Accepted: 6 September 2017

DOI: 10.1111/pai.12800

ROSTRUM

WILEY

Oral challenge without skin tests in children with non-severe beta-lactam hypersensitivity: Time to change the paradigm?

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Abstract

Suspected allergy to penicillins and cephalosporins is very common in childhood. After a proper evaluation, allergy will be confirmed only in a small portion of them. Intradermal tests are usually part of the allergy workup, but they are painful for children and time-consuming, and their role has been debated. A systematic review found only two studies reporting a positive predictive value of skin tests in children of 36% and 33%, respectively, leading to a high rate of inaccurate diagnosis. Moreover, considering that skin tests are negative in more than 90%-95% of cases, an oral provocation test (OPT) is finally needed to confirm tolerance in most of these children. Positive OPT are rare, and even where children demonstrate reproducible signs on challenge, they rarely constitute immediate or serious symptoms. Therefore, OPT to the index antibiotic without skin tests are increasingly being considered an accepted procedure for children with a suspected mild non-immediate reaction related to a beta-lactam antibiotic. Furthermore, a recent research has taken the same approach including children with suspected mild immediate reactions, with similar safety and positive results. In light of recent evidence highlighted, it is now the time for large and multicentric studies to confirm that OPT with the index antibiotic, without skin tests, are safe and convenient for children with a history of a mild reaction with a beta-lactam antibiotic before it can be recommended in pediatric allergy guidelines.

KEYWORDS

beta-lactam hypersensitivity, child, oral challenge, skin tests

Any child goes through multiple infectious diseases, usually viral and mild, along his childhood. Skin manifestations are a common symptom in many of those diseases, much more common than in adults. Antibiotics are commonly prescribed for infections in children. Thus, a significant number of children develop different types of skin rashes while being treated with an antibiotic. The vast majority of these children, concerning about 5% of general pediatric population according to studies based on questionnaire,[1,2] are considered as allergic, mainly due to fear of a more severe reaction, without appropriate allergy testing. After a proper evaluation, allergy will be confirmed only in a small proportion of these children.[3] Intradermal tests, usually performed in the allergy workup, are painful and difficult to interpret in children, especially in infants, and it may decrease the number of children with a suspicion of antibiotic allergy undertaking an allergy workup. However, the role of skin tests in the allergic evaluation of suspected non-severe beta-lactam hypersensitivity (BLH) has been recently highly debated.

1 | WHAT TO DO WITH A CHILD WITH SUSPECTED BLH IN A SPECIALIZED PEDIATRIC ALLERGY CLINIC?

The management of children with a suspicion of BLH has historically been based on data from the adult population and experts' opinions. Thus, skin tests (and possibly in vitro tests) are usually recommended before a drug provocation test, the gold standard, is to be considered.

But adults are much more at risk of serious allergic reactions from drugs and the pediatric population does not have the same cardiovascular risk factors, nor behavioral traits as concerned parents. In benign non-immediate BLH (without any danger sign), the most common clinical scenario in childhood, it has been recommended to perform intradermal tests (delayed-reading) and, if negative, an oral provocation test (OPT) to the index antibiotic. Of note, lymphocyte transformation tests and patch tests have been shown to be not efficient for the diagnosis of benign non-immediate reactions to beta-lactams in children.[4,5] Considering that most children (more than 90%) are not confirmed as allergic, this algorithm is heavily resource-intensive and time-consuming or could even lead to a number of wrong diagnoses of drug hypersensitivity due to uncertain predictive values of skin tests. In recent years, a number of papers have challenged the academic guidelines and have explored the feasibility of performing OPT without skin tests in children with suspicion of a benign non-immediate reaction.[4,6-9] In spite of reported good results, economic savings, and observed satisfaction by parents and doctors, this attitude is still debated and some authors still consider performing intradermal tests, mainly due to fear of severe reactions during OPT.[10] As a result, in current clinical practice, things are not so clear and very different approaches are followed by practicing clinicians.[11]

2 | EVIDENCE FOR THE UTILITY OF SKIN TESTS IN CHILDREN WITH SUSPECTED BLH

What the role is, then, for skin tests in children with suspected BLH? Although the negative predictive value has been shown to be relatively high,[12] very few observational studies investigated the real positive predictive value of skin tests, particularly in the pediatric population. For safety and ethical reasons, OPT is usually not performed in patients with positive skin tests.[13] But this is only because there is a perceived risk of serious reactions during OPT to antibiotics in children, and the evidence increasingly does not support this view. In a study of Caubet and colleagues, both skin tests and OPT were performed in 88 children with a history of mild non-immediate reactions with a betalactam antibiotic: 11 had an immediate positive intradermal test, but only 4 of them had a mild exanthema when challenged, giving a positive predictive value of 36% in that population.[4] If current guidelines would have been followed by Caubet et al and positive skin tests were considered diagnostic, then only 11 OPT would have been avoided (only 4 of them being positive but mild) and 13 diagnoses of BLH would had been formulated, 7 (more than half) of them inaccurately. To evaluate the real diagnostic value of skin tests, they performed a follow-up study to include more patients with a positive OPT. Their results showed that the sensitivity of intradermal test was 50% and the specificity 91.5%.[5] Given the low pretest probability (prevalence of true BLH below 10%), positive predictive values of skin tests are even weaker than their sensitivity, resulting in many inaccurate BLH diagnoses. This is also an issue among adults as highlighted in a recent paper.[14] On the other side, a large number of children have to be skin-tested, but most of them (those with negative results) need an OPT to be anyway performed to identify the small number of patients truly allergic or to formally exclude it. As an example, an analysis over a series of 783 children studied by Zambonino et al[15] showed that if OPT would have been performed directly, 66 in vitro tests and 781 skin tests would have been spared, resulting in only 6 additional OPT (in those few patients with positive in vitro or skin tests) to the other 777 performed.[16] Because of the relative lack of studies, the pediatric guidelines for the management of drug hypersensitivity in children have been based on "expert" opinions held within long-standing practice, resulting in far too many inaccurate and painful intradermal tests among children. But new guidelines are now incorporating recent evidence and OPT without skin tests are recommended for mild non-immediate suspected reactions.[1,2] The determination of the real diagnostic value of skin tests would definitely improve the management of children with suspicion of BLH and possibly decrease medical costs. On the other side, quality of life of children labeled as allergic to beta-lactams has not been formally evaluated,[17] but a relevant impact has been reported on treatments and outcomes in hospitalized patients,[18,19] and the diagnosis persists into adulthood, which should be taken into account when possible false-positive tests are being considered.

3 | SAFETY OF OPT FOR SUSPECTED BLH

As stated above, the use of skin (and in vitro) tests for the workup of children with suspected BLH is intended to avoid as much as possible positive OPT. However, their observed very low performance (more than 90%-95% of skin tests are negative) and lack of (or unknown) accuracy have been shown for a long time, even in the adult population. In this regard, the alleged advantage of trying to avoid OPT relies on the risks attributed to positive OPT. The risk of death due to anaphylactic shock after oral administration of amoxicillin in the general population is extremely low.[20] Under controlled conditions, positive OPT have usually been mild in children with a history of non-severe cutaneous reactions,[4,7,10,15] or even in children with a history of anaphylactic reactions and negative skin tests,[12,21,22] and severe reactions are very uncommon and easily treated.[11,23] On the other hand, OPT have been very rarely performed on children (and adults) with positive skin tests[4] or with a history of severe delayed cutaneous-systemic reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, DRESS syndrome…), in accordance with precautions and contraindications reaffirmed in the last International Consensus on drug allergy.[24]

4 | DIRECT OPT FOR CHILDREN WITH SUSPECTED IMMEDIATE AMOXICILLIN HYPERSENSITIVITY: BREAKING THE DOGMA

For a long time, guidelines for the evaluation of patients with a suspicion of immediate BLH recommend, independently of the severity of the reaction, to perform in vitro tests and skin tests (prick tests

and immediate reading intradermal tests) as a first step. Then, if tests are negative, an OPT can be offered to the patient. But a challenging study has recently been published by Mill and colleagues. A total of 818 children referred to their pediatric allergy clinic with suspected allergy to amoxicillin were subjected directly to a graded OPT with amoxicillin.[25] It must be emphasized that close to 100 of those children had a history of mild immediate amoxicillin reaction (occurring within the first hour following drug administration) and were subjected to the same OPT without performing other previous tests. The results of the work of Mill and colleagues showed, not differently from other known series, that 94% tolerated the amoxicillin challenge, 2% had an immediate reaction, and 4% had a non-immediate reaction. And again, in all cases the positive reactions to the challenge were mild with only skin manifestations. The 17 children with an immediate reaction to the OPT were later skin-tested with benzylpenicillin and benzylpenicilloyl polylysine, and only 1 was positive, giving a poor sensitivity of 6% for the test. Sadly, skin tests with amoxicillin, the implicated antibiotic, were not performed alleging the lack of standardized available intradermal tests for amoxicillin and its sensitivity could not be estimated. They concluded that a graded OPT provides an accurate and safe confirmatory test for immediate and non-immediate, non-severe reactions to amoxicillin, with a clear direct economic benefit. Patients with a history compatible with anaphylaxis were not excluded from the study of Mill et al but, unfortunately, no such case was finally recruited, so their conclusions could not be generalized to those patients. A recent systematic review from Marrs et al concluded that suspected non-serious antibiotic allergy should be primarily investigated using OPT-based clinical protocols.[26] Of interest, it must be recognized that the current classification of BLH reactions as immediate or non-immediate based on the delay from the last dose is not so easy to apply in clinical practice and may be inconsistent.[27] This favors the possibility of an unified management for non-severe cutaneous reactions irrespective of the time elapsed since antibiotic administration.

5 | CONCLUSIONS

Recent works open the possibility for pediatric allergy units to perform OPT to the index beta-lactam with no need of skin tests in children with a history of non-severe skin reaction after the oral intake of a beta-lactam antibiotic, including immediate reactions when no other symptoms of anaphylaxis have occurred. Undoubtedly, these challenges should go on being performed in a medical setting with personnel and equipment able to recognize and treat the unusual but life-threatening anaphylactic reactions possibly to come, in a similar way as pediatric allergists are used to do with food provocation challenges. Children with history of an anaphylactic reaction should be approached with the classical sequential algorithm, including skin tests, and an OPT may be performed if skin test results (and in vitro tests if convenient) are negative.

It is now the time for further large and multicentric pediatric studies to provide strong evidence for making specific recommendations for that large number of children with non-severe skin reactions related to the use of beta-lactam antibiotics. If future studies confirm these findings, OPT may become the standard of care for children with a history of non-immediate (and also immediate) non-severe skin reactions related to the use of a beta-lactam antibiotic.

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How to cite this article: 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;28:724–727. https://doi.org/10.1111/pai.12800