

Review

Evidence Supporting the Use of Cephalosporin Antibiotics in Penicillin-Allergic Patients

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ABSTRACT

The objective was to review the frequency of allergic cross-reactivity between penicillins and cephalosporin antibiotics. MEDLINE and EMBASE databases were searched for all English language articles relevant to penicillin and cephalosporin cross-sensitivity. Among 219 retrieved articles, 103 were included in the review. Based on 38 studies, the evidence suggests that the cross-reactive, immunoglobulin E (IgE)-mediated immune responses between penicillins and cephalosporins are based on molecular side chain similarities of the antibiotics rather than similarities in β lactam rings. Twenty-eight studies examined 5420 patients with a history of penicillin allergy compared to 47,976 without such a history who received cephalosporins; possible allergic reactions were noted in 138 (2.55%) and 654 (1.36%) patients respectively ($p < 0.0001$). However, the risk of a cross-allergic reaction occurred predominantly among patients receiving first-generation cephalosporins with related chemical side chains to penicillin or amoxicillin. The proportion of patients with a cross-allergy to a first generation cephalosporin was increased by 6.1% (95% confidence interval [CI] for difference between penicillin allergic and nonallergic = 5.4%–6.9% $p < 0.0001$) while to second- and third-generation cephalosporins with unrelated chemical side chains, the proportion was decreased by 0.45% (95% CI = –1.2%–0.3%; $p = 0.25$). Cephalosporin skin testing, described in 21 articles, predicts hypersensitivity to the specific cephalosporin skin test reagents or those with similar side chains and based on 3 studies a positive skin test is 10%–38% predictive of a clinical reaction. Experimental and clinical studies suggest that side-chain-specific antibodies predominate in the allergic immune response to cephalosporins thereby explaining the lack of cross-sensitivity between second- and third-generation cephalosporins and penicillins. (Pediatr Asthma Allergy Immunol 2005; 18[4]:230–246.)

INTRODUCTION

RECENT PRACTICE GUIDELINES for the management of acute bacterial sinusitis¹ and acute otitis media (AOM)² endorse the use of selected second-generation and third-generation cephalosporin antibiotics (cefuroxime, cefpodoxime, cefdinir, and ceftriaxone) in penicillin-allergic patients. These recommendations

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are evidence-based and recognize that the cross-reaction rate to second and third generation cephalosporins in penicillin-allergic patients is near zero.

After receiving penicillin, immunoglobulin (Ig)G and IgM antibodies are usually produced without any adverse consequences.³ These antibodies may cross-react with cephalosporin antigens in *in vitro* tests,^{4–14} but the detection of these antibodies does not necessarily predict immunologic cross-sensitivity. The true increased risk of an allergic reaction to a cephalosporin in a penicillin-allergic patient compared to a primary (and unrelated) cephalosporin allergy has not been clearly established despite many studies using different comparison populations.^{15–28} This review will examine the frequency of allergic cross-reactivity between these two classes of antibiotics and the value of cephalosporin skin testing.

MATERIALS AND METHODS

Search strategy

MEDLINE and EMBASE databases were searched for English-language articles using the keywords “cephalosporin and penicillin and allergy and cross-sensitivity” for the years 1960–2005. Among 219 articles identified, 103 were included as source material for this review. Excluded articles were reviews, republication of results, or not relevant to this review.

Classification of reactions

Reactions reported as allergic (type I) after antibiotic administration were often not clearly defined by the authors of the reviewed literature. In this review, pruritic or urticarial rashes were considered as likely allergic. The presence of IgE antibodies as detected by radioallergosorbent assay test (RAST) or skin testing was considered predictive of possible immediate, IgE-mediated hypersensitivity although it is recognized many patients with detectable IgE antibodies will not display a clinical allergic reaction. Cytotoxic IgG antibody (type II) reactions and antigen–antibody (IgG or IgM)-mediated (type III) reactions also can be induced by β lactam antibiotics, but these are not allergic reactions and their occurrence was not evaluated. Contact dermatitis (type IV or delayed hypersensitivity) reactions to penicillins and cephalosporins also can occur, primarily in nurses, pharmacists, and those involved in the drug manufacturing process but they too were not evaluated. Idiopathic reactions occur via unknown mechanisms and their recurrence is not predictable, these are sometimes termed “non-type I allergic reactions” but they are not IgE-mediated, the term “allergic” is misapplied and these reactions were not included.

RESULTS

Reactions to cephalosporins in penicillin-allergic patients

Twenty-eight publications^{4,9,16,29–51} evaluating 5720 patients with a history of “allergic reactions” to penicillin were compared to 47976 patients without a history of penicillin allergy (Table 1). Overall, 138 (2.55%) of the penicillin-allergic patients had a reaction to a cephalosporin versus 654 (1.36%) of the penicillin non-allergic patients (difference = 1.19% $p < 0.0001$). However, the observed difference in reaction rates occurred due to cross reactivity with administered first-generation cephalosporins (Table 2). That is, first-generation cephalosporins that share side chain chemical structure similarity to penicillin and amoxicillin/ampicillin caused the observed increased rate of reactions not observed with other cephalosporins. The proportion of patients with allergic reactions to first generation cephalosporins that had a similar side chain as penicillin and amoxicillin increased by 6.1% (for the difference between penicillin-allergic and nonallergic 95% confidence interval [CI] = 5.4%–6.9%; $p < 0.0001$) and decreased by 0.45% (95% CI = –1.2%–0.3%; $p = 0.256$) for third-generation cephalosporins with dissimilar side chains (Table 2).

The importance of the cephalosporin side chain

A considerable body of evidence has established that the immune response to cephalosporins is more dependent on their side chain substituents than is the case with penicillin.^{9,15–19,21,22,27,28,38,39,41,44–46,48,52–71}

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TABLE 1. CEPHALOSPORIN CHALLENGES IN PENICILLIN ALLERGIC PATIENTS

<i>Author</i>	<i>History</i>	<i>Number</i>	<i>Allergic reaction rate</i>	<i>p value</i>
Walters et al. ³²	Clinical history of penicillin allergy negative, when challenged with cephalothin	4/94	4%	$p = 0.94$
	Clinical history of penicillin allergy, when challenged with cephalothin	0/15	0%	
Griffith and Black ³⁴	Clinical history of penicillin allergy negative, when challenged with cephalothin	0/54	0%	$p = 1.00$
	Clinical history of penicillin allergy when challenged with cephalothin	0/7	0%	
Weinstein et al. ³³	Clinical history of penicillin allergy negative, when challenged with cephalothin	2/78	2.6%	$p = 0.04$
	Clinical history of penicillin allergy when challenged with cephaloridine	0/2	0%	
Thoburn et al. ³⁷	Clinical history of penicillin allergy and penicillin skin test positive when challenged with cephalothin	2/11	18%	$p = 0.42$
	Clinical history of penicillin allergy and penicillin skin test negative when challenged with cephalothin	2/40	5%	
Apicella et al ³⁵	Clinical history of penicillin allergy negative, when challenged with cephalothin	0/72	0%	$p = 1.00$
	Physician diagnosed penicillin allergy, when challenged with cephaloridine	0/20	0%	
Stewart ⁹⁶	Physician diagnosed penicillin allergy, when challenged with cephaloridine	0/4	0%	
Marks and Garrett ⁹⁷	Clinical history of penicillin allergy, when challenged with cephalixin	1/5	20%	
Assem and Vickers ⁴	Clinical history and in vitro or skin test positive for penicillin, challenged with cephaloridine	2/2	100%	
Petz ³¹	Clinical history of penicillin allergy, challenged with cephalothin, cephaloridine, cephalixin, cefazolin, cefamandole	57/701	8.1%	$p < 0.0001$
	Clinical history negative for penicillin allergy, challenged with cephalothin, cephaloridine, cephalixin, cefazolin, cephamandole	285/15007	1.9%	

TABLE 1. CEPHALOSPORIN CHALLENGES IN PENICILLIN ALLERGIC PATIENTS (CONTINUED)

<i>Author</i>	<i>History</i>	<i>Number</i>	<i>Allergic reaction rate</i>	<i>p value</i>
Dash ³⁶	Clinical history of penicillin allergy when challenged with cephalexin or cephaloridine	25/294	8.5%	$p < 0.0001$
	Clinical history of penicillin allergy negative when challenged with cephalexin or cephaloridine	165/17540	1.0%	
Solley ⁴⁵	Clinical history and skin test positive for penicillin allergy when challenged with cephalosporin	0/27	0%	$p = 0.697$
	Clinical history of penicillin allergy but penicillin skin testing negative, challenged with cephalosporins	2/151	1.3%	
Warrington ⁴⁹	Clinical history and skin test positive for penicillin allergy, challenged with cephalosporins	0/3	0%	
Sullivan et al. ⁴³	Clinical history of penicillin allergy but penicillin skin tests negative, challenged with cephalothin	0/23	0%	
Saxon et al. ⁴⁸	Clinical history and skin test positive to penicillin when challenged with cephalosporins	1/62	1.6%	
Blanca ³⁸	Clinical history and skin test or RAST positive for penicillin or amoxicillin allergy, challenged with cefamandole	2/19	10.5%	$p = 0.517$
	with cephaloridine	0/17	0%	
Lin ⁹	Clinical history of penicillin allergy when challenged with ceftazidime	3/521	0.58%	$p = 0.144$
	Clinical history negative for penicillin allergy, when challenged with ceftazidime	57/3427	1.7%	
Martin ⁴⁴	Physician observed anaphylaxis reaction to amoxicillin, challenged with benzylpenicillin	0/6	0%	$p = 1.00$
	ceftazidime	0/6	0%	
Shepherd and Burton ⁴⁶	Clinical history and skin test positive to penicillin, when challenged with cephalosporins	0/9	0%	$p = 0.521$
	Clinical history of penicillin allergy but penicillin skin tests negative, when challenged with cephalosporins	4/159	2.5%	
Audicana ⁴¹	Clinical history and skin test or RAST positive for penicillin and/or amoxicillin, when challenged with cephalexin	1/30	3.3%	$p = 0.987$
	ceftazidime	0/30	0%	

(continued)

TABLE 1. CEPHALOSPORIN CHALLENGES IN PENICILLIN ALLERGIC PATIENTS (CONTINUED)

<i>Author</i>	<i>History</i>	<i>Number</i>	<i>Allergic reaction rate</i>	<i>p value</i>
Anne and Reisman ¹⁶	Clinical history of penicillin allergy, when challenged with ceftazidime	0/11	0%	
Miranda ³⁹	Clinical history and skin test or RAST positive for amoxicillin but not benzylpenicillin, when challenged with cefadroxil	8/21	38%	$p = 0.006$
	cephamandole	0/21	0%	
Sastre et al ⁴²	Clinical history of allergy to amoxicillin and skin test or oral challenge positive to amoxicillin but parenteral challenge negative to penicillin G, when challenged with cephalexin	2/16	12.5%	
Pichichero and Pichichero ⁴⁷	Physician diagnosed allergy to amoxicillin and skin test or oral challenge positive to amoxicillin, when challenged with cephalosporins	1/28	3.6%	$p = 0.899$
	Physician diagnosed allergy to amoxicillin and skin test and oral challenge negative to penicillin and amoxicillin, when challenged with cephalosporin	0/36	0%	
Goodman et al. ⁵⁰	Clinical history of penicillin allergy when challenged with cefazolin	1/412	0.24%	$p = 0.67$
	Clinical history negative for penicillin allergy when challenged with cefazolin	1/2520	0.04%	
Novalbos et al. ⁴⁰	Clinical history of allergy to penicillin and penicillin skin test or challenge positive when challenged with cefazolin	0/41	0%	$p = 1.0$
	cefuroxime	0/41	0%	
	ceftriaxone	0/41	0%	
Romano et al. ⁹⁸	Clinical history of penicillin or amoxicillin allergy and penicillin or amoxicillin skin test positive when challenged with cefuroxime	0/101		$p = 1.00$
	ceftriaxone	0/101		
Daulat et al. ⁵¹	Clinical history of penicillin allergy when challenged with a cephalosporin	1/606	0.17%	
Pichichero ²⁹	Clinical history negative for penicillin/amoxicillin allergy when challenged with cefuroxime	89/5410		$p = 0.879$
	cefprozil	23/1340		$p = 0.884$
	cefpodoxime	20/2025		$p = 0.876$

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TABLE 1. CEPHALOSPORIN CHALLENGES IN PENICILLIN ALLERGIC PATIENTS (CONTINUED)

<i>Author</i>	<i>History</i>	<i>Number</i>	<i>Allergic reaction rate</i>	<i>p value</i>
	Clinical history positive for penicillin/amoxicillin allergy, when challenged with			
	cefuroxime	8/428		
	cefprozil	3/157		
	cefpodoxime	2/234		
	Clinical history positive for penicillin/amoxicillin allergy but penicillin/amoxicillin skin testing negative when challenged with			
	cefuroxime	5/397		<i>p</i> = 0.772
	cefprozil	1/100		<i>p</i> = 0.831
	cefpodoxime	7/497		<i>p</i> = 0.982
	Clinical history positive for penicillin/amoxicillin allergy and penicillin/amoxicillin skin testing positive when challenged with			
	cefuroxime	2/141		
	cefprozil	1/47		
	cefpodoxime	2/188		

RAST, radioallergosorbent assay test.

Cephalosporins bearing a side chain similar to benzylpenicillin are more likely to cross-react with penicillin. For example, cefoxitin, cephalothin, and cephaloridine have side chains that closely resemble the 7-position side chain of penicillin G (Table 3A). Cephalosporins may cross react with each other based on 7-position or 3-position (3B) side chain similarities.

However, the detection of cross-reactive IgE antibody to penicillin or cephalosporins does not necessarily predict a clinical reaction. In a study of 19 well-characterized penicillin-allergic patients, antibenzyl-

TABLE 2. SUMMARY OF STUDIES FOR SPECIFIC CEPHALOSPORINS

<i>Drug (cephalosporin generation)</i>	<i>Penicillin/amoxicillin allergic, by history</i>		<i>Difference (95% CI)</i>	<i>p value</i>
	<i>Yes</i>	<i>No</i>		
Cephalothin (1)	8/160 (5.00%)	27/1343 (2.01%)	3.01% (0.53%–5.5%)	0.035
Cephaloridine (1)	34/390 (8.72%)	178/14,438 (0.12%)	8.6% (8.0%–9.1%)	< 0.0001
Cephalexin (1)	25/365 (6.85%)	160/14,392 (1.11%)	5.74% (4.6%–6.9%)	< 0.0001
Total	67/915 (7.32%)	365/30,173 (1.20%)	6.1% (5.4%–6.9%)	< 0.0001
Cefuroxime (2)	8/428 (1.87%)	89/5410 (1.65%)	0.2% (–1.0%–1.4%)	0.884
Ceftazidime (3)	3/568 (0.54%)	57/3427 (1.66%)	1.12% (–2.2%–0.03%)	0.068
Cefpodoxime (3)	2/234 (0.85%)	20/2025 (0.98%)	0.13% (–1.4%–1.2%)	0.873
Total	13/1230 (1.06%)	166/10,862 (1.53%)	0.45% (–1.2%–0.3%)	0.256

CI, confidence interval.

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TABLE 3A. CHEMICAL STRUCTURE OF SEVEN-POSITION SIDE CHAINS OF U.S. MARKETING PENICILLINS AND CEPHALOSPORINS

<i>Similar side chain structure possible cross-reactivity within group</i>			<i>Dissimilar side chain structures/ unlikely cross-reactivity</i>	
<i>Related</i>	<i>Related</i>	<i>Related</i>	<i>All unrelated</i>	
Penicillin G	Amoxicillin	Cefotaxime	Cefazolin	Ceftazidime
Cephalothin	Ampicillin	Ceftizoxime	Cefotetan	Cefixime
Cefoxitin	Cefaclor	Ceftriaxone	Cefuroxime	Cefmetazole
	Cephalexin	Cefpodoxime	Cefoperazone	Ceftibuten
	Cephadrine	Cefpirome	Cefdinir	Cephmandole
	Cefprozil	Cefepime	Cefditoren	
	Cefadroxil			

TABLE 3B. CHEMICAL STRUCTURES OF THREE-POSITION SIDE CHAINS OF U.S. MARKETING PENICILLINS AND CEPHALOSPORINS

<i>Similar side chain structure/possible cross-reactivity within group</i>						<i>Dissimilar side chain structure/unlikely cross-reactivity</i>
<i>Related</i>	<i>Related</i>	<i>Related</i>	<i>Related</i>	<i>Related</i>	<i>Related</i>	<i>All unrelated</i>
Cephadrine	Cefmetazole	Cefotaxime	Cefuroxime	Cefdinir	Ceftibuten	Cefpodoxime
Cefadroxil	Cefoperazone	Cephalothin	Cefoxitin	Cefixime	Ceftizoxime	Cefprozil
Cephalexin	Cefotetan					Ceftibuten
						Ceftriaxone
						Cefepime
						Cefazolin
						Cefaclor
						Ceftazidime

penicilloyl antibodies were shown to cross-react well with cephaloridine and cefamandole (because they have identical or very similar side chains to penicillin).³⁸ Yet, when challenged with cefamandole, only 2 of 19 (10.5%) patients reacted.³⁸ In another study, the clinical cross-reactivity between amoxicillin and cefadroxil was assessed.⁴² Although these two drugs share an identical side chains, only 2 (12%) of 16 amoxicillin-allergic patients demonstrated an allergic reaction to cefadroxil. In another study, Miranda et al.³⁹ evaluated 21 patients allergic to amoxicillin, for cross-reactivity with cefadroxil and cefamandole; 8 patients (38%) had a positive reaction to cefadroxil (same side chain) and none to cefamandole (different side chain).

Incidence of reactions to cephalosporins

The majority of allergic reactions to penicillins and cephalosporins consist of rashes, occurring in 1.0%–2.8% of patients (Table 4)^{24,25,72–74}; for most the mechanism is idiopathic and not a contraindication for future use.

Studies in animals and with monoclonal antibodies

In the years after the introduction of cephaloridine and cephalothin, anaphylactic reactions were reported in patients who had prior allergic reactions to penicillin.^{75–78} Subsequently, significant antigenic cross-reactivity was observed with *in vitro* tests such as hemagglutination inhibition, quantitative histamine release,

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TABLE 4. RATES OF RASHES TO PENICILLINS AND CEPHALOSPORINS

<i>Author</i>	<i>Variable</i>	<i>Number</i>	<i>Reaction rate</i>
Arndt and Jick ⁷²	Rashes from penicillin G	355/22,227	1.6%
	Ampicillin	1244/22,227	5.6%
	Semisynthetic penicillins	800/22,227	3.6%
	Cephalosporins	289/22,227	1.3%
Platt ²⁴	Rashes from cephalosporins:		
	Cefamandole	1279	1.7%
	Cefoxitin	1615	2.3%
	Cefoperazone	2000	2.0%
	Cefotaxime	1221	1.9%
	Ceftizoxime	1559	<1.0%
	Moxalactam	3558	2.6%
Sanders et al. ⁷³	Rashes from cefamandole	Not stated	2%
	Rashes from cefoxitin	Not stated	2%
Levine ⁷⁴	Urticaria from cefaclor	24/1017	2.3%
	Urticaria from amoxicillin	8/1009	0.8%
Norrby ²⁵	Rashes from Cephalosporins	5063	
	Cefotaxime		1.8%
	Ceftizoxime		3.0%
	Cefuroxime		1.0%
	Cefoperazone		2.8%
	Ceftazidime		2.0%
	Cefoxitin		2.2%

and lymphocyte proliferation in animals (Table 5).^{4-7,13,20,79} The clinical relevance of these cross-reactions was never demonstrated.

Monoclonal antibodies in mice raised to penicillins and cephalosporins have identified virtually no cross-reactive epitopes (Table 6).⁸⁰ Notably, when Mayorga et al.⁸¹ evaluated the antigenic contribution of different regions of amoxicillin-protein conjugate molecules, in 11 (92%) of 12 monoclonal antibodies recognized an epitope in which the side chain was a major constituent, none recognized the thiazolidine ring or the conjugated nuclear region and one recognized all different structures of the penicillin molecule equally.

Cephalosporin skin testing

Penicillin skin testing does not reliably predict cephalosporin allergy. Skin testing for cross-reactivity shows cross-reactivity in some patients between penicillins and first-generation cephalosporins, namely, between ampicillin/amoxicillin and cephalexin/cefadroxil, but not between penicillin/amoxicillin and second-generation or third-generation cephalosporins.^{4,6,20,37,39-45,49,54,58,64,82-85}

Skin testing for cephalosporins has been undertaken in 21 studies^{6,8,12,17,22,30,32,37-40,47,48,58,77,78,86-90} (Table 7) but the positive and negative predictive values of the results are less well established. If the hap- tens that cause cephalosporin allergy were known, cross-reactivity with penicillins could be directly as- sessed. Currently cephalosporin skin tests are done with the native molecule and can only predict hyper- sensitivity to the cephalosporin skin test reagent or cephalosporins with similar side chains.

Predictive value of penicillin skin testing for cephalosporin allergy

Romano et al.⁶³⁻⁶⁵ examined IgE responses in patients with immediate allergic reactions to cephalosporins by performing skin and RAST tests with the responsible drugs. Fewer than 20% of the cephalosporin-al- lergic subjects reacted on skin testing to penicillin determinants, but the majority of cephalosporin-allergic patients had positive results to other cephalosporins with the same or similar side chain structures (ceftri- axone and cefotaxime).

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TABLE 5. ANIMAL DATA

<i>Author</i>	<i>Animal/assay</i>	<i>Test reagent</i>	<i>Conclusions</i>
DeWeck ⁷⁹	Rabbits/ hemagglutination	Benzylpenicillin Phenoxyethylpenicillin Phenoxymethylpenicillin	Side chain plays little role
Batchelor ⁵	Rabbits/ hemagglutination	Benzylpenicillin 6-amino penicillanic acid (penicillin nucleus)	Little cross-reaction between penicillin nucleus and cephalosporins. Cross- reactivity resides in side-chain similarities.
Shibata et al. ¹³	Rabbit and guinea pig/ passive cutaneous anaphylaxis quantitative precipitin hapten inhibition	Cephalothin Penicillin G	Acyl side chain is the important determinant
Hamilton-Miller and Abraham ⁷	Rabbits/ hemagglutination	Benzylpenicillin Carbenicillin Cefazolin Cephaloridine Cephalosporin C Cephalothin Methicillin Oxacillin Phenoxymethylpenicillin	Penicillins cross-reacted with each other but not with cephalosporins unless they contained a chemically related side chain. Cephalosporins only reacted with each other if they shared a chemically related side chain.
Peterson and Graham ¹⁰	Rabbit/ hemagglutination	6-amino-penicillanic acid (6-APA; penicillin nucleus) 7-amino- cephalosporanic acid (7-ACA; cephalosporin nucleus) ampicillin benzylpenicillin cefazolin cephalexin cephaloridine cephalothin phenoxymethylpenicillin	7-ACA and 6-APA nucleus do not cross-react; antibody to penicillin G is directed primarily to the acyl side chain and cross- reacts with the side chain of cephalothin, to a limited degree with cephalexin side chain, and not at all with cefazolin.

Risks of anaphylaxis

The incidence of anaphylaxis to penicillins, calculated from a comprehensive international survey was found to be 0.015%–0.004%, with a fatality rate of 0.002%–0.0015% (Table 8).⁹¹ More limited data suggest the rate of anaphylaxis from cephalosporins is 0.1%–0.0001% (Table 8).²² A summary of cases of anaphylaxis induced by cephalosporins was recently summarized.²⁹ There are more reported cases of anaphylaxis to cephalosporins in patients without a known penicillin allergy compared to those with penicillin allergy.^{16,29}

DISCUSSION

Penicillins and cephalosporins have similar chemical configurations⁹² but differ in that the 5-membered thiazolidine ring of penicillin is replaced with a 6-membered dihydrothiazine ring in the cephalosporins.

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TABLE 6. STUDIES WITH MONOCLONAL ANTIBODIES

<i>Author</i>	<i>Reagent</i>	<i>Conclusions</i>
Nagakura et al. ⁸⁰	6-aminopenicillanic acid (6-APA)	Anticephalexin antibodies recognized three epitopes: the acyl side chain, degraded 7-ACA, and a new antigenic determinant (NAD) formed by conjugation of the beta- lactam and a carrier protein
	7-amino cephalosporanic acid (7-ACA; cephalosporin nucleus)	
	amoxicillin	
	ampicillin	
	benzylpenicillin	
	cefoperazone	
	cefsulodin	
	cephalexin	
	cephalothin	
	6-APA	
	amoxicillin	
Mayorga et al. ⁸¹	ampicillin	92% of the antibodies recognized an epitope in which the side chain was the major constituent; one antibody (8%) recognized all the reagents
	benzylpenicillin	
	butylamine	
	N (p-hydroxyphenyl)-glycine	
	N-phenylglycine	
	phenylacetic acid	
	thiazolidine	

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 ring.²³

This evidence-based review suggests that the incidence of allergic reactions to cephalosporins in 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 with similar side chains the attributable increased risk is 0.5% and for the American Academy of Pediatrics/American Academy of Family Physicians (AAP/AAFP) guideline-endorsed agents for sinusitis and AOM (cefuroxime, cefpodoxime, cefdinir, and ceftriaxone) the risk is near nil. Penicillin skin testing is not predictive for cephalosporin allergy unless the side chain of the penicillin or ampicillin reagent is similar to the cephalosporin side chain under evaluation. Even so, the detection of cross-reactive IgE antibody does not predict a definite clinical reaction. Cephalosporin skin testing may be useful in detecting IgE antibodies to the specific agent used and other cephalosporins with similar side chains. A patient who had 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. Anaphylaxis from cephalosporins is rare. There is no evidence of an increased risk of anaphylaxis to cephalosporins in penicillin-allergic patients.

Two reviews that contributed more than 95% of the patients in the analyses of cephalothin, cephaloridine, cephalexin, cefazolin, and cephmandole largely account for the folklore surrounding the often quoted 10% cross-sensitivity rate between penicillin and cephalosporins. A 1975 review by Dash suggested that the rate of "allergic reactions" to cephalosporins in "penicillin-allergic" patients was 7% as compared with an overall rate of reactions to cephalosporins in nonpenicillin allergic patients of about 1%.³⁶ Petz, in 1971¹¹ and 1978,³¹ reviewed the literature on allergy to cephalosporins in penicillin "allergic and nonallergic patients" that included 15,708 case reports of clinical trials of patients who were treated with cephalothin, cephaloridine, cephalexin, cefazolin, or cephmandole. 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. However, of the 15,007 patients who did not have a history of penicillin allergy, 285 (1.9%)

TABLE 7. SKIN TESTING FOR CROSS-REACTIVITY BETWEEN PENICILLINS AND CEPHALOSPORINS

<i>Author</i>	<i>Antibiotic</i>	<i>Positive rate</i>
Stewart ³⁰	Benzylpenicillin	5/5
	Ampicillin	2/5
	Cephalosporin C	0/5
Thoburn et al. ³⁷	Benzylpenicillin and/or penicillin G	6/6
	Cephalothin	2/6
Greico ²⁰	Benzylpenicillin	1/1
	Ampicillin	1/1
	Oxacillin	1/1
	Cephalothin	1/1
	Cephaloridine	1/1
	Cefamandole	1/1
Pedersen-Bjergaard ⁸²	Benzylpenicillin	13/13
	Cephalothin	8/13
Girard ⁶	Benzylpenicillin and/or MDM	32/32
	Ampicillin	23/32
	Cephalothin	13/32
	Cephaloridine	15/32
	Benzylpenicillin	24/24
Assem and Vickers ⁴	Cephaloridine	11/24
	Benzylpenicillin and/or MDM	3/3
Warrington et al. ⁴⁹	Cephalothin	0/3
	Benzylpenicillin and/or MDM	136/136
Sullivan ⁴³	and/or PPL	
	Ampicillin	41/56
	Carbenicillin	1/6
	Cephalothin	38/74
	Penicillin G and/or MDM	89/89
	and/or PPL	
Solley et al. ⁴⁵	Ampicillin	33/75
	Methicillin	27/73
	Benzylpenicillin and/or MDM	0/6
Martin et al. ⁴⁴	and/or PPL	
	Ampicillin or amoxicillin	4/6
	Ceftazidime	0/6
	Benzylpenicillin and/or MDM	0/2
	and/or PPL	
	Amoxicillin	0/2
Igea et al. ⁵⁸	Cefazolin	0/2
	Cefuroxime	0/2
	Cefotaxime	0/2
	Benzylpenicillin and/or penicillin	11/21
	MDM and/or PPL	
	Ampicillin	8/21
Silivu-Dan et al. ⁵⁴	Amoxicillin	1/21
	Benzylpenicillin and/or MDM	2/54
	and/or PPL	
	Ampicillin	13/54
	Amoxicillin	36/54
	Benzylpenicillin and/or MDM	1
Vega et al. ⁸⁴	and/or PPL	6/34
	Ampicillin	16/34
	Amoxicillin	14/34
	Cephalexin	5/34
	Ceftazidime	0/34
Audicana et al. ⁴¹		

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TABLE 7. SKIN TESTING FOR CROSS-REACTIVITY BETWEEN PENICILLINS AND CEPHALOSPORINS (*CONTINUED*)

<i>Author</i>	<i>Antibiotic</i>	<i>Positive rate</i>
Miranda et al. ³⁹	Amoxicillin	21/21
	Cefadroxil	8/21
	Cefamandole	0/21
Sastre et al. ⁴²	Benzylpenicillin and/or MDM and/or PPL	0/16
	Amoxicillin	16/16
Romano et al. ⁸³	Benzylpenicillin and/or MDM and/or PPL	26/30
	Ampicillin	17/30
	Amoxicillin	17/30
Blanca ³⁸	Benzylpenicillin and/or MDM and/or PPL	55/55
	Amoxicillin	38/55
	Ampicillin	24/55
Romano et al. ⁶³	Ceftriaxone	14/30
	Ceftazidime	7/30
	Cefotaxime	6/30
	Cefuroxime	4/30
	Cephalothin	0/30
	Cefamandole	0/30
	Benzylpenicillin and/or MDM and/or PPL	2/30
	Ampicillin	2/30
	Amoxicillin	0/30
	Benzylpenicillin and/or MDM and/or PPL and/or amoxicillin	41/41
	Benzylpenicillin and/or MDM and/or PPL	23/41
Novalbos et al. ⁴⁰	Amoxicillin	28/41
	Cefazolin	1/41
	Cefuroxime	0/41
	Ceftriaxone	1/41
	0/41	
	Benzylpenicillin and/or MDM and/or PPL	269/269
	Ampicillin	59/269
	Cephalothin	54/269
	Cefuroxime	2/269
	Ceftriaxone	1/269

MDM, minor determinant mixture; PPL, penicilloyl-polylysine.

had an allergic reaction to cephalosporins. The 7% figure by Dash and 8.1% figure by Petz appear to be the basis of the widely cited (and rounded up) figure of a 10% cross-sensitivity between the two drug classes.⁹³ Lost in medical history was the later discovery that penicillin-related compounds were produced by the cephalosporium mold until 1980,⁹¹ and early first-generation cephalosporin antibiotics included in the analyses by Dash³⁶ and Petz^{11,31} contained trace amounts of cephalosporins.^{48,63} Thus, the data by Dash³⁶ and Petz^{11,31} and others until 1980⁹⁴ involving cephalosporins exaggerated cross-sensitivity significantly.⁹⁵

Cephalosporins cause allergic or immune mediated reactions in approximately 1%–3% of patients independent of possible allergy to penicillins. Without the ability to detect patients with IgE antibody to peni-

TABLE 8. RATES OF ANAPHYLAXIS FROM PENICILLINS AND CEPHALOSPORINS

<i>Author</i>	<i>Variable</i>	<i>Number</i>	<i>Reaction rate</i>
Idsoe et al. ⁹¹	Anaphylaxis from penicillin with fatality	Not stated	0.015%–0.04%
Petz ¹¹	History of penicillin allergy followed by anaphylaxis to cephalothin	2/450	0.4%
	No history of penicillin allergy followed by anaphylaxis to cephalothin	2/9388	0.02%
Platt ²⁴	Anaphylaxis from cephalosporins	0/11231	0%
Gadde ⁸⁹	Anaphylaxis from cephalosporins		0.0001%

cillin prospectively and without the ability to distinguish true IgE immunologic reactions from idiopathic reactions in patients given cephalosporins, it is impossible to claim increased immune or IgE-mediated reactions to cephalosporins in penicillin-allergic patients. Nevertheless, this review provides an analysis of evidence to strongly suggest that if cross-allergy exists at all, it is restricted to first-generation cephalosporins that have similar or identical side chains.

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