

The prevalence of antibiotic skin test reactivity in a pediatric population

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ABSTRACT

Although adverse drug reactions (ADRs) are not uncommon, true allergic (i.e., immunologic) reactions are infrequent. Estimates are that only 10% of reported "penicillin (PCN)-allergic" patients have true allergic drug reactions. Most studies of PCN-related ADR have been conducted in adult populations and suggest that the majority of adult patients presenting with PCN allergy history can safely receive the drug. The goal of this study was to examine the outcome of provocative drug challenges to antibiotics in a pediatric population and correlate outcomes with predictive factors. Through chart review, we identified 96 pediatric patients with history of an ADR to antibiotics who underwent skin testing (ST) and/or graded challenges to PCN ($n = 52$), cephalosporins ($n = 7$), azithromycin (AZT; $n = 24$), or clindamycin ($n = 4$). Of these children with an ADR, 87 (90.6%) tolerated provocative drug challenges and 9 (9.4%) were instructed to continue drug avoidance because of positive ST or failed challenge. Eight of the nine patients continued drug avoidance due to positive PCN ST ($n = 4$) or ADR during drug PCN challenge ($n = 4$). All AZT and cephalosporin challenges had negative outcomes, and only one patient did not proceed with the clindamycin challenge after a positive ST. True "antibiotic allergy" denoted by positive ST or failed challenge in patients with a history of ADR occurred in <10% of children included in this study, suggesting that without such testing nearly 90% might be treated with alternative antibiotics unnecessarily.

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An adverse drug reaction (ADR) is defined as any harmful or undesired effect of medications used for prevention, diagnosis, or treatment.¹ ADRs occur in >7% of the general population, affecting 10–20% of hospitalized patients and 17–25% of ambulatory primary care clinic patients.^{2–4} ADRs are classified into predictable reactions (type A) and unpredictable reactions (type B), which include drug hypersensitivity reactions or unpredictable reactions mediated by immunologic mechanisms.^{5,6} Although ADRs are prevalent in the general population, true "drug allergy," defined as an immunologic reaction, is thought to account for only 6–10% of all ADRs.⁷ Antibiotics are associated with a large number of such ADRs, with 10% of the general population reporting an allergy to penicillins (PCNs).^{8,9}

The use of antibiotics is often limited because of questionable history of hypersensitivity and lack of standardized protocols and reagents to verify the history. The only Food and Drug Administration–approved skin testing (ST) reagent for an antimicrobial, PrePen (penicilloyl polylysine; AllerQuest, West Hartford, CT), was withdrawn from the market in 2004 and

was only recently reintroduced in November 2009. In the absence of PrePen, alternative protocols have been proposed to evaluate patients with non-life-threatening reactions to PCN.^{10,11} Commercial ST reagents have never been developed for azithromycin (AZT), clindamycin, or cephalosporins. Because of these deficiencies, patients with ADR to first-line agents are treated with more costly alternative antibiotics, leading to inflated health care costs and suboptimal antimicrobial coverage.

Despite the relatively low prevalence of immunologically mediated ADR, it would be useful to have data on the occurrence of antibiotic allergy in relation to age and sex in children. Risk factors predisposing to immunologic ADR in adult cohort studies include physical and chemical properties of the drug, in addition to patient factors such as atopy, gender, family history, other ADR history, concomitant disease, and need for prolonged or repeated courses of therapy.

Provocation tests remain the gold standard for the diagnosis of current drug allergy and exhibit a low rate of positive outcomes.¹² This study examines the results of ST and outcomes of provocative challenges to PCN, cephalosporin, AZT, and clindamycin in a cohort of children treated in a university-based children's hospital. We also examine demographic and atopic risk factors that may be associated with positive challenges in the hope that this information may help guide clinicians in their approach to patients with suspected antibiotic allergy.

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METHODS

Study Design

An electronic medical record was used to obtain demographic, clinical, and historical information on the patient cohort with suspected antibiotic allergy for the years 2004–2009. Charts of patients who completed a food or drug challenge in addition to charts containing the ICD-9 code 995.20 or “adverse effect of drug” were identified by electronic medical record review. Of the 800 charts reviewed, 96 patients had undergone skin-prick testing (SPT) and/or intradermal (ID) testing and/or completed antimicrobial challenges. These procedures were performed/supervised by one of the study investigators (including years when PrePen was withdrawn from the market). Previous ADR was obtained by history from parents. When available, medical records from the emergency room or primary care physician’s office were used to confirm the ADR history.

Patients had undergone antibiotic SPT if they had a history of an antibiotic associated non-life-threatening ADR and it was thought that future treatment with the antimicrobial might be necessary. Patients with history of Stevens-Johnson syndrome; toxic epidermal necrolysis; or systemic reactions such as vomiting, difficulty breathing, loss of consciousness, or anaphylaxis were excluded. This study was approved by the Institutional Review Board of Alfred I. duPont Hospital for Children.

Method of ST and Challenge

The method of ST for all antibiotics is summarized in Table 1. Patients with history of PCN ADR underwent SPT with saline and histamine (1 mg/mL) controls, PrePen when available, and PCN G (10,000 U/mL). The diameters of the wheals and flares were recorded in millimeters after 20 minutes. Positive responses were read as a wheal ≥ 5 mm. ID testing was performed if SPT was negative (wheal < 5 mm). Positive ID results were defined as a wheal 3 mm greater than the negative control. In the absence of PrePen, two patients had additional SPT and ID with nonirritating concentrations of ampicillin (2.5, 10, and 25 mg/mL).¹³

Patients with a history of ADR to a first- or second-generation cephalosporin underwent SPT and ID with controls and cefazolin (3, 10, and 30 mg/mL). Patients with history of ADR to third- or fourth-generation cephalosporins underwent SPT and ID with controls and cefazolin (3 and 10 mg/mL) of nonirritating concentrations of the antibiotic in question, as described previously by Empedrad *et al.*¹⁴

Patients with ADR to clindamycin underwent SPT, ID, and epicutaneous (patch) testing previously described by a protocol from Lammintausta *et al.*¹⁵ SPTs were placed with controls and clindamycin (150 mg/

Table 1 Summary of skin testing and challenge methods

Antibiotic	Skin-Prick Testing Reagent	Intradermal Skin Testing Reagent	Epicutaneous Patch Testing	Graded Challenge Doses (% of therapeutic dose)
PCN	PrePen PCN G, 10,000 U/mL Ampicillin, 2.5 mg/mL, 10, and 25 mg/mL	PrePen PCN G, 10,000 u/mL Ampicillin, 2.5, 10, and 25 mg/mL	Not done	1, 9, and 90%
Cephalosporins				
First and second generation	3, 10, and 30 mg/mL	3, 10, and 30 mg/mL	Not done	1, 10, and 90%
Third and fourth generation	3 and 10 mg/mL	3 and 10 mg/mL	Not done	1, 10, and 90%
Azithromycin	Not done	Not done	Not done	1, 9, and 90%
Clindamycin	150 mg/mL	15 mg/mL	p.o., 20 and 100% i.v., 1, 10, 20, and 100%	1, 9, and 90%

i.v. = intravenous; PCN = penicillin; p.o. = by mouth.

mL), followed by ID to saline and clindamycin (15 mg/mL). After the negative SPT and ID, patch tests were placed on the upper back using Finn Chambers to evaluate delayed-type hypersensitivity. Patch tests consisted of clindamycin (15 mg/mL oral suspension [p.o.]) tested at full-strength concentrations (100%) and 20% dilution in saline and white petrolatum. Intravenous (i.v.) preparations (150 mg/mL) were also tested at full-strength concentration (100%) and at dilutions of 20, 10, and 1% in saline and white petrolatum. Patch tests were removed after 48 hours and interpreted by a physician at 72 hours. Patients with a history of AZT ADR did not undergo ST because of lack of protocols in the literature and completed graded dose challenges.

After ST patients underwent incremental oral dose challenges of three divided doses (1, 9, and 90%) given at 20-minute intervals to equal a cumulative therapeutic dose. Patients who completed ST and challenges to PCN in the absence of PrePen returned for a second graded challenge 1 month later to confirm tolerance.¹³ After completing the challenge, patients were observed for 1 hour for signs of immediate reactions such as urticaria, angioedema, rhinitis, bronchospasm, or anaphylactic shock. Patients were also advised to monitor for similar symptoms with delayed onset or reactions occurring after 1 hour.¹⁶ Patients who completed incremental challenges without an ADR were advised that they might safely receive that medication, whereas patients who experienced an immediate or delayed ADR were advised to continue drug avoidance. Patients with positive ST were not challenged and were likewise advised to continue medication avoidance.

Demographic Information and Study Variables

The following data were recorded on each patient: age, race, gender, name of suspected antibiotic, date of ADR, date of challenge, the presence of atopy (defined by positive environmental SPT or a diagnosis of allergic rhinitis, asthma, or atopic dermatitis), the coexistence of an illness requiring frequent use of antibiotics (such as sickle cell disease, cystic fibrosis, or malignancy), previous exposures to the suspected antimicrobial, and day of therapy when ADR occurred. The class of antibiotic was categorized into PCNs, cephalosporins, macrolides, or clindamycin. ADRs were classified by reaction type as morbiliform rash, urticaria, pruritus, and angioedema. The corresponding illness during ADR was categorized as acute otitis media, upper respiratory infections, lower airway inflammation (including pneumonia), and other (including cellulitis and peri-/postoperative prophylaxis). The outcome of the challenge was recorded as negative (passed) and positive (failed).

Statistical Analysis

Study variables were characterized by positive and negative outcomes. Categorical variables were summarized using frequencies and percentages, and quantitative variables were summarized using frequency, mean, and SD. The χ^2 -test or Fisher's exact tests were used for categorical variable characterization, and two-sample *t*-test was used for numerical variable characterization. A simple logistic regression model was used to determine the association of predictors with failed challenges. Considering clinical and statistical significance, predictors for failed challenges were adjusted for gender and time elapsed between reaction and challenge dates using a multiple logistic regression model. All tests were performed using a level significance of 0.05. The statistical package, SPSS (Version 17.0; SPSS, Inc., Chicago, IL) was used to analyze the data. The statistical package R (Version 2.8.1) was used for analyzing the variable type of drug challenge.

RESULTS

Demographics

Ninety-six patients were included in our analysis. Their demographic information is summarized in Table 2. The majority of the patients were white and male subjects (84 and 55%, respectively) with history of atopy (55%). The average ADR was reported at age 4.66 years (SD $\pm$ 4.41) and drug challenge was completed at 6.80 years (SD $\pm$ 4.57). Nearly one-half of the patients reported an ADR to more than one antimicrobial (47.9%) and had a family history of ADRs (55.2%). Seventeen patients (17.7%) had prior history of an illness requiring frequent antibiotic use. Thirty-seven patients (38.5%) reported ADR during the first course of the suspect medication. The ADR most commonly reported was rash (92.7%). Over one-third (39.3%) of these patients who experienced rash also reported pruritus. Of the five patients who did not report rash, none reported pruritus. Nearly one-half of patients ($n = 22$; 44.9%) who reported urticaria also reported pruritus, but in the absence of urticaria only 13 patients (28.9%) reported coinciding pruritus. Although not significant ($p = 0.111$), the odds of the prevalence of pruritus was nearly double in the presence of urticaria (odds ratio [OR] = 2.01; 95% CI = 0.85, 4.72). The majority of patients (97.9%) reported either rash or urticaria and about one-half (48.9%) reported a concurrent urticaria with rash. There was a significantly ($p = 0.04$) increased prevalence of pruritus among patients with a coincidence of rash and urticaria (OR = 2.47; 95% CI = 1.04, 5.83) compared with patients with noncoincidence of rash and urticaria.

Table 2 Study variables characterization

	Negative Outcomes	Positive Outcomes	Total patients (<i>n</i> = 96)	<i>p</i> Value*
Drug reaction age (yr)				0.464
<i>n</i>	85	9	96	
Mean (SD)	4.55 (4.32)	5.69 (5.31)	4.66 (4.41)	
Drug challenge age				0.776
<i>n</i>	87	9	96	
Mean (SD)	6.76 (4.55)	7.21 (4.88)	6.80 (4.56)	
Time that elapsed between reaction and challenge (yr)				0.525
<i>n</i>	85	9	94	
Mean (SD)	2.15 (2.87)	1.52 (1.47)	2.09 (2.77)	
Gender				
<i>n</i> (%)				0.468
Male	47 (88.7)	6 (11.3)	53	
Female	40 (93.0)	3 (7.0)	43	
Race				0.695
White	73 (90.1)	8 (9.9)	81	
Other	14 (93.3)	1 (6.7)	15	
Atopy				0.468
Yes	47 (88.7)	6 (11.3)	53	
No	40 (93.0)	3 (7.0)	43	
History of frequent antibiotic use				0.586
Yes	16 (94.1)	1 (5.9)	17	
No	71 (89.9)	8 (10.1)	79	
History of other antibiotic ADR				0.827
Yes	42 (91.3)	4 (8.7)	46	
No	45 (90.0)	5 (10.0)	50	
Family history of other drug allergies				0.739
Yes	31 (91.3)	3 (8.7)	34	
No	47 (88.7)	6 (11.3)	53	
Reaction during first course				0.878
Yes	33 (89.2)	4 (10.8)	37	
No	46 (90.2)	5 (9.8)	51	
Reaction type				
Morbiliform rash				1.000
Yes	80 (89.9)	9 (10.1)	89	
No	5 (100)	0	5	
Urticaria				0.105
Yes	42 (85.7)	7 (14.3)	49	
No	43 (95.6)	2 (4.4)	45	
Pruritus				.055
Yes	29 (82.8)	6 (17.1)	35	
No	56 (94.9)	3 (5.1)	59	
Swelling/angioedema				0.516
Yes	12 (85.7)	2 (14.3)	14	
No	73 (91.3)	7 (8.8)	80	
Type of drug challenged				0.153
Penicillin	52 (86.7)	8 (13.3)	60 (62.5)	
Cephalosporin	7 (100)	0	7 (7.29)	
Zithromax	24 (100)	0	24 (24)	
Clindamycin	4 (80)	1 (20)	5 (9.37)	

*The *p* value is from either two-sample *t*-test, χ^2 -test, or Fisher's exact test. Extended Fisher's exact test was used for calculating *p* value of the variable type of drug challenged.

ADR = adverse drug reaction.

Table 3 Description of positive outcomes (skin test or challenge)

Name of Medication	ST Result	ADR during Challenge
Patient 1, PCN	Negative	Fussiness, vomiting (delayed)
Patient 2, PCN	Positive SPT and ID test	Not challenged
Patient 3, PCN	Negative	Rash (delayed)
Patient 4, PCN	Positive SPT and ID test	Not challenged
Patient 5, PCN	Positive ID	Not challenged
Patient 6, PCN	Negative (no PrePen)	Generalized urticaria (immediate)
Patient 7, Clindamycin	Positive patch test	Not challenged
Patient 8, PCN	Negative	Rash (delayed)
Patient 9, PCN	Positive SPT and ID test	Not challenged

ADR = adverse drug reaction; ID = intradermal; PCN = penicillin; SPT = skin-prick test; ST = skin test.

Table 4 Simple logistic regression model to determine the association of positive outcome challenges with predictors

	Odds Ratio	p Value	95% Confidence Interval
Female patients	0.59	0.472	0.14, 2.50
Atopy	1.70	0.472	0.40, 7.26
Urticaria	3.58	0.124	0.70, 18.25
Swelling/angioedema	1.74	0.520	0.32, 9.38
Pruritus	3.82	0.069	0.90, 16.57
Time that elapsed between ADR and challenge	0.904	0.525	0.663, 1.23

Outcome of Challenges

Results are shown in Table 3. Eighty-seven of 96 patients (90.6%) passed their challenges. Among the patients who underwent evaluation for PCN ADR, 52 of 60 patients (86.7%) had negative ST and experienced no ADR during or after the challenge. No patient experienced an ADR during AZT or cephalosporin challenges. Four of five patients (80%) underwent clindamycin challenges without any reaction. In total, only 9 of the 96 patients (9.37%) were advised to avoid the offending drug because of a positive outcome defined as either a positive ST ($n = 5$) or ADR during/after challenge ($n = 4$). One patient experienced onset of urticaria and generalized pruritus during a PCN challenge, and three patients experienced delayed reactions, as summarized in Table 3.

Predictors of Outcome

Demographic predictors associated with positive outcomes are summarized in Table 4. Although the differences are not significant due to the small cohort of patients, atopic patients (11.3%) were more likely to have positive ST or challenges than nonatopic (7.0%) individuals (OR = 1.70; 95% CI = 0.40, 7.26). Female (7.0%) patients were less likely to have a failed challenge in comparison with their male (11.3%) counterparts (OR = 0.59; 95% CI = 0.14, 2.5). Likewise, patients who reported urticaria, swelling/angioedema, or

pruritus as their initial ADR were more likely to have a positive challenge outcome compared with those who did not report urticaria (OR = 3.58; 95% CI = 0.70, 18.25), swelling (OR = 1.74; 95% CI = 0.32, 9.38), or pruritus (OR = 3.82; 95% CI = 0.90, 16.57). Time that elapsed between ADR and challenge was not associated with positive challenge outcomes ($p = 0.525$). Likewise, history of ADR to other drugs ($p = 0.827$), age during drug reaction ($p = 0.464$), age during drug challenge ($p = 0.776$), race ($p = 0.695$), and family history of ADRs ($p = 0.739$) were not associated with positive challenge outcomes.

Table 5 presents the association of other predictors and type of reaction with positive challenge outcomes after adjustment for gender and time that elapsed between reaction and challenge. Patients with history of pruritus during ADR had significantly more positive challenge outcomes (adjusted OR (AOR) = 4.41; $p = 0.050$, 95% CI = 1.0, 19.43) in the adjusted model. ADRs reported as urticaria were also associated with positive challenge outcomes (AOR = 3.36; $p = 0.166$, 95% CI = 0.61, 18.67), although not significant. Similar to the findings in the unadjusted model (Table 4), patients with atopy (AOR = 1.64; $p = 0.505$; 95% CI = 0.38, 7.09) and swelling (AOR = 1.52; $p = 0.633$; 95% CI = 0.27, 8.48) were again more likely to have positive challenges in the adjusted model (Table 5), although this association also did not reach significance.

Table 5 Multiple logistic regression model to determine the association of positive outcome challenges with predictors after adjustment*

	Odds Ratio	p Value	95% Confidence Interval
Atopy	1.64	0.505	0.38, 7.09
Urticaria	3.36	0.166	0.61, 18.67
Swelling/angioedema	1.52	0.633	0.27, 8.48
Pruritus	4.41	0.05	1.0, 19.43

*Adjusted for gender and time that elapsed.

DISCUSSION

The findings in this study are consistent with previous reports that <10% of patients with a previous history of ADR have reproducible reactions, reflecting a large disparity between “reported” and reproducible ADR.^{17,18} Our study differs from previous reports because it focuses on a pediatric patient population and examines potential risk factors for immunologic drug reactions in children.

Data from adult cohorts propose that age is a risk for an immunologic reaction to medications, suggesting frequent exposure to antibiotics may lead to higher risk of sensitization.^{9,19} Other reports suggest that children may lose specific IgE antibodies to antibiotics more quickly than adults just as children rapidly lose specific IgE antibodies to hymenoptera.²⁰ The findings reported previously, however, do not vary greatly from those in adults. One explanation for discrepancy may be that patients perceive symptoms of the underlying illness, such as rash, as ADRs. Many children treated with antibiotics for viral infections experience symptoms attributed to the medication while the virus itself is responsible for the rash/exanthems. Certain viruses such as EBV, CMV, and HHV6 are known to lower the threshold for drug-induced T-cell activation, which may lead to generalized cutaneous drug hypersensitivity reactions.²¹ Only a minority of such patients will develop a rash or ADR with reexposure of the antibiotic, suggesting that antibiotic allergy is present in a minority of cases.^{22,23}

This study found that atopy, present in 55% of the cohort, was associated with positive challenge outcomes, consistent with previous work focusing on PCN-allergic patients.^{24,25} Although atopic patients, specifically those with asthma, may have an increased risk of PCN anaphylaxis, more recent large-scale studies suggest that atopy is not a clear predisposing factor of drug hypersensitivity, but may be a bias reflective of the majority of such patients being evaluated in allergy practices.^{26,27} It is unclear if the association of atopy and positive outcome challenges reflects a bias in the patient population evaluated by allergists. Of the antibiotic groups included in our study, macrolides, especially AZT, are among the best tolerated in the pediatric

and adult populations.²⁸ Side effects associated with macrolides are usually dose-related and include diarrhea, abdominal pain, and other gastrointestinal symptoms.²⁹ True macrolide hypersensitivity is exceptional³⁰ and is estimated to occur in <3% of all treatment courses.³¹ Few case reports describing macrolide hypersensitivity exist in the literature, including only a single report of hypersensitivity to AZT.^{30,32} Likewise, this study found no ADRs associated with AZT and support that it is one of the best-tolerated antibiotics.

Limitations

Fewer than 100 patients were included in the study, limiting its power. PCN ST was done without the minor determinants penilloate and penicilloate, thereby limiting the predictive values of the ST reagents used. Furthermore, the average time that elapsed between reaction and challenge completion was 2.09 years (± 2.76 years), suggesting that patients may have lost their specific IgE antibodies against the medications and their sensitivity during this time. In considering factors associated with positive ST or challenge, only nine patients were in this category; so significance was not possible to establish. It is our hope that future studies in children with immunologically mediated antibiotic ADRs will permit predictors of antibiotic allergy to be better defined.

CONCLUSION

Drug hypersensitivity can often present diagnostic challenges for allergists. Although most antibiotic ADRs in children are minor and non-life threatening, they are often met with parental and physician trepidation, leading to multiple physician visits and prescription of less desirable and more costly alternative antibiotics. Oftentimes, a child is diagnosed as being allergic to a medication after an ADR unrelated to allergy.¹⁶ As pediatricians and allergists, it is our responsibility to fully evaluate ADRs and advise families on future management through ST and drug challenges. Through our methods we hope to share our protocols for assessing ADR with other allergists con-

fronted with similar clinical scenarios. We find that “true” allergy to antibiotics makes up a small minority of reported ADRs in children. By defining the mechanisms and risk factors for drug allergy, we hope to improve our approach to antibiotic hypersensitivity.

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