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Study Objective. To determine whether a reported antibiotic allergy was likely to have been immunologically mediated.

Design. Questionnaire-based study.

Setting. Tertiary care, freestanding children's hospital.

Patients. One hundred patients aged 1 month–18 years for whom guardians reported an allergy to an antibiotic at the time of hospital admission between October 2009 and March 2010.

Intervention. guardians of the patients were interviewed by using a standardized allergy assessment questionnaire.

Measurements and Main Results. Based on answers to the questionnaire, the reported allergic reactions were categorized to determine if they were true allergies or adverse reactions. Among the 100 patients, reported allergies were categorized as immunologically mediated reactions in 58%, non–immunologically mediated adverse drug reactions in 27%, no reaction in 3%, and unknown in 12%. Reactions to penicillins, cephalosporins, or sulfonamides were reported most frequently and were attributed to immunologically mediated reactions in 68% (26/38), 74% (17/23), and 67% (10/15) of instances, respectively.

Conclusion. Use of the allergy assessment questionnaire determined that 58% of the 100 reported antibiotic allergies fulfilled criteria for an immunologically mediated reaction. These findings underscore the utility of an allergy assessment questionnaire, versus a simple drug history, in improving the accuracy of reported antibiotic reactions.

Allergic reactions are thought to be responsible for 6–10% of adverse reactions to drugs and can be acute, serious, or life-threatening.1 Drug reactions are considered allergic if they are immunologically mediated, as defined by the gell and Coombs classification (Table 1).1 Allergies to penicillin account for 5–20% of the reported drug reactions.2, 3 Approximately 10–30% of patient-reported antibiotic allergies have been found not to be immunologically mediated.2–8 We are aware of no studies that have addressed the validity of reported drug reactions in children, and none that have used a questionnaire to assess the validity of reported reactions.2–8

Although parents or guardians often recall being informed by a health care professional that their child has an antibiotic allergy, many cannot accurately describe the details of these drug reactions. In these settings, parents and health care professionals are often reticent to administer the antibiotic or agents in the same drug class. In most instances, caregivers are unable to distinguish non–immunologically mediated adverse drug reactions from those likely to be allergic reactions. Thereafter, when queried by health care providers, such intolerances may be recorded as drug allergies. Both overreporting and documentation within the medical record

often result in use of alternative agents with wider antimicrobial spectra, narrower safety profiles, and/or higher costs.

The objective of this study was to determine whether a reported antibiotic allergy was likely to have been immunologically mediated by using an allergy assessment questionnaire.

Table 1 Gell and Coombs Classification of Allergic Reactions[1]

Type	Reaction Name	Description	Time to Onset
I	Anaphylactic (IgE mediated)	Allergen binds to IgE on basophils or mast cells and causes inflammatory mediators. This results in anaphylaxis, edema, and bronchospasm. Anaphylaxis can involve a single organ or multiple organs, including the respiratory tract, nasal mucosa, skin, or gastrointestinal tract.	Rapid (within 30 min)
II	Cytotoxic	Reaction involves destruction of host cells, usually blood cells, through cell-associated antigens that initiate cytolysis by antigen-specific antibodies. This can result in hemolytic anemia, agranulocytosis, or thrombocytopenia.	5–12 hrs
III	Immune complexes	Antigen-antibody complexes form and deposit on blood vessel walls. This activates complement and causes localized edematous or erythematous reactions or serum sickness.	3–8 hrs
IV	Cell mediated	Antigens activate lymphocytes, which release inflammatory mediators, leading to dermatologic manifestations involving erythema and indurations.	24–48 hrs
IgE = immunoglobulin E.			

Methods

Study Population and Setting

This study was conducted after receiving approval from the institutional review board of Indiana University–Purdue University, Indianapolis, Indiana. Eligible patients were those aged 1 month–18 years who, on admission to a tertiary pediatric hospital, were reported by a parent or guardian to have previously experienced an allergic reaction to an antibiotic. Exclusion criteria were patients in the neonatal intensive care unit, those who were readmitted after initial study inclusion, and patients whose medical records described adverse reactions that were unlikely to have been immunologically mediated (i.e., vancomycin with a listed reaction of red man's syndrome or macrolide antibiotics in patients receiving cyclosporine or tacrolimus) as determined by study investigators.

One hundred patients were selected by using a randomly generated list of hospital room numbers from among those reporting a history of an antibiotic allergy when being admitted from October 2009 through March 2010. All patients' guardians were interviewed by one pharmacist using a standardized allergy assessment questionnaire (Appendix 1), which was derived from a compilation of recommendations for obtaining an accurate allergy history.2, 4–8

Drug reactions were categorized as either a true allergy or an adverse reaction. Drug reactions that were likely to have been immunologically mediated were considered true allergies as defined by the assessment questionnaire. An adverse reaction was presumed probable if either all reported symptoms were included within the adverse reaction column of the assessment questionnaire, or an antibiotic in the same class (penicillin or cephalosporin) had subsequently been administered without the development of an allergic reaction. For example, if a patient had a reported allergy to penicillin, but had subsequently received amoxicillin without a reaction, the reaction to penicillin would be considered an adverse reaction. Adverse reactions that were considered non–immunologically mediated included vomiting and/or diarrhea, behavioral changes, muscle cramps, or urinary tract symptoms.

Drug reactions were considered "unknown" if not directly observed by the guardian or if the interval between the reaction and antibiotic administration was unclear. "No reaction" was recorded if the patient had never received the drug or was receiving the drug at the time of the interview and no reaction occurred.

Guardians were also queried as to whether the allergic reaction had been"confirmed." This was defined if the guardian recalled being told by a physician or other health care provider that the patient was allergic to the drug. Skin or other challenge tests were not performed.

Statistical Analysis

Descriptive statistics were used for patient demographics, the percentage of reported antibiotic allergies that were assessed to have been true allergies, and the occurrence of true allergies among the antibiotic classes. Statistical analysis was conducted with the Statistical Package for Social Sciences, version 16.0 (SPSS, Inc., Chicago, IL) and Excel 2007 (Microsoft Corp., Redmond, WA).

Results

Patient demographics are summarized in Table 2. guardian-reported reactions in the 100 patients were categorized as true allergy in 58%, adverse reaction in 27%, no reaction in 3%, and unknown in 12%. The reactions were categorized as unknown based on the following criteria: no recollection of the signs or symptoms (five patients); receipt of multiple antibiotics when the reaction occurred (three patients); patient was readmitted to the hospital after undergoing treatment, and it was unclear whether symptoms resulted from an allergic reaction or were attributable to the primary illness (one patient); guardian did not recall the events leading to the history of allergy (one patient); guardian told by primary physician that reaction should be listed as allergy (one patient); and guardian recalled being told that the patient had an allergic reaction, but guardian did not recall the name of the drug (one patient). Medical record–documented drug allergies were most commonly attributed to the penicillin class, cephalosporins, and/or sulfonamides (Table 3); these reactions were categorized as immunologically mediated in 68%, 74%, and 67%, respectively.

Table 2 Demographics of the Study Children

Characteristic	Value
	Mean • ± SD
Age on admission, yrs (n=100)	8.77 ± 4.76
Age when allergic reaction occurred, yrs (n=87)	4.48 ± 3.82
	Percentage of Patients (n=100)
Age group	
1 mo–5 yrs	27
6–11 yrs	37
12–17 yrs	36
Male	57
Interviewee	
Mother	81
Father	13
Both parents	1
Other guardian	5
Medical record–documented antibiotic	91
Specific drug	9
Drug class	33
Specific reaction documented in medical record	

A reaction was recalled by 87 of the 100 guardians interviewed. Among the 87 reported reactions, 40 (46%) were hives or blistering and 39 (45%) were rashes (Table 3). Sixteen patients (18%) were reported to have had both reactions. The interval between drug administration and reaction onset was known in 33 (83%) of the 40 hives or blistering reactions and 31 (79%) of the 39 instances of rash. Of these 33 hives or blistering reactions, 19 (58%) occurred with the first dose and 14 (42%) occurred later in therapy. Of these 31 instances of rash, 12 (39%) occurred after the first dose, 17 (55%) occurred later in treatment, and 2 (6%) occurred after treatment. Rash was most commonly reported with penicillin antibiotics (18/39 [46%]), followed by sulfonamides (8/39 [21%]), and cephalosporins (7/39 [18%]). guardians reported that the reaction was confirmed as a true immunologically mediated reaction in 67 (77%) of the 87 instances, with 36% resulting from a physician visit, 12% over the phone, 16% in an emergency room visit or at another hospital, and 13% at the study hospital. There were no reports of skin testing.

Discussion

Pharmacists and physicians often rely on the guardian’s recollection within the medical record documentation to assess the validity of reported allergies to drugs. The terms “rash” and “hives” are often defined differently by guardians and health care professionals. The results of such inquiries into reported allergies must be objectively interpreted since many are found not to be immunologically mediated. Revalidation of these reports should be conducted at each encounter.

Inaccurate classification of adverse drug reactions as immunologically mediated reactions has been shown to result in substitution of agents with wider spectra of activity, narrower safety profiles, and higher costs.3, 8 Such reports have been shown to alter antibiotic selection in 30% of patients.8 Cross-sensitivity to cephalosporins in patients allergic to penicillin has been reported in as few as 0.5% of patients.9 However, many believe that the range of cross-sensitivity to cephalosporins is higher (8–18%) among patients with penicillin allergy, resulting in limitation of use of penicillins, cephalosporins, and potentially carbapenems from an antibiotic regimen.9

A study performed in an adult acute-care teaching hospital found that 28% of allergy labels could be removed after analyzing the results of a drug allergy assessment.4 Similar studies have concluded that patient-reported drug allergies were found to be valid in 22–50% of instances.2, 4, 5 Similar to our findings, another group of authors determined that β-lactam antibiotics and sulfonamides accounted for 63% of patient- reported allergies, but, in 9% of cases, the patients were found either to be nonallergic or to have not received the drug.6

Our assessment questionnaire examined guardian-recalled historical information in a consistent fashion, which was used to assess the probability of a patient having an immunologically mediated drug reaction. Both for the purpose of our analysis and in an effort to simplify our questionnaire, a detailed description of rashes was not used, rather the presence or absence of cutaneous reactions was noted. Since viral exanthems are common causes of fever in children, it is difficult to differentiate rashes caused by infection and drug allergy.3 One group of authors reported penicillin-associated rashes in 7% of treated children; however, those considered immunologically mediated occurred in only about 3% of treated children.10 The percentage of immunologically mediated drug reactions found in our study (58%) may have been overestimated, since rashes due to the primary disease process could have been attributed to true allergies.

Guardians reported that being told by aphysician or other health care provider that their child had a drug allergy and/or having a physician prescribe an alternative antibiotic was interpreted as validation of a drug allergy. A study that used skin testing and oral antibiotic challenge to confirm immunologically mediated antibiotic reaction found that only 34% of immunologically mediated reactions to penicillins and cephalosporins can be accurately predicted by the appearance of the rash at the time of the presumed reaction.[11] guardians reported that in 12% of instances, confirmation or validation of allergic reactions was based solely on telephone conversations with a care provider. In these instances, guardians should be informed that further evaluation, with use of skin testing or oral challenge, may more accurately assess the validity of the reaction.

Table 3 Characterization of Antibiotic Reaction

Variable	Percentage of Patients with Reaction (n=100)	No. (%) of Reactions Categorized as Immunologically Mediated
Medical record–documented drug allergy		
Penicillins	40	26 (68)
Cephalosporins	25	17 (74)
Sulfonamides	18	10 (67)
Macrolides	9	2 (25)
Vancomycin	4	1 (33)
Clindamycin	2	1 (100)
Fluoroquinolone	1	0 (0)
Metronidazole	1	1 (100)
	(n=87)	
Guardian-described Reaction[3]		
Hives or blistering	46	
Diffuse rash	45	
Otherb	29	
Unknown	15	
Nausea or vomiting	10	
Severe itching	10	
Diarrhea	8	
Shortness of breath	8	
Anaphylaxis	3	
Serum sickness	3	
Drowsiness	2	
Headache	< 1	
Irritability	< 1	
Muscle cramps	< 1	
	(n=100)	
Time to reaction onset		
First dose	33	
During therapy	35	
After completion of therapy	2	
Unknown	30	
Antibiotic rechallenged		
Yes	17	
No	75	
Unknown	8	
	No. (%) of 17 Rechallenges	
Repeat reaction during rechallenge		
Yes	14 (82)	
No	2 (12)	
Unknown	1 (6)	

[a]Multiple reaction symptoms were reported by some guardians.

[b]Included elevated transaminase levels, red man's syndrome, diaper rash, intestinal bleeding, flushing, redness at the injection site, swelling, erythema multiforme, raw and painful skin, facial rash, and seizure.

Limitations

A potential limitation of this study could have been a guardian's inaccurate recollection and/or description of the rash, as well as the recollection of the temporal sequence of events. A previously published assessment of the validity of antibiotic allergies found that 98% of patients recalled the name of the drug and the nature of the allergic reaction.[8] In our study, 87% of the 100 guardians could describe the child's reaction. The reports of "false-positive" allergies to antibiotics other than penicillins, cephalosporins, and sulfonamides appear high, but the percentage of those reports was low at 17%. This may be attributed to the imprecise documentation in the medical record leading to the false-positive allergy. In addition, 12% of 100 reactions were categorized as unknown because limited information was available (i.e., the guardian did not recall specific details) to determine if the reactions were likely to be immunologically mediated.

Conclusion

An allergy assessment questionnaire found that 58% of 100 reported antibiotic allergies fulfilled criteria for an immunologically mediated reaction. There are opportunities to improve the assessment and documentation of reported antibiotic allergies in pediatric patients. Use of an allergy assessment questionnaire may reveal discrepancies necessitating further evaluation, which may impact antibiotic utilization.

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