

**“Penicillin Allergy Evaluation Should Be Performed Proactively in Patients with a Penicillin Allergy Label – A Position Statement of the American Academy of Allergy, Asthma & Immunology”**

Penicillins are the most commonly implicated drugs associated with both immediate and delayed hypersensitivity reactions.<sup>1,2</sup> Penicillin allergy is estimated to affect approximately 10% of the population, and up to 15% of hospitalized patients, are labeled with a penicillin allergy.<sup>1,3</sup> However, when a penicillin allergy evaluation is performed in individuals who report a history of penicillin allergy, the overwhelming majority tolerate penicillins and thus, the allergy label can be removed, and the patient can be “delabeled.”<sup>4</sup> The reasons for the low rate of confirmed penicillin allergy include mislabeling of a side effect as an allergy (e.g., gastrointestinal upset) or a coincidental event (e.g., headache or cutaneous eruption due to underlying infection), reduced rates of exposure to parenteral penicillins, and loss of sensitization with avoidance of penicillins over time.<sup>5</sup>

A penicillin allergy label is associated with poor patient outcomes including increased hospital length of stay, increased perioperative infections, and overall increased mortality.<sup>5-6</sup> Use of alternative antibiotics can be associated with higher costs (due to use of more expensive broad-spectrum antibiotics), inferior efficacy and/or greater risk for untoward effects including antibiotic resistance, *Clostridium difficile*, and side effects.<sup>4,7-8</sup> Penicillin allergy testing is associated with significantly less health care utilization over the next several years and greater use of narrow-spectrum antibiotics. Penicillin allergy testing has a very favorable cost-benefit ratio for the incremental cost of testing versus future health care utilization.<sup>9</sup> Delabeling penicillin allergy is an important component of antibiotic stewardship and is endorsed by many professional organizations and public health bodies<sup>5,10-12</sup> In addition to penicillin allergy evaluation programs, inpatient antibiotic stewardship programs that assist clinicians with pathways and algorithms to allow safe administration of cephalosporins in penicillin allergic patients or provide recommendations for penicillin challenge in low-risk patients, have been successful with improving patient outcomes and delivery of first-line antibiotics.<sup>13-14</sup> Since the last AAAAI penicillin allergy position statement<sup>15</sup>, direct oral challenge without preceding skin testing has been recommended as the preferred approach in low-risk pediatric patients and as a consideration in low-risk adult patients.<sup>4</sup> Low risk patients include those with a remote history (> 5 years) of cutaneous-only reactions such as itching or morbilliform drug eruptions (MDE). A penicillin allergy evaluation is not necessary for patients with a family history of penicillin allergy only or a side effect such as headache or nausea; these patients may simply be delabeled by history alone, although a single step challenge may

be offered to those who are anxious or need additional reassurance.<sup>4</sup> The PEN-FAST rule is a validated tool for clinicians to aid risk stratification of adults with a penicillin allergy label.<sup>16-18</sup> The rate of positive skin test results to penicillin has been declining since the 1990s and directly challenging low risk patients without prior skin testing demonstrates a low reaction rate from 4-10%.<sup>6,19-22</sup> In addition, a recent citation provides further support for the relative predominance of patients with low pre-test probability for having a penicillin allergy and suggests skin testing may be associated with a poor positive predictive value in these low-risk patients.<sup>23</sup> Penicillin skin testing (PST) is reserved for patients with a history of anaphylaxis or a recent reaction suspected to be IgE-mediated. PST may also be preferred for patients with multiple drug allergies and higher risk conditions (for example, patients with active pulmonary or cardiac disease or pregnant patients).<sup>5,24</sup> PST carries minimal risk, and with education and training, can be performed by non-allergist physicians, pharmacists, and advanced practice providers (APPs) depending on local practice patterns and regulations.<sup>25-26</sup> The new option of employing direct oral challenges improves the accessibility of penicillin evaluations, with great promise to increase delabeling.<sup>27-28</sup> Contraindications to an evaluation via PST or direct oral challenge include patients with a history of severe cutaneous adverse reactions to beta-lactams, such as Stevens Johnson Syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms (DRESS).<sup>4</sup>

Penicillin allergy evaluations should be offered proactively to patients during routine visits, in advance of antibiotic need, including to children<sup>4</sup> and pregnant women.<sup>29</sup> Specific programs have been successful to target patients likely to require antibiotics, such as inpatients,<sup>30</sup> ICU patients,<sup>31</sup> oncology patients,<sup>25</sup> pre-operative patients,<sup>32-33</sup> and patients planning for organ transplantation.<sup>34</sup> Importantly, penicillin allergy evaluation by any means has been shown to be a cost-saving intervention.<sup>35-37</sup> The inappropriate re-labeling of penicillin allergy in the electronic health record, even after adequate testing remains a challenge and current efforts are underway to combat this issue.<sup>38-39</sup> Accurate communication of results to delabeled patients and their care team is paramount.

A penicillin allergy evaluation accurately identifies the approximately 9 of 10 patients who, despite reporting a history of “penicillin allergy”, can receive penicillins without allergic reaction. Efforts to delabel can and should be performed by all clinicians, especially for those patients with low-risk histories, not limited to those from Allergy and Immunology. For those clinicians not comfortable performing delabeling procedures, referral to Allergy and Immunology is an appropriate alternative. The

AAAAI encourages widespread and routine penicillin allergy evaluations, which are integral for successful antibiotic stewardship.

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