Original Article

Cross-Reactivity to Cephalosporins and Carbapenems in Penicillin-Allergic Patients: Two Systematic Reviews and Meta-Analyses

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What is already known about this topic? Although many studies have shown that penicillin-allergic patients are at low risk of reacting to most cephalosporins and carbapenems and that there is an increased risk associated with amino-cephalosporins, there is considerable variability in the cross-reactivity rates reported.

What does this article add to our knowledge? In penicillin-allergic patients, the risk of cross-reactivity to cephalosporins varied from 16.45% (95% CI, 11.07-23.75) for aminocephalosporins to 2.11% (95% CI, 0.98-4.46) for low-similarity-score cephalosporins. The risk of cross-reactivity to any carbapenem was 0.87% (95% CI, 0.32-2.32).

How does this study impact current management guidelines? Future guidelines should emphasize the very low risk of cross-reactivity associated with carbapenems and with all low-similarity-score cephalosporins. Caution should be exercised with cephalosporins whose R1 side chain shares similarity with penicillins, especially aminocephalosporins.

BACKGROUND: There is no recent systematic review on the risk of cross-reactivity to cephalosporins and carbapenems in penicillin-allergic patients despite many new studies on the subject. All past reviews have several limitations such as not including any patient with a T-cell–mediated penicillin allergy.
OBJECTIVES: To determine the risk of cross-reactivity to cephalosporins and carbapenems in patients with a proven IgE- or T-cell–mediated penicillin allergy. To measure the association between R1 side chain similarity on cephalosporins and penicillins and the risk of cross-reactivity.
METHODS: MEDLINE and EMBASE were searched from January 1980 to March 2019. Studies had to include at least 10 penicillin-allergic subjects whose allergy had been confirmed by a positive skin test (ST) or drug provocation test (DPT) result. Cross-reactivity had to be assessed to at least 1 cephalosporin or carbapenem through ST or DPT. Both random-effects and fixed-effect models were used to combine data. A bioinformatic model was used to quantify the similarity between R1 side chains.
RESULTS: Twenty-one observational studies on cephalosporin cross-reactivity involving 1269 penicillin-allergic patients showed that the risk of cross-reactivity varied with the degree of similarity between R1 side chains: 16.45% (95% CI, 11.07-23.75) for aminocephalosporins, which share an identical side chain with a penicillin (similarity score = 1), 5.60% (95% CI, 3.46-8.95) for a few cephalosporins with an intermediate similarity score (range, 0.563-0.714), and 2.11% (95% CI, 0.98-4.46) for all those with low similarity scores (below 0.4), irrespective of cephalosporin generation. The higher risk associated with aminocephalosporins was observed whether penicillin allergy was IgE- or T-cell–mediated. Eleven observational studies on carbapenem cross-reactivity involving 1127 penicillin-allergic patients showed that the risk of cross-reactivity to any carbapenem was 0.87% (95% CI, 0.32-2.32).

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Abbreviations used
AR- Absolute risk
DPT- Drug provocation test
IDT- Intradermal test
NPV- Negative predictive value
ST- Skin test

CONCLUSIONS: Although it remains possible that these meta-analyses overestimated the risk of cross-reactivity, clinicians should consider the increased risk of cross-reactivity associated with aminocephalosporins, and to a lesser extent with intermediate-similarity-score cephalosporins, compared with the very low risk associated with low-similarity-score cephalosporins and all carbapenems when using beta-lactams in patients with a suspected or proven penicillin allergy. **(J Allergy Clin Immunol Pract 2019;7:2722-38)**

Key words: *Cross-reactivity; Cephalosporin; Carbapenem; Penicillin; Beta-lactam; Meta-analysis; Systematic review; IgE-mediated; T-cell—mediated*

INTRODUCTION

Increasing antimicrobial resistance is a major and complex public health issue requiring a multifaceted action plan.[1,2] Antimicrobial stewardship programs, by improving the appropriate use of antimicrobials, are one of the main initiatives put forward to tackle this problem.[3,4] An important group of patients that needs to be targeted comprises those allergic to penicillin, who make up around 10% of the adult population.[5-7] These patients are more at risk of being infected by *Clostridium difficile* or colonized by resistant bacteria such as methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus*.[6,8] In addition, they have higher treatment failure rates for certain types of infections.[9] The use of second-line antibiotics such as fluoroquinolones and vancomycin, which also carry additional costs, in place of the preferred beta-lactam provides a plausible explanation for these morbidities.[6,9-11] One way to attenuate these complications is to remove penicillin allergy labels, through allergy testing, in as many patients as possible becausr most will be found to be nonallergic.[12-14] Another way is to provide clinical guides for nonallergists that would facilitate the safe use of beta-lactams in patients with a suspected or proven penicillin allergy.[15] The elaboration of these guides requires that the risk of cross-reactivity between penicillins and other beta-lactams (cephalosporins and carbapenems) be accurately determined.

Few systematic reviews on cross-reactivity to cephalosporins and carbapenems have been published and all have several limitations.[16-18] First, all focus on IgE-mediated reactions,[16-18] providing no information on T-cell—mediated reactions despite their high frequency.[19,20] Second, they all include studies performed on patients with a history of penicillin allergy that was not confirmed by skin test (ST) or a drug provocation test (DPT), introducing a bias that may falsely lower the actual rate of cross-reactivity in penicillin-allergic patients.[16-18] Only the systematic review by Kula et al[16] on cross-reactivity to carbapenems was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[21] However, this study included 12 case reports and excluded patients in whom diagnosis of cross-reactivity was based on a positive ST result, thereby introducing important biases. Finally, since the publication of these reviews, 13 studies[20,22-33] totaling 1282 patients were published on the subject.

The aim of these 2 systematic reviews with meta-analyses was to provide absolute risks (ARs) of cross-reactivity to (1) cephalosporins and (2) carbapenems in patients with a proven penicillin allergy (either IgE- or T-cell—mediated). Because it is increasingly recognized that aminocephalosporins (cefadroxil, cephalexin, cefprozil, cefaclor, and cefatrizine), which share an identical R1 side chain with either amoxicillin or ampicillin (aminopenicillins), carry a higher risk of cross-reactivity compared with other cephalosporins,[17,18,34-38] a secondary objective was to assess the correlation between R1 side chain similarity and risk of cross-reactivity. R2 side chains were not considered because they have only been implicated in cross-reactivity between cephalosporins.[37] These systematic reviews will hopefully facilitate the development of guidelines for using beta-lactams in patients with a suspected or proven penicillin allergy and allow improved decision making among clinicians.

METHODS

Meta-analysis Of Observational Studies in Epidemiology[39] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[21] were followed for the elaboration and reporting of these systematic reviews with meta-analyses.

Search strategy

Search strategy was elaborated in collaboration with a librarian. MEDLINE and EMBASE were searched systematically using the strategy detailed in this article's Online Repository at www.jaci-inpractice.org (see Tables E1 and E2). The search was limited to studies published in English or French between January 1980 and December 2016 and was subsequently updated to include studies published between December 2016 and March 2019. Reference lists of included studies were reviewed for additional articles and authors were contacted to clarify any missing data. Two other databases were searched (Cochrane Library and Google Scholar) to maximize the retrieval of all relevant references. Also, web sites of national agencies and academic societies (see Table E3 in this article's Online Repository at www.jaci-inpractice.org) were searched to retrieve reports of health technology assessment and clinical practice guidelines on the subject matter published between 2010 and 2016.

Inclusion criteria

To be eligible, studies had to include at least 10 penicillin-allergic subjects (children or adults) whose allergy (IgE- or T-cell—mediated) had been confirmed by a positive ST or DPT result. A T-cell—mediated allergy was defined as a positive delayed-reading ST, either intradermal test (IDT) or patch test, or DPT result in patients reporting a history of nonimmediate reaction to any penicillin. Cross-reactivity had to be assessed to at least 1 cephalosporin or carbapenem through ST or DPT. When both tests were performed, DPT was considered the criterion standard to confirm allergy. Subjects in whom penicillin allergy or cephalosporin/carbapenem cross-reactivity was based only on a positive specific IgE assay were excluded because these assays are generally poor predictors of penicillin allergy.[40,41] Subjects had to be evaluated after 1980 given the risk of cephalosporin contamination with penicillins before 1980.[34] Studies were excluded from the meta-analyses if they had fewer than 5 patients who were exposed to the cephalosporin being investigated

because they provide little information and represent an unstable result. For a complete list of inclusion and exclusion criteria, see Tables E4 and E5 in this article's Online Repository at www.jaci-inpractice.org.

Study selection and data extraction

Study selection was performed independently by 2 authors. One author extracted the data using predefined data extraction forms, which were independently checked for accuracy by a second author. The following information was extracted from each study: first author, year of publication, country of origin, study design, patient's characteristics (age, type of penicillin allergy, culprit penicillin), beta-lactam tested for cross-reactivity, ST method used to assess cross-reactivity, and ST and DPT result. Individual participant data were collected from studies that provided information on the allergic profiles of each participant involved. When individual participant data were not reported or could not be inferred, aggregated participant data, compiled and reported by the authors of each study, were used. Any disagreements were resolved by consensus or by a third author.

Risk-of-bias assessment

Two authors performed independently the quality assessment of all included studies using the Effective Public Health Practice Project quality assessment tool for quantitative studies. Final results led to an overall methodological rating of strong, moderate, or weak in 8 sections: selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity, and analysis. When available, any potential conflicts of interest or sources of funding were also identified.

Because DPT was not used systematically to confirm a negative ST result, the risk of underestimating cross-reactivity was assessed for each study and for each beta-lactam. This risk was judged to be low if 70% or more subjects were tested with DPT. If less than 70% of subjects had a DPT, the risk was judged to be either moderate or high depending on the negative predictive value (NPV) of the ST method used for this particular beta-lactam (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). NPVs for each beta-lactam and ST method were derived from the studies included in the meta-analysis (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). Cutoff values were determined by consensus between the study authors. The risk of overestimating cross-reactivity could not be assessed because the positive predictive value of skin testing methods could not be evaluated.

Statistical analysis

Meta-analyses were performed to calculate the AR of cross-reactivity for each cephalosporin and carbapenem in penicillin-allergic patients. Individual participant data and aggregated participant data were used for the penicillin-cephalosporin meta-analysis, whereas only aggregated participant data were used for the penicillin-carbapenem meta-analysis. Subgroup analyses were performed by stratifying by type of penicillin allergy (IgE-vs T-cell−mediated) and by R1 side chain similarity scores. Sensitivity analyses were performed by excluding studies at moderate or high risk of underestimating cross-reactivity for each beta-lactam. If data from a given study were considered at high or moderate risk of underestimating cross-reactivity for a given cephalosporin, it was excluded even if some of those patients had undergone a DPT because we could not exclude a workup bias that could have selected low-risk patients for DPT.

Both random-effects and fixed-effect logistic regression models were used for each analysis. An exact likelihood approach based on a binomial distribution was used to estimate within-study variability because this method is more accurate compared with the approximate approach when the absolute risk of event is low and the sample size is small.[42] Except for cefaclor, ARs are presented according to the random-effects model, because it accounts for intra- and inter-study variability. A fixed-effect model was chosen for cefaclor to counterbalance the weight of small studies, which were all at high risk of bias. Statistical analyses were conducted using the Meta library General Package for meta-analaysis (version 4.5-0) obtained via the Comprehensive R Archive Network (CRAN) (R Foundation, Vienna, Austria).

CIs for individual study results and for combined study results, when no event was observed, were calculated using the Clopper-Pearson method. For each pooled estimate, the extent of heterogeneity was estimated with the Q test (τ^2) and the I^2 statistic. Values of 25%, 50%, and 75% were considered to represent low, moderate, and high heterogeneity, respectively.[43]

Funnel plots and Egger's regression test were used to detect publication bias whenever possible (eg, number of studies $\geq$ 10). Asymmetry in the funnel plot or Egger's test P value of less than .05 is suggestive of a publication bias.

In silico similarity calculation

The isolated R1 (C6/C7) side chain from the studied penicillins and cephalosporins were designed and created with the ChemBioDraw 13.0 software and imported in ChemMine Tools (http://chemmine.ucr.edu) to be compared against each other.[44] Similarity scores between compound pairs were computed using Similarity Workbench of ChemMine Tools based on structural and physicochemical properties (pKa, charge, polarity, hydrophobicity, hydrogen bonds) using the Atom-Pair molecular descriptors and Tanimoto coefficient.[45-47] Given 2 compounds, X and Y, Tanimoto$(X,Y) = z/(x + y - z)$, where x represents the number of bits set to 1 in X, y represents the number of bits set to 1 in Y, and z represents the number of bits set to 1 in both.[48] A final score was obtained, which ranged from 0 to 1, where "0" corresponds to no similarity and "1" to identical side chains.

Additional analyses

The association between the AR of cross-reactivity and R1 side chain similarity was explored by plotting the AR of cross-reactivity against the highest similarity score obtained by a given cephalosporin. A weighted least squares linear regression model was used, with weights being inversely proportional to the estimated cephalosporin standard error obtained from each meta-analysis.

RESULTS

Study selection, characteristics, and risk-of-bias assessment

The literature search yielded a total of 1306 and 760 publications on penicillin-cephalosporin and penicillin-carbapenem cross-reactivity, respectively. After evaluation, 28 different studies involving 2210 penicillin-allergic subjects were selected; 21 were included for the penicillin-cephalosporin meta-analysis, whereas 11 were selected for the penicillin-carbapenem meta-analysis (Figure 1). Four of the 25 selected studies were used to perform both meta-analyses. Excluded studies along with reasons for exclusion are listed in Tables E7 and E8 in this article's Online Repository at www.jaci-inpractice.org.

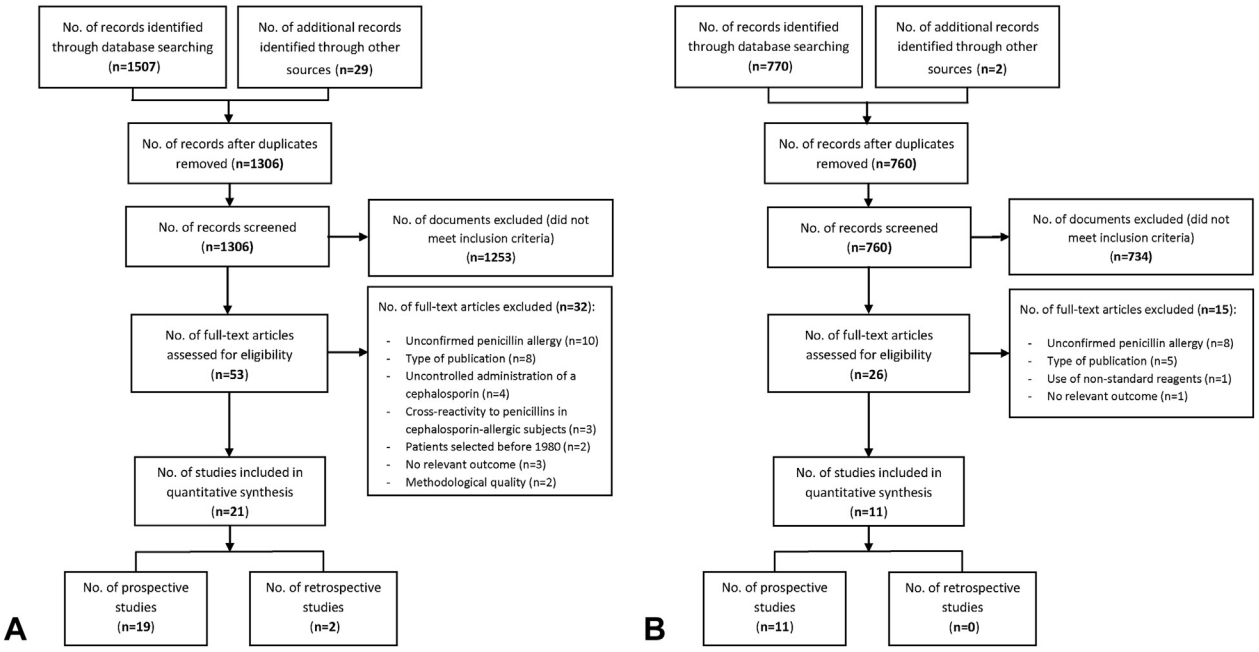


FIGURE 1. Flow diagram of study selection process. **A,** Cross-reactivity to cephalosporins in penicillin-allergic subjects. **B,** Cross-reactivity to carbapenems in penicillin-allergic subjects.

Characteristics of included studies are presented in Table I. Eighty-nine (n = 25) percent of the included studies were performed in Europe, whereas the remaining 11% (n = 3) were performed in Canada. All subjects included in the meta-analyses had a confirmed penicillin allergy based on a positive ST or DPT result to at least 1 penicillin. Penicillin allergy was IgE-mediated in 1269 of 2210 (57.4%) subjects, T-cell–mediated in 857 of 2210 (38.8%) subjects, and was not clearly defined in 84 of 2210 (3.8%) subjects. A total of 13 subjects were excluded from both meta-analyses for the following reasons: (1) penicillin allergy diagnoses based only on a positive specific IgE assay (Buonomo et al,[26] n = 5) and (2) initial allergic reaction was to a cephalosporin and not a penicillin (Buonomo et al,[26] n = 7; Patriarca et al,[55] n = 1). A total of 9 subjects were also excluded from the cephalosporin meta-analysis for the following reasons: (1) penicillin allergy based only on a specific IgE assay (Audicana et al,[51] n = 3; Miranda et al,[53] n = 2) and (2) reaction to a penicillin and a cephalosporin before evaluation for cephalosporin cross-reactivity (Buonomo et al,[26] n = 4).

Almost all allergic reactions to penicillins were to aminopenicillins (amoxicillin, ampicillin, bacampicillin, pivampicillin). Several methods were used to diagnose cross-reactivity (eg, immediate- and delayed-reading skin prick tests, immediate- and delayed-reading IDTs, patch tests, and DPTs) that varied between groups of investigators and type of penicillin allergy studied. Studies also differed in the cephalosporins or carbapenems tested for cross-reactivity.

The quality of all included studies was moderate according to the Effective Public Health Practice Project quality assessment tool for quantitative studies, which identified the lack of blinding as the main weakness of all studies (see Table E9 in this article's Online Repository at www.jaci-inpractice.org). Based on the percentage of subjects tested with DPT and the NPV of the ST used (Figure E1), 11 studies[24-26,28,29,32,52,55-57,61] were considered at high or moderate risk of underestimating cross-reactivity for some cephalosporins (see Table E10 in this article's Online Repository at www.jaci-inpractice.org). In contrast, no study on carbapenems was at high risk of underestimating cross-reactivity and only 2 studies[5,26] were at moderate risk (Table E10). The small number of studies available for most beta-lactams limited the assessment of publication bias (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Also, when the number of studies allowed a funnel plot to be drawn, its interpretation was difficult given that in many studies the rate of cross-reactivity was zero, preventing a logit transformation.

Cross-reactivity to cephalosporins in penicillin-allergic subjects

The AR of cross-reactivity for each cephalosporin is summarized in Table II and is detailed in Table I and Figure E3 in this article's Online Repository at www.jaci-inpractice.org. Although heterogeneity across studies was difficult to assess given the small sample sizes and low number of studies for many cephalosporins,[64-66] it was possibly observed for cefadroxil, cefaclor, cefuroxime, ceftriaxone, and cefepime (Figure E3).

The type of penicillin allergy (IgE- or T-cell–mediated) caused some variation in the AR of cross-reactivity only for some cephalosporins: cefadroxil, cephalothin, and cefamandole (Table III). Almost all subjects showing cross-reactivity to at least 1 cephalosporin had reacted to an aminopenicillin but their pattern of sensitization to penicillins was varied (see Table E11 in this article's Online Repository at www.jaci-inpractice.org). Some reacted only to aminopenicillins, whereas others also reacted to other penicillins.

R1 side chain similarity between penicillins and cephalosporins based on structural and physicochemical properties is presented in Figure 2, *A*. The similarity score was systematically low

TABLE I. Characteristics and outcomes of included studies evaluating cross-reactivity to cephalosporins and/or carbapenems in penicillin-allergic subjects

Study, year (country of origin)	Type of study/data retrieved	N	Age (y), range or mean	Type of penicillin allergy	Culprit penicillin*	Cephalosporins, carbapenems tested (method(s) used)	ST result	DPT result	Cross-reactivity
Atanaskovic-Markovic et al,[49] 2008 (Serbia)	P/APD	108	3-14	IgE	AM: 65/129 PE: 61/129 CE: 3/129	Meropenem (IDT + DPT)	1 of 108 (0.9%)	0 of 107	1 of 108 (0.9%)
Atanaskovic-Markovic et al,[50] 2009 (Serbia)	P/APD	124	3-14	IgE	AM: 75/154 PE: 76/154 CE: 3/154	Imipenem (IDT + DPT)	1 of 124 (0.8%)	0 of 123	1 of 124 (0.8%)
Audicana et al,[51] 1994 (Spain)	P/IPD	31	12-72	IgE	AM: 25/33 PE: 7/33 UN: 1/33	Cephalexin (IDT + DPT)	5 of 31 (16.1%)	1 of 27 (3.7%)	5 of 31 (16.1%)
						Ceftazidime (IDT + DPT)	0 of 31	0 of 27	0 of 31 (0%)
Blanca et al,[52] 1989 (Spain)	P/IPD	19	22-74	IgE	AM: 12/23 PE: 11/23	Cephaloridine (DPT)	ND	0 of 17†	0 of 17†
						Cefamandole (DPT)	ND	2 of 19 (10.5%)	2 of 19 (10.5%)
Buonomo et al,[25] 2014 (Italy)	P/IPD	97	15-75	T-cell	AM: 110/129 PE: 12/129 UN: 7/129	Cephalexin (PT + DPT)	9 of 97 (9.3%)	4 of 38 (10.5%)	13 of 97 (13.4%)
						Cefaclor (PT)	9 of 97 (9.3%)	ND	9 of 97 (9.3%)
						Cefuroxime (PT + DPT)	6/97 (6.2%)	0 of 53	6 of 97 (6.2%)
						Ceftriaxone (PT + DPT)	0 of 97	0 of 31	0 of 97
						Ceftibuten (PT + DPT)	0 of 97	0 of 44	0 of 97
						Cefixime (PT + DPT)	1 of 97 (1.0%)	0 of 52	1 of 97 (1.0%)
						Imipenem (PT + DPT)	4 of 97 (4.1%)	0 of 61	4 of 97 (4.1%)
Buonomo et al,[26] 2016 (Italy)	P/IPD	37‡ 33‡	21-76	IgE	AM: 43/48 PI: 1/48 CE: 4/48‡	Cefazolin (IDT)	0 of 8	ND	0 of 8
						Cephalexin (SPT + DPT)	0 of 27	2 of ?	2 of 27 (7.4%)
						Cefuroxime (IDT)	0 of 14	ND	0 of 14
						Cefaclor (SPT)	0 of 30	ND	0 of 30
						Ceftriaxone (IDT)	2 of 33 (6.1%)	1 of ?	3 of 33 (9.1%)
						Cefepime (IDT + DPT)	0 of 33	1 of ?	1 of 33 (3.0%)
						Imipenem (IDT)	0 of 37	ND	0 of 37
						Meropenem (IDT)	0 of 37	ND	0 of 37
						Ertapenem (IDT + DPT)	0 of 37	0 of 28	0 of 37
Caimmi et al,[27] 2010 (France)	P/APD	69	32-56	NS	NS	Cefuroxime (DPT)	ND	2 of 69 (2.9%)	2 of 69 (2.9%)
Callero et al,[28] 2014 (Spain)	P/IPD	30	1-12	T-cell	AM: 30/30	Cefuroxime (SPT + DPT)	0 of 30	0 of 27	0 of 30

						Cefaclor (SPT + DPT)	0 of 30	0 of 4	0 of 30
						Cefixime (SPT + DPT)	0 of 30	0 of 3	0 of 30
El Fassy et al,[33] 2018 (Canada)	P/APD	53	1-18	T-cell	AM: 53/53	Cefprozil (DPT)	ND	3 of 39 (7.7%)	3 of 39 (7.7%)
Gaeta et al,[22] 2015 (Italy)	P/APD	212	15-80	IgE	AM: 260/279 PE: 3/279 PI: 10/279 CE: 6/279	Imipenem (IDT + DPT)	0 of 212	0 of 211	0 of 212
						Meropenem (IDT + DPT)	0 of 212	0 of 211	0 of 212
						Ertapenem (IDT + DPT)	0 of 212	0 of 211	0 of 212
Martinez et al,[29] 2015 (Spain)	R/IPD	22	7-80	IgE	AM: 21/22 PE: 1/22	Cefuroxime (IDT + DPT)	0 of 22	0 of 19	0 of 22
						Cefixime (SPT + DPT)	0 of 22	0 of 20	0 of 22
						Ceftriaxone (IDT)	0 of 22	ND	0 of 22
						Ceftazidime (IDT)	0 of 22	ND	0 of 22
Meng et al,[30] 2016 (United Kingdom)	R/IPD	15	49.3 ±19.4	IgE	AM: 7/15 PE: 1/15 FL: 1/15 PI: 1/15 UN: 5/15	Cefuroxime (IDT + DPT)	2 of 15 (13.3%)	1 of 13 (7.7%)	3 of 15 (20.0%)
Mill et al,[31] 2016 (Canada)	P/IPD	48	1.0-3.9	IgE: 17 T-cell: 31	AM: 48/48	Cefixime (DPT)	ND	0 of 48	0 of 48
Misirlioglu et al,[32] 2017 (Turkey)	P/APD	29	8.3 ± 5.0	IgE	AM: 28/29 PE: 1/29	Cefuroxime (DPT)	ND	0 of 20	0 of 20
Miranda et al,[53] 1996 (Spain)	P/IPD	19	18-59	IgE	AM: 19/19	Cefadroxil (DPT)	ND	7 of 19 (36.8%)	7 of 19 (36.8%)
						Cefamandole (DPT)	ND	0 of 19	0 of 19
Novalbos et al,[54] 2001 (Spain)	P/IPD	41	19-72	IgE: 39 T-cell: 2	AM: 35/41 CL: 1/41 PE: 3/41 UN: 3/41	Cefazolin (IDT + DPT)	0 of 41	0 of 41	0 of 41
						Cefuroxime (IDT + DPT)	0 of 41	0 of 41	0 of 41
						Ceftriaxone (IDT + DPT)	0 of 41	0 of 41	0 of 41
Patriarca et al,[55] 1999 (Italy)	P/IPD	29	17-63	T-cell	AM: 38/43 PE: 4/43 PI: 1/43	Cephalexin (PT + DPT)	2 of 29 (6.9%)	5 of 29 (17.2%)§	5 of 29 (17.2%)
						Cephalothin (PT + DPT)	1 of 29 (3.4%)	0 of 2	1 of 29 (3.4%)
						Cefadroxil (PT + DPT)	3 of 29 (10.3%)	1 of 13 (7.7%)‖	3 of 29 (10.3%)
						Cefatrizine (PT + DPT)	1 of 29 (3.4%)	0 of 9	1 of 29 (3.4%)
						Cefuroxime (PT + DPT)	2 of 29 (6.9%)	0 of 19¶	1 of 29 (3.4%)
						Cefamandole (PT + DPT)	1 of 29 (3.4%)	0 of 4	1 of 29 (3.4%)

(continued)

TABLE I. *(Continued)*

Study, year (country of origin)	Type of study/data retrieved	N	Age (y), range or mean	Type of penicillin allergy	Culprit penicillin*	Cephalosporins, carbapenems tested (method(s) used)	ST result	DPT result	Cross-reactivity
						Cefaclor (PT + DPT)	0 of 29	0 of 7	0 of 29
						Cefixime (PT + DPT)	0 of 29	0 of 15	0 of 29
						Ceftibuten (PT + DPT)	0 of 29	0 of 14	0 of 29
						Cefotaxime (PT)	0 of 29	ND	0 of 29
						Ceftriaxone (PT + DPT)	0 of 29	1 of 19 (5.3%)	1 of 29 (3.4%)
						Imipenem (PT + DPT)	1 of 29 (3.4%)	0 of 25	1 of 29 (3.4%)
Phillips et al,[56] 2001 (Canada)	P/APD	26	ND	T-cell	AM: 26/26	Cefazolin (IDT)	1 of 26 (3.8%)	ND	1 of 26 (3.8%)
						Cephalexin (PT + DPT)	5 of 16 (31.3%)	0 of 2	5 of 16 (31.3%)
						Cefuroxime (IDT)	0 of 26	ND	0 of 26
						Cefaclor (DPT)	ND	0 of 4	0 of 4#
Romano et al,[57] 2004 (Italy)	P/APD	128	45.5 ±16.7	IgE	AM: 103/128 PE: 19/128 PI: 6/128	Cephalothin (IDT)	8 of 128 (6.3%)	ND	8 of 128 (6.3%)
						Cefuroxime (IDT + DPT)	2 of 128 (1.6%)	0 of 101	2 of 128 (1.6%)
						Cefamandole (IDT)	9 of 128 (7.0%)	ND	9 of 128 (7.0%)
						Ceftriaxone (IDT + DPT)	3 of 128 (2.3%)	0 of 101	3 of 128 (2.3%)
						Ceftazidime (IDT)	2 of 128 (1.6%)	ND	2 of 128 (1.6%)
						Cefotaxime (IDT)	2 of 128 (1.6%)	ND	2 of 128 (1.6%)
Romano et al,[58] 2006 (Italy)	P/APD	112	44.6 ± 15.7	IgE	AM: 117/143 PE: 9/143 PI: 17/143	Imipenem (IDT + DPT)	1 of 112 (0.9%)	0 of 110	1 of 112 (0.9%)
Romano et al,[59] 2007 (Italy)	P/APD	104	14-83	IgE	AM: 116/138 PE: 6/138 PI: 16/138	Meropenem (IDT + DPT)	1 of 104 (1.0%)	0 of 103	1 of 104 (1.0%)
Romano et al,[23] 2013 (Italy)	P/APD	204	15-79	T-cell	AM: 280/298 PE: 4/298 PI: 7/298 PIV: 1/298 CE: 1/298 UN: 5/298	Imipenem (IDT + DPT)	0 of 204	0 of 204	0 of 204
						Meropenem (IDT + DPT)	0 of 204	0 of 204	0 of 204
						Ertapenem (IDT + DPT)	0 of 130	0 of 130	0 of 130
Romano et al,[20] 2016 (Italy)	P/APD	214	15-79	T-cell	AM: 292/307 PE: 4/307 PI: 4/307 PIV: 1/307 UN: 6/307	Cefadroxil (IDT + DPT)	17 of 214 (7.9%)	0 of 170	17 of 214 (7.9%)
						Cephalexin (IDT + DPT)	31 of 214 (14.5%)	0 of 170	31 of 214 (14.5%)

						Cefuroxime (IDT + DPT)	0 of 214	0 of 213	0 of 214
						Cefaclor (IDT + DPT)	39 of 214 (18.2%)	1 of 170 (0.6%)	40 of 214 (18.7%)
						Ceftriaxone (IDT + DPT)	0 of 214	0 of 213	0 of 214
Romano et al,[24] 2018 (Italy)	P/IPD	252	47.7 ± 15.7	IgE	AM: 297/319 PI: 8/319 BA: 5/319 PE: 5/319 UN: 4/319	Cefadroxil (IDT + DPT)	62 of 252 (24.6%)	4 of 167 (2.4%)	66 of 252 (26.2%)
						Cephalexin (IDT)	33 of 252 (13.1%)	ND	33 of 252 (13.1%)
						Cefaclor (IDT + DPT)	38 of 252 (15.1%)	3 of 170 (1.8%)	41 of 252 (16.3%)
						Cefamandole (IDT)	11 of 252 (4.4%)	ND	11 of 252 (4.4%)
						Cefuroxime (IDT + DPT)	2 of 252 (0.8%)	0 of 244	2 of 252 (0.8%)
						Ceftazidime (IDT)	0 of 252	ND	0 of 252
						Ceftriaxone (IDT + DPT)	6 of 252 (2.4%)	0 of 244	6 of 252 (2.4%)
						Cefotaxime (IDT)	3 of 252 (1.2%)	ND	3 of 252 (1.2%)
						Cefepime (IDT)	0 of 252	ND	0 of 252
Sastre et al,[60] 1996 (Spain)	P/IPD	16	3-49	IgE	AM: 16/16	Cefadroxil (DPT)	ND	2 of 16 (12.5%)	2 of 16 (12.5%)
Schiavino et al,[61] 2006 (Italy)	P/IPD	27	14-72	T-cell	AM: 35/35	Cephalothin (PT)	0 of 27	ND	0 of 27
						Cephalexin (PT + DPT)	1 of 27 (3.7%)**	3 of 20 (15%)	3 of 27 (11.1%)
						Cefadroxil (PT + DPT)	0 of 27	0 of 7	0 of 27
						Cefatrizine (PT + DPT)	0 of 27	0 of 3	0 of 27
						Cefradine (DPT)	ND	0 of 1	0 of 1#
						Cefaclor (PT + DPT)	0 of 27	0 of 12	0 of 27
						Cefamandole (PT + DPT)	0 of 27	0 of 1	0 of 27
						Cefuroxime (PT + DPT)	0 of 27	0 of 17	0 of 27
						Cefixime (PT + DPT)	0 of 27	0 of 9	0 of 27
						Ceftibuten (PT + DPT)	0 of 27	0 of 18	0 of 27
						Cefotaxime (PT)	0 of 27	ND	0 of 27
						Ceftriaxone (PT + DPT)	0 of 27	0 of 9	0 of 27
						Cefpodoxime (DPT)	ND	0 of 3	0 of 3#
						Cefepime (DPT)	ND	0 of 1	0 of 1#
						Imipenem (PT + DPT)	0 of 27	0 of 25	0 of 27
Schiavino et al,[62] 2009 (Italy)	P/APD	73	15-74	T-cell	AM: 74/94 PE: 13/94 CE: 2/94 UN: 5/94	Imipenem (PT + DPT)	4 of 73 (5.5%)	0 of 64	4 of 73 (5.5%)
Trcka et al,[63] 2007 (Germany)	P/IPD	71	15-78	T-cell	AM: 71/71	Cefixime (PT + DPT)	0 of 71	1 of 71 (1.4%)	1 of 71 (1.4%)
						Cefpodoxime (PT + DPT)	0 of 71	1 of 71 (1.4%)	1 of 71 (1.4%)

AM, Amoxicillin or ampicillin; *APD*, aggregate participant data (when individual data and detailed allergic profiles of each patient were unavailable); *BA*, bacampicillin; *CE*, cephalosporins; *CL*, cloxacillin; *FL*, flucloxacilline; *IPD*, individual participant data; *ND*, not determined; *NS*, not specified; *P*, prospective study; *PE*, penicillin G or penicillin V; *PI*, piperacillin; *PIV*, pivampicillin; *PT*, patch test; *R*, retrospective study; *SPT*, skin prick test; *UN*, unknown; *?*, the total number of subjects who underwent a DPT is unknown.

*Penicillin responsible for the initial allergic reaction. Some subjects had more than 1 allergic reaction to penicillins. All subjects who reacted to cephalosporins also reacted to at least 1 penicillin.

†Two patients with a positive DPT result to cefamandole did not have a DPT to cephaloridine.

‡A total of 37 patients were included for the carbapenem meta-analysis and 33 for the cephalosporin meta-analysis; 4 patients were excluded from the cephalosporin meta-analysis because they had reacted to a cephalosporin before cross-reactivity to cephalosporins was assessed.

§Includes 2 subjects who were PT+; one had a positive DPT result and the other a negative DPT result.

‖One patient with a positive PT result had a positive DPT result.

¶One patient with a positive ST result to cefuroxime had a negative DPT result.

#Studies with fewer than 5 patients were excluded from meta-analyses because they provide little information and represent an unstable result.

**The patient with a positive ST result had a negative oral challenge to cephalexin.

for all third- and fourth-generation cephalosporins, whereas it varied for first- and second-generation molecules. The degree of R1 side chain similarity with penicillins correlated with the risk of cross-reactivity found in the meta-analyses (regression coefficient $\beta = 15.8$; $P < .0001$) (Figure 2, *B*). The risk was highest for aminocephalosporins (cephalexin, cefadroxil, cefprozil, and cefaclor), which share an identical side chain (similarity score = 1) with an aminopenicillin (risk of cross-reactivity to at least 1 aminocephalosporin: 16.45%; 95% CI, 11.07-23.75) (Figure 3, *A*). It is worth noting that the low risk of cross-reactivity observed for cefatrizine, an aminocephalosporin, is at high risk of being underestimated because all studies[55,61] on cefatrizine are at high risk of bias (Table E10). The risk of cross-reactivity was lower for cefamandole, cephalothin, and cephaloridine, which all have an R1 side chain with a similarity score of around 0.6 compared with that of penicillin G (Figure 2). Also, the R1 side chain of cefamandole has a similarity score of around 0.7 compared with that of ampicillin. The risk of cross-reactivity to at least 1 intermediate-similarity-score cephalosporin (range, 0.563-0.714) was 5.60% (95% CI, 3.46-8.95) (Figure 3, *B*). However, the risk of cross-reactivity observed for cephaloridine and cephalothin could be underestimated because all studies[52,55,57,61] on these cephalosporins were at moderate or high risk of bias (Table E10). The risk was lowest for all cephalosporins with an R1 side chain with similarity scores below 0.4 (cefazolin, cefuroxime, cefixime, cefotaxime, ceftriaxone, ceftazidime, cefpodoxime, ceftibuten, and cefepime), regardless of their generation (risk of cross-reactivity to at least 1 low-similarity-score cephalosporin: 2.11%; 95% CI, 0.98-4.46) (Figure 3, *C*).

Sensitivity analyses were performed by excluding data at risk of bias from 11 studies at risk of underestimating cross-reactivity.[24-26,28,29,32,52,55-57,61] Pooled estimates observed for each cephalosporin were not significantly altered by these analyses (Table IV).

Cross-reactivity to carbapenems in penicillin-allergic subjects

Nine studies evaluated the risk of cross-reactivity to imipenem among 917 penicillin-allergic subjects and found a rate of 0.79% (95% CI, 0.21-2.88) (Figure 4, *A*). Three studies[25,55,62] from the same group of investigators reported rates of cross-reactivity varying between 3.45% and 5.48% and possibly explained the moderate level of heterogeneity observed (Figure 4, *A*). These studies included 199 subjects with a T-cell–mediated penicillin allergy and all cross-reactive subjects were detected through a positive patch test result to imipenem. In contrast, the only other study on imipenem cross-reactivity in subjects with a T-cell–mediated penicillin allergy[23] evaluated 204 subjects with delayed-reading IDTs and performed DPTs, which is considered the criterion standard, in all subjects and found no cross-reactivity.

The risk of cross-reactivity to meropenem and ertapenem was evaluated in 5 and 3 studies, respectively (Figure 4, *B*). The observed rate was 0.30% (95% CI, 0.08-1.19) for meropenem and 0% (0 of 379) (95% CI, 0-0.01) for ertapenem. Given the absence of event, a meta-analysis could not be performed for ertapenem. No evidence of heterogeneity across studies was detected for meropenem although the low number of studies limits our interpretation. Overall, the risk of cross-reactivity to any carbapenem was 0.87% (95% CI, 0.32-2.32) (Figure 4, *C*).

TABLE II. AR of cross-reactivity to cephalosporins in penicillin-allergic patients

Cephalosporin			Cross-reactivity		
Generation	Name	No. of studies	n/N	AR in % (95% CI)*	Proportion of patients tested with DPT
First	Cephalexin	8	97/693	14.00 (11.61-16.79)	288 of 693 (42%)
	Cefadroxil	6	95/557	12.65 (5.85-25.26)	392 of 557 (70%)
	Cephalothin	3	9/184	4.89 (2.56-9.13)	2 of 184 (1%)
	Cefazolin	3	1/75	1.33 (0.19-8.86)	41 of 75 (55%)
	Cefatrizine	2	1/56	1.79 (0.25-11.61)	12 of 56 (21%)
	Cephaloridine	1	0/17	0.0 (0.0-19.5)†	17 of 19 (89%)‡
Second	Cefamandole	6	23/474	4.85 (3.25-7.20)	43 of 474 (9%)
	Cefaclor	7	90/679	13.25 (10.91-16.02)	363 of 679 (53%)
	Cefuroxime	14	16/984	0.96 (0.26-3.51)	835 of 993 (84%)
	Cefprozil	1	3/39	7.69 (1.62-20.87)†	39 of 53 (74%)
Third	Cefpodoxime	1	1/71	1.4 (0.0-7.6)†	71 of 71 (100%)
	Ceftazidime	4	2/433	0.31 (0.02-4.72)	27 of 433 (6%)
	Cefotaxime	4	5/436	1.15 (0.48-2.72)	0 of 436 (0%)
	Cefixime	7	2/324	0.62 (0.15-2.43)	218 of 324 (67%)
	Ceftriaxone	9	13/843	0.99 (0.25-3.87)	659 of 843 (78%)
	Ceftibuten	3	0/153	0.0 (0.0-2.4)†	76 of 153 (50%)
Fourth	Cefepime	2	1/285	0.31 (0.01-10.32)	1 of 285 (0.4%)

n, Number of penicillin-allergic patients who tested positive (ST or DPT) to the cephalosporin; *N*, total number of penicillin-allergic patients who were tested (ST or DPT) to the cephalosporin.
*Random-effects model was used except for cefaclor for which the fixed-effect model was used (random-effects model gave an AR of cross-reactivity of 2.44% [95% CI, 0.26-19.63] for cefaclor).
†No meta-analysis performed because no event or only 1 study was reported. 95% CI calculated by Clopper-Pearson method.
‡Two patients with a positive DPT result to cefamandole did not have a DPT to cephaloridine.

TABLE III. Cross-reactivity to cephalosporins in penicillin-allergic subjects according to the type of penicillin allergy

Cephalosporin		Type of penicillin allergy			
		IgE		T-cell	
Generation	Name	n/N	AR in % (95% CI)	n/N	AR in % (95% CI)
First	Cephalexin	40/310	12.9 (9.6-17.1)	57/383	14.9 (11.7-18.8)
	Cefadroxil	75/287	26.1 (21.4-31.5)	20/270	7.4 (4.8-11.2)
	Cephalothin	8/128	6.3 (2.7-11.9)	1/56	1.8 (0.3-11.6)
	Cefazolin	0/47	0.0 (0.0-7.5)	1/26	3.8 (0.0-19.6)
	Cefatrizine	NA	NA	1/56	1.8 (0.3-11.6)
	Cephaloridine	0/17	0.0 (0.0-19.5)	NA	NA
Second	Cefamandole	22/418	5.3 (3.5-7.9)	1/56	1.8 (0.3-11.6)
	Cefaclor	41/282	14.5 (10.9-19.2)	49/397	12.3 (9.5-16.0)
	Cefuroxime	7/490	1.1 (0.2-5.8)	7/423	0.5 (0.0-8.0)
	Cefprozil	NA	NA	3/39	7.7 (1.6-20.9)
Third	Cefpodoxime	NA	NA	1/71	1.4 (0.0-7.6)
	Ceftazidime	2/433	0.3 (0.0-4.7)	NA	NA
	Cefotaxime	5/380	1.3 (0.6-3.1)	0/56	0.0 (0.0-6.4)
	Cefixime	0/39	0.0 (0.0-9.0)	2/285	0.7 (0.2-2.8)
	Ceftriaxone	12/474	2.5 (1.4-4.4)	1/367	0.2 (0.0-9.5)
	Ceftibuten	NA	NA	0/153	0.0 (0.0-2.4)
Fourth	Cefepime	1/285	0.3 (0.0-10.3)	NA	NA

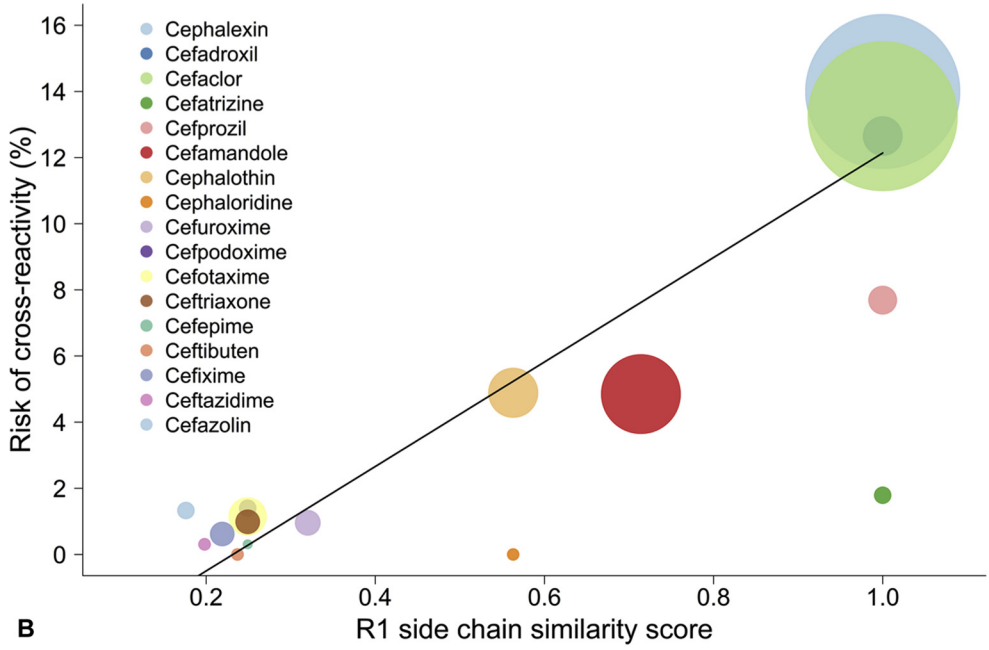
NA, Not applicable.

DISCUSSION

Two systematic reviews with meta-analyses were performed to assess the risk of cross-reactivity to cephalosporins and carbapanems in patients with a proven IgE- or T-cell—mediated penicillin allergy. For cephalosporins, the risk varied with the degree of similarity between R1 side chains of penicillins and cephalosporins. It was highest for aminocephalosporins (high similarity score), lower for a few with an intermediate similarity score (none of which are available in North America), and lowest for all those with low similarity scores, regardless of their

Cephalosporins		Penicillins						
		Penicillin G	Penicillin V	Ampicillin	Amoxicillin	Cloxacillin	Piperacillin	Ticarcillin
1st	Cefadroxil	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cephalexin	0,592	0,333	1,000	0,618	0,208	0,043	0,371
	Cefazolin	0,176	0,110	0,099	0,088	0,078	0,032	0,088
	Cefradine	0,344	0,200	0,517	0,371	0,155	0,082	0,263
	Cephalothin	0,563	0,321	0,337	0,295	0,154	0,035	0,268
	Cefatrizine	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cephaloridine	0,563	0,321	0,337	0,295	0,154	0,035	0,268
2nd	Cefaclor	0,592	0,333	1,000	0,618	0,208	0,043	0,371
	Cefoxitin	0,330	0,245	0,211	0,180	0,148	0,043	0,180
	Cefprozil	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cefuroxime	0,304	0,220	0,274	0,248	0,320	0,044	0,228
	Cefamandole	0,592	0,333	0,714	0,485	0,208	0,043	0,412
3rd	Cefixime	0,110	0,110	0,098	0,157	0,219	0,084	0,138
	Cefotaxime	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Ceftazidime	0,092	0,087	0,092	0,142	0,198	0,064	0,127
	Ceftriaxone	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Cefpodoxime	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Cefdinir	0,147	0,083	0,143	0,156	0,207	0,047	0,238
	Ceftibuten	0,167	0,127	0,148	0,165	0,237	0,079	0,165
4th	Cefepime	0,141	0,090	0,138	0,142	0,249	0,049	0,182

A



B

FIGURE 2. Similarity between R1 side chains of penicillins and cephalosporins and its association with the risk of cross-reactivity. **A,** Heatmap of similarities between R1 side chains. Score of "0" corresponds to no similarity and "1" to identical side chains. **B,** Association between the AR of cross-reactivity and R1 side chain similarity. Weights are inversely proportional to the estimated standard error of the AR of cross-reactivity obtained for each meta-analysis.

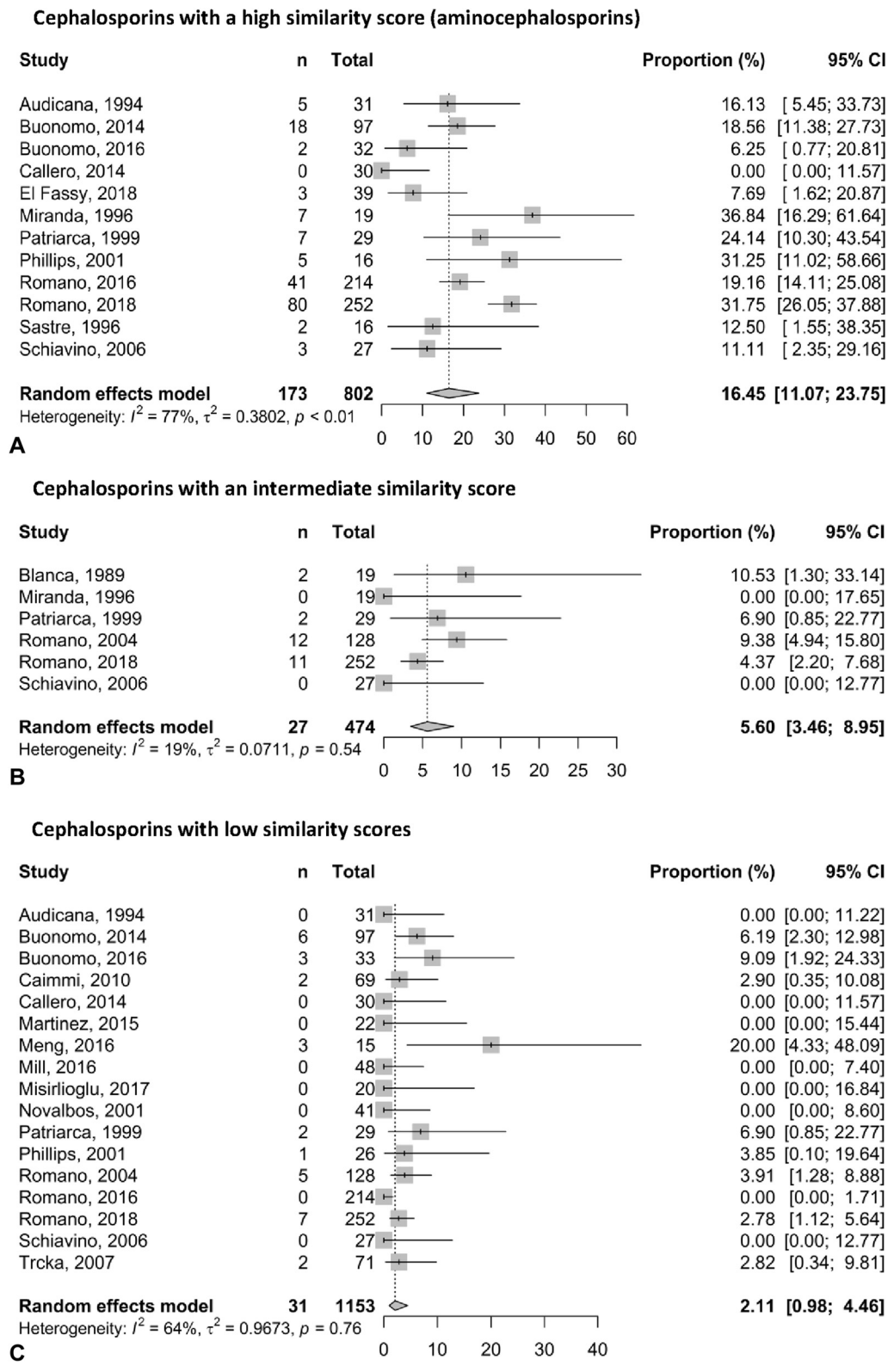


FIGURE 3. Forest plots for pooled effect sizes. Absolute risk of cross-reactivity to at least 1 cephalosporin in penicillin-allergic subjects according to R1 side chain similarity. **A,** Cephalosporins with a high similarity score: cefadroxil, cephalexin, cefatrizine, cefaclor, and cefprozil. **B,** Cephalosporins with an intermediate similarity score: cephalothin, cephaloridine, and cefamandole. **C,** Cephalosporins with low similarity scores: cefazolin, cefuroxime, cefixime, cefotaxime, ceftriaxone, ceftazidime, cefpodoxime, ceftibuten, and cefepime.

TABLE IV. Sensitivity analyses based on the risk of underestimating cross-reactivity*

Cephalosporin			Sensitivity analyses	
		Initial result	High risk excluded	High or moderate risk excluded
Generation	Name	AR in % (95% CI)	AR in % (95% CI)	AR in % (95% CI)
First	Cephalexin	14.0 (11.6-16.8)	13.9 (11.4-16.7)	14.3 (11.2-18.1)
	Cefadroxil	12.7 (5.9-25.3)	18.0 (9.2-32.2)	14.9 (6.0-32.4)
	Cephalothin	4.9 (2.6-9.1)	6.3 (2.7-11.9)	NA
	Cefazolin	1.3 (0.2-8.9)	0.0 (0.0-7.3)	0.0 (8.6)
	Cefatrizine	1.8 (0.3-11.6)	NA	NA
	Cephaloridine	0.0 (0.0-19.5)	NA	NA
Second	Cefamandole	4.9 (3.3-7.2)	5.3 (3.5-7.9)	5.1 (0.9-24.6)
	Cefaclor	13.3 (10.9-16.0)	16.0 (12.3-20.4)	14.4 (8.7-22.7)
	Cefuroxime	1.0 (0.3-3.5)	1.0 (0.3-3.7)	0.7 (0.1-3.9)
	Cefprozil	7.7 (1.6-20.9)	7.7 (1.6-20.9)	7.7 (1.6-20.9)
Third	Cefpodoxime	1.4 (0.0-7.6)	1.4 (0.0-7.6)	1.4 (0.0-7.6)
	Ceftazidime	0.3 (0.0-4.7)	0.3 (0.0-4.7)	0.0 (0.0-11.2)
	Cefotaxime	1.2 (0.5-2.7)	1.3 (0.6-3.1)	NA
	Cefixime	0.6 (0.2-2.4)	0.7 (0.2-2.7)	0.7 (0.1-4.9)
	Ceftriaxone	1.0 (0.3-3.9)	1.0 (0.3-3.9)	1.0 (0.3-4.2)
	Ceftibuten	0.0 (0.0-2.4)	0.0 (0.0-2.4)	NA
Fourth	Cefepime	0.3 (0.0-10.3)	0.3 (0.0-10.3)	NA

NA, Not applicable.
*Based on results presented in Table E10 in this article's Online Repository at www.jaci-inpractice.org.

generation. The risk of cross-reactivity to any carbapenem was very low.

These are the first systematic reviews with meta-analyses on the subject that thoroughly assessed the quality of individual studies and abided by Meta-analysis Of Observational Studies in Epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Moreover, it is the first study to quantify the similarity between R1 side chains of penicillins and cephalosporins on the basis of structural and physicochemical properties and to show a clear association between R1 side chain similarity and risk of cross-reactivity. Although all cephalosporins at a higher risk of cross-reactivity are either first- or second-generation molecules, this finding was attributable to the fact that these molecules had an R1 side chain with a high or intermediate similarity score. Indeed, cefazolin (first-generation), cefuroxime (second-generation), and all third- and fourth-generation cephalosporins have R1 side chains with low similarity scores and carry a very low risk of cross-reactivity. These findings can be extrapolated to estimate the risk of cross-reactivity for cephalosporins for which little or no data are available. For example, no data exist on cefdinir (third-generation) or cefoxitin (second-generation). Because cefdinir and cefoxitin have R1 side chains with low similarity scores (Figure 2), their risk of cross-reactivity can be estimated to be around 2%.

The higher risk of cross-reactivity associated with aminocephalosporins was observed whether penicillin allergy was IgE- or T-cell–mediated. The low risk of cross-reactivity observed for intermediate-similarity-score cephalosporins in patients with a T-cell–mediated penicillin allergy is at high risk of bias given that these patients were evaluated by patch tests (low NPV) and only 2 of 56 (3.6%) had a DPT. Cross-reactivity between aminopenicillins and aminocephalosporins is not restricted to patients selectively allergic to aminopenicillins (eg, tolerant of other penicillins). Indeed, Romano et al[20] showed that sensitivity to penicillin G in patients with a T-cell–mediated aminopenicillin allergy increased the risk of cross-reactivity to aminocephalosporins (odds ratio, 2.7; 95% CI, 1.3-5.5) compared with patients selectively allergic to aminopenicillins.

The relevance of these findings for clinical practice (eg, when facing the decision to prescribe a beta-lactam to a patient with a history of penicillin allergy) will depend on the likelihood that the patient is truly penicillin-allergic and on the severity of the reported reaction to penicillin. If the likelihood of penicillin allergy is low and the reaction was not severe, the probability of causing an allergic reaction with any cephalosporin will be very low and the risk difference between aminocephalosporins and other cephalosporins may not be clinically significant. In contrast, if penicillin allergy is likely or if the reaction was severe, then the risk difference may become clinically relevant and it may be preferable to use low-similarity-score cephalosporins or carbapenems, which have comparable and very low risks of cross-reactivity.

Study limitations

There was considerable variability between studies regarding the beta-lactams that were tested, the methods used to diagnose cross-reactivity, and the populations studied. We tried to control for these variables and to limit heterogeneity by presenting data for individual beta-lactams, by assessing the validity of each method used to diagnose cross-reactivity (see Tables E6 and E10 in this article's Online Repository at www.jaci-inpractice.org), and by stratifying results according to the type of penicillin

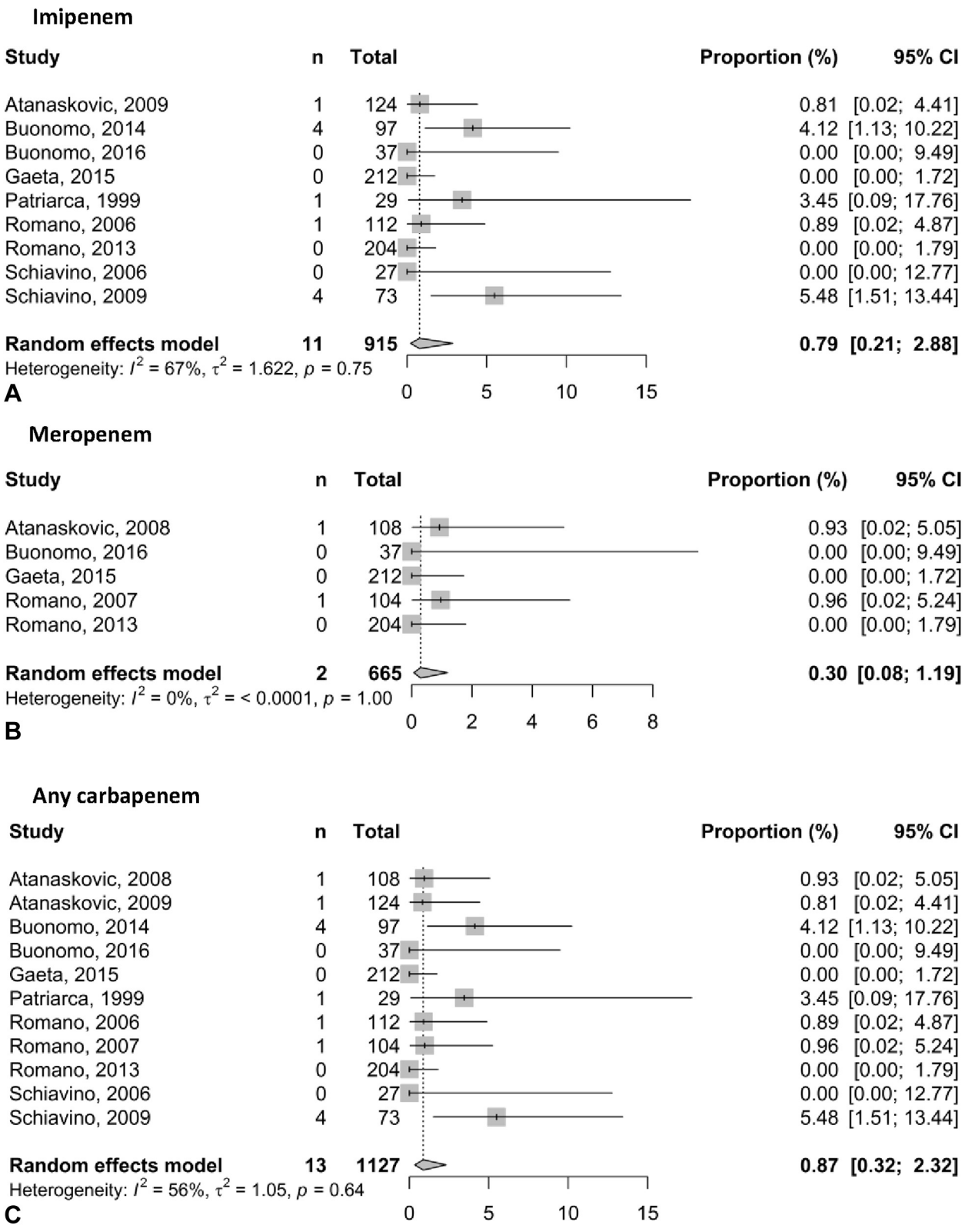


FIGURE 4. Forest plots for pooled effect sizes. AR of cross-reactivity to carbapenems in penicillin-allergic patients. **A,** Imipenem. **B,** Meropenem. **C,** Any carbapenem: imipenem, meropenem, and ertapenem.

allergy (Table III). Statistical assessment of heterogeneity and publication bias was mainly limited by the small number of studies and sample sizes. Also, for several cephalosporins, the risk of cross-reactivity was established on the basis of few studies and patients (Table II).

Although it is unlikely that this meta-analysis underestimated the risks of cross-reactivity, because sensitivity analyses that excluded studies at moderate and high risk of underestimating cross-reactivity did not significantly alter the results (Table IV), overestimation of cross-reactivity cannot be ruled out. For one, most studies diagnosed cross-reactivity on the basis of a positive ST result, which could indicate cross-sensitization rather than cross-reactivity. Also, the risk of a false-positive result increases with the number of STs performed even if IDTs to cephalosporins and carbapenems at the concentrations used in the included studies do not induce positive results in negative controls.[22,67-69] Finally, diagnosing cross-reactivity on the basis of a DPT may require interpretation from the clinician and may be subject to bias as neither the clinician nor the patient was blinded.

Because none of the studies included in these systematic reviews performed *in vitro* mechanistic studies on T-cell lines or specific IgE to prove cross-reactivity, it remains possible that the risk of reactivity to cephalosporins or carbapenems observed in penicillin-allergic patients represent coreactivity rather than cross-reactivity. However, the higher rate of reactivity to aminocephalosporins as well as the structural similarities between those cephalosporins and aminopenicillins argue for cross-reactivity. In contrast, there were several patients in whom many cephalosporins were tested who had a positive ST result to only 1 or a few low-similarity-score cephalosporins while tolerating aminocephalosporins (Table E11). Three possibilities could explain these findings: (1) reactivity to some cephalosporins independent of the penicillin allergy (coreactivity), (2) cross-reactivity attributable to an unrecognized epitope shared by penicillins and some cephalosporins, and (3) a false-positive ST result.

Another limitation is that almost all studies included in this meta-analysis, except 3 studies,[31,33,56] were performed in Europe. Therefore, it remains to be shown that the same patterns of cross-reactivity are seen in other parts of the world. However, 2 Canadian studies[33,56] showed an increased risk of cross-reactivity to aminocephalosporins, supporting the applicability of these findings to populations outside Europe.

Finally, it is unclear how these findings apply to patients allergic to non-aminopenicillins (eg, piperacillin, ticarcillin, penicillin G or V, and cloxacillin) because almost all patients included in this meta-analysis were aminopenicillin-allergic. However, amoxicillin is by far the most frequently prescribed antibiotic in the United States, Canada, and most European countries.[70-72] Therefore, conclusions drawn from this meta-analysis should be applicable to the vast majority of patients claiming a penicillin allergy.

CONCLUSIONS

Cephalosporins cannot be considered a homogeneous group with regard to their risk of cross-reactivity. Future guidelines on beta-lactam use in patients with a suspected or proven penicillin allergy should emphasize the very low risk of cross-reactivity associated with carbapenems and with all low-similarity-score cephalosporins: cefazolin (first-generation), cefuroxime (second-generation), and all third- and fourth-generation cephalosporins. Although it remains possible that this meta-analysis overestimated the risk of cross-reactivity, caution should be exercised with those cephalosporins whose R1 side chain shares similarity with penicillins, especially aminocephalosporins: cefadroxil, cephalexin, cefatrizine, cefprozil, and cefaclor.

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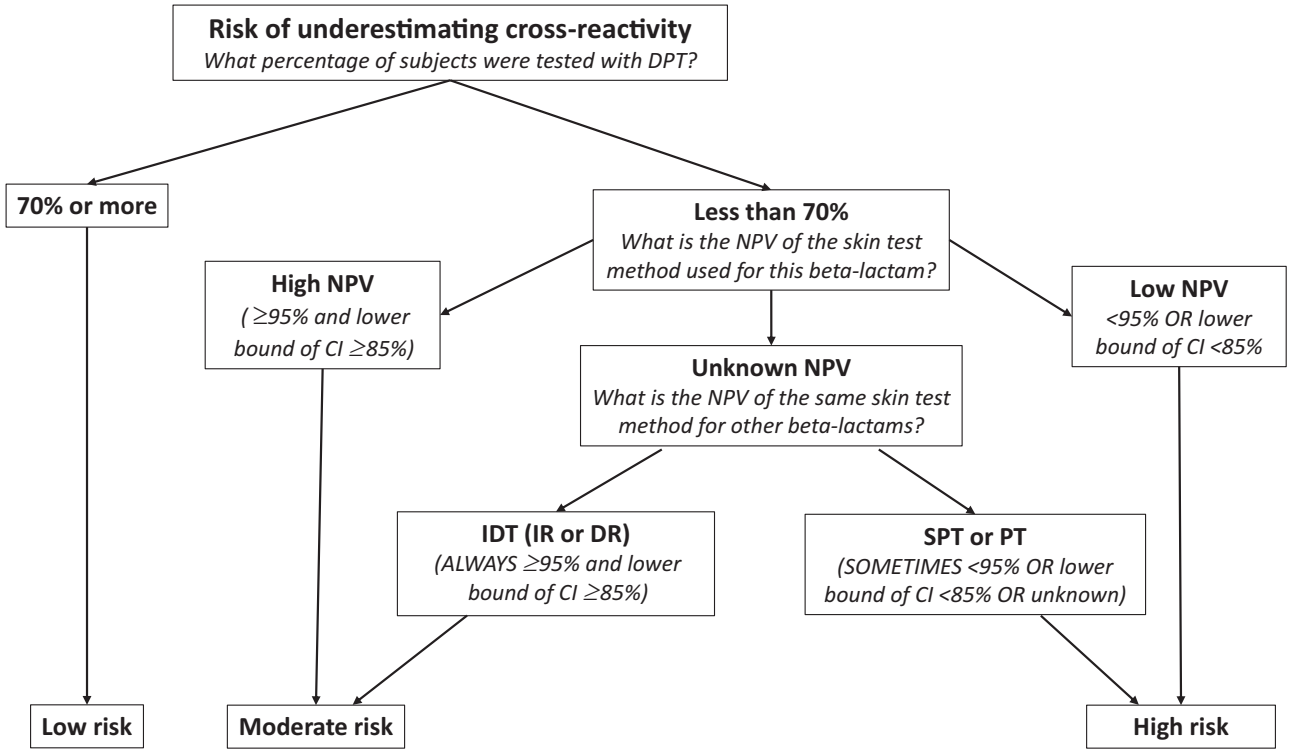


FIGURE E1. Criteria used to evaluate the risk of underestimating cross-reactivity. *DR*, Delayed-reading; *IR*, immediate-reading; *PT*, patch test; *SPT*, skin prick test.

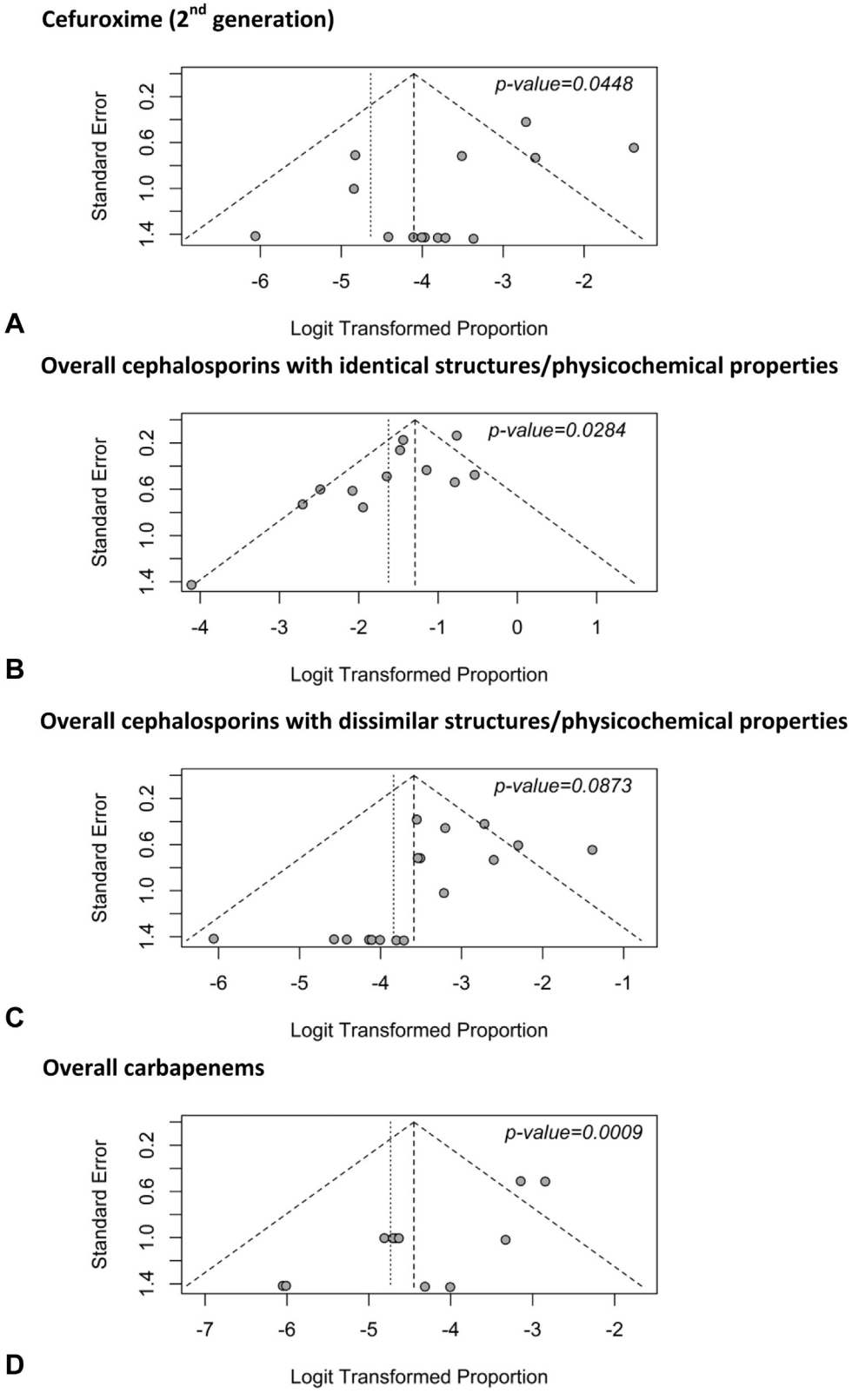


FIGURE E2. Funnel plots for pooled effect sizes and Egger's regression tests (*P* value) when number of studies was 10 or more. **A,** Cefuroxime. **B,** Cephalosporins with identical structures/physicochemical properties. **C,** Cephalosporins with dissimilar structures/physicochemical properties. **D,** Carbapenems.

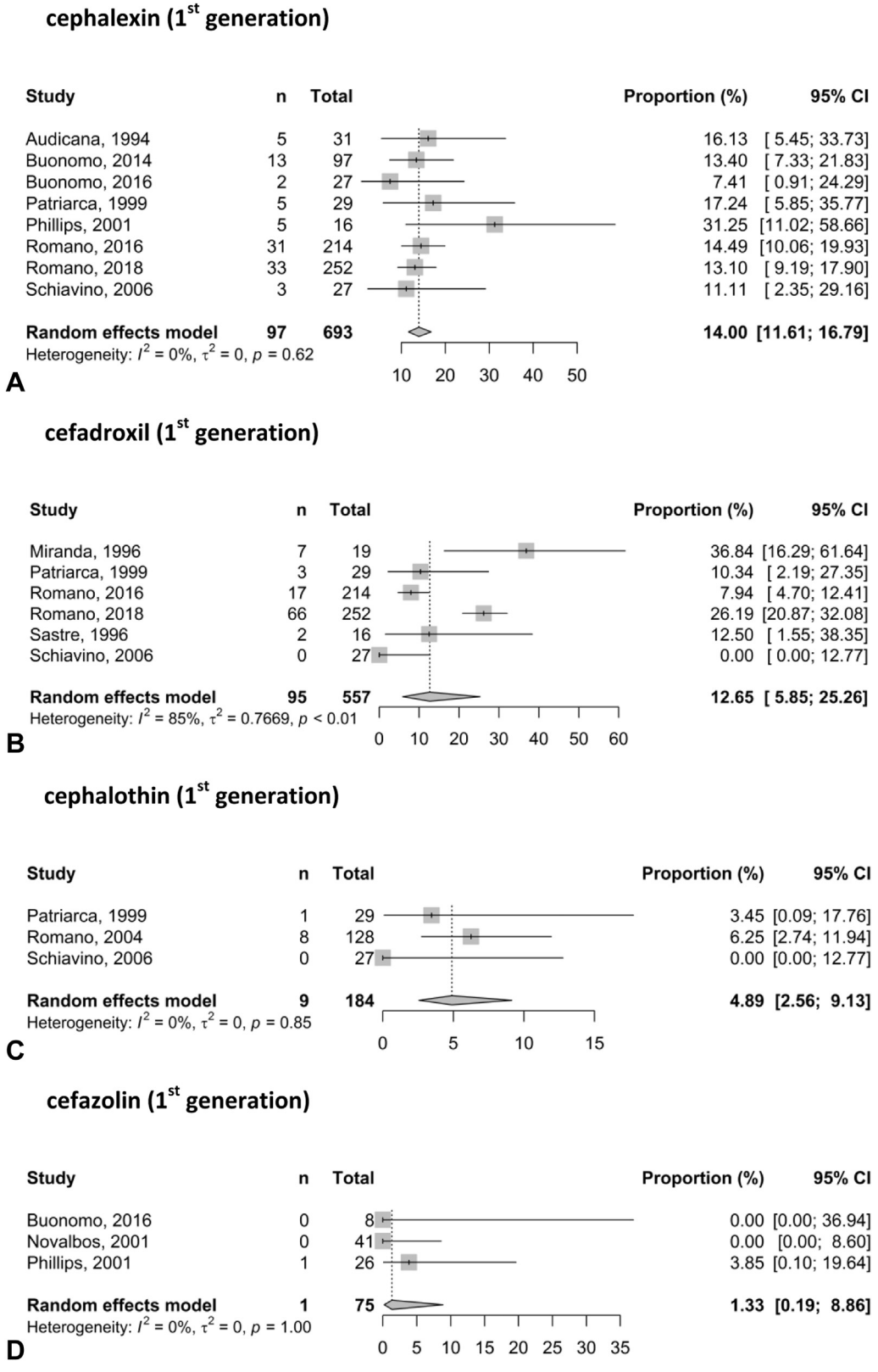


FIGURE E3. Forest plots for pooled effect sizes for each cephalosporin. The random-effects model was preferred except for the cefaclor meta-analysis (Figure E3, *F*). **A,** Cephalexin. **B,** Cefadroxil. **C,** Cephalothin. **D,** Cefazolin. **E,** Cefatrizine. **F,** Cefaclor. **G,** Cefamandole. **H,** Cefuroxime. **I,** Ceftazidime. **J,** Cefotaxime. **K,** Cefixime. **L,** Ceftriaxone. **M,** Cefepime.

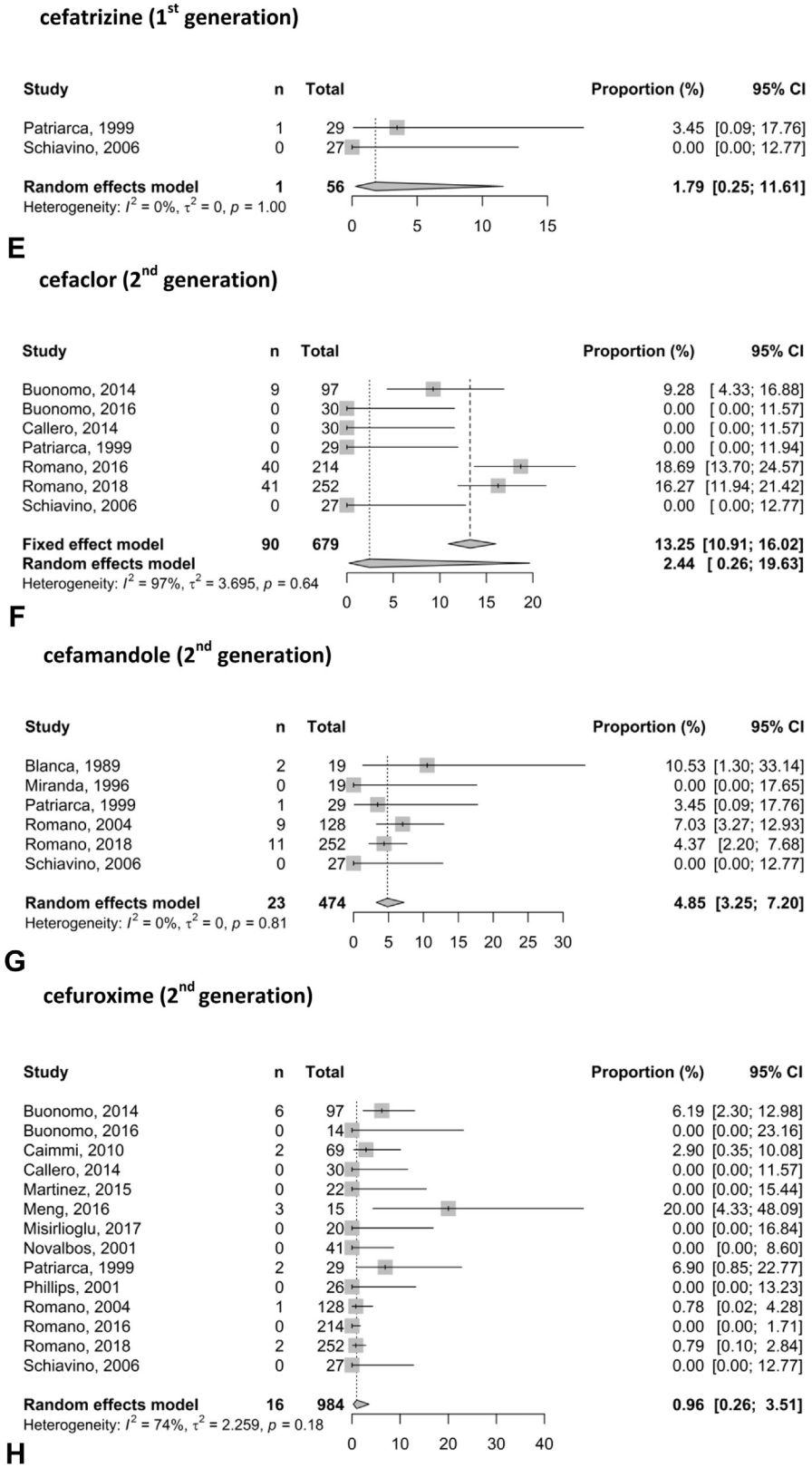
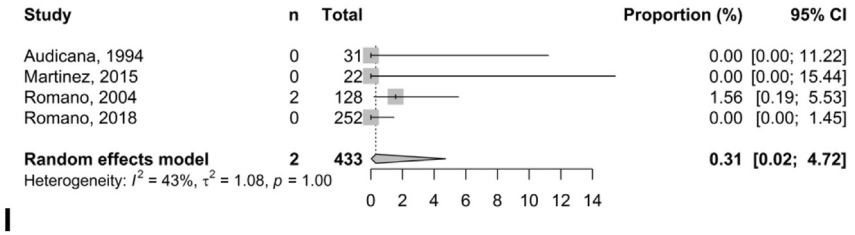


FIGURE E3. (*CONTINUED*).

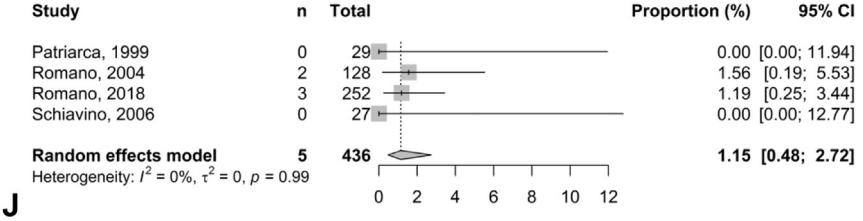
I

ceftazidime (3rd generation)



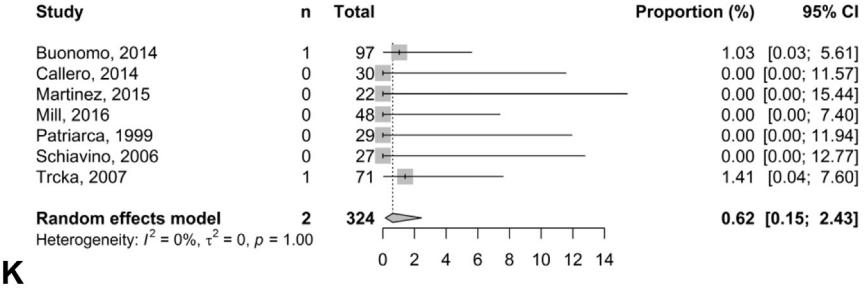
J

cefotaxime (3rd generation)



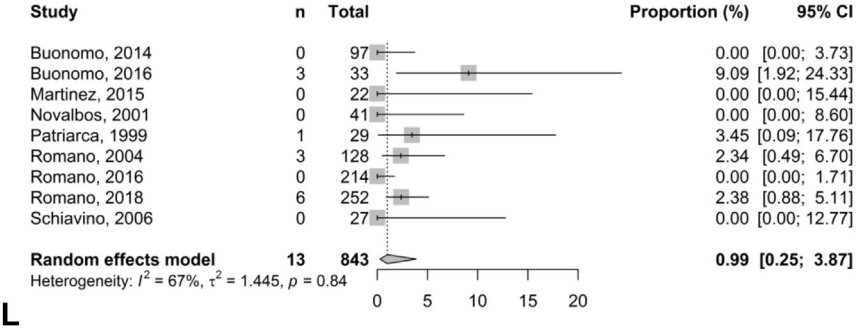
K

cefixime (3rd generation)



L

ceftriaxone (3rd generation)



M

cefepime (4th generation)

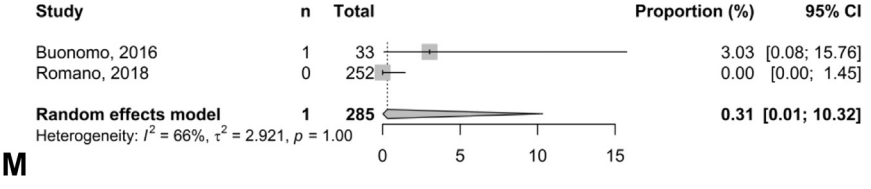


FIGURE E3. (*CONTINUED*).