

## Penicillin Allergy: Asking the Important Questions

Donna Mabe, Pharm.D.

Beta-lactams, including penicillins, cephalosporins, carbapenems, and monobactams are widely prescribed antibiotics and remain the drug of choice for the treatment of many common infections. Unfortunately, due to a fear of penicillin anaphylaxis, the use of these drugs is often limited by a vague history of a penicillin allergy. Although alternative agents are available, they can be associated with undesirable effects, including the development of antibiotic resistance, and tend to be more costly than penicillins. In order to minimize the incorrect labeling of patients as "penicillin allergic," it is important to take a thorough history of the possible penicillin allergy and apply this information to general knowledge regarding penicillin allergies. Differentiating between patients with immediate IgE-mediated penicillin allergies and those with non-IgE mediated penicillin allergies allows one to more accurately assess a patient's risk for cross-reactivity and allergic reaction with other penicillin antibiotics. The key questions to ask regarding a penicillin allergy are shown in Table I.

**Table I: Key Questions to a Penicillin Allergy History**

Question	Significance
At what age did the penicillin reaction occur?	After avoiding penicillins for at least ten years, 9 out of 10 patients who claim to have a penicillin allergy will have a negative skin test and may be able to safely receive a penicillin
Do you remember the reaction? If no, who provided you with this information?	Patients with firsthand recall of their allergic reaction are generally able to provide more reliable information to help confirm symptoms associated with an IgE-mediated reaction
How did the penicillin reaction present?	Anaphylaxis, urticaria, angioedema, wheezing, and hypotension are concerning symptoms for an IgE-mediated hypersensitivity reaction
How long had you been taking penicillin before the reaction occurred?	Allergic reactions occurring >72 hours after administration are generally not IgE-mediated
How was the penicillin administered to you?	IgE-mediated reactions are much more likely with parenteral versus oral administration
For what reason were you taking the penicillin?	Rashes can occur with some viral and bacterial infections and may not be related to a penicillin allergy
Were you taking any other medications when the reaction occurred? If yes, were any of these medications new to you?	Since rashes can occur with a number of medications other than penicillins, another concomitant medication could be the true cause of the allergic reaction
Was the penicillin discontinued? If yes, what was the result?	Penicillin associated maculopapular rashes can spontaneously subside despite continuous therapy with the drug and may not recur upon re-exposure suggesting a non-IgE-mediated allergic reaction
Have you taken any other $\beta$ -lactam antibiotics since the reaction occurred? If yes, did you have an allergic reaction?	Some patients may have been safely treated with another $\beta$ -lactam antibiotic which would argue against a true IgE-mediated penicillin allergy

### How are penicillin allergies classified?

Penicillin allergies have been classified by a number of different systems. Gell and Coombs categorized penicillin hypersensitivity reactions based upon the type of  
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A University of Washington / Harborview Medical Center Drug Information Center publication  
Distributed monthly by authority of the Pharmacy and Therapeutics Committee  
Editor: Nelda A. Murri, Pharm.D. (206) 598-6612 – Asst. Editor: Elizabeth Rudy, D.V.M., R.Ph.  
Department of Pharmacy Services / School of Pharmacy

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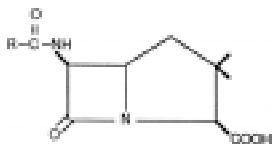
**The most useful information in determining a patient's risk for a true allergic reaction to penicillin is the allergy history.**

**A good understanding of the different types of penicillin allergies promotes the proper evaluation of a patient's risk for an allergic reaction to penicillin.**

reaction, immune mechanism, and clinical syndrome.<sup>1</sup> In contrast, Levine classified penicillin allergies according to their time of onset.<sup>2</sup> Table II below provides a summary of these two classification systems. An understanding of the different types of penicillin allergies is important as it allows the proper evaluation of a patient's risk for an allergic reaction to penicillin and prevents unnecessary withholding of the drug from many patients who could safely receive a penicillin antibiotic.

**Table II: Classification of Penicillin Hypersensitivity Reactions**

Reaction Type (onset)	Classification	Mediator(s)	Clinical Effects	Comments
Immediate (<1 hour)	Type I	IgE	anaphylaxis, urticaria, angioedema, wheezing, hypotension	hallmark of type I reactions is increased number of circulating eosinophils
Accelerated (1-72 hours)	Type I	IgE	urticaria, angioedema, wheezing	fatal penicillin reactions occurring >1 hour after administration are rare
Delayed (>72 hours)	Type II	IgM, complement	cytopenia(s), some organ inflammation	skin testing not useful for types II, III, or IV penicillin allergies
	Type III	IgG, IgM, complement	serum sickness— fever, arthralgias, fatigue	
	Type IV	lymphocytes	contact dermatitis	
Idiopathic (generally >72 hours)	Type V	unknown	maculopapular or morbilliform rash, Stevens-Johnson syndrome, exfoliative dermatitis	common with aminopenicillins



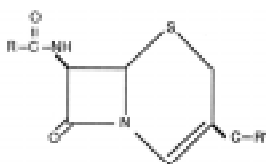
**Penicillins**

Penicillin is a small molecule that acts as a hapten; therefore, it must combine with endogenous proteins to elicit an immune response. Penicillin is largely metabolized (~95%) to a penicilloyl hapten moiety, which then combines with an endogenous protein to form an antigen. This complex is referred to as the major antigenic determinant. In addition, other metabolites of penicillin can form additional antigenic determinants and are termed the minor antigenic determinants. IgE antibodies recognize these major and minor antigenic determinants resulting in a hypersensitivity reaction. Immediate type I reactions are often mediated by IgE antibodies directed to the minor determinant antigens of penicillin, while accelerated type I reactions are often mediated by IgE antibodies directed to the major determinant antigen.

### **What is the cross-reactivity between penicillins and other $\beta$ -lactam antibiotics?**

#### *Cephalosporins*

The exact extent of cross-reactivity between penicillins and cephalosporins remains a matter of debate as contradictory data have been reported. Early studies suggested that 5.4-16.5% of patients with a positive history of a penicillin allergy also demonstrated allergies to cephalosporins, while patients with a negative history reacted at a rate of 1-2.5%.<sup>3</sup> A subsequent review of the literature found that of 15,987 patients who received various cephalosporins, including cephaloridine, cephalexin, cephalothin, cefazolin, and cefamandole, 8.1% of patients with a history of penicillin allergy had a reaction versus 1.9% of patients without a history of penicillin allergy.<sup>4</sup> It also appears that the cross reactivity may be higher for first-generation cephalosporins than for later generations.<sup>5</sup> This issue is further complicated by the fact that some early first-

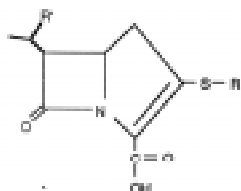


**Cephalosporins**

generation cephalosporins contained trace amounts of penicillin, making initial estimates of penicillin and cephalosporin cross-reactivity unreliable.<sup>6</sup> Although conflicting information exists, it appears that cephalosporins can be safely administered to patients with non-IgE-mediated penicillin allergies. On the other hand, penicillin antibiotics should be avoided in patients with a history of an immediate IgE-mediated penicillin allergy.

*Carbapenems*

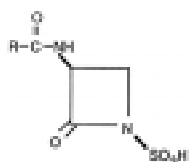
Another class of  $\beta$ -lactam antibiotics is the carbapenems of which imipenem is the prototype. It has been shown that in patients with documented positive penicillin skin tests, there is a significant potential for cross-reactivity and allergic reaction with imipenem. Saxon, et al. studied the potential for IgE-mediated cross-reactivity of penicillin with imipenem.<sup>7</sup> Forty subjects with a history of penicillin hypersensitivity reactions were skin tested with imipenem and penicillin determinants. Twenty subjects had a negative penicillin skin test and did not react to the imipenem skin test. Of the other twenty subjects, all of whom had a positive penicillin skin test, 10 also reacted to the imipenem skin test. Therefore, it was concluded that there is a 50% cross-reactivity between penicillin and imipenem and that imipenem should not be administered to patients with a positive penicillin skin test or a concerning history of a type I allergic reaction to penicillin. In addition, the study showed a good correlation between the penicillin and analogous imipenem determinants to which the patients reacted. It was also noted that the minor antigenic determinants appeared to have the highest degree of cross reactivity with imipenem, possibly suggesting a higher risk of cross reactivity for patients with immediate type I penicillin allergies versus those with accelerated type I penicillin allergies.



**Carbapenems**

*Monobactams*

Aztreonam is the prototype monobactam. Monobactams also belong to the family of  $\beta$ -lactam antibiotics. However, unlike penicillins and cephalosporins, monobactams contain a monocyclic ring structure rather than a bicyclic ring. Unlike the other classes of  $\beta$ -lactam antibiotics, the monobactams appear to lack immune cross-reactivity with the penicillins. Saxon, et al., described 26 patients with positive penicillin skin tests who were safely treated with therapeutic doses of aztreonam.<sup>6</sup> None of the patients developed a clinical reaction to aztreonam. Furthermore, IgE antibodies to aztreonam were not detected by solid phase radioimmunoassay, and levels of preexisting antipenicillin antibodies did not rise. While larger numbers of subjects are needed to define the exact extent of clinically relevant cross-reactivity between penicillins and monobactams, most authorities consider the use of monobactams safe, even in patients with true penicillin allergies.



**Monobactams**

**Which patients should receive penicillin skin testing?**

Penicillin skin testing assesses the presence of IgE antibodies to major or minor antigenic determinants, and thus does not predict the possibility of type II, III, or IV hypersensitivity reactions. It has been reported that of those patients who claim to have a history of a penicillin allergy, 80 to 90% will have a negative penicillin skin test.<sup>6,8</sup> Of those patients with negative penicillin skin tests, 98% can tolerate penicillin without any sequelae.<sup>6,8</sup> Based on this information, it is recommended that a thorough history of the patient's penicillin allergy be taken. In a patient with a history of an adverse reaction to penicillin, the type of reaction and the advantage of a penicillin antibiotic over other antibiotics should guide the decision of whether a skin test should be performed. If a patient's history is concerning for a type I hypersensitivity reaction and penicillin therapy is warranted, skin testing should be considered. Conversely, penicillin skin

**Penicillin skin testing does not predict the possibility of type II, III, or IV hypersensitivity reactions.**

**Of the patients who claim to have a history of a penicillin allergy, 80-90% will have a negative penicillin skin test.**

**If treatment alternatives fail, induce unacceptable side effects, or are clearly less effective, a desensitization protocol should be considered.**

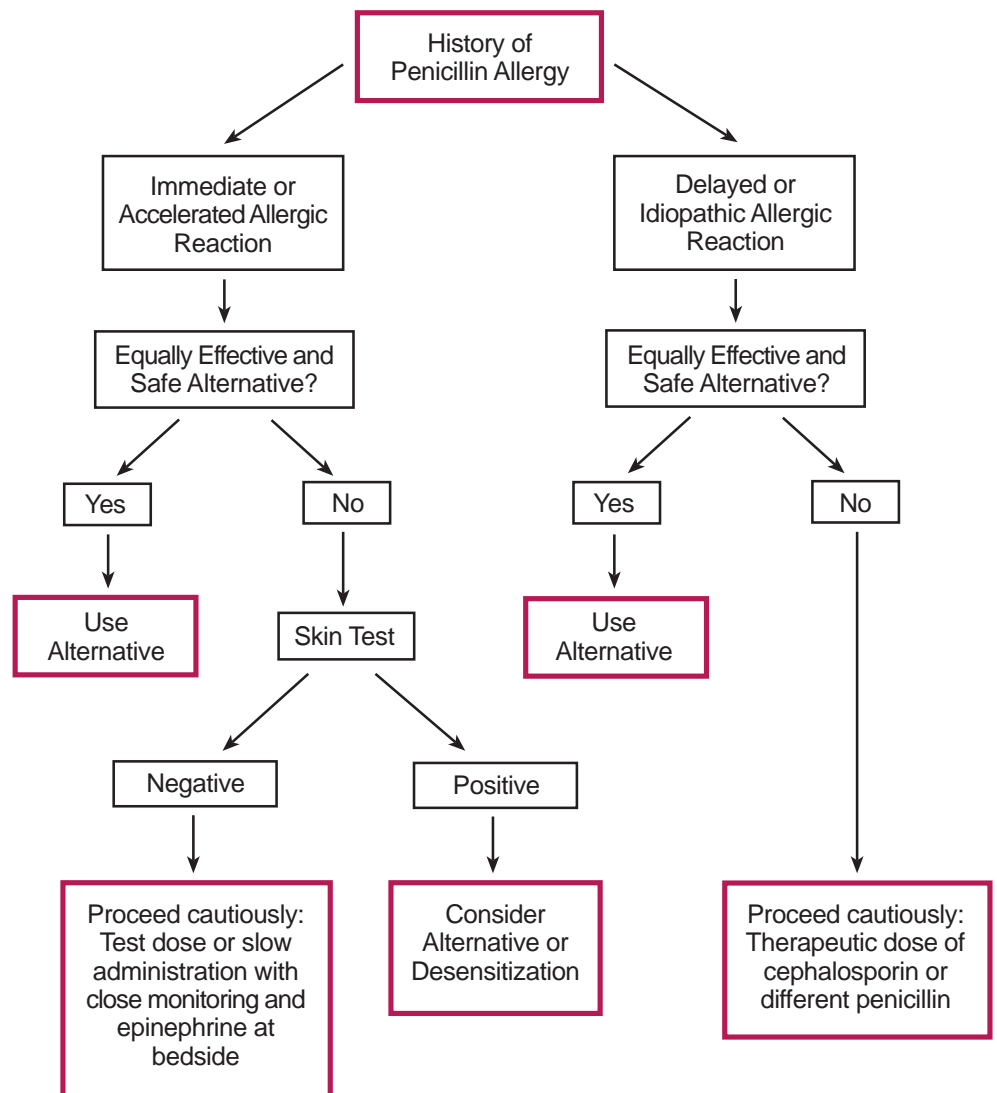
**Desensitization protocols reduce the risk of anaphylaxis, but do not prevent non-IgE mediated reactions from occurring.**

testing is unnecessary in patients with a true history of a life-threatening penicillin allergy, in situations where an equally efficacious and safe alternative is available, and in cases where the skin test results would not affect the physician's decision to withhold penicillin antibiotics. Figure 1 provides a general approach to patients with a positive penicillin allergy history.

**Which patients should be desensitized to penicillin?**

Alternative antibiotics are typically available for the treatment of patients with a true history of a penicillin allergy. However, if these alternatives fail, induce unacceptable side effects, or are clearly less effective, treatment with a penicillin antibiotic utilizing a desensitization protocol should be considered. Some examples of situations in which desensitization may be considered include bacterial endocarditis due to enterococci, brain abscess, bacterial meningitis, overwhelming infections with staphylococci or *Pseudomonas* organisms such as osteomyelitis or sepsis, *Listeria* infections, neurosyphilis or syphilis during pregnancy.<sup>8</sup> It is important to note that desensitization protocols reduce the risk of anaphylaxis, but do not prevent non-IgE-mediated reactions from occurring. Furthermore, a prior history of exfoliative dermatitis or Stevens-Johnson syndrome is a contraindication to the re-administration of any  $\beta$ -lactam antibiotic.

**Figure 1: Approach to Patients with a Positive History of Penicillin Allergy**  
(Adapted from Reference 9)



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**A time dependent decrease in the incidence of positive penicillin skin tests exists—by year 10, less than 20% of patients will react.**

### Are penicillin allergies lifelong?

Sullivan, et al., reported that positive penicillin skin tests occurred 80-90% of the time when conducted within the first 1 to 2 months after an allergic reaction.<sup>10</sup> Following this, a time-dependent decrease in the incidence of positive penicillin skin tests exists, and by year 10, less than 20% of patients will react. Furthermore, according to an article in the Mayo Clinic Health Letter, as many as 9 out of 10 people who believe they have had a prior allergic reaction to penicillin test negative for the allergy after avoiding the drug for 10 years.<sup>11</sup> While skin testing may be a valuable tool to determine if a patient's penicillin allergy is active, it is important to note that some patients can become re-sensitized and develop a hypersensitivity reaction to the drug at some point in the future.

### Conclusion

An inaccurate "penicillin allergy" label denies patients treatment with a safe, effective, and widely prescribed class of antibiotics. Therefore, it is important to accurately assess a patient's penicillin allergy status. The most useful tool in evaluating a patient's potential for a type I, IgE-mediated reaction to penicillin is the allergy history. This allergy history, coupled with an understanding of  $\beta$ -lactam hypersensitivity reactions, enables one to correctly interpret a patient's risk for a true allergic reaction and to use this information to properly guide therapeutic decisions.

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*Note: The editor gratefully acknowledges the assistance of Doug Black, Pharm.D., Tarquin Collis, M.D., and Yvonne Mark, R.Ph. in reviewing this article.*

## Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost <sup>‡</sup>	Therapeutic Classification	Use	Usual Adult Starting Dose*
<b>Iron sucrose (Venofer)</b>	Injection: 100mg elemental iron-\$36.42	Iron replacement	Iron deficiency anemia	100mg elemental iron IV 3 times/week to a total dose of 1000mg in 10 doses
<b>Nesiritide (Natrecor)</b>	Injection: 1.5 mg vial-\$374.56	Recombinant human B-type natriuretic peptide	Acute decompensated congestive heart failure	2mcg/kg IV bolus followed by 0.01mcg/kg/min continuous IV infusion
Formulary Deletions	Dosage Form(s), Strength(s)	Therapeutic Classification	Use	Comment
<b>Iron Dextran (Infed)</b>	All dosage forms and strengths	Iron replacement	Iron deficiency anemia	Replaced by iron sucrose (Venofer)
<b>Daclizumab (Zenapax)</b>	All dosage forms and strengths	Anti-CD25 Monoclonal antibody	Immunosuppression	Replaced by basiliximab (Simulect)

\* Refer to product labeling for full prescribing information. ‡ Costs represent UWMC/HMC outpatient acquisition costs and do not include pharmacy dispensing fees.

### New Director of Pharmacy Operations Appointed at UWMC

Larry Pelham, M.S., R.Ph., FASHP, has been chosen as the new Director of Pharmacy Operations at the University of Washington Medical Center, effective January 28, 2002. The Director of Pharmacy Operations is responsible for the management of clinical and distributive pharmacy services, budget performance, and implementation and management of pharmaceutical care programs. He will report to Shabir Somani, Director of Pharmacy for the Academic Medical Center.

Pelham began his career at the VA Medical Center in Seattle. In 1982 he joined St. Joseph Medical Center in Tacoma as Assistant Director of Pharmacy and later was administrator for their home health division. Most recently he has worked as the Director of Professional Services for NextRx, a pharmacy automation company.

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Supplement:  
Contemporary Issues  
in Drug Therapy



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