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REVIEW ARTICLE

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Management of antibiotic allergy in children: a practical approach

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Abstract
Background: About 10% of children are declared as allergic to antibiotics, with beta(β)-lactams being the most common perpetrators. However, few of these are confirmed by allergy tests. This characteristic of being allergic follows a child well into adulthood, leading to alternative, usually more expensive broad-spectrum antibiotics, contributing to antibiotic resistance and increasing healthcare expenses.
Objective: This review presents a practical approach to managing pediatric patients with antibiotic hypersensitivity reactions.
Material and methods: We updated the guidelines on antibiotic allergy in children by conducting systematic literature research using the best available evidence from PubMed search by entering the keywords "antibiotic allergy" and "children." The search output yielded 5165 citations.
Results: Management of antibiotic allergy depends on the culprit antibiotic, and it includes confirmation of the diagnosis and finding a safe alternative to the culprit antibiotic. In particular patients with a history indicative of penicillin allergy can be treated with cephalosporins as an alternative to penicillin, especially with third-generation cephalosporins, except for those with similar R1 side chains. In patients with a history of immediate-type reactions to cephalosporins who require treatment with cephalosporins or penicillin, skin tests with cephalosporin or penicillin with different side chains should be performed. If allergy to macrolides is suspected, challenge tests are currently the only reliable diagnostic tool. The best strategy for managing patients with sulfonamide hypersensitivity is an alternative antibiotic. The skin prick tests and intradermal tests are not recommended for diagnosis of quinolone allergy, as they can activate dermal mast cells leading to false-positive results. Quinolone challenge test is the most appropriate test for diagnosing quinolone hypersensitivity.
Conclusion: Although adverse drug reactions to antibiotics are frequently documented, immunologically mediated hypersensitivity is unusual. In the event of an reaction, an appropriate diagnostic workup is required to identify the drug's causal role. It is critical to avoid "labeling" a child as allergic without first conducting a proper diagnostic workup.

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Introduction

Adverse drug reactions are rare in the general pediatric population worldwide, with a reported overall incidence of 10%.[1] A prospective study of children and adolescents found that 10.9% of inpatients and 1% of outpatients had adverse drug responses. A percentage of 1.8% of hospitalized children report at least one drug-related adverse reaction.[2] The most typically allergenic antibiotics are beta(β)-lactams. A large cohort study reported that antibiotic allergy between children and adolescents was 16.4%.[3] However, other studies on children and adolescents demonstrated that allergy is confirmed only in a small proportion of reported cases.[4,5] These data indicate that antibiotic allergy is over-diagnosed in children. Marking children as allergic to antibiotics has led to extensive use of alternative, usually broad-spectrum, more expensive, and occasionally less efficient antibiotics.[6] Physicians should be aware of the risks involved in avoiding certain classes of antibiotics, especially when they are first-line agents and an allergy diagnosis is not confirmed.[6] Such an approach can lead to a rise in infections caused by antibiotic-resistant species, such as *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococcus (VRE).[7] The excessive use of broad-spectrum antibiotics, in the long run, causes increased utilization of health care services and added expenditures.[7-9] Hence, a requirement for a generally accepted protocol for the management of antibiotic allergy has become imperative.[10] For reactive haptens, skin prick tests and intradermal testing are especially useful for demonstrating an IgE-dependent mechanism. Owing to its simplicity, low cost, and high specificity, the prick test is suggested for the initial screening of immediate drug hypersensitivity reactions (DHRs). If skin prick tests are negative, intradermal testing is performed. These offers increased sensitivity for drug-specific IgE as compared to skin prick tests. Patch tests and/or late-reading intradermal tests should be used to demonstrate a T-cell-dependent mechanism for non-immediate DHRs.[11,12]

Data collection

We updated the guidelines on antibiotic allergy in children by conducting systematic literature research using the best available evidence from PubMed search by entering the keywords “antibiotic allergy” and “children.” The search output yielded 5165 citations. The selection of articles that serve as bibliographic references that were considered appropriate for inclusion in this integrative review was based on our knowledge and the experience of team members of the allergy unit in the field of drug allergy.

Management in clinical practice

Step 1. Confirming diagnosis

Several studies established that antibiotic allergy is over-diagnosed.[3-5,13,14] Confirming the diagnosis is of paramount importance in managing antibiotic allergy.[15] Drug-associated allergic reactions are unpredictable, dose-independent, and immune-mediated,[15-17] and are divided into immediate and delayed allergic reactions. Immediate reactions are characterized by acute symptoms within an hour of drug administration,[15-17] including anaphylaxis, bronchospasm, urticaria, angioedema, and gastrointestinal manifestations. The delayed drug allergic reactions usually manifest with maculopapular exanthems and contact dermatitis. In contrast, severe reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson syndrome, and toxic epidermal necrolysis, develop rarely.[15-17] It is worth noting that manifestations of antibiotic allergy are not pathognomonic, and should be differentiated from those caused by viral infections, co-administered drugs, and food or inhaled allergens.[18-24] Based on the Gell and Coombs classification system, allergic reactions are classified into the following four classes (type I–V): type I (immunoglobulin E [IgE]-mediated), type II (cytotoxic), type III (immune complex), and type IV (delayed hypersensitivity).[25] Posadas and Pichler further categorized type IV hypersensitivity reactions into the following four subclasses depending on the type of inflammation induced by activated T-cells: type IVa (monocytic), type IVb (eosinophilic), type IVc (cytotoxic), and type IVd (neutrophilic).[26]

Although most antibiotic adverse effects are considered to represent hypersensitivity reactions, allergy has been confirmed by allergic tests in less than 10% of children and adolescents with suspected antibiotic allergy.[3-5] Ponvert et al., based on on the basis of ontheir 20-year experience, reported in on a cohort of 1431 children with suspected β-lactam antibiotic allergy. Skin tests and challenge tests confirmed the diagnosis of β-lactam hypersensitivity in only 15.9% of the cohort, with a higher percentage in those with severe reactions.[14] Caubet et al. found that viral infections were the most common causes (69.6%) of benign skin rashes during treatment with β-lactam antibiotics. Only 6.8% of the studied children had a β-lactam allergy, as verified by skin and provocation tests.[18] Two more studies had comparable results.[4,5] Zambonino et al. found similar outcomes in 783 children with β-lactam hypersensitivity symptoms.[27]

Several studies suggested that penicillin is a low-cost and very effective antibiotic. In this context, ruling out penicillin sensitivity by expanding the application of skin tests could be a useful approach. It is proposed to integrate allergy tests into antimicrobial management protocols in advance.[10,28,29]

Step 2. Finding safe and effective alternative antibiotics

Beta-lactams

β-lactam antibiotics are the most common causes of antibiotic allergic reactions in children.[30] The prevalence of self-reported antibiotic allergies in children ranges from 1.7% to 5.2%. A studyin comprising 2,375,424 children and adults in South California demonstrated a 7.9% prevalence of penicillin allergy.[31]

According to current recommendations, penicillin is the first-line treatment for most pediatric respiratory infections.[32-35] However, it should be noted that antibiotic categories other than the penicillins have limited effectiveness

on respiratory infections.[35] Therefore, another class of β-lactam antibiotics is recommended as the second-line antibiotics. This suggestion is supported by several studies demonstrating that avoidance of cephalosporin administration to patients diagnosed with penicillin allergy is associated with an increased risk of adverse effects and treatment failure.[11,36]

All β-lactam antibiotics share a four-atom β-lactam ring fused with a saturated five-membered thiazolidine ring in penams (penicillins).[37] The side chains discern different groups of penicillins.[31,37,38] The β-lactam ring of cephalosporin antibiotics is bonded to a six-membered dihydrothiazine ring and two side chains, R1 and R2.[37,39] Carbapenems (e.g., imipenem and meropenem) contain a five-membered thiazolidine ring such as in penams, *albeit* sulfur at C-1 in the five-membered ring is replaced by a carbon atom. At the same time, a double bond is introduced. R1 and R2 side chains determine different carbapenems.[37] The monobactam molecule consists of one β-lactam ring without a five- or six-membered ring (Figure 1).[31,37,38]

The antigenic determinants are the β-lactam ring, thiazolidine, dihydrothiazine rings, and side chains. In recent years, the role of side chains as important antigenic sites, especially concerning amoxicillin and cephalosporin hypersensitivity reactions, has been widely recognized. Current evidence suggests that the cross-reactivity of β-lactam antibiotics is associated with side chains, rather than the β-lactam ring.[31,37,38] However, additional epitopes from other molecule parts can also be responsible for cross-reactivity.[31,37,38] For example, ampicillin, amoxicillin, cefalexin, and cefadroxil molecules contain an identical side-chain structure with an amino group. (Figure 2).

Several studies have reported an approximate 10% prevalence of cross-reactivity between penicillin and first- and second-generation cephalosporins. Concerning the third-generation cephalosporins, the incidence of

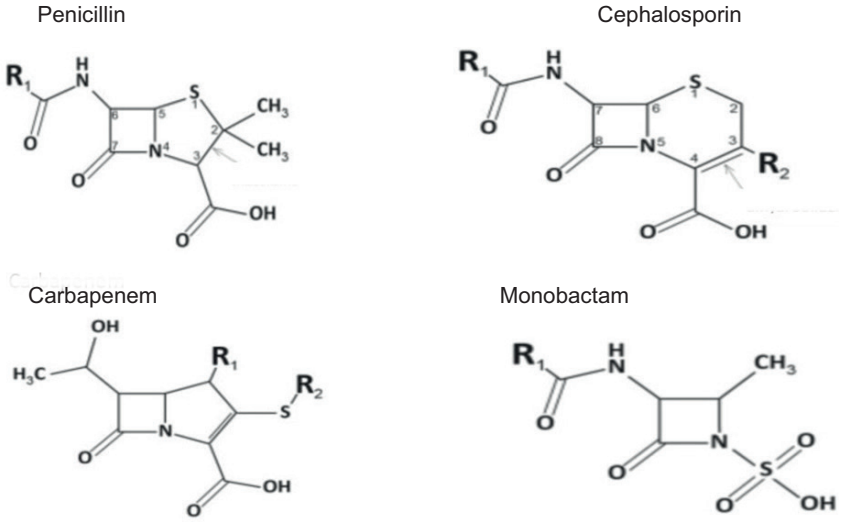


Figure 1 Chemical structure of ß-lactam antibiotics. "R" symbolizes the side chain in the β-lactam molecule.

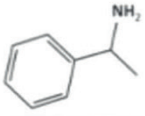
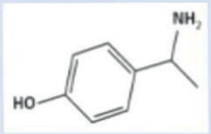
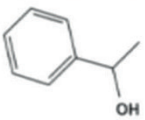
Cephalosporin	R1 chain	Penicillin	
		Identical R1	Similar R1
Cefalexine Cephaloglycin Cefaclor Loracarbef		Ampicillin	Piperacillin
Cefadroxil Cefatrizine Cefprozil		Amoxicillin	Piperacillin
Cefamandole Cefoniside			Ampicillin Amoxicillin

Figure 2 β-lactam antibiotics (penicillins and cephalosporins) with identical (R1) and similar (R2) side chains.

cross-reactivity with penicillin is only 2–3%.[31,37] Other authors have reported a cross-reactivity rate of less than 1%.[38,40] During metabolism of cephalosporins, the β-lactam and dihydrothiazine rings and the R2 side-chain undergo fragmentation, while the R1 component may remain intact and induce cross-reactivity with penicillins.[31,38] The immunogenicity of R2 side chains is controversial.[38] Romano et al. demonstrated that patients allergic to a certain cephalosporin usually tolerate other cephalosporins with different R1/R2 side chains.[37]

Patients with a history indicative of penicillin allergy can be treated with cephalosporins as an alternative to penicillin, especially with third-generation cephalosporins, except for those with similar R1 side chains.[31,32,38] In the presence of a similar R1 side chain, allergy evaluation can help detect the possibility of penicillin/cephalosporin cross-reactivity. In addition to a detailed history, skin testing or administration of a test dose can be safely performed prior to the graded challenge test before cephalosporin treatment.[41] Tables 1 and 2 show the main β-lactam antibiotics being used that share similar or identical R1 and R2 side chains.

Concerning cross-reactions of penicillins and cephalosporins with carbapenems and monobactams, prospective studies demonstrated that these are either rare or lacking,[31,37,38,42] except for ceftazidime, which shares the same R1 side chain with aztreonam.[43]

Recommendations

Third generation cephalosporins can be administered to patients with mild immediate or delayed hypersensitivity to penicillin. However, their use should be avoided in patients with severe skin manifestations secondary to penicillin administration.[15,44]

In patients with a history of immediate-type reactions to penicillin who require cephalosporins, skin testing with or third generation cephalosporins containing a different side chain may be performed. If the result is negative, then the drug can be administered following a graded challenge test.[31,37,38,40,44]

In patients with a history of immediate-type reactions to cephalosporins who require treatment with cephalosporins or penicillin, skin tests with cephalosporin or penicillin with different side chains should be performed. If negative, the antibiotic can be administered following a graded, controlled challenge test.[31,38,40,44]

Patients allergic to penicillin who require treatment with carbapenems or monobactams can undergo skin tests. If negative, the antibiotic can be administered following a graded challenge test under supervision by a trained health professional.[12,37,38,44,45]

Non-β-lactam antibiotics

The prevalence of allergic reactions to non-β-lactam antibiotics is estimated to be about 1–3% in the general population representing approximately 10% of all drug-associated adverse reactions.[40] Of note, viral infections can cause a maculopapular type of rashes, similar to those caused by non-β-lactam antibiotics.[45] Therefore, it is difficult to differentiate between the drug-induced hypersensitivity reactions and skin lesions caused by viral infections.[45]

The main categories of non-β-lactam antibiotics causing hypersensitivity reactions in children include sulfonamides, macrolides, glycopeptides, aminoglycosides, and quinolones.

Macrolides

The structure of macrolides contains a macrocyclic lactone ring with a number of carbon atoms in the lactonic ring constituting the base for classification into different groups: 14 atoms (erythromycin and clarithromycin), 15 atoms (azithromycin), and 16 atoms (spiramycin, rocitamycin, and iosamycin).[46] The prevalence of allergic reactions to macrolides ranges from 0.4% to 3%.[46–48] Existing data indicate that azithromycin-induced hypersensitivity reactions are more frequent than those caused by clarithromycin.[49] Diagnosis of macrolide allergy is difficult due to insufficient validation of skin prick tests and low reliability of *in vitro* diagnostic tests.[6,50] In a study conducted by Mori et al. comprising 64 children with a history of hypersensitivity reactions to clarithromycin. Sensitivity and specificity of 0.5-mg/mL clarithromycin intradermal tests were 75% and 90%, respectively.[51] Published data on the non-irritative concentrations of macrolides used for skin prick tests are limited to children, rendering difficult interpreting the results.[6,52] Consequently, challenge tests are currently the only reliable diagnostic tool.[46,50] It should be noted, though, that since drug administration can elicit an anaphylactic reaction, it is imperative that diagnostic challenge tests

Table 1 Comparison of penicillin side chains. Symbol R1 represents a similar side chain, whereas symbol r1 represents partially identical lateral chain.

		Penicillins					
		Oxacillin	Dicloxacillin	Penicillin G/V	Piperacillin	Ampicillin	Amoxicillin
Penicillins	Oxacillin	x	r1				
	Dicloxacillin		x				
	Penicillin G/V			x	r1	r1	r1
	Piperacillin				x	R1	r1
	Ampicillin			r1	R1	x	r1
	Amoxicillin			r1	r1	r1	x

Table 2 R1 and R2 in bold face indicate identical side chains. R1 and R2 in regular face indicate a similar side group. Bold r1 and r2 represent partially identical lateral chain. Regular r1 and r2 represent partially similar lateral chain.

Cephalosporins		1st generation				2nd generation			3rd generation						4th generation		
		Cefadroxil	Cefalexin	Cefazolin	Cefalotin	Cefuroxime	Cefrozil	Cefaclor	Ceftibuten	Cefixime	Ceftriaxone	Cefotaxime	Cefpodoxime	Ceftazidime	Cefepime	Cefpirome	Aztreonam (Monobactam)
1st generation	Cefadroxil	x	r1				R1	r1									
	Cefalexin	r1	x				r1	R1									
	Cefazolin			x													
	Cefalotin				x	r1r2						R2					
2nd generation	Cefuroxime				r1r2	x				r1	R1	R1r2	R1		R1	R1	
	Cefprozil	R1	r1				x	r1									
	Cefaclor	r1	R1				r1	x									
3rd generation	Ceftibuten								x	R1	R1	R1	R1	R1	R1	R1	R1
	Cefixime					r1			R1	x	R1	R1	R1	R1	R1	R1	R1
	Ceftriaxone					R1			R1	R1	x	R1	R1	R1	R1	R1	R1
	Cefotaxime				R2	R1r2			R1	R1	R1	x	R1	R1	R1	R1	R1
	Cefpodoxime					R1			R1	R1	R1	R1	x	R1	R1	R1	R1
	Ceftazidime								R1	R1	R1	R1	R1	x	R1	R1r2	R1
4th generation	Cefepime					R1			R1	R1	R1	R1	R1	R1	x	R1	R1
	Cefpirome					R1			R1	R1	R1	R1	R1	R1r2	R1	x	R1

should be performed under medical supervision of trained professionals.[45] Although allergic reactions to macrolides are uncommon, cross-reactions between different macrolides have been reported, manifested predominantly as anaphylaxis.[53]

Aminoglycosides

Aminoglycosides are classified into the following two groups: (a) The streptidine group, including streptomycin; and (b) the desoxystreptamine group, including antibiotics amikacin, gentamicin, tobramycin, and neomycin.[54] Hypersensitivity to aminoglycosides is rare, but certain patient groups are at higher risk, such as patients with cystic fibrosis, where aminoglycoside allergy is relatively frequent.[46] Contact dermatitis caused by topical aminoglycosides is the most common clinical manifestation because of the widespread use of neomycin, gentamycin, and tobramycin in creams and ointments as well as eye and ear drops.[54,55] Currently, *in vivo* tests involving aminoglycoside sensitization are not validated. Therefore, the graded challenge test should be performed in children with suspected aminoglycoside allergy.[45] In patients with suspected contact dermatitis, patch tests with the agent in question are recommended.[56]

The reported high prevalence of cross-reactivity among different aminoglycosides (50%) indicates that patients with hypersensitivity to an aminoglycoside should avoid all groups of aminoglycosides.[6,54,56]

Sulfonamides

Sulfonamides are associated with delayed hypersensitivity reactions, such as maculopapular rashes or severe skin manifestations,[57,58] with most allergic reactions being T-cell-mediated ones. Among antibiotics, sulfonamides are the most common cause of the Steven–Johnson syndrome, toxic epidermal necrolysis, and benign skin manifestations.[6]

Cotrimoxazole is the most frequently administered Sulfonamide to children with vesicoureteral reflux for prophylaxis of urinary tract infections (UTI). In addition, it is commonly used for the prevention or treatment of opportunistic infections in patients with severe diseases, including acquired immunodeficiency syndrome (AIDS) and blood malignancies.[40] Concerning patients with AIDS, the prevalence of rashes seems to be higher in those with active, untreated disease and during the acute phase of management in patients with low CD4 (cluster of differentiation 4) cell counts.[58]

The best strategy for managing patients with sulfonamide hypersensitivity is an alternative antibiotic. However, there is no equally effective alternative treatment in certain cases, such as in patients infected with human immunodeficiency virus (HIV).[46] Therefore, various strategies have been suggested to manage patients with mild or moderate non-immediate reactions (e.g., without mucosa or systemic manifestations). In this context, treatment with cotrimoxazole could either be continued at the same doses or be interrupted for a few months, usually 6 months, and then restart with a graded challenge procedure or a desensitizing protocol.[59]

Glycopeptides

The most commonly used glycopeptide is vancomycin, which is often administered in patients infected by either resistant Gram-positive microbes or β-lactam-resistant strains.[46,54] Vancomycin can cause various hypersensitivity reactions, mainly of delayed type.[46,54] Linear bullous dermatosis is the most frequent non-immediate reaction, while red man syndrome (RMS) is the primary immediate reaction.[46,54,60]

In patients with a clinical history indicative of vancomycin hypersensitivity, immediate and delayed-type hypersensitivity reactions can be diagnosed using intradermal (at concentrations equal to or lower than 0.1 mg/mL) and patch tests (at a concentration of 0.005%), respectively.[46] Of note, severe RMS may imitate IgE-induced anaphylaxis, requiring prompt diagnosis and treatment. However, lowering the infusion rate of vancomycin to 500 mg over an hour significantly decreases the risk of RMS, while this does not affect genuine hypersensitivity reactions.[54] Moreover, data regarding the potentially preventing effect of antihistamine medications on RMS is limited.[54]

Rare RMS patients following administration of teicoplanin have also been reported in children with a history of vancomycin hypersensitivity.[45] For this reason, using an alternative antibiotic or applying a desensitization protocol is recommended in patients with vancomycin allergy.[45]

Quinolones

Quinolones are classified into four generations based on their antibacterial spectrum. The first-generation quinolones, with the main representative being nalidixic acid, are used rarely. The second-generation class is the commonly used in clinical practice and includes ciprofloxacin, among many other quinolone antibiotics.

Data from Spain demonstrated that quinolones consist of the third more common cause of drug-induced adverse effects, following anti-inflammatory drugs and β-lactam antibiotics, with a progressively increasing prevalence from 0.53% in 2005 to 5.96% in 2009.[61] A systematic review of studies concerning the prevalence of ciprofloxacin-associated adverse effects, including 16,184 children and adolescents aged less than 18 years, estimated the risk of allergic/anaphylactic reactions as 0.043%.[62] Hypersensitivity reactions to quinolones may be immediate, commonly manifested as anaphylaxis, or delayed presenting with maculopapular rashes.[63]

The skin prick tests and intradermal tests are not recommended for diagnosis of quinolone allergy, as they can activate dermal mast cells leading to false-positive results.[6,63] Quinolone challenge test is the most appropriate test for diagnosing quinolone hypersensitivity.[6,46,63] Estimating the prevalence of cross-reactions among quinolones is not feasible because of the low numbers of patients studied.[63] Therefore, all types of quinolones should be avoided by patients with quinolone hypersensitivity. In cases where quinolones appear as the only choice of treatment, desensitization is required.[63] In addition, cross-reactions have also been reported between quinolones and other drugs, such as β-lactams and neuromuscular blockers.[64]

Conclusions

Antibiotic hypersensitivity is a typical problem for physicians, particularly when considering the future use of antibiotics. It is necessary to ascertain whether the reaction associated with consumption of antibiotics was a type A or type B reaction. Although adverse drug reactions to antibiotics are frequently documented, immunologically mediated hypersensitivity is unusual, and true IgE-mediated antibiotic allergy is confirmed in a small proportion. In the event of a Type B reaction, an appropriate diagnostic workup is required to identify the drug's causal role. This assessment includes determining the most likely drug responsible for allergic reaction, the most plausible mechanism(s), and any potential cross-reactive drugs to avoid in the future. It is critical to avoid "labeling" a child as allergic without first conducting a proper diagnostic workup. After an antibiotic allergy diagnosis is made, prescribing a safe and effective alternative drug is the second step. However, the most significant problem is those who report having a penicillin allergy but do not have one. These individuals suffer from unfavorable consequences throughout their lives, which begin with ineffective and unnecessary use of broad-spectrum antibiotics. The aforementioned cases lead to the global problem of difficult-to-cure inpatient infections, and the development of bacteria resistant to multiple antibiotics. To counter this threat, patients supposed to be allergic to antibiotics should be referred to an allergy specialist for proper evaluation and diagnosis.

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