

Penicillin allergy frameworks enable risk stratification of cephalosporin allergy labels

A history-based risk stratification of cephalosporin allergy labels appeared feasible when using the validated criteria for penicillin allergy, according to a study published in *The Journal of Allergy and Clinical Immunology: In Practice*.

“The field of allergy has known for a while now that most patients who report cephalosporin allergies are unlikely to test positive,” **Cosby A. Stone Jr., MD, MPH**, assistant professor in allergy/immunology with Vanderbilt University Medical Center Drug Allergy Research, told Healio.

Negative predictive values for criteria defining a low-risk CAL:

Patients with a low-risk CAL history



VS

Patients with a low-risk CAL and reaction to an oral cephalosporin



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Data were derived from Koo G, et al. *J Allergy Clin Immunol Pract*. 2022;doi:10.1016/j.jaip.2022.05.032.

The motivation behind the study

Previously, Stone and colleagues found that only approximately 8% to 9% of patients who believed they may be allergic to cephalosporins tested positive to one of these drugs.



Cosby A. Stone Jr.

“After that study, our thought was that taking a careful history with a scheme to separate the stories that people tell us into different risk categories would probably be able to identify a group of patients and stories who are exceedingly unlikely to be allergic when they are tested,” Stone said.

In turn, this would have the potential to make things easier and more efficient for patients and doctors as they decided what to do about a possible allergy when it was blocking them from lifesaving antibiotic treatment, Stone continued.

“When I proposed this idea to the American Academy of Allergy, Asthma & Immunology Foundation, they gave me funding to study it as part of my research program, and I am happy to say that we have been successful in what we proposed to do,” Stone said.

Hospitals commonly use cephalosporins as key [antibiotics in emergencies and critical care treatments](#), Stone explained.

“When you show up with a severe infection in the emergency department, the chance that one of these antibiotics could be used to help save your life is high, especially if you are immune compromised or get frequent infections,” Stone said.

Patients with infections that need treatment who also are possibly allergic to cephalosporins then face big problems, he continued, adding that these medications are the best antibiotics for protecting patients from infections after surgery.

“The alternative antibiotics don't always work as well and may have more side effects, in addition to being more expensive and sometimes harder to use,” Stone said. “Getting your cephalosporin allergy tested before a surgery is a really good idea.”

The study's results

The researchers evaluated 322 patients with 384 cephalosporin allergy labels (CALs) in their outpatient clinic between 2014 and 2019. Of them, 89.4% (n = 288; median age, 57 years; 78.5% female) with 344 CALs had a drug allergy evaluation with completed skin testing or a direct oral challenge, which the researchers used in their analysis.

According to the study, 17% of these 288 patients had more than one cephalosporin label at evaluation, the most common of which included cephalexin at 31.7% and ceftriaxone at 13.7%. Also, the median time between index reaction and testing was 5.14 years.

During the study, 23 patients had positive results on immediate skin testing, delayed skin testing, patch testing or oral challenge, whereas 21 had positive skin or patch testing to the reported label and were not challenged to their index agent.

Also, 77.1% of patients had negative testing and were challenged; 99.1% of the oral challenges were tolerated, which led to label removal. Another 4.9% had negative skin testing and were delabeled afterward because of reported tolerance to a relevant cephalosporin since their index reaction.

Further, 5.6% with negative skin testing did not have an initial oral challenge but later tolerated a cephalosporin treatment, which led to delabeling.

Overall, then, 94.8% of patients had a complete cephalosporin allergy evaluation up to known tolerance or positive testing.

The researchers found that a non-low-risk category or a reaction to IV cephalosporin significantly increased risk for positive cephalosporin testing in their univariate and multivariable logic regression.

Also, they continued, there was a significant association between “non-white” race and increased probability of positive testing on multivariable regression after they had adjusted for other factors.

Next, the researchers categorized 59.4% of the 344 CALs as low risk based on index reaction history, with three testing positive.

“We started by examining a set of criteria that we previously proved to be useful for our program to [remove unnecessary penicillin allergies](#) and found that, indeed, the same criteria worked fairly well to identify low-risk allergies — less than a 1.5% chance of testing positive,” Stone said.

The negative predictive value of a low-risk CAL history, then, was 98.5% (95% CI, 95.8%–99.7%).

“The surprising finding from this study was that we noticed that people who had previously reacted to IV cephalosporins were more likely to test positive (14.9% chance) compared to those who had reacted to an oral cephalosporin (1.4% chance),” Stone said.

“So, the person who is at the lowest risk to be truly allergic is someone who has a low-risk history and their original reaction was to an oral cephalosporin drug. In our study, they had a chance that was lower than 1%. We actually didn’t observe anyone who met those two criteria who ultimately tested positive,” Stone said.

When the researchers excluded patients with reactions to IV cephalosporins from their modified low-risk CAL criteria, they categorized 38.1% of the 344 labels as low risk, with zero positive allergy tests. Therefore, the negative predictive value of a low-risk CAL history and reaction to an oral cephalosporin was 100% (95% CI, 97.2%-100%).

When a CAL was considered low risk if there was a low-risk reaction or the CAL was for an oral drug, 78% of the 344 labels were stratified as low risk and 2.2% of 270 tested positive, with a negative predictive value of 97.8% (95% CI, 95.3%-99.2%).

The study’s implications

Patients with a low-risk history and an oral cephalosporin label may be the safest population for direct challenge protocols using point-of-care cephalosporin delabeling, the researchers wrote, intervening in up to 40% of these labels without preceding skin testing, although patients who only meet one of these criteria may be considered as well.

Also, the researchers advised, doctors could triage patients who do not meet these low-risk criteria for desensitization when they have a high-risk history consistent with anaphylaxis or when they reacted to a nonoral cephalosporin. Patients with the highest risks, the researchers continued, should continue to avoid cephalosporins.

“The most important thing for all doctors is to recognize that not all cephalosporin allergies that a patient reports are equally risky to be a true allergy,” Stone said.

“If a patient needs a cephalosporin drug for their treatment but reports a possible allergy to one, I think that our criteria might be helpful to guide everyone’s decision making about whether or not it could be tried again,” he continued.

In addition to previous research into cephalosporin allergies including cross-reactivity patterns, Stone said, this study provides tools to guide management of allergy risk while giving patients the best care possible.

“However, similar to our earlier stage research on penicillin allergies, the key limitation to our current report is that we did this research retrospectively. Prospective studies will need to be done to make sure that it’s as safe as we currently think it should be,” he said.

The researchers additionally said that future studies are needed to prospectively validate these findings in different populations and compare them with other validated risk criteria such as PEN-FAST.

“Similar to our penicillin research, which is further along at this point, the obvious next question is: Does this mean we can go straight to safely disproving these low-risk cephalosporin allergies by giving an appropriate challenge dose under medical observation?” Stone said.

“I think it’s entirely possible that we can do so safely, and it would hopefully help more patients to get the right antibiotic treatments at the right time,” he continued. “These are the things that I would want to study next.”

Reference:

[Stone CA, et al. *J Allergy Clin Immunol Pract.* 2021;doi:10.1016/j.jaip.2020.07.056.](https://doi.org/10.1016/j.jaip.2020.07.056)

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For more information:

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Pregnant women safely tolerate amoxicillin direct oral challenges

Pregnant women with a history of penicillin allergy safely passed direct oral challenges for amoxicillin without preceding skin testing, according to a study published in *The Journal of Allergy and Clinical Immunology: In Practice*.

“Penicillin allergy delabeling in low-risk patients has been shown to be safe and effective in other patient populations,” **Raymond Mak, MD, FRCPC**, clinical instructor in the division of allergy and immunology in the department of medicine at University of British Columbia in Vancouver, told Healio.

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