

Retrospective stratification of cephalosporin allergy label risk using validated penicillin allergy frameworks

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Clinical Implications

A validated history-based risk stratification approach to penicillin allergy labels is applicable to cephalosporin labels, with an important caveat that cephalosporins administered intravenously are considered higher risk.

Approximately 1% to 2% of the general population reports cephalosporin allergy labels (CALs).¹ Like penicillin allergy labels (PALs), CALs limit delivery of care because cephalosporins are considered first-line antibiotics for many infections.² About 8% of CALs correlate with positive testing results suggesting true allergy; cefazolin and ceftriaxone are the most common culprit drugs associated with positive testing result.¹ Stone et al¹ described testing strategies for evaluating cephalosporin allergies, in particular, the importance of structural similarities in R side chains and time since the index reaction. Increasing time since the initial reaction is associated with decreased odds for a positive skin test result for PALs and CALs.¹ Current literature has explored risk stratification of PALs and described successful delabeling of low-risk labels via oral challenge. However, data on risk stratification of CALs and the potential implications on delabeling efforts are limited.

We aimed to validate whether a history-based risk criteria used for PALs is applicable to CALs, or whether there are additional prognostic features that require consideration.

From 2014 to 2019, a total of 322 patients with a total of 384 CALs were evaluated in our outpatient drug allergy clinic. To be included in our analysis, we required a drug allergy evaluation with completion of cephalosporin allergy skin testing or a direct oral challenge. We also defined a complete cephalosporin allergy evaluation as (1) a patient-provided history of the index reaction to cephalosporin; (2) skin testing using a standardized protocol¹; (3) challenges/tolerance as appropriate, if skin testing result was negative¹; and (4) label removal, or label confirmation, following positive allergy testing results. Subsequent chart review was performed on all eligible patients. Each CAL was categorized into 1 of 3 risk groups using the history-based risk-stratification criteria validated for PALs by Stone et al.³ When the history-based risk-stratification criteria are used for PALs, 60% to 70% of penicillin-labeled patients are classified as low risk.⁴ In addition, these criteria have been shown retrospectively and prospectively to have a negative predictive value (NPV) greater than 99% for any allergic symptoms after an amoxicillin challenge.^{3,5} The outcomes of allergy testing were compared with the history-based risk criteria to estimate the NPV for a positive

cephalosporin allergy skin test result and/or oral challenge among low-risk CAL patients.

As seen in Table 1, 288 of 322 (89.4%) patients with a total of 344 of 384 (89.6%) CALs underwent a drug allergy evaluation with completion of skin testing or a direct oral challenge, and were selected as our analysis set. Forty-nine of 288 (17.0%) patients had more than 1 cephalosporin label at the time of evaluation. Two hundred twenty-six of 288 (78.5%) were female, and the median age was 57 years. The most common cephalosporin labels were cephalexin (109 of 344 [31.7%]) and ceftriaxone (47 of 344 [13.7%]). Cephalosporins that share an identical or similar R1 side chain to cephalexin, known as aminocephalosporins, include cephalexin (109 of 344 [31.7%]), cefaclor (42 of 344 [12.2%]), cefprozil (5 of 344 [1.5%]), and cefadroxil (3 of 344 [0.9%]), which totaled 46.2% (159 of 344) of the labels. The median time between index reaction and testing was 5.14 years.

Twenty-three of 288 (8.0%) patients had positive testing result on either immediate skin testing, delayed skin testing, patch testing, or oral challenge. In terms of challenging the label that was reported, 21 patients had positive skin or patch testing result and were not challenged to their index agent. A total of 222 of 288 (77.1%) patients had negative testing result and were challenged. A total of 220 of 222 (99.1%) oral challenges were tolerated, leading to label removal, with 2 failures. Fourteen of 288 (4.9%) patients had negative skin testing results and were delabeled afterward due to reported tolerance of a relevant cephalosporin since their index reaction. Sixteen of 288 (5.6%) patients with negative skin testing result did not undergo oral challenge initially, but subsequently tolerated a cephalosporin treatment, which would trigger delabeling. Therefore, 273 of 288 (94.8%) patients included for analysis had a complete cephalosporin allergy evaluation up to the level of either known tolerance or positive testing. Only 15 of 288 (5.2%) included patients had complete, negative skin testing result and unknown tolerance of a challenge or treatment.

We next performed univariate logistic regression at the level of the cephalosporin allergy label, to ascertain the relationship between the following variables and the outcome of positive testing: (1) history-based risk category; (2) whether the cephalosporin label was an intravenous (IV) cephalosporin; (3) time since reaction; (4) patient age; (5) sex; (6) race; and (7) recollection of reaction onset in relationship to dose administration. All variables were selected a priori as possible predictors of the outcome of any positive testing result. After univariate analysis, multivariable analysis was performed with the same variables, except for time since reaction, because this variable was included in the risk stratification scheme for categorizing low risk. A non-low-risk history category or a reaction to an IV cephalosporin was significantly associated with increased risk of positive cephalosporin testing result on both univariate and multivariable logistic regression (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Non-White race was also significantly associated with increased probability of positive testing result on multivariable regression after adjustment for the other factors.

TABLE I. Characteristics of cephalosporin allergy labeled cohort tested

Patient characteristics (n = 288)	N (%) or median (IQR)
Age (y)	57 (41-68)
Female sex	226 (78.5)
Self-reported race	
American Indian/Alaska Native	1 (0.4)
Asian	4 (1.4)
Black	15 (5.2)
White	260 (90.3)
Unknown	8 (2.8)
No. of different cephalosporin labels per patient	
1	239 (83.0)
>1	49 (17.0)
CALs (n = 344)	
Cephalexin*	109 (31.7)
Ceftriaxone†	47 (13.7)
Cefaclor*	42 (12.2)
Cefuroxime	28 (8.1)
Cefdinir	25 (7.3)
Cefazolin	25 (7.3)
Cefepime†	21 (6.1)
Unknown cephalosporin	15 (4.4)
Ceftazidime	10 (2.9)
Cefprozil*	5 (1.5)
Ceftaroline	5 (1.5)
Cefadroxil*	3 (0.9)
Cefoxitin	3 (0.9)
Cefixime	2 (0.6)
Cefpodoxime†	2 (0.6)
Cefamandole	1 (0.3)
Cefotaxime†	1 (0.3)
Characteristics of skin testing outcomes	
Time between index reaction and testing (y) (available in n = 245)	5.14 (0.88-20.12)
Total cephalosporin skin tests (prick and/or intradermal) performed (n = 288 patients)	282 (97.9)
Negative	262
Positive	20
Patients evaluated by oral challenge only, without skin testing	6 (2.0)
Characteristics of challenge/tolerance outcomes (n = 288)	
Total oral cephalosporin challenges performed	222 (77.1)
Negative (tolerance)	220
Positive	2
Patients delabeled after negative skin testing result due to known tolerance of a relevant cephalosporin	14 (4.9)

(continued)

TABLE I. (Continued)

Patient characteristics (n = 288)	N (%) or median (IQR)
Patients had negative skin testing result, did not do challenge, but tolerated a subsequent cephalosporin treatment	16 (5.6)
Patients with challenge to index agent not done due to positive skin/patch testing result	21 (7.3)
Patients had negative skin testing result, but tolerance of challenge or treatment unknown	15 (5.2)
Characteristics of positive testing outcomes	
Positive testing result of any kind (immediate n = 18, delayed n = 2, patch n = 1, oral challenge n = 2)	23
Time between reaction and testing in those who skin tested positive (y) (available n = 20)	0.36 (0.12-1.1)
Positive cephalosporin skin test results	20
Immediate	18
Delayed	2
Patch test results positive	1
Cephalexin	1 of 2 patch tests performed—AGEP
Positive oral challenges after negative skin testing results (symptoms during challenge)	2
Cephalexin label (itching and hives)	1
Cefuroxime label (intense itching only)	1
Proportion of labels that were deemed positive after testing/evaluation	
Cefoxitin	1 of 3 (33)
Ceftazidime	3 of 10 (30)
Cefazolin	5 of 25 (20)
Ceftriaxone†	7 of 47 (14.9)
Cefepime†	2 of 21 (9.5)
Cefuroxime	2 of 28 (7.1)
Unknown cephalosporin	1 of 15 (6.7)
Cephalexin*	2 of 109 (1.8)
Other cephalosporin	0 of 86 (0)

*Cephalosporins that share an identical or similar R1 side chain to cephalexin (aminocephalosporins: cephalexin, cefaclor, cefprozil, cefadroxil).

†Cephalosporins that share an identical or similar R1 side chain to ceftriaxone (ceftriaxone, cefepime, cefpodoxime, cefotaxime).

When applying the history-based penicillin risk criteria in Stone et al,³ 204 of 344 (59.4%) cephalosporin labels were categorized as low risk by index reaction history. Only 3 of 204 (1.5%) low-risk CALs tested positive on allergy testing: 1 on immediate skin testing to ceftazidime with a history of

Low risk	High risk	Highest risk
Cephalosporin reaction history - Isolated urticaria more than 5 years ago - Self-limited cutaneous rash at any point in the past without organ involvement or signs of a severe delayed rash - Gastrointestinal symptoms only - Remote childhood reaction with limited details - Family history of cephalosporin allergy only - Avoidant from fear of allergy only - Known tolerance of a cephalosporin since the original reaction occurred - Other nonallergy symptoms Cephalosporin route of administration - Administered orally	Cephalosporin reaction history - Anaphylaxis within the past 5 years - Within 1 hour of cephalosporin administration, the patient developed: - Diffuse hives - Angioedema - Shortness of breath - Wheezing and/or coughing - Hypotension - Weak pulse - Loss of consciousness - Diarrhea and/or vomiting Cephalosporin route of administration - Administered intravenously	Cephalosporin reaction history - Stevens-Johnson syndrome - Toxic epidermal necrolysis - Drug reaction with eosinophilia and systemic symptoms - Acute generalized exanthematous pustulosis - Serum sickness - Immune-mediated kidney injury - Immune-mediated liver injury - Development of severe delayed symptoms - skin or mucosal sloughing - mucosal ulcerations Cephalosporin route of administration - Administered intravenously

FIGURE 1. History-based risk stratification criteria of CALs. *DRESS*, Drug reaction with eosinophilia and systemic symptoms.

delayed-onset urticaria to ceftazidime, 1 on immediate skin testing to ceftriaxone with a history of poorly-recalled rash to ceftriaxone, and 1 during oral challenge to cefuroxime (diffuse pruritus) with a history of rash to cefuroxime with negative immediate skin testing result to all cephalosporins, including cefuroxime. Therefore, the NPV of low-risk CAL history was 201 of 204 (98.5%; 95% CI, 95.8%-99.7%).

We next applied an additional criterion to exclude any patients who reacted to IV cephalosporins to a modified low-risk CAL criteria, whereupon 132 of 344 (38.1%) labels were categorized as low risk and 0 of 132 (0%) tested positive on allergy testing. The NPV of a low-risk CAL history plus a reaction to an oral cephalosporin was therefore 132 of 132 (100%; 95% CI, 97.2%-100%).

Finally, we applied both criteria inclusively, such that a CAL was considered as low risk if either (1) there was a low-risk reaction or (2) the CAL was for an oral drug. With this, 270 of 344 (78%) CALs stratified as low risk, and 6 of 270 (2.2%) labels tested positive, with an NPV of 97.8% (95% CI, 95.3%-99.2%).

History-based risk stratification is a valuable adjunct in the clinical approach to key antibiotic allergies such as penicillin and sulfonamide antibiotics.⁵⁻⁷ In this study, we show that there is the potential for history-based risk stratification of CALs using an approach outlined in Figure 1, to identify those patients who are unlikely to test positive, and that the same historical criteria being used for penicillins appear to apply. However, one caveat is that a reaction to an IV cephalosporin may be inherently more likely to test positive, with 20 of 134 (14.9%) positive test results observed in IV CALs, compared with 3 of 210 (1.4%) positive test results with NPV 98.5% (95% CI, 95.8%-99.7%) in oral CALs.

Limitations of our study include its retrospective nature. Future studies that might seek to risk-stratify and directly challenge low-risk cephalosporin allergies would need to be conducted prospectively. It is our perception that those patients meeting the combined "low-risk history plus oral cephalosporin label" criteria may be the safest population to approach with a direct challenge protocol using point-of-care cephalosporin delabeling, allowing up to 40% of CALs to be intervened on without preceding skin testing. However, patients meeting only 1 criterion (low-risk history or oral CAL) could also be considered. Outside of the allergists' office, patients who do not meet the dual criteria for low risk could be triaged for desensitization when they are either (1) high-risk history consistent with anaphylaxis or (2) reaction was to a nonoral cephalosporin. Those in the highest risk history category would continue their

cephalosporin avoidance (Figure 1). Future studies are needed to validate our findings in different populations, and prospectively, and should compare them to other validated risk criteria, such as PEN-FAST.⁸ An additional key limitation is that our study was done in North America, which may have different cephalosporin sensitization patterns than Australia or Europe.¹

In conclusion, history-based risk stratification of CALs appears to be feasible using the existing validated criteria for penicillin allergy, with the additional caveat that a reported reaction to an IV cephalosporin may be inherently more likely to test positive, and should be scrutinized more carefully. Our study supports the possibility of future prospective studies that could directly challenge and delabel low-risk CALs at the point-of-care.

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TABLE E1. Univariate and multivariate logistic regression analysis of variables predicting positive cephalosporin testing results

Variable	Univariate analysis	Multivariate analysis*
History-based risk category†		
Low risk	1 (reference)	1 (reference)
High risk‡	8.46 (2.33-30.69)	7.97 (1.93-32.91)
Highest risk§	21.44 (5.34-86.12)	12.03 (2.77-52.18)
Patient reacted to IV cephalosporin	11.02 (3.20-37.9)	10.48 (2.74-40.12)
Time since reaction, per year (available in n = 245 labels)*	0.89 (0.80-0.97)	Part of history-based criteria for low risk
Patient age (y)	0.98 (0.96-1.01)	0.99 (0.96-1.01)
Female sex	1.18 (0.39-3.59)	1.81 (0.49-6.61)
Race, non-White	2.79 (0.96-8.08)	4.29 (1.12-16.55)
Patient recollection of reaction onset		
Unknown recall	1 (reference)	1 (reference)
Immediate (<1 h)	5.4 (1.71-16.8)	1.5 (0.42-5.49)
Accelerated (1-4 h)	1	1
Delayed (4+ h)	2.34 (0.76-7.18)	1.66 (0.46-5.99)

DRESS, Drug reaction with eosinophilia and systemic symptoms.

Values are odds ratio (95% CI). Bold values represent findings that met statistical significance.

*Time since reaction was excluded from multivariable analysis because this variable is incorporated in the history-based risk categorization scheme.

†History-based risk category as defined by Figure 1.

‡History potentially consistent with anaphylaxis.

§History potentially consistent with severe delayed reaction (ie, Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS syndrome, etc).