

ADVERSE REACTIONS TO β -LACTAM ANTIBIOTICS

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An adverse drug reaction is any unintended or undesired consequence of drug therapy and can be either predictable or unpredictable. Approximately 80% of drug reactions are predictable; these are reactions that are often dose-dependent or related to the pharmacology of the drug. Examples of these type of reactions are an overdose, side effect, secondary effect, secondary to underlying disease, or drug-to-drug interaction. Unpredictable reactions include drug intolerance, idiosyncratic reactions, pseudoallergic reactions, and allergic reactions. This article focuses mainly on IgE reactions to the β -lactam antibiotics and the management of people with a history of an allergic reaction to a β -lactam antibiotic. The author updates what is new in the management of these patients since the excellent review of this subject by Shepherd in 1991.³⁴

β -lactam antibiotics refers to those antibiotics that have a common β -lactam ring structure (Fig. 1). They include the penicillins, aminopenicillins (e.g., amoxicillin), cephalosporins, carbapenems (e.g., imipenim), and the monobactams (e.g., aztreonam).

PENICILLIN

The majority of people labeled as allergic to penicillin can safely take this antibiotic without fear of a life-threatening reaction because of a variety of reasons^{8, 20, 34}: people lose sensitivity to penicillin with time, a virus or bacteria caused the reaction and not the penicillin, the interaction of penicillin with certain viral infections can cause a reaction, or the reaction was caused by an antibiotic previously taken by the patient and not by the penicillin.^{20, 34} The only way to determine whether a patient with a history of an allergic reaction to penicillin can safely take penicillin without a severe IgE-mediated reaction is

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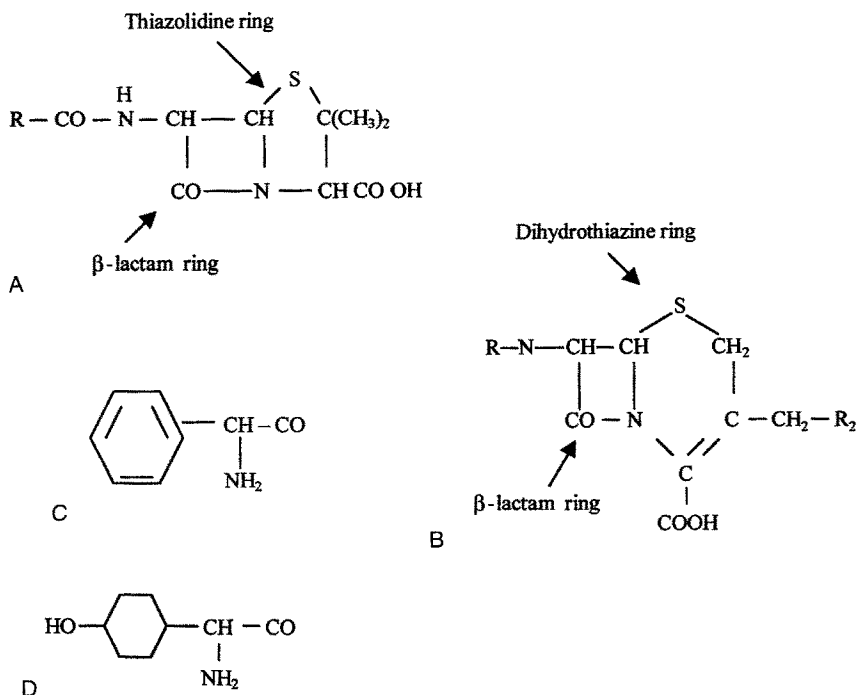


Figure 1. Antibiotics that have a common β -lactam ring structure. Penicillin (A), cephalosporin (B), and the aminopenicillins, ampicillin (C) and amoxicillin (D).

skin testing with appropriate penicillin reagents. Unfortunately, even with those we have known about since the late 1960s, all the necessary skin testing reagents are not available for commercial use, which is mainly caused by the demands that the FDA has put on companies trying to produce these chemicals. Therefore, many people are unnecessarily labeled as allergic to penicillin, and they receive an antibiotic that is frequently not as effective, more expensive, more toxic, and more likely to cause an allergic reaction to an antibiotic for which we cannot skin test. In addition, these patients are put at risk of developing resistance to a newer and possibly more potent antibiotic.

Incidence and Frequency of Allergic Reactions to Penicillin

The chance of developing an allergic reaction to penicillin is approximately 2% per treatment course (0.7–0.8%). The most frequent reactions are rashes, usually maculopapular or urticarial. The frequency of anaphylactic reactions is rare.^{6, 20, 34, 39, 44} In a study of 1740 people on intramuscular (IM) benzathine penicillin prophylaxis for an average of 3.4 years, the incidence of allergic reactions was 3.2%; the incidence of anaphylactic reactions was 1.23/10,000 injections with none occurring in the 600 patients under age 12; and the risk of a fatal reaction was 1/32,000 injections.²² These data and others suggest that the chance of developing a severe allergic reaction to penicillin is rare. On the other

hand, if one relies on the history, the incidence of penicillin allergy is much higher. In a large sexually transmitted disease clinic, 8.3% of the patients gave a history of an allergic reaction to penicillin.⁸ In two large inpatient studies, 10% to 20% of the patients reported a history of an allergic reaction to penicillin.^{8, 34}

Predisposing Factors

Having an antibiotic sensitivity to a non- β -lactam antibiotic increases the likelihood of reacting to a β -lactam antibiotic.⁴⁴ Whether a person with a history of an allergic reaction to penicillin is more likely to develop an allergic reaction to a non- β -lactam antibiotic is controversial. Sullivan suggested that in people allergic to penicillin, there was at least a tenfold increase in reaction rate to non- β -lactam antibiotics.⁴¹ Khoury et al reported no differences in the reaction rate to non- β -lactam antibiotics in people with a history of penicillin allergy with positive and negative skin test and patients with vasomotor rhinitis.¹⁶ There is no evidence that atopic individuals are more likely to react to penicillin than nonatopic individuals, but an atopic background predisposes to a more severe penicillin reaction.⁸

Evaluation of People with a History of Penicillin Allergy

History

Although the history is very important, many people with a history of an allergic reaction to penicillin do not remember the name of the penicillin (e.g., penicillin or amoxicillin) to which they reacted, the type of reaction they had, the number of days they took the drug before they had a reaction, or what they were taking it for. The history is frequently described as: Either my child or I took penicillin for an unknown time for an infection and developed a rash.¹¹ Many patients will say that they are allergic to penicillin and yet can take amoxicillin with no problem. Because people lose their sensitivity to penicillin with time or the infection and not the antibiotic causes the reaction, the history is usually not too helpful in determining whether one is still allergic to penicillin. Any person with a history of a non-IgE reaction to penicillin such as hemolytic anemia, interstitial nephritis, or an exfoliative dermatitis (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis) should not receive penicillin again.^{20, 34, 44}

Skin Testing for Penicillin Allergy

Penicillin has a low molecular weight and is metabolized to form haptens. The metabolism of benzylpenicillin has been studied in detail. Most penicillin (95%) is metabolized to benzylpenicilloyl, which, as a result, is referred to as the *major determinant* or BPO. The remainder stays as the native drug or is metabolized to benzylpenicilloate and benzylpeniloate. These are referred to as the *minor determinants* (MDMs). The MDMs are of major clinical importance because they are associated with the most severe allergic reactions. The BPO is commercially available under the name Pre-Pen. Penicillin G, 10,000 units, is available for skin testing, but the other MDMs are not available for commercial distribution.^{13, 20, 34, 44} Macy et al have recently published a method on how to prepare the MDM.¹⁶ Aged penicillin is not a source for the minor determinants.³¹

It is very safe to skin test people with a history of penicillin allergy using

the BPOs and MDMs when done by prick followed by intradermal skin testing. In over 7000 people with a history of penicillin allergy who were tested, the reaction rate was 0.3% with none being serious.^{20, 40} The accuracy of a negative skin test to BPO and MDM in predicting a life-threatening reaction is greater than 99%.^{20, 34, 44} The use of BPO and 10,000 units of penicillin G without the other MDMs can detect 97% to 99% of potential life-threatening reactions.^{20, 34, 44} In several large studies of people with an allergic reaction to penicillin, 7% to 17% reacted to the MDM, suggesting that skin testing with the other MDM may be less predictive of a clinical reaction.^{8, 23, 28, 36} A positive skin test to the penicillin reagents suggests a reaction rate of 39% to 100%.²⁰ Skin testing predicts only IgE reactions to penicillin; it does not predict the presence of IgG, IgM, or cell-mediated immunity.^{20, 34, 44} Table 1 lists skin testing reagents. Anyone taking antihistamines or medication with antihistamine properties should not be tested.

Evaluation for penicillin allergy by RAST or ELISA is not reliable to rule out allergy because of insensitivity and a lack of an MDM. In addition, it is much more time consuming.¹³

The majority of studies of people with a history of allergic reactions have shown that 80% or more will have a negative skin test.^{20, 34, 44} In a recent study of 326 people with a history of anaphylaxis and or significant urticaria, only 13.2% had a positive skin test. In other words, more than 80% of people labeled as allergic to penicillin should safely be able to take penicillin. In people with no history of penicillin allergy, the incidence of a positive skin test is 1.7% to 4.0%.^{8, 36}

Table 1. β -LACTAM ANTIBIOTIC SKIN TESTS

Skin Testing Reagent*	Method (prick followed by intradermal)†
Pre-Pen (6×10^{-5})	Full strength
Penicillin G 10,000 U‡	Full strength If history of severe reaction, serial tenfold dilution starting a 1/100 (optional)
MDM 10^{-2}	Full strength If history of severe reaction, serial tenfold dilution starting a 1/100 (optional)
Ampicillin 12.5 mg	Full strength If history of severe reaction, serial tenfold dilution starting a 1/100 (optional)
Cephalosporins 3 mg/mL	Full strength If history of severe reaction, serial tenfold dilution starting a 1/100 (optional)
Aztreonam 3 mg/mL	Full strength If history of severe reaction, serial tenfold dilution starting a 1/100 (optional)
Imipenem 1 mg/mL	Full strength If history of severe reaction, serial tenfold dilution starting a 1/100 (optional)

*Skin test volume 0.02 mL for intradermal.

†Positive skin test; prick = 3 mm or greater than negative control, intradermal = wheal 4 mm or greater than control.

‡100,000 units/mL stable at 1 wk in refrigerator and 6 mo frozen. Diluted need to use in 24 h.

Treatment of People with History of Penicillin Allergy Based on Skin Test

Figure 2 outlines a logarithm for the management of patients with a history of penicillin allergy based on skin testing. Ideally, skin testing should be done using all the MDMs. If all the MDMs are not available, and testing is done using only the BPO and 10,000 units of penicillin, then a graded penicillin challenge is suggested if the skin tests are negative. People with a history of a late or mild reaction should be given a graded challenge of penicillin consisting of 1/100th of the desired therapeutic dose first followed in 30 to 60 minutes by 1/10th and then the full therapeutic dose. People with a history of a severe reaction should be either desensitized or given a graded challenge starting with 1/1000th of the dose, preferably in a hospital setting.^{12, 34}

Aminopenicillins

Ampicillin (*a*-aminobenzyl penicillin) and amoxicillin (*p* hydroxy derivative of ampicillin) have replaced penicillin as the most common antibiotic used in the outpatient setting.³ Approximately 5% to 9% of people treated with amoxicillin will develop a nonpruritic maculopapular rash 7 to 10 days into the treatment course. This result increases to 70% to 100% if the patient has a concurrent infection of infectious mononucleosis. The incidence is also high if the patient has chronic lymphocytic leukemia, is treated with allopurinol, or has an elevated uric acid level.^{6, 34, 39} People who have a history of having had the classic, nonpruritic, maculopapular rash to amoxicillin or who developed the maculopapular rash with one of the underlying conditions previously mentioned usually tolerate penicillin or amoxicillin in the future without a severe life-threatening reaction.^{6, 34, 39, 44} The penicillin testing reagents are not as reliable in predicting allergic cutaneous reactions in amoxicillin-allergic individuals. In 750 patients with a history of amoxicillin allergy with negative skin test to the BPOs and MDMs of penicillin, 8% had an IgE reaction when challenged with amoxicil-

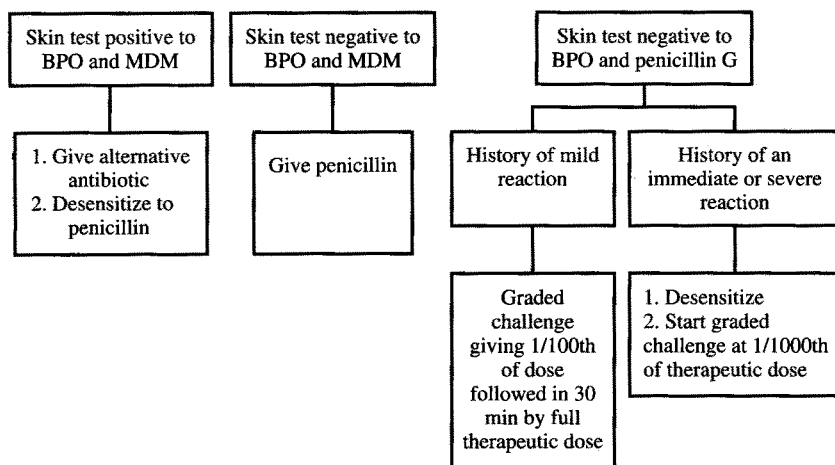


Figure 2. Management of the patient with a history of penicillin allergy based on skin testing.

lin (LM Mendelson, MD, unpublished data). None of the reactions were like threatening. All the reactions were cutaneous, and only 1.5% occurred within 72 hours. Of these patients, 500 had previously tolerated a therapeutic course of penicillin and remained skin-test negative before receiving the amoxicillin. There is immunologic evidence that people with an allergic reaction to amoxicillin have IgE antibodies against the side chains of amoxicillin and not against the β -lactam ring.^{2,3,35} Blanca et al have reported life-threatening reaction to amoxicillin with negative penicillin skin test,^{2,3} but this has not yet been reported in the United States. The data suggest, therefore, that using the penicillin skin tests reagents alone is not as accurate in diagnosing allergic reactions to the aminopenicillins. Figure 3 outlines management of people with a history of an amoxicillin reaction.¹² If there is a history of the classic maculopapular reaction to amoxicillin, skin testing is not necessary. A history of a possible allergic reaction to amoxicillin and skin testing with the BPOs and MDMs of penicillin will predict most life-threatening reactions. The addition of amoxicillin MDM, if available, might add some benefit in predicting IgE reactions. In the author's experience, the use of 12.5 mg/mL of ampicillin for skin testing has not been of any added benefit in predicting an allergic reaction to amoxicillin; however, others claim it is.^{2,3,9,28} Perhaps if amoxicillin were available for skin testing it might be of added value. Some investigators have suggested that delayed reactions to aminopenicillin skin test reagents might be of value in predicting delayed cutaneous reactions to the aminopenicillins.³ Although in the United States life-threatening reactions to amoxicillin are rare, it might be prudent for in patients with a history of a severe reaction to amoxicillin and negative skin tests to the penicillin reagents to do a graded amoxicillin challenge.

Cephalosporin Allergy

Cephalosporins share a common β -lactam ring with the penicillins but have a dihydrothiazine ring instead of the thiazolidine ring of the penicillin molecule (see Fig. 1). Life-threatening reactions rarely occur from the cephalosporins, especially from the second and third generations. The cutaneous reaction for

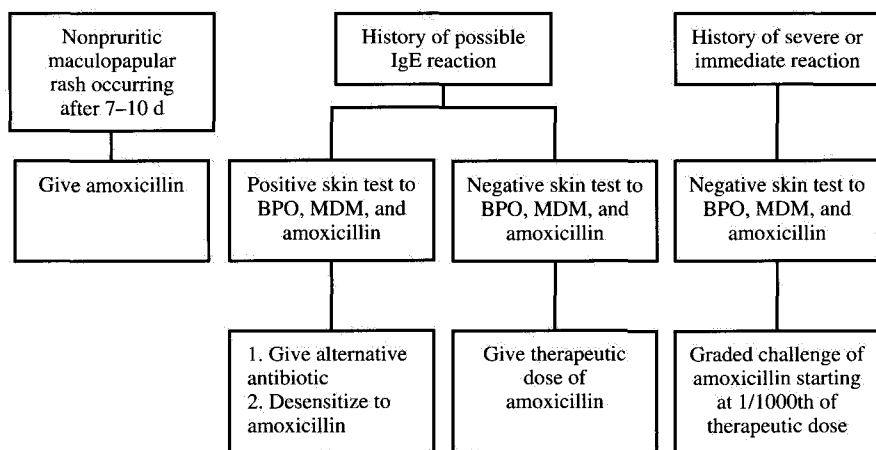


Figure 3. Management of the patient with a history of an amoxicillin reaction.

second and third generation cephalosporins is around 1% to 3%. Although cephalosporins and penicillins have a common β -lactam ring structure, clinical cross-reactivity appears to be much less of a problem. The incidence of reactions to second and third generation cephalosporins in individuals with a history of penicillin allergy and a positive penicillin skin test is 2% in the first 24 hours. Because some of these reactions are life-threatening, cautious graded challenge using a third generation cephalosporin is suggested in penicillin skin-test positive patients if a cephalosporin is required. Because at least 80% of people with a history of penicillin allergy are skin-test negative and only 2% of penicillin skin-test positive patients will react to a cephalosporin, the chance of a person with a history of penicillin allergy reacting to a cephalosporin is probably less than 1%. Ideally, before giving a cephalosporin to a person with a history of an immediate IgE reaction to penicillin, they should be skin tested to penicillin first along with 3 mg/mL of the cephalosporin to be used (Fig. 4). It has been shown that using this concentration of a cephalosporin is nonirritating. Although a positive skin test might be clinically significant, a negative skin test is not because the metabolites of the cephalosporins are not known.

It has been suggested that the majority of reactions to the cephalosporins are caused by antibodies against the side chains. Therefore, in patients with a history of a cephalosporin allergy who need a cephalosporin, a cephalosporin with a different side chain and generation from the one to which the patient reacted should be used. Skin test with 3 mg/mL of the cephalosporin desired using prick followed by intradermal testing might be of additional benefit in these patients. If the skin test is negative, give graded challenge; if the skin test is positive, test with another cephalosporin or desensitize to cephalosporin. Recent data has shed light on the cefaclor (Ceclor) serum sickness-like reactions. These reactions are not IgE-mediated and are specific to a hereditary defect in metabolism in these patients.¹⁵ Patients who have a history of the serum sickness-like reactions to cefaclor can take the other cephalosporins without prob-

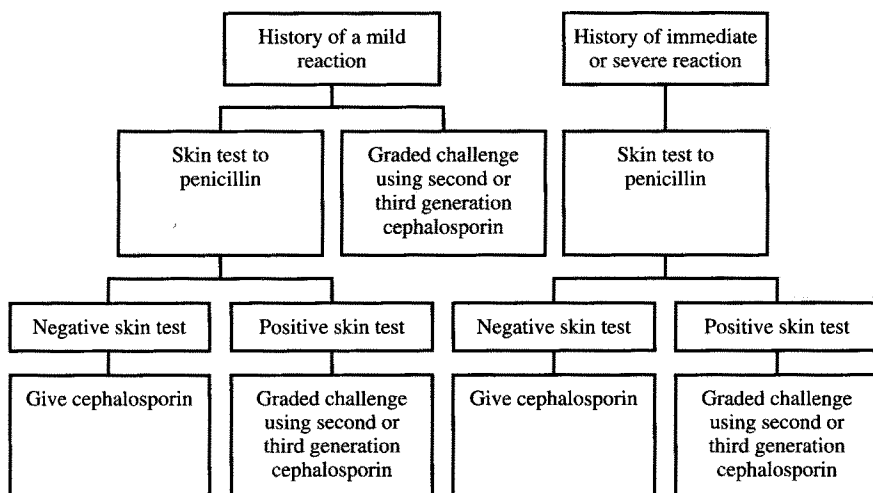


Figure 4. Administration of cephalosporin to a patient with a history of penicillin or amoxicillin allergy.

lems, including loracarbef, which is structurally similar to cefaclor.¹⁵ The management of people with a history of a cephalosporin allergy who need penicillin or amoxicillin is outlined in Figure 5.

In patients with a history of penicillin allergy and a positive skin test to the penicillin metabolites, carbapenem (e.g., Imipenem) should be avoided because it is potentially cross-reactive.³⁴ No cross-reaction between the monobactams (e.g., aztreonam) and the penicillins has been demonstrated³⁴; however, in patients with a history of ceftazidime, there might be a potential clinical problem because they share the same side chains.^{33, 34}

Desensitization to the β -Lactam Antibiotics

When a patient needs penicillin but skin testing reagents are not available or when a penicillin skin test is positive, the use of either oral or intravenous desensitization is recommended. Numerous articles have been published on the safety and method for this procedure. It appears that the oral method might be associated with less problems; however, both methods, when used properly, are safe and allow the majority of patients to be successfully desensitized. Figure 6 and Table 2 outline these procedures.⁴⁴ In patients who need chronic prophylactic β -lactam antibiotics, the administration of a daily oral dose, once desensitization has been completed, seems to maintain a state of desensitization (Table 3).⁴⁴

Risk of Resensitization to Penicillin

A concern has been raised that people who have had a history of a β -lactam allergy and negative skin test, and who have tolerated a therapeutic dose of penicillin have to be retested each time they need penicillin. Because skin testing reagents are only available for penicillin, this is the only one of the β -lactam antibiotics for which this question can be answered. In 240 children with a

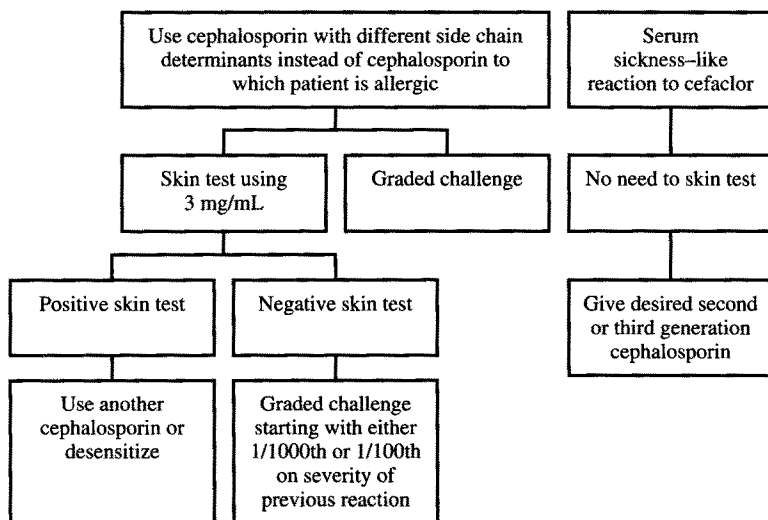


Figure 5. Administration of cephalosporin to a patient with a history of cephalosporin allergy.

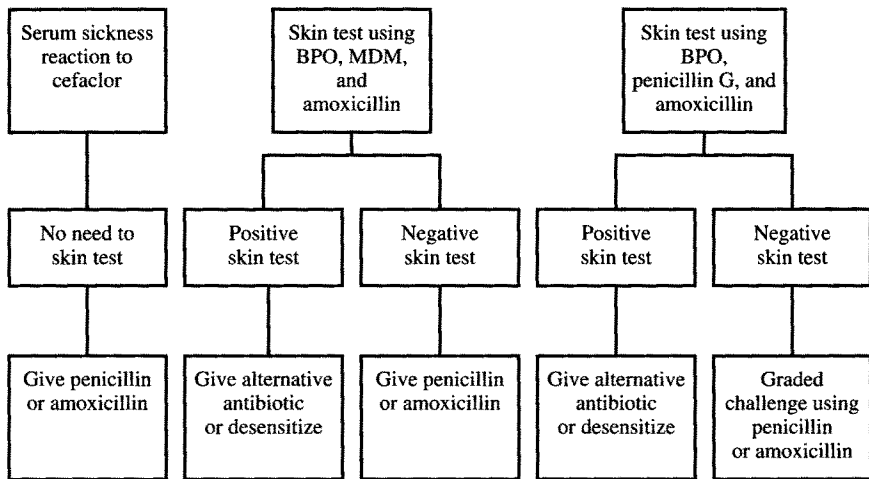


Figure 6. Administration of penicillin or amoxicillin to a patient with a history of cephalosporin allergy.

history of penicillin or aminopenicillin allergy and an additional 1200 unreported cases by the author, the incidence of a positive skin test after successfully completing a therapeutic challenge was 1.02%.^{16, 41} Pichichero and Pichichero have reported a 10.8% resensitization in children after successfully completing a therapeutic challenge.²⁸ In 281 similar cases in adults, the incidence was 5.0%. In seriously ill adults with a history of an allergic reaction to penicillin and initially negative skin tests, 16% had a positive skin test after tolerating a high dose of intravenous β -lactam antibiotics. The chance that those patients who continued with a negative skin test will become resensitized by future intravenous treatments is unknown. The resensitization rate among children who receive high doses of intravenous penicillin is also not known. In penicillin-allergic children who are skin-test positive and, with time, become skin test negative, 20% will become skin-test positive again after successfully completing a therapeutic course of penicillin. It appears that a person with a history of a penicillin allergy after successfully completing a therapeutic course of penicillin, especially intravenously, can be resensitized. If these patients remain skin test negative, however, their chances of developing a life-threatening reaction to further treatments with penicillin, especially oral administration, is no greater than that of a person with no history of penicillin allergy.^{10, 14, 24} Presently, there are no data about the resensitization rate on repeated use of intravenous penicillin in these patients. Presently, it seems prudent to retest patients who receive an intravenous dose of penicillin after completion of a therapeutic course of a β -lactam antibiotic.

When to Test for Penicillin Allergy

Many physicians believe that people with a history of penicillin allergy must be tested immediately before receiving this antibiotic because of fear that future exposure to a food contaminated with penicillin might resensitize the patient. In several studies, especially in children, this has been shown not to be

Table 2. β -LACTAM ORAL DESENSITIZATION PROTOCOL

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Table 3. β -LACTAM INTRAVENOUS DESENSITIZATION PROTOCOL

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Table 4. STEPWISE PROCEDURE FOR ELECTIVE PENICILLIN TESTING

Obtain detailed history
Perform penicillin skin testing (puncture followed by intradermal) using:
Penicilloyl-polylysine
Penicillin G (10,000 units/mL)
Minor determinant mixture (penicilloate and penilloate)
Ampicillin (12.5 mg/mL)
Saline control
Histamine (1 mg/mL, prick, 0.1 mg/mL intradermal)
Administer an oral challenge with up to 250 mg of penicillin or amoxicillin to skin test-negative patients in either single or divided doses—less than 2×125 mg of penicillin
Give a 10-day therapeutic course to patients who tolerate an office challenge (or 2 d more than number of days it took for patient to have initial reaction)
Repeat skin test after completion of therapeutic course (successful or unsuccessful)

the case. People with a history of penicillin allergy who remain skin-test negative after a therapeutic course of penicillin are no more likely to develop a reaction to further courses of oral penicillin than a person without a history of penicillin allergy.^{10, 14, 24} In unpublished data by the author, a follow-up study of 400 children 1 to 10 years after elective testing, there were no life-threatening reactions. Cutaneous reactions occurred in 4%, but most were delayed in onset. In a similar study in 163 children, 1.8% had mild IgE reactions after multiple treatments.²⁴ Because most people who need antibiotics are seen in the outpatient setting and require an oral antibiotic, the ideal time to test people, especially children, is when they are well and not in immediate need of penicillin. It is unlikely that an ill child will willingly staying in the physician's office several more hours to be skin tested, a parent without prior notice will be able to stay several more hours in a physician's office to have their child skin tested and challenged, or that a physician can skin test the patient on a moment's notice. These examples are why many children are given an alternative antibiotic with all its ramifications and keep the label of "penicillin allergy" for most of their lives. The way to prevent the unnecessary labeling of people, especially children, as being penicillin allergic and the risk of developing resistance to our more powerful antibiotics is to do elective penicillin skin testing (Table 4).

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