

Selecting Skin Testing Reagents to Predict Amoxicillin and Cephalosporin Allergy

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ABSTRACT

Objectives: This study assessed the accuracy of a panel of skin testing reagents to detect immunoglobulin E sensitivity to amoxicillin and oral cephalosporins.

Methods: One hundred and eighty-seven children and adolescents experiencing adverse reactions to amoxicillin (or amoxicillin/clavulanate), and/or an oral cephalosporin, that were considered sufficient to preclude further use were studied. Skin testing with penicillin G, commercial benzylpenicilloyl phosphate, penicillin minor determinant mixture (MDM), ampicillin, cefazolin, cefuroxime, and ceftriaxone was performed according to the suspected drug allergy, followed by an oral challenge, repeat skin testing, and prospective follow-up if no reactions were observed.

Results: Fifty-four (33.5%) of 161 patients with suspected amoxicillin reactions and 13 (50%) of 26 suspected cephalosporin reactions had positive skin tests or oral challenges. Positive reactions to only the MDM reagent occurred in 9 amoxicillin- or cephalosporin-allergic patients, to only the ampicillin reagent in 4 amoxicillin-allergic patients, and to only a cephalosporin reagent in 3 cephalosporin-allergic patients. No reactions to oral challenge were severe after negative skin testing. During prospective follow-up, one (0.9%) of 107 patients suspected of amoxicillin allergy who completed our skin testing–oral challenge repeat skin test protocol without a reaction and two (1.8%) patients with borderline reactions subsequently developed urticaria 8–16 months later while taking a course of amoxicillin. Reactions were mild. No test negative patients suspected of cephalosporin allergy developed a reaction with a subsequent course of a cephalosporin. Amoxicillin reactors with positive skin tests or oral challenges (N = 54) received 83 treatment courses of cephalosporins uneventfully in prospective follow-up.

Conclusions: Elective amoxicillin and cephalosporin skin testing and oral challenge protocols are helpful in identifying patients at very low risk for developing subsequent hypersensitivity reactions. *Pediatr Asthma Allergy Immunol* (1997;11[2]:79–93.)

INTRODUCTION

THE IMPORTANCE OF DETECTING β -lactam antibiotic side-chain specific allergy is controversial.^(1–6) The major antigenic determinants for penicillin immune responses are the penicilloyl epitopes, which pri-

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marily include the β -lactam ring and a portion of adjacent protein carrier.⁽⁷⁻⁹⁾ The biologic activity of side-chain specific antibodies are fully inhibitable by the parent β -lactam drug.⁽¹⁰⁾ Furthermore, about 95% of the penicillin bound to tissue protein is in the penicilloyl (the major determinant) form.^(7,11) Clinical studies are generally in good agreement that human immunoglobulin E (IgE) antibody to the major penicillin determinant can be readily identified on skin testing by using a benzyl-penicilloyl polylysine reagent⁽⁸⁾ and to the minor penicillin determinants (penicillin, penicilloate, and penilloate) by using an acid/base-treated penicillin mixture.^(9,12,13) Until 1988,⁽¹⁴⁾ it was widely held that the addition of ampicillin or other β -lactam antibiotics with different side-chain specificities to a skin-testing panel improved sensitivity by only 1.4%–3.7% in identifying IgE-sensitive patients.⁽¹⁵⁻²³⁾ Thereafter, the value and importance of including at least ampicillin as a skin-testing reagent in patients suspected to have ampicillin or amoxicillin hypersensitivity gained support.^(5,24-26)

Cephalosporins are β -lactam antibiotics that differ from penicillins in structure by substitution of a dihydrothiazine ring for the thiazolidine ring of penicillins. Cephalosporins differ from each other chemically based on side-chain substitutions.⁽²⁷⁾ The greater lability of the cephalosporins to degradation may produce more drug-specific and side-chain specific epitopes for the generation of IgE antibody.⁽²⁸⁾ Skin testing with cephalosporins is currently limited to use of the native drugs because the relevant degradation products are unknown. Cross reactivity among cephalosporins and between cephalosporins and the penicillins in terms of IgE hypersensitivity has received limited study; there may be less cross sensitivity among the cephalosporins than the penicillins.^(1,19,22,29-36) Experience with cephalosporin oral challenges of penicillin, amoxicillin, and cephalosporin skin-test positive and negative patients has slowly accumulated (reviewed in reference 6) with results suggesting that early, retrospective studies^(37,38) far overestimated cross reactivity.

In this study, we extend our recent description⁽³⁹⁾ of the reliability of a physician examination-based diagnosis of β -lactam allergy and report the accuracy of a selected skin-testing panel in detecting IgE sensitivity to amoxicillin and cephalosporins. Following the recommended elective skin-test program of Mendelson et al.,⁽⁴⁰⁾ our skin-test negative patients underwent an oral challenge with the β -lactam antibiotic suspected of previously producing a reaction and if no reaction occurred, then repeat skin testing was completed. Penicillin and amoxicillin skin-test and/or oral challenge-positive patients were permitted to receive cephalosporins. Prospective follow-up of skin-test positive and skin-test negative patients for an average of 5.4 years allowed an assessment of the predictive value of our program.

METHODS

Patients

Patients were referred to one of the authors (MEP) from 1988–1996 for elective skin testing and oral challenge as suggested by Mendelson et al.⁽⁴⁰⁾ to detect β -lactam antibiotic allergy. All patients were well and had no need for antibiotics at the time of evaluation (testing and oral challenge). For every patient, the medical record of the primary-care physician was reviewed. Only cases that had a physician examination at the time of the suspected adverse reaction were included in this study and only if the observed reaction led the primary-care physician to advise against further use of antibiotics in the β -lactam class. The procedure of penicillin skin testing and oral challenge and the possible risks were explained to the parents and/or the patients.

Skin testing reagents

The reagents used for skin tests were as follows: (1) normal saline; (2) histamine phosphate (1 mg/mL histamine: Eli Lilly Co., Indianapolis, IN) serving as negative and positive controls, respectively; (3) benzylpenicilloyl polylysine solution (Pre-pen, Kremers-Urban, Milwaukee, WI) at a concentration of 6×10^{-5} M, with a single-dose ampule used for each testing session; (4) potassium benzylpenicillin (Pen G, Eli Lilly Co.), 16.9 mM, of which a stock solution, 10^6 U/ml in normal saline was prepared fresh for each testing session; (5) penicillin minor determinant mixture (MDM) consisting of sodium benzylpenicilloate and sodium benzylpenilloate, each at 10 mM prepared according to the procedure of VanDellen et al.⁽⁹⁾; (6)

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ampicillin (Bristol-Myers Squibb, New Brunswick, NJ) at 10 mg/mL for prick testing and 1 mg/mL for intradermal testing; (7) cefazolin (Bristol-Myers Squibb) at 10 mg/mL for prick testing and 1 mg/mL for intradermal testing; (8) cefuroxime (Glaxo Wellcome, Research Triangle Park, NC) at 10 mg/mL for prick testing and 1 mg/mL for intradermal testing; and (9) ceftriaxone (Roche, Nutley, NJ) at 10 mg/ml for prick testing and 1 mg/ml for intradermal testing.

Procedures for skin test and antibiotic challenge

Patients avoided all antihistamines for 2–4 weeks prior to testing; the longer interval was recommended for antihistamines with longer half-lives. Patients were skin tested on the forearm by the prick (puncture) technique. If after 20 min the erythema and wheal response to the testing materials was greater than 5×5 mm (>25 mm²), the patient was considered to be allergic to the antibiotic and no further testing was done. If the prick test was negative (<25 mm²), then 0.02 ml of the testing material was injected intradermally into the volar aspect of the forearm. After 15 min, the intradermal test was read. An erythema and wheal $>5 \times 5$ mm was considered to be positive and the patient was considered to be allergic to the antibiotic. A reaction greater than 3×3 mm (>9 mm²) but less than 5×5 mm (<25 mm²) was considered to be borderline. Two testing protocols were employed during the time course of the study. In the first skin testing protocol, 68 patients with suspected amoxicillin or amoxicillin/clavulanate allergy were tested with Pen G, Pre-pen and MDM reagents. In the second testing protocol, 93 subjects suspected of amoxicillin or amoxicillin/clavulanate allergy and 26 children suspected of cephalosporin allergy were tested with Pen G, Pre-pen, MDM, ampicillin, cefazolin, cefuroxime, and ceftriaxone reagents. All skin tests were performed and read by trained technicians.

If the intradermal skin test was negative, the patient was then given a penicillin oral challenge (penicillin VK 125 mg white tablet [<40 lbs] or 250 mg [≥ 40 lbs], Eli Lilly Co.) and then observed for 30 min to determine if there was an immediate reaction to the oral challenge. If there was no reaction, a 5–10 day challenge with the appropriate β -lactam antibiotic of concern that previously elicited an adverse reaction was administered in the home setting with diphenhydramine on hand in case of an adverse event. If a patient had experienced an adverse reaction to a single antibiotic, then that antibiotic was administered according to a standard schedule for 10 days. If the patient experienced an adverse reaction to 2 antibiotics, then the patient received a 5-day course with the first (generally amoxicillin) followed by a 3-day washout period and then a 5-day course with the second antibiotic of concern (generally a cephalosporin). The patient was told to discontinue the antibiotic and contact the office immediately if any reaction was experienced during the testing period. Any patient who reported a reaction was examined to document the reaction. After completing the course of antibiotic, the patient returned 3–4 weeks later to be skin tested again as appropriate in a manner identical to the initial evaluations. If the oral-challenge doses of antibiotic were tolerated and the repeat skin test was negative, the patient and parent were told that β -lactam antibiotic use could be resumed. If patients tested positive to penicillin and ampicillin reagents, they were told to avoid these antibiotics but that they could receive oral cephalosporins with the first dose administered under physician supervision and with diphenhydramine kept in the home in case of an adverse reaction that developed later. Cephalosporin skin-test/oral-challenge-positive patients were told to avoid all β -lactam antibiotics.

Prospective follow-up

At the completion of the skin-testing regime, all patient records at the primary-care physician's office were prospectively monitored for a period of 6 months to 8 years (average = 5.4 years), depending on when the initial testing was performed, to ascertain whether oral antibiotics were subsequently administered from the β -lactam class and if any adverse reactions occurred.

RESULTS

One hundred and sixty-one patients with an examination-confirmed adverse reaction to amoxicillin and twenty-six patients with cephalosporin reactions completed our testing protocol. The patients ranged in age

from 6 months to 18 years at the time of skin testing. The most common clinical manifestations of an adverse antibiotic reaction were urticaria and polymorphous rash.

Based on the examination at the time of the adverse reaction, the patients were divided into a group for whom the reaction was of a classically IgE-mediated type (hives, pruritis, angioedema, bronchospasm, or laryngeal edema) and a group for whom the reactions was considered likely not be IgE mediated (polymorphous rash, erythema multiforme, arthralgia, abdominal pain, serum sickness, emesis, or purpura). The results of skin testing in relation to the patient's age and the type of previous reaction suggest that this categorization was inaccurate (Table 1). Fifteen (27.8%) of fifty-four amoxicillin reactors had positive skin tests or oral challenges even though their preceding histories and examinations suggested a non-IgE-mediated adverse event. Similarly, 2 (15.4%) of 13 cephalosporin reactors who had non-IgE type adverse events, nevertheless, were positive on skin testing or oral challenge.

Thirty-four children (21.1%) suspected of amoxicillin allergy were positive on initial skin testing as were eight (30.8%) suspected of cephalosporin allergy. Two (1.2%) of the skin tested children suspected of amoxicillin allergy had an initial skin test reaction which was negative but an IgE-type reaction on oral challenge as did one (3.8%) of the skin-tested children suspected of cephalosporin allergy. After completion of the oral challenge, if no adverse reaction occurred then children returned for repeat skin testing. Eighteen patients (14.4%) of the one hundred twenty-five suspected of amoxicillin allergy returning for another skin-testing challenge were positive, as were four (25%) of the seventeen suspected of cephalosporin allergy.

Table 2A shows the specific skin test reagent reactions of 45 children who had experienced an adverse reaction to amoxicillin (and not a cephalosporin also as shown in Table 2B) and who were skin test positive and 2 children who had reacted to penicillin and amoxicillin. Of the 30 patients positive on initial skin testing who had previously experienced an adverse reaction to amoxicillin, 56% were skin-test positive to a single reagent including one (3%) to MDM only and one (3%) to ampicillin only (Table 2A). Of the 15

TABLE 1. RESULTS OF SKIN TESTING IN RELATION TO PATIENT AGE AND TYPE OF PREVIOUS REACTION TO AMOXICILLIN AND CEPHALOSPORINS

<i>Suspected amoxicillin allergy</i>				
<i>Number of positive skin-test/oral-challenge reactors</i>				
<i>Age (Year)</i>	<i>IgE^a</i>	<i>Non-IgE^a</i>	<i>Both^a</i>	<i>Total</i>
0-6	22	10	4	36
7-12	7	4	3	14
13-19	3	1	0	4
Total	32	15	7	54
<i>Suspected cephalosporin allergy</i>				
<i>Number of positive skin-test/oral-challenge reactors</i>				
<i>Age (Year)</i>	<i>IgE^a</i>	<i>Non-IgE^a</i>	<i>Both^a</i>	<i>Total</i>
0-6	2	2	3	7
7-12	4	0	2	6
13-19	0	0	0	0
Total	6	2	5	13

^aType of previous reaction based on examination. IgE-hives, pruritis alone, angioedema, bronchospasm, and laryngeal edema; Non-IgE-polymorphous rash, erythema multiforme, arthralgia, abdominal pain, serum sickness, emesis, and purpura; both-components of IgE and non-IgE reactions.

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TABLE 2A. COMPARISON OF DRUG ALLERGIC REACTION WITH REACTIVITY TO VARIOUS SKIN-TEST REAGENTS IN SKIN-TEST POSITIVE PATIENTS

<i>Skin-test reagents</i>	<i>Number of patients with drug adverse reaction</i>			
	<i>Amoxicillin (N = 45)^a</i>		<i>Penicillin/ Amoxicillin (N = 2)</i>	
	<i>Initial</i>	<i>Retest</i>	<i>Initial</i>	<i>Retest</i>
Pen G only	8 ^b	2	0	0
Pre-pen only	7	3	0	0
MDM only	1	5	0	0
Ampicillin only	1	2	0	1
Pen G/Pre-pen	6	0	0	0
Pen G/MDM	0	0	0	0
Pen G/Ampicillin	3	0	0	0
Pre-pen/MDM	1	1	0	0
Pre-pen/Ampicillin	0	0	0	0
MDM/Ampicillin	2	0	0	0
Pen G/Pre-pen/MDM	0	0	1	0
Pen G/MDM/Ampicillin	1	0	0	0
Pen G/Pre-pen/ MDM/Ampicillin	0	2	0	0
Total	30	15	1	1

^aTwo patients suspected of amoxicillin allergy were initially skin-test negative but developed an IgE-mediated reaction on oral challenge.

^bNumber of patients with positive reactions to specified skin-test reagent(s).

patients suspected of amoxicillin allergy only who were negative on initial skin testing but positive on repeat skin testing, 10 (67%) were positive to a single skin test reagent, including 5 (33%) who were only positive to MDM and 2 (13%) to ampicillin only (Table 2A).

Reactions to single-skin-test reagents were also observed in those who were suspected of cephalosporin allergy and were skin-test positive on initial or repeat skin testing (Table 2B). Five children in our study were suspected of cephalosporin allergy without concomitant suspicion of penicillin and/or amoxicillin allergy (cephalexin for three cases, cefadroxil for one case, and cefprozil for one case). Two (40%) of the five patients were skin-test positive only to a cephalosporin (cefazolin) skin test reagent. Of the 8 children suspected of a cephalosporin and amoxicillin and/or penicillin allergy, 1 (12.5%) was skin-test positive only to a cephalosporin (cefuroxime) skin test reagent (Table 2B).

Two patients experienced an IgE-mediated reaction in association with the initial skin testing procedure; both patients developed pruritis, were given diphenhydramine, and symptoms resolved while under a 1-h observation. Two patients suspected of amoxicillin allergy and one of cephalosporin allergy had positive oral challenges after negative initial skin tests, all of which were mild; their case histories are presented in Table 3.

Patients who completed our skin testing and oral challenge protocol were prospectively monitored for subsequent adverse reactions to β -lactam antibiotic treatment courses. Multiple courses of penicillin, amoxicillin, and cephalosporins were administered to our patients during a 6-month to 8-year follow-up (mean = 5.4 years).

Patients suspected of amoxicillin allergy who experienced a positive skin test or oral challenge (N = 54) were advised that they could nevertheless receive cephalosporin antibiotics. Eighty-three treatment courses with cephalosporins were administered to these fifty-four patients subsequent to our skin testing protocol

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TABLE 2B. COMPARISON OF DRUG ALLERGIC REACTION WITH REACTIVITY TO VARIOUS SKIN-TEST REAGENTS IN SKIN-TEST POSITIVE PATIENTS

Skin-test reagents	Patients with multiple β -lactam allergy							
	Cephalosporins (N = 5) ^a		Penicillin/ Cephalosporin (N = 3) ^b		Amoxicillin/ Cephalosporine (N = 4) ^c		Penicillin/ Amoxicillin/ Cephalosporin (N = 1) ^d	
	Initial	Retest	Initial	Retest	Initial	Retest	Initial	Retest
Pen G only	0 ^e	0	0	0	1	0	0	1
Pre-pen only	0	0	0	0	0	1	0	0
MDM only	0	1	1	0	1	0	0	0
Amp only	0	0	0	0	0	0	0	0
Pen G/Pre-pen	0	0	0	0	0	0	0	0
Pen G/MDM	0	0	0	0	0	0	0	0
Pen G/Amp	0	0	0	0	0	0	0	0
Pre-pen/MDM	0	0	0	0	0	0	0	0
Pre-pen/Amp	0	0	0	0	0	0	0	0
MDM/Amp	0	0	0	0	0	0	0	0
Pen G/Pre-pen/MDM	0	0	1	0	1	0	0	0
Pen G/MDM/Amp	1	0	0	0	0	0	0	0
Cefazolin	2	0	0	0	0	0	0	0
Cefuroxime	0	0	0	1	0	0	0	0
Ceftriaxone	0	0	0	0	0	0	0	0
Total	3	1	2	1	3	1	0	1

^aCephalosporin allergy suspected were Cephalexin three times, Cefadroxil once and Cefprozil once. After initial skin testing was negative, the patient suspected of Cefprozil allergy developed an IgE-mediated reaction on oral Cefprozil challenge.

^bThree penicillin combinations were penicillin/Cefadroxil, penicillin/Cephalexin and penicillin/Cefuroxime. After initial skin- and oral-challenge to penicillin and Cefuroxime was negative, the retest to Cefuroxime was positive in one patient.

^cFour amoxicillin combinations were amoxicillin/Cefaclor, amoxicillin-Clavulanate/Loracarbef, and amoxicillin/Cephalexin twice.

^dThe suspected cephalosporin was Cefaclor.

^eNumber of patients with positive reactions to specified skin-test reagent(s).

TABLE 3. CASE HISTORIES

Reactions to oral challenge after initial skin testing was negative					
Patient	Suspected drug allergy	Initial skin testing	Challenge drug/dose	Reaction	Onset after challenge
1	Amoxicillin	All negative	Penicillin VK 250 mg tid for 5 days	Itchy eyes and periorbital edema	Fifth day of oral challenge
2	Cefprozil	All negative, including Cefuroxime	Penicillin VK 250 mg bid then Cefprozil 250 mg for 3 days	Hives and angioedema	Tolerated penicillin, then on third day of Cefprozil
3	Amoxicillin	4 × 4 mm intradermal reaction to MDM and negative to remainder	Penicillin VK 250 mg tid for 2 days	Hives	Second day of penicillin

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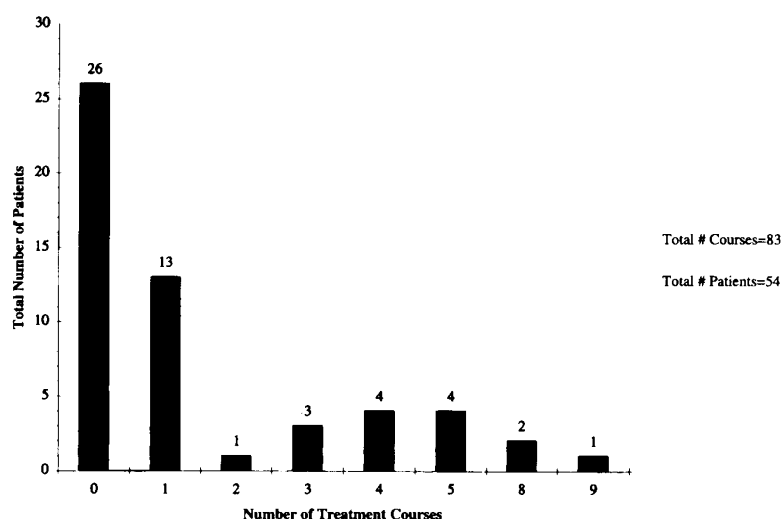


FIG. 1. Suspected amoxicillin/amoxicillin-Clavulanate allergic patients who were skin test or oral challenge positive and received cephalosporins uneventfully. Shown are the cumulative number of treatment courses in patients in the study population receiving cephalosporin antibiotic courses after positive skin testing.

(Fig. 1) and one treatment course (1.2%) in one patient (1.9%) resulted in an IgE-type mediated reaction, which was mild (Table 4). The patient was subsequently skin tested with cefuroxime and the skin testing was positive.

Patients suspected of amoxicillin allergy who were skin-test negative ($N = 107$) and patients suspected of cephalosporin allergy who were skin-test negative ($N = 13$) were advised that they could receive any β -lactam antibiotic prescribed by their physicians. Amoxicillin reactors who were skin-test negative received 231 courses of amoxicillin or penicillin and 93 courses of cephalosporins with no reactions (Fig. 2). Cephalosporin reactors who were skin-test negative received 21 courses of amoxicillin or penicillin and 12 courses of cephalosporins with no reactions (Fig. 3).

Three patients (1.7%) developed urticaria during one of their subsequent courses of β -lactam antibiotics. Two of these patients had borderline positive skin tests and one was completely negative (Table 5).

TABLE 4. CASE HISTORY

<i>Reactions to cephalosporins after positive or borderline penicillin skin testing</i>						
<i>Patient</i>	<i>Subsequent antibiotic treatments</i>		<i>Reaction</i>	<i>Onset after challenge</i>	<i>Prior skin-testing results</i>	
	<i>Time after Testing</i>	<i>Antibiotic</i>			<i>Initial</i>	<i>Prick</i>
1	3 months	Cefaclor	Hives	9 days	Pre-pen MDM Pen G	5×5 3×3 4×4

Had Cefuroxime testing 3 months after Pen testing and 10 days after reaction to Cefaclor, and the results were:

	Prick	ID
Cefuroxime 10 mg/ml	0	3×3 mm
Cefuroxime 1 mg/ml	ND	6×7 mm

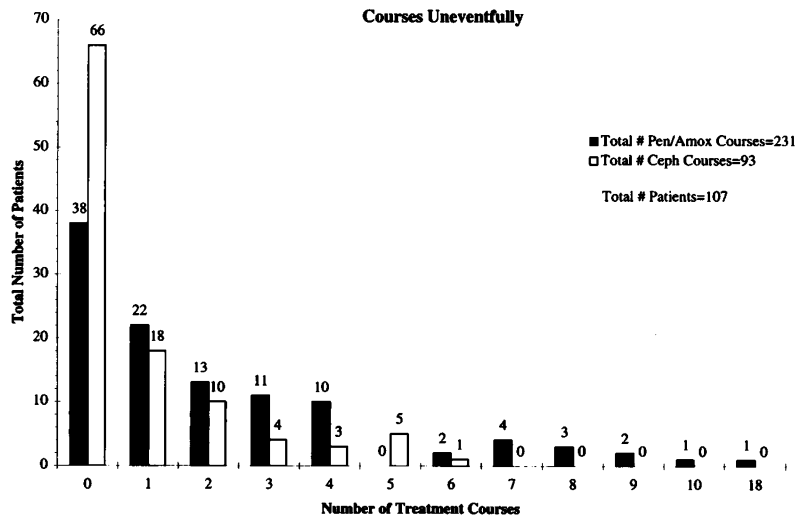


FIG. 2. Suspected amoxicillin/amoxicillin-Clavulanate allergic patients who were skin test or oral challenge negative and received penicillin, amoxicillin, and cephalosporin treatment courses uneventfully. Shown are the cumulative number of treatment courses in patients in the study population receiving β -lactam antibiotic courses after negative skin testing.

DISCUSSION

We recently reported⁽³⁹⁾ that pediatrician-diagnosed allergy to penicillin, amoxicillin, and various oral cephalosporins based on their examination of patients at the time of the reaction was accurate in predicting IgE sensitivity for 84 (34%) of 247 children. Our positivity rate at each testing phase was higher than that observed by Mendelson et al.,⁽⁴⁰⁾ whose referrals were based on history only. Here, we describe skin-testing reagent reactions in detail for our patients suspected of amoxicillin and cephalosporin allergy and our observations for the entire study population during prospective monitoring for reactions to subsequent use of β -lactam antibiotics.

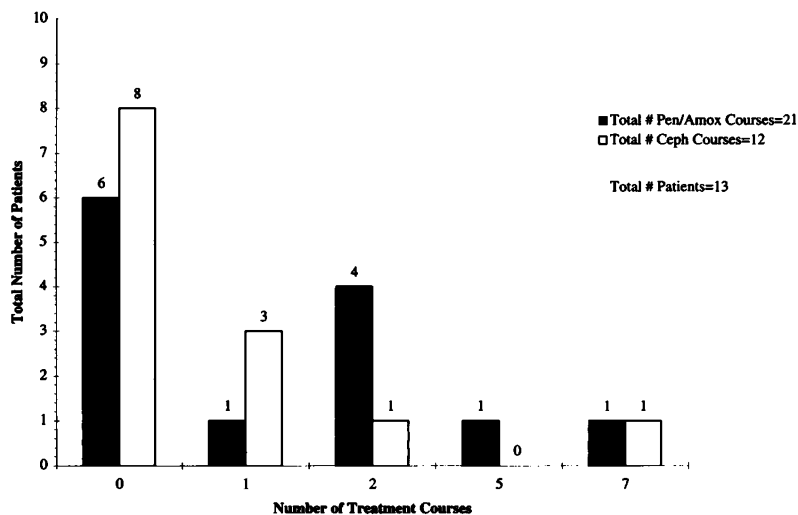


FIG. 3. Suspected cephalosporin allergic patients who were skin test negative and received penicillin, amoxicillin, and cephalosporin treatment courses uneventfully. Shown are the cumulative number of treatment courses in patients in our study population receiving β -lactam antibiotic courses after negative skin testing.

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IgE versus non-IgE reactions

The importance of classifying the adverse reaction to a β -lactam as immunologically versus not immunologically mediated and IgE versus non-IgE mediated has been emphasized.^(1,16,23,24) IgE-mediated reactions include anaphylaxis, laryngeal edema, bronchospasm, angioedema, urticaria, and, in some cases, polymorphous rash. Erythema multiforme, arthralgia, abdominal pain, serum sickness, emesis, and purpura, as well as hemolytic anemia, contact dermatitis, and nephritis, are considered to be non-IgE immunologic-mediated reactions. In addition, idiosyncratic reactions occur to β -lactam antibiotics and most polymorphous rashes are considered to be in this category. If a rash is associated with pruritis, then an IgE mechanism is inferred. Nevertheless, our results and others⁽⁴⁰⁾ support that limiting elective β -lactam antibiotic skin testing to those with typical IgE-type reactions would result in a number of patients with IgE antibody (and potentially at risk) remaining unidentified.

Importance of the oral challenge

IgE hypersensitivity to β -lactam antibiotics wanes (and perhaps can disappear) over time.^(16,21,41,42) Thus, an initial negative skin testing procedure indicates the absence of detectable quantities of IgE antibody; however, memory B-cell clones may be present that are capable of expansion and differentiation, thereby leading to reexpression of IgE antibody. The conversion of skin-test negative patients to skin-test positive status in our study population attests to this idea. If IgE is undetectable by skin testing then an anaphylactic or other serious reaction is unlikely with immediately following oral challenge.⁽⁴³⁾

Skin testing without oral challenge would fail to identify non-IgE immunologic and non-IgE idiosyncratic reproducible reactions. Although all of our positive oral challenges were immunologic, IgE-mediated reactions, the oral challenge afforded an opportunity to detect non-IgE-mediated immunologic and/or idiosyncratic reactions.

TABLE 5. CASE HISTORY

<i>Reaction to oral challenges after completion of testing protocol</i>						
<i>Patient</i>	<i>Time after Testing</i>	<i>Antibiotic</i>	<i>Reaction</i>	<i>Onset after challenge</i>	<i>Prior skin-testing results^a</i>	
					<i>Initial</i>	<i>ID</i>
1	13 months	Cephalexin	none	10 days ^e	Pen G	0
	15 months ^b	Amoxicillin ^c	Hives ^d		Pre-pen	0
	19 months	Cefprozil	none		MDM	3 × 3
					Ampicillin	3 × 3
2					<i>Initial</i>	<i>ID</i>
					PenG	3 × 4
	4 months	Cefixime	none		Pre-pen	3 × 3
	7 months	Amox/clav	none		MDM	0
	15 months	Amoxicillin	none		Ampicillin	3 × 4
	16 months ^b	Amoxicillin ^c	Hives ^d	9 days ^e	<i>Retest</i>	<i>ID</i>
	18 months	Cefadroxil	none		Pen G	3 × 3
	24 months	Cefadroxil	none		Pre-pen	0
3					MDM	0
					Ampicillin	4 × 3
	8 months ^b	Amoxicillin ^c	Hives ^d	9 days ^e	Completely negative	
	skin tests					

^aResults shown are those observed during the initial or repeat skin testing; for interpretation of results see Methods in the text.

^bTime interval between negative result on skin testing and oral-challenge protocol and subsequent reaction to an antibiotic,

^cpositive oral challenge antibiotic, ^dtype of reaction noted, and ^enumber of days on the subsequent antibiotic before the reaction was observed.

Skin testing reagent panel

It is important to select an appropriate skin testing panel of reagents because some patients respond with positive reactions to just one reagent. The value of including MDM in identifying patients at higher risk for serious IgE-mediated reactions has been established in other investigations.^(15,40) Positive reactions to only MDM were seen in 9 of our amoxicillin and cephalosporin-allergic children. The addition of an ampicillin skin test reagent has been advocated for patients who have had adverse reactions to amoxicillin.^(22,24–26) Blanca et al.⁽²⁴⁾ studied 288 patients with a history of allergy to penicillin. Skin tests, specific IgE-antibody measurements, and direct-challenge tests revealed 64 (22%) to be allergic to one or more penicillins. Twenty (31%) of these 64 patients reacted only to ampicillin; thus, 6.9% of the total group of penicillin-allergic patients would have been missed in that study if only benzyl penicillin and phenoxymethyl penicillin were used as diagnostic reagents. Four of our suspected amoxicillin-allergic patients were skin-test positive only to ampicillin.

Predictive accuracy of testing protocol

Nearly all patients with previous reactions to penicillin can subsequently receive the drug safely if they have negative skin tests to the major and minor determinants.^(40,42) The reliability of skin testing with the major determinant alone has been reported to be as high as 97% whereas the addition of Pen G and MDM may bring the reliability to 99%.^(16,18,23,24) In outpatients, the risk of conversion from a negative to a positive skin test following a skin-testing procedure is considered to be negligible. However, this conclusion has been reached after short follow-up.^(40,44) Parker et al.⁽⁴⁴⁾ described three (16%) of 18 patients who had a history of penicillin allergy and who were skin-test negative but converted to skin test positive 1–12 months after receiving a full intravenous course of this antibiotic.

In our study, the predictive accuracy of elective β -lactam antibiotic testing was assessed during 252 subsequent penicillin or amoxicillin and 105 cephalosporin treatment courses following negative testing and oral challenge in 120 patients. We observed only three adverse IgE reactions (0.84%/treatment course and 2.5%/patient), all of which were mild. Eighty-three treatment courses with cephalosporins were uneventfully administered to fifty-four amoxicillin skin-test/oral challenge-positive patients. One adverse reaction (1.2%/treatment course and 1.9%/patient) was observed, which was mild.

Detecting cephalosporin allergy

The cephalosporins are β -lactam antibiotics that differ in structure from the penicillins by the substitution of a dihydrothiazine ring for the thiazolidine ring of penicillins (Fig. 4).

Of concern is the potential for allergic cross reactivity in patients who are considered to be penicillin or cephalosporin-hypersensitive.^(2,3,35) The basic structures of the penicillins and the cephalosporins (6-amino-penicillanic acid and 7-amino-cephalosporanic acid) are similar in several respects. Both classes of antibiotic are of low molecular weight, are highly substituted, possess a β -lactam ring structure on which antimicrobial activity depends, and possess a separate ring structure containing sulfur. However, the chemistry of the degradation and transformation of the penicillins differs from that of the cephalosporins.⁽⁴⁵⁾ After the action of the specific β -lactamases, penicillin forms a stable penicilloate whereas cephalosporin forms an ultraviolet absorption peak that disappears rapidly, a phenomenon indicating fragmentation of the cephalosporin nucleus. Thus, on the basis of the chemical structure and degradation of the penicillins and cephalosporins, differing conclusions might be reached on the likelihood of immunologic cross reactivity.^(31,36,45–47)

Hypersensitivity to first-generation cephalosporins in those patients who have histories of penicillin allergy was reviewed by Petz.⁽³⁸⁾ Among 15,987 patients (from different studies) treated with cephaloridine, cephalothin, cephalexin, and cefazolin, 8.1% of patients with histories of penicillin allergy had reactions compared to 1.9% of patients without such histories.⁽³⁸⁾ Other retrospective studies have suggested that patients with histories of penicillin allergy are 4–8 times more likely to have allergic reactions when given cephalosporins than those without histories of penicillin allergy.^(32,35) However, in those studies the history of penicillin allergy was not confirmed by skin tests and many of the cephalosporin reactions may not have been immunologically mediated. In addition, Smith et al.⁽⁴⁸⁾ showed that individuals with prior adverse re-

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actions to a chemically unrelated drug have about a 3-fold increased risk of penicillin reactions. Norrby's⁽⁴⁾ review of cephalosporin allergy suggested that second- and third-generation cephalosporins cause a lower incidence of allergic reactions than first-generation drugs and the reactions generally consist of rash, urticaria, and pruritis. Lin⁽²⁴⁾ contacted all of the pharmaceutical manufacturers of cephalosporin antibiotics to ascertain the risk of developing a reaction following cephalosporin treatment in penicillin allergic patients. This survey revealed an overall relative risk of 1.6-fold for developing a reaction following cephalosporin therapy in a penicillin-allergic patients for a third-generation cephalosporin; this is decidedly lower than the relative risk of a 4-fold increase noted by Petz⁽³⁸⁾ for first-generation cephalosporins.

Early studies suggested that cephalothin skin test reagent concentrations > 1 mg/mL tended to give false-positive reactions when administered intradermally.^(3,49) Also, contamination of cephalothin with penicillin was known to occur.⁽⁴⁹⁾ It has been stated that it is rare for patients with reactions to cephalosporin side chains not to be picked up by standardized penicillin skin-testing methods.⁽⁵⁾ Skin testing to cephalosporins is not standardized and the results to date have not been validated.⁽¹⁾

Three studies involving 98 skin-test positive patient reagents treated with cephalosporins have been reported.^(3,22,42) Saxon⁽³⁾ challenged 62 such patients and 1 experienced anaphylaxis while Solley et al.⁽²²⁾ treated 27 penicillin skin-test positive patients with cephalosporin antibiotics without an allergic reaction and Shepherd et al.⁽⁴²⁾ challenged 9 patients without adverse consequences.

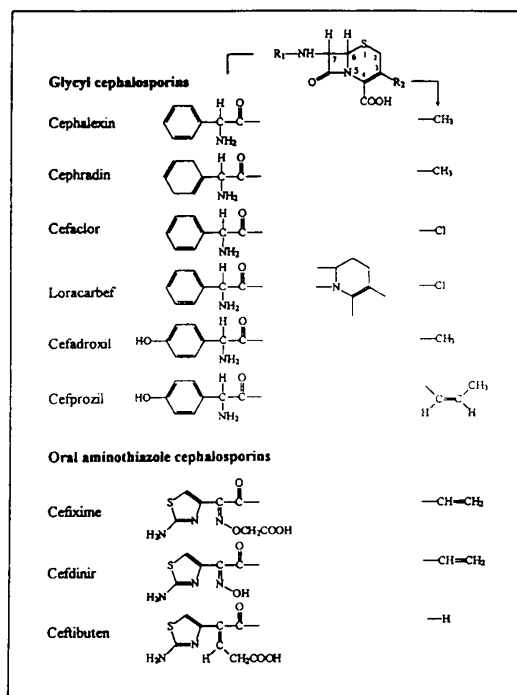
In our study, we elected to perform cephalosporin skin testing with three native compounds: We chose cefazolin for patients reacting to first-generation cephalosporins, cefuroxime for patients reacting to second-generation cephalosporins, and ceftriaxone for patients reacting to third-generation cephalosporins. We elected to use this approach, recognizing that the generation of cephalosporin class does not always correspond with similarities in chemical structure⁽²⁷⁾ (Fig. 4). As has been observed with the use of ampicillin as a skin-testing reagent for ampicillin/amoxicillin allergic patients,⁽²⁴⁾ we found the addition of cephalosporin skin-testing reagents reveals positive reactions that occur only to the cephalosporin skin-test reagent. Also, we identified one patient who had a positive skin test with penicillin determinants who was permitted to receive cephalosporins but then experienced an urticarial reaction on ingestion of cefaclor (Eli Lilly Co., Indianapolis, IN) three months later. That patient, when subsequently skin tested with cefuroxime, showed a positive reaction.

CONCLUSIONS

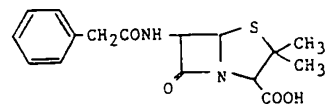
Our investigation leads us to the following conclusions:

- The results of elective β -lactam antibiotic skin testing cannot be predicted based on the type of previous adverse reaction (IgE versus non-IgE) leading to the suspicion of allergy. Seventeen (25%) of sixty-seven skin-test oral challenge-positive patients had a non-IgE-type adverse event leading to their referral.
- A panel of β -lactam antibiotic skin-test reagents, which includes ampicillin, cefazolin, cefuroxime, and ceftriaxone, may detect more test-positive patients suspected of amoxicillin and/or cephalosporin allergy than just the three reagents benzylpenicillin phosphate (major determinant), penicillin G, and penicillin MDM. The addition of ampicillin and cephalosporin reagents identified 7 (3.7%) patients as skin-test positive who otherwise would have been missed.
- The reliability (sensitivity) in predicting which patients with prior suspected β -lactam antibiotic allergy can receive these antibiotics again safely appears to be high. Fifty-four patients skin-test positive to penicillin and/or ampicillin subsequently received eighty-three courses of cephalosporins with 1 reaction. One hundred and twenty skin-test negative patients to cephalosporin and penicillin/ampicillin subsequently received ninety-three courses of cephalosporins with zero adverse reactions and two hundred thirty-one courses of penicillin and/or amoxicillin with three reactions.
- β -lactam antibiotic skin testing is safe. Only 3 reactions occurred in our patients, these reactions were all mild.
- Elective β -lactam antibiotic skin testing is helpful to patients and referring primary-care physicians because it allows the return to use of this valuable antibiotic class in the majority of cases. Four hundred

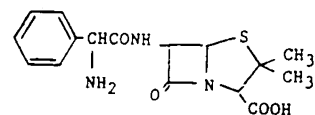
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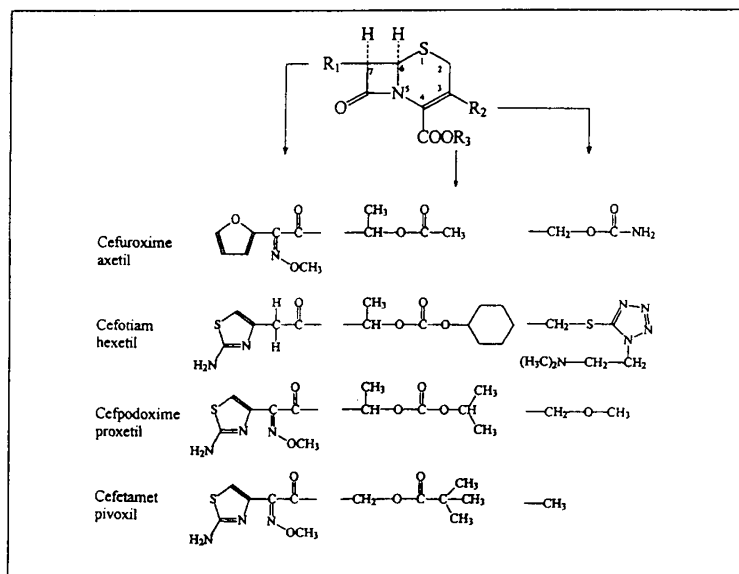
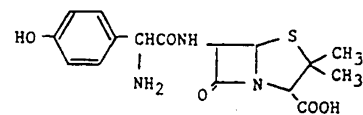
penicillin G



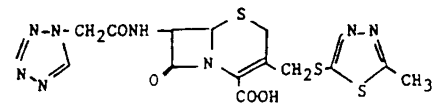
ampicillin



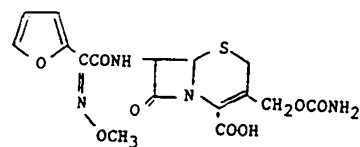
amoxycillin



cefazolin



cefuroxime



ceftriaxone

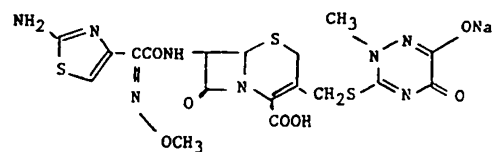


FIG. 4. Chemical structure and relatedness of β -lactam antibiotics.

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forty β -lactam antibiotic courses were given to 174 patients successfully after completion of the testing protocol, whereas, prior to referral and testing, these courses were completely precluded.

ACKNOWLEDGMENTS

This study was made possible through the cooperation of the Elmwood Pediatric Group physicians: Frank A. Disney, M.D.; John L. Green, M.D.; Anne B. Francis, M.D.; Steven M. Marsocci, M.D.; and A. Marie Lynd Murphy, M.D. David Francis assisted in data collection.

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