

Management of Patients with a History of Allergy to Beta-Lactam Antibiotics

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ABSTRACT

Patients with a history of penicillin allergy pose a treatment dilemma. Unnecessary avoidance of this relatively nontoxic class of drugs exposes the patient to potentially more toxic drugs, increases health care costs, and contributes to the development of antibiotic resistance. Yet for those who truly have allergy or other serious adverse reactions to beta-lactams, the use of alternate drugs is a must. This article reviews current management strategies to determine which patients are good candidates for reintroduction of beta-lactams and which patients should continue avoidance.

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KEYWORDS: Adverse drug reaction; Beta-lactam allergy; Cephalosporin allergy; Desensitization; Drug allergy; Late hypersensitivity reaction; Penicillin allergy; Skin testing; Test dosing

INTRODUCTION

Penicillin causes allergy more frequently than any other class of drugs. A history of penicillin allergy is present in approximately 10% of hospitalized patients.¹ Yet only approximately 10% of those with a history of penicillin allergy actually have allergic reactions when treated with a penicillin.² After an allergic reaction to penicillin, penicillin-specific immunoglobulin (Ig)E as demonstrated by positive penicillin skin tests decrease by approximately 10% per year, to approximately 30% after 10 years.¹

Many patients are inappropriately labeled penicillin allergic. For instance, aminopenicillins, such as ampicillin, are associated with a nonallergic rash during some viral illnesses. Patients may have had a side effect to the drug, such as gastrointestinal upset or headache. Therefore, it is important to document exactly what symptoms and signs occurred before labeling a patient penicillin allergic. These findings are useful in deciding whether that drug or a similar drug may be used for future therapy.

PENICILLIN ALLERGENS AND CROSS-REACTIVITY

Immunologically mediated drug reactions may be classified by mechanism (Table 1) or the timing of the reaction (Table 2). Immediate (within 1 hour) and accelerated (1-72 hours) reactions are IgE mediated. Late reactions (after 72 hours) are usually not IgE mediated.³

Symptoms of IgE-mediated drug allergy include flushing, pruritus, urticaria, angioedema, laryngeal edema, wheezing, hypotension, tachycardia, and ventricular arrhythmia. Anaphylaxis implies potentially life-threatening reactions involving 2 or more organ systems. Cutaneous reactions are more common than severe anaphylactic reactions. However, in a given patient, it is impossible to determine whether an acute cutaneous reaction will progress to anaphylaxis. Morbilliform rashes to penicillin are usually not IgE mediated.³

Antibody against native penicillin is directed at the beta-lactam ring (Figure 1), so a patient who is allergic to one type of penicillin is at risk for allergy to any beta-lactam antibiotic. Ninety-five percent of native penicillin is metabolized into benzylpenicilloyl-polylysine, called the "major determinant."^{4,5} Other important penicillin allergens, referred to as "minor determinants," include metabolites penilloate and penicilloate, and native benzylpenicillin. Some patients allergic to semisynthetic penicillins do not have IgE to major or minor determinants of native penicillin but to a side chain or a unique metabolite.^{4,5} With the decreased use

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Table 1 Immunologic Classification of Hypersensitivity Reactions (Gell and Coombs)

Gell-Coombs Classification	Time of Onset	Mediator(s)	Clinical Signs	Skin Testing Indicated
Type I	<1 h	IgE	Anaphylaxis: urticaria, angioedema, wheezing, laryngeal edema, hypotension	Yes
Type II	>72 h	IgG/IgM + complement	Immune cytopenia, some organ inflammation	No
Type III	>72 h	IgG or IgM immune complexes	Serum sickness, drug fever, vasculitis, tissue injury	No
Type IV	>72 h	T cells and cytokines	Contact dermatitis, some organ inflammation	No

Ig = Immunoglobulin.
Beta-lactam antibiotics can cause all 4 types of hypersensitivity reactions. Adapted with permission from Gell PGH, Coombs RRA. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell PGH, Coombs RRA, Lachman PJ, eds. *Clinical Aspects of Immunology*. 3rd ed. Oxford: Blackwell Scientific Publications; 1975:761-781.

of native penicillin, more patients demonstrate allergy to side-chain determinants than in the past.⁴

Cephalosporins cause allergy in 1% to 3% of those exposed.⁶ Although anaphylaxis and death occur, the majority of allergic reactions to cephalosporins are rashes.^{6,7} There is debate over the importance of cross-reactivity between penicillin and cephalosporins, but 5% to 10% of penicillin-allergic patients have allergy to cephalosporins.^{1,5} Cross-reactivity is low between penicillin and the second-, third-, and fourth-generation cephalosporins.⁶ Antibody to the unique side-chain allergens occurs in approximately two thirds of cephalosporin-allergic patients⁸ and is a better predictor of penicillin cross-reactivity in cephalosporin-

allergic individuals (Table 3).^{6,7} One study found that 8% of 24 cephalosporin-allergic patients had allergic reactions when challenged with penicillin.⁸ Penicillin-allergic patients have a 3-fold higher rate of allergic reactions to any drug, even structurally unrelated drugs.⁶ Thus, concomitant penicillin and cephalosporin allergy is not always due to cross-reactivity.

Carbapenem allergy is present in 11% of penicillin-allergic patients and 3% of penicillin non-allergic patients.⁹ Monobactams are tolerated by patients allergic to beta-lactam.^{3,4,6}

ANTIBIOTIC SELECTION IN PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY

Patients labeled penicillin allergic are usually treated with non-beta-lactam antibiotics. Because the overuse of broad-spectrum antibiotics may contribute to the development of microbial resistance and increase health care costs, strategies (including test dosing, skin testing, and desensitization) to determine which patients are candidates for readministration of beta-lactams have been considered (Figure 2). Severe non-

Table 2 Beta-Lactam Reactions Based on Time of Occurrence and Relation to Immunoglobulin-E

Immediate (<1 h) and accelerated (1-72 h), IgE mediated
Urticaria
Angioedema
Laryngeal edema
Bronchospasm
Hypotension
Late reactions (>72 h), possibly IgE mediated
Morbilloform rash
Urticaria
Severe late reactions (>72 h), not IgE mediated
Hemolytic anemia
Neutropenia
Thrombocytopenia
Serum sickness
Interstitial nephritis
Hepatitis
Pulmonary infiltration
Eosinophilia
Vasculitis
Stevens-Johnson syndrome
Drug fever

Ig = Immunoglobulin.
Adapted with permission from Levine BB. Immunologic mechanisms of penicillin allergy. A haptenic model system for the study of allergic diseases of man. *N Engl J Med*. 1966;275:1115-1125.

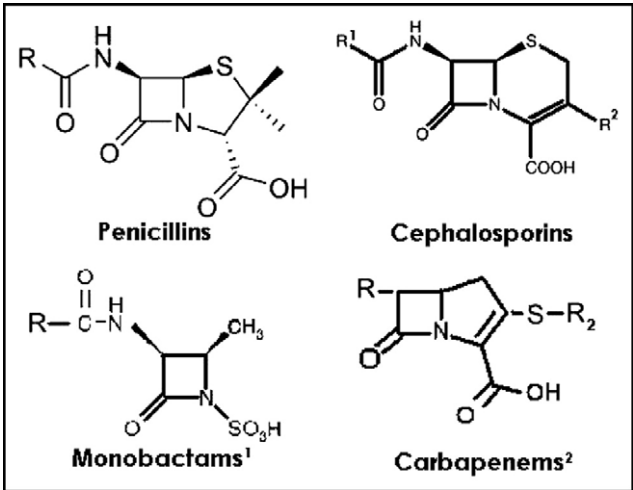


Figure 1 Chemical structures of beta-lactam antibiotics. 1, Monobactam: aztreonam. 2, Carbapenems: imipenem, meropenem.

Table 3 Chemical Similarities of Commonly Used 7-Position (R1) Side Chain Penicillins and Cephalosporins.

Penicillin G	Ampicillin	Ceftizoxime
Cefoxitin	Amoxicillin	Cefepime
Cephalexin	Cefaclor	Cefotaxime
	Cefadroxil	Cefpodoxime
	Cefprozil	Ceftriaxone
	Cephalexin	
Cephalosporins with R-1 Side Chains Chemically Unrelated to Penicillins		
Cefamandole	Cefotetan	
Cefazolin	Ceftazidime	
Cefdinir	Ceftibuten	
Cefixime	Cefuroxime	
Cefonicid	Cephapirin	
Cefoperazone	Moxalactam	

Listed as generic name. Adapted with permission from Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. *Pediatrics*. 2005;115:1048-1057.

IgE-mediated late reactions, including serum sickness, mucocutaneous blistering and skin-sloughing reactions, immune cytopenia, hepatitis, and nephritis, are drug specific, and patients with these reactions should avoid reexposure to the causative drug.

TEST DOSING

Patients with a history of morbilliform rash have a low risk for severe reaction with reexposure to the drug⁶ and might have a gradual dose challenge (also called test dosing) to the drug. The initial dose is usually 0.1% to 1% of the therapeutic dose and is given orally if possible because the risk of severe reaction is lower.¹ If no adverse reaction occurs, the dose is gradually increased (2 to 10-fold) over minutes to days until a therapeutic dose is achieved.¹ There is a small risk for a significant reaction, so this should be performed in a monitored setting and with informed consent regarding the risks and indications. Allergists-immunologists or other physicians knowledgeable in recognizing and treating the symptoms of adverse drug reactions can be useful consultants for this procedure.

SKIN TESTING

Penicillin skin testing detects the presence or absence of penicillin-specific IgE and predicts the likelihood of IgE-mediated allergic reactions to penicillin. Skin testing is used to determine whether a patient with a history of an allergic reaction can tolerate penicillin. A positive penicillin skin test result indicates the presence of IgE to penicillin, but only approximately 60% of patients with a positive skin test result to penicillin will actually have an allergic reaction when penicillin is administered.⁶ Negative skin test results to the major and 3 minor

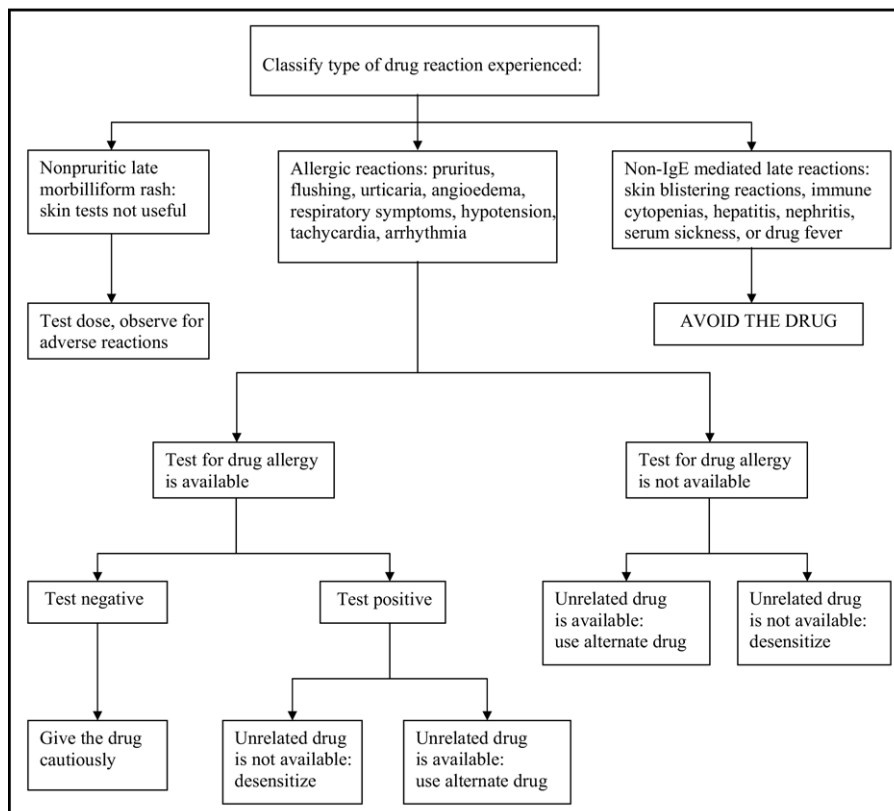


Figure 2 Approach to the patient with a previous beta-lactam reaction who requires treatment for a similar indication. Ig, Immunoglobulin.

penicillin determinants have a negative predictive value of 99% for successful patient tolerance to penicillin.^{2,10} Testing with benzylpenicilloyl-polylysine and benzylpenicillin alone will miss at least 10% of penicillin-allergic patients.² The use of benzylpenicillin and minor determinant mixture without benzylpenicilloyl-polylysine will miss approximately 25% to 60%.¹ Skin testing to amoxicillin helps to detect side chain-specific allergy.^{4,10} Patients who undergo penicillin skin testing in advance of a specific need of antibiotic therapy have a low risk of becoming resensitized to penicillin ($\leq 3\%$).¹⁰ Systemic allergic reactions to penicillin skin testing is low, occurring in 0.12% in one large study of 1710 patients.¹¹

Until September of 2004, benzylpenicilloyl-polylysine was commercially available in the United States as Pre-Pen (Hollister Stier, Spokane, Wash) for skin testing. A new US company (AllerQuest, Plainville, Conn) has purchased the patent rights to produce PrePen, and this should be available in 2008 for skin testing.

Penicillin skin testing does not conclusively determine which patients will have an allergic reaction to cephalosporins.^{7,11} Skin testing to native cephalosporins at 2 mg/mL had a high negative predictive value of more than 80% in one study of 128 patients.¹²

DESENSITIZATION

Patients with positive penicillin skin testing should receive alternate antibiotics if possible. However, when a beta-lactam antibiotic is the *only* indicated antibiotic, or a patient is unable to undergo penicillin skin testing, desensitization to the antibiotic might be attempted. This procedure incurs the risk of anaphylaxis and death, and should only be performed with informed consent, in a closely monitored setting, by a physician experienced in the recognition and treatment of anaphylaxis. The absolute need for the antibiotic should be documented before initiating desensitization. Epinephrine, antihistamine, normal saline, and oxygen must be immediately available, and a large-bore intravenous line must be in place for resuscitation if needed. Beta-blockers should be discontinued, because they complicate treatment of anaphylaxis. Desensitization can be performed intravenously or orally, but the oral route has a lower risk for anaphylaxis.⁵ Most regimens begin with a dilute concentration of drug, and the dose is doubled every 15 to 30 minutes until a full therapeutic dose is reached (Table 4). Desensitization is usually successful, although mild reactions, such as pruritus and urticaria, are seen in 30% of patients during and after desensitization. Non-IgE-mediated immunologic reactions occurred in 5% of patients. None of the reactions were fatal.¹³ Long-term desensitization may be maintained with chronic twice-daily dosing of penicillin.¹³

CONCLUSIONS

Management of patients with a history of adverse drug reaction is a frequent dilemma in medical practice. Detailed documentation of the adverse reaction will help in the future

Table 4 Protocol for Oral Desensitization to Beta-Lactam Antibiotic*

Step	Concentration of Drug (mg/mL)	Amount (mL)	Dose Given (mg)	Cumulative dose (mg)
1	0.5	0.1	0.05	0.05
2	0.5	0.2	0.10	0.15
3	0.5	0.4	0.20	0.35
4	0.5	0.8	0.40	0.75
5	0.5	1.6	0.80	1.55
6	0.5	3.2	1.60	3.15
7	0.5	6.4	3.20	6.35
8	5.0	1.2	6.00	12.35
9	5.0	2.4	12.00	24.35
10	5.0	4.8	24.00	48.35
11	50.0	1.0	50.00	98.35
12	50.0	2.0	100.00	198.35
13	50.0	4.0	200.00	398.35
14	50.0	8.0	400.00	798.35

Observe patient for 30 minutes, and then administer 1 g of same agent intravenously.

*Interval between doses is 20 to 30 minutes.

Drug suspension diluted in 30 mL of water for oral ingestion.

Adapted with permission from Sullivan TJ. Drug allergy. In: Middleton EJ, Reed CE, Ellis EF, et al, eds. *Allergy: Principles and Practice*. 4th ed. St Louis: CV Mosby; 1993:1726.

when similar drug therapy is indicated. Many patients may tolerate careful readministration of penicillin or may be candidates for desensitization. Allergists-immunologists may be helpful when chemically unrelated alternative drugs are not appropriate. Evidence-based testing, challenge, and desensitization procedures are available and aid practitioners in the management of these challenging clinical situations.

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