

Parent-Reported Penicillin Allergy Symptoms in the Pediatric Emergency Department

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ABSTRACT

OBJECTIVE: Children often present to the pediatric emergency department (ED) with a reported penicillin allergy. The true incidence of pediatric penicillin allergy is low, and patients may be inappropriately denied first-line antibiotics. We hypothesized that more than 70% of reported penicillin allergies in the pediatric ED are low risk for true allergy.

METHODS: Parents of children presenting to the pediatric ED with parent-reported penicillin allergy completed an allergy questionnaire. The questionnaire included age at allergy diagnosis, symptoms of allergy, and time to allergic reaction from first dose. The allergy symptoms were dichotomized into high and low risk in consultation with a pediatric allergist before questionnaire implementation.

RESULTS: A total of 605 parents were approached; 500 (82.6%) completed the survey. The median (interquartile range) age of the children at diagnosis was 1 year (7 months, 2 years); 75% were diagnosed before their third birthday. Overall, 380

(76%) (95% confidence interval 72.3, 79.7) children had exclusively low-risk symptoms. The most commonly reported symptoms were rash (466, 92.8%) and itching (203, 40.6%). Of the 120 children with one or more high-risk symptom, facial swelling (50, 10%) was the most common. Overall, 354 children (71%) were diagnosed after their first exposure to penicillin. Symptom onset within 24 hours of medication administration occurred in 274 children (54.8%).

CONCLUSIONS: Seventy-six percent of patients with parent-reported penicillin allergy have symptoms unlikely to be consistent with true allergy. Determination of true penicillin allergy in patients with low-risk symptoms may permit the increased use of first-line penicillin antibiotics.

KEYWORDS: pediatric emergency department; penicillin allergy

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WHAT'S NEW

Seventy-six percent of children in the emergency department with a reported penicillin allergy have low-risk symptoms that may not reflect true penicillin allergy. The majority of these allergies were diagnosed before the child was 3 years old while receiving antibiotics for an ear infection.

CHILDREN OFTEN PRESENT to the pediatric emergency department (ED) with a parent-reported allergy to various medications. Penicillin allergy is the most commonly reported medication allergy, reported in 5% to 20% of patients.^{1–6} Because physicians rely on these patient- or parent-reported allergies when making treatment decisions, many people are denied first-line antibiotic therapy resulting from misunderstood or misdiagnosed penicillin allergy.⁷ As a consequence, these patients are prescribed second- or third-line medications that are more expensive and not the antibiotic of choice for their bacterial infection. Specific to penicillin allergy, more than 95% of patients may actually tolerate a penicillin, either because they

were never allergic or because they had an earlier allergy that subsequently resolved.⁸

Drug-related hypersensitivity reactions are an important health problem, but epidemiologic data on drug allergy are scarce. A study of 10,059 6th to 8th grade children found parent-reported allergy in 792 children (7.9%).⁹ However, parent surveys revealed a clinical history suggestive of drug allergy in only 117 children (1.2%) and a true frequency of immediate-type drug hypersensitivity in 0.11%. Other studies also support the notion that a large number of adverse drug reactions are not consistent with an allergic reaction.^{10–12} Examples of adverse drug reactions classified as allergies include rash, an episode of emesis with medication administration, or the development of antibiotic-associated diarrhea. Several studies have shown that rash associated with amoxicillin is rarely reproducible with allergy testing and that it is a common adverse reaction that results in no patient harm with continuation of the medication.^{13,14}

The ascertainment of medication allergy information is commonly performed during triage in the ED setting. Provider reliance on parental report of allergy greatly affects

the care of their children.⁹ In addition, there is typically no standardized question format used when ascertaining a true medication allergy, resulting in varying responses from patients and their caregivers. A study of adult surgical patients found that approximately 50% of reactions labeled by surgical interns as allergic were deemed not allergic when assisted by a structured allergy questionnaire.¹⁵ That study and others support the need for a structured questionnaire to help differentiate true allergic reactions from adverse reactions.¹⁶⁻¹⁸

This study utilized a self-reported penicillin allergy questionnaire to identify and classify patients with reported penicillin allergy into high- and low-risk groups. We know of no previous study that has assessed the percentage of children presenting to a pediatric ED with parent-reported allergies who have exclusively low-risk symptoms. We hypothesized that more than 70% of penicillin allergy as reported by families in a pediatric ED are low risk for a true penicillin allergy.

METHODS

STUDY DESIGN

We conducted a cross-sectional study of children birth to 18 years old inclusive with a history of parent- or guardian (hereafter termed parent)-reported allergy to penicillin who presented to an urban pediatric ED between April 1, 2015, and March 31, 2016. Children were excluded if the family did not speak English or if the child was a ward of the state, currently in foster care, or in police or detention custody. The study was approved by the hospital's institutional review board.

Trained research staff, available in the ED from 8 AM to 11 PM on weekdays and 11:30 AM to 10 PM on weekends, identified a convenience sample of eligible children by chart review for penicillin allergy and approached parents for consent, and children for assent when applicable, in the ED. Consented parents completed an allergy questionnaire administered via an electronic tablet, and the results were uploaded to a secure online database. If two parents were present in the ED, only one parent completed the survey; thus, one survey was completed per child. Research staff abstracted age, recorded in years, and sex from the medical record (Table 1).

Table 1. Characteristics of Child Questionnaire Participants

Characteristic	Overall	High Risk	Low Risk	P*
Age, y, median (IQR)				
Survey completion	6 (3, 11)	7 (3,11)	6 (3,11)	.378
Allergy diagnosis	1 (7 mo, 2yr)	1 (8 mo, 2yr)	1 (7 mo, 2yr)	.205
Race, n (%)				<.05
White	260 (52.0)	49 (40.8)	211 (55.5)	
African American	109 (21.8)	40 (33.3)	69 (18.2)	
Hispanic	67 (13.4)	17 (14.2)	50 (13.2)	
Asian	7 (1.4)	3 (2.5)	4 (1.1)	
American Indian	3 (0.6)	1 (0.8)	2 (0.5)	
Other	54 (10.8)	10 (8.3)	44 (11.6)	
Female, n (%)	222 (44.4)	58 (48.3)	165 (43.4)	.345

*Comparison between high- and low-risk groups.

PENICILLIN ALLERGY QUESTIONNAIRE

The allergy questionnaire included 17 items assessing allergy history and parent report of their child's race (using National Institutes of Health classifications). Allergy-related questions included: age of child when allergy was diagnosed (reported in years, or months if under 1 year old), name of the antibiotic the child was taking when the allergy was diagnosed (eg, penicillin, amoxicillin, amoxicillin/clavulanate [Augmentin, GlaxoSmithKline, Research Triangle Park, NC]), indication of antibiotic prescription for the child (eg, ear infection, throat infection, chest infection), symptoms of allergic reaction, time to allergic reaction from first dose, and whether a parent, physician, or both diagnosed the allergy. There was no limit to the number of allergy symptoms a parent could report. An initial list provided 17 allergy symptoms and parents were allowed to select "other" and add additional symptoms if needed.

Questionnaire symptom responses were dichotomized into high or low risk in consultation with a pediatric allergist before questionnaire implementation (Table 2). This designation was based on the reported organ system involved and the potential for severe immunoglobulin E (IgE)-mediated or a T-cell-driven reaction. The term "high risk" was used to refer to reported reactions, either IgE-mediated or T-cell driven, that bore high clinical risk for readministration of penicillin by any route. The term "low risk" referred to reactions that were not likely to represent a severe IgE-mediated or T-cell-driven process.

For potentially IgE-mediated symptoms, respiratory or cardiovascular involvement was deemed to be high risk (ie, wheezing, difficulty breathing, airway swelling,

Table 2. Symptoms at Time of Allergy Diagnosis, as Reported by Parents

Symptom	n (%)*
Low-risk symptoms	
Nonhive rash	304 (65.2)
Itching	203 (40.6)
Hive rash	135 (29.0)
Diarrhea	57 (11.4)
Vomiting	33 (6.6)
Runny nose	26 (5.2)
Nonspecified rash	25 (5.0)
Nausea	25 (5.0)
Cough	19 (3.8)
No symptoms but family history of penicillin allergy	11 (2.2)
Headache	11 (2.2)
Dizziness	8 (1.6)
High-risk symptoms	
Facial swelling	50 (10.0)
Difficulty breathing	37 (7.4)
Lip swelling	29 (5.8)
Wheezing	27 (5.4)
Throat swelling	24 (4.8)
Skin peeling	15 (3.0)
Mouth blisters	7 (1.4)
Drop in blood pressure	1 (0.2)

*More than 1 symptom could be selected, so the items are not mutually exclusive.

syncope, and drop in blood pressure). Cutaneous involvement with a severe reaction was also deemed to be high risk (ie, orofacial or limb angioedema). Any report of anaphylaxis was also classified as high risk. Urticarial reactions, while potentially IgE mediated, were classified as low risk in the absence of other high-risk symptoms. When rash was reported, parents selected from an unlabeled picture chart of hives, maculopapular rash, or other to specify the rash most similar to what their child had. While all rashes were considered low risk, we wanted to understand the distribution of rash types.

For potentially T-cell-mediated symptoms, any report consistent with a bullous cutaneous reaction was classified as high risk; this is in consideration of Stevens-Johnson syndrome and toxic epidermal necrolysis, a severe reaction that would contraindicate all future administration of that class of drug. Any report of diffuse erythema could represent drug reaction with eosinophilia and systemic symptoms; this was also classified as high risk. Symptoms consistent with possible fixed drug eruptions, which are typically benign, were classified as low risk.

Reported symptoms that may have led to the diagnosis of penicillin allergy but may have been the result of an adverse effect or concomitant viral or bacterial illness, such as rhinorrhea, cough, nausea, emesis, or diarrhea, were classified as low risk. Allergy symptoms reported as “other” were individually reviewed and classified as high or low risk by the study’s principal investigator. An additional choice of “cannot remember” was also listed in the questionnaire. Parents were neither aware of the symptom risk classification nor the names of the rashes shown in the pictures. A subset of children’s pediatricians was selected at random and called to check agreement between the child’s medical record and parental questionnaire response regarding who reported the child’s allergy.

The primary outcome was the percentage of children with exclusively low-risk allergy symptoms to penicillin. Other outcomes included age at allergy diagnosis, reason for antibiotic prescription, name of penicillin antibiotic for which an allergy was reported, onset of allergy symptoms in relation to taking the medication, and who diagnosed their child’s allergy.

DATA MANAGEMENT

Data were collected and managed using REDCap (Research Electronic Data Capture), hosted at the Medical College of Wisconsin.¹⁹

DATA ANALYSIS

Sample size calculations resulted in an estimated need for 500 completed surveys. Five hundred patients would ensure that we had enough subjects with different reasons for believing they had an allergy to ensure a full investigation of allergy symptoms. Five hundred patients allowed for a confidence interval less than 0.1 in width irrespective of the proportion values. The power calculation was made using PASS 11 (NCSS 11 statistical software; NCSS, Kaysville, Utah).

Descriptive statistics were used to summarize baseline patient characteristics and allergy questionnaire data. The frequency of high- and low-risk allergy symptoms was analyzed and reported using a 95% confidence interval. The Mann-Whitney test was used to compare the median age of allergy diagnosis between high- and low-risk groups. Chi-square tests were used to compare group differences by risk level for race, sex, whether or not this was the child’s first exposure to the antibiotic, and symptom onset. SPSS 22 was used to perform all analyses (IBM SPSS, Chicago, Ill).

RESULTS

During the study period, 66,419 children visited the pediatric ED. A total of 605 parents reported penicillin allergy and were approached for participation; 500 (82.6%) were enrolled and completed the allergy questionnaire (Fig). Of those enrolled, 260 (52.0%) were white, 109 (21.8%) African American, and 67 (13.4%) Hispanic (Table 1). The median (interquartile range [IQR]) child age at time of survey administration was 6 years (3, 11). The median (IQR) age at allergy diagnosis was 1 year (7 months, 2 years).

Overall, 380 parents (76.0%) (95% confidence interval [CI] 72.3, 79.7) reported exclusively low-risk allergy symptoms. The remaining 120 parents (24.0%) (95% CI 20.3, 27.7) reported 1 or more high-risk allergy symptoms. Among all children, the most common reported low-risk symptoms were rash (464, 92.8%) and itching (203, 40.6%) (Table 2). The most frequently reported high-risk symptoms were facial swelling (50, 10.0%) and difficulty breathing (37, 7.4%). Analysis of age at allergy diagnosis showed that of all children, 75% were diagnosed as penicillin allergic before their third birthday, and 344 (68.8%) were given this medicine for an ear infection (Table 3).

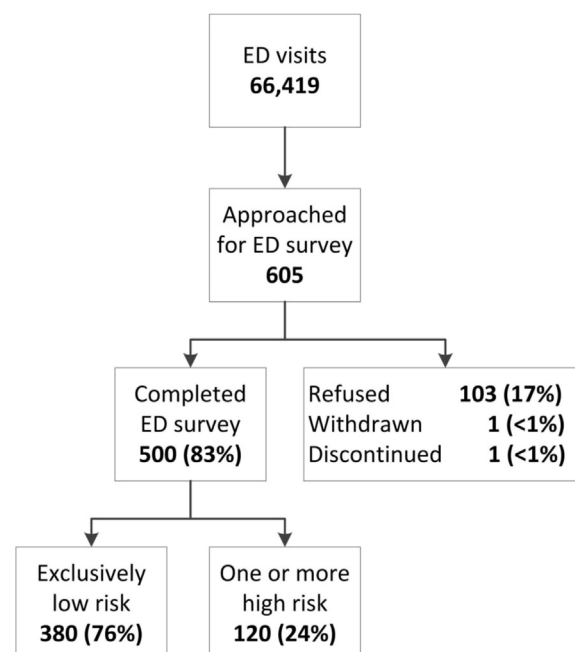


Figure. Symptom designation as high or low risk.

Table 3. Indication for Antibiotics Reported by Parents

Indication	n (%) [*]
Ear infection	344 (68.8)
Throat infection	49 (9.8)
Cannot remember	46 (9.2)
Chest infection	32 (6.4)
Other infection	23 (4.6)
Skin infection	11 (2.2)
Urine infection	4 (0.8)

^{*}More than 1 indication could be selected, so the items are not mutually exclusive.

Amoxicillin and amoxicillin/clavulanate were the most commonly reported antibiotic allergies (402, 80.4%), followed by the generic name, penicillin (95, 19%). Families identified their primary care physician as the person who diagnosed the allergy in 435 children (87.0%). A sample of 178 primary care physicians was called for allergy verification, and 145 (81.4%) reported that parents diagnosed the allergic reaction in their child.

The age at allergy diagnosis did not differ when analyzed by risk group (Table 1). The percentage of parents who reported that the allergy diagnosis occurred after their child's first exposure to penicillin was similarly high in both risk groups (high risk, 70.0%; low risk, 72.0%; $P = .779$) (Table 4). Symptoms were reported to have occurred within 24 hours of the first dose of penicillin in 201 children (53.0%) with low-risk symptoms and 73 children (60.8%) with high-risk symptoms ($P < .05$).

DISCUSSION

Our results demonstrate that 76% of children presenting to the pediatric ED with parent-reported penicillin allergy exhibited exclusively low-risk symptoms. The most common low-risk symptoms were rash and itching. The most common high-risk symptoms were facial swelling and difficulty breathing. Symptoms occurred before 24 hours more frequently in children with high-risk symptoms compared to low-risk symptoms. This may reflect the quicker onset of true IgE-mediated reactions. These penicillin "allergies" are being diagnosed at a young age, with half diagnosed by the first birthday and three-quarters before the third birthday. Approximately 70% of these reported allergy diagnoses resulted from use of an antibiotic for an ear infection.

Table 4. Allergy Symptom Onset and Previous Penicillin Use

Characteristic	High Risk, n (%)	Low Risk, n (%)	<i>P</i>
First-time penicillin use			.779
Yes	84 (70.0)	270 (71.1)	
No	30 (25.0)	83 (21.8)	
Cannot remember	6 (5.0)	22 (5.8)	
Missing	...	5 (1.3)	
Symptom onset			<.05
Less than 24 h	73 (60.8)	201 (52.9)	
More than 24 h	40 (33.3)	140 (36.8)	
Cannot remember	5 (4.2)	30 (7.9)	
Missing	2 (1.7)	9 (2.4)	

By definition, drug allergies are immunologically mediated hypersensitivity reactions that usually occur after sensitization from previous exposure to the allergen.²⁰ The true incidence of anaphylactic (life-threatening) reactions to penicillin is in the range of 0.004% to 0.015%.^{21–23} With the incidence of true allergic reactions being low, it is likely that parent-reported penicillin allergy may be a misdiagnosed adverse reaction or a consequence of a viral infection that should not prevent a patient from receiving the medication.^{10–12}

Our study found that approximately 94% of patients reported a rash as a symptom of allergy to penicillin. Two-thirds of those rashes were identified as maculopapular. One of the explanations for the presence of a maculopapular rash in the context of penicillin treatment may be that it is an adverse reaction to the medication that is not consistent with true allergy. An additional explanation for the presence of a maculopapular rash may have been that it was caused by a viral infection. Bass et al¹³ demonstrated an occurrence of maculopapular rash in 3% to 7% of children provided amoxicillin. All patients who developed this maculopapular rash were able to complete their course of antibiotics with no other adverse effects. Those findings support the notion that penicillin allergy is overdiagnosed and that a maculopapular rash may be indicative of an adverse reaction and not an allergic reaction.

In our study, after review of the literature and consultation with a pediatric allergist, hives were categorized as a low-risk symptom when no high-risk symptoms were concomitantly reported. While the presence of hives may be the result of an IgE-mediated reaction, it is more frequently due to other causes. Our study showed that over 70% of patients in both the high- and low-risk groups were taking penicillin for the first time, which would decrease the chances that they were having an IgE-mediated response to penicillin. A likely explanation for the hives witnessed during administration of penicillin is that it may have been a rash associated with a viral illness as opposed to true allergic response. Hives being caused by a viral illness is supported by a study by Caubet et al,¹⁴ who found that 67% of children who presented to a pediatric ED with a rash had a viral infection at the time of allergy diagnosis, and that upon oral challenge with penicillin, a rash was only reproducible 6.8% (6/88) of the time.

Our study showed that 75% of children were diagnosed with penicillin allergy before their third birthday and that 68.8% of children were given the antibiotic for an ear infection. Otitis media typically occurs as a complication of a resolving viral upper respiratory infection.²⁴ The reliability of the diagnosis of penicillin allergy was found to be in question for the majority of the participants in this study. Notably, 87% of parents reported a physician-diagnosed allergy. However, when a sample of primary care offices was called to confirm how the allergy was diagnosed, 81% reported never witnessing any symptoms of allergic reaction. This finding indicates symptoms of penicillin allergy were often low risk by parental report, as confirmed over the phone by a physician's office. However, most symptoms

were not verified in person by a physician, leading to uncertainty in the diagnosis of true allergic reaction.

This study is limited because it was conducted at a single center. In addition, patients were chosen as a convenience sample; however, there was no way before enrollment for the research staff to know which allergy symptoms would be reported by the parent, making bias in enrollment less likely. Additionally, the study depended on parental recall, which in some instances required parents to recall events from several years before, potentially leading to misidentification of initial symptoms of allergic reaction or the name of antibiotic to which their child was allergic. We are confident, however, that even if the family incorrectly remembered the name of the specific antibiotic, the reported reaction occurred in relation to a medication in the penicillin family.

CONCLUSIONS

Our results suggest that the symptoms of parent-reported penicillin allergy in the pediatric ED frequently do not reflect those that would be expected from a true penicillin allergy. At this time, the questionnaire should not change pediatric ED management of reported penicillin allergy. However, this study does provide evidence that penicillin allergy in the pediatric ED should be investigated further. Future steps would involve testing children with low-risk allergy symptoms for true penicillin allergy and comparing these results to our questionnaire results.

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