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A Review of Evidence Supporting the American Academy of Pediatrics Recommendation for Prescribing Cephalosporin Antibiotics for Penicillin-Allergic Patients

Michael E. Pichichero, MD

ABSTRACT. The American Academy of Pediatrics, evidence-based guidelines endorse the use of cephalosporin antibiotics for patients with reported allergies to penicillin, for the treatment of acute bacterial sinusitis and acute otitis media. Many physicians, however, remain reluctant to prescribe such agents. Although such concern is understandable, lack of consistent data regarding exactly what constitutes an initial penicillin-allergic reaction and subsequent cross-sensitivity to cephalosporins may be preventing many patients from receiving optimal antibiotic therapy. This article reviews evidence in support of the American Academy of Pediatrics recommendation. Included is an examination of the types and incidence of reactions to penicillins and cephalosporins; the frequency of cross-reactivity between these 2 groups of agents; experimental and clinical studies that suggest that side chain-specific antibodies predominate in the immune response to cephalosporins, thereby explaining the lack of cross-sensitivity between most cephalosporins and penicillins; the role of skin testing; and the risks of anaphylaxis. Specific recommendations for the treatment of patients on the basis of their responses to previously prescribed agents are summarized. *Pediatrics* 2005;115:1048–1057; *penicillin, cephalosporin, allergy.*

ABBREVIATION. AAP, American Academy of Pediatrics.

The American Academy of Pediatrics (AAP) practice guidelines for the management of acute bacterial sinusitis¹ endorse the use of selected second-generation and third-generation cephalosporin antibiotics (cefuroxime, cefpodoxime, and cefdinir) for penicillin-allergic patients as long as the penicillin reaction is not severe. Severe reactions include anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug-induced hypersensitivity syndrome with multiorgan involvement. The AAP guideline for acute otitis media² endorses the use of cefuroxime, cefpodoxime, and cefdinir for patients with “non-type I allergy” and ceftriaxone as an alternative for patients with penicillin allergy. These recommendations are evidence based and rec-

ognize that the often-cited 8%³ to 18%⁴ rates of cross-sensitivity to cephalosporins among penicillin-allergic patients are lacking in accuracy and require revision.

Much of the confusion about cephalosporin allergy among penicillin-allergic patients is attributable to the term “allergic reaction” having been applied uncritically to any adverse reaction⁵ and clinically relevant “cross-sensitivity” to the detection of any cross-reactive antibody. Indeed, in daily practice and in many epidemiologic surveys, patients with histories of penicillin or cephalosporin “allergy” have experienced nonimmunologic side effects (eg, vomiting, diarrhea, or nonspecific rash), toxic effects, or contemporaneous adverse experiences occurring during antibiotic therapy that are attributed inappropriately to the drug.

After receiving penicillin, most humans produce IgG and IgM antibodies without experiencing any adverse consequences.⁶ These antibodies may cross-react with cephalosporin antigens.^{3,7–16} Therefore, their detection does not necessarily predict immunologic or allergic cross-sensitivity. When an allergic reaction to a cephalosporin occurs in a penicillin-allergic patient, it may be coincidental. The true increased risk of an allergic reaction to a cephalosporin among penicillin-allergic patients must take into account the possibility of a primary (and unrelated) cephalosporin allergy. Despite many studies using different comparison populations,^{17–30} the risk attributable to penicillin hypersensitivity when an allergic reaction follows cephalosporin treatment has not been established clearly.

In this review, evidence supporting the AAP recommendation of cephalosporin use for individuals labeled as penicillin allergic is discussed. Specifically, this article examines the types of reactions these antibiotics cause, the incidence of reactions, and the frequency of allergic cross-reactivity between these 2 classes of antibiotics.

TYPES OF REACTIONS

The classification of immunologically mediated drug reactions described by Gell and Coombs³¹ is shown in Table 1. IgE-mediated (type I) reactions are the most dangerous, with clinical manifestations ranging from urticaria to anaphylaxis. Appropriate synonyms for IgE-mediated reactions include allergic and/or immediate hypersensitivity reactions. The presence of IgE antibodies to penicillins and cephalosporins is predictive of possible subsequent,

From the University of Rochester, Elmwood Pediatric Group, Rochester, New York.

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Address correspondence to Michael E. Pichichero, MD, University of Rochester Medical Center, Elmwood Pediatric Group, 601 Elmwood Ave, Box 672, Rochester, NY 14642. E-mail: michael.pichichero@urmc.rochester.edu
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TABLE 1. Classification Scheme for Adverse Drug Reactions Described by Gell and Coombs³¹

Classification	Time of Onset, h	Mediator(s)	Clinical Signs	Skin Testing Useful	Comments
Allergic immediate (type I)	<1	Antibiotic-specific IgE antibodies	Anaphylaxis and/or hypotension, laryngeal edema, wheezing, angioedema, or urticaria	Yes	Much more likely with parenteral than oral administration; fatal outcome in 1 per 50 000 to 1 per 100 000 treatment courses with penicillin; accelerated reactions occurring 1–72 h after exposure may be IgE mediated
Late (type II)	>72	IgG, complement	Increased clearance of red blood cells and platelets by lymphoreticular system	No	IgE not involved
Type III	>72	IgG and IgM immune complexes	Serum sickness, tissue injury	No	Tissue lodging of immune complexes; drug fever; IgE not involved
Type IV	≥72		Contact dermatitis	No	IgE not involved
Other (idiopathic)	Usually >72		Maculopapular or morbilliform rashes	No	1–4% of all patients receiving penicillins and cephalosporins

immediate, IgE-mediated, allergic hypersensitivity reactions, but many patients with detectable IgE antibodies do not display a clinical allergic reaction. IgG and IgM antibodies do not induce allergic reactions; only IgE binds to mast cells and basophils to produce such reactions. Cytotoxic IgG antibody (type II) reactions and antigen-antibody (IgG or IgM)-mediated (type III) reactions are induced by β -lactam antibiotics, albeit rarely, and are difficult to predict prospectively; these are not allergic reactions. The occurrence of type II or III reactions should lead to avoidance of future use of the drug. An example of such a reaction is the serum sickness-like reaction to cefaclor caused by a heredity defect in metabolism of the drug.³² Patients who have a history of such reactions to cefaclor can take other cephalosporins without difficulty, including loracarbef, although it is structurally similar to cefaclor.³² Contact dermatitis (type IV or delayed hypersensitivity) reactions to penicillins and cephalosporins occur primarily among nurses, pharmacists, and those involved in the drug-manufacturing process; these are not allergic reactions. Idiopathic reactions occur through unknown mechanisms, and their recurrence is not predictable. These are sometimes termed “non-type I allergic reactions,” but they are not IgE mediated and are not truly allergic. For antibiotic cross-reactivity, the focus for clinicians should be on allergic reactions to penicillin that are predictive of an increased likelihood of allergic, IgE-mediated, type I reactions to cephalosporins.

Another useful classification scheme for reactions to antibiotics uses the timing of their occurrence (Table 2).³³ Reactions that begin within the first 1 hour after administration are IgE mediated and may progress to anaphylaxis, including wheezing, hypotension, laryngoedema, and dysphasia. Accelerated reactions occur 1 to 72 hours after administration, which indicates that they are almost always associated with previous sensitizations; these reactions are also IgE mediated. Late reactions, which occur beyond 72 hours, may be attributable to the new onset of IgE-mediated hypersensitivity (although this is very unusual)³⁴ or type II, III, or IV and/or idiopathic mechanisms.

TABLE 2. Types of Allergic Reactions to Penicillins and Cephalosporins³³

Immediate (within 1 h) and accelerated (1–72 h), IgE mediated
Urticaria
Laryngeal edema
Bronchospasm
Hypotension
Local swelling
Late (after 72 h)
Morbilliform rash
Serum sickness
Urticaria
Other late reactions
Stevens-Johnson syndrome
Interstitial nephritis
Pulmonary infiltration
Vasculitis
Hemolytic anemia
Neutropenia
Thrombocytopenia

Reactions to antibiotics that manifest as rashes can be difficult to assess and present clinicians with a conundrum.³⁵ Maculopapular rashes that are not pruritic occur among 3% to 7% of children taking ampicillin³⁶ and emerge during antibiotic treatment. These rashes are very unlikely to be IgE mediated and are most likely idiopathic. Therefore, they are not a contraindication for the future use of the drug.³⁷ If the patient has taken the antibiotic in the past or if the rash develops in the second week of the initial course of the antibiotic and is pruritic, then it is possibly an allergic reaction.³⁸ However, the immune response that a patient mounts to a viral infection can alter the immune response to an antibiotic, resulting in an allergy-like reaction specifically to that antibiotic, one that is highly unlikely to recur. The most well-known example of this is the rash that develops among patients with acute Epstein-Barr virus infection after they receive amoxicillin.³⁹ This rash is usually maculopapular, rather than urticarial, but it is often pruritic. These patients are not allergic to amoxicillin.

INCIDENCE OF REACTIONS TO PENICILLIN

The true incidence of penicillin allergy among patients with that history is often $\leq 10\%$.^{38,40–45} In a

cohort of 298 children with a history of side effects associated with prior oral penicillin administration, only 1 (0.3%) had a positive radioallergosorbent test for penicillin.⁴⁶ In another study, 4 of 132 patients (3%) referred for a penicillin allergy evaluation were confirmed to have an allergy through radioallergosorbent testing.⁴⁷

PENICILLIN SKIN TESTING

Skin tests are an important means of confirming or refuting a history of penicillin allergy and of predicting which patients are at risk of developing IgE-mediated reactions to penicillin. Such tests yield positive results for a variable percentage (1–20%) of patients reporting an allergic reaction to penicillin or its derivatives, depending on the study population.* In subsequent challenge studies, positive skin tests appear to be ~60% predictive of clinical hypersensitivity.^{41–45} It is important to emphasize that skin testing and/or rechallenge with penicillin should not be performed for patients with a history of Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatitis, hemolytic anemia, or interstitial nephritis. Skin testing is usually performed with penicillin G, the major determinant of benzylpenicillin (benzylpenicilloyl), a minor determinant mixture of benzylpenicillin, and often also with ampicillin.^{23,28,38,49,51,55–62} Salkind et al⁶³ conducted an evidence-based analysis of the likelihood of penicillin allergy on the basis of clinical history. Positive and negative likelihood ratios were calculated by evaluating studies that compared clinical history and skin tests for penicillin allergy among patients with or without a positive history of penicillin allergy. A history of penicillin allergy had a positive likelihood ratio of 1.9 (95% confidence interval: 1.5–2.5), whereas an absence of penicillin allergy had a negative likelihood ratio of 0.5 (95% confidence interval: 0.4–0.6), as validated with appropriate skin testing.

CEPHALOSPORIN SKIN TESTING

Skin testing for cephalosporins has been undertaken in a number of studies,[‡] but the positive and negative predictive values of the results are less well established than those of penicillin. If the haptens that cause cephalosporin allergy were known, cross-reactivity with penicillins could be assessed directly. Currently, cephalosporin skin tests are performed with the native molecule. Unlike penicillins, cephalosporins lose both ring structures during degradation,^{9,10,25,73} which may generate unique haptens⁷⁴ or neoantigens or may make the cephalosporin ring structure clinically irrelevant.

INCIDENCE OF REACTIONS TO CEPHALOSPORINS

The majority of allergic reactions to cephalosporins consist of rashes, which occur for 1.0% to 2.8% of patients.²⁴ In most cases, the mechanism is idiopathic and the reaction is not a contraindication for future use. Type II reactions occur for 1% to 2% of patients. Retrospective studies of different cephalosporins and

information provided by pharmaceutical companies were reviewed by Anne and Reisman,¹⁸ who calculated the incidence of immune-mediated adverse reactions to cephalosporins to be 1% to 3% for all patients.¹⁸

CROSS-REACTIVITY OF PENICILLINS AND CEPHALOSPORINS

Penicillins and cephalosporins have similar chemical configurations. Both classes of antibiotic are of low molecular weight, are highly substituted, and possess a β -lactam ring, on which antimicrobial activity depends.⁷⁵ Cephalosporins and penicillins differ in that the 5-membered thiazolidine ring of penicillin is replaced with a 6-membered dihydrothiazine ring in the cephalosporins. However, after degradation, penicillin forms a stable penicilloate ring, with preservation of the thiazolidine ring, whereas cephalosporins undergo rapid fragmentation of the β -lactam and dihydrothiazine rings.^{9,10,25,73} On the basis of these differences in degradation, immunologic cross-reactivity between β -lactam rings of these compounds might be minimal, a finding supported by clinical and monoclonal antibody analysis (discussed later).

In the years following the introduction of cephaloridine and cephalothin, anaphylactic reactions were reported for patients who had prior allergic reactions to penicillin.^{64,65,76,77} Subsequently, significant antigenic cross-reactivity between penicillin and those cephalosporins was observed with *in vitro* tests such as hemagglutination inhibition, quantitative histamine release, and lymphocyte proliferation.^{7,9,22} The clinical relevance of these *in vitro* cross-reactions was never demonstrated, and skin tests with cephalosporin C among penicillin-sensitive patients failed to confirm any allergic cross-reactivity.⁶⁶

Numerous studies of patients with a history of allergy to penicillin or skin test confirmation of being penicillin allergic who received cephalosporins have been reported. In Table 3, a summary of data from 25 studies[§] evaluating “allergic reactions” to cephalosporins is presented. The term allergic is used here as applied by the authors, but review of the articles indicates that a proportion of the reactions were not allergic, and these findings are likely overestimates. The rates of reactions among penicillin-allergic patients (with history or skin test confirmation) appear to differ according to cephalosporin generation. First-generation agents demonstrate an increased rate of reaction that is not observed for second- or third-generation drugs. However, there is a threefold increased coincidental risk of adverse reactions to unrelated drugs among penicillin-allergic patients.⁴¹ If this nonspecific increased reaction risk is taken into account, then the proportion of allergic reactions most likely directly attributable to first-generation cephalosporins among penicillin-allergic patients can be recalculated (Table 3). Two seminal reviews that contributed >95% of the patients in the first-generation cephalosporin analyses are noteworthy.

*Refs 11, 12, 21, 23, 29, 38, 40–45, and 48–54.

‡Refs 4, 5, 9, 11, 14, 19, 24, 31, 46, 48, 49, and 64–72.

§Refs 4, 5, 7, 12, 18, 43–45, 58, 66, 67, 69–72, 74, and 78–84.

TABLE 3. Proportions of Patients With "Allergic Reactions" to Cephalosporins, Stratified According to Cephalosporin Generation, Penicillin Allergy History, and Penicillin Skin Test Results

Cephalosporin Generation	Penicillin Allergy History But No Skin Testing, No. (%)		P Value	Penicillin Allergy Skin Test Confirmed, No. (%)		P Value
	Yes	No		Yes	No	
First						
Reported proportion	83/1043 (7.9)*	458/3288 (1.4)†	<.0001	15/138 (10.9)‡	2/63 (3.2)§	.12
Attributable proportion	21/1088 (1.9)	458/32 885 (1.4)	.18	4/138 (2.9)	2/63 (3.2)	.73
Second	11/585 (1.9)	112/675 (1.7)	.82	5/269 (1.9) ¶	6/497 (1.2)	.69
Third	5/772 (0.6) #	77/5452 (1.4) **	.12	2/259 (0.8) ††	7/497 (1.4)	.68
Unspecified				2/129 (1.6)‡‡	6/341 (1.8)§§	.81

Excluding anaphylaxis case reports presented in Table 9.

* From refs 66, 72, 74, and 78 to 81.

† From refs 4, 72, and 78 to 81.

‡ From refs 4, 7, 67, 69, 70, 82, and 83.

§ From refs 4 and 44.

|| Data included from author's unpublished prospective case series with history and skin-testing techniques, as described in ref 38.

¶ From refs 67, 69, and 70.

From refs 12, 18, and 58.

** From ref 12.

†† From refs 70 and 82.

‡‡ From refs 5, 43, 45, 71, and 84.

§§ From refs 43, 71, and 84.

TABLE 4. Frequency of Reactions to Cephalosporins Among Patients With a History of Penicillin Allergy⁸¹

Drug	No History of Penicillin Allergy		History of Penicillin Allergy		P Value
	No. of Patients	Reaction to Cephalosporins, No. (%)	No. of Patients	Reaction to Cephalosporins, No. (%)	
Cephalexin	6573	73 (1.1)	69	5 (7.2)	<.0001
Cephaloridine	10 967	92 (0.8)	255	20 (7.8)	<.0001
Total	17 540	165 (0.9)	324	25 (7.7)	<.0001

A 1975 review by Dash⁸¹ suggested that the rate of "allergic reactions" to cephalosporins among "penicillin-allergic" patients was 7%, compared with an overall rate of reactions to cephalosporins among non-penicillin-allergic patients of ~1% (Table 4).⁸¹ In 1971³ and 1978,⁷⁴ Petz reviewed the literature on allergy to cephalosporins among penicillin-allergic and nonallergic patients, including 15 708 cases in clinical trials of patients who were treated with cephalothin, cephaloridine, cephalexin, cefazolin, or cefamandole. Table 5 shows the number of "allergic" reactions reported after administration of these cephalosporins to putative penicillin-allergic and nonallergic patients. Of the 15 708 patients, 701 (4.5%) had a history of allergy to penicillin and 57 (8.1%) of those had an allergic reaction to administration of the specified cephalosporin. Of the 15 007 patients who did not have a history of penicillin allergy, 285 (1.9%) had an allergic reaction to cephalosporins. Many of these reactions were rashes (without specification as pruritic or urticarial). The 8.1% figure from that article appears to be the basis of the widely cited (and rounded up) figure of 10% cross-sensitivity between the 2 drug classes.⁸⁵ Although many interpreted the risk of reactions to cephalosporins to be increased fourfold among patients who were allergic to penicillin, this was not the interpretation by Petz. He stated, "These data superficially suggest cross-allergenicity but such a conclusion is not warranted."³ Most importantly, it was later discovered that, because penicillin-related compounds are produced by

the *Cephalosporium* mold,²⁴ the early first-generation cephalosporin antibiotics included in the analyses by Dash⁸¹ and Petz^{3,74} contained trace amounts of penicillin.^{5,86} Therefore, the data reported by Dash⁸¹ and Petz^{3,74} and others until 1980⁸⁷ for first-generation cephalosporins overestimated cross-sensitivity, significantly weakening the conclusions.⁸⁸ The cross-reactivity rates between penicillin and most second-generation and third-generation cephalosporins appear very low and may actually be lower than the cross-reactivity rate between penicillins and other classes of antibiotics,³⁰ although the cross-reactivity rate may not be 0.

THE IMPORTANCE OF THE CEPHALOSPORIN SIDE CHAIN

During the past decade, a considerable body of evidence has established that the immune response to cephalosporins is more dependent on their side chain molecular structure than is the case with penicillin.|| That is, cephalosporins bearing a side chain similar to benzylpenicillin may be more likely to cross-react with penicillin. For example, cephalothin and cephaloridine have identical thiophene 2-acetic acid side chains at the 7-position of the β -lactam ring, which closely resemble the phenylacetic acid side chain of benzylpenicillin (Table 6); therefore, these 2 cephalosporins may have a 0.5% to 6.5% greater

||Refs 5, 12, 17–21, 23, 24, 29, 30, 38, 43, 50, 51, 56, 58–60, 67–69, 82, 84, 86, and 89–100.

TABLE 5. Cephalosporin Allergy Among Penicillin-Allergic Patients^{3,74}

Cephalosporin and History of Penicillin Allergy (<i>n</i>)	Adverse Reactions, No. (%)	Type of Reaction (No.)	<i>P</i> Value*
Cephaloridine			
No (3471)	86 (2.6)	No data	
Yes (109)	14 (13.0)†	Rash (11), urticaria (6), fever (1)	<.001
Cephalothin			
No (1045)	21 (2.0)	Anaphylaxis (2), rash or urticaria (14), unspecified (5)	.016
Yes (138)	8 (5.8)	Anaphylaxis (2), rash or urticaria (5), unspecified (1)	
Cephalexin			
No (7819)	87 (1.1)‡	Rash (37), urticaria (12), miscellaneous (12)	<.0001
Yes (291)	19 (6.5)§	Rash (8), urticaria (1), miscellaneous (2)	
Cefazolin			
No (1369)	8 (0.6)	No data	.08
Yes (74)	3 (4.0)	No data	
Cefamandole			
No (1303)	83 (6.4)	No data	.017
Yes (89)	13 (14.6)	No data	
Overall cephalosporins			
No (15 007)	285 (1.9)		.0001
Yes (701)	57 (8.1)		

* Comparing those with and without a history of penicillin allergy.

† In ref 3, there were 18 patients in this group; in ref 74, there were 14 patients in this group.

‡ In ref 3, there were 61 patients in this group; in ref 74, there were 87 patients in this group.

§ In ref 3, there were 11 patients in this group; in ref 74, there were 19 patients in this group.

TABLE 6. Chemical Structures of 7-Position Side Chains of Penicillins and Cephalosporins

Similar Structure/Possible Cross-Reactivity With Group			Dissimilar Structures/Unlikely Cross-Reactivity	
Related	Related	Related	Not Related	Not Related
Penicillin G	Amoxicillin	Cefotaxime	Cefsulodin	Cefotiam
Cephaloridine	Ampicillin	Ceftizoxime	Cefazolin	Ceftazidime
Cephalothin	Cefaclor	Ceftriaxone	Cefonicid	Cefamandole
Cefoxitin	Cephalexin	Cefpodoxime	Cefotetan	Cephapirin
	Cephadrine	Cefpirome	Cefuroxime	Cefixime
	Cefprozil	Cefepime	Cefoperazone	Cefmetazole
	Cefatrizine	Cefetamet	Cefdinir	Ceftibuten
	Cefadroxil	Cefteram		Moxalactam

TABLE 7. Chemical Structures of 3-Position Side Chains of Penicillins and Cephalosporins

Similar Structure/Possible Cross-Reactivity Within Group							Dissimilar Structure/ Unlikely Cross-Reactivity: Not Related
Related	Related	Related	Related	Related	Related	Related	
Cephadrine	Cefmetazole	Cephapirin	Ceftazidime	Cefuroxime	Cefdinir	Ceftibuten	Cefatrizine
Cefadroxil	Cefoperazone	Cefotaxime	Cefsulodin	Cefoxitin	Cefixime	Ceftizoxime	Cefotiam
Cephalexin	Cefotetan	Cephalothin					Cefpodoxime
	Cefamandole						Cefprozil
							Ceftibuten
							Ceftriaxone
							Cefonicid
							Cefepime
							Cefotiam
							Cefazolin
							Cephaloridine
							Cefaclor

likelihood of producing an allergic reaction among penicillin-allergic patients (Table 3). Cefadroxil, cephalexin, cefaclor, cephradine, cefprozil, cefatrizine, and cefadroxil have 7-position side chains similar to those of ampicillin and amoxicillin (Table 6); therefore, these cephalosporins may have a 0.5% to 6.5% greater likelihood of producing allergic reactions among amoxicillin-allergic patients (Table 3). In contrast, a cephalosporin such as cefdinir (endorsed by the AAP for treatment of acute sinusitis and otitis

has a dissimilar 7-position side chain, compared with penicillin or amoxicillin (Table 6); therefore cefdinir is highly unlikely to produce an allergic reaction among either penicillin-allergic or amoxicillin-allergic patients. Cefdinir has a 3-position side chain similar to that of cefixime (Table 7); therefore, cefdinir has a greater likelihood of producing an allergic reaction among cefixime-allergic patients. Side chain structure, and thus possible allergic cross-reactivity, does not correlate with the antimicrobial classifica-

TABLE 8. Classification of Cephalosporins

First Generation	Second Generation	Third Generation	Fourth Generation
Cephalothin	Cefaclor	Ceftazidime	Cefepime
Cephapirin	Cefamandole	Cefsulodin	Cefpirome
Cefadroxil	Cefmetazole	Cefoperazone	
Cephalexin	Cefonicid	Cefdinir	
Cefazolin	Cefotetan	Cefetamet	
Cefatrizine	Cefoxitin	Ceftibuten	
Cephaloridine	Cefprozil	Cefixime	
Cephradine	Cefuroxime	Cefpodoxime	
	Loracarbef	Ceftriaxone	
		Cefotaxime	
		Ceftizoxime	
		Moxalactam	
		Cefotiam	

tion of the cephalosporins as first, second, third, or fourth generation (Table 8), which is a system of classification more familiar to most clinicians.

The detection of IgE antibody to penicillin or cephalosporins or of cross-reactive IgE antibody does not predict a definite clinical reaction. Blanca et al⁶⁷ studied 19 well-characterized, penicillin-allergic patients for their sensitivity to cephalosporins containing potentially cross-reactive side chains. Antibenzylpenicilloyl antibodies cross-reacted well with cephaloridine and cefamandole, which have side chains identical or very similar to those of penicillin. When challenged with the drug, only 2 of the 19 (10.5%) reacted to cefamandole; the others tolerated both cephalosporins with no adverse effects. Sastre et al⁸³ studied the clinical cross-reactivity between amoxicillin and cefadroxil among 16 patients allergic to amoxicillin, with good tolerance of penicillin. Although these 2 drugs share an identical side chain, only 2 (12%) of the amoxicillin-allergic patients demonstrated an allergic reaction to cefadroxil, which suggests that the side chain of aminopenicillins was clinically relevant for 12% of the patients. Miranda et al⁶⁹ evaluated 21 patients allergic to amoxicillin for allergenic cross-reactivity to cefadroxil and cefamandole; 8 patients (38%) had a positive response to cefadroxil (same side chain) and none to cefamandole (different side chain).

STUDIES WITH MONOCLONAL ANTIBODIES

Experimental studies in mice with monoclonal antibodies identified cephalosporin epitopes that indicate that nearly all antibodies recognize structures unique to cephalosporins, with little or no recognition of penicillins.¹⁰¹ Using monoclonal antibodies raised against amoxicillin-protein conjugates, Mayorga et al¹⁰² evaluated the antigenic contribution of different regions of the penicillin molecule, analyzing their specificities in detail. Eleven of 12 monoclonal antibodies (92%) recognized an epitope in which the side chain was a major constituent, none recognized the thiazolidine ring or the conjugated nuclear region of the penicillins, and 1 recognized all different structures of the penicillin molecule equally.

CROSS-REACTIVITY TO PENICILLIN AMONG CEPHALOSPORIN-ALLERGIC PATIENTS

Few studies have been conducted to evaluate cross-reactivity with penicillin among patients with

primary hypersensitivity to cephalosporins. Romano et al^{86,93,94} examined IgE responses among patients with immediate allergic reactions to cephalosporins by performing skin tests and radioallergosorbent tests with the responsible drugs; the responses to other cephalosporins and to the classic penicillin determinants were also assessed. Less than 20% of the cephalosporin-allergic subjects reacted to penicillin determinants in skin testing, but the majority had positive responses to other cephalosporins with the same or similar side chain structure (ceftriaxone and cefotaxime) (Table 6).

PREDICTIVE VALUE OF PENICILLIN SKIN TESTING FOR CEPHALOSPORIN ALLERGY

The results of penicillin skin testing do not predict cephalosporin allergy reliably. Skin testing for cross-reactivity between penicillins and cephalosporins generally shows some cross-reactivity between penicillins and first-generation cephalosporins, ie, between ampicillin/amoxicillin and cephalexin/cefadroxil, but not between penicillin/amoxicillin and second-generation or third-generation cephalosporins.¶ The value of penicillin skin testing in predicting an allergy to cephalosporins among patients with a history of penicillin allergy therefore is controversial. If the penicillin or amoxicillin side chain is identical or similar to that of the cephalosporin, then such testing is of possible value.

RISKS OF ANAPHYLAXIS

In a comprehensive international survey, the incidence of anaphylaxis with penicillins was 0.015% to 0.004%, with a fatality rate of 0.002% to 0.0015%.⁴⁰ More limited data suggested that the rate of anaphylaxis with cephalosporins was 0.1% to 0.0001%.²⁴ Cases of anaphylaxis induced by cephalosporins# are summarized in Table 9. Of course, these findings are subject to reporting bias,¹²⁷ but there are more reported cases of anaphylaxis with cephalosporins among patients without a known penicillin allergy than among those with penicillin allergy. Anne and Reisman¹⁸ identified 1 of 98 patients (1%) with positive penicillin skin tests who developed anaphylaxis after cephalosporin challenge, compared with 6 of 310 patients (2%) with negative penicillin skin tests.

¶Refs 4, 7, 9, 22, 43–45, 51, 58, 68–70, 82, 83, 93, and 103–106.

#Refs 3, 9, 12, 45, 59, 64, 67, 74, 76, 77, 86, 89, 94, 96, and 106–127.

TABLE 9. Anaphylaxis With Cephalosporins Among Penicillin-Allergic and Nonallergic Patients

Cephalosporin Generation	Penicillin Allergic			Not Penicillin Allergic			Penicillin Allergy Status Not Specified			Total
	Adults	Children	Unknown	Adults	Children	Unknown	Adults	Children	Unknown	
First	8*		3†	10‡				6§		27
Second	1	1¶		8#	1**		3††	4‡‡	12§§	30
Third	0			3	1¶¶		15##	6***	20†††	35
Unknown	1†††		5‡‡‡			2§§§				8
Total	11	1	8	19	2	2	18	16	32	

* From refs 9, 64, 65, 76, 77, and 107 to 109.

† From refs 74 and 110.

‡ From refs 3, 45, 108, and 111 to 116.

§ From ref 59.

|| From ref 67.

¶ From ref 117.

From refs 86, 89, 96, 106, 118, and 119.

** From ref 120.

†† From ref 94.

‡‡ From refs 59 and 121.

§§ From refs 12 and 122.

||| From refs 123 to 125.

¶¶ From ref 94.

From refs 86 and 126.

*** From refs 59 and 86.

††† From ref 12.

‡‡‡ From ref 127.

§§§ From ref 3.

No case of fatal anaphylaxis with a cephalosporin has been reported for a child.¹²⁸

MEDICOLEGAL CONSIDERATIONS

The package inserts of first- and second-generation cephalosporins and of penicillin and ampicillin/amoxicillin suggest a 10% cross-sensitivity rate as a possible contradiction to the use of those cephalosporins among penicillin/amoxicillin-allergic patients. In contrast, the package insert of an AAP-endorsed, third-generation cephalosporin, ie, cefdinir, states that, "in penicillin-allergic patients, caution should be exercised" for use. Guidelines establish a standard of care, and the standard of care is the primary, overriding, medicolegal standard for appropriate practice.

CONCLUSIONS

If a patient experienced a reaction to a penicillin or cephalosporin that was not IgE mediated and was not serious, it is safe to administer repeated courses of that antibiotic and related antibiotics. Only IgE-mediated reactions are likely to become more severe with time and to result in anaphylaxis. An IgE-mediated reaction manifests as bronchospasm, angioedema, hypotension, urticaria, or a pruritic rash. If the rash is nonurticarial and nonpruritic, then it is almost certain that the rash is not IgE mediated and the risk of recurrence of the same rash with repeated courses of the same antibiotic is not increased. In uncertain cases, elective penicillin skin testing is advisable.

If the patient has a history that is consistent with a severe, IgE-mediated reaction to a penicillin, then cephalosporins with a similar 7-position side chain on the β -lactam ring (cephaloridine, cephalothin, and cefoxitin) should be used with caution. If the allergic reaction followed administration of ampicillin or amoxicillin, then cephalosporins with a similar

side chain (cephalexin, cephadrine, cefatrizine, cefadroxil, cefaclor, and cefprozil) should be used with caution. Other cephalosporins with different side chains are not more likely to produce allergic reactions among penicillin- or amoxicillin-allergic patients than among nonallergic patients.

A cephalosporin may be given to a patient who has experienced a non-IgE-mediated adverse reaction to a penicillin, ie, a type II, III, or IV or idiopathic reaction such as hemolytic anemia, serum sickness, contact dermatitis, or morbilliform or maculopapular rash. In uncertain cases, elective penicillin skin testing is advisable.

When patients give a history of penicillin allergy, it is advisable to probe the authenticity of this information, because very often the drug was not actually taken or a recognized nonimmunologic side effect (eg, vomiting, diarrhea, or a nonspecific rash) occurred. Penicillin skin testing can be useful to identify more accurately allergic patients, and testing is ~60% predictive for clinical hypersensitivity. Cephalosporins cause allergic or immune-mediated reactions among ~1% to 3% of patients, even if the patients are not allergic to penicillins. Without the ability to detect prospectively patients with IgE antibodies to penicillin and without the ability to distinguish true IgE immunologic reactions from idiopathic reactions among patients given cephalosporins, it is impossible to claim increased immune- or IgE-mediated reactions to cephalosporins among truly penicillin-allergic (IgE) patients.

The incidence of allergic reactions to cephalosporins among penicillin-allergic patients, attributable to cross-reactive antibodies, varies with the chemical side chain similarity of the cephalosporin to penicillin or amoxicillin. For first-generation cephalosporins, the attributable increased risk is 0.4%; for the AAP-endorsed agents for sinusitis and acute otitis

media (cefuroxime, cefpodoxime, and cefdinir), the risk is nearly nil.

A patient who experienced an allergic reaction to a specific cephalosporin probably should not receive that cephalosporin again; however, the risk of a drug reaction when a different cephalosporin is administered appears to be very low or nonexistent if the side chains of the drugs are not similar. Penicillin skin testing is not predictive of cephalosporin allergy unless the side chain of the penicillin or ampicillin reagent is similar to the side chain of the cephalosporin under evaluation. Even so, detection of cross-reactive IgE antibodies does not predict a definite clinical reaction. Cephalosporin skin testing may be useful for detecting IgE antibodies to the specific agent used in testing and other cephalosporins with similar side chains (not all cephalosporins are available as parenteral preparations amenable for use in skin testing).

Anaphylaxis with cephalosporins is rare. There is no evidence of an increased risk of anaphylaxis with cephalosporins among penicillin-allergic patients, and no case of fatal anaphylaxis with a cephalosporin has been reported for a child.

From a medicolegal viewpoint, coincidental allergic reactions to cephalosporins occur among penicillin/amoxicillin-allergic patients. A predictable, immunologically causal link for allergic reactions may occur with early-generation cephalosporins (0.5% increased attributable risk) but has no evidence base for most second- and third-generation agents.

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Submitted by Student

**A Review of Evidence Supporting the American Academy of Pediatrics
Recommendation for Prescribing Cephalosporin Antibiotics for
Penicillin-Allergic Patients**

Michael E. Pichichero
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