

Once You Label Me...



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Recent studies have reinforced the message that we should no longer be complacent when encountering a patient with a label of penicillin allergy.¹ Up to 10% of all patients and 15% of hospitalized patients self-report “penicillin allergy,”² and on this basis are predisposed to experience untoward health care outcomes.¹ Thankfully, via appropriate allergy/immunology evaluation, including performance of immediate hypersensitivity skin testing, 90% of these individuals are found to be able to tolerate penicillin and penicillin-like antibiotics.³

Beta-lactams are among the leading causes of drug-induced anaphylaxis, including fatalities. Specifically, in the United States, it has been estimated that 500 to 1000 deaths per year are due to penicillin-induced anaphylaxis.⁴ Cephalosporins have recently also emerged as an important cause of anaphylaxis, especially in the perioperative setting.⁵

If a patient with a label of penicillin allergy is not tested to resolution, use of alternative antibiotics is the only option. In a retrospective, matched cohort study of patients admitted to Kaiser Foundation hospitals in Southern California, Macy and Contreras⁶ found that a label of penicillin allergy was associated with statistically significantly greater use of fluoroquinolones, clindamycin, and vancomycin ($P < .001$), 23.4% (95% CI, 15.6%-31.7%); more *Clostridium difficile*, 14.1% (95% CI, 7.1%-21.6%); more methicillin-resistant *staphylococcus aureus*; 30.1% (95% CI, 12.5%-50.4%) more vancomycin-resistant *enterococcus* infections; and 0.59 (9.9%; 95% CI, 0.47-0.71) more total hospital days compared with matched controls without a penicillin allergy label. Similar outcomes have recently been seen in a cohort of children with a label of antibiotic allergy.⁷ Furthermore, in a recent retrospective cohort study examining patients who underwent hip arthroplasty, knee arthroplasty, hysterectomy, colon surgery, and coronary artery bypass grafting in a tertiary care hospital, when comparing patients with and without a reported penicillin allergy, those with a label of penicillin allergy experienced 50% increased odds of

surgical-site infection, which was attributable to the receipt of second-line perioperative antibiotics.⁸ For this reason, the Centers for Disease Control and Prevention in a recent statement recommended: “Before prescribing broad-spectrum antibiotics to a patient thought to be penicillin-allergic, evaluate the patient for true penicillin allergy (IgE-mediated) by conducting a history and physical, and, when appropriate, a skin test and challenge dose.”⁹

Because most diagnostic evaluation for penicillin allergy, including skin testing and challenge, is performed by allergists in a community practice setting, with less support available compared with a hospital outpatient or inpatient setting, there is rightful concern for the potential this evaluation could result in a systemic reaction—including anaphylaxis. Thus, when considering the utility of skin testing as a diagnostic discriminator for moving forward with challenge, allergists are most concerned about avoiding a false-negative result. We know that most patients with a penicillin allergy label can tolerate penicillin without adverse reaction, but a minority do have the potential for serious and even life-threatening reactions. For this reason, providing a tool that aids in reducing the risk for true penicillin-allergic patients undergoing a penicillin challenge is what is most desired, to allay this concern for both the allergist and the patient. Penicillin allergy skin testing continues to be underused, with one of the major reasons being the lack of commercially available, Food and Drug Administration—approved, skin testing materials. It is well known that penicillin spontaneously breaks down to form several active moieties, both the major determinant (penicilloyl) and the minor determinants (including penicilloate and penilloate)—so named on the basis of their abundance rather than their clinical importance. It is important to remember that previous studies have demonstrated that positive skin test response to the minor determinant has been associated with anaphylaxis.¹⁰ Presently, we have a Food and Drug Administration—approved major determinant (PrePen), but no minor determinant is available. Diluted penicillin G is used as a surrogate for the minor determinant mixture by most allergists.

In the study by Solensky et al,¹¹ which appears in this issue of the journal, the authors present data from a prospective, multicenter, open-label regulatory trial for the “Penicillin Skin Test Kit.” Specifically, they investigated the negative predictive value of this kit, which included penicilloyl-polylysine 60 $\mu\text{mol/L}$, a tripartite minor determinant mixture consisting of penicillin G, penicilloate, and penilloate lyophilized powder (each 10 mmol/L), and amoxicillin sodium powder (20 mg/mL). In 455 subjects (18 years or older) with a history of penicillin allergy, 13.8% had 1 or more positive skin test result—65% of these positive test results were to the minor determinant mixture and/or amoxicillin. As per the study protocol, only those subjects negative to all the skin test materials underwent challenge, and in this subgroup the negative predictive value was 98%.

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Alert readers will note 2 important features of this study.

1. The rate of wheal/flare reaction to penicillin skin testing observed was higher than that in a number of other studies. This is likely explained by the inclusion criteria used in this study compared with those used in previously reported studies,¹²⁻¹⁴ in which patients with unverified penicillin allergy underwent skin testing regardless of whether history of reaction was compatible with IgE-mediated pathogenesis.
2. This study did not strive to address the positive predictive value of skin testing to penicillin by carrying out oral challenges in patients in whom a wheal/flare reaction was observed. The positive predictive value of a test indicates the likelihood that a patient with a positive test result actually has the condition of interest, in this case: IgE-mediated potential to penicillin (or amoxicillin). In other words, this statistic provides an answer to the following question: "Skin testing is positive, what is the certainty this patient has penicillin allergy?" Answering this question would have required oral challenges in subjects with positive skin test results. These challenges have not generally been carried out on the basis of ethical considerations and concerns for patient safety¹⁵; the potential benefit in determining the positive predictive value of penicillin skin testing is outweighed by the potential for harm (severe or even life-threatening anaphylactic reaction). Indeed, it is standard of care to regard individuals with a positive penicillin skin test result to be candidates for alternative antibiotics, or desensitization should penicillin be indicated without an equally efficacious alternative¹⁶—a recommendation supported by findings of a recent literature review.¹⁷ It is important to note that in critically appraising the utility of a screening test, our focus is primarily directed to the negative predictive value: the likelihood a negative test result identifies a patient who does not have IgE-mediated potential to penicillin. We commonly prioritize the utility of a screening test for ruling out the presence of a condition, with the understanding that our screening test may be overly sensitive. For instance, a rapid streptococcal antigen test used to evaluate a 50-year-old man with sore throat is associated with a positive predictive value of only 64%, but a negative predictive value of 98%.¹⁸ The negative predictive value of 98% reported by Solensky et al¹¹ answers the question: "Skin testing is negative, how certain are we the patient does not have penicillin allergy?" This is the question of greatest concern for the patient with unverified penicillin allergy and also for the allergist.

Søren Kirkegaard said: "Once you label me, you negate me."¹⁹ However, evidence indicates that for the overwhelming majority with "penicillin allergy," this label should not be viewed as negating the possibility that penicillin and penicillin-like drugs will be well tolerated. The availability of diagnostic reagents associated with a more optimal negative predictive value will facilitate our ability to more efficiently and safely evaluate these

patients. For this reason, the Penicillin Skin Test Kit will be a welcome addition to the armamentarium of the practicing allergist.

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