

REVIEWS OF THERAPEUTICS

Penicillin Allergy Skin Testing: What Do We Do Now?

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Drug-induced anaphylaxis remains a relatively infrequent event. However, penicillin and associated β -lactam antibiotics remain a primary cause of anaphylaxis. Penicillin allergies are undoubtedly overreported, and patients with suspected penicillin allergy can be treated with antibiotic alternatives. Penicillin allergy skin testing is a simple and effective way to identify true penicillin allergy. Skin testing involves testing for both major and minor determinants and should be conducted in a facility with available life-support equipment. The commercial major determinant product, benzylpenicilloyl-polylysine, was removed from the market in 2004; this action compromised the ability of clinicians to evaluate a patient's likely response to penicillin therapy. Alternatives to skin testing include laboratory synthesis of major determinants, use of the radioallergosorbent test (RAST), or a combination of RAST and minor determinant skin testing. Patients with suspected penicillin allergy can undergo desensitization if they require penicillin therapy. The planned return of a commercial major determinant will hopefully resolve this issue.

Key Words: PrePen, benzylpenicilloyl-polylysine, penicillin allergy, skin test, radioallergosorbent test, RAST.

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Penicillin is a frequent cause of anaphylaxis and is responsible for an estimated 75% of anaphylactic deaths in the United States.^{1, 2} Prevalence of penicillin allergy varies from

1–10% based on patient reports.³ Patient drug allergy histories are often limited to simply asking the patient about any drug allergies, with little or no follow-up, and thus are often unreliable. Over 80% of patients with a suspected history of penicillin allergy do not have penicillin-specific immunoglobulin E antibodies on skin testing.^{2, 4, 5} This misinformation may cause clinicians to forgo β -lactam antimicrobials in patients with self-reported penicillin allergy. Unfortunately, this practice results in increased health care costs, risks the development of bacterial resistance, and may require treatment with an alternative and possibly inferior antibiotic.⁶

The advent of penicillin allergy skin testing allowed clinicians to discern a true allergy from an adverse event. Use of accurate skin test results may increase β -lactam treatment and limit unnecessary prescribing of broad-spectrum agents. One study showed that skin testing reduced treatment with vancomycin and fluoroquinolones by 96% in patients with

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negative skin test results.⁴ Use of penicillin allergy skin testing can reduce adverse events, spare administration of broad-spectrum agents, and lower health care costs, making these tests an invaluable component of health care.⁶⁻⁹

The only available penicillin allergy skin test in North America contained the commercial major determinant product, benzylpenicilloyl-polylysine (PrePen; HollisterStier Laboratories, Spokane, WA). Unfortunately, this product was suspended by the U.S. Food and Drug Administration in 2000 because of production irregularities.¹⁰ In 2004, commercial benzylpenicilloyl-polylysine (CBP) was subsequently removed from the market. Without approved alternative products available, many clinicians have been forced to abandon penicillin allergy skin testing.

Data concerning alternatives to skin testing are scarce, but *in vitro* and laboratory options are available. In addition, patients with suspected penicillin allergy can undergo desensitization if they require penicillin therapy. However, many clinicians would prefer that CBP return to the market.

Skin Testing for Major and Minor Determinants

Allergic reactions to penicillin are caused by two factors: major and minor determinants.¹¹ The primary metabolic product of penicillin *in vivo* is benzylpenicilloyl. The combination of benzylpenicilloyl with protein forms an antigenic hapten known as the major determinant. Numerous other metabolic products along with unmetabolized penicillin make up the minor determinants. Testing for reactivity to both factors is vital in correctly identifying penicillin allergy.

The CBP consisted of benzylpenicilloyl bound to polylysine for the major determinant.¹⁰ A mixture of 10⁻² M benzyl penicilloate, benzyl penilloate, and benzyl-*N*-propylamine are used for the minor determinant. Penicillin G diluted to 10,000 U/ml has been used in conjunction with CBP. Minor determinant tests are not available commercially and may vary among institutions as a result of extemporaneous compounding. Information regarding preparation of the minor determinant test has been previously published.^{12, 13}

Before any penicillin skin test is begun, clinicians should ensure that appropriate measures to manage anaphylactic reactions are immediately accessible. The first step in the skin test is the prick or epicutaneous test. At least 15

minutes should elapse before the result is read. A negative prick test should be followed by an intradermal test; the latter should never be attempted first because it could result in a serious reaction. If either step produces a wheal 3 mm or larger compared with the negative control, the test is considered positive. Both major and minor determinants should be tested. Histamine and saline, respectively, serve as positive and negative controls.

The skin test of major and minor determinants is the gold standard for detecting penicillin allergy. Major determinant testing alone identifies over 90% of potential reactors; addition of a minor determinant test brings the accuracy to nearly 100%.¹⁴ Between 97% and 99% of patients with a negative skin test result can tolerate penicillin.^{3, 14-16} Many clinicians administer a two-dose oral penicillin challenge to patients with a negative result.

Alternatives to the Commercial Major Determinant Test

Laboratory-Synthesized Major Determinant Test

The removal of a CBP from the market has led some researchers to prepare their own versions. One group compounded benzylpenicilloyl-polylysine in the laboratory for use in skin testing.¹¹ They then compared CBP with their laboratory-synthesized benzylpenicilloyl-polylysine (SBP). Two control patients with no history of penicillin allergy had negative results on prick and intradermal tests for both products. One patient with a history of reactivity to CBP was administered prick tests using CBP and three dilutions of SBP. Results were negative for both CBP and SBP. An intradermal test yielded positive results for both CBP and SBP (concentration of 5 mg/ml).

Ten additional patients with a history of reaction to CBP were then tested. Two were prick-test positive to both CBP and SBP. The remaining eight patients tested positive to both products intradermally (CBP and SBP 5 mg/ml). Finally, enzyme-linked immunosorbent assay was used to compare the binding of polyclonal rabbit anti-penicillin antibody to CBP and concentrations of SBP of 2.5, 5.0, and 10.0 mg/ml. Results were similar for CBP and all concentrations of SBP.

Although this study raised hope for an alternative to CBP, several potential pitfalls must be considered. The number of patients in this study was small; in addition, the authors stated

that their work was preliminary, and further study was required. Also, the process provided by the authors for manufacturing SBP may prove difficult. Smaller health care centers lacking experienced personnel and proper equipment may be unable to produce SBP as directed. Finally, the belief that CBP will return to the market may limit further research in this area.

Radioallergosorbent Test

The radioallergosorbent test (RAST) uses penicillin-specific antibodies to detect immunoglobulin E reactivity. Numerous trials have compared RAST with skin testing. In one study, 98% of patients with a negative skin test result also had a negative RAST result.¹ However, only 65% of patients with a positive skin test result were also RAST positive. This problem was evident in those who experienced urticaria when exposed to penicillin. Of 23 patients with urticaria, 14 had positive skin test results, but only eight had positive RAST results. Nevertheless, the authors found 92% overall agreement between the two tests.

In another study, patients with a positive skin test result for the major determinant always had a positive RAST result.¹⁷ Unfortunately, only three of 11 patients who reacted to the minor determinant skin test had a positive RAST. Overall, a correlation of 95% was found between skin test and RAST results in this study. One other study found that skin tests did not provide more information on reactivity than RAST.¹⁸

The main drawback of RAST is that it can test only for the major determinant. Consequently, there is a strong correlation between negative skin test results and negative RAST results, but a wide disparity between positive skin test results for the minor determinant and RAST outcomes. A practice guideline on management of drug hypersensitivity developed jointly by the American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology describes RAST as unreliable due to its insensitivity and inability to test the minor determinant.² Thus, RAST alone should not be used to rule out penicillin allergy.

Combination Approach

Studies have shown a strong correlation between the results of RAST and skin tests for the major determinant. Thus, a combination

approach involving RAST and minor determinant skin testing may be useful in the absence of CBP. The use of both tests would address possible shortcomings of either test used alone and would provide a more accurate picture of a patient's sensitivity to penicillin. However, this approach has not been tested in a controlled clinical trial.

Return of the Commercial Major Determinant Test to the Market

The withdrawal of CBP from the market led a group of allergy specialists and physicians to form AllerQuest (West Hanford, CT), whose goal is to return CBP to the market. Indications are that CBP could return to the market by 2007 (N. F. Adkinson, AllerQuest, personal communication, May 6, 2006). A plan to bring a commercial product for the minor determinant was mentioned, although no time frame was provided. The use of RAST as an alternative was also mentioned but the lack of testing for the minor determinant and decreased sensitivity compared with the skin test was reiterated.

Clinicians would welcome the return of CBP. However, various marketing and regulatory forces remain that could further delay or even prevent the return of this product to the market.

Desensitization

Desensitization is an option for patients who require β -lactam treatment but have a suspected or proven penicillin allergy. In brief, the process involves administration of steadily increasing doses of penicillin, which renders mast cells unresponsive to penicillin antigens. A patient who has undergone proper desensitization may then receive penicillin therapy. Numerous desensitization protocols have been published.^{13, 19–21} However, due to the risk of serious adverse events, the process should be attempted only in a health care center with immediate access to life support and ventilator equipment.

Conclusion

The withdrawal of CBP from the U.S. market has left many clinicians without a reliable means to test for penicillin allergy. Several alternatives have been studied, but all have shortcomings. Laboratory production of the major determinant is promising, but the data are preliminary and have not been validated in a large-scale clinical trial. In addition, producing the major determinant may not be possible for many health care centers

for technical reasons. The RAST is not as sensitive as skin tests, and the lack of a test for the minor determinant means that many patients could have a negative RAST result and still experience serious adverse events. The combination of RAST and minor determinant skin testing makes sense but lacks supporting clinical data.

Clinicians should be vigilant in attempting to discern true penicillin allergy. A thorough history combined with available testing methods could be helpful in identifying patients at risk of penicillin-induced anaphylaxis. The option of desensitizing patients to penicillin remains a viable option for those who require the drug.

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