Pro/Con Review

Minor Determinants Are Essential for Optimal Penicillin Allergy Testing: A Pro/Con Debate

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At the American Academy of Allergy, Asthma, and Immunology 2015 Annual Meeting in Houston, Texas, we debated the following issue: "Minor determinants are essential for optimal penicillin allergy testing." The pro position was defended by Roland Solensky, and the con position was defended by Eric Macy. We considered the existing data on the safety and efficacy of using a complete panel of penicillin allergy skin test reagents including penicilloyl-poly-lysine (PPL), native penicillin G, penilloate, penicilloate, and amoxicillin versus using only the currently commercially available materials, PPL and native penicillin G, followed by an oral challenge if the skin test result is negative. The present article is an account of the debate and does not constitute a systematic review of the literature.

This review will restrict the word "allergy" to mean a clinically significant IgE-mediated reaction. When *allergy* is used in italics, it will refer to what is noted in a medical record pertaining to an adverse reaction or intolerance associated with the previous use of a specific medication or medication class without verification of an IgE-mediated mechanism responsible.

THE PRO POSITION

Approximately 10% of the population self-reports a history of penicillin *allergy*. However, when formally evaluated for penicillin allergy, 90% or more of these individuals are found to not be allergic and able to tolerate penicillins.[1,2] This observation is partly because the penicillin-specific-IgE level wanes over time and therefore penicillin allergy resolves in most, but not all, patients.[3] It is also likely that some patients were mislabeled as being penicillin allergic at the time of the reaction because their symptoms may have been due to the underlying illness or an interaction between the antibiotic and an infectious agent. The best-characterized example of this is the development of a nonpruritic morbilliform cutaneous eruption when patients actively infected with EBV are treated with ampicillin.[4]

The label of penicillin *allergy* is not benign. Patients with a history of penicillin *allergy* are more likely to be treated with clindamycin, as well as broad-spectrum antibiotics such as fluoroquinolones, vancomycin, and third-generation cephalosporins.[5-19] In addition, when compared with controls, patients with a history of penicillin *allergy* have higher costs, longer hospital stays, and higher rates of development of vancomycin-resistant enterococcus, *Clostridium difficile*, and methicillin-resistant *Staphylococcus aureus* infections.[7] Research has shown that penicillin skin testing, by virtue of ruling out penicillin allergy in the vast majority of subjects, greatly reduces the use of fluoroquinolones and vancomycin.[10-13]

Under physiologic conditions, penicillins spontaneously degrade to reactive intermediates that act as haptens and covalently bind to tissue and serum proteins.[14,15] These complexes may elicit immune responses, such as production of specific-IgE antibodies or drug-specific T cells. About 95% of penicillin degrades to the penicilloyl moiety, which is referred to as the "major antigenic determinant." The remaining portion of penicillin degrades to several other derivatives, of which penicilloate and penilloate are the most important in inducing allergic responses. Penicilloate and penilloate, along with penicillin itself, are called the "minor antigenic determinants." [Note: MDM refers to minor determinant mixture, and this may include only penicilloate + penilloate or penicilloate + penilloate + penicillin G.]

The elucidation of the immunochemistry of penicillin led to the development of skin test reagents for penicillin skin testing in the late 1960s and early 1970s. PPL and penicillin G detected most, but not all, penicillin-allergic patients. The first description of penicillin-allergic patients detected by penicilloate and penilloate but not PPL or penicillin G was given by Levine et al[16] and Levine and Zolov.[17] Using PPL and MDM (consisting of all 3 minor determinants), 218 patients with a history of penicillin allergy underwent skin testing and 32 were skin test–positive (8 PPL+/MDM+, 17 PPL+/MDM−, 7 PPL−/MDM+). Among the 7 patients positive solely to MDM, at least 3 underwent skin testing with the individual minor determinants and were positive only to penicilloate (negative to penicillin G and penilloate). There is no indication whether the remaining 4 patients underwent similar skin testing with the separate MDM components. Subsequently, large-scale studies have found that about 10% of penicillin skin test–positive patients are positive to only penicilloate and/or penilloate (negative to PPL and penicillin G) (Table I).

One method to assess the utility of penicillin minor determinants is the positive predictive value. The positive predictive

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Abbreviations used
MDM- Minor determinant mixture
NPV- Negative predictive value
PPL- Penicilloyl poly-lysine

value of penicillin skin testing is approximately 50%, which is comparable to food and hymenoptera skin testing. Because of ethical concerns of challenging skin test–positive patients, the positive predictive value is based on a limited number of challenges.[27] In addition, the vast majority of subjects challenged with penicillins were skin test–positive to either PPL or penicillin G and not the other minor determinants. It is difficult to find published reports of penicillin challenges in patients who were positive to only penicilloate and/or penilloate. There are several reasons for this—namely, that only one tenth of penicillin skin test–positive patients react solely to penicilloate and/or penilloate; some studies used MDM consisting of all 3 minor determinants (and there is no way to determine which minor determinant(s) the patients reacted to)[2,3]; and many studies did not skin test with minor determinants aside from penicillin G.[28]

In the published literature, I am aware of 4 patients who were selectively skin test–positive to penicilloate or penilloate and were subsequently challenged with penicillins.[16,17,29] Three of the 4 patients experienced immediate reactions: (1) wheezing and flushing, (2) urticaria, and (3) flushing.[16,17] Each of the patients was skin test–positive to penicilloate (negative to PPL, penicillin G, and penilloate), and parenteral penicillin was administered via a type of escalating graded challenge in 2 of the 3 cases. The fourth patient, who was selectively skin test–positive to penilloate, tolerated oral amoxicillin 5 years after her skin test and intravenous ampicillin 7 years after the skin test.[29] The time lapse between the skin test and the challenges raises the possibility that she had outgrown her allergy by the time she was treated.

Another method by which the utility of penicillin minor determinants can be assessed is the negative predictive value (NPV). In other words, how does the NPV of PPL + penicillin G compare with the NPV of PPL + penicillin G + MDM? The NPV of skin testing with the full set of penicillin skin test reagents has been reported in many studies, and it is generally more than 95%, meaning that very few skin test–negative subjects react and the reactions are usually mild and not life-threatening.[1,2,26,30,31] There are only 3 large-scale published studies that have reported the NPV of skin testing with only PPL and penicillin G, and it was also more than 95%.[10,28,32]

However, because of the reasons outlined below, it is not appropriate to directly compare the NPV obtained when MDM was used versus when it was not. First, all the studies were observational in nature, without attempts to match patient characteristics or include a control group. The subjects were not all comers with a history of penicillin *allergy*, or consecutive patients whose reaction history qualified them to undergo skin testing. Rather, they were simply patients in "real-life" clinical settings who were arbitrarily chosen by practicing allergists to undergo penicillin skin testing. It is not unreasonable to think that clinicians without access to MDM might hesitate and be less likely to skin test or challenge patients with recent reaction histories or history of severe penicillin-induced anaphylaxis. This selection bias may have excluded patients who would have reacted to penicilloate and/or penilloate. The consequence of underrepresentation of patients with more severe reactions in the PPL/penicillin G studies is an artificially inflated NPV. Second, in only 1 of the 3 PPL/penicillin G studies were all the skin test–negative patients challenged with penicillins.[32] In the other 2 studies, only about half the subjects[10] and one third of the subjects,[28] respectively, were challenged, and no formal criteria or reasons were given for not administering at least a single dose of penicillin. Third, although Macy et al challenged all the patients, the average time from index reaction to evaluation was more than 20 years, and the findings may not extend to patients with more recent reactions. Last, the NPV, unlike sensitivity or specificity, is dependent on the prevalence of the disease, which (penicillin allergy) was very low in this population (1%-2%), and this limits the generalizability of the results.

TABLE I. Selected large-scale studies demonstrating that about 10% of the patients with positive penicillin skin test results are uniquely positive to penicilloate and/or penilloate (negative to PPL and penicillin G)

Reference	No. of skin test–positive patients	No. (%) of patients positive to only penicilloate and/or penilloate (%)
Sullivan et al[18]	469	34 (7.2)
Mendelson et al[19]	23	3 (13)
Macy et al[20]	60	11 (20)
Macy and Burchette[21]	101	11 (10.9)
Bousquet et al[22]	136	9 (6.6)
Jost et al[23]	171	15 (8.8)
Park et al[24]	64	7 (10.9)
Matheu et al[25]	64	8 (12.5)
Fox and Park[26]	66	7 (10.6)
Total	1125	105 (9.3)

Amoxicillin and ampicillin are also considered minor determinants in the evaluation of penicillin *allergy*. Skin testing with native amoxicillin/ampicillin may identify patients who are selectively allergic to these semisynthetic penicillins. In other words, there are patients who are skin test–negative to PPL, penicillin G, and MDM and tolerate penicillin VK, but they react to amoxicillin on skin testing and oral challenge.[33] Selective IgE-mediated allergy to amoxicillin seems to be much more common in some parts of Europe, compared with North America. Up to 50% of the patients positive on penicillin skin testing from centers in Southern Europe are uniquely positive to amoxicillin (ie, negative to PPL, penicillin G, and MDM),[33] whereas in the United States, the proportion of amoxicillin-only skin test–positive patients is an order of magnitude less.[24,26,33,34] The reasons for these observed differences are unclear.

Despite the public health implications of penicillin *allergy*,[35] penicillin skin testing is greatly underutilized in the United States. I would argue one reason for this is the commercial unavailability of MDM and amoxicillin skin test reagents. Rightly or not, clinicians seem uncomfortable relying on only PPL and penicillin G in the evaluation of patients with penicillin *allergy*. A 1994 survey of the American Academy of Allergy, Asthma, and Immunology members and fellows found that 92% of the respondents performed penicillin skin testing using PPL and 40% used MDM.[36] In contrast, according to Allerquest, the