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EDITORIAL

# Allergy to beta-lactam antibiotics in children: Looking for a practical approach

According to the World Health Organization (WHO), an adverse drug reaction (ADR) is defined as a harmful or undesired effect following the administration of a drug at therapeutic, diagnostic or prophylactic doses.[1]

Adverse drug reactions include drug hypersensitivity reactions (DHRs) characterized by severity which ranges widely from common and mild problems to serious skin reactions mediated by immune (allergic reactions) or non-immune mechanisms (non-allergic hypersensitivity reactions). Both types are a growing and important source of demand for care in our pediatric allergy units, and account for between 8–10% of all consultations.[2] However, as evidenced by a number of studies in children with suspected DHRs subjected to testing (allergic tests and drug provocation tests [DPTs]), approximately 90% of the patients are tolerant.[3,4]

There are shortcomings in our knowledge of the epidemiology of these processes in the pediatric population. While prospective studies on cutaneous adverse drug reactions are scarce, purported DHRs in children do pose a health problem of some importance.

The most common clinical manifestations of hypersensitivity reactions are referred to the skin, with a number of morphological and chronological features ranging from erythema to maculopapular exanthema or rash (MPR), urticaria, angioedema, blister, pustules, mucous membrane involvement, etc. In the pediatric population, DHRs often coexist with infectious processes, many of which are caused by viruses, and the administration of antibiotic treatment — particularly beta-lactams.[5,6]

It is not clinically possible to distinguish whether the cause of the reaction is the drug, or whether the virus is directly responsible for lymphocyte activation that triggers the symptoms or interaction with metabolism of the drug. In the study published by Bass et al.,[7] between 3–7% of the children administered oral ampicillin developed maculopapular rash. All of them completed the seven-day treatment cycle without other adverse effects. Rash in this case was interpreted as an adverse drug reaction, not as an allergic reaction to the medication. Thus, in order to define the situation of these patients, studies are needed, and it is particularly important to eliminate false diagnoses of drug allergy.

In the present number of Allergologia et Immunopathologia, Dias de Castro et al. present the results of their retrospective study entitled: ''Allergy to beta-lactam antibiotics in children'', involving 220 patients. The objectives of the study included definition of the frequency of beta-lactam allergy in their population, evaluation of the safety of using a less broader testing protocol in patients with mild reactions, and identification of the possible risk factors predicting test positivity.

The number of children included in the study makes it possible to conclude that skin reactions are the most frequent problem, representing 96.9% of the cases — with maculopapular rash being the predominant manifestation. Non-immediate reactions accounted for close to 60% of the cases, although it is important to mention that the type of reaction could not be established in 30% of the patients, probably due to the time elapsed from reaction onset to evaluation of the lesions (2.9 years on average).[8] Difficulties in remembering what happened so long ago might also interfere with data collection. The diagnosis of beta-lactam allergy was confirmed in only 23 of the children (10.5%) — this was consistent with the data found in the literature.[3,4] Of these cases, three constituted immediate reactions while 14 were non-immediate reactions. The question here is whether these data also could be influenced by the long-time interval between onset of the reactions and their study. Approximately 50% of all children with mild non-immediate hypersensitivity reactions to penicillins may tolerate the implicated drug after some time.[9]

The retrospective study design and few positive patients imply a need for caution in drawing certain conclusions. The study does not describe the diagnostic procedures used to consider a positive family history of drug allergy; no mention is made of how many patients had mild reactions; and the criteria used for considering a given reaction to be mild are not specified.

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An interesting finding is the fact that only 4.2% of the patients with mild reactions yielded a positive DPT, with manifestations similar to those of the reaction for which patient evaluation was indicated in the first place — although one patient with a presumably mild reaction (patient 19) did not undergo DPT due to the presence of positive skin testing.

Although maculopapular rash in children is secondary to infection in over 50% of all cases,[10] its relation to Stevens–Johnson syndrome and toxic epidermal necrolysis is subject to controversy, and there is some evidence that these severe forms of drug hypersensitivity are clinically and etiologically distinct from maculopapular rash.[11] It is important to bear in mind the recommendations and contraindications of DPT, and of course we must never forget the principle of ''*primum non nocere*''.

In cases with anaphylactic symptoms, particularly when there has been more than one episode and/or the study is carried out more than one year after the reaction, it is advisable to repeat specific IgE testing and skin tests before performing DPT.[12]

There is growing evidence – and the mentioned study corroborates this – on the importance of simplifying the study of beta-lactam antibiotic allergy in the pediatric population. In this regard we need more prospective studies, seeking to identify not only genetic risk factors. Genotyping is indicated in specific populations, but not all carriers develop symptoms — thus suggesting the importance of cofactors.[13] It is essential to unify methodologies and criteria referred to both the diagnosis of the skin lesions[14] and the tests to be made,[15,16] in order to establish which patients should undergo DPT – which is regarded as the gold standard for drug hypersensitivity diagnosis – directly, and if possible on the same day of first patient consultation, since doing so avoids undue discomfort for the patients and families, and results in considerable health resource savings. It also remains to be clarified whether DPT should be made in single dose form or stepwise; establish what the duration should be (one day, three days, or for as long as the patient presented the symptoms, according to the chronology of the suspected allergic reaction); and define when the study should be repeated in patients that prove positive or experience mild non-immediate reactions. Another issue is whether the decision-making algorithms in these patients should focus priority on the type of reaction (immediate or non-immediate) or on the symptoms of the reaction.

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