

Original Article

Tolerability of Cefazolin and Ceftributen in Patients with IgE-Mediated Aminopenicillin Allergy

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What is already known about this topic? Penicillin-allergic subjects may cross-react with cephalosporins, especially with those that share identical or similar side chains with the responsible penicillins.

What does this article add to our knowledge? All but 1 penicillin-allergic patients had negative skin test results to cefazolin and ceftributen, which are among the cephalosporins with side chains dissimilar from those of penicillins. One subject was skin-test positive to all reagents tested, indicating a sensitivity to an antigenic determinant of the common β -lactam ring.

How does this study impact current management guidelines? The possibility of this sensitivity, even though extremely rare, and that of coexisting sensitivities suggests that alternative cephalosporins should be tested before giving them to subjects with a confirmed penicillin allergy, even if they have side chains different from those of the responsible penicillins.

BACKGROUND: Side-chain similarities or identities constitute the predominant factor for cross-reactivity between penicillins and cephalosporins, whereas differences in the side-chain structure seem to account for the absence of such cross-reactivity. **OBJECTIVE:** We sought to assess the cross-reactivity between penicillins and 2 cephalosporins (ie, cefazolin and ceftributen) that have side chains different from those of penicillins, as well as to evaluate the possibility of using these cephalosporins in penicillin-allergic subjects.

METHODS: We conducted a prospective study of 131 consecutive subjects who had suffered 170 immediate reactions (mostly anaphylaxis) to penicillins and had positive skin test results to at least 1 penicillin reagent. All patients underwent skin tests with cefazolin and ceftributen. Patients with negative results were challenged with them.

RESULTS: One participant had positive skin test results to cefazolin and ceftributen, as well as to all other reagents tested, including aztreonam and carbapenems. All 129 subjects who

underwent challenges with cefazolin and ceftributen tolerated them. One subject refused cephalosporin challenges.

CONCLUSIONS: Subjects with an IgE-mediated hypersensitivity to penicillins could be treated with cephalosporins such as cefazolin and ceftributen, which are among the cephalosporins that have side-chain determinants different from those of penicillins. Nevertheless, in patients with such hypersensitivity who need these alternative β -lactams, pretreatment skin tests are advisable because of the possibility of coexisting sensitivities or, much less frequently, of a sensitivity to an antigenic determinant of the common β -lactam ring. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Cefazolin; Ceftributen; Challenges; Cross-reactivity; Penicillin allergy; Skin tests; Tolerability

INTRODUCTION

In β -lactam-allergic subjects, the literature data indicate that cross-reactivity as a result of antibody recognition is more closely related to side-chain identity or similarity than to the common β -lactam ring.¹⁻⁴

In studies performed since 1990 on subjects with a documented IgE-mediated hypersensitivity to penicillins,⁵⁻¹⁰ the rate of positive challenges to cephalosporins in a total of 553 patients, who had negative skin test results to the cephalosporins concerned, was 0.8% (11 of 1306 challenges) (see Table E1 in this article's Online Repository at www.jaciinpractice.org).

In other studies,¹¹⁻¹⁴ where a total of 138 patients with a documented penicillin allergy underwent challenges or treatments with cephalosporins without previous skin testing with the cephalosporin concerned, the rate of positive responses to cephalosporin challenges was 9.8% (17 of 173 challenges).

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*Abbreviations used**BP-OL- Benzylpenicilloyl-octa-L-lysine*

Nevertheless, there is still a debate on the usefulness of performing skin tests with cephalosporins before giving them to penicillin-allergic patients.¹⁵

The present prospective study was conducted to further assess the cross-reactivity between penicillins and cephalosporins with side chains dissimilar from those of penicillins (Figure 1), as well as to evaluate the tolerability of these cephalosporins in patients with a documented IgE-mediated allergy to penicillins. To address this question, a group of such subjects was evaluated by skin tests with cefazolin and ceftibuten, to assess any cross-reactivity. Patients with negative results were challenged with cefazolin and ceftibuten to ascertain whether negative skin test results could be a reliable indicator of the tolerability of these alternative cephalosporins. Cefazolin is a first-generation cephalosporin for parenteral use, very effective against gram-positive staphylococci and streptococci. Ceftibuten is a third-generation cephalosporin administered orally, mainly effective against gram-negative bacteria, less against gram-positive pathogens.

Patient selection

We studied all participants older than 17 years who came to the allergy units of the Columbus Hospital, Rome, Italy, IRCCS Oasi Maria S.S., Troina, Italy, and Istituto Dermatologico dell'Immacolata, Rome, Italy, between January 2015 and June 2019 because of histories of immediate reactions to penicillins. Anaphylactic reactions were diagnosed according to the clinical criteria proposed by Sampson et al¹⁶ and classified as mild, moderate, and severe, as previously described.¹⁷ The inclusion criterion was a positive skin test result to at least 1 penicillin reagent. An indication for cephalosporin treatment was not a criterion of inclusion. The exclusion criteria were a history of hypersensitivity reactions to cephalosporins, pregnancy, and severe cardiovascular, renal, or respiratory compromise. Before the study, all subjects received information about possible risks of allergy tests, and a written informed consent was obtained from each patient. The respective institutional review boards approved the protocol.

Skin tests

We performed skin testing on 3 different days, as previously described.¹⁸

On the first day, prick and intradermal tests were carried out using benzylpenicilloyl-octa-L-lysine (BP-OL, DAP, Diater, Leganés, Spain), the minor determinant sodium benzylpenilloate (DAP), and benzylpenicillin. The final concentrations were 8.64×10^{-5} mol/L (ie, undiluted), 1.5×10^{-3} mol/L (ie, undiluted), and 10,000 international unit/mL, respectively.

On the second day, we tested ampicillin and amoxicillin, at concentrations of 1 and 20 mg/mL. Piperacillin, at concentrations of 1 and 20 mg/mL, was also used in subjects who had experienced adverse reactions to it, as previously described.¹⁹

On the third day, subjects with positive skin test results to at least 1 penicillin reagent were tested with cefazolin and ceftibuten at concentrations of 2 and 20 mg/mL.

We diluted all reagents with 0.9% NaCl no more than 2 hours before administration, as previously described.¹⁸

All the above reagents were initially tested on volar forearm skin by the prick method and reactions were considered positive when a wheal larger than 3 mm in diameter with surrounding erythema was present 20 minutes later. When prick test results were negative, 0.02 mL of the reagent solution was injected intradermally on volar forearm skin. Readings were made 20 minutes after injections. The wheal of the injected area was outlined on a transparent adhesive tape immediately and 20 minutes after testing. Results were considered positive when the maximum diameter of the wheal produced by the injection increased by 3 mm or more, accompanied by erythema.²⁰

The concentrations used for cephalosporins had proved to be nonirritating in previous studies.²¹⁻²⁴

Positive controls for prick and intradermal tests were done with histamine (at 10 and 1 mg/mL, respectively). As a negative control for prick and intradermal tests, 0.9% NaCl was used.

Detection of total and specific IgE in serum

We performed assays for serum total and specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, and amoxicilloyl with ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) in all subjects. We considered a positive result to be a value of 0.35 kUA/L or greater.

Cephalosporin-controlled administrations (challenges)

Challenges with cefazolin (intramuscularly) and ceftibuten (orally) were carried out, each on a different day, in subjects who displayed negative results in cephalosporin skin testing. We administered an initial dose of one-hundredth of the maximum single unit dose (1 g and 400 mg, respectively), that is, 0.01 g of cefazolin or 4 mg of ceftibuten. In cases with negative results, 1 hour later we administered one-tenth, that is, 0.1 g of cefazolin or 40 mg of ceftibuten, and if the result was again negative, 1 hour later we gave a full dose. After the first 30 challenges, we modified the challenge protocol and gave initially one-tenth of the maximum single unit dose, and if the result was again negative, 1 hour later we gave a full dose. For cefazolin intramuscular challenges, one-hundredth and one-tenth concentrations of the maximum single unit dose were injected in deltoid muscles and the full dose in the gluteus, as previously described.¹⁸

Patients were carefully monitored during all allergy testing, and for 2 hours after challenges; complete equipment for cardiopulmonary resuscitation was immediately available.

Statistical analysis

We collected the data prospectively and analyzed them using Stata software (StataCorp, College Station, Texas). We have presented the frequency of positive results as a percentage and exact 95% CI. Age has been reported as the mean $\pm$ SD, and the time interval between the last adverse reaction and testing as the median and range.

RESULTS

We examined a total of 132 participants ranging in age from 18 to 77 years, with histories of immediate reactions to penicillins. These 132 subjects constituted 72.9% of an outpatient population of 181 adults recruited prospectively between January 2015 and June 2019 in the aforesaid allergy units because of such histories. Of the 132 penicillin-allergic subjects, 91 were diagnosed in the Columbus Hospital, 14 in the IRCCS Oasi Maria

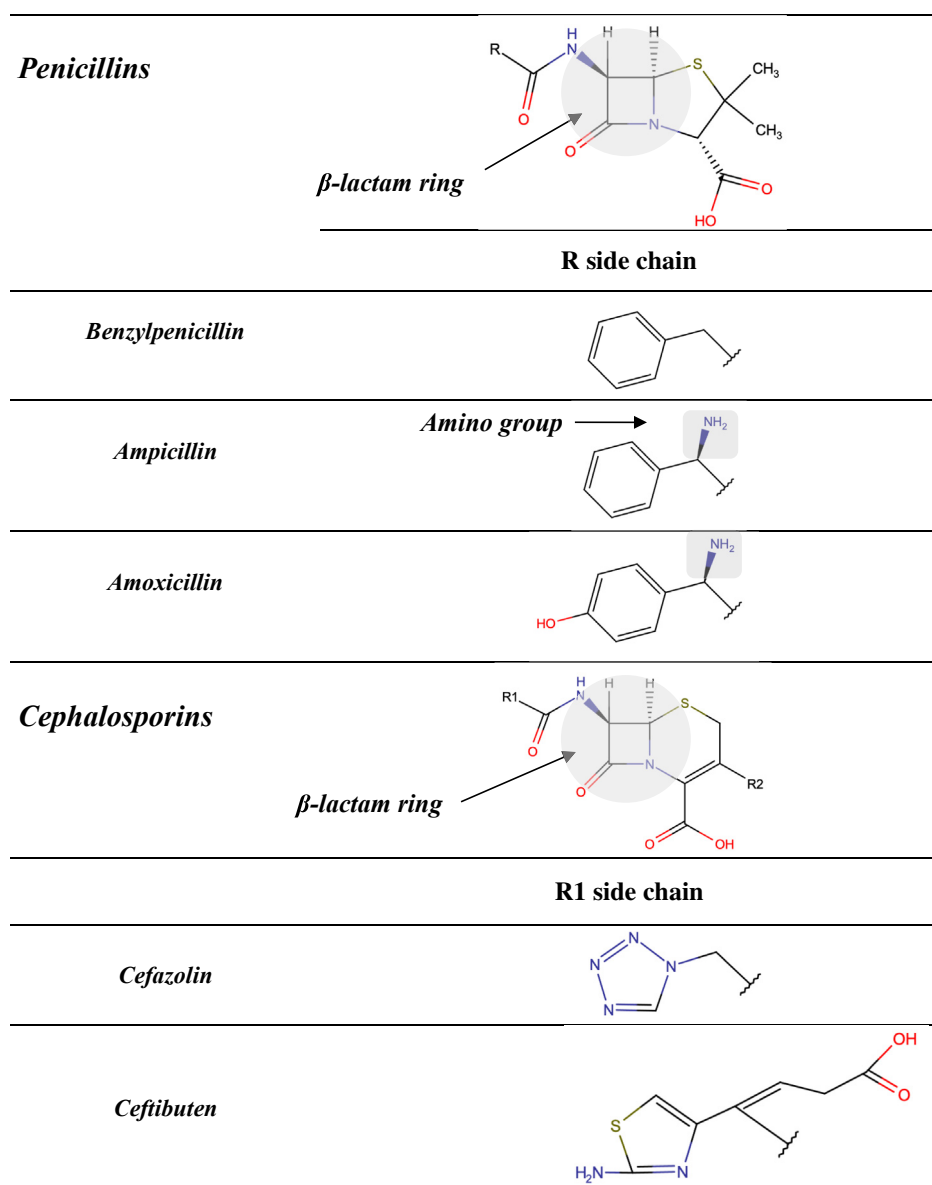


FIGURE 1. Chemical structures of penicillins, cefazolin, and ceftibuten. The common β -lactam ring and the amino group are highlighted in gray.

S.S, and 27 in the Istituto Dermopatico dell'Immacolata. One subject was excluded because of a history of immediate reactions to both penicillins and cephalosporins. None of the remaining 131 cases had any exclusion criterion.

The clinical data and allergy test results are presented in Table I.

One hundred twenty-nine subjects (98.5%) reported hypersensitivity reactions only to aminopenicillins (amoxicillin, ampicillin, or bacampicillin), 1 to benzylpenicillin, and the remaining 1 to piperacillin.

The 131 participants had experienced a total of 170 immediate reactions to penicillins (Table I).

One hundred eight patients (82.4%) had had anaphylactic reactions. The remaining 23 patients had developed urticaria and/or angioedema.

All subjects had positive skin test results to at least 1 of the penicillin reagents tested (Table I): 71 subjects were positive only to semisynthetic penicillins (amoxicillin, ampicillin, and/or piperacillin), 57 to both classic penicillin reagents (BP-OL, minor determinant, and benzylpenicillin) and semisynthetic penicillins, and 3 only to classic penicillin reagents.

One subject (0.8%; 95% CI, 0.13%-4.1%) was skin-test positive to cefazolin and ceftibuten. He was a 53-year-old man who had experienced 2 anaphylactic reactions to amoxicillin and amoxicillin plus clavulanic acid, respectively. He was skin-test positive to all other reagents tested on the first day (ie, BP-OL, minor determinant, and benzylpenicillin) and the second day (ie, ampicillin and amoxicillin). He underwent skin tests with aztreonam, imipenem/cilastatin, meropenem, and ertapenem, as previously described,¹⁹ with positive responses to them.

TABLE I. Clinical data and allergy test results of the 131 patients

Age (y), mean $\pm$ SD	50.1 $\pm$ 14.1	
Sex: women, n (%)	84 (64.1)	
Time since last penicillin reaction,* median (range) [25th, 75th percentile]	2 (1-240) [1, 8]	
Family history of allergic diseases, n (%)	52 (39.7)	
Personal history of allergic diseases, n (%)	23 (17.6)	
Responsible β -lactams, n (%)	All reactions (170)	
Amoxicillin	161 (94.7) [127 plus clavulanic acid]	
Ampicillin	4 (2.4)	
Bacampicillin	3 (1.8)	
Benzylpenicillin	1 (0.6)	
Piperacillin	1 (0.6)	
Manifestation, (%)	All reactions (170)	
Anaphylaxis	132 (77.6) [63 mild, 42 moderate, 27 severe]	
Urticaria	21 (12.4)	
Urticaria-angioedema	16 (9.4)	
Angioedema	1 (0.6)	
Positive skin test results, n (%)		
BP-OL	22 (16.8)	
Sodium benzylpenilloate (MD)	11 (8.4)	
Benzylpenicillin	48 (36.6)	
Amoxicillin	123 (93.9)	
Ampicillin	91 (69.5)	
Piperacillin	1 (0.8)	
Positive specific IgE assay results, n (%)	Threshold value of 0.35 kUA/L	Threshold value of 0.10 kUA/L
Penicilloyl G	25 (19.1)	44 (33.6)
Penicilloyl V	32 (24.4)	51 (38.9)
Ampicilloyl	27 (20.6)	56 (42.7)
Amoxicilloyl	36 (27.5)	62 (47.3)

MD, Minor determinant.

*Time (months) elapsed between last adverse penicillin reaction and current allergy workup.

As far as *in vitro* assays are concerned, considering a positive result to be a value of 0.35 kUA/L or greater, 52 patients (39.7%) were positive (Table I): 27 to both penicillins and aminopenicillins, 12 only to amoxicillin, 8 only to penicillin G and/or penicillin V, and 5 only to ampicillin. Choosing as the threshold value 0.1 kUA/L, 84 patients (64.1%) were positive (Table I): 48 to both penicillins and aminopenicillins, 12 to both amoxicillin and ampicillin, 12 only to amoxicillin, 7 only to penicillin G and/or penicillin V, and 5 only to ampicillin.

Of the 130 patients with negative cephalosporin skin test results, 129 agreed to undergo challenges with cefazolin and ceftibuten and tolerated them. One subject refused cephalosporin challenges. She had experienced 2 anaphylactic reactions to amoxicillin plus clavulanic acid and was skin-test positive to BP-OL, amoxicillin, and ampicillin.

DISCUSSION

In the present study, 1 (0.8%) of the 131 participants displayed positive skin test results to both cefazolin and ceftibuten.

He was skin-test positive to all reagents tested, including aztreonam and carbapenems. Therefore, we can speculate that he had IgE antibodies against an antigenic determinant of the common β -lactam ring, which has not been clearly identified. Regarding its identification, we have to highlight the limitation of any 2-dimensional structural formula, which cannot depict a complex 3-dimensional molecular structure interacting with IgE antibodies. Interestingly, cross-reactivity related to an antigenic determinant of the β -lactam ring, which entails positive allergy test results to all β -lactams, is very rare in subjects with an IgE-mediated hypersensitivity and has not been described in those with a T-cell-mediated hypersensitivity.²

Notably, almost half the subjects of the present study, who had reacted to aminopenicillins, displayed positive responses to benzylpenicillin in skin tests and ImmunoCAP. The phenomenon of an IgE response not directed only to the culprit β -lactam, but also to benzylpenicillin, is probably due to a previous exposure to the latter and was already observed by Antúnez et al.²⁵ According to them,²⁵ it can be explained by the theory of original antigenic sin²⁶: in case of an antibody response, memory B cells are more easily triggered than naive B cells. The above phenomenon can also be explained by the fact that aminopenicillins and benzylpenicillin share similar antigenic determinants. For example, ampicillin and benzylpenicillin have similar side-chain structures, which are benzyl derivatives.²⁷

We selected cefazolin and ceftibuten as alternative cephalosporins because they have side chains different not only from those of penicillins (Figure 1) but also from those of the other cephalosporins, except ceftazidime, which shares an identical R1 side chain and a similar R2 side chain with cefazolin.³

Regarding our allergy workup, it should be noted that all skin-test reagents can be tested sequentially in 1 day without a significant increase in the risk of systemic reactions and that cefazolin challenges can be done also safely intravenously.

The rate of positive responses to skin tests for cephalosporins found in the present study (0.8%) is similar to that (0%) found in 2 studies,^{6,8} which assessed the cross-reactivity between penicillins and cephalosporins, such as cefazolin, cefuroxime, and ceftriaxone, in 110 subjects with an IgE-mediated hypersensitivity to penicillins (see Table E1).

Nevertheless, in 2 previous studies of ours,^{7,9} 12 (3.2%) of a total of 380 participants with a well-demonstrated IgE-mediated hypersensitivity to penicillins displayed positive skin test results to cephalosporins, such as cefuroxime, ceftriaxone, ceftazidime, and cefotaxime, which have side chains different from those of penicillins (see Table E1). Specifically, 1 subject was positive to all reagents tested⁷; the remaining 11 participants presented different patterns of positivity, which indicated the possibility of coexisting sensitivities, likely because of previous exposures to the cephalosporins concerned. In effect, Italy is the European country with the highest consumption of third-generation cephalosporins.²⁸ Because of possible coexisting sensitivities, we suggest performing pretreatment skin tests with cephalosporins, even with those selected on the basis of side-chain differences, before their administration to patients with confirmed penicillin allergy based on clinical history and positive skin-test results. In fact, even though skin tests with cephalosporins are not as well validated as those with penicillins,²⁹⁻³² studies carried out on at least 20 subjects demonstrated that cephalosporin skin testing is reliable and effective for diagnosing immediate hypersensitivity to these β -lactams,^{18,33-35} as well as selecting alternative

cephalosporins either in penicillin-allergic subjects⁵⁻¹⁰ or in cephalosporin-allergic subjects.^{23,36}

CONCLUSIONS

Our study demonstrated a 0.8% rate of cross-reactivity between penicillins and cefazolin and ceftibuten, as well as the tolerability of these cephalosporins in all subjects with IgE-mediated hypersensitivity to penicillins displaying negative cephalosporin skin test results. Nevertheless, in patients with such hypersensitivity who need these alternative β -lactams, we recommend pretreatment skin tests because of the possibility of coexisting sensitivities or, much less frequently, of a sensitivity to an antigenic determinant of the β -lactam ring.

REFERENCES

- Pichichero ME, Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: a meta-analysis. *Otolaryngol Head Neck Surg* 2007;136:340-7.
- Romano A, Gaeta F, Arribas Poves MF, Valluzzi RL. Cross-reactivity among beta-lactams. *Curr Allergy Asthma Rep* 2016;16:24.
- Zagursky RJ, Pichichero ME. Cross-reactivity in β -lactam allergy. *J Allergy Clin Immunol Pract* 2018;6:72-81.e1.
- Picard M, Robitaille G, Karam F, Daigle JM, Bédard F, Biron É, et al. Cross-reactivity to cephalosporins and carbapenems in penicillin-allergic patients: two systematic reviews and meta-analyses. *J Allergy Clin Immunol Pract* 2019;7:2722-38.
- Audicana M, Bernaola G, Urrutia I, Echechipia S, Gastaminza G, Muñoz D, et al. Allergic reactions to betalactams: studies in a group of patients allergic to penicillin and evaluation of cross-reactivity with cephalosporin. *Allergy* 1994;49:108-13.
- Novalbos A, Sastre J, Cuesta J, De Las Heras M, Lluch-Bernal M, Bombín C, et al. Lack of allergic cross-reactivity to cephalosporins among patients allergic to penicillins. *Clin Exp Allergy* 2001;31:438-43.
- Romano A, Guéant-Rodriguez RM, Viola M, Pettinato R, Guéant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med* 2004;141:16-22.
- Caimmi S, Galéra C, Bousquet-Rouanet L, Arnoux B, Demoly P, Bousquet PJ. Safety of cefuroxime as an alternative in patients with a proven hypersensitivity to penicillins: a DAHD cohort survey. *Int Arch Allergy Immunol* 2010;153:53-60.
- Romano A, Valluzzi RL, Caruso C, Maggioletti M, Quarantino D, Gaeta F. Cross-reactivity and tolerability of cephalosporins in patients with IgE-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol Pract* 2018;6:1662-72.
- Al-Ahmad M, Rodriguez-Bouza T. Drug allergy evaluation for betalactam hypersensitivity: cross-reactivity with cephalosporines, carbapenems and negative predictive value. *Asian Pac J Allergy Immunol* 2018;36:27-31.
- Blanca M, Fernandez J, Miranda A, Terrados S, Torres MJ, Vega JM, et al. Cross-reactivity between penicillins and cephalosporins: clinical and immunologic studies. *J Allergy Clin Immunol* 1989;83:381-5.
- Sastre J, Quijano LD, Novalbos A, Hernandez G, Cuesta J, de las Heras M, et al. Clinical cross-reactivity between amoxicillin and cephadroxil in patients allergic to amoxicillin and with good tolerance of penicillin. *Allergy* 1996;51:383-6.
- Miranda A, Blanca M, Vega JM, Moreno F, Carmona MJ, García JJ, et al. Cross-reactivity between a penicillin and a cephalosporin with the same side chain. *J Allergy Clin Immunol* 1996;98:671-7.
- Park MA, Koch CA, Klemawesch P, Joshi A, Li JT. Increased adverse drug reactions to cephalosporins in penicillin allergy patients with positive penicillin skin test. *Int Arch Allergy Immunol* 2010;153:268-73.
- Macy E, Blumenthal KG. Are cephalosporins safe for use in penicillin allergy without prior allergy evaluation? *J Allergy Clin Immunol Pract* 2018;6:82-9.
- Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.
- Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;114:371-6.
- Romano A, Guéant-Rodriguez RM, Viola M, Amoghly F, Gaeta F, Nicolas JP, et al. Diagnosing immediate reactions to cephalosporins. *Clin Exp Allergy* 2005;35:1234-42.
- Gaeta F, Valluzzi RL, Alonzi C, Maggioletti M, Caruso C, Romano A. Tolerability of aztreonam and carbapenems in patients with IgE-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol* 2015;135:972-6.
- Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;57:45-51.
- Empedrad R, Darter AL, Earl HS, Gruchalla RS. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. *J Allergy Clin Immunol* 2003;112:629-30.
- Testi S, Severino M, Iorno ML, Capretti S, Ermini G, Macchia D, et al. Nonirritating concentration for skin testing with cephalosporins. *J Investig Allergol Clin Immunol* 2010;20:171-2.
- Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Zaffiro A, Caruso C, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of alternative cephalosporins. *J Allergy Clin Immunol* 2015;136:865-891.e3.
- Uyttebroek AP, Decuyper II, Bridts CH, Romano A, Hagendorens MM, Ebo DG, et al. Cefazolin hypersensitivity: toward optimized diagnosis. *J Allergy Clin Immunol Pract* 2016;4:1232-6.
- Antúnez C, Fernández T, Blanca-López N, Torres MJ, Mayorga C, Canto G, et al. IgE antibodies to betalactams: relationship between the triggering hapten and the specificity of the immune response. *Allergy* 2006;61:940-6.
- Fazekas de St Groth, Webster RG. Disquisitions of original antigenic sin, I: evidence in man. *J Exp Med* 1966;124:331-45.
- Guéant JL, Mata E, Masson C, Gérard P, Moneret-Vautrin DA, Mouton-Faivre C, et al. Non-specific cross-reactivity of hydrophobic serum IgE to hydrophobic drugs. *Mol Immunol* 1995;32:259-66.
- Versporten A, Coenen S, Adriaenssens N, Muller A, Minalu G, Faes C, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient cephalosporin use in Europe (1997-2009). *J Antimicrob Chemother* 2011;66:vi25-35.
- Solensky R, Khan DA, Bernstein IL, Bloomberg GR, Castells MC, Mendelson LM, et al. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105:259-73.
- Solensky R. Allergy to β -lactam antibiotics. *J Allergy Clin Immunol* 2012;130:1442-2.65.
- Pichichero ME, Zagursky R. Penicillin and cephalosporin allergy. *Ann Allergy Asthma Immunol* 2014;112:404-12.
- Khan DA, Banerji A, Bernstein JA, Bilgicir B, Blumenthal K, Castells M, et al. Cephalosporin allergy: current understanding and future challenges. *J Allergy Clin Immunol Pract* 2019;7:2105-14.
- Antunez C, Blanca-López N, Torres MJ, Mayorga C, Perez-Inestrosa E, Montañez MI, et al. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. *J Allergy Clin Immunol* 2006;117:404-10.
- Romano A, Gaeta F, Valluzzi RL, Alonzi C, Viola M, Bousquet PJ. Diagnosing hypersensitivity reactions to cephalosporins in children. *Pediatrics* 2008;122:521-7.
- Mori F, Liccioli G, Piccorossi A, Sarti L, Barni S, Giovannini M, et al. The diagnosis of ceftriaxone hypersensitivity in a paediatric population. *Int Arch Allergy Immunol* 2019;178:272-6.
- Sadler PH, Clarke RC, Platt PR. Cefalotin as antimicrobial prophylaxis in patients with known intraoperative anaphylaxis to cefazolin. *Br J Anaesth* 2016;117:464-9.

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TABLE E1. Rate of cephalosporin positive skin test results in penicillin-allergic patients and rate of cephalosporin positive challenges in those with negative skin test results to the cephalosporin concerned

Study (reference)	Patients, n	Skin testing				Challenge		
		Penicillin reagents	Tested cephalosporin(s)	Positive patients,* n (%)	Positive cephalosporins,† (n positivities)	Administered cephalosporin(s)	Administration route	Reactions, n/challenges, (%)
Audicana et al ^{E1}	34	PPL, MDM, AM, AX	Cephalexin, ceftazidime	5 (14.7)	Cephalexin (5)	Cephalexin, ceftazidime	Oral, intravenous	0/29 0/30
Novalbos et al ^{E2}	41	PPL, MDM, BP, AX	Cefazolin, cefuroxime, ceftriaxone	0	None	Cefazolin, cefuroxime, ceftriaxone	Intramuscular, intramuscular, intramuscular	0/41 0/41 0/41
Romano et al ^{E3}	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	Oral, intramuscular	0/101 0/101
Caimmi et al ^{E4}	69	PPL, MDM, BP, AX	Cefuroxime	0	None	Cefuroxime axetil	Oral	2/69 (2.9)
Romano et al ^{E5}	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), cephalexin (33), cefamandole (11), ceftriaxone (6), cefotaxime (3), cefuroxime (2)	Cefaclor, cefadroxil, cefuroxime axetil, ceftriaxone	Oral, oral, oral, intramuscular	3/170 (1.8) 4/167 (2.4) 0/244 0/244
Al-Ahmad and Rodriguez-Bouza ^{E6}	29	PPL/BP-OL, MDM/MD, BP, AM, AX	Cefuroxime	1 (3.4)	Cefuroxime (1)	Cefuroxime	Intramuscular	2/28 (7.1)
Present study	131	BP-OL, MD, BP, AM, AX, PP	Cefazolin, ceftibuten	1 (0.7)	Cefazolin (1), ceftibuten (1)	Cefazolin, ceftibuten	Intramuscular, oral	0/129 0/129
Total	684			105 (15.4)				11/1564 (0.7)

AM, Ampicillin; AX, amoxicillin; BP, benzylpenicillin; MD, minor determinant; MDM, minor determinant mixture; PP, piperacillin; PPL, benzylpenicilloyl-poly-L-lysine.

*Patients with positive skin test results to at least 1 cephalosporin.

†Cephalosporins found positive to skin tests.

REFERENCES

- E1. Audicana M, Bernaola G, Urrutia I, Echechipia S, Gastaminza G, Muñoz D, et al. Allergic reactions to betalactams: studies in a group of patients allergic to penicillin and evaluation of cross-reactivity with cephalosporin. *Allergy* 1994; 49:108-13.
- E2. Novalbos A, Sastre J, Cuesta J, De Las Heras M, Lluch-Bernal M, Bombín C, et al. Lack of allergic cross-reactivity to cephalosporins among patients allergic to penicillins. *Clin Exp Allergy* 2001;31:438-43.
- E3. Romano A, Guéant-Rodriguez RM, Viola M, Pettinato R, Guéant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med* 2004;141:16-22.
- E4. Caimmi S, Galéra C, Bousquet-Rouanet L, Arnoux B, Demoly P, Bousquet PJ. Safety of cefuroxime as an alternative in patients with a proven hypersensitivity to penicillins: a DAHD cohort survey. *Int Arch Allergy Immunol* 2010;153: 53-60.
- E5. Romano A, Valluzzi RL, Caruso C, Maggioletti M, Quarantino D, Gaeta F. Cross-reactivity and tolerability of cephalosporins in patients with IgE-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol Pract* 2018;6:1662-72.
- E6. Al-Ahmad M, Rodriguez-Bouza T. Drug allergy evaluation for betalactam hypersensitivity: cross-reactivity with cephalosporines, carbapenems and negative predictive value. *Asian Pac J Allergy Immunol* 2018;36:27-31.