

## Putting Penicillin Allergies to the Test

Penicillin is the most common drug allergy documented in hospital admissions and leads to frequent use of alternate, less effective therapies.<sup>1,2</sup> Documented penicillin allergies also lead to longer hospital stays, higher overall hospitalization costs, increased incidence of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Clostridioides difficile*, and mortality.<sup>1,3-6</sup> Unfortunately, much of this alternate therapy is unnecessary since fewer than 10% of penicillin allergies are confirmed by formal testing results.<sup>7</sup>

Assessing and clarifying penicillin allergy is an important component of antibiotic stewardship and recommended by the American Academy of Allergy, Asthma, and Immunology, the Infectious Diseases Society of America, and the Centers for Disease Control and Prevention.<sup>8-10</sup> Stewardship programs have identified many approaches to tackle optimization of therapy in these patients ranging from identifying appropriate beta-lactam agents with low risk of cross-reactivity to clarifying penicillin allergy through elaborate medication history and in some cases penicillin skin testing. Our [June 2017 DASON newsletter](#) discussed types of allergic reactions and beta-lactam cross-reactivity in detail. Resource limitations have made penicillin skin testing impractical in many facilities and settings. For this newsletter, we will focus on two recent papers that propose potential strategies for penicillin allergy clarification in low risk patients without performing penicillin allergy testing.

For a more comprehensive resource if your facility is considering starting a penicillin allergy assessment program, please speak with your DASON Liaison and check out our [Toolkit](#).

## Development and Validation of a Penicillin Allergy Clinical Decision Rule

PEN-FAST is a simple rule designed to accurately identify low-risk penicillin allergies that do not require formal allergy testing. The rule was derived and validated from a multicenter antibiotic-allergy tested cohort of 622 patients from 2 tertiary care sites in Melbourne, Australia. Characteristics associated with positive penicillin allergy tests were evaluated in univariate and multivariate analysis and the 4 features associated with a positive penicillin allergy test were summarized with the PEN-FAST mnemonic (Table 1). Next, the rule was externally validated in a retrospective, penicillin-allergy tested cohort of 945 patients from Sydney and Perth, Australia and Nashville, Tennessee. The study collected data from June 26, 2008 to June 3, 2019. Patients who reported penicillin allergy in the trial received penicillin allergy testing that consisted of skin prick, intradermal, or patch testing and/or oral challenge administered directly or after skin testing. The study determined that a cut-off of less than 3 points on the PEN-FAST scale identified a low risk of penicillin allergy in which only 17 of 460 patients (3.7%) experienced positive allergy tests, with a negative predictive value of 96.3%. The findings of the external validation were similar. The study limitations include exclusion of non-penicillin beta-lactam allergies and intravenous penicillins that could not be confirmed with oral challenges, limited number of patients with SCAR-like phenotypes, predominance of inpatient testing, inclusion of adult patients only, and lack of validation in an ethnically diverse patient population where penicillin allergy phenotypes may vary. The authors concluded that a PEN-FAST score of less than 3 is associated with a high negative predictive value and could be useful to identify patients at low risk for a positive penicillin allergy test and may be eligible for allergy de-labeling by means other than PST.<sup>11</sup>

**Table 1.** PEN-FAST Penicillin Allergy Clinical Decision Rule<sup>11</sup>

Mnemonic	Assessment	Scoring
<b>PEN</b>	Patient reports penicillin allergy	If yes, proceed with assessment:
<b>F</b>	Five years or less since reaction	2 points
<b>A</b> <b>S</b>	Anaphylaxis <b>OR</b> Severe Cutaneous Adverse Reaction (SCAR)*	2 points
<b>T</b>	Treatment required for reaction	1 point

\*SCAR includes forms of delayed reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction that caused eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis, and severe delayed rashes with mucosal involvement. Patients were excluded from this analysis if they experienced acute interstitial nephritis, drug induced liver injury, serum sickness, or isolated drug fever as allergy phenotypes.

**Table 2.** PEN-FAST Score Interpretation and Risk of Positive Penicillin Allergy Test<sup>11</sup>

Score	Interpretation	Risk of Allergy
0	Very low risk	<1%
1 - 2	Low risk	5%
3	Moderate risk	20%
4	High risk	50%

### Direct Challenge to Penicillin-Based Antibiotics in the Inpatient Setting

The final step in penicillin skin testing is to complete an oral challenge of the beta-lactam to ensure no reaction. As an alternative to the full testing protocol, several groups have suggested low-risk patients could begin with the oral challenge in appropriate clinical scenarios. The efficacy and safety of a direct challenge of was tested in a prospective, single-center study conducted at 528-bed Rochester General hospital from February 2018 to May 2019.<sup>12</sup> Infectious diseases (ID) pharmacists identified patients who met study inclusion criteria and recommended penicillin allergy consultation to the hospitalist team. Consults were performed by an allergist practicing in the outpatient setting via tele-health technology. Patients with a history of cutaneous-only reactions (e.g. rash, itching, urticaria, or other unknown reaction) more than 20 years prior were able to receive a 3-step challenge with amoxicillin. Patients with cutaneous reactions less than 20 years prior or those

with allergy histories of angioedema and extracutaneous IgE-mediated reactions underwent traditional penicillin skin testing (PST) followed by oral challenge. A total of 372 patients were evaluated and 100 patients consented to remote allergy consult. Of the 52 patients receiving PST, 44 (84.6%) were PST negative. In the direct challenge group, 47 of 48 (97.9%) patients initially tolerated amoxicillin and 2 (4.2%) experienced delayed reactions. The one patient with an immediate reaction received an antihistamine and required no additional intervention.

The study demonstrated antibiotic cost savings of \$23,375.27 as part of their secondary outcomes. One limitation noted by the authors is the study included a small sample size and was likely underpowered given the low risk of severe reaction in this patient population. Other limitations include short follow-up period (14 days) which may have missed some delayed reactions, a conservative allergy history period of 20 years, pushing some low risk patients to PST where it may not be needed, and using the institution-specific 3-step challenge instead of a 2-step challenge as described by other researchers.<sup>13</sup> The authors concluded that direct challenge is a safe, effective, and less expensive than PST to de-label penicillin allergies in low-risk patients with a history of cutaneous-only reactions more than 20 years prior as compared to PST.<sup>12</sup>

### Summary

- Penicillin allergy labels are associated with many negative outcomes for patients, including increases in hospital costs, adverse events, drug-resistant infections, and mortality.
- Allergy assessments should be prioritized by antimicrobial stewardship programs to ensure patients receive the best care possible.
- If PST is not available or feasible, PEN-FAST and direct challenge may offer alternate strategies for clarifying penicillin allergies.
- Allergy clarification may not be feasible for all inpatients; however, certain patients may benefit from an outpatient allergist consultation to review penicillin allergies.

- The DASON Penicillin Allergy Assessment Toolkit provides additional resources to assist hospitals in allergy de-labeling and includes a questionnaire for patients with reported beta-lactam allergy, allergy assessment flowchart, an example allergy assessment policy, and educational slides.

## References:

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