

Bringing Data to Bear on the Mushy Middle: Riskier Immediate Reactions to Penicillin



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Risk-stratified approaches to penicillin allergy labels have a solid premise and a growing evidence base. Such approaches posit that patients with low-risk penicillin allergy histories can be challenged directly without prior skin testing, historical reactions consistent with anaphylaxis should be skin tested before rechallenge, and reactions consistent with severe delayed hypersensitivity should lead to continued avoidance. When using skin testing, our testing paradigms continue to improve as well; knowledge of cross-reactivity patterns among β -lactams demonstrates that many reactions are drug specific or restricted to R-side chains.¹⁻³ Within this context, the work by Romano et al⁴ in this issue of *The Journal of Allergy and Clinical Immunology: In Practice* highlights key findings that help allergy/immunology physicians risk stratify further. The paper provides specific chronologic characteristics to apply when evaluating reactions consistent with anaphylaxis not immediately classified as low-risk. They might best be classified as dwelling in a “mushy middle” zone (Figure 1) of potentially higher risk for IgE-mediated allergy.

The key findings in this paper come from focusing on probabilities for positive skin testing and a presumably true allergy based on the chronological features of time from administration to onset of symptoms. In their analysis, the authors studied adult patients presenting for penicillin allergy evaluations and divided them into 4 groups. Group A included patients with reaction onset <1 hour after an initial dose; group B included patients with reaction onset <1 hour after a subsequent dose; group C included patients with reaction onset >1 hour $\leq$ 6 hours after an initial dose; and group D included patients with reaction onset >1 hour $\leq$ 6 hours after a subsequent dose. Two key features

based on group A emerged. First, immediate hypersensitivity reactions were much more likely to correspond with positive skin testing when they appeared within an hour of dose administration. Second, immediate hypersensitivity reactions were much more likely to correspond with positive skin testing when those symptoms appeared on the first dose of a new treatment course. When comparing the extremes of this paradigm, the authors noted that the probability of positive testing ranged from 75% positive testing in group A to 3% positive testing in group D, with groups B and C having 26% and 33% positives, respectively. This is exceedingly valuable pretest information.

These findings are slightly limited by the categorical nature of the data obtained, in that the data were not collected in a continuous fashion, only to the level of key cut points of $\leq$ 1 hour or >1 hour to $\leq$ 6 hours. Hence, statistical models using regression techniques to create a continuous model of risk for positive allergy testing based on time between administration of the drug and the onset of the symptoms were not possible, and we are left to presume that perhaps a reaction at 2 hours might be riskier for positive testing than a reaction at 5 hours. However, one could imagine in future directions that our field could create a multifactorial model of pretest probability for a positive penicillin allergy test in a patient reporting immediate-type symptoms. Such a construct could build upon this data and other models such as PEN-FAST,⁵ to more critically evaluate the “mushy middle” zone of reactions, represented in this study by groups B and C (Figure 1). The goal would be to further refine when an allergist really needs to perform either skin testing or desensitization. PEN-FAST is a clinical decision tool where patients with a history of penicillin allergy are risk stratified based on point totals. A reaction <5 years is assigned 2 points, a history of anaphylaxis/angioedema or a severe cutaneous reaction is assigned 2 points, and a reaction requiring treatment is assigned 1 point. Totals of 0-2 are considered low risk, and patients may be directly challenged to penicillin-based antibiotics. Separate work has shown that recalling the name of the antibiotic causing a reaction, a history of anaphylaxis, and <1 year since a reaction are predictors for true penicillin allergy.⁶ Prospectively validated current models of risk stratifying penicillin allergy labels can currently carve off 60% to 70% of adult penicillin allergy labels as low risk enough to be acceptable for a direct oral challenge, but perhaps a multifactorial model based on the data from Romano et al and others could add an additional 10% to 15% of systematically identified low-risk patients. Future studies of positive penicillin allergy testing should therefore seek to obtain 2 key chronological features: time in minutes-hours from administration to the onset of symptoms and also time that has elapsed between the reaction and an allergy/immunology evaluation. Based on the analysis by Romano et al, both of these continuous time variables appear to play a key role in

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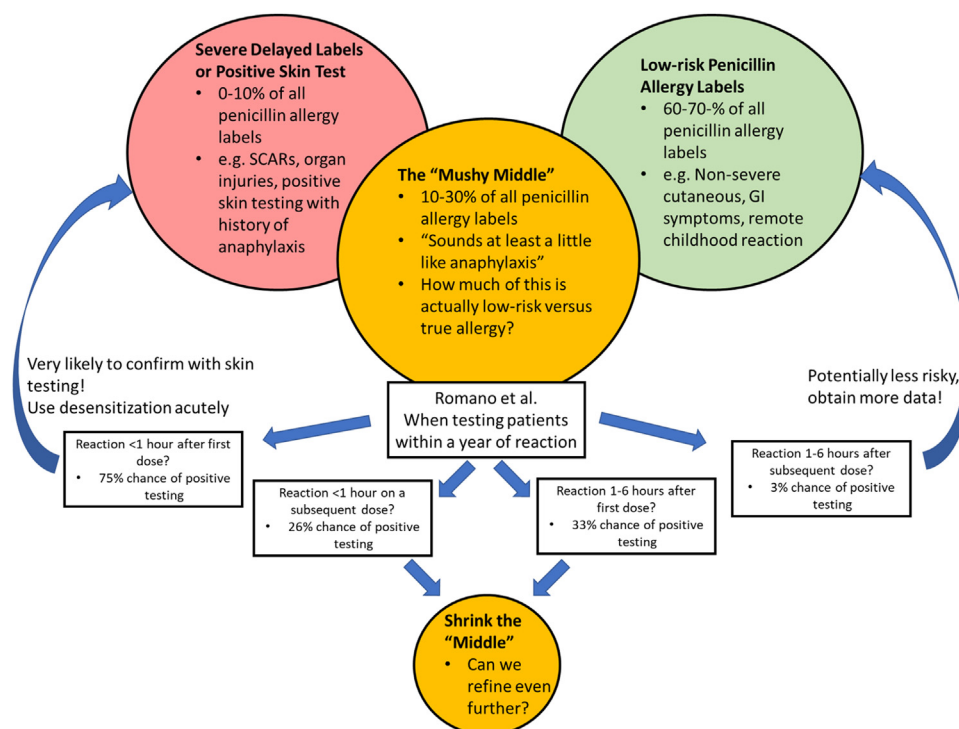


FIGURE 1. Improving on the “mushy middle” of penicillin allergy labels. Greater understanding of the features of skin test positive allergies where the recalled events are similar to anaphylaxis (such as in the paper by Romano et al) will allow for improved stratification of those patients who are likely to test positive from those who are safe enough for a direct challenge. Greater knowledge of pretest probabilities will inform and improve resource utilization by guiding the need for a direct challenge, skin testing, desensitization, or continued avoidance. *GI*, Gastrointestinal; *SCAR*, severe cutaneous adverse reaction.

whether or not a patient reporting immediate-type symptoms will have a positive penicillin skin test.

The model of care described by Romano et al also suggests that expeditious evaluation of penicillin allergy may be crucially important in finding patients who are truly allergic. Because Romano et al’s team has structured their capture of patients to allow for rapid evaluation of recent reactions, they captured many patients with positive testing. In addition, this strategy mitigates the potential issue of poor patient recall, as it is likely that details may be forgotten the further out a patient is from a reaction. With their quick follow-up, Romano et al also demonstrate some thought-provoking findings. A subset of group A (patients experiencing symptoms <1 after administration on the first dose) demonstrated negative skin testing followed by negative oral challenges with penicillins. They were then followed up 2–4 weeks later, with 20% showing some evidence of sensitization upon repeat testing. This raises the question as to whether patients who fall into this high-risk group should be routinely re-evaluated, or whether they were evaluated too early to show sensitization, or sensitized without clinical allergy. It is also puzzling, given their tolerance of a challenge.

Finally, another key finding from this paper is in the details. Perhaps most important to determining what should be included in a patient’s skin testing panel, the authors verified what has been reported in other studies to date, namely, that piperacillin allergies appear to demonstrate selectively positive skin testing to piperacillin^{7,8} and not always to other reagents, and that

aminopenicillin reactors were very likely to test positive only to aminopenicillins (Table VI, Romano et al).⁴ The aminopenicillin findings may be less important in the United States because of differences in observed sensitization patterns and β -lactam utilization (intravenous [IV] amoxicillin and amoxicillin-clavulanate are not in use for treatment in the United States).⁹ However, Romano et al’s findings strongly suggest that piperacillin needs to be included in a patient’s testing plan when it was the culprit drug, and that aminopenicillins have additional utility for testing a concerning severe clinical history of an immediate aminopenicillin reaction to avoid a reaction during an amoxicillin challenge.¹⁰ It is also increasingly feasible that sensitization patterns to β -lactams vary by a country’s β -lactam utilization. The IV route, when available, may be more likely to result in a sensitization that corresponds with positive allergy testing, as was recently observed for cephalosporins.¹¹

In conclusion, Romano et al provide key pieces of information that should be welcomed as a step in the right direction. They highlight that “everything that sounds like anaphylaxis in terms of symptomatology” is not equally risky in terms of “chronology.” They also highlight that we still have much to learn about sensitization patterns to penicillins and that what we should be including in our “standard” testing panels may vary both by the culprit drug and by geographic variations in antibiotic use. Romano et al’s excellent paper also brings helpful data highlighting the potential for additional precision in our risk stratification. Such precision will help to firm up the current “mushy middle.”

REFERENCES

1. Stone CA Jr, Trubiano JA, Phillips EJ. Testing strategies and predictors for evaluating immediate and delayed reactions to cephalosporins. *J Allergy Clin Immunol Pract* 2021;9:435-44.e13.
2. Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Zaffiro A, Caruso C, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of alternative cephalosporins. *J Allergy Clin Immunol* 2015;136:685-91.e3.
3. Romano A, Valluzzi RL, Caruso C, Maggioletti M, Quarantino D, Gaeta F. Cross-reactivity and tolerability of cephalosporins in patients with IgE-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol Pract* 2018;6:1662-72.
4. Romano A, Valluzzi RL, Gaeta F, Caruso C, Zaffiro A, Quarantino D, et al. The combined use of chronological and morphological criteria in the evaluation of immediate penicillin reactions: evidence from a large study. *J Allergy Clin Immunol Pract* 2022;10:3238-48.
5. Trubiano JA, Vogrin S, Chua KYL, Bourke J, Yun J, Douglas A, et al. Development and validation of a penicillin allergy clinical decision rule. *JAMA Intern Med* 2020;180:745-52.
6. Siew LQC, Li PH, Watts TJ, Thomas I, Ue KL, Caballero MR, et al. Identifying low-risk beta-lactam allergy patients in a UK tertiary centre. *J Allergy Clin Immunol Pract* 2019;7:2173-81.e1.
7. Gallardo A, Moreno EM, Laffond E, Munoz-Bellido FJ, Gracia-Bara MT, Macias EM, et al. Sensitization phenotypes in immediate reactions to piperacillin-tazobactam. *J Allergy Clin Immunol Pract* 2020;8:3175-7.
8. Casimir-Brown RS, Kennard L, Kayode OS, Siew LQC, Makris M, Tsilochristou O, et al. Piperacillin-tazobactam hypersensitivity: a large, multi-center analysis. *J Allergy Clin Immunol Pract* 2021;9:2001-9.
9. Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. *J Allergy Clin Immunol Pract* 2013;1:258-63.
10. Khan DA, Banerji A, Blumenthal KG, Phillips EJ, Solensky R, White AA, et al. Drug allergy: a 2022 practice parameter update. *J Allergy Clin Immunol* 2022; 150:1333-93.
11. Koo G, Yu R, Phillips EJ, Stone CA Jr. Retrospective stratification of cephalosporin allergy label risk using validated penicillin allergy frameworks. *J Allergy Clin Immunol Pract* 2022;10:2472-5.e1.