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

Leticia Vila,1 Vanesa Garcia,1 Oihana Martinez Azcona,2 Loreley Pineiro,2 Angela Meijide,3 Vanesa Balboa4

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 (STs) show low sensitivity. Our aim was to assess the performance of drug provocation tests (DPTs) 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 2013 were reviewed. Prick, intradermal and patch tests were performed with major determinant penicilloypolylysine, minor determinant mixture, amoxicillin (AMX), cefuroxime, penicillin G and AMX-clavulanate. 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%). 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

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.3 5

In the paediatric population, antibiotics, mainly beta-lactam (BL) and especially amoxicillin (AMX),6 7 are the most commonly involved drugs, followed by non-steroidal anti-inflammatory drugs.1 3 Unlike adults, children usually experience mild non-immediate skin reactions, as maculopapular exanthema and non-immediate urticarial rash.5 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 of 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, the diagnosis of immediate IgE-mediated reactions to BLs should be based on clinical history, skin tests (STs) (skin prick test [SPT] and intradermal tests [IDTs]), in vitro laboratory tests as serum specific IgE determination and drug provocation tests (DPTs).11

For the diagnosis of non-immmediate reactions, there are no standardised 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 sensitivity4 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 standardisation 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 paediatric patients evaluated for BL allergy in the Complexo Hospitalario Universitario A Coruña (CHUAC) between the years 2011 and 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.

To cite: Vila L, Garcia V, Martinez Azcona O, et al. Mild to moderate hypersensitivity reactions to beta-lactams in children: a single-centre retrospective review. BMJ Paediatrics Open 2019;3:e000435. doi:10.1136/bmjpo-2019-000435

© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

1 Complexo Hospitalario Universitario A Coruña, A Coruña, Spain
2 Pediatrics, Complexo Hospitalario Universitario A Coruña, A Coruña, Spain
3 Allergy, Complexo Hospitalario Universitario A Coruña, A Coruña, Spain
4 Epidemiology and Biostatistics, Complexo Hospitalario Universitario A Coruña, A Coruña, Spain

Correspondence to Dr Leticia Vila; leticiavila@yahoo.com
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 2013 were reviewed. Patients with severe non-immediate reactions (drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, generalised exanthematic pustulosis and Steven-Johnson syndrome) were excluded from the study.

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 hospitalisation was needed) or severe (reaction required treatment in hospital, was life threatening or resulted in death).

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

Skin tests
For immediate reactions, SPTs were performed with the major determinant penicilloyl-polylysine (Diater, Madrid, Spain), minor determinant mixture (Diater) and the suspected drug at the following concentrations: AMX (20 mg/mL), cefuroxime (2.5 mg/dL), penicillin G (10 000 IU/mL) and AMX–clavulanate (20 mg/mL). Children older than 12 years also underwent IDT testing in case of negative SPT.

Readings were made 15 min after. STs were considered positive if weal diameter was ≥5 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 were 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: AMX, 50 mg/kg/dose; AMX–clavulanate, 50 mg/kg/dose; cefuroxime, 15 mg/kg/dose; cefaclor, 8 mg/kg/dose. They stayed for 1 hour of observation at the hospital setting.

In cases of severe immediate reactions, doses were fractionated: one-tenth, one-half and total dose, administered every 30 min, with 1 hour of observation.

Patients reporting non-immediate reactions received a full dose of the antibiotic calculated by weight and they were observed during 1 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, the 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, STs 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 means±SD, median and range, and qualitative variables as absolute frequencies and percentages.

The association between qualitative variables was analysed with the χ2 test or Fisher’s exact test. Means were compared with the Mann-Whitney U 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. Statistical analysis was performed with the SPSS V.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 BL antibiotics were reviewed. There were 108 girls (50.7%) and 105 boys (49.3%). Mean age at the time of the reaction was 3.6±3.06 years. Mean age at the time of the allergic work-up was 6.26±3.9 years. Demographic characteristics are summarised in table 1.

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

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

Skin tests
For immediate reactions, SPTs were performed with the major determinant penicilloyl-polylysine (Diater, Madrid, Spain), minor determinant mixture (Diater) and the suspected drug at the following concentrations: AMX (20 mg/mL), cefuroxime (2.5 mg/dL), penicillin G (10 000 IU/mL) and AMX–clavulanate (20 mg/mL). Children older than 12 years also underwent IDT testing in case of negative SPT.

Readings were made 15 min after. STs were considered positive if weal diameter was ≥5 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 were 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: AMX, 50 mg/kg/dose; AMX–clavulanate, 50 mg/kg/dose; cefuroxime, 15 mg/kg/dose; cefaclor, 8 mg/kg/dose. They stayed for 1 hour of observation at the hospital setting.

In cases of severe immediate reactions, doses were fractionated: one-tenth, one-half and total dose, administered every 30 min, with 1 hour of observation.

Patients reporting non-immediate reactions received a full dose of the antibiotic calculated by weight and they were observed during 1 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, the 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, STs 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 means±SD, median and range, and qualitative variables as absolute frequencies and percentages.

The association between qualitative variables was analysed with the χ2 test or Fisher’s exact test. Means were compared with the Mann-Whitney U 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. Statistical analysis was performed with the SPSS V.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 BL antibiotics were reviewed. There were 108 girls (50.7%) and 105 boys (49.3%). Mean age at the time of the reaction was 3.6±3.06 years. Mean age at the time of the allergic work-up was 6.26±3.9 years. Demographic characteristics are summarised in table 1.

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 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 summarised in table 2.

### Testing results

Regarding ST, 32 children older than 12 years with non-immediate skin reactions underwent IDT. All IDTs 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 with BL 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 generalised urticaria and oedema 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 summarised in table 3.

Two patients (11.8%) with confirmed BL allergy reported family history of drug allergy. There were non-significant differences regarding family history of...
Table 2  Clinical characteristics of children with suspected hypersensitivity reactions to beta-lactam antibiotics

| Number of reactions | N=232 |
|---------------------|-------|
| Age at reaction     | Mean±SD (years) 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 78 (33.6%) |
|                     | Angioedema 31 (13.4%) |
|                     | Serum sickness like 15 (6.5%) |
| Antibiotics         | Amoxicillin/clavulanate 147 (63.4%) |
|                     | Amoxicillin 45 (19.4%) |
|                     | Cefuroxime 16 (6.9%) |
|                     | Cefadroxil 11 (4.7%) |
|                     | Cefixime 6 (2.6%) |
|                     | Penicillin V 3 (1.3%) |
|                     | Cefotaxime 1 (0.4%) |

Table 3  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        |

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 results. This diagnostic work-up has been reconsidered since STs are not efficient for the diagnosis of mild and moderate non-immediate reactions to BLs in children, they are time consuming, and IDTs 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 recognised by the immune system since BLs are haptons 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 results. Recently, Caubet et al48 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 al19 also reported that three children with positive ST to BLs tolerated the antibiotic on DPT. Given these observations, we wonder if the three patients with positive ST in our study (two with delayed reactions and one reporting immediate reaction) would have tolerated the suspected antibiotic on DPT.

Based on our findings, since 2014 we do not perform ST in children referred to us with non-immediate 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 on 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 standardised 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,\(^{11}\) 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\(^{22}\) 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\(^{23}\) reported high negative predictive value (96.7%) of a 2-day DPT but still, 4% of children with negative DPT reacted when re-treated at home with the suspected antibiotic.

Mori et al\(^{24}\) 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 misdiagnosis.

To minimise adverse reactions as diarrhoea 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 BL allergy in children, Faitelson et al\(^{25}\) recently found significant association between family history of drug allergy and Mill et al\(^{26}\) reported the same observation. Among patients diagnosed with BL allergy by DPT included in the present study, 11.8% (two 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 overestimate the incidence of true allergy.\(^{21}\)

In summary, skin tests are not useful for the diagnosis of non-immediate hypersensitivity reactions to BLS 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 minimising the potential adverse drug reactions.

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

Contributors All authors have significantly contributed to the study.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Ethics approval The study was approved by the Hospital’s Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There are no additional data from the study.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES
1. Rebelo GE, Fonseca J, Araujo L et al. Drug allergy claims in children: from self-reporting to confirmed diagnosis. Clin Exp Allergy 2008;38:191–8.
Open access

2. Orphan F, Karakas T, Cakir M, et al. Parental-reported drug allergy in 6- to 9-yr-old urban schoolchildren. Pediatr Allergy Immunol 2008;19:82–5.

3. Erkoç&flu01;lg&flu01; M, Kaya A, Clivelek E, et al. Prevalence of confirmed immediate type drug hypersensitivity reactions among school children. Pediatr Allergy Immunol 2013;24:168–77.

4. Zambonino MA, Corzo JL, Muñoz C, et al. Diagnostic evaluation of hypersensitivity reactions to beta-lactam antibiotics in a large population of children. Pediatr Allergy Immunol 2014;25:80–7.

5. Caubet J-C, Kaiser L, Lemaître B, et al. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. J Allergy Clin Immunol 2011;127:218–22.

6. Ponvert C, Perrin Y, Bados-Albiero A, et al. Allergy to beta-lactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. Pediatr Allergy Immunol 2011;22:411–8.

7. Caubet J-C, Eigenmann PA. Managing possible antibiotic allergy in children. Curr Opin Infect Dis 2012;25:279–85.

8. Mori F, Cianferoni A, Barni S, et al. Amoxicillin allergy in children: five-day drug provocation test in the diagnosis of nonimmediate reactions. J Allergy Clin Immunol Pract 2015;3:375–80.

9. Dibek Mısırlıoglu E, Guvenir H, Özkan Parla&flu01;ay A, et al. Incidence of antibiotic-related rash in children with Epstein-Barr virus infection and evaluation of the frequency of confirmed antibiotic hypersensitivity. Int Arch Allergy Immunol 2018;176:33–8.

10. Norton AE, Konvinse K, Phillips EJ, et al. Antibiotic allergy in pediatrics. Pediatrics 2018;141:e20172497.

11. Gomes ER, Brockow K, Kuyucu S, et al. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. Allergy 2016;71:149–61.

12. Blanca M, Romano A, Torres MJ, et al. Update on the evaluation of hypersensitivity reactions to beta-lactams. Allergy 2009;64:183–93.

13. Moral L, Caubet J-C. Oral challenge without skin tests in children with non-severe beta-lactam hypersensitivity: time to change the paradigm? Pediatr Allergy Immunol 2017;28:724–7.

14. Callero A, Berroa F, Infante S, et al. Tolerance to cephalosporins in nonimmediate hypersensitivity to penicillin in pediatric patients. J Investig Allergol Clin Immunol 2014;24:122–41.

15. Mil&flu01; C, Pr&u00e9ame M-N, Medoff E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in children. JAMA Pediatr 2016;170:e160033–8.

16. Macy E, Shu Y-H. The effect of penicillin allergy testing on future health care utilization: a matched cohort study. J Allergy Clin Immunol Pract 2017;5:705–10.

17. Ariza A, Mayorga G, Fernandez TD, et al. Hypersensitivity reactions to ß-lactams: relevance of hapten–protein conjugates. J Investig Allergol Clin Immunol 2015;25:12–25.

18. Caubet J-C, Frossard C, Fellay B, et al. Skin tests and in vitro allergy tests have a poor diagnostic value for benign skin rashes due to ß-lactams in children. Pediatr Allergy Immunol 2015;26:80–2.

19. Vyles D, Adams J, Chiu A, et al. Allergy testing in children with low-risk penicillin allergy symptoms. Pediatrics 2017;140.10.1542/peds.2017-0471.

20. Ve&flu01;r E, Dibek Mısırlıoglu E, Clivelek E, et al. Direct oral provocation tests in non-immediate mild cutaneous reactions related to beta-lactam antibiotics. Pediatr Allergy Immunol 2016;27:50–4.

21. Marrs T, Fox AT, Lack G, et al. The diagnosis and management of antibiotic allergy in children: systematic review to inform a contemporary approach. Arch Dis Child 2015;100:583–6.

22. Tonson la Tour A, Michelet M, Eigenmann PA, et al. Natural history of benign nonimmediate allergy to beta-lactams in children: a prospective study in retreated patients after a positive and a negative provocation test. J Allergy Clin Immunol Pract 2017;5:789–4.

23. Faitelson Y, Boaz M, Dalal I. Asthma, family history of drug allergy, and age predict amoxicillin allergy in children. J Allergy Clin Immunol Pract 2018;6:1363–7.

24. Meng J, Thudford D, Lukawska JJ. Allergy test outcomes in patients self-reported as having penicillin allergy: two-year experience. Ann Allergy Asthma Immunol 2016;117:273–9.