
Penicillin allergy: clinical quandaries

Before the commercialization of penicilloyl-polylysine in the 1960s, penicillin skin testing was unreliable. Early cephalosporins were thought to have a high rate of cross-reactivity with penicillins.^{1,2} Before 1970, the consensus approach for patients with a history of penicillin allergy was to give a non- β -lactam antibiotic without bothering to skin test for penicillin allergy. Surprisingly, in the study by Puchner and Zacharisen³ published in this issue of the *Annals*, this approach remains the option favored by >60% of the 378 surveyed physicians, including community and academic internists, pediatricians, medical students, residents, and even allergists.

The Puchner survey illustrates well some of the current quandaries associated with the diagnosis of penicillin allergy. Which previous reactions have inferential value? Who requires skin testing? When is the best time to proceed with testing? How significant is the cross-reactivity with cephalosporins? Should children with a history of penicillin allergy be approached differently than adults?

The clinical manifestations of the previous allergic reaction clearly impacts the approach to penicillin-allergic patients. In the study by Puchner, very few (2 to 8%) of the respondents chose to skin test a patient with sinusitis/bronchitis with a past history of maculopapular rash, whereas up to 21% would skin test if the same patient had a history of systemic allergic reaction. Delayed maculopapular rashes are probably mediated by a T cell immune response.⁴⁻⁶ Immunoglobulin (Ig)E antibody tests would therefore not be suitable for identifying such reactors. Positive penicillin skin tests in patients with a history of maculopapular rash range from 0 to 7%.⁷⁻⁹ Although the yield is low, pa-

tients with penicillin-specific IgE are at some increased risk for severe reactions. Ideally, they should be identified by skin testing. Realistically, it is understandable that not all such patients are skin tested as resources are reserved for patients with histories of IgE-mediated reactions.

In the survey, skin testing was more commonly chosen for patients with systemic allergic reactions. Only 21% of pediatricians and none of the internists would choose to skin test a patient requiring a cephalosporin for sinusitis/bronchitis who had penicillin-induced chest and throat tightness; nevertheless, 88% avoided prescribing the needed cephalosporin because of that previous reaction. The low incidence of requests for penicillin skin tests among nonallergist respondents in the Puchner study can, to some degree, be explained by a lack of knowledge about penicillin allergy and skin testing. Only 56% of pediatricians and 52% of internists knew that penicillin allergy is not lifelong. Approximately 35% of internists and pediatricians did not know that standardized skin tests for penicillin were available. These beliefs discourage the use of penicillin skin tests in most cases.

More surprisingly, only 13% of allergists would choose to skin test the sinusitis/bronchitis patient with a history of a systemic penicillin reaction. This differs significantly from the results of a 1994 survey by Wickern et al¹⁰ in which 88% of allergists chose to skin test patients with a history of anaphylaxis. The questionnaires and targeted populations were different, but if this contrast truly reflects an abandonment of the use of penicillin skin testing over the past decade, this is worrisome.

The recently published practice parameter on management of drug hyper-

sensitivity recommends that patients with a history of penicillin allergy should be skin tested only in the case that there is no effective alternative antibiotic.¹¹ Performing penicillin skin test immediately before treatment and only when no other antibiotics are suitable alternatives is the example illustrated in case 4 of the Puchner study. Appropriately, 90% of the allergists included a skin test for penicillin in their management, as compared with <40% of nonallergist respondents. Practically, nonallergist physicians are the ones who must make such decisions. Even if they are well educated about penicillin allergy and skin testing, an allergist may not be readily available to perform skin testing. These realities, in our opinion, recommend the use of elective penicillin skin testing for patients with histories of penicillin allergy and a likelihood of recurrent antibiotic therapy. A detailed history of the reaction coupled with penicillin skin testing results provide sufficient information to an allergist to provide advice about subsequent management of penicillin therapy: liberal use, graded challenge, or desensitization. This approach eliminates unnecessary "penicillin allergic" labels and, consequently, the use of less effective, more expensive, and often more toxic alternatives.

One interesting finding of the Puchner study is the fact that some questions were answered differently by pediatricians and internists. More pediatricians than internists would prescribe a cephalosporin both to patients with a history of maculopapular rash (56% vs 22%), and to those with cases of systemic allergic reactions (19% vs 7%). The belief that children are at low risk for IgE-mediated reactions to penicillin antibiotics^{12,13} could explain the liberal use of cephalosporins by pedi-

atricians. More recent studies have shown that 13 to 34% of children with a history of adverse reactions to β -lactams have positive skin tests or challenges.^{14,15} This range is comparable with major adult studies.^{7,16,17} Therefore, we believe that guidelines for the evaluation and management of children with β -lactam allergy should not differ from guidelines for adults.

There is no consensus regarding the administration of cephalosporins to patients with a good history of an IgE-mediated reaction to a penicillin.¹¹ The options are to use a non- β -lactam antibiotic (the most popular among the Puchner-surveyed physicians), to give the cephalosporin directly (chosen by 20 to 56% pediatricians, depending on the situation), or to skin test for penicillin and/or cephalosporin allergy.¹¹ The most convenient and safest option when faced with non-severely ill patients who require antibiotics for sinusitis is certainly to give non- β -lactam antibiotics. In the Puchner study, 53 to 56% chose to treat the patient with sinusitis/bronchitis with a macrolide. This is troubling because macrolides do not provide first-line coverage for the most common pathogens causing sinusitis.¹⁸ This faux pas of prescribing less effective antibiotics again argues for referral for penicillin skin testing to remove, if appropriate, incorrect labels of "penicillin allergy." If cephalosporins are judged to be the best alternative and penicillin skin tests are not readily available, a graded challenge with the chosen cephalosporin offers a prudent option. Desensitization is even safer, but also more laborious. Unfortunately, only 43% of pediatricians and 56% of internists knew that patients with cephalosporin allergy can be desensitized. This misconception can have serious consequences if a severely ill patient with a convincing risk of systemic allergy to the culprit cephalosporin is given a less effective antibiotic.

We allergists must educate our primary-care colleagues about β -lactam allergy, skin testing, and desensitization. Physicians who completed an allergy rotation during their training did

not respond differently in the survey by Puchner. This calls attention to the need to provide specific educational sessions about drug allergy to primary-care residents rotating through an allergy-immunology division. Ideally, drug allergy education should be part of the curriculum of all generalists, as most physicians, regardless of their specialty, will at some time have to prescribe antibiotics for a patient with a history of drug allergy. The best way to provide such education is probably through case consultations. Even when it is not the primary reason for consultation, attention should be paid to the drug allergy history of each patient seen in consultation by an allergist. The consultation report should include specific impressions and management recommendations about any drug allergy reported by the patient. If the impression, based on the history and/or skin test, is that the patient should avoid the culprit antibiotic or its whole class, the possibility of safe desensitization if the antibiotic is urgently needed should be emphasized.

Finally, another critical problem which has emerged since the time of the survey is the discontinued production of the sole commercial source of penicilloyl-polylysine (PrePen, Mequon, WI) in the United States. Of patients with positive penicillin skin tests, 75% react only to penicilloyl-polylysine.⁷ Minor determinant mixture can therefore identify only 25% of penicillin-allergic patients. However most allergists have access only to penicillin G to evaluate minor determinant sensitivity.¹⁰ Of patients with a positive skin test to a tripartite minor determinant mixture, 66% will be detected with penicillin G alone (unpublished data). Therefore, <17% of penicillin-allergic patients detectable by an optimal skin test regime would be identified if penicillin G alone is used. Until this PrePen shortage situation is resolved, allergists and other physicians will have to rely more and more on clinical judgment. Unfortunately, history alone is not a very good predictor of the presence of penicillin IgE antibodies. Indeed, one-third of indi-

viduals who have positive penicillin skin tests have a vague history of penicillin allergy.¹⁹ Use of alternative antibiotics and gradual dose escalation regimens ("desensitization") seem to be the most prudent options until the PrePen crisis is resolved.

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