



Diagnostic issues in pediatric drug allergy

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Purpose of review

The serious health hazards posed by drug allergies have long been recognized and are commonly encountered in daily pediatric practice. Our general lack of knowledge of the pathomechanisms greatly hampers our ability to correctly diagnose allergic drug reactions. The present review addresses the most recent literature regarding the diagnosis of allergy for the most commonly implicated drugs in children, that is, antibiotics, nonsteroidal anti-inflammatory drugs (NSAID) and vaccines.

Recent findings

Systematic approaches have been proposed and, if implemented, will likely reduce the number of children being inappropriately labeled as 'drug allergic'. In case of suspicion of an allergy, a complete allergy work-up should always be performed. This evaluation based on carefully selected diagnostic tests will differ according to the drug involved and the mechanisms suspected. The drug provocation test remains the gold standard and has gained in importance, particularly in children presenting with a benign rash while taking antibiotic treatment. Several new diagnostic tools are currently under investigation and provide promising results.

Summary

Accurate diagnosis of drug allergy is important not only to prevent serious or even life-threatening reactions, but also to avoid unnecessary drug restriction associated with increased resistance and healthcare costs.

Keywords

allergy, antibiotics, drugs, nonsteroidal anti-inflammatory drugs, vaccine

INTRODUCTION

Adverse drug reactions (ADR) are inevitable consequences of pharmacotherapy as all drugs carry the potential to produce both desirable and undesirable effects. The serious health hazards posed by ADR have long been recognized and are commonly encountered in daily pediatric practice. Although representing only a small proportion of all adverse reactions (less than 15%), drug allergic reactions represent a major public health problem associated with substantial morbidity and mortality. Estimates of the prevalence of drug allergy vary widely in the pediatric population. Recent cross-sectional surveys revealed that the incidence of self-reported drug allergy ranged between 2.5 and 10.2% of children [1[¶]]. However, parental or patients' reports of drug allergies always overestimate the true frequency in the community [1[¶],2]. This is mostly due to the fact that patients who experience any adverse drug reactions often label themselves as being allergic without subsequent physician verification. Nevertheless, the term 'drug allergy' refers only to adverse immunologic reactions, either antibody-mediated or cell-mediated and should be distinguished from other

adverse reactions (i.e. nonallergic hypersensitivity reactions) that do not relate to an immunological mechanism [3]. From a medical point of view, diagnosis of drug allergy is difficult and occurrence of some adverse drug reactions may result in labeling a child as allergic because of the lack of a better explanation of the event [4]. Subsequently, clinicians are often hesitant to prescribe a drug to patients with suspected, but unproven, allergy and most of the time, this diagnosis persists into adulthood. Accurate diagnosis of drug allergy is important not only to prevent serious or even life-threatening reactions, but also to avoid unnecessary drug restriction that may affect patients' health and results in increased medical costs.

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KEY POINTS

- Several recent studies confirmed that drug allergy in children is clearly overdiagnosed.
- The drug provocation test remains the gold standard in the diagnosis of drug allergy and should be considered particularly in children with a history of mild cutaneous eruption to β -lactams.
- As for antibiotic, NSAID provocation tests have been recently shown to have a high negative predictive value.
- Skin testing with influenza vaccine prior to administration in patients with egg allergy is no longer recommended.

Systematic approaches have been proposed and, if implemented, will likely reduce the number of children being inappropriately labeled as 'drug allergic'. Currently the diagnosis of drug allergy is based on the clinical history, in-vivo tests (i.e. skin tests), in-vitro tests (i.e. mainly specific IgE, basophil activation test and lymphocyte transformation test) and drug provocation tests, considered as the gold standard. The evaluation will differ according to the drug involved and the mechanisms suspected. The present review addresses the most recent literature regarding the diagnosis of allergy for the most commonly implicated drugs in children, that is, antibiotics, nonsteroidal anti-inflammatory drugs (NSAID) and vaccines.

ALLERGY TO β -LACTAMS ANTIBIOTICS

The most frequently incriminated drugs in children are antibiotics, particularly the β -lactams group, largely because of their increased use in the last decades [1[•],5]. Skin rashes are frequently observed in children treated with β -lactams, mainly as delayed-onset urticarial or maculopapular rashes. In this situation, most of the children are labeled as penicillin allergic without further testing. However, an allergic reaction can only be demonstrated by an oral provocation test in less than 10% of the patients developing a rash while on β -lactams [6,7^{••},8^{••}]. The cause is more likely to be related to the underlying infection rather than to an allergic reaction to the antibiotic [7^{••}]. Although a recent study [9] investigated diagnostic tests to differentiate between a viral and a drug-induced exanthema, no test has been validated so far. Those patients should undergo an allergy work-up, mainly based on drug provocation test given the low sensitivity of skin tests confirmed by several recent studies

[10–12]. Drug provocation test without previous skin testing has been shown to be a well tolerated procedure in children with a history of mild cutaneous eruption to β -lactams (Fig. 1) [6,7^{••},8^{••},13,14]. However, the investigating physician should ensure that the patient's reaction history is consistent with a benign rash, by excluding a severe reaction. This level of certainty about the initial reaction history is only possible if he observed the reaction first hand, or if there is clear documentation of the rash in the medical record. When doubtful, it is recommended to perform skin tests, mainly to exclude an immediate reaction (Fig. 1). High negative predictive value of β -lactams provocation tests has been confirmed in recent large studies [15,16] and most of the reactions reported by patients were nonimmediate and not severe. This information should reassure the patients and/or their parents and their doctors in prescribing antibiotics with negative allergy work-up. In addition, a recent study [17] showed that most patients were satisfied with a drug provocation test for diagnostic purposes, independently of the outcome of the test. To be noted, several in-vitro tests, that is, lymphocyte transformation test (LTT), the flow cytometric lymphocyte activation test (LAT) and the enzyme-linked immunospot (ELISPOT) assays, have shown promising results in the diagnosis of nonimmediate allergy that will need to be confirmed in the pediatric population [18,19].

For evaluating patients with severe skin reactions [e.g. acute generalized exanthematic pustulosis (AGEP), drug-induced hypersensitivity syndrome (DIHS), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)], patch tests should be used as the first line of investigation [20^{••}]. In case of patch test negativity, intradermal tests can be performed starting with the highest dilution due to high risk of systemic reaction. Recently, Ponvert *et al.* [8^{••}] proposed a provocation test in children reporting reactions to essential β -lactams and with negative skin tests results. However, these data have to be confirmed with further studies and based on current literature, drug provocation tests are contraindicated in severe skin reactions because of the high risk of recurrence [21].

Immediate-reading skin tests (prick and intradermal tests) are indicated in children with suspicion of anaphylactic reaction to β -lactams, using a combination of the penicillin major determinant benzylpenicilloyl conjugated to poly-L-lysine (PPL), mixture of minor determinants (MDM) and side-chain structures (i.e. amoxicillin and culprit drug such as cephalosporins) [20^{••},22–26]. Selective allergy to clavulanic acid has been recently reported [8^{••},27,28] and should be considered in patients

Clinical history	Immediate reactions <1 hour	Nonimmediate reactions >1 hour	
Symptoms	Anaphylaxis and/or cutaneous	Mild cutaneous rash	Other nonimmediate reactions
<i>In vivo</i> tests	Immediate reading skin tests (SPT/IDT)	No	Delayed reading skin tests (IDT/patch tests)*
<i>In vitro</i> tests	Specific IgE/ BAT	No	LTT, LAT
Confirmation by challenge test	Yes, with caution	Yes	Yes, with caution
Procedure with limited validity			

FIGURE 1. Algorithm for the diagnosis of immediate and nonimmediate allergic reactions to β -lactams. *Regarding severe reactions [acute generalized exanthematic pustulosis (AGEP), drug-induced hypersensitivity syndrome (DIHS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)], patch tests should be used as the first line of investigation. BAT, basophils activation tests, BAT; IDT, intradermal tests; LAT, lymphocyte activation test; LTT, lymphocyte transformation test; SPT, skin prick tests.

who reacted to the combination of amoxicillin-clavulanic acid but have negative skin tests to classical reagents and/or a negative oral provocation test to amoxicillin. To be noted, safety of skin testing has been confirmed recently in a large cohort of pediatric patients [8²²]. Although the negative predictive value of skin tests has been shown to be high (>90%), the sensitivity is relatively low [8²²,25,29–31]. The main issue with skin testing is the lack of data on the positive predictive value due to ethical concerns of challenging those patients with incriminated antibiotic. Serum specific IgE is still the most common in-vitro method for evaluating immediate reaction. Some cases have been reported with negative skin tests and positive IgE; it is therefore still recommended to measure specific IgE in addition to skin testing in order to improve the sensitivity of the allergy work-up [20²²,22,23]. Basophil activation test (BAT) is another more recently developed in-vitro test proposed for the diagnosis of β -lactams allergy. A recent review [32] has shown that the BAT sensitivity in β -lactams allergy is 50% and that its specificity ranges from 89 to 97%. Although these tests are promising, particularly for the diagnosis of allergy to cephalosporin [33], they still need to be validated in large-scale pediatric studies. In a child with negative testing, the absence of allergy should be confirmed by administering an age-appropriate dose of the

β -lactams to which the patient initially reacted, followed by an observation period to ensure that an immediate reaction does not occur [34]. A follow-up phone call/visit is needed to exclude any delayed reactions that may have occurred after completion of the provocation test.

Identification of well tolerated alternative β -lactams is important when β -lactams allergy has been diagnosed. Recently, it has been shown that carbapenems do not exhibit a significant degree of cross-reactivity with penicillin and after skin tests with the relevant carbapenem, a provocation test should be considered [35,36]. Monobactams (i.e. aztreonam) are very weakly cross-reactive with other β -lactams and generally well tolerated by patients with penicillin allergy [37]. Ceftazidime, the only exception, shares an identical side chain and has shown some cross-reactivity potential [38]. Second or third-generation cephalosporins may also be considered as they have demonstrated less cross-reactivity to penicillin than first-generation agents, particularly those with side chains different from the offending penicillin [39,40,41²⁴,42]. On the contrary, Romano *et al.* [42] found that 25% of patients with cephalosporin allergy had positive results to penicillins. The authors conclude that in patients requiring alternative β -lactams, pretreatment skin tests are advisable because negative results indicate tolerability of the incriminated β -lactams.

ALLERGY TO NON-β-LACTAMS ANTIBIOTICS

Apart from the β-lactams antibiotics, sulfonamides and macrolides are the two most commonly implicated antibiotics in pediatric drug allergy, although the exact incidence is not known. The majority of allergic reactions to these antibiotics are non-IgE-mediated reactions, mainly maculopapular or delayed urticarial rashes. To be noted, sulfonamides were identified as the antibiotic group, which is most strongly associated with SJS. Quinolones have been increasingly used in children, particularly in those with cystic fibrosis and allergic reactions have become more commonly reported in the past decade [43]. The lack of reliable diagnostic tests for non-β-lactams antibiotics makes the diagnosis more challenging. The most important issue in diagnosis is that skin tests are not standardized and most of the diagnosis of non-β-lactams allergy relies upon drug provocation tests [43–45]. In the testing of nonstandardized drug preparations, false positives can occur from irritating properties of the incriminated drug. However, nonirritating intradermal skin test concentrations have been reported for some of these antibiotics [46,47].

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS HYPERSENSITIVITY

Although reported less frequently than in adults, hypersensitivity reactions to NSAID in children rank

second after antibiotics among self-reported adverse reactions in children [48^{***}]. The reported prevalence of NSAID hypersensitivity among otherwise healthy children is about 0.3% [49,50], acetylsalicylic acid and ibuprofen being the most frequently reported drugs. The prevalence has been shown to be higher in asthmatic children, around 5% as assessed by provocation test [50]. All manifestations of NSAID hypersensitivity described in adulthood are also observed in children (Fig. 2), with a high occurrence of isolated periorbital angioedema in pediatric patients [51,52]. The need for a firm diagnosis of NSAID hypersensitivity in children is especially important as these drugs are frequently used during viral infection for their antipyretic, anti-inflammatory, and analgesic properties.

Classification of NSAID hypersensitivity distinguishes immediate (appearing from a few minutes to several hours after the last dose) from delayed (appearing after 24 h) reactions [20^{***}]. Immediate reactions are further classified into one of four categories according to the clinical reaction, underlying disease and suspected mechanisms (Fig. 2). Similarly to antibiotic allergy, diagnosis and management of NSAID hypersensitivity depend on the confirmed or supposed mechanism of the reaction (Fig. 2). A recent study confirmed that clinical histories are not reliable tools for diagnosing NSAID hypersensitivity [53], except for patients presenting multiple reactions in the past [52]. Diagnosis of NSAID hypersensitivity is mainly based on a

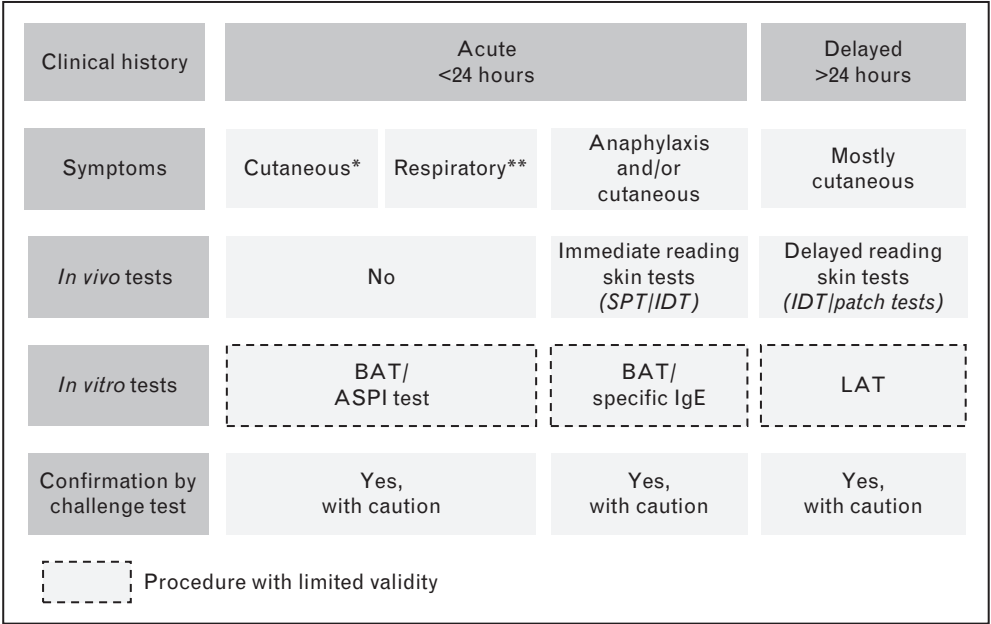


FIGURE 2. Algorithm for the diagnosis of acute and delayed hypersensitivity to NSAID (adapted with authorization from [48^{***}]). *Underlying chronic urticaria; **Underlying asthma, chronic rhinosinusitis. ASPI test, Aspirin-Sensitive Patient Identification Test; BAT, basophil activation tests; IDT, intradermal tests; LAT, lymphocyte activation test; SPT, skin prick tests.

provocation test with the culprit drug. As for anti-biotic, the negative predictive value of drug provocation testing has been recently shown to be high (>97%) [54[■]]. Skin testing (i.e. skin prick tests and intradermal tests) and/or specific IgE testing should be restricted to suspected IgE-mediated reactions, although the validity is not well established [55]. Several new in-vitro tests [i.e. BAT [32], Aspirin-Sensitive Patients Identification Test or ASPITest (based on 15-HETE release measurement from peripheral blood leukocytes) [56], LTT [18]] have been evaluated in the diagnosis of NSAID hypersensitivity mainly in adults, but are not yet validated [32] (Fig. 2).

Safety of the alternative drug should be confirmed by a drug provocation test. Because acute urticarial or anaphylactic reactions in otherwise healthy individuals are believed to be drug specific, it is reasonable to perform a graded drug provocation test with another NSAID. Not uncommonly, children with acute urticarial reactions are mistakenly told to avoid all NSAID indefinitely. In contrast, reactions that are caused by modifying effects on arachidonic acid metabolism (i.e. respiratory or urticarial reactions) involve increased risk of reaction to other NSAID, particularly those with strong COX-1 inhibitor activity, as one would expect [57]. Acetaminophen is considered the drug of choice but further studies of other alternatives in children are required [48[■]]. In particular, COX-2 inhibitors, for example, celecoxib can be tested in selected patients, particularly those suffering from rheumatic diseases. However, it should be noted that these medications are not registered for use in young children.

ALLERGY TO VACCINES

Although the prevalence is estimated to be approximately 0.65 events per 1 million administrations, allergy to vaccines represents a common problem in daily pediatric practice [58]. The diagnosis of allergies to a vaccine is complex and these allergies are often overdiagnosed, mainly due to fear of severe anaphylaxis. Particularly, local reactions to vaccination such as swelling and redness at the injection site are common and should not be considered reasons for avoiding administration of further doses of the vaccine [59].

Possible sources of allergenic proteins in vaccines include gelatin, egg or chicken proteins, preservatives, antimicrobial agents, yeast, and natural rubber latex as well as bacterial or viral proteins used for eliciting vaccine responses, for example, tetanus and diphtheria toxoids [59–61]. Allergy to one of these constituents should be

excluded by skin tests and/or specific IgE. Hen's egg allergy is a major issue and the most frequent discussed constituent, in terms of allergic reactions to vaccines. Several studies have demonstrated that egg allergy is not a contraindication for measles, mumps, and rubella (MMR) vaccination, as it is manufactured in insignificant amounts of egg cross-reacting proteins [62]. Regarding influenza vaccine, the amount of egg protein in the vaccine has decreased significantly over the years, and all vaccines now have low ovalbumin levels. Skin testing with influenza vaccine prior to administration in patients with egg allergy is no longer recommended [63[■],64–66]. Skin testing with the vaccine is still appropriate when evaluating a patient with a history of a reaction to the influenza vaccine itself as opposed to a history of reaction to egg. From another point of view, a recent case series raised the possibility that residual casein could be responsible for some anaphylactic reactions to the diphtheria/tetanus vaccines in patients with severe milk allergy and high level of cow's milk specific IgE [67]. The results of this study require confirmation [68].

In patients with a positive history of reactions, and who must receive further doses of a vaccine, skin testing with the incriminated vaccine should be performed. To be noted, skin tests are not standardized for vaccine and should follow international guidelines. If the intradermal test with the vaccine is negative, the chance that the patient has IgE antibody to any vaccine constituent is negligible, and the vaccine can be administered in the usual manner. If vaccine or vaccine-component skin tests are positive, alternatives to vaccination should be considered. However, if indispensable, the vaccine can still be administered, using a graded dose protocol.

CONCLUSION

In children, true drug allergies are relatively rare and several recent publications confirmed that they are clearly overdiagnosed. The economic burden and the impact on health, both from an individual point of view but also in terms of public health, are very important. Therefore, the proper identification, evaluation and management of patients with a suspected drug allergy based on the history are essential components of patient care. In case of suspicion of a drug allergy, the child should be referred to the allergist in order to perform a complete allergy work-up, based on carefully selected diagnostic tests depending on whether an immediate or a nonimmediate reaction is suspected. The drug provocation test remains the gold standard and has gained in importance, particularly in children presenting with

a benign rash while taking antibiotic treatment. A drug provocation test potentially exposes subjects to a risk of severe anaphylactic reactions, particularly in the absence of well validated negative skin tests. Drug provocation tests also incur costs, and are time consuming as the parent/child needs to take time off work/school. New diagnostic in-vitro or in-vivo tests are required to assess the presence and severity of drug allergy. Currently, research efforts focus on improving diagnostic tests and on developing new tools that provide better prognostic performance, in particular in children.

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Conflicts of interest

There are no conflicts of interest.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 440).

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