

Allergy to antibiotics in children: Perception versus reality

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Antibiotics are the most commonly prescribed drugs in children and are most likely to be associated with adverse reactions (1-3). Less than 25% of all adverse drug reactions are due to allergies to the drugs (4). Although these illnesses are usually not severe enough to lead to hospital admission (5), they are a concern for parents, and children who are antibiotic-allergic have an increased number of medical visits and antibiotic prescriptions, and higher antibiotic costs (6) than other children. Clinicians are often hesitant to prescribe an antibiotic to patients with suspected, but unproven, immunoglobulin E (IgE)-mediated allergies (7,8) because of the potential risk of life-threatening anaphylaxis. The consequence of avoiding first-line agents is that alternative antibiotics are usually more expensive, have a broader spectrum of antimicrobial coverage and, therefore, are more likely to alter normal flora, and to have more side effects (9). The purpose of this note is to review briefly antibiotic allergy in children and clinical approaches to children with suspected antibiotic allergies.

An adverse reaction to an antibiotic is "any response to a drug which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis, or treatment" (10). Generally, hypersensitivity or allergic drug reactions are categorized according to the immunopathogenic mechanisms outlined by Gell and Coombs (11) (Table 1), and more than one mechanism can be operating simultaneously (4). The true prevalence of antibiotic allergy is unknown. In ambulatory children followed in prospective studies, the incidence of adverse drug reactions ranges from 0.75% to 4.5% (1-3,12,13). The percentage of those attributable to drug allergy is not known because few population-based studies are available, and most reports are of individual patients or groups of patients. Furthermore, the

pathophysiological basis of adverse reactions to many antibiotics is not known, although it may be labelled as allergic in nature. For example, the serum sickness-like illness that occurs in about 0.06% of children receiving cefaclor (14) is likely due to a cytotoxic effect of the drug on cells (15), rather than immune complex deposition. Some commonly used antibiotics and the types of allergies associated with their use can be found in Table 2.

Parental or patient reports of drug allergies always overestimate the true frequency. For example, when children with reported allergies to penicillin are subjected to skin testing, a range of 0% to 34% will have an IgE-type reaction (16-20). A small number of children have allergies to multiple antibiotics (21); the etiology of this phenomenon is not clear.

The variation in the reported frequency of allergies among those who are labelled as antibiotic-allergic before skin testing is likely due, in some part, to differences in physician management of the initial clinical event that leads to suspicion of drug allergy. Physician documentation of the clinical findings of the suspected allergic reaction

TABLE 1
Classification of allergic drug reactions

Type I:	IgE-mediated (eg, anaphylaxis to penicillin)
Type II:	cytotoxic antibodies (eg, penicillin-hemolytic anemia)
Type III:	antigen-antibody complexes (eg, serum sickness)
Type IV:	cell-mediated immune reactions (eg, gramicidin/neomycin sulfate/polymyxin B sulfate [Neosporin Cream, Glaxo Wellcome, Canada] contact dermatitis)

IgE Immunoglobulin E

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TABLE 2
Allergic reactions to some commonly used antibiotics in children

Antimicrobial (reference)	Reaction type				Incidence of anaphylaxis
	I*	II	III	IV	
Penicillin (35)	X (3.2%)	X	X		1.23/10,000 injections
Cephalosporins (all) (36)	X (1%–2.8%)				0.0001% to 0.1%
Cefixime (37)	2.8%				
Cefaclor (38)	X (1.5%)				
Sulphonamide (39,40)	X (4.6/100 person- years at risk)		X		1/100,000
Macrolides					
Erythromycin (41)	X				
Azithromycin (42)	0.5%				
Clarithromycin (42)	2.8%				

*Incidence is in brackets

may be incomplete (9), making interpretation difficult for subsequent care providers. Discrepancies between parental reporting of antibiotic allergy and confirmation in the health record (6) suggest either poor documentation or miscommunication as to the likely diagnosis when adverse drug reactions occur.

Clinical diagnosis of adverse reactions to antibiotics is difficult, and this may result in labelling the child as allergic for lack of a better explanation of the event. Antibiotics are prescribed frequently for febrile infectious illnesses in childhood, and many of these are associated with urticarial or other rashes. A morbilliform, nonurticarial rash may occur in up to 13% of patients who receive amoxicillin or ampicillin. These patients are not considered to be at risk for a life-threatening reaction to penicillin. The interaction between viral infections and certain antibiotics can result in adverse events that appear to be specific to certain viruses, for example, cutaneous reactions to ampicillin in acute infectious mononucleosis and to sulphonamides in patients with HIV infection (22). Reactions may be caused by excipients and additives in the antibiotic preparation, or by a drug previously taken by the patient (19). Although frequently a cause of physician and parent anxiety, the incidence of allergic cross-reactions to cephalosporins in patients who are allergic to penicillin is less than 2% (4).

The clinical evaluation of adverse drug reactions is difficult; therefore, systematic approaches have been proposed (23,24) and, if implemented, will likely reduce the number of children being inappropriately labelled as allergic to antibiotics. Detailed algorithms have also been reported,

but none has proven to be sufficiently sensitive and specific (24). An approach to the clinical evaluation of suspected adverse drug reactions is presented in Table 3.

There is no single test or clinical finding that leads to a diagnosis of antibiotic allergy (23,25-27). The only validated method for determining drug allergy in clinical practice is skin testing for IgE-mediated allergy to penicillin (4,28). The radioallergosorbent test for serum IgE to penicillin is not recommended because of poor sensitivity and because it is only available for the major determinant of penicillin (4). There are no reliable skin tests routinely available for assessing allergic reactions to other antimicrobial agents (25). The development of immunological diagnosis of antibiotic allergy is limited because most drugs are incomplete antigens, or haptens (15). Haptens cannot stimulate hypersensitivity reactions until they bind to a carrier molecule. With the exception of penicillin, immunoreactive molecules have rarely been identified (28).

If the child's history is suggestive of an IgE-mediated allergy to penicillin, skin testing is an established method to determine whether a specific IgE response exists and to determine type I hypersensitivity (4,28). The negative predictive value of a negative skin test is greater than 99% (29). Skin testing cannot detect non-IgE-mediated immunological reactions such as serum sickness and hemolytic anemia. The procedure consists of a scratch test on the volar surface of the forearm using preparations of the major and minor determinants of penicillin, and positive (histamine) and negative (saline) controls. If scratch testing is negative after 15 min, intradermal testing is completed with the same agents. If no reaction is observed during the skin tests, an oral challenge with a standard dose of penicillin is given, and the child is observed for 1 h. Generally, this clinic visit takes approximately 2.5 h. If no adverse reaction is observed, then the family can be told that the risk of a life-threatening or serious reaction if the child takes penicillin is no greater than that of the general population. It is important that the parent and child are educated about the meaning of negative and positive test results, and that a system is in place to update the child's health record if penicillin allergy warning labels are to be removed from the chart (16,30) and subsequent prescribing behaviour is to change.

Skin testing must be conducted by personnel who are familiar with the techniques in a setting capable of managing rare systemic reactions and with appropriate test materials (4,28). Up to 90% of systemically administered penicillin is excreted in the urine, and a fraction is metabolized. The remaining fraction undergoes spontaneous degradation. The degradation products react with host proteins to form the penicilloyl group (major determinants) or form penicilloate, penicilloylamine and penicilloate (minor determinants) (31). Because no commercially available formulation of a minor determinant mixture is available, various locally prepared reagents have been used, and only 40% of allergists surveyed in the United States use a minor determinant mix-

TABLE 3
Approach to a suspected adverse drug reaction

1) Clinical diagnosis	Obtain a detailed history of the name of the drug(s), indications for the drug, concurrent infections and other clinical features, time lapse between when the drug was taken and the onset of the reaction, and history of resolution of symptoms with drug withdrawal
	Perform physical examination for skin rashes (urticaria, angioedema, maculopapular rashes, dermatitis and vasculitis) and their distribution. Drug reactions may involve any system
2) Analysis of drug exposure	Review current and past exposures to this drug (name, formulation, concentration, dose and known excipients)
3) Differential diagnosis	Consider all possible clinical diagnoses, including the underlying condition. Is the reaction in keeping with known adverse reactions to the drug? If Stevens-Johnson syndrome, exfoliative dermatitis, hepatotoxicity or anaphylaxis occurred, refer the patient to a specialist for assessment
4) Literature review	Search medical literature for evidence showing that the drug in question is associated with the adverse event. If there is no association, reconsider the diagnosis and consider additives to the drug preparation
5) Confirmation	Complete skin testing for penicillin, refer to specialist
6) Report to drug regulatory authorities and the drug manufacturer	
7) Advice to the patient	Notify the patient and other health care professionals involved in the patient's care (MedicAlert, MedicAlert Foundation, USA). Determine alternate antibiotic choices if necessary

Data from references 23,25,43

ture when they perform skin testing (8). Although only 14% of true penicillin allergy is to a minor determinant, these responses have a higher likelihood of being anaphylactic reactions. Only minor determinant mixtures are recommended to detect allergy to minor determinants (4,28). In Canada, a number of physician specialists (paediatric allergists and immunologists, pharmacologists, infectious disease specialists) (20,21) provide skin testing for penicillin allergy and evaluation of patients with suspected drug hypersensitivity.

RECOMMENDATIONS

Use antibiotics wisely. The Canadian Paediatric Society recommends that antimicrobial therapy should be limited to situations in which there is a clear indication and should be administered for the shortest effective duration (32). The appropriate use of antimicrobial agents decreases the incidence of adverse drug reactions.

If a suspected allergic adverse drug reaction occurs in a child taking antimicrobial agents, perform a careful clinical assessment to determine whether the clinical event is an adverse drug reaction and whether it is potentially allergic in nature. The nature of the reaction should be carefully documented in the child's health record. Suspected adverse drug reactions should be reported to the Canadian Adverse Drug Reaction Monitoring Program of Health Canada. These reactions can be reported whether they are expected or not, regardless of their severity. Canadian Adverse Drug

Reaction reporting forms can be downloaded from the Therapeutic Products Directorate Web site (http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/guides/adr/adr_guideline_e.html), copied from the Compendium of Pharmaceuticals and Specialties (33) or obtained from regional or national adverse drug reaction units.

If the adverse drug reaction is to penicillin and is thought to be a manifestation of an IgE-mediated allergy, arrange for skin testing. This may require referral to an adverse drug reaction clinic, an allergist or another specialist. Skin testing should only be conducted in settings in which personnel are familiar with the technique, use appropriate materials and are able to manage life-threatening drug reactions.

If the adverse drug reaction is to an antimicrobial agent other than a penicillin and is thought to be allergic in nature, avoid the use of the drug. If the patient is likely to need antibiotics in the future (eg, recurrent urinary tract infections), then the patient may benefit from referral to a specialist to determine which antimicrobial agent(s) is the most effective and safe choice.

If a child is allergic to an antibiotic and it is the only therapeutic choice, desensitization may be necessary. Desensitization protocols are available for several antibiotics, and describe administration of the drug in progressively increasing doses given by mouth (34) and intravenously (28). These protocols must be performed in a hospital setting by experienced personnel.

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The recommendations in this note do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate. This article also appears in *Paediatr Child Health* 2002;7(4):233-237.



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