



Managing possible antibiotic allergy in children

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Purpose of review

In children, allergic reactions to antibiotic are rare and several recent publications confirmed that they are clearly overdiagnosed, representing a major public health problem. Highlighting the most recent literature, the present review addresses the management of children with a possible antibiotic allergy.

Recent findings

In diagnosis of antibiotic allergy, the patient's history is central although not sufficient. In case of suspicion of an allergy, the child should be referred to an allergist in order to perform a complete allergy workup, based on carefully selected diagnostic tests depending on whether an immediate or a nonimmediate reaction is suspected. The antigen challenge test remains the gold standard and has gained in importance, particularly in children presenting a benign rash while taking antibiotic treatment. However, this test potentially exposes individuals to a significant risk of severe reaction and has relevant cost and is time consuming. Several new diagnostic tools are currently under investigation and provide promising results.

Summary

Accurate diagnosis of antibiotic 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 health costs.

Keywords

allergy, antibiotics, betalactams, children, diagnosis, hypersensitivity, penicillin

INTRODUCTION

Antibiotics are among the most widely and heavily prescribed drugs worldwide, particularly in the pediatric population [1,2]. Since their introduction, these drugs have been associated with a wide range of adverse reactions. Although representing only a small proportion of all adverse reactions (less than 15%), allergic reactions to antibiotics represent a major public health problem associated with substantial morbidity and mortality. Estimates of the prevalence of antibiotic allergy vary widely. A few large cross-sectional surveys revealed that the incidence of self-reported antibiotic allergy ranged between 2.5 and 10.2% of children [3]. However, parental or patients' reports of antibiotics allergies always overestimate the true frequency [4–6]. This is mostly due to the fact that patients who experience any adverse reactions often label themselves as being allergic to antibiotic. Nevertheless, the term 'antibiotic allergy' refers only to adverse immunologic reactions to antibiotics, either antibody-mediated or cell-mediated, and should be distinguished from other adverse reactions that do not have an immune basis. From a medical point of view, diagnosis of antibiotic allergy is difficult

and occurrence of some adverse reactions to antibiotic may result in labeling a child as allergic for lack of a better explanation of the event. Subsequently, clinicians are often hesitant to prescribe an antibiotic to patients with suspected, but unproven, antibiotic allergy and most of the time this diagnosis persists until adulthood. Accurate diagnosis of antibiotic allergy is important not only to prevent serious or even life-threatening reactions, but also to avoid unnecessary drug restriction resulting in increased resistance to antibiotics and increased health costs.

Systematic approaches have been proposed and, if implemented, will likely reduce the number of children being inappropriately labeled as allergic to antibiotic. Currently, the diagnosis of antibiotic

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KEY POINTS

- Several recent studies confirmed that antibiotic allergy in children is clearly overdiagnosed.
- In case of suspicion of an allergy, the child should be referred to an allergist in order to perform a complete allergy workup, based on carefully selected diagnostic tests depending on whether an immediate or a nonimmediate reaction is suspected.
- The antigen challenge test remains the gold standard and should be considered, particularly, in children with a history of mild cutaneous eruption to betalactams.

allergy is based on in-vivo tests (i.e. skin tests), in-vitro tests [i.e. specific immunoglobulin E (IgE) and basophils activation tests] and antigen challenge tests, considered as the gold standard. The present review addresses the most recent literature regarding the management of suspicion of antibiotic allergy in children and often refers to the general guidelines.

CLINICAL HISTORY

In the diagnosis of antibiotic allergy, no single investigation is fully reliable alone and a stepwise approach, similar to those for other allergic disorders, is recommended [7,8]. The diagnostic workup of suspected antibiotic allergy should always start with a detailed history. Table 1 summarizes key clinical diagnostic points. To facilitate recording medical history, a specific questionnaire

Table 1. Key clinical diagnostic points

Clinical dataset	Complete history of the drug reaction, including the timing of onset of the reaction The dose and route of antibiotic List of concomitant medication Previous exposure to the same antibiotic or structurally similar antibiotics, with or without reactions Signs and symptoms involved, as precisely as possible Any treatment given and response to that treatment, including the duration of the reaction Exclude severe reactions to antibiotics ^a
Nonspecific laboratory tests	Eosinophilia, ESR, tryptase, proteinuria

ESR, erythrocyte sedimentation rate.
^aSuch as acute generalized exanthematic pustulosis, drug-induced hypersensitivity syndrome, Stevens–Johnson syndrome and toxic epidermal necrolysis.

has been developed by the European Network on Drug Allergy and is available in many different languages [9]. The primary purpose of the clinical history is to identify the disease as a hypersensitivity reaction and then to assess what type of reaction the child likely experienced. According to Coombs and Gell [10], antibiotic allergic reactions can be classified into four categories that reflect distinct immune mechanisms [11]. However, many reactions that appear to have an immunologic component cannot be classified because of our lack of mechanistic information. Recently, distinction between immediate and nonimmediate reactions based upon the timing of the appearance of symptoms has been recommended [7,8]. Although this classification is not strict and overlaps exist, this has proved not only to be useful clinically but also to be in good agreement with the mechanisms responsible for the reaction.

- (1) Immediate reactions occur within 1 h after drug intake and are manifested by various combinations of IgE-mediated symptoms, that is urticaria and/or angioedema, rhinitis, wheezing and hypotension. Although rare, identification of these reactions is important because they carry the risk of life-threatening anaphylaxis if the patient is re-exposed.
- (2) Nonimmediate reactions are those occurring more than 1 h after antibiotic intake and are supposed to be caused totally or partially by a delayed cell-mediated hypersensitivity. The skin is the organ most frequently involved in these reactions, with a large spectrum of clinical manifestations ranging from benign skin rashes such as maculopapular rashes and delayed-onset urticaria to other less common but more severe entities such as acute generalized exanthematic pustulosis (AGEP), drug-induced hypersensitivity syndrome (DIHS), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Despite the importance of the clinical history, it has been demonstrated in several studies that the presence of antibiotic allergy cannot be accurately predicted based upon history alone [4–6]. Referral to an allergist/immunologist is necessary to perform a complete workup based on carefully selected diagnostic tests depending on whether an immediate or a nonimmediate reaction is suspected (Table 2) [8]. Indeed, various diagnostic algorithms have been proposed for the evaluation of immediate and nonimmediate reactions that will differ depending on the antibiotic class involved (Figs 1 and 2).

Table 2. Diagnostic tests of antibiotic allergy

Type of reaction	Type of test	
Immediate	In-vitro	Specific IgE assays
	In-vivo	Flow cytometric basophils
		Activation tests
		Skin tests
Nonimmediate		Drug provocation tests
	In-vitro	Lymphocyte transformation or activation tests
	In-vivo	Delayed-reading intradermal tests
		Patch tests
		Antigen challenge test

IgE, immunoglobulin E. Adapted from [8[■]].

BETALACTAMS ANTIBIOTICS

The most common groups of antibiotics associated with allergic reactions are the betalactam antibiotics [3]. This is mainly due to the characteristics of these molecules having a high propensity to undergo haptenization. In addition, the increased use of betalactam antibiotics [12] results in a relevant number of allergic reactions, particularly in the pediatric population.

Suspicion of immediate reaction to betalactams

Four main groups of betalactams are described [11[■]]. They include low molecular weight structures that share the same betalactam nuclear ring. The side-chains contribute to the name of the specific penicillin and might be of immunological relevance,

contributing to the epitope's structure. Under physiological conditions, betalactam antibiotics have the capacity to bind easily to serum and cell membrane proteins. Binding occurs by the spontaneous opening of the betalactam ring in order to form stable covalent drug–protein conjugates that may elicit various immune responses including the production of specific IgE antibodies (hapten concept) [11[■]]. From the betalactam ring, the major determinant known as benzylpenicilloyl epitope (accounting for 95% of haptened penicillin) as well as a series of minor determinants (e.g. penilloate, penicilloate, penicillin, penicanyl) are derived [11[■]].

Immediate-reading skin tests (prick and intradermal tests) are indicated in children with symptoms suggesting immediate allergic reactions (Fig. 1). The current recommended reagents used for skin testing comprise a combination of PPL (the penicillin major determinant benzylpenicilloyl conjugated to poly-L-lysine), MDM (mixture of minor determinants) and side-chain structures (i.e. amoxicillin and culprit drugs such as cephalosporins) [7,8[■],13–16]. With the increased use of amoxicillin and cephalosporins, side-chain structures as specific determinants play an increasingly important role, whereas the accountability of major and minor determinants of penicillin (PPL and MDM) is markedly decreased [17] of note, recent studies highlighted the role of clavulanic acid in several immediate reactions. It has been proposed to test this component, particularly in children with negative skin tests to amoxicillin [18,19,20[■]].

The negative predictive value of skin tests is very high (>90%) and serious immediate-type reactions in patients challenged with penicillin following negative skin testing have not been reported [20[■],21,22[■],23]. Data on the positive predictive value of skin testing are limited due to ethical concerns of challenging those patients with incriminated antibiotic. Ideally, skin tests should be performed 4–6 weeks after the reaction [20[■]] and, in any case, as soon as possible within that timeframe because of the loss of sensitivity over time [24].

Serum-specific IgE is still the most common in-vitro method for evaluating an 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 workup [7,8[■],13]. New in-vitro tests have an increasing importance for the diagnosis of allergy to betalactam, particularly the basophils activation test (BAT). A recent review [25] has shown that the BAT sensitivity in betalactam allergy is 50% and that its specificity ranges from 89 to 97%.

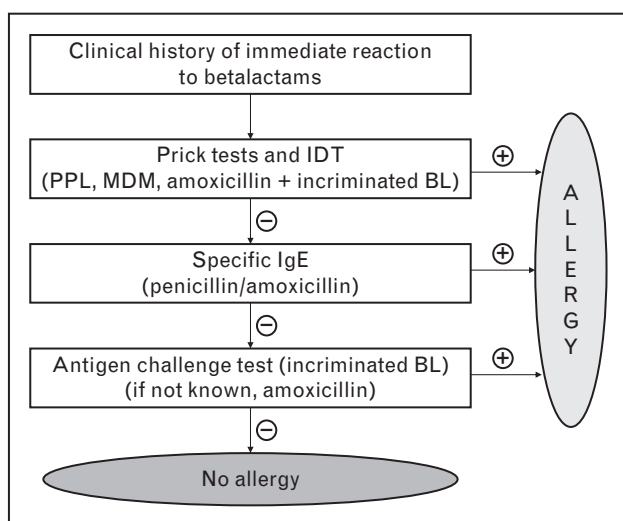


FIGURE 1. Algorithm for the diagnosis of immediate allergic reactions to betalactams. BL, betalactams; IDT, intradermal test.

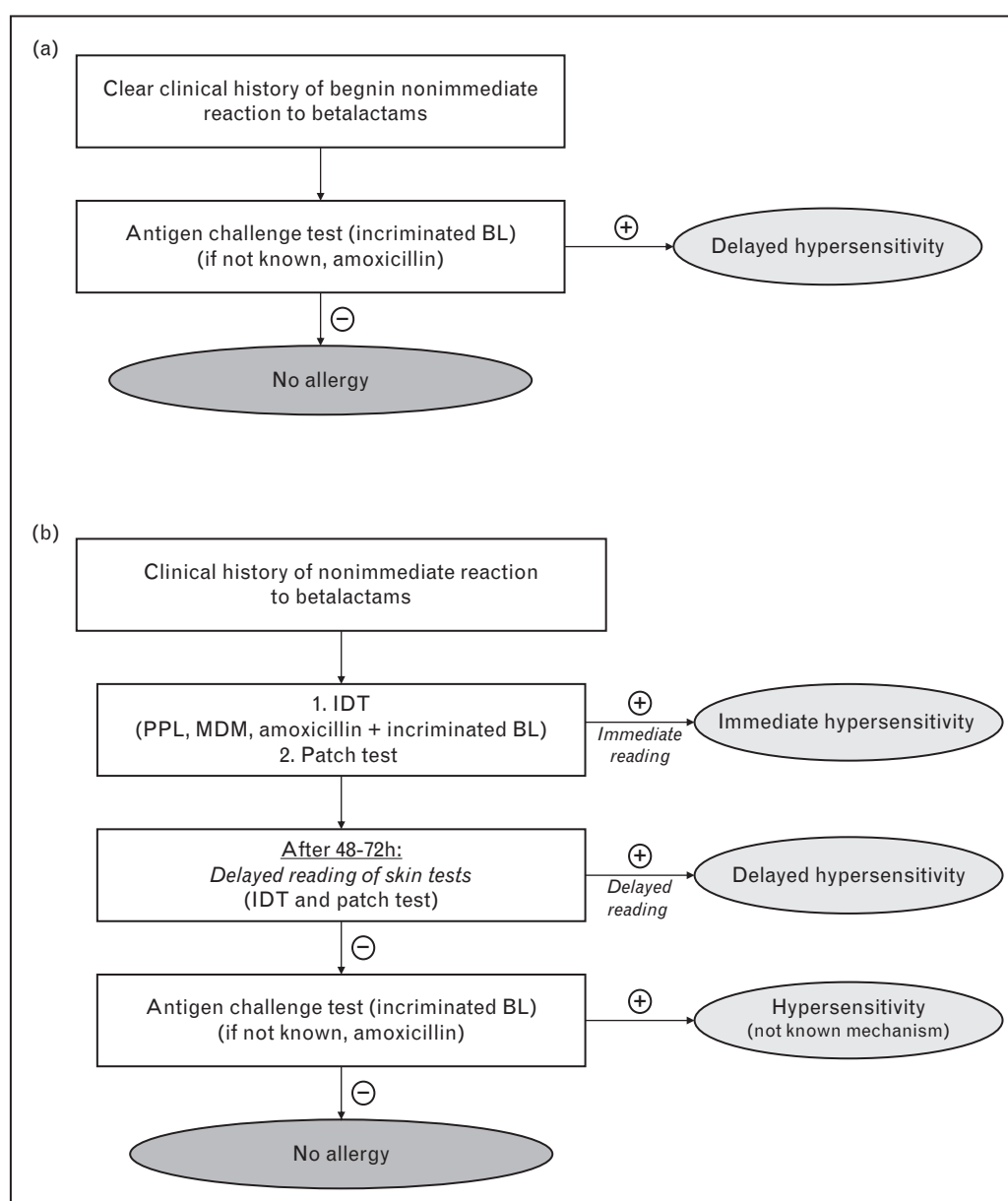


FIGURE 2. Algorithm for the diagnosis of nonimmediate allergic reactions to betalactams (BL). Short algorithm in children with a history of mild cutaneous eruption to BL (a) and long algorithm in presence of any doubts (b). IDT, intradermal test.

Although these tests are promising, particularly for the diagnosis of allergy to cephalosporin, they still need to be validated in large-scale studies including children.

In a child with negative testing, the absence of allergy should be confirmed by administering an age-appropriate dose of the betalactam to which the patient initially reacted, followed by an observation period to ensure that an immediate reaction does not occur [26]. It must be noted that skin tests and antigen challenge tests with antibiotics carry a relatively high risk of severe anaphylactic reactions

and should always be performed by well trained physicians and emergency equipment must be readily available [8¹¹,16,17,20¹¹].

Cross reactivity between betalactams

Identification of a well tolerated alternative betalactam is important when betalactam allergy has been diagnosed. Carbapenems do not exhibit a significant degree of cross-reactivity with penicillin and after skin tests with the relevant carbapenem, a challenge test should be considered [27,28].

Monobactams (i.e. aztreonam) are very weakly cross-reactive with other betalactams and generally well tolerated by patients with penicillin allergy. Ceftazidime, the only exception, shares an identical side-chain and has shown some cross-reactivity potential [29]. Second-generation 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 dissimilar to the offending penicillin [30,31,32[■],33[■]]. From another point Romano *et al.* [33[■]] found that 25% of individuals with cephalosporin allergy had positive results to penicillins. The authors conclude that in patients requiring alternative betalactam, pretreatment skin tests are advisable because negative results indicate tolerability of the incriminated betalactam.

Suspicion of nonimmediate reaction to betalactams

Delayed-onset urticarial or maculopapular rashes are frequently observed in children treated with betalactam. There are many causes of pediatric rashes, especially among children with a concomitant illness treated by antibiotic, making diagnosis difficult and often elusive. Viral infections are the most common cause of maculopapular or urticarial eruptions, independent of the medication. An allergic reaction is a far more common cause for a rash after intake of a betalactam antibiotic in adults than in children [34,35]. In children, allergic reactions can be demonstrated by an oral antigen challenge test in less than 10% of the patients developing a rash while on a betalactam [20[■],22[■],36]. Finally, and most likely, the rash may result from an interaction between the virus and drug-induced immune activation. The best known example is an Epstein–Barr virus infection, known as a risk factor for cutaneous drug reactions.

Although a recent study investigated diagnostic tests to differentiate between a viral and a drug-induced exanthema, no test has been validated so far [37]. Regarding allergic reaction, skin tests (delayed reading intradermal and/or patch tests) have been widely used for many years in the evaluation of nonimmediate reactions to betalactam [38]. However, several recent pediatric studies have demonstrated the limited contribution of skin testing in diagnosis of nonimmediate reactions to betalactam [20[■],22[■],36,38,39]. Although the negative predictive value was found to be high (above 90%), a low sensitivity (around 2–10%) was reported.

Because of the low sensitivity of skin testing, the oral antigen challenge test is the most important diagnostic tool in nonimmediate reaction to

betalactam [17,38,40]. Antigen challenge testing without previous skin testing is considered a relatively well tolerated procedure in children with a history of mild cutaneous eruption to betalactam (Fig. 2a) [20[■],22[■],36,41,42]. However, the clinician should be certain that the patient's reaction history is consistent with a benign rash, excluding a severe reaction. This level of certainty about the initial reaction history is only possible if the clinician observed the reaction first hand, or if there is clear documentation of the rash in the medical record. In presence of any doubts, it is recommended to perform skin tests, mainly to exclude an immediate reaction (Fig. 2b). High negative predictive value of betalactam antigen challenge tests of 98 and 94% has been confirmed in recent large studies involving 256 children [35] and 457 patients [43[■]], respectively, and most of the reactions reported by patients were nonimmediate and not severe. This information should reassure the patients and their doctors in prescribing antibiotics with negative allergy workup [17]. In addition, a recent study showed that most patients were satisfied with an antigen challenge test for diagnostic purposes, independent of the outcome of the test [44].

For a long time, the role of T cells in non-immediate allergic reaction has been highlighted in several studies. Several in-vitro tests have been investigated to assess cellular response involving drug-related T-cell activity, that is, lymphocyte transformation test and the flow cytometric lymphocyte activation test [45,46]. Recently, the enzyme-linked immunospot assays has also been proposed to analyze the frequency of antigen-specific, cytokine-producing cells [47]. Although giving promising results, these tests are still under investigation and further studies are required before use in clinical practice, particularly in the pediatric population.

For evaluating patients with severe skin reactions (e.g. AGEF, DIHS, SJS, TEN), patch tests should be used as the first line of investigation [8[■]]. In case of patch test negativity, intradermal tests can be performed starting with the highest dilution due to high risk of systemic reaction. Provocation tests must not be performed due to high risk of recurrence [48]. However, Ponvert *et al.* [20[■]] recently proposed a provocation test in children with negative skin tests results and reported reactions to essential betalactam. These data have to be confirmed by further studies.

NON-BETALCTAM ANTIBIOTICS

Any non-betalactam antibiotic has the potential of causing immediate and nonimmediate drug

allergies in children. Sulfonamides and macrolides are among the most commonly implicated antibiotics in pediatric drug allergy after betalactams, although the exact incidence is not known. They rarely cause IgE-mediated reactions and more commonly result in maculopapular or delayed urticarial rash. To be noted, sulfonamides were identified as the antibiotic group that 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 [49]. For the diagnosis of non-betalactam antibiotics, less data are available. The most important issue in diagnosis is that skin tests are not standardized and most of the diagnosis relies upon antigen challenge tests [49–51]. In the testing of nonstandardized drug preparations, false-positive results can occur from irritating properties of the incriminated drug. However, nonirritating intradermal skin test concentrations are reported for some of these antibiotics.

CONCLUSION

In children, true allergy to antibiotic is rare and several recent publications confirmed that they are clearly overdiagnosed. The negative consequences of this include the development of resistance by unnecessary use of broad-spectrum antibiotics and increased medical costs. Therefore, the proper identification, evaluation and management of patients with a reported history of antibiotic allergy are essential components of patient care. In case of suspicion of an allergy, the child should be referred to the allergist in order to perform a complete allergy workup, based on carefully selected diagnostic tests depending on whether an immediate or a nonimmediate reaction is suspected. The antigen challenge test remains the gold standard and has gained importance, particularly in children presenting a benign rash while taking antibiotic treatment. However, an antigen challenge test potentially exposes individuals to a significant risk of severe anaphylactic reactions and, moreover, has relevant costs and is time consuming. New diagnostic tests are required to assess the presence and severity of an antibiotic allergy. Currently, research efforts focus on improving diagnostic tests and on developing new tools that provide better prognostic performance.

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Conflicts of interest

There are no conflicts of interest.

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