Clinical Commentary Review

Cross-reactivity in β-Lactam Allergy

Robert J. Zagursky, PhD, and Michael E. Pichichero, MD *Rochester, NY*

β-Lactam drugs (penicillins, amoxicillin, and cephalosporins) account for 42.6% of all severe drug-induced anaphylaxis. In this review, we focus on clinically significant immunologic cross-reactivity in patients with confirmed penicillin allergy to cephalosporins, and the structural involvement of the R_1 and R_2 chemical side chains of the cephalosporins causing IgE-mediated cross-reactivity with penicillin and other cephalosporins. Skin tests predict IgE-mediated reactions and showed cross-reactivity between penicillins and early generation cephalosporins that shared side chains, but confirmatory challenge data are lacking. Later-generation cephalosporins, which have distinct side chains, do not have any skin test cross-reactivity with penicillin/amoxicillin. There is debate as to the involvement of R_2 side chains as the antigenic determinants that cause IgE-mediated hypersensitivity with various cephalosporins. Avoidance of cephalosporins, when they are the drug of choice in a penicillin-allergic individual, results in significant morbidity that outweighs the low risk of anaphylaxis. We conclude that there is ample evidence to allow the safe use of cephalosporins in patients with isolated confirmed penicillin or amoxicillin allergy. **© 2017 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2018;6:72-81)**

Key words: *Anaphylaxis; β-Lactam allergy; Penicillin; Cephalosporin*

INTRODUCTION

In 2011, penicillins and cephalosporins were the top 2 classes of antibacterial drugs sold in the United States, making up nearly 60% of all the antibacterial drug market[1] and accounted for 55% of global antibiotic drugs consumed in 2010.[2] As of May 2017, the Food and Drug Administration has approved more than 34 β-lactam compounds as active ingredients in drugs for human use.[3] In a report by the Allergy Vigilance Network of the European registry of recorded drug-induced severe anaphylaxis from 2002 to 2010, 42.6% of the cases were caused by β-lactam drugs: amoxicillin, other penicillins, and cephalosporins.[4] This provides strong evidence for the need for allergy assessment. Performance of penicillin allergy testing has shown that approximately 90% of patients with a reported history of penicillin are not allergic to penicillin. This has important ramifications because increased usage of non−β-lactam drugs encourages the development of antibiotic-resistant organisms and use of alternative antibiotics that have serious side effects.[5] The same concern should be applied to patients with a reported history of cephalosporin allergy.

The 2013 American Academy of Pediatrics Sinusitis Guideline[6] endorsed the use of specific cephalosporin antibiotics for the treatment of patients even if there is a report of type I (IgE-mediated) allergy or non−type I penicillin reactions; however, for unclear reasons the endorsement in older guidelines excludes penicillin reactions that are type I allergic reactions (2004 American Academy of Pediatrics and American Academy of Family Physicians,[7] 2013 American Academy of Pediatrics Acute Otitis Media Guidelines, and the 2010 Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology[8]). Our previous review focused on the immunologic cross-reactivity of patients with a penicillin allergy to certain cephalosporins and the structural involvement of the R_1 cephalosporin site for this cross-reactivity.[9] Here, we include type I allergy reactions with penicillins and cephalosporins including the R_2 chemical groups as well as cross-reactivity among cephalosporins.

PENICILLINS, CEPHALOSPORINS, AND OTHER β-LACTAMS: STRUCTURE

Early production of natural penicillin resulted in different structures depending on the liquor used during fermentation. That changed with the production of semisynthetic penicillins with different side chains. Today there are a number of different penicillins (penams) (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Shortly after bacterial resistance to penicillin started to emerge, a new class of natural penicillin-like antibiotics called cephalosporins was discovered. Both penicillins and cephalosporins share a common β-lactam ring that is attached to either a 5-membered thiazolidine ring or a 6-membered dihydrothiazine (cephem) ring, respectively (Figure 1). These β-lactam antibiotics inhibit the bacterial transpeptidases (also called penicillin-binding proteins) that catalyze the peptidoglycan cross-linking reaction involved in bacterial cell wall biosynthesis. Another difference between penicillins and cephalosporins is that cephalosporins contain additional modifications at the R_2 chemical group. These modifications have resulted in antibiotic therapy with broader spectrum of activity targeting gram-positive and gram-negative bacteria and better pharmacokinetic properties.[10] Cephalosporins can be roughly

Rochester General Hospital Research Institute, Center for Infectious Diseases and Immunology, Rochester, NY

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Corresponding author: Michael E. Pichichero, MD, Research Institute, Rochester General Hospital, 1425 Portland Ave, Rochester, NY 14621. E-mail: Michael.Pichichero@RochesterRegional.org.

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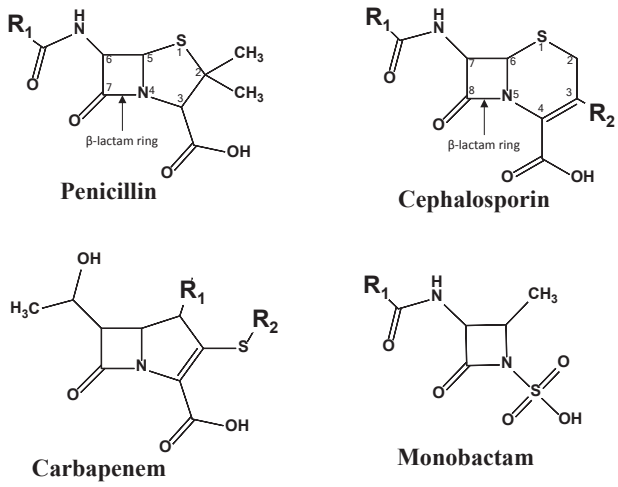


FIGURE 1. Chemical core structures of β-lactam and monobactam antibiotics. The β-lactam ring shown and present in all structures. "R" represents side chains that differ among the antibiotics.

classified into various generations on the basis of their appearance in time (see Table I). The earliest generation focused mainly on the R_1 chemical group, whereas the later generations focused on modifications at both the R_1 and R_2 groups. Today, there are more than 50 cephalosporin antibiotics, 18 licensed in the United States (see Figure E1).

Additional modifications to the basic core structures of both penicillins and cephalosporins have been made. Examples of these are the prodrugs of penicillin that contain changes at the C_3 carboxy position and in cephalosporins that contain a 7-α-methoxy group at C_7 (cephamycins) or where the sulfur atom at position 1 is replaced with an oxygen atom (oxacephems). Other types of β-lactam—containing antibiotics are carbapenems such as meropenem, imipenem, and ertapenem and monobactams such as aztreonam.

Carbapenems are similar to penicillins but the β-lactam ring is attached to a 5-member carbon-only cyclic ring and a sulfur atom linked to C_2. Prospective studies of carbapenems suggest that attributable cross-reactivity is very unlikely or absent between these β-lactams and penicillins/cephalosporins.[12-15]

Monobactams are structurally unique in that the β-lactam ring is not fused to another ring structure. Monobactams do not have cross-allergy with penicillins or most cephalosporins,[8,15] with the exception of ceftazidime, which shares an identical R_1 side chain as aztreonam.[16]

Most β-lactamase inhibitors that are themselves β-lactams, such as clavulanic acid, tazobactam, and sulbactam, and although alone are poor antibiotics, in combination with a β-lactam antibiotic may overcome the bacterial resistance. Examples of such combination drugs are Augmentin, which contains amoxicillin and clavulanic acid, Zosyn, which contains piperacillin and tazobactam, and Avycaz, which contains ceftazidime and avibactam (non-β-lactam).[17,18]

PENICILLIN AND CEPHALOSPORIN ALLERGY TESTING

Both the American Joint Task Force (American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology)[8] and the European Network for Drug Allergy and the European Academy of Allergy and Clinical Immunology[19,20] guidelines for skin testing (prick or intradermal) for penicillin reactivity include a minor determinant mixture of the natural metabolized penicillin G products along with penicilloyl polylysine (also known by its trade name Pre-Pen)[21] and other possible β-lactam drugs for initial skin testing. However, the recommendation is complicated by the fact that the minor determinant mixture is not commercially available in the United States. As an alternative, skin testing using penicilloyl polylysine, penicillin, and amoxicillin without using minor determinant mixture, and if negative, followed by oral amoxicillin challenge has been proposed.[22] A penicillin skin test result is considered positive if a greater than or equal to 5 mm wheal surrounded by erythema is observed.[23]

Cephalosporyl is a natural metabolized determinant product of a cephalosporin but is unstable and undergoes multiple fragmentations of the dihydrothiazine ring and the haptenic determinants are unknown.[24,25] Thus, a "minor determinant mixture" consisting of a partially fragmented β-lactam ring does not exist for cephalosporins. However, unlike the R_2 side chain which may be eliminated, the R_1 side-chain structure of cephalosporins usually remains intact and is the major factor for cross-reactivity between cephalosporins and penicillins.[19,24,26-29] Skin testing for cephalosporins has been undertaken in more than 20 studies but the positive and negative predictive values of the results are less well established.[30] Currently, cephalosporin skin tests are done with the native molecule (intravenous preparations or crushed tablets solubilized in buffer) and can predict hypersensitivity only to the specific cephalosporin skin test reagent or cephalosporins with similar side chains. The European Network on Drug Allergy recommends using a nonirritating skin test concentration of 2 mg/mL for all cephalosporins, but increasing the concentration may identify additional skin test positive patients as reported using a nonirritating concentration of 20 mg/mL cefazolin.[31] We and others have used 1 to 20 mg/mL for scratch and intradermal testing, whereas others have used a 10-fold dilution.[30,32-35]

Skin testing predicts only IgE reactions and shows cross-reactivity in some patients between penicillins and early generation cephalosporins that share side-chain identity, namely, between ampicillin/amoxicillin and cephalexin/cefadroxil. This is normally not the case with later-generation cephalosporins that have distinct side chains from those of penicillin/amoxicillin.[36-41] The fragmented β-lactam ring with associated side chain normally binds *in vivo* to a protein to produce a hapten that elicits an antibody reaction.[27] Although penicilloyl polylysine, minor and major determinants, and benzylpenicillin are typically used for penicillin testing and accepted as valid reagents, for cephalosporins only the native molecule is available.[27] Hence, skin testing with native molecule cephalosporins has yet to be standardized and test concentrations remain to be widely accepted.[31,42]

Other methods that may be used to test for IgE antibodies to penicillin include the early radio-allergosorbent test, the more current fluorescent enzyme immunoassay, or ELISA. These *in vitro* techniques are not as reliable as skin or oral testing and may be susceptible to loss or decomposition of important antigenic structural features.[24,27-29,43,44]

TABLE I. Human cephalosporins*

Generation	USA	Brand name	Generic name (www.drugs.com)
First			
Cefadroxil	Yes	Duricef, etc	Cephadroxil, cefadroxilum
Cefalexin (Cephalexin)	Yes	Keflex, Panixine, Biocef, Zartan	
Cefaloglycin (Cephaloglycin)†		Not on market	Not on market
Cefaloridine (Cephaloridine)†		Cephalin, Ceporan	Cephalomycine, cefaloridina, cefaloridimum
Cefalotin (Cephalothin)†		Keflin, etc	
Cefapirin (Cephapirin)†		Cefadyl	
Cefatrizine		Trizicef, Trizin, etc	Cefatrizina, cefatrizin, cefatrizinum
Cefazedone‡		Kukje, Pazeron, Refosporen, Zenocef	
Cefazolin	Yes	Ancef, Kefzol	Cefazoline, cephazolin
Cefradine (Cephradine)†		Velosef	Cefradina
Cefroxadine		Tiroxin, Oraspor	
Ceftezole		Cetrazole, Tezacef, etc	Ceftezolo
Second			
Cefaclor	Yes	Raniclor, Ceclor, etc	Cefacloro, cefeaclor, cephaclor, cefaclorum
Cefamandole†		Mandol, etc	
Cefprozil	Yes	Cefzil, etc	Cefprozilum
Cefuroxime	Yes	Ceftin, Kefurox, Zinacef	Cefuroxima, cefuroxime axetil§
Cefonicid†		Monocid, etc	Cefonicide
Cefmetazole†‖		Zafazone, etc	
Cefotetan‖	Yes	Cefotan, etc	Cefotetan
Cefoxitin‖	Yes	Mefoxin, etc	Cefoxitina, cefoxitine, cefoxitinum
Loracarbef†¶		Lorabid, Lorbef	Loracarbef
Cefminox		Tancef, Meicelin, etc	Cefminox
Cefbuperazone		Tomiporan, Zinperazone	
Flomoxef#		Flumarin	
Third			
Cefcapene‡		Flomox, etc	
Cefdinir	Yes	Omnicef, etc	
Cefditoren	Yes	Spectracef, etc	Cefoviten
Cefetamet‡		Altamet, etc	
Cefixime	Yes	Suprax, etc	Cefixim
Cefmenoxime†		Bestron, Bestcall, etc	Cefmenoxim
Cefoperazone†		Acebis, Cefobid, etc	Cefoperazonum
Cefotaxime	Yes	Claforan, etc	Cefotaximun
Cefpiramide†		Cefpiran, etc	
Cefpodoxime	Yes	Vantin, etc	Cefpodoximun
Cefsulodin‡		Not on market	Not on market
Ceftibuten	Yes	Cedax, etc	Ceftibutene
Ceftizoxime†		Cefizox, etc	Ceftizoxima
Ceftriaxone	Yes	Rocephin, etc	Ceftriaxonum
Latamoxef†# (Moxalactam)		Latamoxef	
Ceftazidime**	Yes	Fortaz, Tazicef, Ceptaz, Avycaz	Ceftazidima, ceftazidimum
Cefodizime		Diezime, Kenicef, Timecef	
Cefdaloxime		Not on market	Not on market
Ceftiolene		Not on market	Not on market
Cefteram		Teracefron, Celat, etc	
Fourth			
Cefepime	Yes	Maxipime	
Cefluprenam‡		Not on market	Not on market
Cefozopran‡		Firstcin	
Cefpirome‡		Cefrom, Keiten, Broact, Cefir	
Cefclidine		Not on market	Not on market
Cefoselis		Not on market	Not on market

(continued)

TABLE I. *(Continued)*

Generation	USA	Brand name	Generic name (www.drugs.com)
Fifth			
Ceftaroline fosamil§ (Ceftaroline)	Yes	Teflaro, Zinforo	
Ceftobiprole‡		Zevtera, Mabelio	
Ceftolozane††	Yes	Zerbaxa	Ceftolozane and tazobactam
Cefiderocol‡‡		Not on market	Not on market

*Names are international nonproprietary names except those in parentheses are US names. Generations from WHO Collaborating Centre for Drug Statistics Methodology.[11]
†Discontinued in the United States (www.fda.gov/Drugs).
‡Not approved in the United States.
§Prodrug for improved oral bioavailability.
||Cephamycins have a 7-alpha-methoxy group that gives resistance to β-lactamases and makes them different from other cephalosporins.
¶Loracarbef is a carbacephem although typically grouped with cephalosporins.
#Oxacephem: where the sulfur atom of the cephalosporin core is replaced with an oxygen atom.
**Combined with avibactam, a β-lactase inhibitor, and given the trade name Avycaz.
††Combined with tazobactam, a β-lactase inhibitor, and given the trade name Zerbaxa.
‡‡Novel siderophore in now in phase II and III clinical studies.

ANTIBIOTIC DRUG ALLERGY

R_1 cross-reactive moiety

Classifications of β-lactam adverse reactions are based on the immunopathologic events of the patient responding to the allergen as originally proposed by Coombs and Gell.[45] Type I (hypersensitivity) is an IgE-mediated reaction, with onset occurring minutes to hours after exposure. These IgE-mediated reactions are clinically represented as urticarial rash, hives, wheezing, hypotension, rhinitis, bronchospasm, angioedema, and anaphylactic shock.[8,46] Traditionally, skin tests have been used for type I immune testing (see below). Today, the criterion standard test is an oral challenge with a therapeutic dose of the test antibiotic after skin testing.[22]

There have been many misconceptions regarding penicillin and cephalosporin allergies. Early dogma that cephalosporin allergy occurs in approximately 10% of penicillin-allergic patients has been shown to be incorrect because (1) 90% to 99% of patients reporting being allergic to penicillin can tolerate penicillins due to misclassification of reaction and natural waning of type I allergy,[47] and (2) most of the reported cases of penicillin-allergic patients who did experience an adverse reaction to a cephalosporin were given an early generation cephalosporin drug. In the latter case, reactivity was most likely the result of structurally similar antigenic R_1 groups of the cephalosporin and penicillin drugs,[9,48] or contamination of early generation cephalosporins by penicillin because the early manufacturing processes used penicillium mold to produce a parent compound that was subsequently chemically modified to create a cephalosporin ring structure.[25,49,50] The actual rate of cross-reactivity is probably less than 1%.[8,51] Figure 2 lists cephalosporins with identical or similar R_1 groups to penicillins.

However, not all structurally related side chains will have cross-reactivity to penicillins because compounds with dissimilar structures yet similar bioisostere properties (similar 3-dimensional electronic and steric properties) might result in cross-reactivity. An example of this is the benzyl group of penicillin G and the thiophene side chain of cephalothin.[26,52,53] It has also been suggested that the cross-reactivity between penicillin G and cephalothin may be due to the common methylene group within the side chains.[53] Indeed cephalothin is a special case in the debate about cephalosporin cross-reactivity with penicillin because cephalothin was the first cephalosporin marketed in the United States (in 1964) and it was contaminated with benzylpenicillin and that alone would explain the reports of cross-reactivity.[25,49,50]

Evidence that the β-lactam ring is not the major antigenic determinant comes from trials of patients with positive penicillin skin test results and subsequent testing for sensitivity to a carbapenem that only shares the common β-lactam ring structure.[11,13,54,55] The low rate of cross-reactivity (0.8%-1%) between penicillins and carbapenems could be attributable to unique separate sensitivities to the 2 antibiotic classes in the same patients.[56] These results are consistent with studies of penicillin-allergic patients where skin and *in vitro* tests established that the IgE response was directed toward the R_1 side chain of structurally related penicillins.[57]

In cases where a patient may react in tests to both penicillin and cephalosporin with dissimilar structures, it is not clear whether there is true cross-reactivity or natural coexisting sensitivity to both drugs.[58] In a study of penicillin-allergic patients, 11% displayed positive skin test responses to cephalosporins[59] and 64% of the patients reacted to cefamandole, which contains a benzyl R_1 structure similar to many of the penicillins, and/or cephalothin, which contains a thiophene R_1 structure similar to the R_1 of ticarcillin or temocillin penicillins. The remainder of patients who had positive skin test results to cephalosporins had different patterns of skin positivity to ceftazidime, ceftriaxone, cefuroxime, and cefotaxime, which all contain a methoxyimino R_1 group that is similar as a bioisostere to the methyl-isoxazole R_1 group of oxacillin.[27] When cefamandole or cephalothin skin test positive patients and patients who had negative cephalosporin skin test results received challenges to cefuroxime and ceftriaxone, none of the 101 challenged patients experienced an adverse reaction.[59]

R_2 cross-reactive moiety

There has been much attention and reports directed at the R_1 moiety being responsible for hypersensitive cross-reactivity.[9,35,58,60] This is also due in part to the proposed structure of the cephalosporin-hapten complex. Aminolysis is the process by which binding of the amino group of the carrier protein results in the opening of the β-lactam ring and subsequent breakdown of the dihydrothiazine ring with the proposed loss of the R_2 group.[27,28,61] However, there is debate as to the

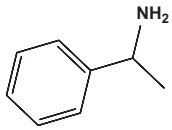
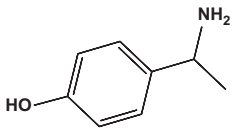
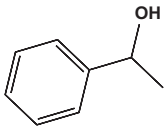
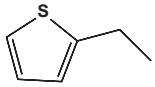
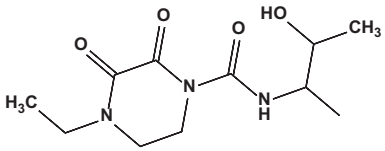
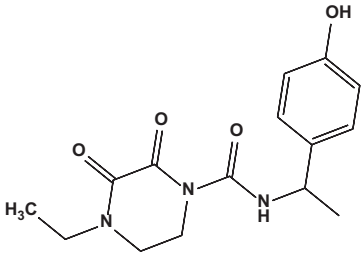
Cephalosporin	R_1 Structure	Penicillin Identical R_1	Penicillin Similar R_1
Cephalexin Cephaloglycin Cefaclor Loracarbef		Ampicillin Pivampicillin*† Bacampicillin*‡ Talampicillin*†	Mezlocillin‡ Piperacillin Azlocillin‡
Cefadroxil Cefatrizine Cefprozil		Amoxicillin	Mezlocillin Piperacillin Azlocillin
Cefamandole Cefonicid			Ampicillin Amoxicillin Pivampicillin Bacampicillin Talampicillin
Cefoxitin Cephaloridine Cephalothin			Ticarcillin‡ Temocillin†
Cefbuperazone			Piperacillin
Cefoperazone§			Piperacillin

FIGURE 2. Cephalosporin and penicillin R_1-like structures. R_1 cephalosporin structures that are either identical or similar to penicillin R_1 side chains. *Prodrug, breaks down to ampicillin. †Not approved in the United States. ‡Discounted in the United States. §Aside from the ethyl-dioxopiperazine moiety that is identical to piperacillin, also contains hydroxyl-benzyl (phenol) group that is identical to amoxicillin and similar to piperacillin's benzyl group.

involvement of R_1 and/or R_2 as antigenic determinants that cause type I hypersensitivity for various cephalosporins, which is essential to know for prescribing these antibiotics in patients who have cephalosporin allergy. In an early report using an *in vitro* inhibition immunoassay, serum IgE from a subject with type I reaction to cephalothin was tested.[62] Cephalothin was bound to Sepharose for chromatographic analysis and various cephalosporins tested for inhibition of patient's serum IgE antibodies binding to cephalothin-Sepharose. Drugs that had identical R_1 groups elicited inhibition, but cephaloglycin and cephapirin, which do not have a similar R_1 group but do have an identical R_2 group, showed significant inhibition. The same group has also suggested contributions of both R_1 and R_2 groups involved in *in vitro* sera cross-reactivity studies.[27]

In a study of patients with immediate reactions to cephalosporins evaluated on the basis of skin test and Sepharose radioimmunoassay, 70 (92%) of 76 patients showed IgE hypersensitivity, with more than 90% of the cross-reactivity due to R_1 side-chain structure similarities.[56] Additional studies have been reported evaluating the cross-reactivity of patients with immediate allergic reactions to cephalosporins and are summarized in Table II. In Table II we chose to report only skin test responses versus *in vitro* IgE studies because (1) skin tests are easily performed in a clinical setting and the patient can be monitored for

TABLE II. R_1/R_2 Similar groups and positive skin test results in subjects with type I reaction to cephalosporin drug

	Skin tests†								
Culprit*	Cefoperazone	Cefonicid	Cefatrizine	Cefodizime	Cephalexin	Cefaclor	Cephalothin	Cefamandole	Ceftazidime
Cefoperazone[a,b]	2/2‡	ND	R_1 ND	ND	0/1	R_1 0/1	0/1	**R_2** 2/2	0/2
Cefonicid[a,c]	ND	1/2‡	R_1 ND	ND	ND	R_1 0/1	0/1	**R_1** 0/1	0/2
Cefatrizine[a]	R_1 ND	R_1 ND	1/3‡	ND	R_1 ND	R_1 ND	0/3	0/3	0/3
Cefodizime[a,b]	ND	ND	ND	6/6‡	ND	ND	1/5	1/5	R_1 2/6
Cephalexin[a,b,d]	ND	ND	R_1 ND	ND	2/3‡	**R_1** 1/1	1/2	R_1 2/3	1/4
Cefaclor[a-d]	R_1 ND	R_1 0/7	R_1 ND	ND	**R_1** 3/3	10/13‡	0/3	R_1 1/6	0/13
Cephalothin[a]	ND	ND	ND	ND	ND	ND	1/1‡	0/1	0/1
Cefamandole[a]	**R_2** ND	**R_1** ND	ND	ND	R_1 ND	R_1 ND	1/3	2/3‡	1/3
Ceftazidime[a,c]	ND	0/2	ND	R_1 ND	ND	0/2	1/15	1/15	11/17‡
Ceftriaxone[a-c,f]	ND	0/3	ND	**R_1** ND	0/4	1/7	0/18	2/22	R_1 5/48
Cefuroxime[a-i]	ND	0/13	ND	R_1 2/5	1/1	1/14	(R_1/R_2) 1/8	0/9	0/29
Cefotaxime[a-c,h]	ND	0/3	ND	R_1 1/1	ND	0/3	**R_2** 0/14	0/14	R_1 2/19
Cefazolin[d,j]	ND	ND	ND	ND	ND	ND	0/2	0/2	0/3

ND, No data.
[a]Data from 70 adults[56]; [b]Data from 32 adults[35]; [c]Data from 24 adults[29]; [d]Data from 6 adults[63]; [e]Data from 1 adult[60]; [f]Data from 2 adults[28]; [g]Data from 1 adult[64]; [h]Data from 1 adult[61]; [i]Data from 1 adult[65]; [j]Data from 10 adults.[66]
*Subjects with a single cephalosporin drug involved in the type I reaction.
†Cephalosporins used for skin testing.
‡Identical drugs. Numbers shown are the number of patients with a positive reaction over total number of patients tested for this drug. Drugs tested that have identical or similar R groups to the culprit drug are noted R_1 and/or R_2 as follows: identical—bolded; very similar or bioisostere (parentheses)—not bolded.

any adverse reaction; (2) in *in vitro* IgE studies, the R_2 side chain may be lost during conjugation of the cephalosporin to a carrier or Sepharose[27,29]; and (3) the R_2 group may be sterically shielded because of the R_1 group.[52] It is important to note, as reported by Romano et al,[67,68] that skin test responses can be affected by the time interval between the last reaction and the allergy tests.

Cephalosporin challenge studies

In a retrospective review of patients who were penicillin allergic and received a preoperative cephalosporin treatment of cefazolin or cefoxitin, no cases of anaphylaxis were reported.[69] There was 1 case of a patient with development of hives and erythema (0.6%), thus demonstrating the rarity in cross-reactivity and the occurrence may have been due to an independent hypersensitivity and not true cross-reactivity.

In a study of 1421 patients who had no previous allergy to β-lactam antibiotics and required preoperative cephalosporin prophylaxis, all were skin tested with 4 cephalosporins (ceftezol, cefotetan or cefamandole, ceftriaxone or cefotaxime, and flomoxef) and penicillin G.[70] Five percent of patients were positive to at least 1 cephalosporin. All patients were then challenged intravenously with the scheduled cephalosporin and only 0.3% had an immediate hypersensitivity reaction and none of those who reacted had been skin test positive. Thus, in that study, skin test results demonstrated 0% sensitivity for predicting an immediate hypersensitivity of a cephalosporin.

In a prospective study of 622,456 patients exposed to 901,908 courses of oral cephalosporins and 326,867 patients exposed to 487,630 courses of parenteral cephalosporins, there were 13 (0.0009%) physician-documented cephalosporin-associated anaphylaxis cases.[71] Of these 13 cases, none was in 3,313 patients tested with history of cephalosporin allergy and 3 were in 65,915 patients tested with history of penicillin allergy. These data support the authors' recommendation on the safe use of cephalosporins in individuals with a history of penicillin or other cephalosporin allergy.[72]

CLINICAL RECOMMENDATIONS

There is ample evidence to allow the safe use of all but a few early generation cephalosporins in patients with penicillin or amoxicillin allergy.[40,41,48,73] Patients with a history of penicillin allergy do have a general elevated risk of allergic reaction and may develop an allergic response to cephalosporins by coincidence[51] but the risk is comparable to that of receiving a sulfonamide antibiotic.[74] Thus, the attributable risk of an allergic

TABLE II. Continued.

	Skin tests†							
Culprit*	**Ceftriaxone**	**Cefuroxime**	**Cefotaxime**	**Cefazolin**	**Cefepime**	**Cefadroxil**	**Ceftibuten**	**Cefoxitin**
Cefoperazone[a,b]	0/2	0/2	0/2	0/1	0/1	0/1	0/1	ND
Cefonicid[a,c]	0/2	0/2	0/2	ND	ND	ND	ND	ND
Cefatrizine[a]	0/3	0/3	0/3	ND	ND	**R_1** ND	ND	ND
Cefodizime[a,b]	**R_1** 3/6	R_1 3/6	R_1 4/6	ND	0/1	ND	ND	ND
Cephalexin[a,b,d]	1/4	0/4	0/4	0/2	0/1	R_1 0/1	0/2	ND
Cefaclor[a-d]	0/13	2/14	1/13	0/4	0/3	R_1 1/3	0/3	ND
Cephalothin[a]	0/1	R_1/R_2 0/1	**R_2** 0/1	ND	ND	ND	ND	**R_1**/R_2 ND
Cefamandole[a]	1/3	1/3	1/3	ND	ND	ND	ND	ND
Ceftazidime[a,c]	R_1 4/17	2/17	R_1 2/17	ND	R_1 ND	ND	ND	ND
Ceftriaxone[a-c,f]	46/48‡	(R_1) 13/48	**R_1** 32/48	0/4	**R_1** 14/27	0/4	R_1 1/4	ND
Cefuroxime[a-i]	R_1 7/29	26/29‡	R_1/(R_2) 15/29	0/5	R_1 2/10	0/6	0/1	ND
Cefotaxime[a-c,h]	**R_1** 9/19	(R_1/R_2) 10/19	14/19‡	ND	**R_1** 0/3	0/1	ND	ND
Cefazolin[d,j]	0/8	1/8	1/5	8/11‡	ND	ND	ND	0/2

cross-reactivity between penicillins and cephalosporins, for all but a few cephalosporins with similar side-chain structures to penicillin, is essentially nil. Therefore, virtually every patient reporting a history of or who is skin test positive to penicillins may receive a cephalosporin antibiotic as a replacement with the exception of those showing R_1 side-chain similarity. To aid in choosing a penicillin or cephalosporin drug based on a subject having had an allergic reaction to one of these drugs, we have devised a chart that lists many of the major drugs used today and whether the R_1 or R_2 side chains are identical or similar (Figure 3). We also subdivided R_1 if it contained multiple chemical moieties where each moiety alone has the potential to be responsible for cross-reactivity.[64,65] However, we did not take into account possible cross-reactivity due to bioisosteric structures such as the methyl-substituted isoxazole R_1 of oxacillin with the methoxyimino R_1 of cefuroxime, ceftriaxone, cefepime, and cefotaxime,[27,65] or the postulated benzene and thiophene ring bioisosterism of benzylpenicillin and cephalothin that may be due to contamination and not bioisosterism.[27,65] Whether the cross-reactivity is due to bioisosterism or unreported prior exposure to other drugs containing similar cross-reactive moieties, the chart is a guide to help choose a drug with dissimilar R side-chain groups.

Clinical data and side-chain analysis of cross-reactivity between penicillins and cephalosporins allows prescribing specific cephalosporin antibiotics for the treatment of patients with reported type I or non−type I penicillin allergies as endorsed in the 2013 American Academy of Pediatrics Sinusitis Guideline.[6] Other agencies, such as the American Academy of Allergy, Asthma & Immunology, that have not endorsed this approach recommend skin testing and challenge studies before cephalosporin treatment.[8] Reconsideration of those recommendations appears warranted.

Based on a clearer understanding of penicillin, cephalosporin, and β-lactam allergy, it is now known that an allergy diagnosis based on skin testing and oral/parenteral challenge rather than a patient's reported history will permit more than 95% of patients labeled as allergic to be delabeled.[75] To clear the way for wide acceptance and adoption of delabeling practices, we propose the following key points:

1. Clinical evaluation of patients reporting a penicillin antibiotic allergy should include skin testing and oral challenge if the drug is orally available.[5,22,76,77] A negative penicillin test result removes a patient as being labeled as penicillin allergic with reasonable medical certainty and allows one to prescribe

		Penicillins							1st							2nd								3rd										4th		5th			Mono
		Nafcillin	Oxacillin	Dicloxacillin	Penicillin G / V	Piperacillin	Ampicillin	Amoxicillin	Cefadroxil	Cefatrizine	Cephalexin	Cefazolin	Cefazole	Cephalothin	Cephapirin	Cefprozil	Cefuroxime	Cefotetan	Cefprozil	Cefaclor	Cefonicid	Cefamandole	Cefoperazone	Ceftibuten	Cefdinir	Cefixime	Ceftriaxone	Cefditoren	Cefodizime	Ceftazime	Cefpodoxime	Ceftazidime	Cefepime	Cefpirome	Ceftaroline fosamil	Ceftolozane	Cefiderocol	Aztreonam
PCN	Nafcillin																																						
	Oxacillin			r1																																			
	Dicloxacillin		r1																																				
	Penicillin G / V					r1'	r1'	r1'	r1	r1	r1								r1	r1	r1	r1	r1'																
	Piperacillin				r1'		R1'	r1'	r1'	r1'	R1'								r1'	R1'	r1'	r1'	R1"																
	Ampicillin				r1'	R1'		r1'	r1	r1	R1								r1	R1	r1	r1	r1'																
	Amoxicillin				r1'	r1'	r1'		R1	R1	r1'								R1	r1	r1	r1	R1'																
1st	Cefadroxil				r1	r1	r1	R1		R1	r1								R1	r1	r1	r1	R1'																
	Cefatrizine				r1	r1'	r1	R1	R1		r1								R1	r1	r1	r1	R1'																
	Cephalexin				r1	R1'	R1	r1	r1	r1									r1	R1	r1	r1	r1'																
	Cefazolin												R1r2																										
	Ceftezole											R1r2																											
	Cephalothin														R2	R1r2	r1'r2														R2								
	Cephapirin													R2		r2	r2														R2								
2nd	Cefoxitin													R1r2	r2		r1'R2														r2								
	Cefuroxime													r1'r2	r2	r1'R2										r1"	R1"	R1"	R1"	R1"r2	R1"		R1"	R1"	r1"				
	Cefotetan																				r2	R2	R2																
	Cefprozil				r1	r1	r1	R1	R1	R1	r1									r1	r1	r1	R1'																
	Cefaclor				r1	R1'	R1	r1	r1	r1	R1								r1		r1	r1	r1'																
	Cefonicid				r1	r1	r1	r1	r1	r1	r1							r2	r1	r1		R1r2	r1'r2																
	Cefamandole				r1	r1	r1	r1	r1	r1	r1							R2	r1	r1	R1r2		r1'R2																
3rd	Cefoperazone				r1'	R1"	r1'	R1'	R1'	R1'	r1'							R2	R1'	r1'	r1'r2	r1'R2																	
	Ceftibuten																								R1'	R1'	R1'	R1'	R1'	R1'	R1'	R1'	R1'	R1'	r1'	r1'	R1'	R1'
	Cefdinir																							R1'		R1'R2	R1'	R1'	R1'	R1'	R1'	R1'	R1'	R1'	r1'	r1'	R1'	R1'
	Cefixime																r1"							R1'	R1'R2		R1'	R1'	R1'	R1'	R1'	R1'	R1'	R1'	r1	r1	R1'	R1'
	Ceftriaxone																R1"							R1'	R1'	R1'		R1	R1	R1	R1	R1'	R1	R1	r1	r1	R1'	R1'
	Cefditoren																R1"							R1'	R1'	R1'	R1		R1	R1	R1'	R1'	R1	R1	r1	r1	R1'	R1'
	Cefodizime																R1"							R1'	R1'	R1'	R1	R1		R1	R1'	R1'	R1	R1	r1	r1	R1'	R1'
	Cefotaxime													R2	R2	r2	R1"r2							R1'	R1'	R1'	R1	R1	R1		R1'	R1'	R1	R1	r1	r1	R1'	R1'
	Cefpodoxime																R1"							R1'	R1'	R1'	R1	R1	R1	R1		R1'	R1	R1	r1	r1	R1'	R1'
	Ceftazidime																							R1'	R1'	R1'	R1'	R1'	R1'	R1'	R1'		R1'	R1'r2	r1	R1'	R1	R1
4th	Cefepime																R1"							R1'	R1'	R1'	R1	R1	R1	R1	R1	R1'		R1	r1	r1	R1'r2	R1'
	Cefpirome																R1"							R1'	R1'	R1'	R1	R1	R1	R1	R1	R1'r2	R1		r1	r1'	R1'	R1'
5th	Ceftaroline fosamil																r1"							r1'	r1'	r1'	r1	r1	r1	r1	r1	r1	r1	r1		R1'	r1	r1'
	Ceftolozane																							r1'	r1'	r1'	r1'	r1'	r1'	r1'	r1'	R1'	r1'	r1'	R1'		R1'	R1'
	Cefiderocol																							R1'	R1'	R1'	R1'	R1'	R1'	R1'	R1'	R1	R1'r2	R1'	r1	R1'		R1
Mono	Aztreonam																							R1'	R1'	R1'	R1'	R1'	R1'	R1'	R1'	R1	R1'	R1'	r1'	R1'	R1	

FIGURE 3. Comparison of R_1 and R_2 structural similarities between β-lactam drugs. Drugs that have identical R_1 or R_2 structures are listed as R1 (red cell) or R2 (gold cell). If only the ring or branch chain moiety of the R_1 structure is identical, it is listed as R1′ or R1″, respectively. Drugs that have similar R_1 or R_2 structures are listed as r1 or r2. If only the ring or branch chain moiety of the R_1 structure is similar, it is listed as r1′ or r1″, respectively. Blank cells imply no R_1 or R_2 structural similarities.

penicillins. This procedure should be considered electively rather than urgently.

2. Clinical evaluation of patients reporting a cephalosporin allergy should include cephalosporin skin testing with the native molecule and oral challenge if the drug is orally available.[36,40,41] A negative cephalosporin test result removes a patient as being labeled allergic to that cephalosporin and other cephalosporins with similar R_1 and R_2 side chains. This procedure should be considered electively rather than urgently.
3. The notion that penicillin-allergic patients must avoid all cephalosporins because of potential cross-reactivity among the molecules should be dismissed as a myth. Cross-reactivity between penicillins and cephalosporins occurs rarely and when it occurs it is due to similarity in the R_1 side chain of the molecules.
4. The notion that a patient allergic to a specific cephalosporin must avoid all cephalosporins because of potential cross-reactivity among the molecules should be dismissed as a myth. Cross-reactivity between cephalosporins occurs rarely and when it occurs it is due to similarity in the R_1 or R_2 side chain of the molecules. The important take-home message that is evidence based is the need to perform a skin test to confirm the safety of any drug if a patient has been labeled as allergic and then an oral provocation test under physician supervision. This may occur in an outpatient setting as long as there is preparedness for treatment of anaphylaxis. Similarly, in the hospital setting after skin testing, if negative, parenteral drugs provocation testing may be used to permit the use of a test β-lactam and delabeling.
5. Carbapenem and monobactams are β-lactams but their molecular structure is sufficiently dissimilar from those of penicillins and cephalosporins that cross-allergy among these molecules would not be predicted.
6. Performing these tests will reduce the use of less effective, more toxic, broader antimicrobial spectrum and more costly alternative antibiotic drugs, and will support good antimicrobial stewardship guidelines.[75]
7. The risks of medicolegal prosecution are always a concern for clinicians and part of the decision-making paradigm. It should be recognized that patients with a bona fide allergy to a β-lactam antibiotic may experience an allergic reaction to a different β-lactam antibiotic as an independent hypersensitivity reaction that is not related by cross-allergy. The old adage, "true, true and unrelated" can and does occur in patients.

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FIGURE E1. β-Lactam structures. The names of the compounds are shown along with the (generation number) for each cephalosporin. R_1 and R_2 groups have been highlighted in red and blue, respectively. The cephalosporins were arranged on the basis of the R_1 ring moiety and then on the R_1 branch chain. Atoms shown in green are modifications at the β-lactam or cephem rings. Structures drawn using ChemBioDraw Ultra software and shown for best viewing and may not be the actual structural conformation.

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