

Original Article

Testing Strategies and Predictors for Evaluating Immediate and Delayed Reactions to Cephalosporins

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What is already known about this topic? Testing strategies for cephalosporin allergy have been poorly defined. Previous studies have suggested that cephalosporin cross-reactivity was primarily based on common shared R1 groupings.

What does this article add to our knowledge? In 2 separate cohorts, allergy to ceftriaxone with R1 cross-reactivity and selective cefazolin allergy were the most common. Selective ampicillin intradermal test positivity in cephalosporin-allergic patients was limited to the Australian cohort, and this was associated with aminopenicillin-aminocephalosporin R1 cross-reactivity.

How does this study impact current management guidelines? Cephalosporin skin testing and ingestion challenge using approaches that account for structural similarities in R side chains is a safe and efficacious mechanism to evaluate cephalosporin allergy.

BACKGROUND: Although 1% to 2% of the general population carries a cephalosporin allergy label (CAL), we lack validated testing strategies and predictors of true allergy.

OBJECTIVE: To identify cross-reactivity patterns and predictors of skin test positive (STP) in geographically disparate patients with a CAL.

METHODS: A total of 780 adult patients labeled with a CAL or penicillin allergy label (PAL) with unknown tolerance of cephalosporins identified from the Austin Hospital (Melbourne, Australia) (n = 410) and Vanderbilt University Medical Center (Nashville, TN) (n = 370) between 2014 and 2018 underwent a standardized skin testing.

RESULTS: Of 328 patients with a CAL, 29 (8.8%) tested STP to ≥1 cephalosporin(s). There were no cefazolin or ceftriaxone STP, 0 of 452 (0%), in patients with a PAL only. Of 328 patients with a

CAL, 16 (4.8%) were ampicillin STP. Eleven of 16 of these patients had an initial allergy label to cephalosporin. Twenty of 29 cephalosporin STP patients demonstrated tolerance to a cephalosporin with a different R1 side chain, and 8 of 14 ampicillin STP patients demonstrated tolerance to ≥1 non-amino R1 group cephalosporin. Eleven of 13 patients STP to cefazolin were skin and ingestion challenge negative to all other penicillins and cephalosporins predicted by its distinct R1/R2 groups. Seven of 15 ceftriaxone STP patients demonstrated cross-reactivity with R1-similar cephalosporins. Time since the original reaction predicted STP testing to both penicillins, adjusted odds ratio (aOR) per year 0.93 (95% confidence interval [CI]: 0.90, 0.97), and cephalosporins, aOR per year 0.71 (95% CI: 0.56, 0.90). **CONCLUSIONS:** Cephalosporin cross-reactivity is based on shared R1 groupings. Increasing time since the original reaction

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Abbreviations used

CAL- Cephalosporin allergy label
 CI- Confidence interval
 DRESS- Drug reaction with eosinophilia and systemic symptom
 IDT- Intradermal test
 OR- Odds ratio
 SPT- Skin prick testing
 STP- Skin test positive
 VUMC- Vanderbilt University Medical Center

and the presence of a PAL with unknown cephalosporin tolerance predict a lower likelihood of cephalosporin STP. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Cephalosporin; Beta-lactam; Immediate hypersensitivity; Allergy; Penicillin; Skin testing; Cross-reactivity

Between 1% and 2% of the general population are labeled as cephalosporin allergic,¹ but specific and validated testing strategies for both immediate (IgE-mediated) and delayed (T-cell-mediated) cephalosporin allergy are less well defined.² Current drug allergy guidelines from the American Academy of Allergy, Asthma, and Immunology² and European Academy of Allergy and Clinical Immunology³ each note the need for additional evidence on cephalosporin cross-reactivity patterns when using nonirritating drug concentrations and systematic skin testing approaches.^{3,4} To date, immediate cephalosporin hypersensitivity testing strategies using specific IgE and basophil activation, although safe, have both lacked sensitivity and specificity for diagnosing cephalosporin allergy.⁵⁻⁸ Furthermore, although there is general agreement as to the highest nonirritating concentrations for most cephalosporins, *in vivo* testing such as prick and intradermal testing (IDT) has varied widely as to the types and concentrations of cephalosporins employed.⁹⁻¹¹ Studies suggest that cephalosporin skin test positivity is predictable primarily based on known R1 side chain cross-reactivity patterns such as those reported in European populations by Romano et al;¹²⁻¹⁷ however, the generalizability and prevalence of positive skin testing across different populations is unknown particularly in the United States where these testing practices are not common.^{14,18,19}

We reviewed 2 large and geographically disparate adult drug allergy cohorts using similar approaches to cephalosporin skin testing and ingestion challenge, with the specific purpose of evaluating the safety and efficacy of testing and the cross-reactivity between cephalosporins sharing similar side chains. Time since the original reaction has been reported as an important predictor for skin test positivity to beta-lactams in the past.¹³ We therefore aimed to evaluate the extent to which positive cephalosporin allergy skin testing decreases over time since the original reaction in a cohort of consecutively tested patients. Furthermore, cephalosporin allergy cross-reactivity with penicillins has been hypothesized to be restricted to drugs that share R1 side chains, such as the aminopenicillin side chain shared by ampicillin, amoxicillin, cefadroxil, cefaclor, cephalixin, and cefprozil.²⁰ Other cephalosporin R1 side chain families are not shared with penicillins. Examples include the methoxyimino side chain family shared by cefuroxime, ceftriaxone, cefotaxime,

cefepime, and cefpodoxime; the R1 side chain of cefazolin that is shared by no other drug; and the R1 side chain of ceftazidime that is shared with aztreonam. Hence, we sought to evaluate the extent to which patients who are history or skin test positive (STP) to cephalosporins would have positive skin testing and/or ingestion challenge to penicillins. Finally, although it is not universally standard practice, in view of previously published higher cross-reactivity patterns between penicillins and cephalosporins, our original protocols tested for cephalosporin allergy in patients with penicillin allergy and unknown tolerance of cephalosporins. This was done to evaluate whether a penicillin allergy history alone would result in positive cephalosporin skin tests other than the shared aminopenicillin/aminoccephalosporin R1 side chain.

METHODS

We performed a retrospective 2 center cohort study evaluating cephalosporin testing strategies. From 2014 to 2018, across 2 geographically disparate beta-lactam testing cohorts, the Austin Hospital (Melbourne, Australia) and Vanderbilt University Medical Center (VUMC), Nashville, TN, all patients reporting a cephalosporin or penicillin allergy with unknown tolerance of cephalosporins underwent a standardized skin testing and ingestion challenge protocol (Figures 1 and 2). Of a total of 1301 patients seen at these 2 sites from 2014 to 2018 for any drug allergy, 780 (60%) had a history of beta-lactam allergy consisting of either a reported cephalosporin allergy (n = 328) or penicillin allergy with unknown tolerance of cephalosporins (n = 452) and were subject to the retrospective review. A standardized chart review was performed to obtain patient age, sex, race, penicillin and cephalosporin labels, reaction history, which was classified as immediate or delayed, time since reaction, and testing outcomes from standardized skin testing and ingestion challenge protocols.

Skin testing reagents and protocols

Skin testing was defined as a standardized combined skin prick testing (SPT) and IDT approach that we employed. All 780 penicillin or cephalosporin allergy-labeled patients received a standard testing panel. The standard protocol consisted of Pre Pen²¹ or DAP major determinant (Diater),²² minor determinant mix²³ either Diater (Austin) or an in-house stock prepared solution of benzyl penicilloate (VUMC), ampicillin (25 mg/mL), and penicillin G (1000 and 10,000 IU/mL), cefazolin (1 mg/mL), and ceftriaxone (2.5 mg/mL) via SPT and IDT using nonirritating concentrations as per previously published protocols.^{24,25} Concentrations of additional cephalosporins tested based on an individual's history or initial testing results can be found in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org).

Skin testing methods

Penicillin and cephalosporin testing was performed by SPT and IDT using nonirritating concentrations (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).²⁰ Prick testing was performed first when a higher severity immediate hypersensitivity to a beta-lactam such as immediate multisystem involvement on history or administration of epinephrine consistent with anaphylaxis was reported. Otherwise, patients only received IDTs.

All patients with cephalosporin allergy labels (CALs) were tested to 2 standard cephalosporins, as outlined in Figure 1, which were cefazolin and ceftriaxone. When the cephalosporin that the patient

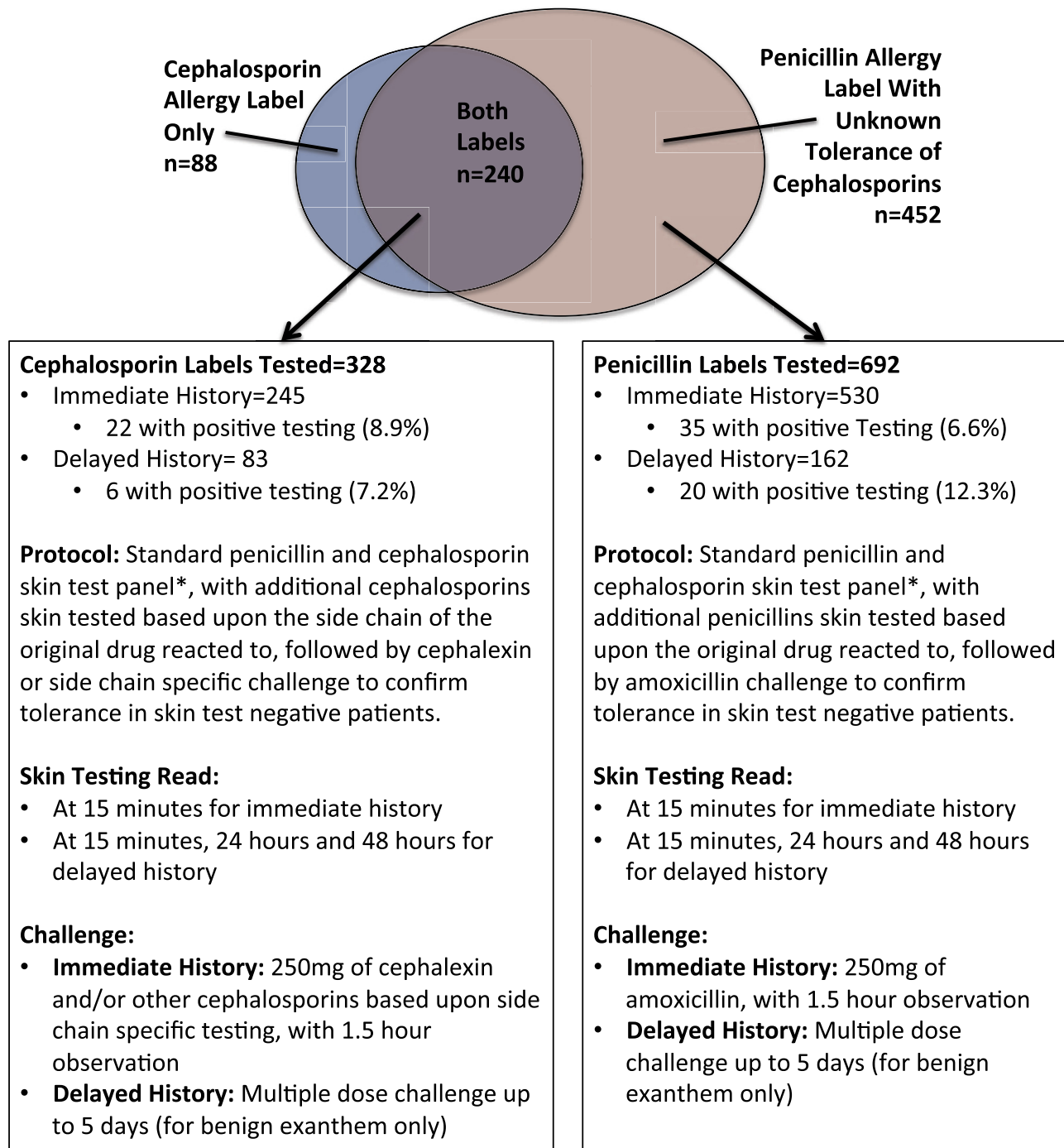


FIGURE 1. Flow diagram for selection of penicillin/cephalosporin testing as described in this article. The standard panel of testing included Pre Pen²¹ or DAP major determinant (Diater),²² minor determinant mix²³ either Diater (Austin) or an in-house stock prepared solution of benzyl penicilloate (VUMC), ampicillin (25 mg/mL), and penicillin G (1000 and 10,000 IU/mL), cefazolin (1 mg/mL), and ceftriaxone (2.5 mg/mL) via skin prick and intradermal tests. Every skin test negative penicillin allergy was challenged with amoxicillin. Every skin test negative cephalosporin allergy was challenged with cephalexin. Additional skin test reagents and additional drugs were used to disprove side chain–specific allergies by selecting either the exact same drug as the patient’s index reaction, or a drug with the same side chain, based on availability in oral and sterile IV preparation, respectively. Note that 0 of 452 patients tested for a penicillin allergy label and unknown tolerance of cephalosporins had positive testing to cefazolin or ceftriaxone. *Concentrations for testing additional specific cephalosporins based on the R side chain structure are found in [Table E1](#) (available in this article’s Online Repository at www.jaci-inpractice.org). IV, Intravenous; VUMC, Vanderbilt University Medical Center.

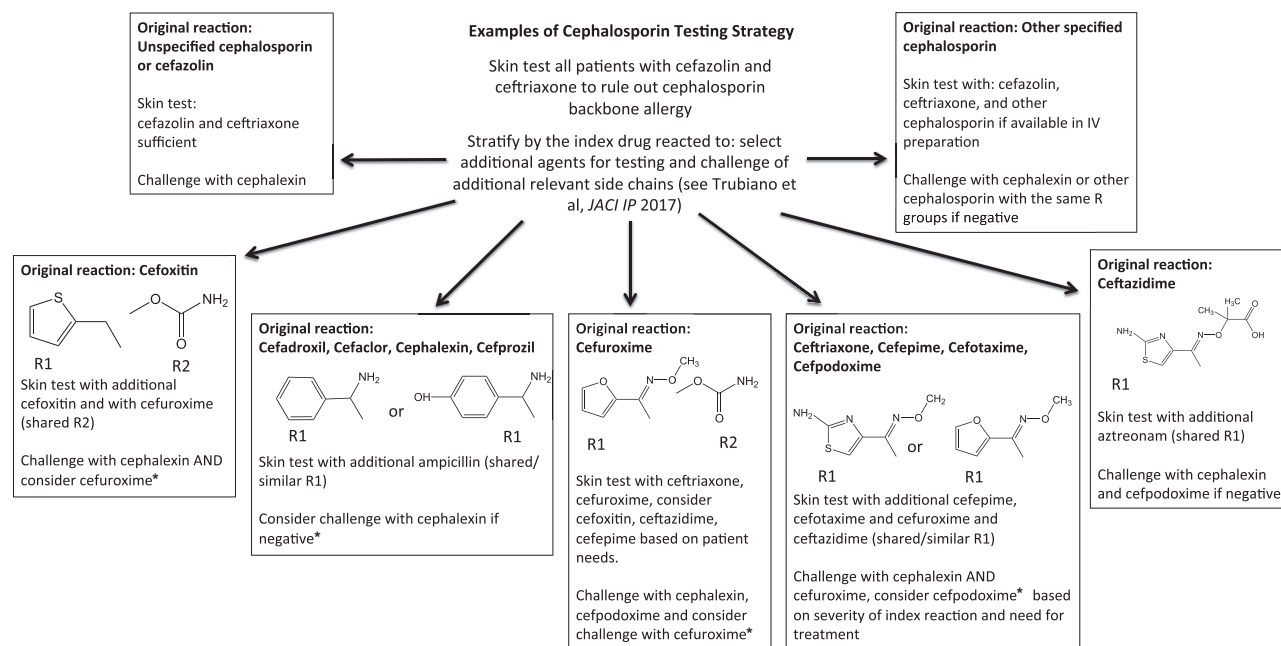


FIGURE 2. Examples of side chain–specific cephalosporin skin tests, added in addition to the standard protocol in Figure 1, derived from published side chain patterns.²⁰ *Challenges using the same R1 side chain should be considered when index reactions are of low-moderate severity when skin testing is negative, or when the patient has a specific clinical need for the implicated drug or same R1 side-chain drugs. Note: there are currently no oral drugs containing the ceftazidime/aztreonam R1.

originally reacted to, their “label,” was not cefazolin or ceftriaxone, the patient was also tested against the implicated cephalosporin when it was available in sterile intravenous preparation (Figure 2; Table E1, available in this article’s Online Repository at www.jaci-inpractice.org).

In cases where the standard approach above was positive to any penicillin or cephalosporin, additional testing with cephalosporins that had shared R1/R2 side chains was performed when possible (Figure 2; Table E1, available in this article’s Online Repository at www.jaci-inpractice.org). This was done with prick testing, followed by immediate IDTs, in 2 separate testing steps, for immediate hypersensitivity, and in a single delayed IDT and/or patch testing for delayed hypersensitivity. The potential for structural cross-reactivity amongst other penicillins and cephalosporins was defined by previously published reports on R-group side chain similarity.^{12–17,20}

Patients with a penicillin-only reaction history and unknown tolerance of cephalosporins were tested for cephalosporin reactivity via IDT to cefazolin and ceftriaxone only, without preceding SPTs.

Delayed readings of IDTs were performed at 24 and 48 hours in settings where the history suggested a delayed hypersensitivity.

Ingestion challenges

Ingestion drug challenges were performed in cases of negative skin testing as the gold standard procedure to rule out allergy and lead to removal of the cephalosporin and/or penicillin allergy label. Our overarching premises in challenges were as follows: (1) after negative skin testing, any cephalosporin can be used to rule out an allergy directed against the cephalosporin ring, and (2) when a cephalosporin skin test was positive to agents with R-side chain structural similarity but not to cephalosporins with different R-side chains, oral challenges with the skin test negative R-side chain containing

cephalosporins should be performed when possible/available. Standard challenges included 250 mg of amoxicillin to rule out a penicillin allergy, and 250 mg of cephalexin to rule out a primary cephalosporin ring allergy, when the respective skin testing was negative. A 250 mg penicillin VK challenge step was used in selected cases where skin tests were selectively positive to ampicillin and negative to other determinants. At the Austin Hospital Australia, where penicillin is still the primary drug used for community-acquired infections including community-acquired pneumonia, a penicillin VK 250 mg as an oral ingestion challenge was also used where the primary implicated penicillin was penicillin VK or penicillin G or if the reaction was before the widespread use of amoxicillin in 1972.

This article reflects an institutional review board–approved retrospective review on real clinical practice and not an interventional study. No ingestion challenges were conducted to the identical cephalosporin drug in the case of a positive skin test to that drug, either by the prick test or IDT, such as might be done in the context of a prospective study. No intravenous or intramuscular challenges were performed due to the outpatient clinic setting of both cohorts. Therefore, when skin testing and cephalexin challenge were negative, or skin testing was positive in a pattern suggestive of an R-side chain specific allergy, additional selective ingestion challenges of other oral cephalosporins beyond cephalexin were used to ascertain tolerance of cephalosporins with different R1 and/or R2 side chains, as needed for the patient’s treatment. For example, cefpodoxime challenge (which shares an R1 side chain with ceftriaxone) was sometimes used (particularly when patient need for the drug dictated this in the context of real clinical practice) in addition to cephalexin to determine tolerance of cephalosporins and tolerance of the shared ceftriaxone R1 side chain in immediate reactions to ceftriaxone of

TABLE I. Combined and separate characteristics of 2 beta-lactam skin testing cohorts in Nashville, TN, and Melbourne, Australia

	Combined cohort (n = 780)	Vanderbilt (n = 370)	Austin (n = 410)	P value comparing subcohorts
Age (y)				
Median [IQR]	59 [46, 69]	59 [45,69]	58 [47, 69]	.81
50 or older	538 (69%)	251 (68%)	287 (70%)	
Between 25 and 50	190 (24%)	95 (26%)	95 (23%)	
25 and younger	52 (7%)	24 (6%)	28 (7%)	
Sex (female)	527 (67%)	280 (76%)	247 (60%)	<.005
Race				<.005
Black	18 (2%)	17 (5%)	1 (0%)	
White	728 (93%)	340 (92%)	388 (95%)	
Asian	27 (3%)	6 (2%)	21 (5%)	
Other/mixed	7 (1%)	7 (2%)	0	
Hispanic ethnicity	5 (1%)	5 (1%)	0	.02
By cephalosporin allergy history				
Anaphylaxis	37 (5%)	23 (6%)	14 (3%)	
Angioedema/swelling	31 (4%)	21 (6%)	10 (2%)	
Blistering rash/skin sloughing	7 (1%)	6 (2%)	1 (0%)	
Diffuse itchy rash or disseminated itching	59 (8%)	34 (9%)	25 (6%)	
Diffuse, nonitchy rash	57 (7%)	35 (9%)	22 (5%)	
DRESS syndrome	8 (1%)	5 (1%)	3 (1%)	
Drug fever	7 (1%)	3 (1%)	4 (1%)	
Fixed drug eruption	5 (1%)	3 (1%)	2 (0%)	
Nausea/vomiting/diarrhea only	13 (2%)	6 (2%)	7 (2%)	
Respiratory symptoms only	12 (2%)	11 (3%)	1 (0%)	
Urticaria only	76 (10%)	48 (13%)	28 (7%)	
Other/unknown	16 (2%)	11 (3%)	5 (1%)	
Penicillin allergy label with unknown tolerance of cephalosporins	452 (58%)	164 (44%)	288 (70%)	
Original cephalosporin allergy labels (some patients report multiple labels)				
Cephalexin	136 (17%)	78 (21%)	58 (14%)	
Ceftriaxone	61 (8%)	39 (11%)	22 (5%)	
Cefazolin	43 (6%)	18 (5%)	25 (6%)	
Cefaclor	33 (4%)	24 (6%)	9 (2%)	
Cefuroxime	23 (3%)	21 (6%)	2 (0%)	
Cefdinir	21 (3%)	21 (6%)	0 (0%)	
Cefepime	18 (2%)	16 (4%)	2 (0%)	
Ceftazidime	10 (1%)	8 (2%)	2 (0%)	
Cefpodoxime	3 (0%)	3 (1%)	0 (0%)	
Cefoxitin	3 (0%)	3 (1%)	0 (0%)	
Cefotaxime	2 (0%)	2 (1%)	0 (0%)	
Patient reports a previous reaction to an unknown cephalosporin	36 (5%)	33 (9%)	3 (1%)	

DRESS, Drug reaction with eosinophilia and systemic symptom; IQR, interquartile range.

high index severity, when skin testing was negative. Cefuroxime challenge was commonly used in Austin in patients whose testing pattern was suggestive of an aminopenicillin/aminoccephalosporin allergy, as it has a dissimilar R1 side chain. This was a minor variation in protocol between our 2 testing sites that was necessitated by the higher rate of selective aminopenicillin and immediate anaphylactic aminoccephalosporin reactions.

Statistical analysis

Descriptive statistics assessing differences between the 2 cohorts were performed using Fisher's exact test for comparisons of categorical variables and the Wilcoxon rank-sum test for comparisons

amongst continuous variables. Comparisons amongst the number of positive skin tests to beta-lactam type by site were performed using a 2-sided test of proportions (Table I).

The specific time that had elapsed since the original reaction to a penicillin or cephalosporin leading to allergy labeling was known and reported by 427 of 530 (81%) of patients with a history of immediate penicillin allergy and 217 of 245 (89%) of patients with a history of immediate cephalosporin allergy. We therefore modeled the relationship between time since the original reaction and the outcome of skin test positivity in patients with a reported immediate reaction to penicillins or cephalosporins using univariate logistic regression. We then adjusted for covariates of age (continuous), sex,

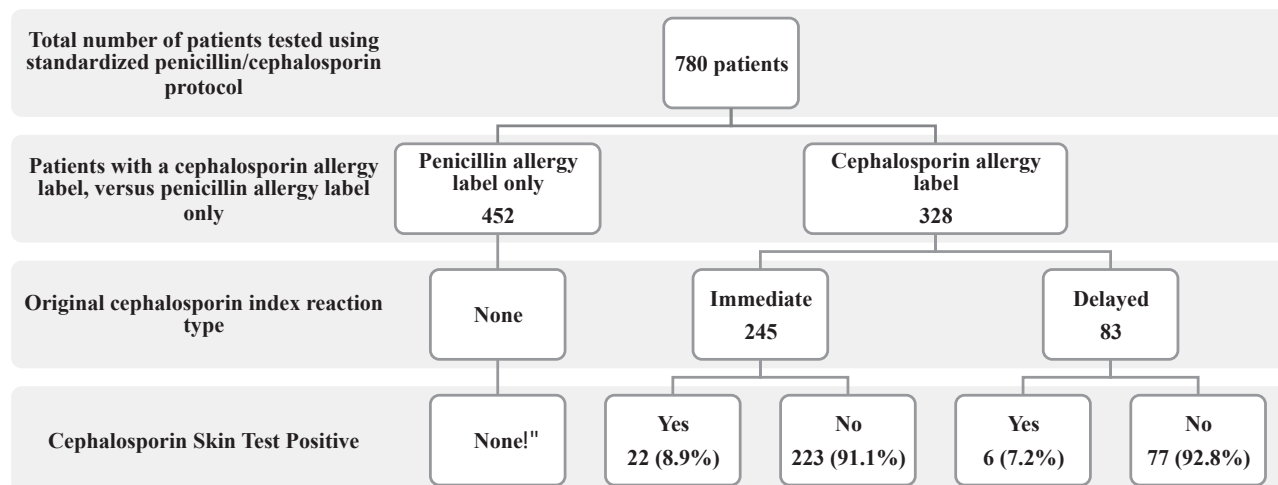


FIGURE 3. Flow diagram outlining cephalosporin testing results in patients with penicillin and cephalosporin allergy histories. *Patients with penicillin allergy label were tested with cefazolin and ceftriaxone only.

race, and testing site. These covariates were selected *a priori* to examine their potential as predictors of skin test positivity based on clinical experience during the performance of the challenges, and to avoid overfitting. We also performed an analysis stratified by site. Our multivariable logistic regression therefore used either 6 or 7 degrees of freedom depending on whether testing site was included. The minimum sample size analyzed in this way, with 6 degrees of freedom, was 55 participants. Statistical analysis was performed using STATA statistical software version 15.0.²⁶

RESULTS

A total of 780 patients received standardized skin testing for a label of penicillin or cephalosporin allergy from 2014 to 2018. Of our investigated cohort, 692 of 780 (89%) had a history of penicillin allergy and 328 of 780 (42%) had a reported history of cephalosporin allergy, with a total of 396 CALs reported amongst these 328 patients (Table I). In terms of cephalosporin allergy, 88 reported cephalosporin allergy only, 240 of 780 (34%) reported allergy to both penicillins and cephalosporins, and 452 of 780 (58%) reported a penicillin allergy with unknown tolerance of cephalosporins. Amongst our cohort, 69% were 50 or older (median age, 59 years [interquartile range: 46, 69]), 93% were white, and 67% were female (Table I). The VUMC US cohort had a higher proportion of patients referred with CALs (56%) than the Australian cohort (30%) ($P < .0005$). Amongst cephalosporin allergy-labeled patients, only 29 of 328 (8.8%) demonstrated positive allergy skin testing to a cephalosporin. There were no positive cefazolin or ceftriaxone skin tests in patients with a penicillin allergy and an unknown tolerance of cephalosporins, 0 of 452 (0%) (Figure 3).

Immediate hypersensitivity cephalosporin labels

There were 245 patients with a CAL with a history of immediate hypersensitivity. Twenty-two of 245 (9.0%) had positive immediate hypersensitivity skin testing to a cephalosporin (Figure 4; Table E2, available in this article's Online Repository at www.jaci-inpractice.org). This rate increased to 16 of 59 (27%) among patients with a history of an immediate hypersensitivity to a cephalosporin and a reported reaction with 1 year of testing. Among 22 patients with a confirmed allergy to

either cefazolin, cefuroxime, ceftriaxone, ceftazidime, or cefepime, 17 tolerated an ingestion challenge to cephalixin, which has a non-cross-reactive R1 side chain with all of these cephalosporins. Another patient with a confirmed cefazolin allergy tolerated an ingestion challenge to cefuroxime. These patients were advised that they could take all cephalosporins in the future except those sharing an R1 or R2 group with the implicated cephalosporin (Figure 4; Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Representative skin test images can be found in Figures E1 and E2 (available in this article's Online Repository at www.jaci-inpractice.org).

The other 223 of 245 patients with a history of immediate reaction to a cephalosporin had negative SPT and IDT to both penicillins and cephalosporins. This negative skin testing included the standard panel along with at least 1 drug containing the index reaction drug's R1 side chain, when it was known. Of 223 of these patients, 139 (62%) underwent oral challenge to 250 mg penicillin VK or amoxicillin, followed by oral challenge to 250 mg cephalixin or another cephalosporin, and tolerated these challenges uneventfully, leading to delabeling of their cephalosporin allergy. A further 75 of 223 (34%) uneventfully tolerated oral challenge with penicillins but for logistical reasons have not yet not undergone oral challenge to a cephalosporin. These patients were advised it was safe to take all penicillins and advised to avoid cephalosporins pending further testing. Six of 223 (3%) have yet to undergo any oral challenge and have been advised to avoid both penicillins and cephalosporins pending further testing. There were no reactions observed during skin testing or ingestion challenges, either immediate or delayed, which were consistent with a true allergic reaction.

Delayed hypersensitivity cephalosporin labels

There were 83 patients with a history of delayed hypersensitivity to a cephalosporin; 7 of 83 (8%) had positive delayed IDT to a cephalosporin (Figure 4; Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Among 7 patients with a confirmed allergy to either cefazolin, cefoxitin, ceftriaxone, or cefepime, 2 underwent an ingestion challenge with cephalixin and both tolerated it. Representative skin test images can be

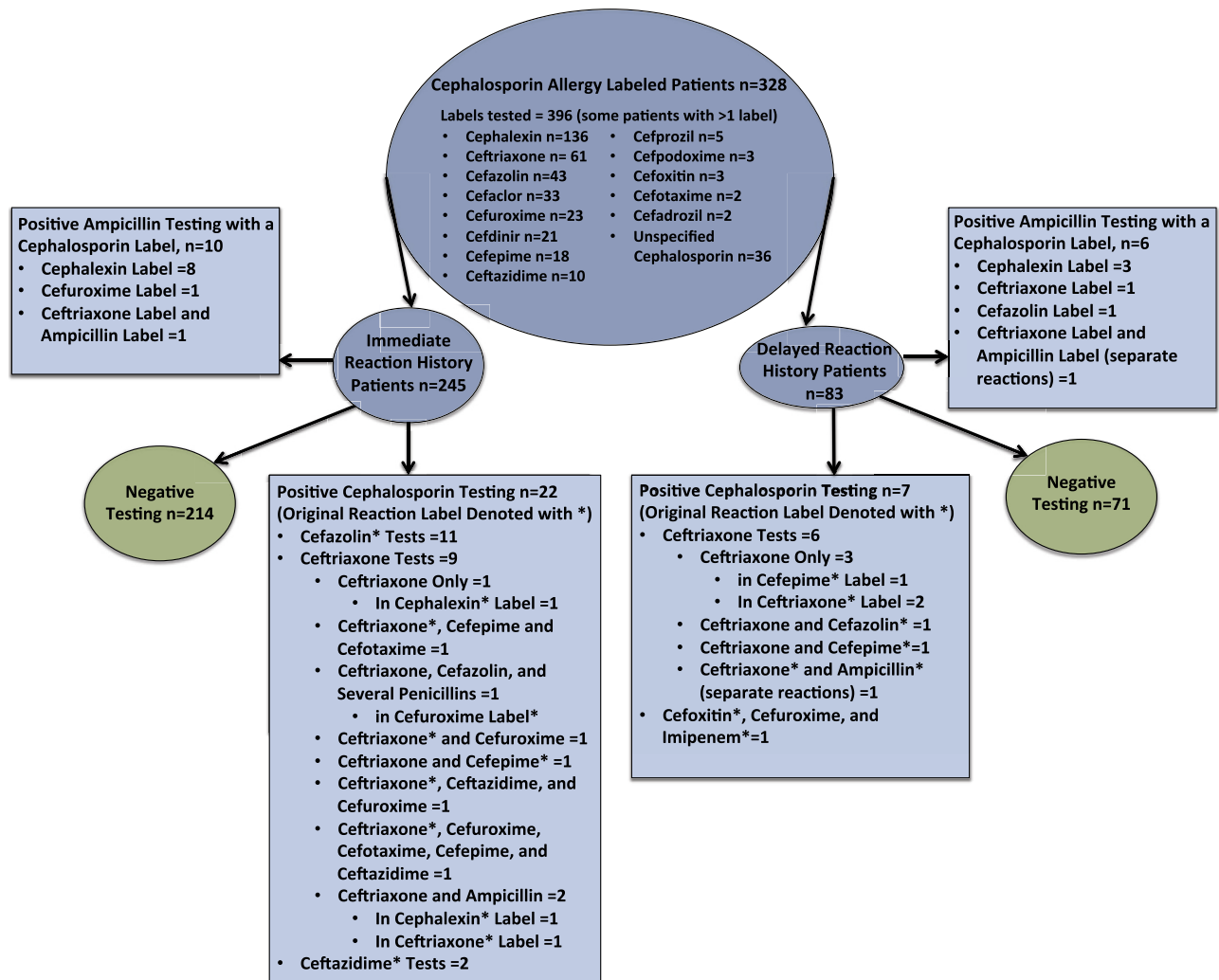


FIGURE 4. Outcomes of immediate and delayed cephalosporin testing in this cohort. For individual-level data on labels, testing, and outcomes, please see [Tables E2](#) and [E5](#) (available in this article's Online Repository at www.jaci-inpractice.org).

found in [Figure E3](#) (available in this article's Online Repository at www.jaci-inpractice.org).

Skin testing results in patients labeled allergic to aminocephalosporins

Among patients who were initially labeled as allergic to aminocephalosporins (cefaclor, cefadroxil, cephalexin, cefprozil) and tested, 11 of 174 (6%) had positive skin testing to ampicillin, all of whom had carried cephalexin allergy labels, and 2 had positive skin testing to ceftriaxone ([Figure 4](#)). Sixteen patients had a STP to ampicillin with a primary reaction history to a cephalosporin. Of these, 10 (62.5%) had an immediate history and were positive on immediate SPT or IDT, with 8 of 10 (80%) reporting a primary reaction to cephalexin (an aminocephalosporin) and 1 to cefuroxime only. Another patient had a labeled history of immediate hypersensitivity reactions to both ceftriaxone and amoxicillin, but was positive to ampicillin skin testing only, and subsequently tolerated penicillin, flucloxacillin, cephalexin, and cefuroxime on test challenge in clinic and a subsequent therapeutic regimen of ceftriaxone ([Tables E4](#) and [E5](#), available in this article's Online Repository at

www.jaci-inpractice.org). Six of 16 (37.5%) had a delayed reaction history and were positive on delayed IDT to ampicillin within 24 and 48 hours of application. Of these, 3 (60%) reported a primary reaction to cephalexin, 1 to ceftriaxone only, and 1 to cefazolin only. The final patient reported separate delayed onset reactions to amoxicillin (drug reaction with eosinophilia and systemic symptom [DRESS]) and ceftriaxone (maculopapular exanthem), with positive tests to both drugs. Of these 16 cephalosporin-labeled patients who tested positive to ampicillin, only 2 had positive skin testing to a cephalosporin. In both of these cases, the patient reported an additional ceftriaxone allergy and tested positive to ceftriaxone. Testing strategies and specific modalities employed for each case are described in [Tables E5](#) and [E6](#) (available in this article's Online Repository at www.jaci-inpractice.org).

There was notable geographic variation in positive ampicillin testing. Among all patients with ampicillin positive testing regardless of their initial penicillin or cephalosporin label, 32 of 420 (7.6%) ampicillin tests resulted positive in Melbourne versus 8 of 370 (2.2%) in Nashville, Fisher's exact test P value < .005 ([Table E3](#), available in this article's Online Repository at

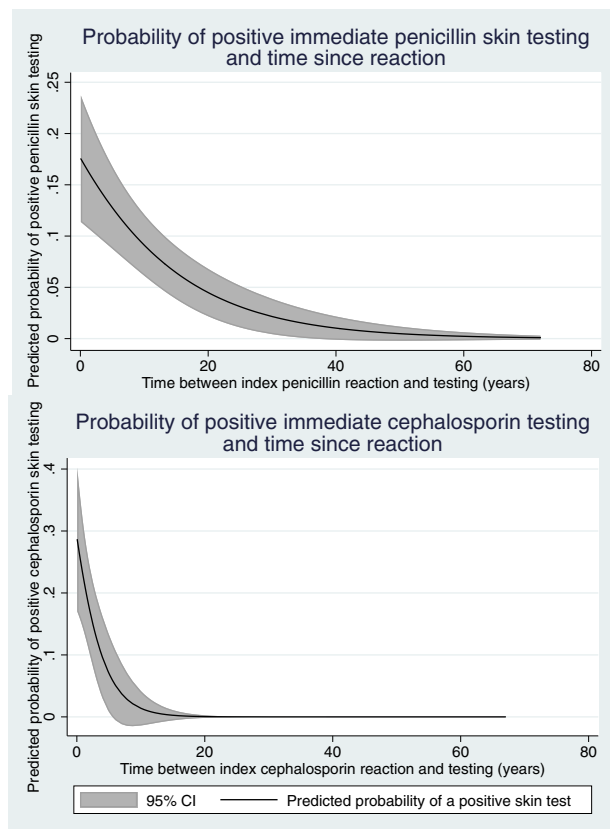


FIGURE 5. Probability of obtaining positive immediate hypersensitivity skin testing in patients with an immediate reaction history (penicillins in the top panel, cephalosporins in the bottom panel). Predicted probabilities obtained via multivariable logistic regression modeling with adjustment for age, sex, race, and site.

www.jaci-inpractice.org). Within the subgroup of cephalosporin-labeled, ampicillin-positive patients with delayed and immediate reaction histories, 14 of 16 (93%) of these were Australian cases and only 2 were from VUMC.

Results from penicillin and cephalosporin allergy challenges

In total, of 328 patients with an initial reported label of cephalosporin allergy, 305 (80%) underwent an uneventful penicillin allergy challenge and 192 (59%) underwent an uneventful cephalosporin allergy challenge, leading to delabeling of their cephalosporin allergy. Of a total of 678 amoxicillin challenges and 230 cephalosporin challenges performed, only 1 beta-lactam challenge performed during our study elicited any significant symptoms: a patient with a history of cephalixin allergy and negative skin testing was challenged with amoxicillin and developed symptoms of pruritus, which was attributed to a nonimmunological effect (Austin Case 413, [Table E5](http://www.jaci-inpractice.org), available in this article's Online Repository at www.jaci-inpractice.org) due to the absence of other clinical findings and resolution without treatment. The rest were tolerated uneventfully.

Characteristics of cefazolin and ceftriaxone positive cases

The most common STP cephalosporins in our cohort were cefazolin ([Figure E1](http://www.jaci-inpractice.org), available in this article's Online Repository at

www.jaci-inpractice.org) and ceftriaxone ([Figure E2](http://www.jaci-inpractice.org), available in this article's Online Repository at www.jaci-inpractice.org), which comprised 25 of 29 (86%) of all positive cases. Cefazolin was the most common drug to have positive immediate hypersensitivity skin testing, with 12 immediate cases observed and 1 delayed case observed. Of 43 cefazolin allergy labels tested, 30% resulted in positive testing. Ceftriaxone skin testing demonstrated 9 cases with positive immediate hypersensitivity skin testing and 6 with positive delayed hypersensitivity skin testing, making ceftriaxone the most common cephalosporin in our cohort to have a positive delayed hypersensitivity skin test. Of 61 ceftriaxone allergy labels tested, 9 (15%) resulted in positive testing, with 6 ceftriaxone positive skin tests in patients with primary labels to other cephalosporins ([Figure 4](http://www.jaci-inpractice.org); [Table E2](http://www.jaci-inpractice.org), available in this article's Online Repository at www.jaci-inpractice.org). Seven of 15 (46%) of ceftriaxone STP patients demonstrated historical or skin test–based evidence of cross-reactivity with R1-similar cephalosporins such as cefepime, cefuroxime, or ceftazidime. There were 2 cases, both from Melbourne, who did not follow the typical pattern of side-chain cross-reactivity: patient 574, who had immediate skin test positivity to cefazolin, ceftriaxone, and penicillins in the absence of dermatographism, and patient 114, with a history of a delayed exanthem to cefazolin and meropenem DRESS that had a delayed skin test response to cefazolin, ceftriaxone, and meropenem. A more extensive panel of IDT and patch testing to other beta-lactams in these cases was not done due to lack of availability of the patients to return for further testing ([Tables E2 and E3](http://www.jaci-inpractice.org), available in this article's Online Repository at www.jaci-inpractice.org).

Eleven of 11 cases who had clear isolated immediate skin test positivity to cefazolin also had clear histories of immediate reactions to cefazolin and were all negative on skin testing and oral challenge to other cephalosporins and penicillins, demonstrating the selective nature of immediate reactions to cefazolin consistent with the findings of other groups.^{13,14,19,27} Nine of 11 (82%) of these selective immediate cefazolin cases had their index reaction within the year before testing. An additional 2 cases with positive cefazolin skin testing had positive skin testing to other cephalosporins and/or beta-lactams as described above.

Predictive modeling: time since reaction

In univariate logistic regression analysis, increasing time since the original reaction in patients reporting immediate reactions was associated with decreased odds for a positive skin test to both penicillins (odds ratio [OR], 0.93 per year; 95% confidence interval [CI]: 0.89, 0.96) and cephalosporins (OR, 0.71 per year; 95% CI: 0.57, 0.90) ([Figure 5](http://www.jaci-inpractice.org)). We observed that adjustment for age, sex, race, and site did not alter these findings significantly ([Table E6](http://www.jaci-inpractice.org), available in this article's Online Repository at www.jaci-inpractice.org), except for a less significant relationship between time since reaction and penicillin testing at the Vanderbilt site. Our observed decrease in the probability of positive testing over time was consistent when stratified across both the US and Australian sites ([Table E6](http://www.jaci-inpractice.org), available in this article's Online Repository at www.jaci-inpractice.org). More details about individual STP penicillin cases can be found in [Table E5](http://www.jaci-inpractice.org) (available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

Similar to penicillins, adult patients referred with a label of cephalosporin allergy can safely have their risk of a suspected

IgE-mediated reaction or T-cell-mediated reaction assessed using a combination of skin testing and ingestion challenges. Only 1 patient with negative skin testing using our protocol had noteworthy symptoms during a challenge; challenges were otherwise well tolerated with rare reports of self-limited gastrointestinal discomfort or subjective self-resolving pruritus. In our 2-site study, only 28 of 328 (8.5%) patients referred for a labeled cephalosporin allergy had positive cephalosporin skin testing, with 22 immediate hypersensitivity and 7 delayed hypersensitivity cases detected. Immediate skin test positivity was largely driven by time since the original reaction, with 18 of 22 (81%) immediate cephalosporin STP patients having their reaction within the last year (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Cefazolin and ceftriaxone were the most common cephalosporins to test positive, which corresponded in every case but one with the suspected cephalosporin based on history, with an average time since index reaction of 0.57 years for cefazolin and 1.57 years for ceftriaxone (more delayed reactions to ceftriaxone were observed). There were no patients with a suspected false-positive immediate reaction to cephalosporins in our cohort, based on the recency and high severity of the index reactions, and our pretest causality assessment. In keeping with previous reports, 11 of 11 patients with a combination of a reported immediate reaction to cefazolin and positive skin testing to cefazolin were 100% selective to cefazolin with negative skin testing to ceftriaxone and ingestion challenges to other penicillins and cephalosporins (cephalexin) because cefazolin does not share a side chain with these drugs, a finding consistent with the reports of other groups.^{13,14,19,27}

Our data do not support the idea that patients with a history of penicillin allergy and unknown tolerance of cephalosporins should be routinely tested for cephalosporin allergy, with 419 of 452 (92.7%) of patients being negative on skin testing and oral challenge to penicillins and 452 of 452 (100%) of such patients having negative cephalosporin skin testing to cefazolin and ceftriaxone. The exception to this might be patients with recent (within last 5 years) and immediate reactions to aminopenicillins where the risk of cross-reactivity to aminocephalosporins is still significant and may be geographically driven as reinforced by our study's finding of 32 of 420 (7.6%) ampicillin positive skin tests in Melbourne versus 8 of 370 (2.2%) in Nashville despite our cohorts being of similar size. There is currently no validated strategy for skin testing aminocephalosporins that are only available as oral preparations; skin testing with a filtered preparation in at least 1 study has been shown to have low sensitivity,¹⁹ even though this has shown a high negative predictive value for other cephalosporins.^{13,17,28} Therefore, in these cases, we would recommend skin testing to parenterally available aminopenicillins and cephalosporins followed by oral challenge to cephalosporins not sharing the R1 aminocephalosporin side chain when aminopenicillin testing is positive. The flipside of this is that 16 of 328 (4.5%) patients with a history of cephalosporin allergy tested STP to ampicillin, 10 immediate and 6 delayed. Of all 16 ampicillin positive tests in patients with a CAL, 11 (69%) corresponded with an aminocephalosporin allergy history (cephalexin), suggesting that although the cross-reactivity may be low that this is a relevant strategy to pick up aminocephalosporin allergy. This phenomenon was predominantly observed in our Australian site cohort and is likely reflective of patterns reported previously in previous and Australian and European studies,^{14,17,24,29} where

cross-reactivity between aminopenicillins such as ampicillin and aminocephalosporins such as cephalexin is more frequently observed.^{13,30} In the United States, because of differences in skin testing patterns and infrequent use of ampicillin as a testing reagent as well as lack of commercially available sterile reagents to perform IDT with aminocephalosporins, there is limited information from contemporary practice on the epidemiology of aminocephalosporin allergy and true cross-reactivity between aminocephalosporins and cephalosporins such as cefazolin and ceftriaxone. Similar to our study, however, previous studies have also suggested that the aminopenicillin/aminocephalosporin pattern of sensitization is infrequent in the United States.³¹

Our study was limited by the absence of universal oral challenge for all cephalosporin tested patients and focused on testing strategies using commercially available sterile intravenous cephalosporin reagents, specifically cefazolin and ceftriaxone. We used single-dose oral challenges, which are effective to rule out anaphylaxis, but a single-dose challenge has the potential to miss delayed onset reactions. We were further limited by the absence of an oral challenge strategy to account for the ceftazidime/aztreonam R1 side chain. In cases where skin testing was negative, we delabeled patients of allergy to intravenous drugs such as ceftriaxone based on oral tolerance of identical R1-containing oral drugs such as cefpodoxime, without direct intravenous or intramuscular challenge to the primary agent. Because this was a real-world retrospective cohort study at 2 clinical sites, the return of patients to complete follow-up testing was based in part on the clinical need of the patient as well as their ability to return. Not every patient with an initial positive skin test was able to return and complete follow-up testing to every relevant cephalosporin in our protocol. All patients with positive immediate or delayed skin testing had convincing recent histories of more recent immediate or delayed reactions, and in view of this high pretest probability and the high probability of inducing a clinical reaction, we did not directly challenge the specific cephalosporins where skin testing was positive. Given the severity of the immediate or delayed clinical reaction history many of these cases and high pretest probability, they were not challenged to confirm a systemic response. Contrary to previous studies, however,³² using criteria for a positive immediate skin test of a wheal ≥ 3 mm baseline and flare ≥ 5 mm baseline we did not see any STP to cephalosporins in patients with low probability or remote histories, and whenever possible all patients went onto ingestion challenge. Therefore, both the false negative and positive rates from skin testing would be predicted to be low using clinical history and ingestion challenge as the gold standard. For patients with a history of certain severe delayed reactions (eg, DRESS and acute granulomatous exanthematous pustulosis), we did not perform alternative cephalosporin challenges even when skin or patch testing was negative to an implicated drug, but would have considered doing so in the presence of a compelling clinical need where the benefit to be gained by treatment appeared to outweigh the risk.

However, the strengths of our study are that we observed that all our cases with positive immediate or delayed skin tests to cephalosporins already carried a preexisting label of cephalosporin allergy, typically acquired within 1 year of testing 22 of 29 (76%) had side chain-specific skin testing usually related to the R1 side chain, and 82% were proven to tolerate structurally dissimilar cephalosporins and penicillins. The strength of our study also lies in the overall similarity between 2 geographically

distinct cohorts using the same testing protocols. Our findings are in keeping with previous studies that have reported loss of STP penicillin and cephalosporin allergy over time, and are limited for the time being to the risk factors that we report.³³ In addition, although previous studies have reported loss of skin test reactivity over time, they have not followed patients with ingestion challenge. A number of questions remain unanswered such as risk factors for reactions to specific cephalosporins and the likelihood of positive cephalosporin testing. In addition, although previous studies have suggested significant loss of skin test reactivity over time, these have not been paired to demonstrated loss of ingestion challenge reactivity; therefore, longitudinal follow-up of our cohort is planned and will be important. Our retrospective 2-site study demonstrated that testing was safe and no patients experienced a systemic or severe reaction from immediate or delayed IDT or patch testing. Therefore, we believe that allergist knowledge of cephalosporin side chain groupings, specific testing protocols, and time since reaction are crucial elements of cephalosporin allergy management and provide insights into the mechanisms of these important drug allergies.

CONCLUSIONS

We demonstrate that cephalosporin skin testing and ingestion challenge is a safe mechanism to both delabel patients with cephalosporin allergy and identify patients with R1 side chain selective cross-reactivity who will tolerate non-R1 side chain sharing cephalosporins and penicillins. Although cefazolin and ceftriaxone were the most common cephalosporins associated with positive testing in both the Australian and US cohorts, geographical differences appeared for selective aminopenicillin allergy presenting with aminocephalosporin cross-reactivity. Selectively positive aminopenicillin skin testing, both immediate and delayed, and the potential for cross-reactivity with aminocephalosporins such as cephalixin appear to be much more common in Australia than the United States and may reflect differing utilization of parenteral aminopenicillins such as amoxicillin and amoxicillin-clavulanate that are widely used in Europe and Australia but not available in the United States.

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FIGURE E1. These 2 patients with a history of intraoperative anaphylaxis had positive intradermal skin tests to cefazolin 1 mg/mL (labeled Cp and Ceph in these images), with negative skin testing to other penicillin reagents, ceftriaxone, and intraoperative agents. Both tolerated penicillin VK and cephalexin oral challenges (250 mg) and were given advice to selectively avoid cefazolin. Images taken at 15 minutes after application.



FIGURE E2. This patient, with a history of ceftriaxone anaphylaxis, was prick test positive to ceftriaxone, with positive intradermal testing to cefepime. He tolerated 250 mg oral challenges with amoxicillin, cephalexin, and cefuroxime, and was advised to selectively avoid ceftriaxone, cefotaxime, cefuroxime, cefpodoxime, and cefepime (shared R1). Images taken at 15 minutes after application.



FIGURE E3. This patient had a history of large B-cell lymphoma, status post autologous peripheral blood stem cell transplant (2014) and developed rigors, fevers 103.2°F, facial edema, diffuse exanthem on day 9 of cefepime/metronidazole, and on the same day as vancomycin infusion (without the previous known history of vancomycin exposure) and bone marrow engraftment. Diagnosed with DRESS due to rash, peripheral eosinophilia, elevated liver enzymes, and impaired renal function. The patient developed post-DRESS autoimmune thyroiditis (Graves' disease). Delayed intradermal skin tests were negative to all of the received agents and standard test agents except for cefepime 10 mg/mL. Sequential images taken of the same skin test at 24 hours (left panel), 48 hours (middle panel), and 8 days (right panel) after application. She was advised to avoid cefepime and shared R1 agents. *DRESS*, Drug reaction with eosinophilia and systemic symptom.

TABLE E1. Concentrations of standard panel and other beta-lactams used in this report

Drug	Skin prick	Immediate intradermal	Delayed intradermal	Oral challenge
Controls				
Histamine	6 mg/mL	6 mg/mL		
Saline	Undiluted	Undiluted	Undiluted	
Standard testing panel				
Pre-Pen or Diater	Undiluted	Undiluted	Undiluted	
Minor Determinant Mix	Undiluted	1:100	1:100	
Penicillin G	10,000 IU/mL	1000 and 10,000 IU/mL	10,000 IU/mL	
Penicillin VK				250 mg
Ampicillin	25 mg/mL	25 mg/mL	25 mg/mL	
Amoxicillin				250 mg
Cephalexin				250 mg
Cefazolin	1 mg/mL	1 mg/mL	10 mg/mL	
Ceftriaxone	2.5 mg/mL	2.5 mg/mL	10 mg/mL	
Other penicillins				
Nafcillin	0.025 mg/mL	0.025 mg/mL	0.025 mg/mL	
Flucloxacillin	2 mg/mL	2 mg/mL	2 mg/mL	
Ticarcillin	20 mg/mL	20 mg/mL	20 mg/mL	
Piperacillin-tazobactam	4.5 mg/mL	4.5 mg/mL	4.5 mg/mL	
Other cephalosporins				
Cefepime (shared R1 with ceftriaxone)	1 mg/mL	1 mg/mL	10 mg/mL	
Cefpodoxime (shared R1 with ceftriaxone)				100 mg
Cefuroxime (shares methoxyimino portion of R1 side chain with ceftriaxone)	10 mg/mL	10 mg/mL	10 mg/mL	250 mg
Cefoxitin (shares R2 with cefuroxime)	1 mg/mL	1 mg/mL	10 mg/mL	
Ceftaroline	1 mg/mL	1 mg/mL	10 mg/mL	
Ceftazidime	1 mg/mL	1 mg/mL	10 mg/mL	
Monobactams				
Aztreonam (shared R1 with ceftazidime)	1 mg/mL	1 mg/mL	10 mg/mL	
Carbapenems				
Imipenem	0.5 mg/mL	0.5 mg/mL	0.5 mg/mL	
Meropenem	2.5 mg/mL	2.5 mg/mL	2.5 mg/mL	

TABLE E2. Outcomes of cephalosporin label testing

	Total	VUMC	Austin
Total cephalosporin allergy labels tested (immediate or delayed history)	328	206	122
Immediate cephalosporin labels tested	245	172	73
Positive immediate cephalosporin skin tests	22 (8.9%)	10 (5.8%)	12 (16.4%)
Cefazolin only	11	5	6
Ceftriaxone only	2		2
Ceftriaxone and cefazolin	1		1
Ceftriaxone and cefuroxime	1	1	
Ceftriaxone and cefepime	1	1	
Ceftriaxone, cefepime, and cefotaxime	1	1	
Ceftriaxone, cefuroxime, and ceftazidime	1	1	
Ceftriaxone, cefepime, cefotaxime, cefuroxime, and ceftazidime	1	1	
Ceftazidime	2	2	
Ceftriaxone and ampicillin	1		1
Delayed cephalosporin labels tested	83	34	49
Positive delayed cephalosporin skin tests	7 (7.2%)	3 (5.9%)	4 (8.1%)
Ceftriaxone only	3		3
Ceftriaxone and cefazolin	1		1
Ceftriaxone and cefepime	1	1	
Cefoxitin, cefuroxime, and imipenem	1	1	
Ceftriaxone and ampicillin (2 separate reactions)	1	1	

VUMC, Vanderbilt University Medical Center.

TABLE E3. Positive cephalosporin skin tests, excluding aminoccephalosporin testing with ampicillin

Case	Age	Sex	Race	Original reaction	Skin test positive to which drug*	Time since index reaction (y)	Cephalosporin challenge tolerance	Conclusion
Austin—immediate cephalosporins								
117	34	Female	White	Anaphylaxis to cefazolin	Cefazolin	0.87	Cephalexin	Selective avoidance of cefazolin
615	30	Male	White	Anaphylaxis to cefazolin	Cefazolin	0.37	Cephalexin	Selective avoidance of cefazolin
236	38	Female	White	Anaphylaxis to cefazolin	Cefazolin	0.27	Cefuroxime	Selective avoidance of cefazolin
146	39	Female	White	Anaphylaxis to cefazolin	Cefazolin	1.36	Cephalexin	Selective avoidance of cefazolin
52	62	Female	White	Anaphylaxis to cefazolin	Cefazolin	0.49	Cephalexin	Selective avoidance of cefazolin
440	86	Male	White	Anaphylaxis to cefazolin	Cefazolin	0.06	Cephalexin	Selective avoidance of cefazolin
457	78	Female	White	Anaphylaxis to cephalexin, delayed rash to flucloxacillin	Ceftriaxone-immediate Flucloxacillin-delayed	0.08	Not done	Continued avoidance of all cephalosporins/penicillins in the absence of challenge
376	54	Female	White	Anaphylaxis to cephalexin	Ceftriaxone, ampicillin	1.07	Not done	Continued avoidance of all cephalosporins
53	58	Male	White	Anaphylaxis to ceftriaxone	Ceftriaxone, ampicillin	0.95	Not done	Continued avoidance of all cephalosporins in the absence of challenge
574	70	Male	White	Anaphylaxis to cefuroxime	Ceftriaxone, cefazolin, ampicillin, penicillin 10,000, flucloxacillin	1.12	Not done	Continued avoidance of all cephalosporins in the absence of challenge
Austin—delayed cephalosporins								
265	62	Male	White	Diffuse MPE to cefepime	Ceftriaxone	0.36	Cephalexin	Selective avoidance of ceftriaxone, cefepime, cefotaxime Cefpodoxime (identical R1) and cefuroxime, ceftazidime (nonidentical but cross-reactive methoxyimino)
358	69	Male	White	Fixed drug eruption to ceftriaxone	Ceftriaxone	0.73	Cephalexin	Selective avoidance of ceftriaxone, cefepime, cefotaxime Cefpodoxime (identical R1) and cefuroxime, ceftazidime (nonidentical but cross-reactive methoxyimino)
51	72	Female	White	DRESS syndrome to ceftriaxone	Ceftriaxone	0.18	Not done	Continued avoidance of all cephalosporins in the absence of challenge
114	74	Male	White	MPE to cefazolin, DRESS to meropenem	Cefazolin, ceftriaxone, meropenem	0.75	Not done	Continued avoidance of all cephalosporins and meropenem
VUMC—immediate cephalosporins								
12	41	Female	Asian	Anaphylaxis to cefazolin	Cefazolin	0.66	Cephalexin	Selective avoidance of cefazolin

2	70	Female	White	Anaphylaxis to cefazolin	Cefazolin	0.08	Cephalexin	Selective avoidance of cefazolin
11	71	Female	White	Anaphylaxis to cefazolin	Cefazolin	0.08	Cephalexin	Selective avoidance of cefazolin
8	74	Male	White	Anaphylaxis to cefazolin	Cefazolin	0.08	Cephalexin	Selective avoidance of cefazolin
3	80	Female	White	Anaphylaxis to cefazolin	Cefazolin	1.17	Cephalexin	Selective avoidance of cefazolin
9	21	Female	White	Anaphylaxis to cefepime	Cefepime, ceftriaxone	1	Cephalexin	Selective avoidance of ceftriaxone, cefepime, cefotaxime Cefpodoxime (identical R1) and cefuroxime, ceftazidime (nonidentical but cross-reactive methoxyimino)
10	46	Female	White	Anaphylaxis to ceftriaxone	Ceftriaxone, cefepime, cefuroxime, cefotaxime, ceftazidime	0.25	Cephalexin	Selective avoidance of ceftriaxone, cefepime, cefotaxime Cefpodoxime (identical R1) and cefuroxime, ceftazidime (nonidentical but cross-reactive methoxyimino)
7	48	Female	White	Anaphylaxis to ceftriaxone	Ceftriaxone, cefepime, cefotaxime	0.58	Cephalexin	Selective avoidance of ceftriaxone, cefepime, cefotaxime Cefpodoxime (identical R1) and cefuroxime, ceftazidime (nonidentical but cross-reactive methoxyimino)
379	38	Male	Black	Anaphylaxis to ceftriaxone	Ceftriaxone, cefuroxime	10	Cephalexin	Selective avoidance of ceftriaxone, cefepime, cefotaxime Cefpodoxime (identical R1) and cefuroxime, ceftazidime (nonidentical but cross-reactive methoxyimino)
47	51	Male	White	Anaphylaxis to ceftazidime	Ceftazidime	6	Cephalexin	Selective avoidance of ceftazidime and aztreonam (shared R1)
4	35	Female	White	Anaphylaxis to ceftazidime	Ceftazidime	0.25	Cephalexin	Selective avoidance of ceftazidime and aztreonam (shared R1)
5	40	Female	White	Anaphylaxis to ceftriaxone	Ceftriaxone, ceftazidime, cefuroxime	1	Cephalexin	Selective avoidance of ceftriaxone, cefepime, cefotaxime Cefpodoxime (identical R1) and cefuroxime, ceftazidime (nonidentical but cross-reactive methoxyimino)
VUMC—delayed cephalosporins								
1	45	Female	Asian	DRESS syndrome to cefepime	Ceftriaxone, cefepime	2	Not done	Continued avoidance of all cephalosporins in the absence of challenge

(continued)

TABLE E3. (Continued)

Case	Age	Sex	Race	Original reaction	Skin test positive to which drug*	Time since index reaction (y)	Cephalosporin challenge tolerance	Conclusion
6	73	Female	White	DRESS syndrome to cefoxitin with coadministered imipenem	Cefoxitin, cefuroxime, imipenem	0.25	Not done	Continued avoidance of all cephalosporins and imipenem in the absence of challenge
27	25	Male	White	Delayed ceftriaxone MPE, and a separate delayed amoxicillin clavulanate DRESS	Ampicillin Ceftriaxone	0.17	Not done	Continued avoidance of all cephalosporins in the absence of challenge

DRESS, Drug reaction with eosinophilia and systemic symptom; MPE, maculopapular exanthema; VUMC, Vanderbilt University Medical Center.

*Standard skin test panel was used in every patient, and these drugs were negative if not listed.

TABLE E4. Outcomes of penicillin allergy label testing

Total penicillin allergy labels tested (immediate or delayed history)	692	319	373
Immediate penicillin labels tested	530	288	242
Positive immediate penicillin tests	35 (6.6%)	6 (2.1%)	29 (12.0%)
Ampicillin only	14	2	12
Flucloxacillin only	1		1
PPL only	4	1	3
Penicillin G only	1	1	
Piperacillin/tazobactam only	1		1
Ampicillin and penicillin G	5	2	3
Ampicillin and PPL	3		3
Ampicillin and flucloxacillin	1		1
PPL and MDM	2		2
PPL and penicillin G	1		1
Ampicillin, penicillin G, and flucloxacillin	1		1
Ampicillin, PPL, and MDM	1		1
Ampicillin and ceftriaxone	2		2
Delayed penicillin labels tested	162	31	131
Positive delayed penicillin tests	20 (12.3%)	6 (19.3%)	14 (10.7%)
Ampicillin only	5	4	1
Flucloxacillin only	3		3
Piperacillin/tazobactam only	2	2	
Ampicillin and penicillin G	2		2
Ampicillin and PPL	1		1
Ampicillin and flucloxacillin	1		1
Ampicillin and piperacillin/tazobactam	3		3
Ampicillin, penicillin G, and flucloxacillin	1		1
Ampicillin, penicillin G, and PPL	1		1
Ampicillin, penicillin G, and piperacillin/tazobactam	1		1
Ampicillin and ceftriaxone (2 separate reactions)	1	1	

MDM, Minor determinant mixture; PPL, penicilloyl-polylysine.

TABLE E5. Penicillin skin test positive patients, with original labels and subsequent challenge tolerance

Case	Age	Sex	Race	Pretest penicillin labels, type, and drug	Pretest cephalosporin labels, type, and drug	Skin test positive to which drug (negative otherwise)	Challenges and tolerance	Conclusion
Austin: of positive penicillin tests 32/43 (75%) positive for an aminopenicillin								
9	63	M	W	Delayed flucloxacillin	Delayed cefepime	Delayed flucloxacillin	Penicillin VK, amoxicillin, cephalexin	Selective avoidance of flucloxacillin
11	70	M	W	Immediate amoxicillin		Immediate ampicillin	Not done	Continued avoidance of all penicillins and aminocephalosporins
29	36	F	W	Immediate amoxicillin/clavulanate		Immediate ampicillin	Penicillin VK, cefuroxime	Selective avoidance of aminopenicillins and aminocephalosporins
32	60	F	W		Immediate cephalexin	Immediate ampicillin, penicillin 10,000	Not done	Avoidance of all penicillins and cephalosporins in the absence of challenge
37	18	F	W		Immediate cephalexin	Immediate ampicillin, penicillin 10,000	Cefuroxime	Avoidance of all penicillins and aminocephalosporins
53	58	M	W		Immediate ceftriaxone	Immediate ampicillin, ceftriaxone	Penicillin VK, flucloxacillin	Selective avoidance of aminopenicillins and avoidance of all cephalosporins in the absence of challenge
55	65	M	W	Immediate amoxicillin	Immediate ceftriaxone	Immediate ampicillin	Penicillin VK, cephalexin, cefuroxime, flucloxacillin treatment Ceftriaxone treatment tolerated	Selective avoidance of aminopenicillins
56	46	F	W	Unknown amoxicillin		Immediate ampicillin, flucloxacillin	Penicillin VK, cephalexin	Selective avoidance of aminopenicillins
63	61	M	W	Immediate penicillin		Immediate ampicillin, PPL	Cephalexin	Continued avoidance of all penicillins
74	71	M	A	Immediate amoxicillin/clavulanate		Immediate ampicillin	Penicillin VK	Selective avoidance of aminopenicillins and aminocephalosporins
77	64	F	W		Delayed cephalexin MPE	Delayed ampicillin, penicillin 1000, PPL	Cefuroxime	Continued avoidance of all penicillins and aminocephalosporins
83	38	F	W	Immediate amoxicillin/clavulanate		Immediate ampicillin	Penicillin VK	Selective avoidance of aminopenicillins and aminocephalosporins

95	43	F	W	Immediate penicillin		Immediate PPL	Not done	Continued avoidance of all penicillins
102	62	M	W	Delayed piperacillin/ tazobactam DRESS		Delayed ampicillin, piperacillin- tazobactam	Not done	Continued avoidance of all penicillins and tazobactam
105	79	M	W	Immediate piperacillin/ tazobactam		Immediate piperacillin- tazobactam	Penicillin VK, amoxicillin, cephalexin	Selective avoidance of piperacillin/ tazobactam
113	63	F	A	Immediate amoxicillin/ clavulanate		Immediate ampicillin, flucloxacillin	Cefuroxime	Continued avoidance of all penicillins
116	57	M	W	Immediate amoxicillin	Immediate ceftriaxone	Immediate ampicillin	Cephalexin	Continued avoidance of all penicillins
129	55	M	W	Immediate amoxicillin		Immediate PPL, penicillin G	Not done	Continued avoidance of all penicillins
138	73	F	W	Immediate penicillin		Immediate PPL, MDM	Cefuroxime	Continued avoidance of all penicillins
144	38	F	W	Delayed piperacillin/ tazobactam DRESS		Delayed ampicillin, penicillin neat, 1000, 10,000, piperacillin- tazobactam	Cefuroxime	Continued avoidance of all penicillins and tazobactam
154	52	M	W		Immediate cephalexin	Immediate ampicillin	Penicillin VK, cefuroxime	Selective avoidance of aminopenicillins and aminocephalosporins
172	59	F	W	Delayed amoxicillin DRESS		Immediate ampicillin	Not done	Continued avoidance of all penicillins and aminocephalosporins
185	40	F	W	Immediate amoxicillin		Immediate PPL, MDM	Cephalexin cefuroxime	Continued avoidance of all penicillins
212	66	F	W	Immediate amoxicillin/ clavulanate		Immediate ampicillin, PPL	Not done	Continued avoidance of all penicillins
217	91	F	W	Immediate penicillin		Delayed ampicillin, penicillin 10,000	Penicillin VK	Selective avoidance of aminopenicillins
218	30	M	W	Delayed amoxicillin MPE		Delayed ampicillin, penicillin 10,000	Penicillin VK, ampicillin, cefuroxime	No avoidance needed
242	75	M	W	Delayed piperacillin/ tazobactam DRESS		Delayed ampicillin, piperacillin- tazobactam	Cephalexin	Continued avoidance of all penicillins and tazobactam
250	54	F	W	Immediate penicillin		Immediate PPL	Cephalexin	Continued avoidance of all penicillins
255	72	F	W	Immediate penicillin		Immediate ampicillin, PPL	Cefuroxime	Continued avoidance of all penicillins
258	61	F	W	Immediate amoxicillin	Immediate cephalexin	Immediate PPL	Cephalexin cefuroxime	Continued avoidance of all penicillins

(continued)

TABLE E5. (Continued)

Case	Age	Sex	Race	Pretest penicillin labels, type, and drug	Pretest cephalosporin labels, type, and drug	Skin test positive to which drug (negative otherwise)	Challenges and tolerance	Conclusion
262	67	F	W	Delayed flucloxacillin MPE		Delayed flucloxacillin	Penicillin VK, cephalixin	Selective avoidance of flucloxacillin
274	68	M	W	Immediate amoxicillin		Immediate ampicillin	Penicillin VK	Selective avoidance of aminopenicillins and aminocephalosporins
308	58	M	W	Delayed MPE implicating augmenting, followed by MPE implicating piperacillin-tazobactam vs ceftriaxone	Delayed piperacillin-tazobactam vs ceftriaxone MPE	Delayed ampicillin	Cefuroxime	Selective avoidance of all penicillins and aminocephalosporins
333	40	M	W	Immediate flucloxacillin		Immediate flucloxacillin	Penicillin VK	Selective avoidance of flucloxacillin
376	54	F	W		Immediate cephalixin	Immediate ampicillin, ceftriaxone	Penicillin VK	Selective avoidance of aminopenicillins and all cephalosporins
380	76	M	W		Immediate cephalixin	Immediate ampicillin	Cefuroxime, flucloxacillin treatment	Selective avoidance of aminopenicillins and aminocephalosporins
413	53	F	W		Immediate cephalixin	Positive amoxicillin oral challenge, negative immediate skin testing	Penicillin VK	Selective avoidance of aminopenicillins and aminocephalosporins
439	74	F	W	Delayed flucloxacillin DRESS syndrome	Delayed cephalixin MPE	Delayed ampicillin, flucloxacillin, penicillin, penicillin 1000, penicillin 10,000	Not done	Continued avoidance of all penicillins and cephalosporins
442	67	F	W	Immediate amoxicillin		Immediate ampicillin	Penicillin VK amoxicillin	No avoidance needed
457	78	F	W	Delayed unknown penicillin	Immediate cephalixin	Flucloxacillin—delayed Ceftriaxone—immediate	Not done	Continued avoidance of all penicillins and cephalosporins
459	52	M	W		Immediate cephalixin	Immediate ampicillin	Penicillin VK, cefuroxime	Selective avoidance of aminopenicillins and aminocephalosporins
504	52	F	W	Immediate penicillin	Delayed cefazolin MPE	Immediate ampicillin, penicillin 10,000	Cephalixin	Continued avoidance of all penicillins

506	55	M	W	Delayed piperacillin tazobactam MPE		Delayed ampicillin, tazobactam	Cephalexin	Continued avoidance of all penicillins and tazobactam
574	70	M	W	Immediate penicillin	Immediate cefuroxime	Immediate ceftriaxone, cefazolin, ampicillin, penicillin 10,000, flucloxacillin	Not done	Continued avoidance of all penicillins and cephalosporins
VUMC: of positive penicillin tests 8/12 (75%) positive for an aminopenicillin								
24	40	F	W		Delayed cephalexin AGEP after a spider bite	Positive ampicillin delayed IDT and negative cephalexin patch test	Not done	Selective avoidance of aminopenicillins and aminocephalosporins spider bite considered potentially causal
27	25	M	W	Delayed amoxicillin/ clavulanate DRESS	Separate delayed ceftriaxone MPE	Delayed ampicillin/ ceftriaxone	Not done	Continued avoidance of penicillins and cephalosporins in the absence of challenge
49	86	F	W	Immediate penicillin	Immediate cefuroxime, cefdinir	Immediate penicillin G, Pre-pen	Cephalexin	Continued avoidance of all penicillins
130	64	F	W	Delayed penicillin/ amoxicillin MPE		Delayed ampicillin IDT and patch tests positive	Penicillin VK	Selective avoidance of aminopenicillins and aminocephalosporins
216	23	M	O	Immediate amoxicillin		Immediate ampicillin	Not done	Selective avoidance of aminopenicillins
219	70	F	W	Immediate penicillin		Immediate ampicillin	Penicillin VK, cephalexin	Selective avoidance of aminopenicillins
235	34	F	W	Immediate ampicillin sulbactam		Immediate ampicillin, penicillin	Not done	Selective avoidance of aminopenicillins and aminocephalosporins
299	66	F	W	Immediate amoxicillin		Immediate PPL	Amoxicillin	Continued avoidance of penicillin VK
340	57	F	W	Delayed onset AGEF to piperacillin/ tazobactam		Delayed piperacillin/ tazobactam	Penicillin VK	Selective avoidance of piperacillin/ tazobactam
341	74	M	W	Delayed amoxicillin clavulanate MPE		Delayed ampicillin IDT positive and positive patch test to ampicillin and amoxicillin, negative to cephalexin	Not done	Selective avoidance of aminopenicillins and aminocephalosporins

(continued)

TABLE E5. (Continued)

Case	Age	Sex	Race	Pretest penicillin labels, type, and drug	Pretest cephalosporin labels, type, and drug	Skin test positive to which drug (negative otherwise)	Challenges and tolerance	Conclusion
344	57	F	W	Delayed desquamating rash to piperacillin tazobactam		Delayed piperacillin/tazobactam	Penicillin VK and amoxicillin	Selective avoidance of piperacillin/tazobactam
378	33	F	W	Immediate amoxicillin		Immediate ampicillin, penicillin 10,000	Cefuroxime	Avoidance of penicillins, aminopenicillins, and aminocephalosporins

AGEP, Acute granulomatous exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptom; IDT, intradermal test; MPE, maculopapular exanthema; PPL, penicilloyl-polylysine; VUMC, Vanderbilt University Medical Center.

TABLE E6. Time since initial reaction and the odds of a positive immediate penicillin or cephalosporin skin test**Odds of positive immediate hypersensitivity penicillin skin testing in all immediate penicillin history patients and the passage of time: OR represents a 1 year increase**

	Vanderbilt (n = 279)	Austin (n = 148)	Combined (n = 427)
Unadjusted odds ratio (95% CI)	0.97 (0.91, 1.02)	0.92 (0.87, 0.97)	0.93 (0.90, 0.96)
Adjusted odds ratio* (95% CI)	0.98 (0.90, 1.03)	0.92 (0.87, 0.97)	0.93 (0.90, 0.96)

Odds of positive immediate hypersensitivity cephalosporin skin testing and the passage of time: OR represents a 1 year increase

	Vanderbilt (n = 160)	Austin (n = 55)	Combined (n = 217)
Unadjusted odds ratio (95% CI)	0.78 (0.65, 0.96)	0.31 (0.09, 1.06)	0.71 (0.57, 0.90)
Adjusted odds ratio* (95% CI)	0.78 (0.64, 0.95)	0.32 (0.09, 1.12)	0.71 (0.56, 0.90)

CI, Confidence interval; OR, odds ratio.

*Adjusted for patient age, sex, race in single site analysis, adjusted for age, sex, race, and site in combined site analysis.