was used for immediate reactions.[15] Non-immediate reactions were graded as mild (no treatment required), moderate (patient responded readily to appropriate treatment and no hospitalisation was needed), or severe (reaction required treatment in hospital, was life-threatening or resulted in death). Anaphylaxis was defined as a severe, life-threatening generalised or systemic hypersensitivity reaction.[16]

Skin tests

Skin tests were performed according to ENDA recommendations,[9] first as prick tests and, if negative, were followed by intradermal tests (IDT). Prick and intradermal tests were performed into the non-irritative concentrations.[7] A prick test was considered positive if after 15 min the size of the wheal was at least 3 mm in diameter. For IDT, positivity was considered when the size of the initial wheal increased by at least 3 mm in diameter after 20 min. Late reading was performed in those who mentioned a positive result in the following 72 h.

Drug provocation tests

Drug provocation tests were performed according to recommendations.[17] Patients' parents signed informed consent before the DPT. The DPT entails ingesting increasing doses of the antibiotic, every 30 min, until the appropriate cumulative dose per weight was reached. At home, daily therapeutic doses were prescribed for 5 days. Parents were advised to stop treatment, to contact their doctor, and to take oral antihistamines and/or corticosteroids if they experienced a reaction. Administration was performed on an open challenge protocol by a physician, with full resuscitation back-up. Patients not skin tested or with negative skin tests to betalactams were proposed to be tested with the culprit antibiotic. Those patients with positive skin tests to betalactams or in whom their parents refused to be tested with the culprit drug were submitted to an alternative betalactam antibiotic.

The DPT result was considered positive if any symptom or sign of a drug reaction was clearly documented by a physician (urticaria, maculopapular eruption, bronchospasm, rhinoconjunctivitis, laryngeal oedema, or anaphylaxis)

and occurred during the challenge or within 48 h after the end of the antibiotic intake.

Statistical analysis

An exploratory analysis of the variables of interest was carried out. Frequencies, percentages, and means were calculated using classical statistics.[18] The Fisher exact test was used to compare proportions. The Mann-Whitney was used to compare means in different groups.

The level of significance considered was $\alpha = 0.05$ although p-values greater than 0.05 and lower than 0.1 were considered in order to indicate trends.[18] SPSS (Statistical Package for the Social Sciences, 15.0; Chicago, Illinois, USA) for Windows was used to analyse the data.

Results

The study flow chart is presented in Figure 1. Between January 2002 and April 2008, 161 children were referred to our department for a compatible past clinical history of betalactam allergy. The majority were boys (60%), with a median age of 3 years at the time of the reaction (Table 1). With respect to the chronology of the adverse reaction, 33 patients (20.5%) had immediate reactions, and 33 non-immediate reactions (20.5%). Ninety-five (59%) patients could not remember the time elapsed between antibiotic intake and their subsequent reaction(s). Aminopenicillins and benzylpenicillin counted for more than 75% of the implicated antibiotics. Out of the total of 161 patients, 47 (29%) were skin tested to betalactams.

Isolated skin eruptions (maculopapular exanthema, urticaria, angio-oedema, undefined rash) were the most frequent clinical presentations, in 140 patients (87%). For the most part these were immediate reactions and according to the Ring and Messmer classification these were Grade I. There was one anaphylaxis. The non-immediate reactions were mild and moderate in all cases.

Allergic diseases, namely asthma, occurred in 25.5% of the children, which is higher than the Portuguese paediatric asthma prevalence. Skin tested children to betalactams were older and had a higher frequency of asthma compared to those who were not skin tested (42.6% versus 18.4%). The same was true for allergic rhinitis (46.8% versus 23.7%); atopic eczema (14.9% versus 5.3%); and positive airborne allergen skin tests (51% and 16.7%). Patients not skin tested to betalactams had more IgE mediated food allergy. The implicated food allergens were milk, egg and fish.

Of the 47 children skin tested to betalactams, eight (17%) had a positive reaction, all with intradermal tests (Table 2): four to PPL, two to MDM, and another two for amoxicillin with clavulanic acid. No delayed skin reactions documented. Specific IgE to penicillin was performed in 106 (66%) of the patients and was positive in only two (1.9%), both with positive skin tests to betalactams. Specific IgE to penicillin was positive in a significantly higher number of children with a positive skin test (7.7% against 0%). From those with a negative IgE, 12.5% had a positive skin test.

The majority of patients included in this study were submitted to a DPT with the culprit drug. 3.4% of the patients skin tested to betalactams had a positive challenge against 13.4% in those not skin tested. Skin tests were negative in those patients with a positive DPT. About 40% of the patients were tested with an alternative drug. This was the choice even in nine patients with negative skin tests to betalactams, as their parents feared a serious reaction. Most of the patients who underwent the alternative DPT were challenged with cephalosporin and were negative (98.4% of patients had a negative DPT with an alternative drug). At the time of the DPT with the culprit drug, skin tested children were older (median age of 7 years versus 4 years), which may represent a longer delay until the diagnosis.

The median time that elapsed between the reaction and the allergy work up (time delay) was significantly higher for children skin tested to betalactams (not skin tested: median of one year; skin tested: median of two years).

Among the 12 patients with a positive DPT with the culprit drug, four had an immediate adverse drug reaction (ADR), in one a non-immediate ADR, and in seven it was unknown. The severity of those ADR was mild. The DPT reaction occurred in all cases one hour after the intake. Skin eruption was the manifestation in all cases. In all the positive DPT with the culprit drug, specific IgE to penicillin was negative.

When we analyse only the group of children not skin tested to betalactams and submitted them to a DPT with the culprit antibiotic (Table 3), we found no find significant gender and age differences between positive and negative DPT groups. Concerning the chronology of ADR, immediate reactions represented 36% of the positive DPT and 17% of the negative DPT. There was a trend towards higher prevalence of asthma in those with a positive DPT (36.4% in the positive

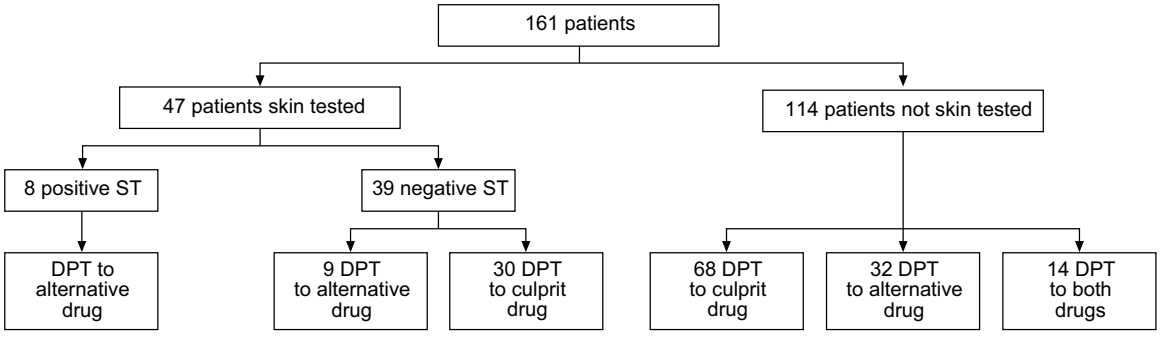

Figure 1 Study flow chart. DPT: drug provocation test; ST: skin tests to betalactams.

Table 1 Clinical characteristics of all the patients

	Total	Not skin tested	Skin tested	*p*-value
Total number	161	114 (70.8%)	47 (29.2%)	
Gender				0.425
Male	96 (59.6%)	69 (60.5%)	27 (57.4%)	
Female	65 (40.4%)	45 (39.5%)	20 (42.6%)	
Age at the time of the ADR – years (Q1–Q3)	3 (1–6)	2 (1–4)	4.5 (2–6.5)	0.001
≤3 years old	85 (74.8%)	65 (57%)	20 (42.6%)	
≥4 years old	62 (38.5%)	36 (31.6%)	26 (55.3%)	
Unknown	14 (8.7%)	13 (11.4%)	1 (2.1%)	
Implicated antibiotic – n (%)				0.012
Unknown	5 (3.1%)	1 (0.9%)	4 (8.5%)	
Amoxicillin	40 (24.8%)	32 (28.1%)	8 (17.1%)	
Amoxicillin+clavulanic acid	73 (45.3%)	50 (43.9%)	23 (48.9%)	
Benzylpenicillin	10 (6.2%)	4 (3.5%)	6 (12.8%)	
Flucloxacillin	4 (2.5%)	3 (2.6%)	1 (2.1%)	
Cephalosporin	29 (18%)	24 (21%)	5 (10.6%)	
Chronology of the ADR				0.906
Immediate	33 (20.5%)	25 (21.9%)	8 (17%)	
Non-immediate	33 (20.5%)	22 (19.3%)	11 (23.4%)	
Unknown	95 (59%)	67 (58.8%)	28 (59.6%)	
Classification of the reaction				
Immediate				1.000
Grade I	28 (17.4%)	22 (19.3%)	6 (12.7%)	
Grade II	0 (0%)	0 (0%)	0 (0%)	
Grade III	5 (3.1%)	3 (2.6%)	2 (4.2%)	
Grade IV	0 (0%)	0 (0%)	0 (0%)	
Non-immediate				0.608
Mild	15 (9.3%)	10 (8.8%)	5 (10.6%)	
Moderate	18 (11.2%)	12 (10.5%)	6 (12.8%)	
Severe	0 (0%)	0 (0%)	0 (0%)	
Clinical presentation of the ADR				0.272
Unknown	5 (3%)	2 (1.8%)	3 (6.4%)	
Skin eruption	140 (87%)	103 (90.3%)	37 (78.7%)	
Gastrointestinal	12 (7.5%)	8 (7%)	4 (8.5%)	
Respiratory	3 (1.9%)	1 (0.9%)	2 (4.3%)	
Anaphylaxis	1 (0.6%)	0 (0%)	1 (2.1%)	
Airborne allergen skin tests				0.000
Positive	43 (26.7%)	19 (16.7%)	24 (51%)	
Negative	54 (33.5%)	44 (38.6%)	10 (21.2%)	
Not performed	64 (39.8%)	51 (44.7%)	13 (27.6%)	
Asthma diagnosis				0.002
Yes	41 (25.5%)	21 (18.4%)	20 (42.6%)	
No	120 (74.5%)	93 (81.6%)	27 (57.4%)	
Allergic rhinitis diagnosis				0.005
Yes	49 (30.4%)	27 (23.7%)	22 (46.8%)	
No	112 (69.6%)	87 (76.3%)	25 (53.2%)	
Atopic eczema diagnosis				0.056
Yes	13 (8%)	6 (5.3%)	7 (14.9%)	
No	148 (92%)	108 (94.7%)	40 (85.1%)	
Food allergy diagnosis				0.234
Yes	15 (9.3%)	13 (11.4%)	2 (4.3%)	
No	146 (90.7%)	101 (88.6%)	45 (95.7%)	

Q1: 1st quartile; Q3: 3rd quartile; ADR: adverse drug reaction.

group versus 14.1% in the negative group, p=0.087). A diagnosis of food allergy was associated with a positive DPT (27.3% in the positive group versus 5.6% in the negative group, p=0.047).

Discussion

Adverse drug reactions are an important public health issue. They are considered somewhere between the fourth and

Table 2 Results of the investigation performed to all the patients

	Total	Not skin tested	Skin tested	*p*-value
Skin test results (betalactams)				
Positive	8 (17%)	–	8 (17%)	
Negative	39 (83%)	–	39 (83%)	
IgE penicillin[a] result				0.058
Positive	2 (1.9%)	0 (0%)	2 (7.7%)	
Negative	104 (98.1%)	80 (100%)	24 (92.3%)	
Result of the DPT – Culprit betalactam				0.179
Positive	12 (8.9%)	11 (13.4%)	1 (3.4%)	
Negative	100 (91.1%)	71 (86.6%)	29 (96.6%)	
Result of the DPT – Alternative antibiotic				0.303
Positive	1 (1.6%)	0 (0%)	1 (6.3%)	
Negative	62 (98.4%)	46 (100%)	16 (95%)	
Time delay in the diagnosis – years (Q1–Q3)	1 (0–2)	1(0–2)	2(1–4)	0.006
<One year	42 (26.1%)	37 (32.6%)	6 (12.8%)	
>One year	105 (65.2%)	65 (57.0%)	40 (85.1%)	
Unknown	14 (8.9%)	13 (11.4%)	1 (2.1%)	
Age at the time of the DPT – years (Q1–Q3)[b]	5 (3–7)	4 (2–6)	7 (5–9)	0.000

[a]Amoxicillin, Penicillin G and V.
[b]Age at the time of the DPT with the culprit drug; Q1: 1st quartile; Q3: 3rd quartile; DPT: Drug provocation test.

Table 3 Clinical characteristics of the patients not skin tested to betalactam and submitted to a DPT with the culprit antibiotic

	Total	DPT positive	DPT negative	*p*-value
Total number	82	11	71	
Gender				0.516
Male	47 (57.3%)	5 (45.5%)	42 (59.2%)	
Female	35 (42.7%)	6 (54.5%)	29 (40.8%)	
Age at the time of the DPT – years (Q1–Q3)	4 (2-6)	3 (2-4)	4 (3-6)	0.327
Age at the time of the ADR				0.709
≤3 years old	49 (59.8%)	7 (63.6%)	42 (59.2%)	
≥4 years old	23 (28.0%)	2 (18.2%)	21 (29.6%)	
Unknown	10 (12.2%)	2 (18.2%)	8 (11.2%)	
Chronology of the ADR				0.279
Immediate	16 (19.5%)	4 (36.4%)	12 (16.9%)	
Non-immediate	15 (18.3%)	1 (9.0%)	14 (19.7%)	
Unknown	51 (62.2%)	6 (54.5%)	45 (63.4%)	
Asthma diagnosis				0.087
No	68 (82.9%)	7 (63.6%)	61 (85.9%)	
Yes	14 (17.1%)	4 (36.4%)	10 (14.1%)	
Allergic rhinitis diagnosis				1.000
No	61 (74.4%)	8 (72.7%)	53 (74.6%)	
Yes	21 (25.6%)	3 (27.3%)	18 (25.4%)	
Atopic eczema diagnosis				1.000
No	77 (93.9%)	11 (100%)	66 (93.0%)	
Yes	5 (6.1%)	0 (0%)	5 (7%)	
Food allergy diagnosis				0.047
No	75 (91.5%)	8 (72.7%)	67 (94.4%)	
Yes	7 (8.5%)	3 (27.3%)	4 (5.6%)	

DPT: drug provocation test; ADR: adverse drug reaction; Q1: 1st quartile; Q3: 3rd quartile.

sixth leading cause of death in the USA, even when the drugs are used in a proper manner, in appropriate doses and for approved indications.[19] According to a meta-analysis,[20] the overall incidence of ADR in hospitalised children was 9.53% and severe reactions accounted for 12.29%. The overall rate of paediatric hospital admissions due to ADRs was 2.09%;

39.3% of these were life-threatening reactions. For outpatient children the overall incidence of ADR was 1.46%.

It is well known that most patients with a suspected drug allergy have negative responses in skin and challenge tests. This is true for adults[21] and for children. In a Portuguese study, only 7% of the children with a self-reported drug allergy had a confirmed diagnosis.[22] In children, true non-immediate allergic drug reactions associated with skin eruptions seem lower than in adults and are commonly attributed to infections.[4] The diagnostic work up for drug allergy is complex and time consuming. A diagnostic protocol which includes skin testing to betalactams is considered useful in clarifying the nature of the reaction.[14]

In the present study we have studied 161 consecutive children seen at our outpatient clinic referred for a suspected betalactam antibiotic allergy. A drug allergy diagnosis was established in only 13% of the patients non-skin tested and in 19% of the skin tested to betalactams (nine children: eight by skin tests and in one trough DPT). This fact supports the idea that most of the suspected reactions to this class of antibiotics are not a true allergic phenomenon and are probably related with the infectious process.[3,4] Our results are slightly lower than the results of Pichichero[23] and differ from those found by other authors.[10,24] We should note that the frequency of positive tests to betalactams found in the present study is similar to the results reached in adult studies.[21,25]

Despite the lower incidence of all positive DPT in the group skin tested, they have a higher time delay to the diagnosis than the non-skin tested group. That could be due to the fact that skin tests to betalactams are not readily available and a ''waiting strategy'' was taken in skin-tested children in order to achieve an older age. The younger age at the time of the ADR is according to the fact that most of the DPTs were negative and an older age is associated with a higher antibiotic exposition. It was, however, surprising that 64% of the positive DPT were in children younger than 3 years.

Most of the patients were boys and this reflects the characteristics of our outpatient clinic. Despite not reaching statistical significance, girls had a higher occurrence of positive DPT with the culprit drug when non-skin tested to betalactams. Being female is usually considered a risk factor for drug allergy in adults.[26]

Seventy-five percent of the non-skin tested children to betalactams were aged six years or less. The decision not to perform skin tests in these children was related to the idea that such tests are generally considered difficult to perform in children younger than six years of age.[7] Skin tested children were older and this might partly explain the higher prevalence of allergic diseases and positive skin tests to airborne allergens.

Specific IgE for penicillin was positive only in a minority of the cases. This is possibly due to methodological problems and also depends upon the availability of the relevant antigens.[27] We should also note that most of the studied reactions were non-immediate.

The role of atopy is still under debate. Atopic disease is not generally considered a risk factor for the development of ADRs.[28] However, atopy seems to constitute a significant risk factor in ADR to NSAIDs[29] and more recently seems to be linked to a history of penicillin allergy.[30] Asthma appears to be a risk factor for severe reactions[31] and in Singaporean children with a reported ADR, they were more likely to have a diagnosis of asthma compared to the control group.[32] In this study, a positive DPT was associated not only with asthma but also with a diagnosis of food allergy. Factors such as concurrent drug intake, infection, exercise and physical activity and underlying food allergy may synergistically interact with each other and precipitate a hypersensitivity reaction or increase its severity.[2]

From our results, DPTs seem a safe procedure in the paediatric population. Despite the lowest rate of DPTs in skin tested children to betalactams, the number of positive DPTs in the non-skin tested children was extremely low and demonstrates that the majority of the suspected allergic ADR are non-reproducible in a subsequent exposure. Our finding supports the idea that most children with a suspected drug allergy with betalactam are not truly allergic. The decision to perform a DPT without previous skin testing may be considered a relatively safe procedure in children with a history of a low grade severity reaction, namely that of an isolated cutaneous presentation. This approach could be time saving and is less invasive. This is in accordance with recent studies in paediatric age group.[33] We should remember that skin tests to betalactams in children face non-collaboration which is unusual in adults and can thus raise interpretation difficulties.

Conclusions

Our results reinforce the need to perform appropriate investigations in all children with a clinical history compatible with betalactamic allergy. DPT seems a safe procedure even in the absence of antecedent skin testing and this could be a practical option in infants and pre-school children, where skin testing could be painful and difficult to perform. Our data suggests that more caution should still be exercised in children with asthma and a history of food allergy.

References

1. International Rheumatic Fever Study Group. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. Lancet. 1991;337:1308–10.
2. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol. 2005;5:309–16.
3. Romano A, Quaratino D, Papa G, Di Fonso M, Venuti A. Aminopenicillin allergy. Arch Dis Child. 1997;76:513–7.
4. Romano A. Recognising antibacterial hypersensitivity in children. Paediatr Drugs. 2000;2:101–12.
5. Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy Jama. 2001;285:2498–505.
6. MacLaughlin EJ, Saseen JJ, Malone DC. Costs of beta-lactam allergies: selection and costs of antibiotics for patients with a reported beta-lactam allergy. Arch Fam Med. 2000;9:722–6.
7. Torres MJ, Blanca M, Fernandez J, Romano A, Weck A, Aberer W, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. Allergy. 2003;58:961–72.
8. Blanca M, Romano A, Torres MJ, Fernandez J, Mayorga C, Rodriguez J, et al. Update on the evaluation of hypersensitivity reactions to betalactams. Allergy. 2009;64:183–93.

9. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy. 2002;57:45–51.
10. Ponvert C, Le Clainche L, de Blic J, Le Bourgeois M, Scheinmann P, Paupe J. Allergy to beta-lactam antibiotics in children. Pediatrics. 1999;104:e45.
11. Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity: questionnaire. EAACI interest group on drug hypersensitivity. Allergy. 1999;54:999–1003.
12. Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Gotz M, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. Allergy. 2008;63:5–34.
13. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, et al. Standardization of food challenges in patients with immediate reactions to foods–position paper from the European Academy of Allergology and Clinical Immunology. Allergy. 2004;59:690–7.
14. Romano A, Blanca M, Torres MJ, Bircher A, Aberer W, Brockow K, et al. Diagnosis of nonimmediate reactions to beta-lactam antibiotics. Allergy. 2004;59:1153–60.
15. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet. 1977;1: 466–9.
16. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113:832–6.
17. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy. 2003;58:854–63.
18. Altman DG. In: Practical Statistical for Medical Research. London: Chapman & Hall; 1990.
19. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. Jama. 1998;279:1200–5.
20. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol. 2001;52:77–83.
21. Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. Ann Intern Med. 2004;140:1001–6.
22. Rebelo Gomes E, Fonseca J, Araujo L, Demoly P. Drug allergy claims in children: from self-reporting to confirmed diagnosis. Clin Exp Allergy. 2008;38:191–8.
23. Pichichero ME, Pichichero DM. Diagnosis of penicillin, amoxicillin, and cephalosporin allergy: reliability of examination assessed by skin testing and oral challenge. J Pediatr. 1998;132:137–43.
24. Mendelson LM, Ressler C, Rosen JP, Selcow JE. Routine elective penicillin allergy skin testing in children and adolescents: study of sensitization. J Allergy Clin Immunol. 1984;73:76–81.
25. Co Minh HB, Bousquet PJ, Fontaine C, Kvedariene V, Demoly P. Systemic reactions during skin tests with beta-lactams: a risk factor analysis. J Allergy Clin Immunol. 2006;117:466–8.
26. Barranco P, Lopez-Serrano MC. General and epidemiological aspects of allergic drug reactions. Clin Exp Allergy. 1998;28(Suppl 4):61–2.
27. Blanca M, Mayorga C, Torres MJ, Reche M, Moya MC, Rodriguez JL, et al. Clinical evaluation of Pharmacia CAP System RAST FEIA amoxicilloyl and benzylpenicilloyl in patients with penicillin allergy. Allergy. 2001;56:862–70.
28. Haddi E, Charpin D, Tafforeau M, Kulling G, Lanteaume A, Kleisbauer JP, et al. Atopy and systemic reactions to drugs. Allergy. 1990;45:236–9.
29. Sanchez-Borges M, Capriles-Hulett A. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. Ann Allergy Asthma Immunol. 2000;84:101–6.
30. Apter AJ, Schelleman H, Walker A, Addya K, Rebbeck T. Clinical and genetic risk factors of self-reported penicillin allergy. J Allergy Clin Immunol. 2008;122:152–8.
31. Adkinson Jr. NF. Risk factors for drug allergy. J Allergy Clin Immunol. 1984;74(4 Pt 2):567–72.
32. Kidon MI, See Y. Adverse drug reactions in Singaporean children. Singapore Med J. 2004;45:574–7.
33. Blanca-Lopez N, Zapatero L, Alonso E, Torres MJ, Fuentes V, Martinez-Molero MI, et al. Skin testing and drug provocation in the diagnosis of nonimmediate reactions to aminopenicillins in children. Allergy. 2009;64:229–33.