
Elective penicillin skin testing in a pediatric outpatient setting

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Background: Adverse reactions associated with penicillin-type antibiotics are common in pediatric practice, leading to the subsequent unnecessary use of alternative antibiotics. IgE-mediated penicillin allergy represents only a fraction of these adverse reactions.

Objectives: To examine (1) the trend of penicillin skin test reactivity during a recent 10-year interval, (2) the relative distribution of specific reagents related to a positive skin test result, and (3) skin test reactivity as a function of reaction history.

Methods: Penicillin testing using 3 reagents—benzylpenicilloyl polylysine, penicillin G, and sodium penicilloate (penicillin A)—was conducted in a prospective study of 359 consecutive patients referred to an outpatient pediatric allergy clinic between January 1, 1993, and May 31, 2003. We also retrospectively reviewed penicillin skin test results for 562 children previously tested between January 1, 1979, and December 31, 1992.

Results: Between 1993 and 2003, the prevalence of penicillin skin test sensitivity markedly declined. Of all the positive skin test results between 1979 and 2002, either penicillin G or sodium penicilloate or both identified 34%, with sodium penicilloate alone responsible for 8.5%. The rate of positive skin test reactions was not significantly different between patients with vs without a history of suggestive IgE-mediated reactions.

Conclusions: A marked decline in penicillin skin test sensitivity in the pediatric age group is identified. The minor determinant reagents penicillin G and sodium penicilloate are both necessary for determining potential penicillin allergy. Relating history alone to potential penicillin sensitivity is unreliable in predicting the presence or absence of a positive skin test result.

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INTRODUCTION

Adverse reactions occurring during penicillin therapy are common. An estimated 8% to 10% of patients visiting subspecialty clinics, urgent care centers, and hospitals believe themselves to be allergic to penicillin.^{1–3} Most of these adverse reactions are exanthematous, and the event may lead to a lifetime diagnosis of penicillin allergy, forcing the choice of alternative antimicrobial drug therapy for infectious illness. Yet, in most reported series, only 7% to 21% of patients reporting a history of penicillin allergy are found to have a positive skin test result confirming an IgE-mediated allergy.^{2,4–13} This discrepancy between history and skin test results is an important issue for patients in need of penicillin-type antibiotic treatment and for the treating physician, causing uncertainty in the decision-making process.

Skin testing for penicillin allergy has been available at St Louis Children's Hospital (SLCH) Allergy Clinic for more than 30 years. In 1993 we began a medical record review of all previously referred patients and set up a database to be used for all future referrals. This database was intended to serve as a prospective evaluation of pediatric patients referred as being allergic to penicillin antibiotics. On reviewing our

experience after several years, we found a marked change in the prevalence of skin test reactivity. In addition, sufficient data were available to review the utility of specific minor determinant reagents (MDRs) in identifying patients with positive skin test results.

METHODS

Study Population

We present data from 2 consecutive study populations referred to the SLCH Allergy Clinic for elective penicillin skin testing. Patient data were collected prospectively between January 1, 1993, and May 31, 2003, and retrospectively from clinic records between January 1, 1979, and December 31, 1992.

Skin Testing

Three separate penicillin reagents were used throughout both study periods. The major determinant of penicillin, benzylpenicilloyl polylysine, was purchased as PrePen from Kramers-Urbach Co (Milwaukee, WI) before 2001 and thereafter from Hollister-Stier Laboratories LLC (Spokane, WA). Two MDRs were used separately: penicillin G and sodium penicilloate (penicillin A). Penicillin G was purchased from Sigma-Aldrich Corp, St Louis, MO (1,653 U/mg). Sodium penicilloate was prepared by means of alkaline hydrolysis of penicillin G.^{14,15} Penicillin G and sodium penicilloate were stored in dried form and were reconstituted at a concentration of 3.3 mg/mL in phosphate-buffered saline (concentrate). Solutions of penicillin G and sodium penicilloate were dis-

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carded after 24 hours. These reagents have been prepared and used at Washington University School of Medicine since 1969.

All the patients were asked to refrain from using antihistamines for at least 1 week and antibiotics for 8 weeks before skin testing. Histamine (1 mg/mL) and saline served as positive and negative controls, respectively. Reagents were applied sequentially at 15-minute intervals. Skin prick testing (SPT) with concentrate was performed initially. A wheal measuring 3 mm or greater than the negative saline control was interpreted as a positive SPT reaction. If the SPT gave a negative reaction, intradermal testing (IDT) followed using a volume of 0.02 mL and producing a 3-mm bleb.¹⁶ Dilutions of concentrate at 1:10,000 and 1:100 were applied sequentially for IDTs before the concentrate if the history suggested a severe IgE-mediated process. The IDTs were applied in duplicate, and if either test site was reactive the test result was judged to be positive. The IDTs were interpreted by comparing the wheal diameter after 15 minutes with the initial injection site. A wheal, which during the following 15-minute observation period increased in diameter by at least 2 mm, was interpreted as a positive IDT reaction.¹⁷

One experienced technician performed all the tests between January 1, 1979, and October 31, 2001. Another experienced technician performed all the tests between November 1, 2001, and December 31, 2003. All the tests from 1993 forward were examined and interpreted, as described, by the same physician (G.R.B.).

Database

All the patients in the prospective cohort were interviewed by the same physician (G.R.B.) using standardized inquiry. The histories were entered into a relational database (Microsoft Access; Microsoft Corp, Redmond, WA). Age at initial reaction as recalled by a parent and age at the time of testing were recorded. Antibiotic histories were divided into groups based on whether the child had a reaction to (1) a penicillin or aminopenicillin only and no other antibiotics, (2) cefaclor specifically, or (3) a penicillin antibiotic initially and then subsequent antibiotics as well. Some parents could not recall the name of the antibiotic that their child had received but knew only that "a penicillin" was prescribed. Records were not regularly available for confirmation because many patients experienced the reaction several years previously, had changed physicians, or had changed geographic locale. Children with a history where the parents could not recall the antibiotic related to the reaction are included in the analysis only for their skin test result.

Reaction histories were recorded in the parents' own words and were entered as (1) rash without a history of hives; (2) hives; (3) joint pain or joint swelling; (4) wheeze or any respiratory distress; (5) angioedema; (6) gastrointestinal symptoms, such as vomiting, abdominal pain, and diarrhea; and (7) shock. Reactions described as consistent with hives, angioedema, wheezing, or anaphylaxis were characterized as being consistent with an IgE/mast cell-related mechanism.

Parental recollection of pruritus or no pruritus was not used in distinguishing urticarial from nonurticarial reactions because many parents found it difficult to remember this particular symptom, particularly if there had been a substantially long interval between the event and the clinic visit or if the child was in infancy when the reaction occurred. Parents also described pruritus in children with diffuse morbilliform rash in the absence of urticaria.

Skin test results were entered for each reagent tested (positive or negative), as were the concentration of the test reagent and, for positive test results, the type of skin test (SPT or IDT). Medical records of patients tested before 1993 were also reviewed, and available data were entered into the database as part of the retrospective analysis. This study was approved by the Human Studies Committee of Washington University School of Medicine.

Statistical Analyses

The χ^2 test was used to test for statistically significant differences in reaction history between groups (eg, skin test result negative vs skin test result positive). Analyses were performed using SPSS for Windows version 13.0 (SPSS Inc, Chicago, IL). For cases in which the expected value in a cell was less than 5, a Fisher exact test was used. For all reported statistics, $P \leq .05$ was considered statistically significant.

RESULTS

Demographics and Reaction History

The 359 patients who were personally interviewed and underwent skin testing between January 1, 1993, and May 31, 2003, are described in Table 1. A specifically identified antibiotic was reported by 316 patients. Penicillin, ampicillin, amoxicillin, and amoxicillin-clavulanic acid (group 1) were solely implicated in 34% of the cases. Cefaclor alone (group

Table 1. Demographic Characteristics and Antibiotic Histories of the 359 Study Patients, 1993–2003

Characteristics	Patients, No. (%)
Age, y	
<1	4 (1)
1–4	101 (28)
5–9	167 (47)
10–15	76 (21)
16–18	11 (3)
Sex	
M	179 (50)
F	180 (50)
Antibiotic group*	
Group 1	123 (34)
Group 2	10 (3)
Group 3	183 (51)
Antibiotic not identified	43 (12)

* Group 1 received penicillin, ampicillin, amoxicillin, and amoxicillin-clavulanic acid; group 2, cefaclor only; and group 3, a reaction to any of the group 1 agents and a reaction to a subsequently administered cephalosporin other than cefaclor.

2) accounted for 3% of referred patients. A reaction to more than 1 antibiotic (including a penicillin drug from group 1) was reported by 51% of the patients (group 3). Forty-three patients (12%) could not give specific information other than that their child had received a "penicillin"-type drug.

A full reaction history was available for 330 patients, of which 326 had cutaneous reactions that were partitioned as rash only or urticaria, each with associated other reactions (Table 2). Four patients without rash or urticaria reported other reactions (see the footnote in Table 2). Twenty-nine patients could not recall the reaction in enough detail to enter a reliable history. Thirty-eight percent of the patients reported more than 1 type of reaction or organ system involvement (eg, hives and gastrointestinal symptoms). Two thirds of the patients reported a history that was consistent with IgE-mediated symptoms (ie, hives, wheezing, and/or angioedema).

Skin Test Results: Reactivity vs Reaction Trend

Twenty-three (6%) of the 359 prospectively evaluated children had a positive skin test reaction. Twenty-two reactions occurred in the first year of the study (1993) and 1 occurred in 2002 (Fig 1). We then reviewed penicillin skin tests in the 562 children referred to the SLCH Allergy Clinic between January 1, 1979, and December 31, 1992. During this period, 154 children (27%) had positive test results (Fig 1). A downward trend beginning early in the 1980s is apparent, with 2 alternate years of increase (1991 and 1993) just before all skin test results were negative in 1994.

Table 2. Reaction Histories of 359 Children Referred for a Penicillin Antibiotic Reaction

History	Patients, No.
Rash (no urticaria)	117
Rash only	86
Rash and associated symptoms	31
Angioedema*	13
Wheeze*	3
Joint symptoms	4
Gastrointestinal symptoms	11
Urticaria*	209
Urticaria only	117
Urticaria and associated symptoms	92
Angioedema	46
Wheeze	12
Joint symptoms	12
Gastrointestinal symptoms	22
Nonrash, nonurticarial reaction†	4
Nondefinitive reaction history	29

* A total of 227 patients or 68% of the known reaction history group (ie, IgE related) had hives, angioedema, or wheeze.

† These 4 patients had negative skin test results and did not report urticaria or maculopapular rash (1 had purpura, bruises, and blood in stool and urine; 1 had redness only of the face, neck, and chest; 1 had intraoperative anaphylaxis; and 1 had asthma and angioedema).

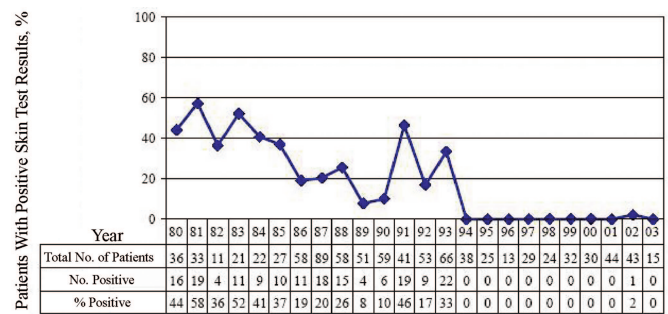


Figure 1. The rate of positive skin test reactions for all patients who underwent skin testing for penicillin allergy between 1980 to 2003.

Skin Test Results: Reactivity vs Reagent

In the entire group of 921 patients, the MDRs penicillin G and sodium penicilloate identified 177 patients with penicillin reactivity (Fig 2). Of these 177 positive skin test reactions, 116 or 66% were identified with benzylpenicilloyl polylysine reagent. Overall, 40% were positive with benzylpenicilloyl polylysine and the MDR, 26% were benzylpenicilloyl polylysine positive alone, and 34% were MDR positive alone. From this group of positive-reacting skin tests, 8.5% were identified only by sodium penicilloate.

Skin Test Results: Reactivity vs Reaction History

Thirteen (56%) of the 23 penicillin skin test-reactive patients in the prospective data were among the group who could not recall a definitive, reliable history of the antibiotic reaction. Definitive reaction histories were known for 10 of 23 patients with positive test results in the prospective analysis. Of these 10 patients, 9 reported urticaria, angioedema, or wheeze and

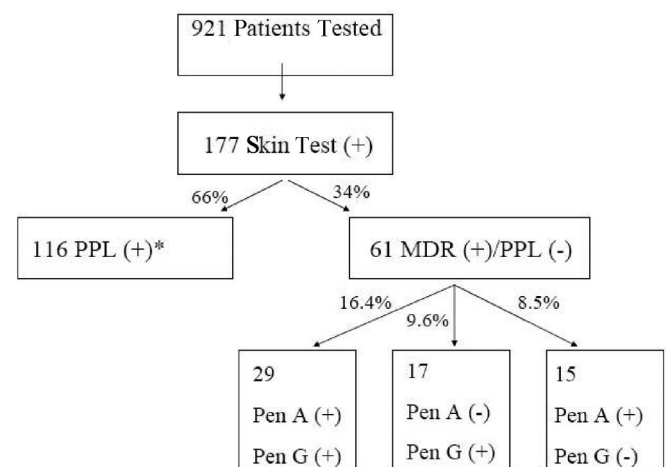


Figure 2. Penicillin skin test results according to reagent for 921 patients tested between 1980 and 2003. PPL indicates benzylpenicilloyl polylysine; Pen G, penicillin G; Pen A, sodium penicilloate; MDR, minor determinant reagents; (+), positive reaction; (-), negative reaction. *Forty-six patients had PPL (+)/MDR (-) results and 70 had PPL (+)/MDR (+) results.

1 reported rash only. Four of the 9 patients with urticaria or angioedema also experienced gastrointestinal symptoms.

An IgE-mediated reaction was considered likely if the patient had any 1 report of urticaria, angioedema, wheeze, and/or anaphylaxis (Table 2). A non-IgE-mediated reaction was considered with a history of nonurticarial rash with or without the presence of gastrointestinal symptoms or joint swelling. When histories were grouped to reflect the likelihood of an IgE-mediated reaction, 9 of the 227 patients with suggestive IgE-mediated symptoms reacted to penicillin skin tests, whereas only 1 of the 103 with a nonsuggestive IgE-mediated reaction had a positive reaction to penicillin reagents (Table 3). There was no significant difference between these 2 groups (Fisher exact test, $P = .14$).

Skin Test Reactivity and Interval Since Initial Reaction

The interval between the index reaction and skin testing was unrelated to the probability of a positive skin test result (Fig 3). In the prospective group of children, those who were tested within 1 year of their index reaction had a positive skin test reaction 7% of the time compared with 8% of children tested more than 8 years later ($\chi^2_1 = 0.05$; $P > .75$).

DISCUSSION

Three outstanding findings from this prospective study and retrospective review are apparent. First, there has been a marked decline in the prevalence of penicillin sensitization. Second, testing with a second MDR identified 8.5% of sensitized patients who would not be recognized by using the major determinant (benzylpenicilloyl polylysine) and penicillin G alone. Third, history alone is not a reliable predictor of penicillin test results.

The most remarkable finding is the steady decline in skin test sensitivity. Positive reactivity to penicillin skin testing in this clinic population has steadily declined for 2 decades and, after 1993, penicillin sensitivity all but disappeared except for 1 patient in 2002. Plausible considerations for this occurrence involve the possibility of unrecognized changes in the internal protocol and the presence of evolving changes in pediatric antibiotic prescribing practices.

Since the period before 1979 and as reported by Sullivan et al in 1981,¹⁸ the same reagents have been in use through the

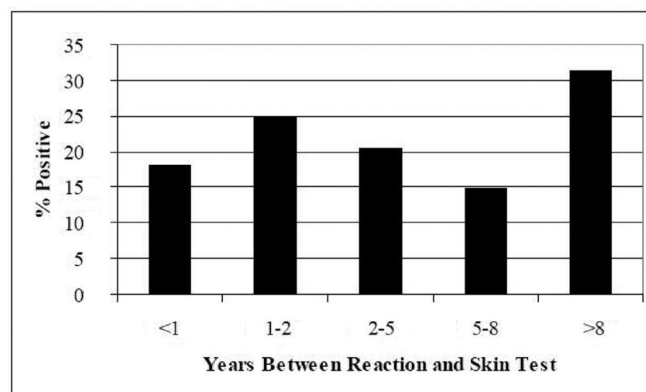


Figure 3. The percentage of the 23 patients with positive skin test results in the prospective patient cohort (1993–2003) related to the interval between the reported year of the initial penicillin reaction and the year of penicillin skin testing.

present. The MDRs have been prepared by one of us (H.J.W.) or by Dr Sullivan during this entire period. These reagents also are used for penicillin skin testing by the Department of Internal Medicine, and between January 1, 1999, and December 31, 2003, 23 of 164 adult inpatients tested for penicillin sensitivity had a positive test result. In addition, the same skin test method was used by a single technician at SLCH before and after 1993, the year that the reaction rate changed so markedly in this series, and there was 1 more positive reactor at SLCH in 2002. One physician supervised, examined, and interpreted penicillin skin tests throughout the study period and several years previously. Therefore, it seems unlikely that a change in reagents or testing procedure accounts for the persistent absence of positive penicillin skin test results after 1993.

Children may also be receiving less sensitizing forms of penicillin. There is evidence of declining use of injectable penicillin G as supported by the steady decrease in prescription volume of Bicillin preparations (Prescription Sales Audit, 2003, IMS Health and NDC Health, Fairfield, CT). In this prospective series, few parents reported that their child had received “a shot of penicillin.” Intramuscular penicillin given as a repository injection may be more sensitizing and may result in longer-lasting sensitization than penicillin given orally.^{19,20}

The increasing use of oral antibiotics, particularly amoxicillin and amoxicillin–clavulanic acid, is also considered. The association of rash with aminopenicillins has repeatedly been reported and estimated to have a 3% to 9% incidence in children.^{21–23} This rash, usually described as maculopapular, can sometimes be difficult to discern from an urticarial appearance. During this series, amoxicillin and cephalosporins have increasingly been the antibiotics most commonly prescribed.^{24,25} The US National Ambulatory Medical Care Survey demonstrated a steady increase in amoxicillin prescribing rates (53 prescriptions per 1,000 population increasing to 172

Table 3. Skin Test Reactivity by Presumed IgE-Mediated Symptoms vs Presumed Non-IgE-Mediated Symptoms*

	Skin test result positive	Skin test result negative	Total
IgE mediated†	9 (4)	218 (96)	227 (100)
Non-IgE mediated‡	1 (1)	102 (99)	103 (100)
Total	10 (3)	320 (97)	330 (100)

* Data are given as number (percentage). Fisher exact test $P = .18$.

† Defined as any 1 report of urticaria, angioedema, or wheeze.

‡ Defined as nonurticarial and any 1 of the following: gastrointestinal, joint, or other symptoms considered non-IgE mediated.

per 1,000 population) coincident with a continuing decline in penicillin use (81 per 1,000 population to 25 per 1,000 population) between 1980 and 1992.²⁵ A follow-up survey reported a 69% increase in the use of amoxicillin-clavulanic acid between January 1, 1992, and December 31, 2000.²⁶ Together, these 2 factors—the decrease in the use of a sensitizing penicillin preparation and the increased use of aminopenicillins—has generated a population of pediatric patients with rash reactions that are not related to IgE directed to the β -lactam core yet that raise concerns about anticipated serious adverse reactions should there be a need for further administration.

All the patients throughout both series were tested with 3 reagents: benzylpenicilloyl polylysine, penicillin G, and sodium penicilloate. Of the 177 children with penicillin sensitivity, 34% reacted to 1 or both of the MDRs (penicillin G and sodium penicilloate); 8.5% reacted only to sodium penicilloate. In the review by Shepherd²⁷ and in studies of children by Mendelson et al⁹ and Chandra et al,¹⁰ MDRs other than penicillin G are needed to detect all positive penicillin reactors. The increase in the rate of positive skin test results that an additional MDR to penicillin G contributes suggests the need to consider its use necessary. However, what is not known is the positive predictive value for patients with sensitivity only to sodium penicilloate. Because penicillin G is the only MDR generally available for penicillin skin testing, the issue of necessity for MDR testing with reagents other than penicillin remains unresolved.

In this prospective study, 330 patients with complete reaction histories were available for analysis. In this group there were 23 patients with reactive tests confirming penicillin IgE-mediated sensitivity. Among patients reporting a definitive reaction history there was no statistically significant difference in the skin test result between those with a suggestive IgE-mediated reaction and those without the characteristic IgE-mediated signs and symptoms. These numbers are small but caution that a history of rash without urticaria may still represent IgE-mediated allergy.

Of particular concern is the group referred for penicillin allergy but with no recall of specific history. Positive skin test results in this group are not an unusual event as reported by other researchers.^{2,13,28–30} One study²⁹ found that in “patients in whom penicillin allergy was reported but who could not remember or did not know the details of the reaction,” 13.6% had positive skin test results. This study also noted that there were no significant differences in the types of clinical reactions between patients with positive and negative skin test results. The meta-analysis by Solensky et al³⁰ found that one third of the patients with positive skin test results had “vague” reaction histories. A retrospective study³¹ reported that 6.7% of patients with a vague history of penicillin allergy had a positive penicillin skin test result. The present results confirm the need for serious consideration of IgE-mediated allergy in patients reporting penicillin allergy but who cannot recall the specific reaction event.

Limitations of this study consist of (1) a lack of medical records pertaining to the reaction event and (2) the absence of challenge procedures. Medical records were seldom available, and data by parent report are subject to recall bias. However, this is often the case with allergy histories. Parents were interviewed throughout the prospective period by the same physician, and consistency and experience in data collection served to reduce variation. Follow-up reports of the outcome of testing were not systematically obtained, and provocation testing was not used owing to clinic procedural conditions.

In conclusion, 2 decades of experience with penicillin skin testing in an allergy referral clinic at one institution is reported. We note an almost complete disappearance of penicillin allergy as reflected by penicillin skin test reactivity. The disappearance of skin test reactivity was noted early in data collection, and reporting of this result was delayed several years to confirm that this was not an aberrant observation. Plausible explanations for this trend include the declining use of injectable repository penicillin and the increasing use of aminopenicillins that cause cutaneous reactions based on side chain reactions and non-IgE-related mechanisms.³² It seems that pediatricians, at least in our community, have become increasingly willing to continue prescribing β -lactam antibiotics such as cephalosporins or macrolide antibiotics with indication for referral when further rashes occur or when they prefer to again have amoxicillin or amoxicillin-clavulanate available. Nevertheless, the marked decline in penicillin skin test sensitivity among children, if confirmed, may have implications for the future prevalence of penicillin allergy in the adult population.

Analysis of the pattern of skin test reactions for those with positive skin test results indicates that using only benzylpenicilloyl polylysine and penicillin G as reagents will miss 8.5% of potential reactors. Even if the positive predictive value for this group of patients is unknown, it, nevertheless, is a caution in proceeding to treat patients tested with only benzylpenicilloyl polylysine and penicillin G.

It is important that more attention be given to the initial reaction event. Limited documentation of drug-allergic events will lead to the use of alternative antibiotics.³³ Although physician-diagnosed allergic reactions to β -lactam antibiotics overestimate the rate of IgE-mediated allergy, it is still more accurate than patient history alone.¹² The common practice of simply instructing patients to discontinue using the antibiotic when a rash occurs without further examination or other means of documentation (ie, digital photograph) leads to a lifelong diagnosis of allergy with ramifications concerning subsequent antibiotic use.

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