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Case Series

Beta-lactam allergy in children: is it temporary? A case series

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ABSTRACT

Beta-lactam antibiotics are the most frequently prescribed antimicrobials in pediatric practice. Although hypersensitivity reactions are commonly reported, true beta-lactam allergy is confirmed in a minority of cases and may resolve over time. This prospective case series aimed to evaluate the persistence or resolution of beta-lactam hypersensitivity in children and to characterize cases with persistent allergy followed at a Pediatric Allergy consultation, in a tertiary hospital. Children diagnosed with beta-lactam hypersensitivity who underwent a follow-up oral provocation test (OPT) at least 12 months after the initial diagnosis were included. Demographic data, clinical presentation, results of the initial and follow-up OPTs, and characteristics of persistent cases were analyzed. Fourteen children were included. At follow-up, 64% tolerated amoxicillin, with a mean interval of 18 months between the initial and repeat OPTs. Five children showed persistent hypersensitivity, predominantly presenting with non-immediate cutaneous reactions. Some persistent cases also had a personal or family history of hypersensitivity to other antibiotics or foods. These findings suggest that beta-lactam allergy in children may be transient. Periodic re-evaluation with OPT enables delabeling in a significant proportion of patients, thereby optimizing antibiotic selection. Further studies are needed to determine the ideal retesting interval and identify predictors of persistent hypersensitivity.

Keywords: Beta-lactam allergy, Children, Drug hypersensitivity, Oral provocation test, Transient allergy

INTRODUCTION

Beta-lactam antibiotics are the most commonly prescribed antimicrobial agents in pediatric populations.[1] Reported hypersensitivity reactions occur in about 11% of children, and the diagnostic label of beta-lactam allergy is associated with important clinical consequences: use of broader-spectrum or less effective antibiotics, higher treatment costs, increased bacterial resistance and longer hospital stays.[2,3]

Recent studies suggest that beta-lactam allergy often resolves over time in children. Some studies demonstrated that up to 30% of IgE-mediated reactions may be lost after one year and up to 60% after five years, with tolerance rates approaching 80–90% over longer follow-up periods.[4,5] The Canadian Paediatric Society suggests 5 years after the diagnosis to re-access individuals who have been diagnosed with penicillin allergy.[6] Nevertheless, the optimal timing to repeat the oral provocation test (OPT) and the factors associated with persistent hypersensitivity remain unknown.

This study aimed to evaluate the natural history of beta-lactam hypersensitivity in a pediatric population by

assessing tolerance on follow-up OPT and to describe cases with persistent reactions.

CASE SERIES

A prospective observational case series was conducted at the Pediatric Allergy Consultation of Hospital Pediátrico de Coimbra (ULS Coimbra), a tertiary referral center. Children with a previous diagnosis of beta-lactam hypersensitivity were prospectively followed and reassessed, focusing on the natural evolution of beta-lactam hypersensitivity reactions.

Participants were eligible for inclusion if they were younger than 18 years, had a history of a non-immediate hypersensitivity reaction to amoxicillin, had a positive initial oral provocation test (OPT), and accepted to repeat OPT at least 12 months after the initial diagnostic OPT. Patients with a history of severe immediate reactions, such as anaphylaxis, or severe delayed reactions, including Stevens–Johnson syndrome, toxic epidermal necrolysis, or DRESS, were excluded. All patients performed a standardized diagnostic approach, according to current EAACI recommendations: a direct oral provocation testing, without prior skin testing, was performed, given the benign nature of the initial reactions.

Amoxicillin was used in the OPT as it is the most frequently prescribed and implicated beta-lactam. The test consisted of incremental dosing up to half weight-appropriate therapeutic dose, followed by clinical observation in the following 2 hours, and parental report of delayed symptoms, via e-mail, in the succeeding days. The OPT duration was adjusted to the initial episode characteristics, up to 5 days. All patients were also tested with cefuroxime, as an alternative beta-lactam, in case they had not yet been exposed to it, using a similar protocol.

Fourteen children were included in the study, 64% (n=9) male, aged between 8 months and 12 years at the time of the first reaction. The primary indication for amoxicillin treatment was acute otitis media; all patients developed a benign cutaneous reaction after a mean of 4.9 days of treatment. In the first OPT, the mean time to reaction was 2.3 days, and all patients presented with a similar cutaneous reaction maculopapular exanthema. One patient presented with serum sickness–like disease, characterized by maculopapular exanthema, fever, localized edema, and arthralgia.

Table 1 summarizes the clinical characteristics of the initial reaction and first oral provocation test of the cohort.

Resolution of hypersensitivity

All children performed a second OPT, at least 12 months after the one that confirmed the hypersensitivity, with a mean interval between OPT's of 16 months (12-30 months).

Nine children (64%) had a negative follow-up OPT, tolerating amoxicillin after a mean interval of 18 months (13-30 months) from the initial OPT.

Persistent hypersensitivity

Five children (36%) showed persistent hypersensitivity on follow-up OPT, with a mean interval of 12 months (12-13months) between tests.

In the second OPT, as in initial reaction and first OPT, clinical manifestations mainly included urticaria, maculopapular exanthema, and generalized pruritus. One patient presented with a serum sickness–like reaction (fever, edema, and arthralgia). This patient underwent repeat testing because, although serum sickness–like reactions may present with marked clinical features, they are generally considered a benign manifestation of hypersensitivity3. Additionally, during the first OPT, parents did not fully describe the symptoms; these were more accurately reported when compared with the follow-up OPT.

One patient had a family history of beta-lactam allergy, a known risk factor for hypersensitivity to this drug class.[7] Another child developed a reaction to cefuroxime during the OPT to an alternative beta-lactam.

Table 2 summarizes the clinical characteristics of the children with persistent beta-lactam hypersensitivity and their follow-up OPT.

Table 1: Clinical characteristics of the cohort in the initial reaction and first oral provocation test. Mo - month, d - days; y - years

Mean age at first reaction (years)	**4.9 [8mo - 12y]**
Indication	OMA (n=5); Streptococcal tonsillitis (n=5); Cervical adenitis, Upper respiratory infection, Pneumonia, Periorbital cellulitis (n=1)
Mean Time until reaction (days)	5.8 [2-10]
Mean time until reaction in the 1st OPT (days)	2.3 [1h - 7d]

Table 2: Clinical characteristics of children with persistent beta-lactam hypersensitivity and their follow-up OPT.

Mean age at first reaction (years)	**3.9 (8-11 months)**
Interval between OPTs (months)	12.2 (12-13)
Mean time until reaction	28.8 (6-96 h)

DISCUSSION

This prospective case series demonstrates that beta-lactam hypersensitivity in children is frequently transient, with 64% of patients tolerating amoxicillin on follow-up OPT after a mean interval of 16 months. These findings are consistent with previous studies describing a high rate of resolution of beta-lactam allergy in pediatric populations.

International guidelines emphasize that most beta-lactam allergies in children, particularly non-immediate benign cutaneous reactions, are not persistent and recommend active de-labeling strategies using OPT.[6-9] Our results support this approach, showing that systematic reassessment leads to removal of the allergy label in 2 in every 3 children, within a short follow-up period. The literature reports that children with benign non-immediate reactions frequently tolerate beta-lactams on re-exposure, even after an initially positive provocation test, highlighting the dynamic nature of drug hypersensitivity. The resolution rate observed in our cohort aligns with other recent data.[4,5,10]

Persistent hypersensitivity was observed in 36% of children, who exhibited symptoms comparable to those observed during the first OPT. Some of these patients presented at the extremes of pediatric age, with earlier onset of reactions, more exuberant clinical presentations, or family history of beta-lactam allergy. However, none of these factors were consistently present across cases and therefore can only be suggested as potential predictors of persistent hypersensitivity. Given the limited sample size, definitive risk factors could not be established. It is important to emphasize that cross-reactivity or multiple beta-lactam sensitivities can occur, as it happened with one child. This reinforces the importance of individualized assessment and cautious use of alternative beta-lactams.[10] The optimal timing for repeat OPT remains uncertain. Our data, and the existing literature, indicate that a 12-24-month interval is effective in resolution of the hypersensitivity in most children.[11] Larger prospective studies are needed to define evidence-based retesting intervals and predictors of delayed resolution.

Limitations

We acknowledge some limitations to our study. First, the sample size was small (n=14), reflecting the experience of a single center in which the diagnostic protocol was changed in spring 2024 in accordance with emerging evidence from the literature. Second, the follow-up period was relatively short, and therefore most patients had not yet required amoxicillin as the antibiotic of choice following the negative OPT.

CONCLUSION

Beta-lactam allergy in pediatric patients is frequently transient. Repeating OPT allows safe delabeling in approximately two-thirds of children with a previous diagnosis, improving antimicrobial stewardship and clinical outcomes. Further prospective studies with larger cohorts are needed to identify predictors of persistent allergy and to establish evidence-based retesting intervals.

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