



Allergic reactions to antibiotics in children

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Purpose of review

To analyze recent findings on antibiotic hypersensitivity reactions in children focusing on betalactams, with regard to clinical entities, antibiotics involved and diagnostic methods.

Recent findings

Betalactams are the most frequent cause of antibiotic hypersensitivity, more specifically amoxicillin alone or with clavulanic acid, with selective reactions to clavulanic acid also recently reported. Cephalosporins are the second most frequent group involved, especially in countries with high consumption. Other antibiotics such as sulphamides and macrolides although involved are less common. There are two types of reactions, immediate and nonimmediate, the latter being more frequent. Diagnosis is complex and is confirmed in less than 10% of children evaluated, twice as often in immediate than in nonimmediate reactions. Clinical history is often unreliable. Regarding other methods, skin testing and in-vitro methods can be useful for immediate reactions; however, most nonimmediate reactions need drug provocation tests for diagnosis. There are different degrees of cross-reactivity between penicillin and cephalosporins, with the side-chain being critical for determination.

Summary

Betalactams are the antibiotics most frequently involved in hypersensitivity reactions with amoxicillin being the main culprit drug. Immediate reactions, although less frequent, are more often confirmed, with skin testing still relevant for their diagnosis. Nonimmediate reactions are usually diagnosed by drug provocation test.

Keywords

antibiotics, betalactams, hypersensitivity, immediate, nonimmediate

INTRODUCTION

The prevalence of drug hypersensitivity in children is not known mainly because most studies have dealt with adverse drug reactions rather than hypersensitivity specifically [1]. In fact, adverse drug reactions are frequently reported in hospitalized children (10.2%) and outpatients (1.5%) [2,3]. Other difficulties for prevalence estimation are that most studies are performed in adults and only consider some types of reactions.

In children, there is an overestimation of drug hypersensitivity [4] and compared with adults, it is 1.5 times less likely to be confirmed, being particularly lower in those with maculopapular exanthema (MPE) [5]. The parental reporting of allergy is 10.2% compared with confirmed drug allergy of 6% [6]. Even after ruling out a diagnosis of drug allergy, parents still refuse their administration. Only 45% of children for whom penicillin hypersensitivity was ruled out went on to receive this drug again [7].

Hypersensitivity reactions are classified as immunologically mediated or allergic, and non-immunologically mediated or nonallergic. The former can be immediate or nonimmediate according

to the time between drug intake and the appearance of symptoms [8]. Immediate reactions usually appear within 1 h of drug intake and are mediated by specific IgE antibodies. Urticaria and anaphylaxis are the most commonly reported entities. Nonimmediate reactions (NIRs) usually occur 24–48 h after drug intake, although the time interval can be as short as 1 or 2 h; they are usually T-cell-mediated and the most frequent entities are MPE [9,10].

IMPLICATED DRUGS

In a recent study [11] evaluating a large population of children with hypersensitivity reactions to drugs, those most frequently involved were nonsteroidal

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KEY POINTS

- Betalactams are the drugs most frequently involved in allergic reactions in children inducing both IgE and T-cell-mediated reactions. Amoxicillin, alone or associated with clavulanic acid, was the betalactam most frequently involved, followed by cephalosporins.
- Immediate reactions, although less frequent, are confirmed nearly twice as often compared with NIR.
- Skin testing is a useful approach for confirming diagnosis for immediate reactions. DPT appears to be the only approach for diagnosing NIR to betalactams, especially in mild reactions.
- Non betalactam antibiotics such as sulphonamides and macrolides are also involved in allergic reactions in children producing mainly NIR.
- Desensitization has been shown to be useful in children, particularly when no other alternative treatment is available.

anti-inflammatory drugs (NSAIDs) (44.53%), betalactams (42.97%) and macrolides (1.56%). The most common confirmed diagnosis was NIR to betalactam (42.19%) followed by cross-intolerance reactions to NSAIDs (34.38%). These data are similar to those found in adults from the same population, although in adults immediate reactions to betalactams were more frequent [12].

Betalactams were the most frequent cause of IgE and T-cell-mediated immunological reactions [11]. The high frequency of immunological reactions compared with other antibiotics could be because of the high capacity of betalactam molecules for inducing hapten-protein conjugates [13] and their high consumption in the pediatric population [14]. However, a recent study [15[•]] has shown that the prevalence of these reactions is slightly lower in children with cystic fibrosis than in the general population (0.71 versus 1) in spite of their high consumption.

Other antibiotics inducing hypersensitivity reactions in children are macrolides and sulphonamides, although with much lower frequency.

BETALACTAM HYPERSENSITIVITY

Betalactams are frequently prescribed in children in the context of an infection, despite the fact that these are often caused by viruses. Hypersensitivity to this class of drugs is reported by parents and doctors, although the rate of confirmed diagnosis after an allergological study may vary from 7 to 60% [16–22,23^{••}]. These differences may be because of the mechanisms involved, the type of reactions, the betalactam involved and the diagnostic approach.

Mechanisms

Betalactams are haptens that cannot be recognized by the immunological system by themselves, but when they bind spontaneously to exogenous or endogenous proteins, they form a complex that can later be processed and presented to T lymphocytes. They can induce all the reactions described by Gell and Coombs [24], although those mediated by specific IgE antibodies (Type I) or T cells (Type IV) are the most frequent (Fig. 1). The type of reaction elicited occurs in the first stages of the immunological response, wherein dendritic cells, as antigen-presenting cells, and naive T lymphocytes are key players, regulating both IgE production and T-effector cell differentiation, depending on their profile of cytokine production.

For IgE-mediated reactions, dendritic cells present the drug to T cells within the context of a Th2 response. These T cells will proliferate and interact with B cells by two signals (CD40-CD40L and the Th2 cytokines) inducing isotype IgE switching and leading to the production of drug-specific IgE antibodies [25]. These antibodies bind to high-affinity Fcε-Receptor I on the surface of mast cells and basophils during the sensitization phase. During further re-exposures, the antibiotic–protein complex cross-links with two or more IgE molecules, leading to the release of presynthesized inflammatory mediators such as histamine, tryptase, quimase and heparins or newly synthesized as prostaglandins and leukotriens, which are responsible for the symptoms of the reaction.

T-cell-mediated reactions (Type IV) have been further sub-classified as [26]: Th1 reactions with macrophage activation (Type IVa), eosinophil-rich exanthems (Type IVb), bullous skin diseases (Type IVc) as well as neutrophil-rich inflammations like acute generalized exantematic pustulosis (Type IVd). Different studies have shown the presence of activated T cells expressing the cutaneous lymphocyte antigen (CLA) with an increased production of interferon-γ, tumor necrosis factor-α, interleukin-2, the transcription factor T-bet, and the cytotoxic markers perforin and granzyme B [7[•],27]. In MPE, a mononuclear infiltrate can be found, mainly consisting of CD4+ T cells [28]. These cells release Th1 and skin-homing chemokines and cytokines in the affected tissue (the skin), and their corresponding receptors are expressed in both skin and peripheral blood.

Types of reactions

The skin is the organ most often affected. Urticaria/angioedema and anaphylaxis are the clinical entities most often appearing in immediate reactions, whereas MPEs are more common in NIRs (Table 1).

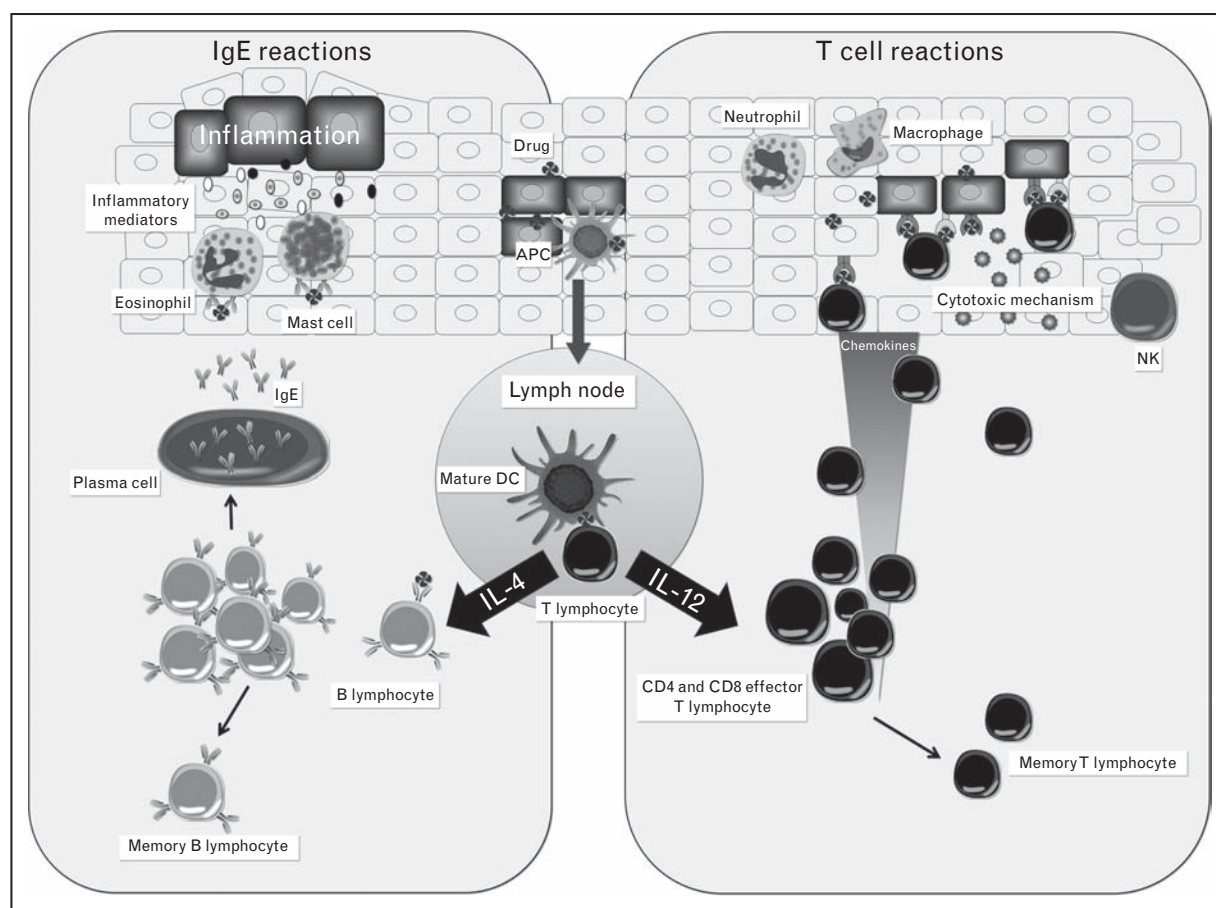


FIGURE 1. Mechanisms involved in immediate and nonimmediate reactions to antibiotics. APC, antigen-presenting cell; DC, dendritic cell; NK, natural killer cell.

Immediate reactions, although less frequent, are confirmed nearly twice as often compared with NIRs (13.64 versus 7.39%) [23^{***}]. Related to this, it has been reported that the likelihood of betalactam hypersensitivity is significantly higher in children reporting immediate reactions (30.9%) than in NIRs (13.9%) [20]. Similar results have been described for cephalosporins [18], wherein 76.7% of the children with immediate reaction were confirmed as allergic, but only 1% of those who had experienced NIR were confirmed.

Considering specific types of reactions, the likelihood of betalactam hypersensitivity is significantly higher in anaphylaxis, serum sickness-like reaction and potentially harmful skin reactions compared with urticarial or MPEs [20]. Given that there are many potential causes of exanthema in children receiving betalactams for an infection, such as viruses, it is important to consider other differential diagnoses for the exanthema [29,30].

Anaphylaxis is not a frequently confirmed diagnosis, varying from 11.1 to 22% [20,23^{***}]. In a survey of severe drug-induced anaphylaxis that included children, antibiotics (49.6%) were the most frequent

culprits, of which the most common were betalactams (86.6%), followed to a much lesser extent by quinolones (9.1%) [31].

Betalactams involved

Penicillins and to a lesser extent cephalosporins are the betalactams most frequently involved [18,20–22] (Table 1). In fact, it has been shown that amoxicillin (AX), alone or associated with clavulanic acid (CLV), was the betalactam most frequently involved (64.9%), followed by third-generation cephalosporins (21.5%) [20]. In a recent study [23^{***}], 89.65% of reactions were induced by AX or AX-CLV, in 8.43% by cephalosporins and in 1.92% by benzylpenicillin. When evaluating children with MPE, AX or AX-CLV was responsible for 87.5% of the reactions and cephalosporins for rest (12.5%) [19]. As in adults [32,33], selective reactions to CLV may appear in children [20,23^{***}]; whether these reactions will increase as AX-CLV is more prescribed remains to be seen.

Regarding cephalosporins, differences have been observed between countries. In Italian children

Table 1. Description of type of reactions, clinical symptoms, betalactam involved as well as percentage of children finally confirmed as allergic from recent studies published each with a large number of patients

	N	Immediate reaction/NIR	Symptoms	Drugs	Confirmed
Caubet <i>et al.</i> JACI, 2011 [19]	88	Not clarified	Urticaria (53.4%), MPE (46.6%)	AX (48.5%), AX-CLV (38.8%), Cef (12.5%)	6.8%
Ponvert <i>et al.</i> Pediatr Allergy Immunol, 2011 [20]	1431	Immediate reaction = 162 (11.3%), NIR = 1269 (88.7%)	Anaphylaxis (6.9%), urticaria (70.8%), MPE (18.4%), severe (3.8%)	AX & AX-CLV (64.9%), Ceph (21.5%), others (13.6%)	15.9%
Zambonino <i>et al.</i> Pediatr Allergy Immunol, 2014 [23 [■]]	783	Immediate reaction = 66 (8.4%), NIR = 717 (91.6%)	Anaphylaxis (0.6%), urticaria (28.6%), exanthema (69.5%) other (1.3%)	BP (1.9%), AX (43.4%), AX-CLV (46.2%), Cef (8.4%)	7.92%
Matar <i>et al.</i> Pediatr Allergy Immunol, 2014 [15 [■]]	19 with 23 reactions (children with cystic fibrosis)	Immediate reaction = 13 (56.5%), NIR = 10 (43.5%)	Anaphylaxis (39.1%), urticaria (60.9%)	Pip-tazo (17.4%), Cefta (34.8%), Aztr (21.7%), Tic/tem (8.7%), AX (8.7%), Oxa (4.3%), Pip (4.3%)	47%

AX, amoxicillin; Aztr, aztreonam; BP, benzylpenicillin; Cefta, ceftazidime; Ceph, cephalosporines; CLV, clavulanic acid; MPE, maculopapular exanthema; NIR, nonimmediate reaction; Oxa, oxacillin; Pip, piperacillin; Tazo, tazobactam; Tem, temocillin; Tic, ticarcillin.

diagnosed with immediate reaction to cephalosporins, 51.4% were induced by cefaclor and 37.1% by ceftriaxone [18]. In Serbian children, 29.2% of them were allergic to cefaclor, 25.8% to cephalexin, 1% to ceftriaxone and 0.3% to cefotaxime. Both studies showed that anaphylactic reactions to cefaclor in children were not as rare as previously believed, especially in countries with high consumption [34]. In France, only 1.2% of children with immediate reaction to betalactams were allergic to cephalosporins [20], compared with 11% in Spain [23[■]]. These variations in the betalactams involved in allergic reactions are likely to be due to the changes in their patterns of prescription and consumption [12,35].

Children may develop hypersensitivity to betalactams and to one or more chemically different drugs. This has been deemed multiple drug hypersensitivity, and can appear when drugs are administered simultaneously or sequentially. It has been recently shown that from 292 children with a history of multiple drug hypersensitivity only 2.5% were confirmed (28.6% simultaneously and 71.4% sequentially). Betalactams were the drugs involved in 71.4% of the reactions [36[■]].

Diagnostic work-up

The diagnostic work-up of betalactam hypersensitivity has become complex, time-consuming and sometimes risky, requiring skilled personnel and an appropriate setting [32]. This includes a detailed clinical history, followed by skin testing, in some

cases in-vitro evaluation, and a drug provocation test (DPT) [32] (Fig. 2). However, in daily practice, it is often based solely on the clinical history, which is unreliable and leads to over-diagnosis [37].

Considering immediate reaction, in-vitro IgE determination by CAP-FEIA (ThermoFisher Scientific, Waltham, Massachusetts, USA) is one potential approach; however, it suffers from low sensitivity [38] and may induce false-positive results, especially with penicillin V [39,40]. In a recent study, 22% of children with immediate reaction were diagnosed by in-vitro tests and 22% by skin testing. This figure would probably have been higher if skin testing had also been performed on those diagnosed by in-vitro testing [23[■]]. Other authors found skin test positivity in 86% of those finally confirmed as immediate reaction, 4.6% by prick test and 93% by intradermal test [20]. All these results indicate that skin testing in immediate reactions is a useful approach for confirming diagnosis.

Skin test in NIRs has a very low sensitivity, and in most instances, patients are diagnosed by DPT [19,21]. Delayed reading intradermal test positivity may vary from 3.8 to 33.8%, according to recent studies, although the latter study used high drug concentrations, which may have led to a number of false positives [20,23[■]]. Higher values of positive results have been reported in more severe reactions, such as erythema multiforme and acute generalized exanthematous pustulosis [20]. Therefore, DPT seems the only approach for diagnosing NIR to betalactams, especially in mild reactions. Analyzing the time of symptom appearance after DPT, it has

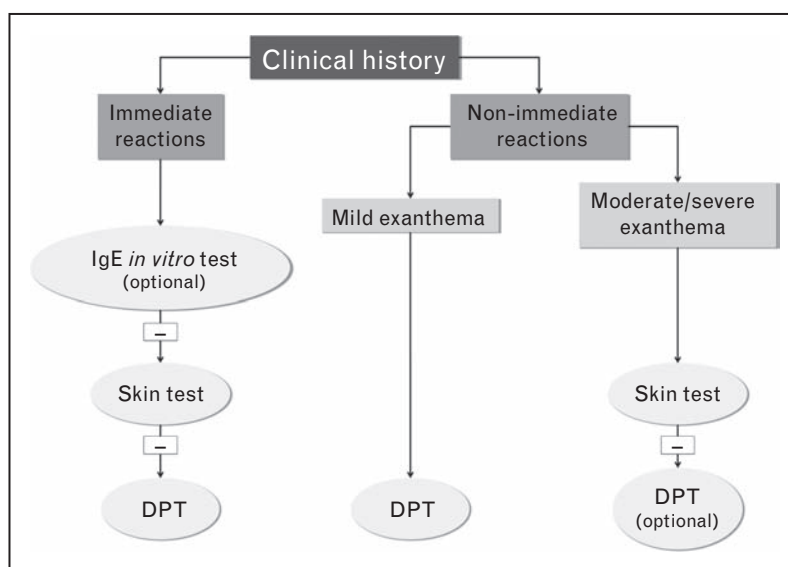


FIGURE 2. Allergological work-up for diagnosing immediate and nonimmediate reactions to betalactams in children. DPT, drug provocation test.

been shown that 65% of the children reacted within 6–24 h, and 10% from 24–48 h. These results indicate that a 3-day DPT protocol (one in the hospital and two at home) is well tolerated and accurate for diagnosis [23[■]].

It is interesting to analyze whether skin test positivity can predict betalactam tolerance. In one prospective study [19], DPT with betalactams was performed in 88 children with delayed-onset urticarial or maculopapular rashes, independently of the skin test results. They found that 11 children had immediate intradermal test responses, although only four of them developed a positive DPT (one immediate reaction and three NIRs). Delayed reading intradermal tests and patch testing were negative in all children. Taken together, these results suggest that immediate reading of intradermal skin tests should be performed only for immediate reactions.

A second allergological work-up in patients with negative test results is recommended in order to be certain that they are not allergic. However, this is particularly recommended for severe immediate reactions and for patients with a long interval between the reaction and the study because of the clearance of the IgE antibody over time [41]. Taking into account that in children most cases are NIRs, this procedure does not seem to be useful. In fact, in a retrospective study, it has been found that only 0.4–2.1% of children were diagnosed in the retest [42,43].

Cross-reactivity

The degree of cross-reactivity between penicillin and cephalosporin has been evaluated in children.

Ponvert *et al.* [20] found cross-reactivity in 28.2% of the betalactam allergic children. This was higher for those with immediate reactions (76%) than those with NIRs (14.7%). Atanaskovic-Markovic *et al.* [44] found that cross-reactivity between cephalosporins and penicillins varied between 0.3 and 23.9%, being higher among penicillins and between first-generation and second-generation cephalosporins. However, as previously reported [18,20,44,45], it has recently been shown that all penicillin allergic children tolerated cefuroxime, a cephalosporin with a different side chain [23[■]]. All these studies indicate that cross-reactivity is higher in immediate reactions and when penicillins and cephalosporins are identical or similar in the R1 side chain, as happens with the first and second-generation cephalosporins.

Regarding carbapenems, cross-reactivity with penicillins in children is very low: 0.9% for meropenem [46] and 0.8% for imipenem [47]. These results demonstrate that the practice of avoiding meropenem in children with penicillin immediate reaction should be abandoned.

NONBETALACTAM ANTIBIOTICS

The two important groups of nonbetalactam antibiotics in the induction of allergic reactions in children are macrolides and sulphonamides.

Macrolides are highly prescribed for children with upper respiratory tract infections, and hypersensitivity is estimated to occur in 0.4–3% of pediatric patients [48]. The majority of cases reported are NIRs, such as MPE and urticarial exanthema. The incidence of anaphylactic reactions is extremely low [49,50].

The allergological evaluation is difficult because skin tests have not been validated, especially for those that are presented in noninjectable forms, and in-vitro tests have shown inconsistent results [51]. Studies [52–54] of patients with suspected macrolide allergy indicate that only 7.5–13.7% were finally confirmed as allergic, mainly by DPT. This has also been confirmed recently in children. Out of those confirmed as allergic, azithromycin was involved in 2.3% of cases [11]. Cross-reactivity between the different macrolides is variable and little information is available [55,56]; however, a case with an immediate reaction to roxithromycin with positive prick test to erythromycin and clarithromycin has been reported [57].

Sulphonamides also mainly produce NIRs. Generalized maculopapular or urticarial exanthema is the most common manifestation [58]. In addition, these drugs have been shown to cause severe drug allergic reactions such as drug hypersensitivity syndrome and Stevens–Johnson syndrome [59]. In a study [60] analyzing medications as risk factors for Steven-Johnson syndrome/toxic epidermal necrolysis in children, sulphonamides and anticonvulsants were the most frequent drugs involved. Moreover, in another study in children diagnosed with Steven Johnson syndrome/toxic epidermal necrolysis, anticonvulsants were the most common (50%), followed by antibiotics (36%) and NSAIDs (21%). From the antibiotic group, sulphonamides were responsible for 20% and macrolides 40% of reactions [61]. However, another study [62] showed that antibiotics had the third largest adjusted odds ratio, with betalactams and macrolides involved in 27.7% of cases. The possibility of cross-reactivity between antibacterial and nonantibacterial sulfonamides has been suggested, but it was impossible to determine whether the reaction to two sulfonamide derivatives was coincidental or may be a multiple drug allergy syndrome [63].

DESENSITIZATION

This procedure, although not free of risk, is particularly important for children for whom the drug is essential and there is no other alternative treatment. This is often the case for multiresistant bacteria or multiple antibiotic allergies. In children, there are scarce data on desensitization, with the majority related to antibiotics such as betalactams [64–66] and ciprofloxacin in cystic fibrosis [67,68]. Success has been found mainly for children with IgE-mediated reactions and ranges from 50 to 100% [69], although because of the low number of cases, these data could be overestimated.

This procedure must be performed after establishing a risk/benefit analysis and only in hospitals by well trained personnel [70,71]. It is based on the administration of increasing doses of the culprit antibiotic until the therapeutic dose is achieved and tolerated over a short period of time [71]. The protocols used in children are, in general, similar to those used for adults, but dosage is adapted to the child's requirements and the oral route is used when possible, although dosage must be adapted to take into account gastrointestinal absorption [69,70].

CONCLUSION

Out of a large number of children with a history of hypersensitivity drug reactions, few were finally confirmed as truly allergic. Antibiotics, in particular betalactams, were the drugs most frequently involved. The majority of the allergic reactions are NIRs and a drug provocation test has been shown to be a necessary and well tolerated tool to diagnose these children.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. *Br J Clin Pharmacol* 2011; 71:684–700.
2. Clavenna A, Bonati M. Adverse drug reactions in childhood: a review of prospective studies and safety alerts. *Arch Dis Child* 2009; 94:724–728.
3. Impicciatore P, Choonara I, Clarkson A, *et al.* 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.
4. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol* 2005; 5:309–316.
5. Rubio M, Bousquet PJ, Gomes E, *et al.* Results of drug hypersensitivity evaluations in a large group of children and adults. *Clin Exp Allergy* 2012; 42:123–130.
6. Rebelo Gomes E, Fonseca J, Araujo L, Demoly P. Drug allergy claims in children: from self-reporting to confirmed diagnosis. *Clin Exp Allergy* 2008; 38:191–198.

7. Picard M, Paradis L, Nguyen M, *et al*. Outpatient penicillin use after negative skin testing and drug challenge in a pediatric population. *Allergy Asthma Proc* 2012; 33:160–164.

This study evaluated the use of penicillin in children studied and diagnosed as nonallergic. Penicillin was only used in 45% of children and 18% of parents refused their administration because they still feared an adverse reaction. Thus, less than 50% of children who had allergy ruled out received penicillin.

8. Torres MJ, Blanca M. The complex clinical picture of beta-lactam hypersensitivity: penicillins, cephalosporins, monobactams, carbapenems, and clavams. *Med Clin North Am* 2010; 94:805–820.
9. Fernandez TD, Canto G, Blanca M. Molecular mechanisms of maculopapular exanthema. *Curr Opin Infect Dis* 2009; 22:272–278.
10. Gomez E, Blanca-Lopez N, Salas M, *et al*. Induction of accelerated reactions to amoxicillin by T-cell effector mechanisms. *Ann Allergy Asthma Immunol* 2013; 110:267–273.
11. Zambonino MAMC, Corzo JL, Requena G, *et al*. Analysis of drug hypersensitivity reactions in a large series of children. *J Allergy Clin Immunol* 2014; 133:AB263.
12. Dona I, Blanca-Lopez N, Torres MJ, *et al*. Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. *J Invest Allergol Clin Immunol* 2012; 22:363–371.
13. Ariza A, Garzon D, Abanades DR, *et al*. Protein haptenation by amoxicillin: high resolution mass spectrometry analysis and identification of target proteins in serum. *J Proteomics* 2012; 77:504–520.
14. Adriaenssens N, Coenen S, Tonkin-Crine S, *et al*. European Surveillance of Antimicrobial Consumption (ESAC): disease-specific quality indicators for outpatient antibiotic prescribing. *BMJ Qual Saf* 2011; 20:764–772.
15. Matar R, Le Bourgeois M, Scheinmann P, *et al*. Beta-lactam hypersensitivity in children with cystic fibrosis: a study in a specialized pediatric center for cystic fibrosis and drug allergy. *Pediatr Allergy Immunol* 2014; 25:88–93.

In this study, children with cystic fibrosis and a history of betalactam reaction were evaluated by skin tests and DPT. The prevalence in this population was quite low (0.71%) and this may be attributed to the tolerance induced by prolonged betalactams treatments. However, it was confirmed in 47.3%, a percentage higher than in the general population.

16. Zambonino MA, Torres MJ, Munoz C, *et al*. Drug provocation tests in the diagnosis of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs in children. *Pediatr Allergy Immunol* 2013; 24:151–159.
17. Corzo JL, Zambonino MA, Munoz C, *et al*. Tolerance to COX-2 inhibitors in children with hypersensitivity to nonsteroidal anti-inflammatory drugs. *Br J Dermatol* 2014; 170:725–729.
18. Romano A, Gaeta F, Valluzzi RL, *et al*. Diagnosing hypersensitivity reactions to cephalosporins in children. *Pediatrics* 2008; 122:521–527.
19. Caubet JC, 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; 127:218–222.
20. Ponvert C, Perrin Y, Bados-Albiero A, *et al*. Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. *Pediatr Allergy Immunol* 2011; 22:411–418.
21. Blanca-Lopez N, Zapatero L, Alonso E, *et al*. Skin testing and drug provocation in the diagnosis of nonimmediate reactions to aminopenicillins in children. *Allergy* 2009; 64:229–233.
22. Romano A, Quaratino D, Papa G, *et al*. Aminopenicillin allergy. *Arch Dis Child* 1997; 76:513–517.
23. Zambonino MA, Corzo JL, Munoz C, *et al*. Diagnostic evaluation of hypersensitivity reactions to beta-lactam antibiotics in a large population of children. *Pediatr Allergy Immunol* 2014; 25:80–87.

In this study, a large cohort of children ($N = 783$) with a history of hypersensitivity reactions to betalactams were evaluated and only 7.92% were confirmed as being allergic, 14.52% with immediate reaction and 85.48% with NIR. In immediate reaction, in-vitro and skin test were useful for diagnosis, whereas in NIRs, DPT was essential. In this study, amoxicillin or amoxicillin-CLV was the betalactam most frequently involved.

24. Coombs PRGP. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: RR G, editor. *Clinical aspects of immunology*. Oxford: Oxford Univ; 1968. pp. 575–596.
25. Vercelli D. The regulation of IgE synthesis. *Clin Allergy Immunol* 2002; 16:179–196.
26. Pichler WJ. Delayed drug hypersensitivity reactions. *Ann Intern Med* 2003; 139:683–693.
27. Mayorga C, Torres MJ, Fernandez J, *et al*. Cutaneous symptoms in drug allergy: what have we learnt? *Curr Opin Allergy Clin Immunol* 2009; 9:431–436.
28. Fernandez TD, Mayorga C, Torres MJ, *et al*. Cytokine and chemokine expression in the skin from patients with maculopapular exanthema to drugs. *Allergy* 2008; 63:712–719.
29. Torres MJ, Corzo JL, Leyva L, *et al*. Differences in the immunological responses in drug- and virus-induced cutaneous reactions in children. *Blood Cells Mol Dis* 2003; 30:124–131.
30. Romano A. Recognising antibacterial hypersensitivity in children. *Paediatr Drugs* 2000; 2:101–112.
31. Renaudin JM, Beaudouin E, Ponvert C, *et al*. Severe drug-induced anaphylaxis: analysis of 333 cases recorded by the Allergy Vigilance Network from 2002 to 2010. *Allergy* 2013; 68:929–937.

32. Blanca M, Romano A, Torres MJ, *et al*. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy* 2009; 64:183–193.
33. Torres MJ, Ariza A, Mayorga C, *et al*. Clavulanic acid can be the component in amoxicillin-clavulanic acid responsible for immediate hypersensitivity reactions. *J Allergy Clin Immunol* 2010; 125:502–505; e2.

34. Novembre E, Mori F, Pucci N, *et al*. Cefaclor anaphylaxis in children. *Allergy* 2009; 64:1233–1235.

35. Blanca M. Allergic reactions to penicillins. A changing world? *Allergy* 1995; 50:777–782.

36. Atanaskovic-Markovic M, Gaeta F, Gavrovic-Jankulovic M, *et al*. Diagnosing multiple drug hypersensitivity in children. *Pediatr Allergy Immunol* 2012; 23:785–791.

In this study, children with a history of multiple drug hypersensitivity syndrome were evaluated confirming 2.5% of them, betalactams being the drugs most frequently implicated drug.

37. Seitz CS, Brocker EB, Trautmann A. Diagnosis of drug hypersensitivity in children and adolescents: discrepancy between physician-based assessment and results of testing. *Pediatr Allergy Immunol* 2011; 22:405–410.

38. Fontaine C, Mayorga C, Bousquet PJ, *et al*. Relevance of the determination of serum-specific IgE antibodies in the diagnosis of immediate beta-lactam allergy. *Allergy* 2007; 62:47–52.

39. Vultaggio A, Matucci A, Virgili G, *et al*. Influence of total serum IgE levels on the in vitro detection of beta-lactams-specific IgE antibodies. *Clin Exp Allergy* 2009; 39:838–844.

40. Johansson SG, Adedoyin J, van Hage M, *et al*. False-positive penicillin immunoassay: an unnoticed common problem. *J Allergy Clin Immunol* 2013; 132:235–237.

41. Fernandez TD, Torres MJ, Blanca-Lopez N, *et al*. Negativization rates of IgE radioimmunoassay and basophil activation test in immediate reactions to penicillins. *Allergy* 2009; 64:242–248.

42. Iglesias-Souto J, Gonzalez R, Poza P, *et al*. Evaluating the usefulness of retesting for beta-lactam allergy in children. *Pediatr Infect Dis J* 2012; 31:1091–1093.

43. Ponvert C, Weilenmann C, Wassenberg J, *et al*. Allergy to betalactam antibiotics in children: a prospective follow-up study in retreated children after negative responses in skin and challenge tests. *Allergy* 2007; 62:42–46.

44. Atanaskovic-Markovic M, Velickovic TC, Gavrovic-Jankulovic M, *et al*. Immediate allergic reactions to cephalosporins and penicillins and their cross-reactivity in children. *Pediatr Allergy Immunol* 2005; 16:341–347.

45. Pichichero ME, Pichichero DM. Diagnosis of penicillin, amoxicillin, and cephalosporin allergy: reliability of examination assessed by skin testing and oral challenge. *J Pediatr* 1998; 132:137–143.

46. Atanaskovic-Markovic M, Gaeta F, Medjo B, *et al*. Tolerability of meropenem in children with IgE-mediated hypersensitivity to penicillins. *Allergy* 2008; 63:237–240.

47. Atanaskovic-Markovic M, Gaeta F, Gavrovic-Jankulovic M, *et al*. Tolerability of imipenem in children with IgE-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol* 2009; 124:167–169.

48. Periti P, Mazzei T, Mini E, Novelli A. Adverse effects of macrolide antibacterials. *Drug Saf* 1993; 9:346–364.

49. Craft JC, Siepmann N. Overview of the safety profile of clarithromycin suspension in pediatric patients. *Pediatr Infect Dis J* 1993; 12:S142–S147.

50. Mori F, Barni S, Pucci N, *et al*. Sensitivity and specificity of skin tests in the diagnosis of clarithromycin allergy. *Ann Allergy Asthma Immunol* 2010; 104:417–419.

51. Araujo L, Demoly P. Macrolides allergy. *Curr Pharm Des* 2008; 14:2840–2862.

52. Seitz CS, Brocker EB, Trautmann A. Suspicion of macrolide allergy after treatment of infectious diseases including *Helicobacter pylori*: results of allergological testing. *Allergol Immunopathol* 2011; 39:193–199.

53. Benahmed S, Scaramuzza C, Messaad D, *et al*. The accuracy of the diagnosis of suspected macrolide antibiotic hypersensitivity: results of a single-blinded trial. *Allergy* 2004; 59:1130–1133.

54. Messaad D, Sahla H, Benahmed S, *et al*. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Int Med* 2004; 140:1001–1006.

55. Sanchez-Morillas L, Laguna-Martinez JJ, Reano-Martos M, *et al*. Hypersensitivity to spiramycin with good tolerance of other macrolides. *J Invest Allergol Clin Immunol* 2007; 17:417–418.

56. Holmes NE, Hodgkinson M, Dendle C, Korman TM. Report of oral clarithromycin desensitization. *Brit J Clin Pharmacol* 2008; 66:323–324.

57. Kruppa A, Scharffetter-Kochanek K, Krieg T, Hunzelmann N. Immediate reaction to roxithromycin and prick test cross-sensitization to erythromycin and clarithromycin. *Dermatology* 1998; 196:335–336.

58. Rieder MJ, Shear NH, Kane A, *et al*. Prominence of slow acetylator phenotype among patients with sulfonamide hypersensitivity reactions. *Clin Pharmacol Ther* 1991; 49:13–17.

59. Caubet JC, Eigenmann PA. Managing possible antibiotic allergy in children. *Curr Opin Infect Dis* 2012; 25:279–285.

60. Levi N, Bastuji-Garin S, Mockenhaupt M, *et al*. Medications as risk factors of Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a pooled analysis. *Pediatrics* 2009; 123:e297–e304.

61. Ferrandiz-Pulido C, Garcia-Fernandez D, Dominguez-Sampedro P, Garcia-Patos V. Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of the experience with paediatric patients in a university hospital. *J Eur Acad Dermatol Venereol* 2011; 25:1153–1159.
 62. Raucci U, Rossi R, Da Cas R, *et al.* Stevens-johnson syndrome associated with drugs and vaccines in children: a case-control study. *PLoS One* 2013; 8:e68231.
- This is a multicenter study in which cases with a diagnosis of SJS were retrieved from all children hospitalized through the emergency departments, and provide risk estimates of drugs associated with SJS or TEN. Although anticonvulsants were associated with the highest adjusted odds ratio, significantly elevated risks were also estimated for antibiotics. Betalactams were the most frequently implicated followed by macrolides.
63. Wulf NR, Matuszewski KA. Sulfonamide cross-reactivity: is there evidence to support broad cross-allergenicity? *Am J Health Syst Pharm* 2013; 70:1483–1494.
 64. De Maria C, Lebel D, Desroches A, Gauvin F. Simple intravenous antimicrobial desensitization method for pediatric patients. *Am J Health Syst Pharm* 2002; 59:1532–1536.
 65. Stark BJ, Earl HS, Gross GN, *et al.* Acute and chronic desensitization of penicillin-allergic patients using oral penicillin. *J Allergy Clin Immunol* 1987; 79:523–532.
 66. Turvey SE, Cronin B, Arnold AD, Dioun AF. Antibiotic desensitization for the allergic patient: 5 years of experience and practice. *Ann Allergy Asthma Immunol* 2004; 92:426–432.
 67. Bircher AJ, Rutishauser M. Oral 'desensitization' of maculopapular exanthema from ciprofloxacin. *Allergy* 1997; 52:1246–1248.
 68. Erdem G, Staat MA, Connelly BL, Assa'ad A. Anaphylactic reaction to ciprofloxacin in a toddler: successful desensitization. *Pediatr Infect Dis J* 1999; 18:563–564.
 69. de Groot H, Mulder WM. Clinical practice: drug desensitization in children. *Europ J Pediatr* 2010; 169:1305–1309.
 70. Cernadas JR. Desensitization to antibiotics in children. *Pediatr Allergy Immunol* 2013; 24:3–9.
 71. Cernadas JR, Brockow K, Romano A, *et al.* General considerations on rapid desensitization for drug hypersensitivity – a consensus statement. *Allergy* 2010; 65:1357–1366.