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ORIGINAL ARTICLE

AMOXICILLIN ALLERGY IN CHILDREN - A 22 MONTH STUDY

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ABSTRACT

Introduction: Unconfirmed amoxicillin allergy is an important public health problem due to the limitations it imposes on therapeutic choice. The aim of this study is to characterize the pediatric population suspected of amoxicillin allergy.

Methods: Observational, retrospective, descriptive and analytical study of the pediatric population with suspected amoxicillin allergy referred by general pediatrics to immunoallergology consultation between January 2018 and October 2019 in a tertiary care center.

Results: 224 patients (50% female) were studied. Most had atopy (n=159; 71%), however, the likelihood of drug allergy was not significantly higher in these children (p = 0.749). The median age of reaction was 22 months (minimum 4 months; maximum 17.7 years). The reaction was non-immediate in 99.6% and immediate in only one patient. The most frequent symptom was exanthema (96.4%); anaphylaxis occurred in one patient. 35.3% patients were previously exposed to the same antibiotic class. In ambulatory management, only one patient had positive specific IgE to ampicillin; all skin tests performed (n=25) were negative; four of the 138 amoxicillin oral provocation tests were positive; in 18 patients an alternative challenge was performed with cefuroxime and cefixime, which was negative. 41 patients did not undergo the oral provocation test. Allergy was confirmed in 5.4% patients (n=12).

Conclusions: Our results were consistent with international studies. Amoxicillin allergy, although rare in children, requires an accurate diagnosis, emphasizing the importance of approaching it in a specialized consultation to avoid severe adverse reactions, reduce the misdiagnosis of amoxicillin allergy patients and provide alternative treatment options.

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amoxicillin allergy, beta-lactam, children, drug allergy, hypersensitivity

ABBREVIATIONS

BL - β-lactam

DHR - Drug hypersensitivity reactions

NSAIDs - Non-steroidal anti-inflammatory drugs

OPC - Oral provocation challenge

Introduction

Drug hypersensitivity reactions (DHR) are often overestimated in children, as only a small number of cases are actually confirmed through diagnostic work-up. A study conducted on pediatric patients suspected of having a penicillin allergy showed that approximately 95% of the cases were negative. Labeling a child as having a drug allergy can lead to negative clinical outcomes, especially in the case of antibiotics. This can result in the increased use of broad-spectrum antibiotics, which in turn can lead to higher rates of bacterial resistance, increased risk of infections from drug-resistant pathogens, greater morbidity, toxicity, longer hospital stays, and higher healthcare costs. Additionally, there is often an incorrect association between drug allergies and predictable adverse reactions, such as gastrointestinal reactions from macrolides, tendinous rupture from fluoroquinolones, and ototoxicity from aminoglycosides. Therefore, it is crucial to confirm or exclude a diagnosis of drug allergy.[1,2,3,4,5,6]

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The most frequently implicated drugs are β-lactam (BL) antibiotics, especially amoxicillin, followed by non-steroidal anti-inflammatory drugs (NSAIDs) and non-BL antibiotics. Unconfirmed amoxicillin allergy, which is one of the most frequently prescribed drugs, poses a significant public health concern as it limits treatment options. The diagnosis of DHR is confirmed through positive skin tests and/or specific IgEs or oral provocation challenge (OPC).[1,2,3] This study aimed to assess and characterize pediatric patients with suspected amoxicillin allergy and determine the prevalence of amoxicillin allergy.

Methods

An observational, retrospective, descriptive and analytical study was conducted. The sample included the pediatric population with suspected amoxicillin allergy referred by general pediatrics to Immunoallergology consultation between January 2018 and October 2019 in a tertiary care center.

The study variables were: gender, personal and family history of atopy, usual medication, age at the reaction, suspected drug, reaction timing, reaction symptoms, prescription reason, previous exposure to the suspected drug, previous exposure to the same and another antibiotic class, reaction treatment,

relapse, later tolerance to the drug or another drug class, specific IgE to amoxicillin ampicillin and penicillin determinants, skin tests and OPC results.

Patient clinical data collection was carried out by consulting the clinical process. Statistical analysis of collected data was performed using Microsoft Excel® and SPSS statistical software version 21 (IBM, Armonk, NY, USA)®. Some variables were compared using Fisher's exact test. Significance was set at $p < 0.05$.

Ethical Principles and Good Clinical Practices in order to comply with the precepts of the Declaration of Helsinki,[7] the Convention on Human Rights and Biomedicine,[8] the Council for International Organizations of Medical Sciences guidelines[9] and the Good Clinical Practice Guide (ICH, GCP)[10] were safeguarded during the study. The study was approved by the Ethics Committee of Hospital de Braga.

Results

The sample included 224 patients, 112 female, and 112 males. Most had a personal history of atopy (n=159; 71%); 57 children (25.4%) had a family history of atopy. There was no statistically significant association between drug allergy and personal or family history of atopy (p=0.749 and p=1.000, respectively). Most children were not taking regular medication (n=191; 85.3%). The reaction median age was 22 months, a minimum of 4 months and a maximum of 17.7 years. In 114 cases amoxicillin and clavulanic acid combination was prescribed and in 110 patients only amoxicillin. The reaction was non-immediate in 99.6% (23 patients after treatment discontinuation) and immediate in only one patient. The most frequent symptom was exanthema (96.4%); anaphylaxis occurred in one patient - Table 1.

Table 1. Symptoms during suspected hypersensitivity reaction.

Symptom	n	%
Exanthema	216	96,43
Pruritus	76	33,93
Fever	19	8,48
Vomiting	12	5,36
Anaphylaxis	1	0,45

The most frequent prescription reasons were acute otitis media and acute pharyngitis - Table 2.

Table 2. Amoxicillin prescription reasons.

Prescription reasons	n	%
Acute otitis media	73	32,59
Acute pharyngitis	72	32,14
Upper respiratory infection	23	10,27
Urinary tract infection	12	5,36
Pneumonia	10	4,46
Acute otitis media and acute pharyngitis	4	1,79
Cellulitis	2	0,89
Scarlet fever	2	0,89
Dental abscess	1	0,45
Acute bronchiolitis	1	0,45
Periorbital cellulitis	1	0,45
Chalazion	1	0,45
Epistaxis	1	0,45
Exanthem subitem	1	0,45
Pharyngitis	1	0,45
Sinusitis	1	0,45
Unknown	18	8,04

35.3% (n=79) patients were previously exposed to the same antibiotic class; 7.6% (n=17) were previously exposed to another class.

In children who underwent adverse reaction treatment, the most used drugs were antihistamines. In 59% cases, no treatment was needed - Table 3.

Table 3. Drugs used in reaction treatment.

Drugs used in reaction treatment	n	%
Antihistamines	61	27,23
Antihistamines + systemic corticosteroids	26	11,61
Corticosteroids	3	1,34
Epinephrine + antihistamines + systemic corticosteroids	1	0,45
Unknown	74	33,04
None	59	26,34

Eight-point nine percent (n=20) patients were re-exposed to the same antibiotic and had a similar reaction.

Later tolerance to the same antibiotic class was verified in 17.9% (n=40) patients and to another class in 55.8% (n=125).

In the allergy diagnostic work-up, only one patient had positive specific IgE to ampicillin. All skin tests performed (n=25) were negative. In 138 diagnostic OPC performed, only 4 were positive; in 18 patients, an alternative challenge was performed with cefuroxime or cefixime, which was negative - Table 4. Legend: OPC – oral provocation challenge

Allergy was confirmed in 5.4% of patients (n=12): four with positive OPC, one with positive specific IgE, one had a type III hypersensitivity reaction, three had reproducible reactions, one had anaphylaxis, one had a reaction in the first hour and one had positive lymphocyte transformation test. Seven patients were female and five were male.

Discussion

DHRs occur less frequently in children compared to adults and may be mistakenly overestimated by confusing an adverse effect with an allergic reaction.

Table 4. Ambulatory complementary diagnostic exams.

Complementary diagnostic exams	Result	n
Specific IgE	Positive	1
	Negative	124
Skin tests	Positive	-
	Negative	25
Diagnostic OPC (amoxicillin)	Positive	4
	Negative	134
Alternative OPC (cefixime)	Positive	-
	Negative	10
Alternative OPC (cefuroxime)	Positive	-
	Negative	8
Lymphocyte transformation test	Positive	1
	Negative	-

Approximately 10% of parents report that their child has experienced at least one DHR, but very few are confirmed after undergoing allergy diagnostic work-up.[1] BL adverse reactions are common in children but less than 10% of cases are truly allergic.[1,2,4] In this study, the confirmed DHR due to amoxicillin was 5.4%, which aligns with the available data. Limited pediatric data describe the impact of age and sex on antibiotic allergy rates.[11] Some studies suggest a similar gender distribution in pediatric populations[3,11], as confirmed in this study. Drug allergic reactions can occur at any age.[2] According to Lucas et al[11], an increasing prevalence of antibiotic allergy labeling with age has been observed. An American study analyzing data from both adults and children found that increasing age was significantly associated with a higher prevalence of reported antibiotic allergy.[12]

Patients with a prior atopy history do not have an increased risk of drug allergy, although they may have more severe IgE-mediated reactions.[2] According to Dias de Castro E et al, BL allergy probability is significantly higher in children with drug allergy family history.[4] In this study, although most children had an atopy personal history (71%), their allergy likelihood was not significantly higher (p=0.749). Likewise, no statistically significant association was found between allergy and atopy family history (p=1.000).

BL (including penicillins, cephalosporins, carbapenems, and monobactams) are the antibiotics most commonly associated with allergic reactions, which can be mediated by IgE or T cells.[1,2] In one study, more than half of the children reacted upon their first exposure to amoxicillin, suggesting that these reactions are unlikely to be IgE-mediated, since they require prior exposure to generate drug-specific IgE.[1] The increased frequency of immunological reactions compared to other antibiotics may be due to the high production capacity of hapten-protein conjugates and their very frequent prescription in the pediatric population.[2] Over 80% of children report only mild to moderate and often none IgE-mediated adverse reactions to antibiotics (commonly rashes).[13] The most frequent reactions are non-immediate, such as maculopapular exanthema or delayed urticaria, which might be related to the underlying infection rather than a true allergy to the antibiotic.[4] A classic example of this phenomenon is the well-established association of maculopapular exanthema after several days of treatment with amoxicillin during Epstein–Barr virus infection. The likelihood of not confirmed allergy is higher in children with less severe reactions and with maculopapular exanthema.[4] In this study, the reaction was non-immediate in 99.6% of cases, occurring even after discontinuation in 23 patients. It can be assumed that the patient had a delayed maculopapular skin reaction when the history clearly suggests macular or papular lesions limited to the skin, with or without pruritus, that began more than one hour (typically, several hours) after the last administration of the antibiotic and has no urticaria, angioedema, systemic symptoms or more severe delayed reactions warning signs.[3] Nonimmediate skin reactions resolve upon discontinuation of the involved drug, usually within one or two weeks, although symptoms may worsen for a few days even after drug withdrawal.[1] Immediate reactions with urticaria or anaphylaxis are far less frequent in children, but the likelihood of confirming an allergy in these cases is higher.[2] True IgE-mediated BL allergic reactions are uncommon and anaphylaxis, although not well-documented, is exceedingly rare, accounting for approximately 0.001% of parenteral exposures and 0.0005% of oral exposures. Fatal outcome is extremely rare.[14,15,16] Anaphylaxis is a systemic reaction of sudden onset with the involvement of two or more systems. In most cases, anaphylaxis presents with mucocutaneous symptoms (80-90%), often associated with one or more other organ symptoms. Respiratory symptoms of the upper or lower airways are observed in 40-60% of patients, and additional manifestations, such as cardiovascular, gastrointestinal, and neurological symptoms may also occur in up to one-third of cases. In this study, anaphylaxis occurred in only one patient. Severe cutaneous adverse reactions are very uncommon in childhood, with only isolated cases or small series related to different drug data available. Typically, the drugs implicated are BL antibiotics, NSAIDs, and antiepileptics.[2] Some severe forms of non-immediate reactions may initiate with a maculopapular exanthema and then progress to more severe clinical signs and symptoms. Warning signs of severe and life-threatening drug reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis include fever (>38°C), mucosal involvement, skin tenderness or pain, and blistering.[1] In this study, none of the patients had a severe cutaneous adverse reaction.

Our data showed that the most frequently reported symptom was exanthema (96.4%), which is consistent with available evidence where the most common manifestations are cutaneous. Aminopenicillins have been associated with maculopapular eruptions in up to 5 to 10% patients, particularly in children, often in the context of a viral infection.[17] In patients with concomitant fever (8.48%), we have to consider the occurrence of symptoms induced by pathogens, which is a much more prevalent situation.[3] Adverse reactions such as isolated episodes of vomiting or diarrhea should not be interpreted as DHR.[2]

The most frequent prescription reasons were acute otitis media and acute pharyngitis. It should be noted that most of these infections in children are

of viral etiology, which are frequently responsible for exanthems appearance.

About half of the participants (42.9%) had been previously exposed to antibiotics. Only five of the 12 patients with confirmed allergy had previous exposure to the same class of antibiotic, while the remaining data are unknown. The reaction occurred on first exposure to amoxicillin in 65 participants, making the IgE-mediated reaction unlikely; and in 52 participants previously exposed to another class.

DHR diagnosis is based on clinical history, in vitro tests (specific IgE test, basophil activation test, lymphocyte transformation test), and in vivo tests (skin tests - prick, intradermal, epicutaneous, and OPC). Clinical history alone is insufficient for establishing a DHR diagnosis or adverse drug reactio[2,5], but is sufficient for its exclusion when symptoms and timeline do not suggest drug hypersensitivity, such as type A reactions or clinical signs of infection.[2] It's of main importance to collect as much information as possible regarding the ADR symptoms, detailing the chronology of allergy-related symptoms, identifying the potential drugs involved and assessing the patient›s medical history. The selection of specific tests to perform depends on the suspected drug and reaction type; OPC is the gold standard for diagnosis.[2] DHR diagnosis is established when skin tests and/or specific IgEs or OPC are positive.[4] Diagnosis usually requires OPC due to the lack of standardized and widely available in vivo and in vitro tests.[3] OPC should always be performed in a hospital center, equipped for the treatment of possible anaphylaxis, under medical supervision.[2]

In this study, 125 patients underwent a specific IgE test, which was positive in only one patient.

Performing OPC without in children with a history of mild non-immediate reactions, without prior blood tests or skin tests, has been shown to be both safe and efficient.[18] All skin tests performed were negative, which further reinforces the safety of conducting OPC without preceding tests.

Of the 138 diagnostic OPC performed, only 4 were positive. According to Lutfeali & Khan, among the 818 children challenged with amoxicillin, 94,1% tolerated the challenge with 2,1% experiencing immediate (<1 hour) reactions and 3.8% having delayed reactions.[3] In 18 cases, OPC was performed using an alternative antibiotic, all these challenges produced negative results. According to Lutfeali & Khan, cefuroxime was tolerated by all but one of the penicillin-allergic patients who were administered the cefuroxime challenge.[3] The OPCs performed in this study were one-day challenges. However, five-day OPC may increase the detection of non-immediate reactions. Mori and colleagues[19] showed an increase in the detection of nonimmediate reactions from 35.7% to 100% with the use of prolonged five-day challenges in a European pediatric cohort of 200 patients with suspected amoxicillin allergy.[3,19] Confino-Cohen and colleagues also found an increased detection of nonimmediate reactions, an additional 6.1% of cohort patients developed mild delayed reactions during a prolonged five-day challenge compared with the one-day challenge.[3,20]

Among the 165 participants with available data, later tolerance to the same antibiotic class was found in 17.9% patients and to another antibiotic class in 55.8% patients.

In non-immediate reactions, the preferred alternative drug are cephalosporins, avoiding first-generation ones, particularly those with a similar side chain to amoxicillin (such as cefadroxil, cefprozil, cefazolin).[1,2] As for immediate reactions, it is advisable to avoid cephalosporins, particularly in the case of anaphylactic reactions. However, in the presence of a severe infection, in which a BL treatment is necessary, a cephalosporin with a different side chain or a carbapenem can be considered, with the initial administration conducted under close supervision.[2] Cephalosporins are also contraindicated in severe non-immediate reactions, and their management should follow a similar approach as for immediate reactions[2] In systemic or generalized blistering diseases, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms / drug hypersensitivity syndrome all BL should be avoided.[1] In all cases, a non-BL alternative can be administered without any restrictions. However, in situations where an alternative BL is required, structural similarities should be avoided.[5] Desensitization, defined as the temporary induction of tolerance (which can be maintained through continuous drug exposure), may be considered when there is no alternative drug available.[3] However, this approach should only be pursued in cases of immediate allergic reactions, and it is consistently contraindicated in the context of delayed organ-specific reactions or severe cutaneous or systemic reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and drug rash with eosinophilia and systemic symptoms.[2]

Cases of suspected DHR should be promptly referred for management in an immunoallergology consultation. This referral is crucial, regarding the consequences of forbidding a drug: economic, essential drug, irreplaceable or frequently used drug, use of alternatives with a higher risk of resistance.

One limitation of this study was the small number of children with a confirmed allergy which precluded the possibility of conducting a multivariate analysis. Furthermore, the retrospective design of the study meant that data collection relied on pre-existing clinical records.

Conclusion

The results obtained are consistent with international research findings. Allergy to amoxicillin, although rare in children, requires a precise diagnosis, emphasizing the importance of referral to specialized consultation. Profound comprehension of pediatric drug allergies and their precise confirmation, is crucial to prevent overdiagnosis. It is essential to make an accurate diagnosis of drug hypersensitivity or allergy, not only to prevent severe reactions but also to minimize the occurrence of mislabelled patients and to provide appropriate therapeutic alternatives.

Compliance with Ethical Standards
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Conflict of Interest None

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