

# $\beta$ -Lactam Allergy and Cross-Reactivity: A Clinician's Guide to Selecting an Alternative Antibiotic

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**Abstract:**  $\beta$ -Lactams which include penicillins, cephalosporins, carbapenems, and monobactams are the most common antibiotic classes reported to cause allergic reactions to drugs. This review is mainly about published studies assessing the cross-reactivity among  $\beta$ -lactams in penicillin- or cephalosporin-allergic subjects by carrying out diagnostic tests with alternative  $\beta$ -lactams and, if appropriate, graded challenges. Several studies demonstrated that cross-reactivity connected with the  $\beta$ -lactam ring, causing positive responses to allergy tests with all  $\beta$ -lactams, is infrequent in subjects with an IgE-mediated allergy and anecdotal in those with a T-cell-mediated allergy. Identities or similarities of  $\beta$ -lactam side-chain structures are mainly responsible for cross-reactivity among these antibiotics. For example, in aminopenicillin-allergic subjects, cross-reactivity with aminoccephalosporins could possibly be over 30%. On the other hand, in a few prospective studies of penicillin-allergic individuals, less than 1% of cases show a cross-reactivity between penicillins and both aztreonam and carbapenems. Particular patterns of allergy-test positivity observed in some studies that assessed cross-reactivity among  $\beta$ -lactams seem to indicate that prior exposures may be responsible for coexisting sensitivities. Therefore, pre-treatment skin tests with the related  $\beta$ -lactams are suggested before administering them via graded challenges to  $\beta$ -lactam-allergic patients who need alternative  $\beta$ -lactams.

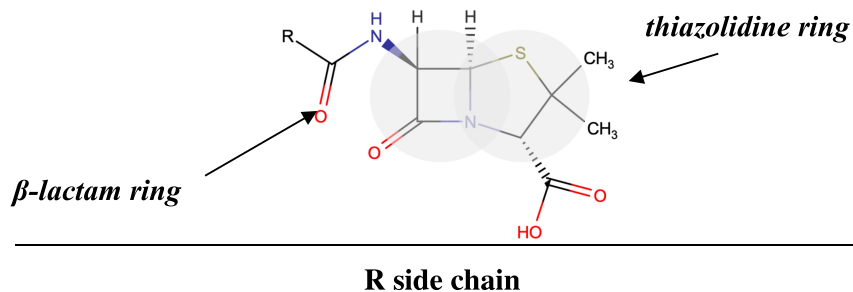
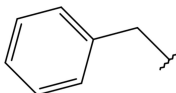
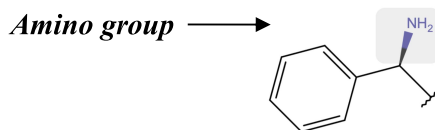
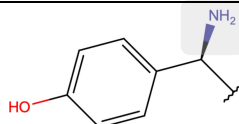
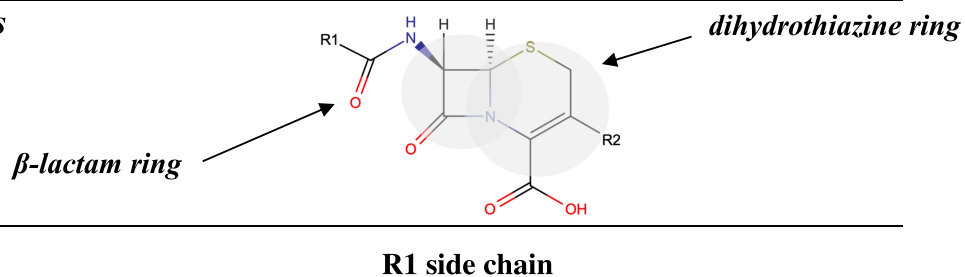
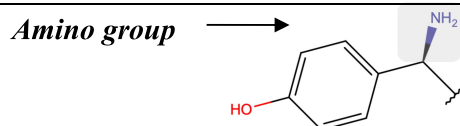
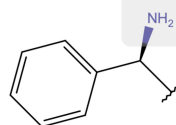
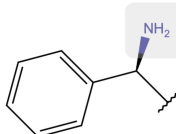
**Keywords:** aztreonam,  $\beta$ -lactams, carbapenems, cephalosporins, cross-reactivity, hypersensitivity, penicillins, skin tests

## Introduction

$\beta$ -Lactams which include penicillins, cephalosporins, carbapenems, and monobactams, are the most common antibiotic classes reported to cause allergic reactions to drugs. All  $\beta$ -lactams share a 4-membered  $\beta$ -lactam ring. In penicillins, it is attached to a 5-membered thiazolidine ring; the side chain (R) differentiates the penicillins (Figure 1). Instead of the 5-membered thiazolidine ring of penicillins, cephalosporins have a 6-membered sulfur-containing dihydrothiazine ring and 2 side chains (R1 and R2), which distinguish the different compounds (Figures 1, 2A and B). Carbapenems (eg, imipenem, meropenem, ertapenem, and doripenem) contain a carbon double bond instead of sulfur in the 5-membered thiazolidine ring and have a side chain (R), which distinguishes the different carbapenems (Figure 3). Aztreonam is the only monobactam commercially available; it contains only the  $\beta$ -lactam ring (Figure 3).

Penicillins and cephalosporins are frequently responsible for hypersensitivity reactions (HSRs).<sup>1</sup> IgE-mediated ones occur within 6 hours after the last drug administration (ie, immediate reactions), though typically occur within one hour

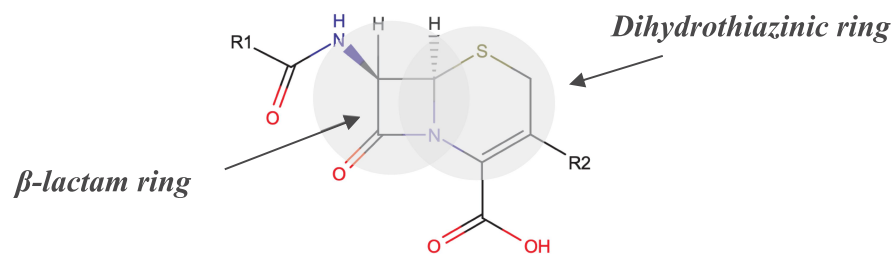
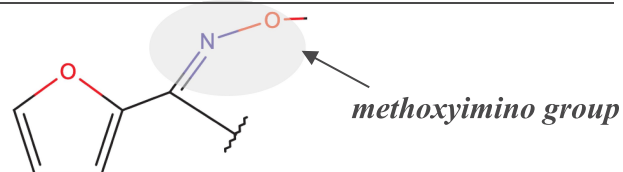
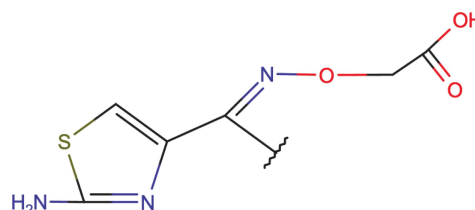
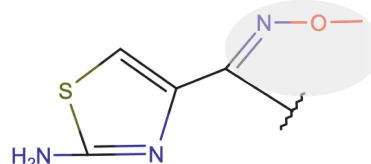
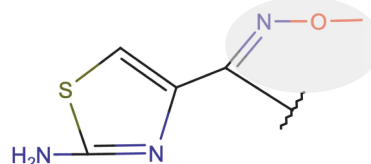
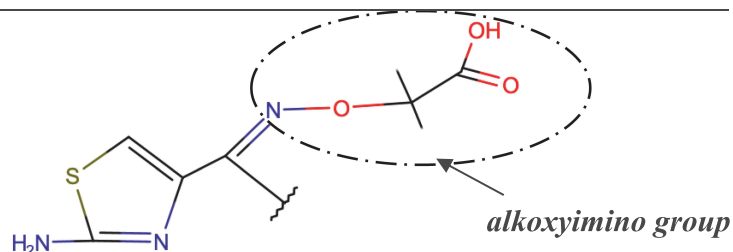
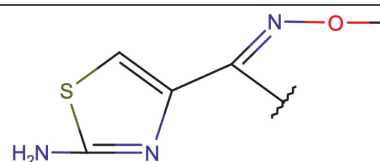
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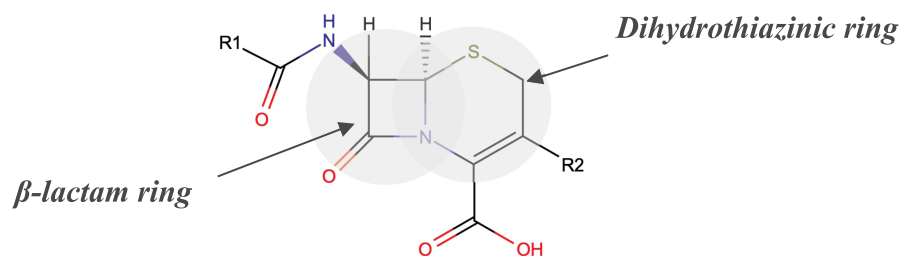
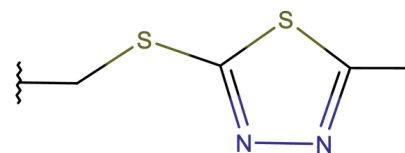
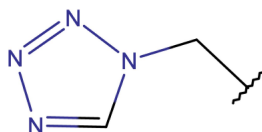
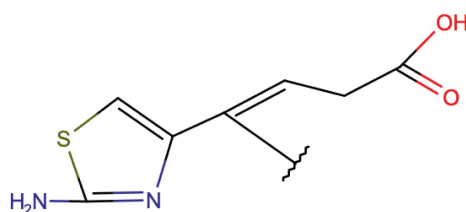
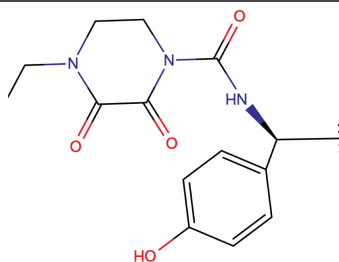
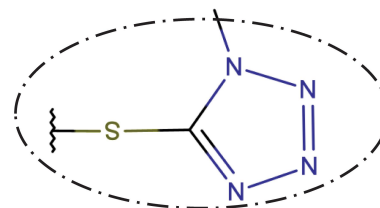
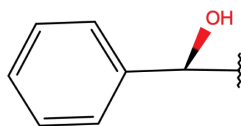
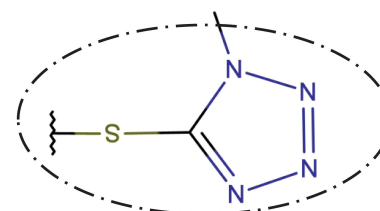
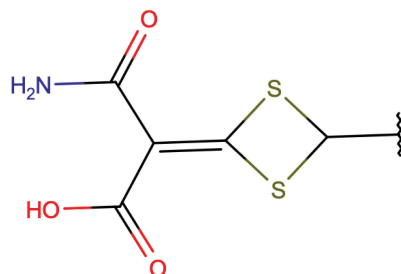
**Penicillins****Benzylpenicillin****Ampicillin****Amoxicillin****Aminocephalosporins****Cefadroxil****Cephalexin****Cefaclor**

**Figure 1** Chemical structures of penicillins, with the amino group of ampicillin and amoxicillin, as well as that of cephalosporins of group B (ie, aminocephalosporins) highlighted in gray.

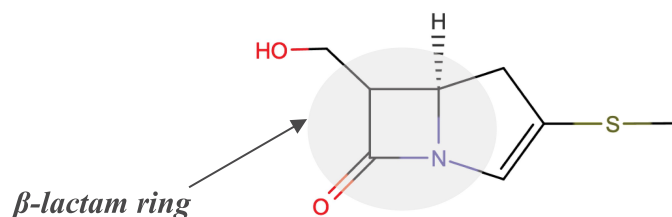
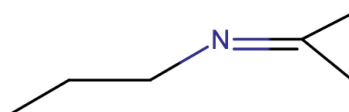
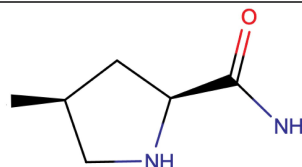
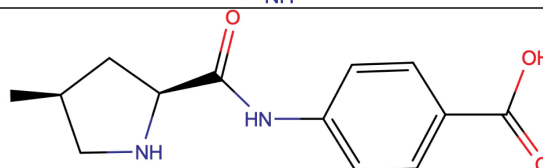
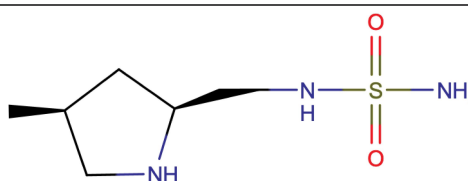
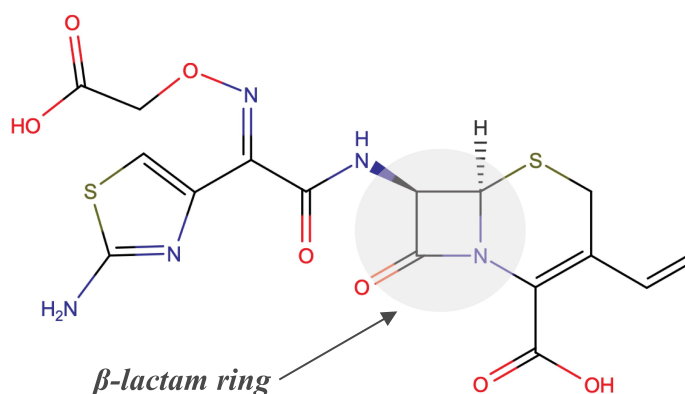
of the first dose of a new treatment course.<sup>2–4</sup> These reactions are characterized by a silent sensitization, with a transient mast-cell unresponsiveness to the initial

administration of the drug.<sup>5</sup> They usually manifest as cutaneous (eg, itching, hives, angioedema, generalized erythema), respiratory (eg, nasal congestion, rhinorrhea,

**A*****Cephalosporins*****R1 side chain***Cefuroxime**Cefixime**Cefotaxime**Ceftriaxone**Ceftazidime**Cefpodoxime***Figure 2 Continued.**

**B****Cephalosporins****R1 side chain****R2 side chain****Cefazolin****Ceftibuten****Cefoperazone****N-methyltetrazole-thiol group****Cefamandole****Cefotetan**

**Figure 2 (A and B)** Chemical structures of cephalosporins other than aminocephalosporins, with the methoxyimino group of cephalosporins of group A highlighted in gray and the alkoxyimino group of ceftazidime and N-methyltetrazole-thiol group of cefamandole and cefoperazone circled in black.

**Carbapenems****Imipenem****Meropenem****Ertapenem****Doripenem****Aztreonam**

**Figure 3** Chemical structures of carbapenems and aztreonam.

sneezing, hoarseness, cough, wheezing), gastrointestinal (eg, nausea, diarrhea, mild abdominal pain, vomiting), cardiovascular (eg, tachycardia, hypotension) symptoms, which may appear isolated or in combination as in anaphylaxis.<sup>4</sup> T-cell-mediated HSRs may occur at any time from 1 hour after the first drug administration (ie,

nonimmediate reactions), commonly after many days of treatment.<sup>3</sup> In this case, cytotoxic and cytokine-secreting T cells orchestrate the inflammatory cells (ie, T cells, PMN, eosinophils).<sup>5</sup> Maculopapular exanthema (MPE) and delayed-appearing urticaria are the most frequent non-immediate reactions.<sup>3,6</sup> Severe cutaneous adverse reactions

(SCARs), ie acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome or drug rash with eosinophilia and systemic symptoms (DRESS), are the most serious expressions of  $\beta$ -lactam nonimmediate reactions.

The  $\beta$ -lactam ring, the thiazolidine/dihydrothiazine rings, and the side-chains can all sensitize subjects treated with  $\beta$ -lactams. In particular, side chains contribute significantly to immunological recognition and therefore the structures are most frequently responsible for allergic cross-reactivity.<sup>1,7–12</sup>

In  $\beta$ -lactam-allergic patients, the diagnostic workup with alternative drugs shows the cross-reactivity and, above all, allows to treat patients with safe drugs.<sup>4,13</sup>

This review is mainly about prospective studies which assessed the cross-reactivity among  $\beta$ -lactams in penicillin- or cephalosporin-allergic subjects by carrying out in vivo tests and, if available, in vitro ones with alternative  $\beta$ -lactams and, in case of negative results, administering them via graded challenges.

## Selecting Alternative $\beta$ -Lactams in $\beta$ -Lactam-Allergic Subjects

In subjects reporting HSRs to  $\beta$ -lactams, the two main goals of the diagnostic workup are to confirm or exclude allergy to the  $\beta$ -lactam concerned and, in case of allergy diagnosis, to find safe alternatives, particularly among other  $\beta$ -lactams.<sup>4</sup> An accurate clinical history is crucial for the assessment of subjects reporting HSRs to  $\beta$ -lactams, followed by skin tests (STs) and/or patch tests (PTs). In selected cases presenting negative results, challenges with the suspected  $\beta$ -lactams can be considered for the final diagnosis.<sup>4</sup> Subjects with suspected IgE-mediated reactions are evaluated by immediate-reading skin prick tests and intradermal tests (IDTs) by immediate-reading are performed in subjects with suspected IgE-mediated reactions, whereas those with nonimmediate reactions by delayed-reading STs and/or PTs.<sup>4,14</sup>

In vitro tests can be used as a complement to the above diagnostic tests. The main in vitro tests for assessing subjects with immediate reactions to  $\beta$ -lactams are the serum specific IgE (sIgE) assay and the basophil activation test. The lymphocyte transformation test and the enzyme-linked immunosorbent spot assay can be used for evaluating subjects with nonimmediate reactions.<sup>4</sup>

There are few prospective studies of  $\beta$ -lactam-allergic subjects which assessed cross-reactivity among  $\beta$ -lactams by carrying out allergy tests with  $\beta$ -lactams other than

those responsible and, in case of negative results, by performing graded challenges with them.<sup>4,9–12</sup>

## Penicillin-Allergic Subjects

Individuals with histories of penicillin allergy are more likely to receive alternative broad-spectrum antibiotics, including vancomycin and quinolones, which can lead to higher costs, prolonged hospitalizations, and elevated number of infection with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and *Clostridioides difficile* (formerly *Clostridium difficile*).<sup>15–17</sup> Although a large number of patients are labeled as allergic to penicillin, more than 95% of them can tolerate penicillin after an appropriate evaluation.<sup>18</sup> Due to the low prevalence of true penicillin allergy and the disadvantage from using alternative antibiotics, all subjects who report HSRs to penicillins should be evaluated in order to confirm or exclude a penicillin-allergy diagnosis.<sup>19,20</sup>

### Selecting Alternative Penicillins

Several studies found a greatness of cross-reactivity between benzylpenicillin (penicillin G [PG]) and semisynthetic penicillins, as well as among the latter, in particular aminopenicillins (ie, amoxicillin, ampicillin, bacampicillin, and pivampicillin) which share an amino group in their side chain (Figure 1).<sup>9–12</sup> However, there are studies in which participants with either an IgE-mediated<sup>21</sup> or a T-cell-mediated allergy to aminopenicillins<sup>22,23</sup> showed negative results at in vivo tests with PG and/or phenoxymethylpenicillin (penicillin V [PV]) and tolerated graded challenges with them. Specifically, Blanca-Lopez et al<sup>21</sup> diagnosed hypersensitivity in 58 subjects reporting immediate reactions to amoxicillin or amoxicillin/clavulanic acid. Of these 58 individuals, 7 were positive to PG determinants, 40 were positive to amoxicillin and tolerated both PG and PV, and the remaining 11 were positive only to clavulanic acid and tolerated PG, PV, and amoxicillin.

In two studies of more than 30 subjects with a T-cell-mediated allergy to aminopenicillins,<sup>22,23</sup> the rate of cross-reactivity to PG and/or PV was 9.1% and 28.2%, respectively. Specifically, in a study of ours,<sup>22</sup> 33 of the 60 participants reporting MPEs associated with aminopenicillin therapy were positive to PTs and delayed-reading IDTs with ampicillin and amoxicillin, and 3 also to those with PG; 17 subjects negative to PG reagents accepted challenges with PV and tolerated them. In another study,<sup>23</sup> of the 71 participants with a delayed allergy to aminopenicillins, 16 presented positive PTs or IDTs to both PG and

PV and 4 only to PG. All 51 subjects who underwent challenges with PV tolerated them.

Concerning subjects allergic to penicillins other than aminopenicillins, in a recent study by Kennard et al,<sup>24</sup> 4 patients with an immediate hypersensitivity to flucloxacillin and one with a delayed hypersensitivity to it tolerated challenges with amoxicillin and PG, respectively, found negative in allergy tests.

### Selecting Cephalosporins

The data concerning the measure of cross-reactivity between penicillins and cephalosporins differ markedly and are frequently inaccurate.<sup>25</sup> A meta-analysis of articles published between 1966 and 2005, which compared HSRs to cephalosporins in penicillin-allergic and non-penicillin-allergic patients, showed a considerable rise (odds ratio = 4.8) in allergic reactions to all first-generation cephalosporins plus cefamandole, but no increment with second- or third-generation.<sup>26</sup> Nonetheless, the adulteration of these early cephalosporins with trace amounts of PG it may have led to an overset of the degree of cross-reactivity between these  $\beta$ -lactams. Furthermore, this meta-analysis<sup>26</sup> comprehended retrospective studies, in which the diagnosis of penicillin allergy was based only on the clinical history. A recent meta-analysis<sup>12</sup> of 21 studies on cephalosporin cross-reactivity performed between January 1980 and December 2016, which included 1269 penicillin-allergic patients, showed that the rate of cross-reactivity varied with the degree of similarity between R1 side chains. In effect, such risk was 16.5% for aminocephalosporins (ie, cephalixin, cefadroxil, cefprozil, and cefaclor), which share an identical side chain (similarity score = 1) with an aminopenicillin, 5.6% for cephalothin, cephaloridine, and cefamandole, which have an R1 side chain with a similarity score of around 0.6 compared with that of PG, and 2.1% for all those (ie, cefazolin, cefuroxime, cefixime, cefotaxime, ceftriaxone, ceftazidime, cefpodoxime, ceftibuten, and cefepime) with low similarity scores (below 0.4), irrespective of cephalosporin generation (Figures 1, 2A and B).

Note that this meta-analysis<sup>12</sup> included studies on at least 10 subjects (children and adults) with a documented penicillin allergy (IgE- or T-cell-mediated). In studies carried out since 1990 on more than 25 subjects with proven IgE-mediated allergy to penicillins,<sup>27–34</sup> the rate of positive cephalosporin STs ranged from 0%<sup>28,30</sup> to 33.3% (Table 1).<sup>31</sup> The highest rate was found in the study of

ours,<sup>31</sup> in which participants underwent STs with a panel of 9 cephalosporins, including 3 aminocephalosporins (ie, cephalixin, cefadroxil, and cefaclor) that share similar or identical side-chain determinants with the aminopenicillins that were responsible for HSRs in 96% of the 252 patients assessed. In the aforesaid studies,<sup>27–34</sup> 821 penicillin-allergic subjects negative to cephalosporin STs underwent a total of 1825 graded challenges with the related cephalosporins; only 11 challenges (0.6%) were positive. Specifically, there were 7 positive challenges (1.9%) out of 366 performed with aminocephalosporins, and 4 positive challenges (0.3%) out of 1459 carried out with cephalosporins like cefazolin, cefuroxime, ceftriaxone, and ceftazidime that have side chains different from those of penicillins. In other studies,<sup>35–38</sup> penicillin-allergic subjects underwent challenges or treatments with cephalosporins, such as cephalixin, cefadroxil, cefamandole, and ceftriaxone, without previous STs with the related cephalosporins. The rate of positive responses to cephalosporin challenges ranged from 5.6% (5 of 85)<sup>38</sup> to 38% (8 of 21).<sup>37</sup> The highest rate of cephalosporin positive challenges was observed in the study by Miranda et al,<sup>37</sup> who administered cefadroxil to 21 subjects allergic to amoxicillin.

All this should end the debate on the usefulness of performing STs with cephalosporins before giving them to penicillin-allergic patients, which has also recently taken place.<sup>39</sup>

To be noted that in a study concerning the cross-reactivity and tolerability of cefazolin and ceftibuten in 131 penicillin-allergic patients,<sup>33</sup> one participant was ST positive to all reagents tested, including carbapenems and aztreonam, which indicates a sensitivity to an antigenic determinant of the  $\beta$ -lactam ring.

With regard to T-cell-mediated allergy, of the 3 studies<sup>23,40,41</sup> that evaluated cross-reactivity with cephalosporins in adults with such allergy – by carrying out STs and/or PTs with cephalosporins and, in case of negative results, challenges with all tested cephalosporins –<sup>40,41</sup> found a rate of cross-reactivity with aminocephalosporins of 19.1% and 31.2%, respectively. Specifically, in an aforementioned study,<sup>41</sup> 214 consecutive adults with proven T-cell-mediated hypersensitivity to penicillins underwent STs with cephalixin, cefaclor, cefadroxil, cefuroxime, and ceftriaxone. Most subjects had experienced MPEs, whereas 5 had had a TEN, and 2 an AGEP (one of the latter had experienced 2 episodes). All participants were negative to STs with cefuroxime and

**Table 1** Rate of Cephalosporin Positive Skin Tests in Patients with Confirmed IgE-Mediated Hypersensitivity to Penicillins and Rate of Cephalosporin Positive Graded Challenges in Those with Negative Skin Tests to the Cephalosporin Concerned

Study (Reference)	Patients, n	Skin Testing		Challenge			
		Penicillin Reagents	Tested Cephalosporin(s)	Positive Patients,* n (%)	Positive Cephalosporins, <sup>†</sup> (n Positives)	Administered Cephalosporin(s)	Reactions, n/Challenges, (%)
Audicana et al <sup>27</sup>	34	PPL, MDM, AM, AX	Cephalexin, ceftazidime	5 (14.7)	Cephalexin (5)	Cephalexin, ceftazidime	0/29 0/30
Novalbos et al <sup>28</sup>	41	PPL, MDM, BP, AX	Cefazolin, cefuroxime, ceftriaxone	0	None	Cefazolin, cefuroxime, ceftriaxone	0/41 0/41 0/41
Romano et al <sup>29</sup>	128	PPL, MDM, BP, AM, AX	Cephalothin, cefamandole, cefuroxime, ceftazidime, ceftriaxone, cefotaxime	14 (10.9)	Cefamandole (9), cephalothin (8), ceftriaxone (3), cefuroxime (2), ceftazidime (2), cefotaxime (2)	Cefuroxime axetil, ceftriaxone	0/101 0/101
Caimmi et al <sup>30</sup>	69	PPL, MDM, BP, AX	Cefuroxime	0	None	Cefuroxime axetil	2/69 (2.9)
Romano et al <sup>31</sup>	252	PPL/BP-OL, MDM/MD, BP, AM, AX, PP	Cephalexin, cefadroxil, cefaclor, cefamandole, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, cefepime	84 (33.3)	Cefadroxil, (62) cefaclor (38), cephalothin (33), cefamandole (11), ceftriaxone (6), cefotaxime (3), cefuroxime (2)	Cefaclor, cefadroxil, cefuroxime axetil, ceftriaxone	3/170 (1.8) 4/167 (2.4) 0/244 0/244
Rodriguez-Bouza <sup>32</sup>	29	PPL/BP-OL, MDM/MD, BP, AM, AX	Cefuroxime	1 (3.4)	Cefuroxime (1)	Cefuroxime	2/28 (7.1)
Romano et al <sup>33</sup>	131	BP-OL, MD, BP, AM, AX, PP	Cefazolin, ceftibuten	1 (0.7)	Cefazolin (1), ceftibuten (1)	Cefazolin, ceftibuten	0/129 0/129
Sánchez de Vicente et al <sup>34</sup>	137	PPL, MDM, AX	Cefuroxime, ceftriaxone	2 <sup>‡</sup> (1.5)	Cefuroxime (1), ceftriaxone (1)	Cefuroxime, ceftriaxone	0/136 0/125
<b>Total</b>	<b>821</b>			<b>107 (13)</b>			<b>11/1825 (0.6)</b>

**Notes:** \*Patients with positive skin tests to at least one cephalosporin. <sup>†</sup>Cephalosporins found positive to skin tests. <sup>‡</sup>One subject had experienced immediate reactions to both amoxicillin and cefuroxime. **Abbreviations:** AM, ampicillin; AX, amoxicillin; BP, benzylpenicillin; BP-OL, benzylpenicilloyl-octa-L-lysine; MD, minor determinant; MDM, minor determinant mixture; PP, piperacillin; PPL, benzylpenicilloyl-poly-L-lysine.

ceftriaxone and tolerated challenges with them. Forty (18.7%) of the 214 participants were positive to aminoccephalosporin STs (Table 2). Two of these 40 participants had experienced an AGEP and 2 a TEN. Of the 174 participants negative to aminoccephalosporin STs, 170 accepted challenges; one reacted to cefaclor. Challenges with aminoccephalosporins found negative in skin testing were not carried out in 3 subjects with TEN as index reaction. In the aforementioned studies,<sup>23,40,41</sup> only 3 (0.3%) out of 1083 cephalosporin challenges were positive (Table 2).

In penicillin-allergic patients, therefore, skin testing with cephalosporins – such as cefazolin, cefuroxime, ceftazidime, cefpodoxime, cefixime, ceftriaxone, and ceftibuten that have side chains different from those of penicillins – followed, in case of negative results, by graded challenges has proved to be a safe method to administer these alternative  $\beta$ -lactams.<sup>4,9</sup> Note that this approach is the one recommended by both the European Academy of Allergy and Clinical Immunology<sup>4,13</sup> and the British Society for Allergy and Clinical Immunology.<sup>8</sup> It is also one of three options in the US practice parameter<sup>42</sup> concerning cephalosporin administration to patients with histories of penicillin allergy.

In graded challenges, usually, an initial dose of one tenth of the maximum single unit dose (MSUD) is administered and, in case of a negative result, 1 hour later a full MSUD.

In patients with mild/moderate nonimmediate reactions to penicillins who require a cephalosporin, if there's no time to wait for the delayed reading of pre-treatment STs, giving a full dose of a structurally non-related cephalosporin under close surveillance can be considered, as the increased risk does not concern an immediate reaction, such as anaphylaxis, but that of an exanthema recurrence. In a study by Blumenthal et al,<sup>43</sup> 17 patients treated with nafcillin were switched to cefazolin because of non-IgE-mediated HSRs, which included MPE (n = 10), immune-mediated nephritis (n = 3), isolated eosinophilia (n = 2), immune-mediated hepatitis (n = 1), and a serum sickness-like reaction (n = 1). All but one patient (94.1%) who switched to cefazolin tolerated a therapeutic course with it.

Patients with histories of SCARs associated with penicillin treatments should generally avoid all penicillins and cephalosporins, especially those structurally related to the responsible penicillin, because of the severity of the reported reaction and the not yet well defined sensitivity of allergy tests. Exceptions are possible only after consultation with an allergist experienced in drug allergy. In a study by Trubiano et al,<sup>44</sup> 6 patients with

**Table 2** Rate of Cephalosporin Positive Patch Tests and/or Skin Tests in Patients with Confirmed T-Cell-Mediated Hypersensitivity to Penicillins and Rate of Cephalosporin Positive Graded Challenges in Those with Negative Allergy Tests to the Cephalosporin Concerned

Study (Reference)	Patients, n	Responsible Penicillins	Tested Cephalosporin(s) (Methods)	Positive Patients,* n (%)	Cephalosporin Challenges		
					Administered Cephalosporin(s)	Administration Route	Reactions, n/Challenges, (%)
Phillips et al <sup>40</sup>	16	Aminopenicillin	Cephalexin (patch tests)	5 (31.2)	Cephalexin	Oral	0/6
Trcka et al <sup>23</sup>	71	Aminopenicillins	Cefpodoxime, cefixime (patch tests)	0	Cefpodoxime, cefixime	Oral, oral	1/71 (1.4) 1/71 (1.4)
Romano et al <sup>41</sup>	214	Aminopenicillins, benzylpenicillin, piperacillin	Cephalexin, cefaclor, cefadroxil (skin tests and patch tests) Cefuroxime, ceftriaxone (skin tests)	40 (18.7%) [16 to cephalexin and cefaclor, 15 to cephalexin, cefaclor, and cefadroxil, 7 to cefaclor, 1 to cefaclor and cefadroxil, and 1 to cefadroxil]	Ceftriaxone, cefuroxime axetil, cephalexin, cefaclor, cefadroxil	Intramuscular, oral, oral, oral, oral	0/213 0/213 0/170 1/170 (0.6) 0/169
<b>Total</b>	<b>301</b>			<b>45 (15)</b>			<b>3/1083</b>

Note: \*Patients with positive patch tests and/or skin tests to at least one cephalosporin.

SCARs (3 with DRESS and 3 with AGEP) associated with penicillins (3 with piperacillin/tazobactam, 2 with flucloxacillin, and 1 with amoxicillin) underwent delayed-reading IDTs with a panel of penicillins and cephalosporins. All were positive to PG, ampicillin, and flucloxacillin; the 3 subjects who had reacted to piperacillin/tazobactam were also positive to this combination. All 6 subjects were negative to cefazolin and ceftriaxone; 5 of them underwent oral challenges with cephalosporins (3 with cephalexin and 2 with cefuroxime) and tolerated them.

In a recent retrospective study,<sup>45</sup> 13 of the 29 subjects with SCARs (3 with DRESS and 10 with AGEP) were positive to allergy tests with the responsible  $\beta$ -lactams – 9 to amoxicillin, 1 to cloxacillin, 1 to cefoxitin, 1 to cefuroxime, and 1 to ceftriaxone (11 to PTs and 2 to delayed-reading IDTs) – and underwent PTs and STs with a panel of reagents which included penicillins, cephalosporins, aztreonam, and carbapenems. One of the 2 patients with DRESS and 5 of those with AGEP associated with amoxicillin were also positive to other penicillins. Only one subject who had reacted to both amoxicillin and cefpodoxime was positive to a cephalosporin (ie, cefotaxime). In this study,<sup>45</sup> however, unlike in aforementioned studies,<sup>41,44</sup> penicillin-allergic subjects negative to allergy tests with cephalosporins did not undergo challenges with them.

### Selecting Carbapenems or Aztreonam

Until 15 years ago, carbapenems were considered potentially dangerous for individuals with penicillin allergy<sup>46</sup> because in a study by Saxon et al<sup>47</sup> 9 (47.4%) out of 19 subjects with such allergy were ST positive to imipenem and/or its metabolites. Subsequent prospective studies,<sup>48–52</sup> each performed on more than 100 subjects with a well-demonstrated IgE-mediated penicillin allergy, found a rate of cross-reactivity between penicillins and carbapenems lower than 1% by carrying out STs with different compounds (ie, imipenem/cilastatin, meropenem, and ertapenem).

Regarding aztreonam, in a study of ours,<sup>52</sup> 212 consecutive adults with proven IgE-mediated allergy to penicillins, mostly aminopenicillins, displayed negative STs to aztreonam.

In the aforementioned studies,<sup>48–52</sup> all participants tolerated challenges with the alternative  $\beta$ -lactams found negative in skin testing, including 211 subjects who underwent aztreonam challenges.

According to a recent review on penicillin allergy,<sup>53</sup> patients with reported immediate reactions to penicillin have a <1% risk of IgE-mediated cross-reactivity to carbapenems and 0% to monobactams. However, in a study that assessed the tolerability of meropenem in 104 subjects with an IgE-mediated penicillin allergy,<sup>49</sup> 1 participant (0.9%) presented a positive reaction to the IDT with meropenem and had positive results to all penicillin reagents in both in vivo and in vitro tests, as well to STs with imipenem/cilastatin and cephalosporins. Therefore, this subject probably had IgE antibodies to an antigenic determinant of the common  $\beta$ -lactam ring like the one described above.<sup>33</sup>

With regard to the cross-reaction between penicillins and either carbapenems or aztreonam in subjects with a nonimmediate hypersensitivity, the literature data are less robust. Two studies regarding more than 200 subjects<sup>41,54</sup> presented no cross-reactivity with these alternative  $\beta$ -lactams. In particular, all patients were ST negative to carbapenems (ie, imipenem/cilastatin, meropenem, and ertapenem) and aztreonam and tolerated challenges with the alternative  $\beta$ -lactams concerned. Considering the results of a study of ours,<sup>54</sup> the positive responses to PTs with imipenem/cilastatin previously observed by Schiavino et al<sup>55</sup> in 4 of 73 subjects with a delayed penicillin allergy appear unreliable. In fact, it seems unlikely that all 4 patients of the aforesaid study<sup>55</sup> positive to imipenem/cilastatin PTs were negative to delayed-reading IDTs, which are more sensitive than PTs.<sup>6</sup> Moreover, Schiavino et al<sup>55</sup> found 2 PT positivities to benzylpenicilloyl-poly-L-lysine (PPL). However, as noted by Levine<sup>56</sup> in delayed reactions to penicillins, polylysine is a nonimmunogenic carrier. Therefore, the positivity to PTs with imipenem/cilastatin may have been false, as that to PTs with PPL.

Concerning subjects with SCARs, in the study by Bérot et al<sup>45</sup> none of the 13 patients with such reactions and positive allergy tests with the responsible  $\beta$ -lactams was positive to aztreonam and carbapenems. In this study,<sup>45</sup> subjects displaying negative results in allergy tests with these alternative  $\beta$ -lactams did not undergo challenges with them, whereas in a study of ours,<sup>41</sup> 7 subjects with a T-cell-mediated hypersensitivity to aminopenicillins (5 with TEN and 2 with AGEP) tolerated challenges with aztreonam found negative in skin testing. However, Fernando<sup>57</sup> described a case that reported a history of a generalized rash associated with PG and cephalexin, respectively, as well as that of an AGEP

associated with ertapenem. He underwent patch testing with an unspecified reagent panel and was positive at 48 hours to PG, cephalothin, meropenem, and ertapenem. Moreover, Sameed et al<sup>58</sup> reported a case of meropenem-induced SJS/TEN in a patient with a history of SJS from amoxicillin. This patient did not undergo allergy evaluation. Therefore, a concomitant sensitization to different  $\beta$ -lactams cannot be excluded in these 2 subjects.

## Cephalosporin-Allergic Subjects

HSRs to cephalosporins are becoming increasingly common, with approximately 1–3% of the population reporting them.<sup>11</sup> In particular, cephalosporins are one of the leading causes for perioperative anaphylaxis and SCARs.<sup>59</sup> Even though STs with cephalosporins are not as well validated as those with penicillins,<sup>7,42,59</sup> studies carried out on at least 20 subjects demonstrated that they are reliable and effective for diagnosing both immediate<sup>60–65</sup> and delayed hypersensitivity<sup>66</sup> to these  $\beta$ -lactams. Of note, in a Korean study,<sup>67</sup> 74 (5.2%) of 1421 participants who underwent preoperative cephalosporin STs were positive to at least one cephalosporin. However, all 74 subjects tolerated a challenge dose of the same or different cephalosporin found positive in skin testing.

### Selecting Penicillins

In subjects with proven IgE-mediated allergy to cephalosporins, a few studies assessed the cross-reactivity between cephalosporins and the other classes of  $\beta$ -lactams by performing graded challenges with alternative  $\beta$ -lactams found negative in allergy tests. In a study by Antunez et al,<sup>61</sup> 2 of 24 cephalosporin-allergic subjects were ST positive to penicillin reagents, while 22 were ST negative to them and tolerated PG challenges. In a study of 98 subjects with proven cephalosporin allergy who underwent sIgE assays and STs with penicillin reagents as well as STs with carbapenems and aztreonam,<sup>68</sup> 25 participants (25.5%) had positive allergy tests to penicillins. All 73 subjects negative to penicillin reagents tolerated amoxicillin challenges.

Yuson et al<sup>64</sup> diagnosed a hypersensitivity to the index cephalosporins in 24 (46.3%) of 55 subjects with histories of cephalosporin immediate reactions. Among them, twenty-three subjects were ST negative to penicillin reagents; 7 of them underwent challenges with amoxicillin (6 subjects) or flucloxacillin (one subject) and tolerated them. The remaining subject was ST positive to amoxicillin and was not challenged.

Li et al<sup>69</sup> assessed the safety and feasibility of amoxicillin challenges without penicillin STs in 40 patients with anaphylactic reactions to cefazolin and positive STs to it. This study<sup>69</sup> also included 2 patients with cephalothin anaphylaxis, and 2 with ceftriaxone anaphylaxis; all 4 patients had positive STs to the responsible cephalosporins and negative penicillin STs. All 44 patients underwent a 3-day amoxicillin challenge without reporting immediate reactions. One patient experienced a delayed benign rash at 24 hours and ceased amoxicillin.

### Selecting Carbapenems or Aztreonam

A systematic review<sup>70</sup> of all published data on children and adults reporting immediate reactions to penicillins and/or cephalosporins who were subsequently given a carbapenem showed that for patients with previous proven, suspected, or possible IgE-mediated cephalosporin reactions ( $n = 12$ ), the incidence of any type of HSR to a carbapenem was 25% (3 of 12); this included 2 non-IgE-mediated reactions and 1 possible IgE-mediated reaction.

In an aforementioned study concerning 98 cephalosporin-allergic subjects,<sup>68</sup> 1 participant was ST positive to both meropenem and imipenem/cilastatin, as well as to all the other reagents tested, which indicates a sensitivity to an antigenic determinant of the  $\beta$ -lactam ring, and 3 subjects were positive to aztreonam: the one just mentioned, another with positive allergy test results also to cefodizime and PV, and the last with positive STs to both aztreonam and ceftazidime, the responsible drugs. Of note, the other 10 subjects who were allergic to ceftazidime were ST negative to aztreonam. In this study,<sup>68</sup> all subjects tolerated the alternative  $\beta$ -lactams concerned found negative in skin testing, with the exception of 1 subject who reacted to imipenem/cilastatin.

### Selecting Alternative Cephalosporins

There are few studies in which at least 5 patients with cephalosporin allergy were challenged with alternative cephalosporin found negative to STs.

A study<sup>71</sup> evaluated 102 adults with immediate reactions to cephalosporins and positive STs to the responsible drugs by performing cefaclor sIgE assays and STs with a panel of 11 cephalosporins. On the basis of the results of both allergy tests, subjects were classified into four groups: group A (73 subjects), positive to one or more of ceftriaxone, cefuroxime, cefotaxime, cefepime, cefodizime, and ceftazidime; group B (13 subjects), positive to aminoccephalosporins; group C (7 patients), positive to cephalosporins other than those belonging to the aforementioned

groups; and group D (9 participants), positive to cephalosporins belonging to two different groups. In group A, 41 subjects were positive only to the responsible cephalosporins and 32 presented a pattern of cross-reactivity. In group B, 11 subjects were positive only to the culprit aminocephalosporins and 2 presented a pattern of cross-reactivity. Of the 7 subjects of group C, 6 were positive only to the responsible compound (5 to cefazolin and 1 to cefamandole), and the remaining subject, who had reacted to cefoperazone, was positive to both cefoperazone and cefamandole. Group D subjects displayed different patterns of positivity, most of which cannot be explained by either similar or identical side chains or by the common  $\beta$ -lactam ring. These cases suggest the possibility of coexisting sensitivities; therefore, the rate of positive allergy test responses to other cephalosporins is not associated only with the chemical similarities among side-chain determinants. In this study,<sup>71</sup> group A subjects underwent challenges with cefaclor, cefazolin, and ceftibuten; group B participants with cefuroxime axetil, ceftriaxone, cefazolin, and ceftibuten; and group C and D subjects with some of the aforementioned cephalosporins selected on the basis of their patterns of positivity. A total of 323 challenges with alternative cephalosporins (ceftibuten in 101, cefazolin in 96, cefaclor in 82, and cefuroxime axetil and ceftriaxone in 22 subjects) were well tolerated. These data indicate that cephalosporin hypersensitivity is improbable to be a class hypersensitivity. In effect, 2 groups (or subclasses) of cephalosporins were identified: group A, which includes those with a methoxyimino group in their R1 side chains plus ceftazidime, whose R1 side chain does not have a methoxyimino group but instead has an alkoxyimino group (Figure 2A and B), and group B, which is composed of aminocephalosporins. The limited number of subjects sensitive to cephalosporins other than those belonging to the aforementioned groups did not allow to identify further groups. However, based on the case of a group C subject who had reacted to cefoperazone and was ST positive to both cefoperazone and cefamandole, one could hypothesize additional groups, such as one consisting of cephalosporins like cefamandole, cefoperazone, and cefotetan that share an identical R2 side chain with an N-methyltetrazole-thiol group (Figure 2A and B).

Subsequently, in a study by Sadleir et al,<sup>72</sup> 21 subjects diagnosed with immediate hypersensitivity to cefazolin, including 19 subjects with confirmed anaphylaxis, were negative to IDTs with cephalothin and tolerated challenges with it. Van Gasse et al<sup>73</sup> administered ceftazidime to 5

patients who had experienced immediate HSRs to cefuroxime and displayed positive STs to cefuroxime and negative ones to ceftazidime. All subjects tolerated challenges with ceftazidime. This study<sup>73</sup> proved that small structural dissimilarities might result in a lack of cross-reactivity and clinical tolerance. In a study by Stone et al,<sup>65</sup> among 22 patients with a confirmed immediate allergy to either cefazolin, cefuroxime, ceftriaxone, ceftazidime, or cefepime, 17 tolerated an oral challenge with cephalixin, which has a R1 side chain different from those of the responsible cephalosporins. Another patient with a confirmed cefazolin allergy tolerated a cefuroxime challenge.

However, even though literature data<sup>9–12,60,61,65,74</sup> indicate that cross-reactivity among cephalosporins is mainly connected with their R1 side chains, cases of cross-reactivity related to the R2 side chain, such as the one observed in the aforementioned study of ours,<sup>71</sup> are possible.<sup>75</sup>

The above studies<sup>65,71–73</sup> demonstrated the usefulness of considering the antigenic determinants of both R1 and R2 side chains when selecting alternative cephalosporins in cephalosporin-allergic subjects and the capability of STs to detect fine structural differences among cephalosporins in allergic subjects. In effect, a total of 367 challenges were performed with alternative cephalosporins found negative to STs, and none caused symptoms. Therefore, cephalosporin STs appear to be reliable and effective for selecting alternative cephalosporins in cephalosporin-allergic subjects. In a large Korean study,<sup>76</sup> however, routine screening IDTs with cephalosporins before administration of the cephalosporin concerned was not clinically useful for the prevention of anaphylaxis and related mortality.

Regarding individuals with a delayed allergy to cephalosporins, in the above study,<sup>65</sup> among 7 patients with such allergy to either cefazolin, cefoxitin, ceftriaxone, or cefepime, 2 underwent an oral challenge with cephalixin and both tolerated it. Concerning subjects with SCARs, in the aforementioned study by Bérot et al,<sup>45</sup> of the 3 subjects who had experienced a DRESS from cefoxitin, cefuroxime, and ceftriaxone, respectively, one presented a selective response to PT with cefoxitin, another was positive to cefuroxime, as well as to ceftriaxone and penicillins, and the last was positive to ceftriaxone, cefuroxime, ceftazidime, cefotaxime, and cefoxitin. In this study,<sup>45</sup> however, subjects displaying negative results in allergy tests with cephalosporins other than those responsible did not undergo challenges with them.

## Conclusions

In choosing an alternative  $\beta$ -lactam for a  $\beta$ -lactam-allergic patient, it is important to consider its potential cross-reactivity to the responsible drug.

The literature data<sup>9–12</sup> indicate that similarities or identities of  $\beta$ -lactam side-chain structures are the main responsible for cross-reactivity among these antibiotics. In particular, the similarity or identity of the branch chain moiety of cephalosporin R1 structure is more frequently connected with cross-reactivity among cephalosporins than the similarity or identity of the ring of the R1 structure.<sup>9,10,76</sup>

Instead, the cross-reactivity related to the common  $\beta$ -lactam ring, which entails positive responses to all  $\beta$ -lactams tested, is very rare in subjects with an IgE-mediated allergy and appears to be even rarer or absent in those with a T-cell-mediated allergy.<sup>9</sup> Notably, in 3 studies,<sup>33,49,68</sup> 2 subjects with an IgE-mediated allergy to penicillins and 1 to cephalosporins, respectively, were ST positive to all reagents tested, including carbapenems and aztreonam. These 3 subjects probably had IgE antibodies to an antigenic determinant of the common  $\beta$ -lactam ring. Therefore, unlike what has been believed so far,<sup>18,53,77</sup> there appears to be an immunologic cross-reactivity related to the common  $\beta$ -lactam ring not only between penicillins and carbapenems but also between penicillins and the monobactam aztreonam, as well as between cephalosporins and both carbapenems and aztreonam, although it is very rare.

In some studies that assessed cross-reactivity among  $\beta$ -lactams,<sup>23,29,30,68,71</sup> there were particular patterns of allergy-test positivity which cannot be explained by either similar or identical side chains or by the common  $\beta$ -lactam ring. Such patterns seem to indicate the possibility of coexisting sensitivities to different  $\beta$ -lactams likely due to previous exposure to them. Because of this possibility or, much less frequently, of a sensitivity to an antigenic determinant of the  $\beta$ -lactam ring, an allergist dealing with a  $\beta$ -lactam-allergic patient who needs an alternative  $\beta$ -lactam should perform STs with this drug, even if it has a different side chain from that of the culprit drug; if ST results are negative, she/he can give the  $\beta$ -lactam concerned with a graded challenge.

If is not possible to perform a complete allergy workup, individuals who report immediate reactions to penicillins and have a pressing need for a cephalosporin or another alternative  $\beta$ -lactam can be evaluated by STs with cephalosporins (or carbapenems, or aztreonam) that

do not share similar or identical side chains with the culprit penicillins, and, in case of negative results, can undergo graded challenges with the alternative  $\beta$ -lactam concerned. A similar approach can be chosen in patients with histories of cephalosporin allergy who need an alternative  $\beta$ -lactam, including another cephalosporin.

In patients with mild nonimmediate reactions to  $\beta$ -lactams who require an alternative  $\beta$ -lactam, if there's no time to wait for the delayed reading of pre-treatment STs, giving a full dose of a structurally non-related  $\beta$ -lactam under close surveillance can be considered.

## Abbreviations

AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction (or rash) with eosinophilia and systemic symptoms; HSR, hypersensitivity reaction; IDT, intradermal test; MPE, maculopapular exanthema; MSUD, maximum single unit dose; PG, penicillin G (or benzylpenicillin); PT, patch test; PV, penicillin V (or phenoxymethylpenicillin); PPL, benzylpenicilloyl-poly-L-lysine; SCAR, severe cutaneous adverse reaction; sIgE, serum specific IgE; SJS, Stevens-Johnson syndrome; ST, skin test; TEN, toxic epidermal necrolysis.

## Disclosure

All authors declare no personal or professional conflicts of interest for this work.

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