JAMA Surgery | Original Investigation

Assessment of the Frequency of Dual Allergy to Penicillins and Cefazolin
A Systematic Review and Meta-analysis

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IMPORTANCE Cefazolin is the preoperative antibiotic of choice because it is safer and more efficacious than second-line alternatives. Surgical patients labeled as having penicillin allergy are less likely to prophylactically receive cefazolin and more likely to receive clindamycin or vancomycin, which results in higher rates of surgical site infections.

OBJECTIVE To examine the incidence of dual allergy to cefazolin and natural penicillins.

DATA SOURCES MEDLINE/PubMed, Web of Science, and Embase were searched without language restrictions for relevant articles published from database inception until July 31, 2020.

STUDY SELECTION In this systematic review and meta-analysis, a search of MEDLINE/PubMed, Web of Science, and Embase was performed for articles published from database inception to July 31, 2020, for studies that included patients who had index allergies to a natural penicillin and were tested for tolerability to cefazolin or that included patients who had index allergies to cefazolin and were tested for tolerability to a natural penicillin. A total of 3228 studies were identified and 2911 were screened for inclusion.

DATA EXTRACTION AND SYNTHESIS Data were independently extracted by 2 authors. Bayesian meta-analysis was used to estimate the frequency of allergic reactions.

MAIN OUTCOMES AND MEASURES Dual allergy to cefazolin and a natural penicillin.

RESULTS Seventy-seven unique studies met the eligibility criteria, yielding 6147 patients. Cefazolin allergy was identified in 44 participants with a history of penicillin allergy, resulting in a dual allergy meta-analytical frequency of 0.7% (95% credible interval [CrI], 0.1%-1.7%; I^2 = 74.9%). Such frequency was lower for participants with unconfirmed (0.6%; 95% CrI, 0.1%-1.3%; I^2 = 54.3%) than for those with confirmed penicillin allergy (3.0%; 95% CrI, 0.01%-17.0%; I^2 = 88.2%). Thirteen studies exclusively assessed surgical patients (n = 3884), among whom 0.7% (95% CrI, 0%-3.3%; I^2 = 85.5%) had confirmed allergy to cefazolin. Low heterogeneity was observed for studies of patients with unconfirmed penicillin allergy who had been exposed to perioperative cefazolin (0.1%; 95% CrI, 0.1%-0.3%; I^2 = 13.1%). Penicillin allergy was confirmed in 16 participants with a history of cefazolin allergy, resulting in a meta-analytical frequency of 3.7% (95% CrI, 0.03%-13.3%; I^2 = 64.4%). The frequency of penicillin allergy was 4.4% (95% CrI, 0%-23.0%; I^2 = 75%) for the 8 studies that exclusively assessed surgical patients allergic to cefazolin.

CONCLUSIONS AND RELEVANCE These findings suggest that most patients with a penicillin allergy history may safely receive cefazolin. The exception is patients with confirmed penicillin allergy in whom additional care is warranted.

JAMA Surg. doi:10.1001/jamasurg.2021.0021
Published online March 17, 2021.

Supplemental content

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More than 17 million surgical procedures are performed each year in the US.[1] The Centers for Disease Control and Prevention health care–associated infection prevalence survey estimated that there were 110 800 surgical site infections associated with inpatient operations.[2] Cefazolin, a first-generation cephalosporin, is the guideline-recommended antibiotic for most surgical procedures.[3,4] Cefazolin is the first-line treatment because it is the most widely studied, has the appropriate spectrum of activity against organisms commonly encountered in surgical site infections, is well tolerated, and has a low acquisition cost. However, the 10% of patients reporting a penicillin allergy are less likely to receive cefazolin and more likely to receive clindamycin or vancomycin, resulting in increased odds of developing a surgical site infection.[5,6]

Avoidance of cefazolin in patients with penicillin allergy is grounded in evidence from more than 40 years ago and is being increasingly called into question. Research from the 1960s and 1970s reported a cross-reactivity rate of 8% between penicillins and cephalosporins.[7,8] The production process of penicillins included using a cephalosporin mold and has been blamed for the high rates of cross-reactivity observed before synthetic manufacturing of β-lactams became standard in the middle 1980s.[9] Regardless of manufacturing improvements, the current US Food and Drug Administration label for all cephalosporins warns of a 10% cross-reactivity between penicillins and cephalosporins.[9,10] Contemporary data have established that cross-reactivity between penicillins and cephalosporins is primarily based on the R1 side chain, not the shared β-lactam ring structure.[11,12] Cefazolin does not share an R1 side chain with other penicillins or cephalosporins.[9,13,14] This difference in R1 side chains should make cefazolin safe to administer in patients with a penicillin allergy. However, few studies have been published evaluating the incidence of allergy, or hypersensitivity, to natural penicillins (ie, penicillin, amoxicillin, and ampicillin) and cefazolin.

The primary outcome of this systematic review and meta-analysis is the incidence of dual allergy to cefazolin and natural penicillins. In addition, we aimed to identify variables associated with between-study differences in dual allergy between penicillins and cefazolin. The term *cross-reactivity* was not used as the primary outcome because it implies a biological reaction based on a common chemical structure that is unlikely between cefazolin and penicillins.

Key Points

Question What is the incidence of dual allergy to cefazolin and natural penicillins?

Findings This systematic review and meta-analysis included 6147 patients from 77 studies. Forty-four patients were identified as allergic to a natural penicillin and cefazolin, resulting in a meta-analytical frequency of 0.7%.

Meaning The low frequency of penicillin-cefazolin dual allergy suggests that most patients should receive cefazolin regardless of penicillin allergy history.

Methods

Eligibility Criteria

We included observational studies in which the primary outcome of dual allergy to a natural penicillin (penicillin, amoxicillin, or ampicillin) and cefazolin could be assessed. Included studies consisted of (1) those assessing patients with self-reported or confirmed allergy to a natural penicillin who were exposed to cefazolin or tested for cefazolin allergy and (2) those assessing patients with self-reported or confirmed cefazolin allergy who were exposed to, or tested for, penicillin allergy. We did not apply exclusion criteria based on publication date, status, or language. This systematic review with meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline.

Information Sources and Search Methods

Two of us (B.S.-P. and M.N.J.) searched 3 electronic bibliographic databases (MEDLINE/PubMed, Web of Science, and Embase) for articles published from database inception to July 31, 2020. Search queries are listed in eTable 1 in the Supplement. Searches on electronic bibliographic databases were complemented by reviewing the references of included primary studies and by contacting authors.

Study Selection and Data Collection

After duplicates were removed, each study was independently assessed by 2 reviewers (all authors in pairs), first by title and abstract screening and second by full-text reading. Non–English-language articles were translated before full-text reading. Data from included primary studies were independently extracted by 2 reviewers (all authors in pairs) using purposely built online forms. For each study, we retrieved information on variables that potentially explained differences in the results, including publication year, country, sampling method (consecutive or convenience), clinical setting, participants' age group, and characteristics of the index reactions. Index reaction details included culprit drugs, diagnostic tests, clinical manifestations, and timing of allergic reaction. Immediate reactions were defined as those occurring during the first hour after exposure to the culprit drug, with the remaining reactions classified as nonimmediate.

For studies in which the index allergic reaction was a penicillin, we retrieved data on the number of patients with self-reported or confirmed penicillin allergy as well as the number of those who also had a cefazolin allergy, gathering information about whether the latter was confirmed by skin testing, in vitro testing (ie, specific IgE test), drug challenges (ie, a controlled or stepwise drug exposure), and/or drug exposure for prophylactic or therapeutic purposes. Likewise, for studies in which the index allergic reaction was cefazolin, we retrieved information on the number of patients with cefazolin allergy and those who also had a penicillin allergy (as well as on how the latter was confirmed).

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Disagreements between reviewers in data selection or extraction were solved by consensus. Authors of primary studies were contacted to provide missing information, including from unpublished studies.

Quality Assessment

The quality of included primary studies was independently assessed by 2 researchers (B.S.-P., K.G.B., and/or M.N.J.) using an adaptation from the checklist developed by Hoy et al[15] for prevalence studies. Of the 11 items, we used 5 that were deemed adequate for this study, namely (1) if the sample was representative of the target population; (2) if random or consecutive sampling methods were used; (3) if the likelihood of nonresponse bias was minimal (ie, if >75% participants with index allergy to penicillins underwent testing and/or exposure to cefazolin or vice versa); (4) if an acceptable or sufficiently complete definition of allergic or hypersensitivity reaction was used in the study; and (5) if the same methods of assessment and data collection were used for all study participants.

Quantitative Synthesis of Results

We performed bayesian meta-analysis following a random-effects model based on a binomial likelihood to estimate the frequency of allergic reactions to cefazolin in patients with history of penicillin allergy and the frequency of allergic reactions to penicillins in patients with history of cefazolin allergy.[16] We opted for this approach because it can more adequately handle proportions equal to 0, which were frequent in included primary studies. By contrast, a frequentist approach would require adding a continuity correction (eg, 0.5) to the proportions equal to 0, which might bias meta-analytical results.

Bayesian methods yield probability distributions of the parameters of interest (posterior probabilities) based on prior probability distributions and on the observed data. In this study, we used meta-analytical methods to estimate the posterior probabilities of the frequency of developing allergic reactions. Of those posterior probabilities, we retrieved the median value and the respective 95% credible intervals (CrIs) (range of values within which, with 95% probability, the true frequency of allergic reactions lies). For building bayesian models, we used uninformative prior distributions for the effect size measure and for the tau parameter (dnorm [0,0.00001] and dgamma [0.00001,0.00001], respectively).

We assessed heterogeneity (existence of differences beyond those that would be expected by random sampling only) by computing estimates of the I^2 statistic, with I^2 greater than 50% indicative of severe heterogeneity. Heterogeneity sources were explored by means of meta-regression methods and subgroup analysis. Exponentials of meta-regression coefficients were interpreted as odds ratios (ORs).

Meta-analysis was performed using the rjags package of R software, version 4.0.0 (R Foundation for Statistical Computing). For each analysis, we ran at least 30 000 iterations with a burn-in of 15 000 sample iterations.

Results

The search yielded 3218 records, of which 307 were duplicates (**Figure 1**). After the screening phase, 317 articles remained. A total of 77 met the inclusion criteria and were included in this systematic review. Of note, the full texts of 9 articles were not available even after contacting the authors. Eight articles were not included despite meeting the eligibility criteria of this systematic review because the participants had also been assessed in included publications with larger samples.

Of the 77 included primary studies, 43 were cohort studies (eTable 2 in the Supplement), which were quantitatively assessed by meta-analysis. The remainder were case reports, whose description is available in eTable 3 in the Supplement.

Frequency of Cefazolin Allergy in Patients With Penicillin Allergy

We included 30 primary studies[17-46] that assessed the frequency of cefazolin allergy in series of patients with self-reported or confirmed penicillin allergy (**Table 1**). The included primary studies[17-46] had been published between 1976 and 2020, assessing a total of 6001 participants. In 9 studies,[18,20,25,34,36,38-40,44] penicillin allergy was confirmed by diagnostic testing (skin, in vitro, and/or drug challenges). In 13 studies,[18,20,22,23,25,31,32,34,37-40,44] cefazolin allergy was assessed by means of skin tests or drug challenges, whereas prophylactic or therapeutic introduction of cefazolin occurred in 18 studies.[17,19,21,24,26-30,33,35-37,41-43,45,46]

Cefazolin allergy was identified in 44 participants, resulting in a meta-analytical frequency of 0.7% (95% CrI, 0.1%-1.7%; I^2 = 74.9%) (**Figure 2**A). Such frequency was lower for participants with self-reported penicillin allergy (0.6%; 95% CrI, 0.1%-1.3%; I^2 = 54.3%) than for those with confirmed allergic reactions (3.0%; 95% CrI, 0.01%-17.0%; I^2 = 88.2%) (OR, 0.4; 95% CrI, 0.02-1.8; 92% probability of OR <1).

Thirteen studies[17,19-21,25,29-31,33,35,41,42,46] exclusively assessed surgical patients (n = 3884), among whom 0.7% had confirmed allergy to cefazolin (95% CrI, 0%-3.3%; I^2 = 85.5%). Unconfirmed penicillin allergy was associated with lower risk of cefazolin allergy (OR, 0.01; 95% CrI, <0.01-0.1). Ten studies[17,19,21,29,30,33,35,41,42,46] described patients with unconfirmed penicillin allergy who had been exposed to perioperative cefazolin, resulting in a dual allergy frequency of 0.1% (95% CrI, 0.1%-0.3%; I^2 = 13.1%).

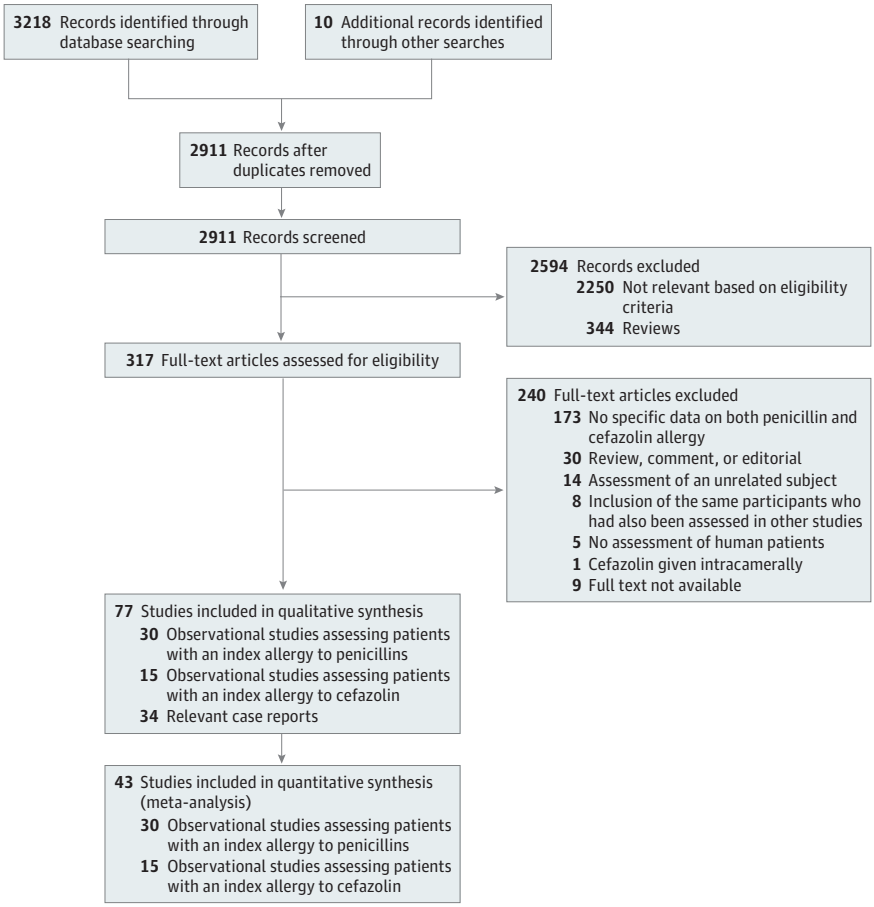
Frequency of Penicillin Allergy in Patients With Cefazolin Allergy

We included 15 primary studies[25,39,47-59] that assessed the frequency of penicillin allergy in series of patients with cefazolin allergy (**Table 2**). The included primary studies[25,39,47-59] assessed a total of 146 participants. All patients had confirmed cefazolin allergy. Seven studies[47,49,50,52,53,57,58] included only patients who had had anaphylactic reactions to cefazolin. Penicillin allergy was assessed by means of drug challenge or exposure in 9 studies.[47,49-54,57,59] Thirteen studies[25,39,48-51,53-59] assessed penicillin allergy status by skin tests.

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram for Study Selection



Two studies assessed both patients with index allergy to penicillins tested for cefazolin and patients with index allergy to cefazolin tested for penicillins.

Penicillin allergy was confirmed in 16 participants, corresponding to a meta-analytical frequency of 3.7% (95% CrI, 0.03%-13.3%; I^2 = 64.9%) (Figure 2B). Lower heterogeneity was observed when assessing studies that only assessed immediate reactions (subgroup frequency, 2.8%; 95% CrI, 0.8%-4.9%; I^2 = 3.4%).

Eight studies[25,47,49,50,52,53,57,58] exclusively assessed surgical patients (n = 104), among whom 4.4% had confirmed allergy to penicillins (95% CrI, 0%-23.0%; I^2 = 75.5%). In all surgical studies[25,47,49,50,52,53,57,58] that exclusively assessed immediate reactions to cefazolin, all participants had anaphylaxis as their index reaction. Among these patients, 2.7% (95% CrI, 0.8%-3.9%; I^2 = 0.9%) had confirmed allergy to penicillin.

Quality Assessment

A risk of bias graph is presented in **Figure 3**, whereas the risk of bias summary for each included primary study is presented in eTable 4 in the Supplement. Overall, the items with the largest number of studies classified as having a high risk of bias concerned the sampling methods and the possibility of nonassessment bias. Eight studies[38,40,44,50,52,53,57,59] had all items classified as low risk of bias.

Discussion

This systematic review and meta-analysis assessed the frequency of patient allergies to a natural penicillin and cefazolin. The study assessed 6001 patients with an allergy to a natural penicillin who subsequently received or were tested for an allergy to cefazolin. Forty-four of these patients were identified as allergic to cefazolin, resulting in a meta-analytical frequency of 0.7%. The frequency of dual allergy was higher among patients with confirmed penicillin allergies (3.0%) compared with patients with self-reported or unconfirmed penicillin allergies (0.6%). The meta-analytical frequency of dual allergy for surgical patients was 0.7%, with surgical patients with unconfirmed penicillin allergies having an even lower rate of dual allergy (0.1%). A total of 146 patients had an index allergy to cefazolin and subsequently received or were tested for an allergy to a natural penicillin; in this cohort, the frequency of dual allergy was 3.7% and 4.4% considering surgical patients only. These results are consistent with those from Picard et al,[60] who identified a dual allergy frequency for penicillin-cefazolin of 1.3% based on 3 primary studies that involved a total of 75 patients.

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Table 1. Meta-regression and Subgroup Analyses for the Frequency of Cefazolin Allergy in Patients With Index Self-Reported or Confirmed Allergy to Penicillins

Variable[a]	No. of studies	No. of patients	Subgroup analyses		Univariable meta-regression, OR (95% CrI)	Probability of OR <1, %
			Severe reaction, % (95% CrI)	I^2, %		
All primary studies						
All	30	6001	0.7 (0.1-1.7)	74.9	NA	NA
Year of publication	30	6001	NA	NA	1.00 (0.98-1.02)	49
Geographic region						
North America	21	5547	0.8 (0.1-2.2)	75.2	5.03 (0.11-28.00)[b]	37
Europe	7	431	0.6 (0-1.0)	7.9	NA	
Setting						
Surgical patients	13	3884	0.7 (0-3.3)	85.5	2.39 (0.09-12.01)[b]	48
Pregnant women	3	1405	0.7 (0-2.3)	29.2	NA	NA
Referenced patients to an outpatient clinic	7	490	1.0 (0-4.8)	81.1	NA	NA
Inpatients and ED patients	7	222	2.7 (0.7-6.1)	16.8	NA	NA
Sampling method						
Convenience	20	5450	0.5 (0.1-1.4)	74.6	2.27 (0.03-9.01)[b]	67
Consecutive	6	520	2.5 (0-14.7)	77.3	NA	
Index allergy to penicillins						
Unconfirmed by diagnostic tests	21	5487	0.6 (0.1-1.3)	54.3	0.36 (0.02-1.83)[b]	92
Confirmed by diagnostic tests	9	514	3.0 (0-17.0)	88.2	NA	NA
Exclusion of studies assessing nonimmediate index reactions[c]	26	5843	0.7 (0.2-1.8)	72.5	NA	NA
Assessment of cefazolin allergy						
Skin tests	8	455	3.7 (0-28.9)	91.4	8.75 (0.41-42.67)	9
Prophylactic or therapeutic exposure	18	5266	0.4 (0.1-0.8)	41.0	0.19 (0.01-0.82)	98
Studies' methodologic quality	30	6001	NA	NA	0.91 (0.30-2.37)[d]	69
Classification for most items						
Low risk of bias	16	3607	0.7 (0.1-1.9)	62.5	1.54 (0.08-8.99)[b]	63
High risk of bias	14	2394	0.8 (0-3.3)	83.5	NA	NA
Studies exclusively assessing surgical patients						
Year of publication	13	3884	NA	NA	0.98 (0.96-0.99)	99
Geographic region	13	3884	NR[e]	NR[e]	NR[e]	NA
Sampling method						
Convenience	10	3738	0.4 (0-2.1)	86.8	1.30 (<0.01-6.00)[b]	93
Consecutive	2	141	NR[f]	NR[f]	NR[f]	NA
Index allergy to penicillins						
Unconfirmed by diagnostic tests	11	3860	0.3 (0-1.0)	66.5	0.01 (<0.01-0.06)[b]	99
Confirmed by diagnostic tests	2	24	NR[f]	NR[f]	NR[f]	NA
Exclusion of studies assessing nonimmediate index reactions	11	3749	1.3 (0-6.1)	85.3	NA	NA
Assessment of cefazolin allergy						
Skin tests	2	24	NR[f]	NR[f]	NR[f]	NA
Prophylactic or therapeutic exposure	10	3721	0.1 (0.1-0.3)	13.1	0.01 (<0.01-0.06)[b]	>99
Studies' methodologic quality						
Classification of most items						
Low risk of bias	7	2966	0.8 (0-9.4)	77.3	NR[f]	NA
High risk of bias	6	918	2.0 (0-12.5)	95.7	NR[f]	NA

Abbreviations: CrI, credible interval; ED, emergency department; NA, not applicable; NR, not reported; OR, odds ratio.

[a] For some variables, the number of studies and patients in the categories do not sum to 30 and 6001, respectively, because there were studies belonging to other categories (with insufficient numbers of patients to be used in subgroup analyses or meta-regression) or with missing information.

[b] Compared with all other categories of the respective variable.

[c] Subgroup analysis restricted to data from participants with index reactions of immediate type (available from 4 studies) of 0.6% (95% CrI, 0.1%-1.1%). Subgroup analysis restricted to data from participants with index reactions of nonimmediate type (available from 6 studies) of less than 0.1% (95% CrI, 0%-1.2%).

[d] Meta-regression on the number of items classified as low risk of bias.

[e] All studies that exclusively assessed surgical patients were performed in North America.

[f] Analysis not possible on account of the insufficient number of primary studies or participants.

Debate about cross-reactivity vs dual allergy among β-lactam antibiotics remains a contemporary issue.[61] It is possible that some patients experience a cross-reactivity to the β-lactam ring structure based on the higher frequency of dual peni-

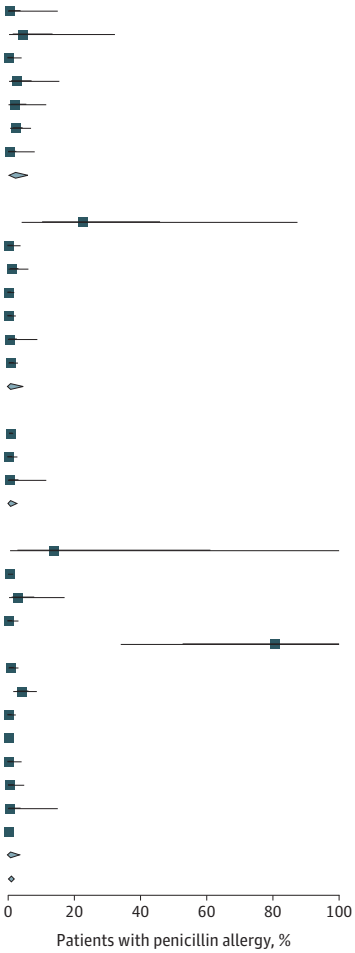
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Figure 2. Forest Plots on the Frequency of Dual Allergy to Penicillins and Cefazolin

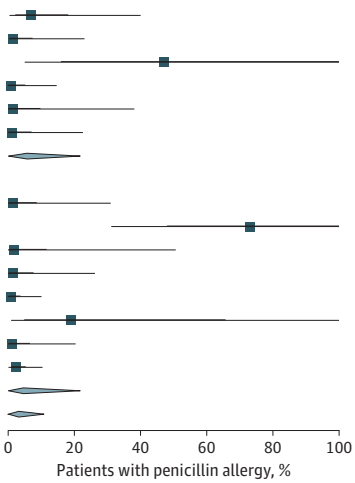
A Cefazolin allergy in patients with allergy to penicillins

Study	Patients with penicillin allergy, No./total No.	Patients with penicillin allergy, % (95% CrI)
Inpatients and ED patients		
Castleton et al,[24] 1976	0/5	0.4 (0-13.5)
Pines et al,[37] 1977	1/10	4.4 (0.2-32.6)
Fonacier et al,[28] 2005	0/37	0.2 (0-3.6)
Blumenthal et al,[23] 2015	1/21	2.5 (0.1-15.1)
Turner et al,[45] 2018	1/29	1.9 (0.1-11.2)
Blumenthal et al,[22] 2019	3/106	2.4 (0.6-6.6)
Maguire et al,[32] 2020	0/14	0.3 (0-7.2)
Subtotal 2.7% (95% CrI, 0.7%-6.1%); I^2 = 16.8%		
Mixed outpatients		
Aihara and Ikezawa,[18] 1987	3/11	23.4 (4.4-88.6)
Novalbos et al,[34] 2001	0/41	0.2 (0-3.4)
Park et al,[36] 2010	1/59	1.1 (0.1-5.8)
Ponvert et al,[38] 2011	0/150	0.1 (0-1.2)
Jimenez-Rodriguez et al,[39] 2019	0/86	0.2 (0-1.9)
Trubiano et al,[44] 2019	0/12	0.3 (0-8.0)
Romano et al,[40] 2020	1/131	0.6 (0-1.7)
Subtotal 1.0% (95% CrI, 0%-4.8%); I^2 = 81.1%		
Pregnant women		
Desai et al,[26] 2017	10/1332	0.7 (0.4-1.3)
Desravines et al,[27] 2019	0/65	0.2 (0-2.3)
Thellier et al,[43] 2020	0/8	0.4 (0-10.3)
Subtotal 0.7% (95% CrI, 0%-2.3%); I^2 = 29.2%		
Surgical patients		
Beam and Spooner,[20] 1984	1/2	14.9 (0.4-100)
Goodman et al,[29] 2001	1/299	0.3 (0-1.3)
Park et al,[35] 2006	1/19	2.7 (0.2-16.9)
Haslam et al,[30] 2012	0/54	0.2 (0-2.7)
Cook et al,[25] 2014	11/22	82.6 (34.6-100)
Beltran et al,[21] 2015	1/127	0.6 (0.1-2.8)
Laaouaj et al,[31] 2016	6/139	4.0 (1.5-8.5)
Michaud and Yen,[33] 2017	0/81	0.2 (0-2.0)
Anstey et al,[19] 2019	2/2570	0.1 (0-0.2)
Schlosser et al,[41] 2020	0/38	0.2 (0-3.5)
Stone et al,[42] 2019	0/28	0.3 (0-4.4)
Ahmad et al,[17] 2020	0/5	0.4 (0-13.6)
Lam et al,[46] 2020	0/500	0.1 (0-0.5)
Subtotal 0.7% (95% CrI, 0%-3.3%); I^2 = 85.5%		
All studies 0.7% (95% CrI, 0.1%-1.7%); I^2 = 74.9%		



B Penicillin allergy in patients with index cefazolin allergy

Study	Patients with penicillin allergy, No./total No.	Patients with penicillin allergy, % (95% CrI)
Mixed outpatients		
Pipet et al,[54] 2011	1/10	6.8 (0.4-40.3)
Romano et al,[55,56] 2010	0/8	1.1 (0-18.7)
Chng et al,[48] 2016	2/4	47.4 (4.9-100)
Laguna et al,[51] 2018	0/11	0.9 (0-14.4)
Jimenez-Rodriguez et al,[39] 2019	0/3	1.5 (0-37.8)
Yuson et al,[59] 2019	0/6	1.2 (0.-23.0)
Subtotal 6.4% (95% CrI, 0.1%-23.1%); I^2 = 37.3%		
Surgical patients		
Warrington and McPhillips,[58] 1996	0/4	1.4 (0-29.8)
Cook et al,[25] 2014	11/24	73.6 (31.2-100)
Alves et al,[47] 2015	0/2	1.7 (0-51.7)
Kuhlen et al,[50] 2016	0/5	1.3 (0-25.4)
Uyttebroek et al,[57] 2016	0/19	0.7 (0-9.8)
Farinha et al,[49] 2018	1/3	18.7 (0.9-100)
Mota et al,[53] 2018	0/7	1.1 (0-20.1)
Li et al,[52] 2019	1/40	2.2 (0.2-10.1)
Subtotal 4.4% (95% CrI, 0%-23.0%); I^2 = 75.5%		
All studies 3.7% (95% CrI, 0%-13.3%); I^2 = 64.9%		



CrI indicates credible interval; ED, emergency department. The width of the diamonds corresponds to the length of the 95% CrI for the meta-analytical pooled result. Thin lines indicate the length of the 95% CrI for each primary study. Thick lines indicate the length of the 68% CrI for each primary study.

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Table 2. Meta-Regression and Subgroup Analyses for the Frequency of Penicillin Allergy in Patients With Index Cefazolin Allergy

Variable[a]	No. of studies	No. of patients	Subgroup analyses		Univariable meta-regression, OR (95% CrI)	Probability of OR <1, %
			Severe reaction, % (95% CrI)	I^2, %		
All	15	146	3.7 (0-13.3)	64.9	NA	NA
Year of publication	15	146	NA	NA	0.98 (0.95-1.01)	85
Geographic region						
Europe	9	63	3.7 (0-11.0)	11.1	3.53 (<0.01-8.11)[b]	86
North America	3	33	NR[c]	NR[c]	NA	NA
Setting						
Surgical patients	8	104	4.4 (0-23.0)	75.5	NR[c]	NA
Referenced patients to an outpatient clinic	7	42	6.4 (0.1-23.1)	37.3	NA	NA
Sampling method						
Convenience	8	64	10.0 (0-54.1)	70.6	NR[c]	NA
Consecutive	5	77	1.1 (0-4.7)	22.4	NA	NA
Timing of index reactions						
Immediate	12	115	2.8 (0.8-4.9)	3.4	0.04 (0.01-0.11)[b]	99
Immediate and nonimmediate	3	31	NR[c]	NR[c]	NA	NA
Clinical manifestations of index reactions						
Anaphylaxis only[d]	7	80	2.7 (0.8-3.9)	0.9	3.46 (<0.01-10.50)[b]	87
Different reactions	8	66	10.6 (0-48.8)	66.4	NA	NA
Assessment of penicillin allergy						
Skin tests	13	104	3.7 (0-16.6)	72.1	NR[c]	NA
Drug challenge or exposure	9	103	2.5 (0.7-5.6)	3.5	0.67 (0.01-1.46)[b]	96
Studies' methodologic quality						
Classification of most items						
Low risk of bias	11	109	4.6 (0.3-9.4)	11.9	0.49 (0.09-1.40)[e]	95
High risk of bias	4	37	15.2 (0-100)	93.4	NA	NA

Abbreviations: CrI, credible interval; NA, not applicable; NR, not reported; OR, odds ratio.

[a] For some variables, the number of studies and patients in the categories do not sum to 15 and 146, respectively, because there were studies belonging to other categories (with insufficient numbers of patients to be used in subgroup analyses or meta-regression) or with missing information.

[b] Compared with all other categories of the respective variable.

[c] Analysis not possible on account of the insufficient number of primary studies or participants.

[d] All primary studies concerned surgical patients.

[e] Meta-regression on the number of items classified as low risk of bias.

cillin and cefazolin hypersensitivity from studies[12,18,25,62] that used skin testing as their diagnostic method. However, it may be that this higher risk is only observed in patients with IgE-mediated allergies or that it may mirror false-positive results because the positive predictive value of skin tests appears limited.[63] An alternative explanation of a higher dual allergy rate for patients with a confirmed penicillin allergy is multiple drug hypersensitivity syndrome. The prevalence of multiple drug hypersensitivity syndrome was 1.2%, according to a study by Blumenthal et al[64] that assessed nearly 800 000 patients.

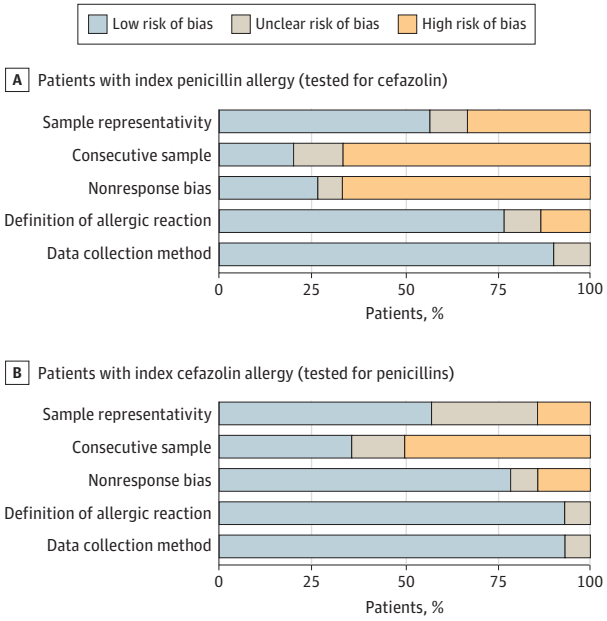
One of the most intriguing studies to assess the controversy of cross-reactivity and multiple drug allergy syndrome is from Strom et al,[65] who analyzed the United Kingdom General Practice Research Database. This large case-control study found that patients with no history of drug allergy had a lower frequency of allergic reactions to sulfonamide nonantibiotics (1.1%) compared with patients with history of allergic reactions to sulfonamide antibiotics (9.9%) and patients with a history of penicillin allergy (14.2%). Because penicillins and sulfa drugs are not chemically similar, the authors concluded that the high rate of allergic reactions between sulfa antibiotics and sulfa nonantibiotics was attributable to a greater predisposition to allergic reactions in general among patients with a history of medication allergies.[66,67] Although the current meta-analysis did not assess the frequency of allergic reactions to a non-β-lactam, we were able to identify 19 primary studies (among the 240 articles that were fully read in the selection stage of this systematic review) that reported on the frequency of cefazolin allergic reactions in patients with no registration of penicillin allergy. On the basis of data from 13 149 patients, we obtained a meta-analytical frequency of 0.6% (95% CrI, 0.1%-1.2%; I^2 = 59.0%), close to that observed for patients with penicillin allergy. In addition, our observed low rate of dual allergy should increase practitioner confidence in using cefazolin in patients allergic to penicillins, particularly when data suggest cefazolin is the optimal antibiotic, such as perioperative prophylaxis.

In the performed meta-analyses, severe heterogeneity was observed. A meta-regression and subgroup analyses were performed to identify potential variables that could explain dif-

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Figure 3. Risk of Bias for Included Primary Studies



ferences across primary studies. Higher rates of dual allergy were seen with studies from the 1970s and 1980s[18,20,37] and those with small samples.[25,48,49,54] We also observed that having an unconfirmed penicillin allergy and being prophylactically or therapeutically exposed to cefazolin without previous testing was associated with lower risk of developing a cefazolin hypersensitivity reaction. This finding may be attributable to a selection bias in the real-world observational studies, with practitioners selecting lower-risk patients with penicillin allergy to prophylactically or therapeutically receive cefazolin. Notably, severe heterogeneity was not identified when performing a meta-analysis limited to surgical patients who self-reported penicillin allergy and received cefazolin without previous testing. Unfortunately, there was no information available in the primary studies on several variables that may also contribute to explain heterogeneity, such as the proportion of patients with allergy to other medications or the presence of other immunologic comorbidities.

Strengths and Limitations

This study has strengths. To our knowledge, this is the most extensive systematic review and meta-analysis conducted to assess the frequency of cross-reactivity between natural penicillins and cefazolin and the first fully dedicated to this research question with the aim of improving perioperative antibiotic prophylaxis. One prior study[60] assessed the cross-reactivity rate for penicillin-cefazolin in 3 primary studies that involved a total of 75 patients, finding a 1.3% reaction rate. Our bayesian methods allowed us to appropriately summarize data that included 0 cells. We also performed meta-regression and subgroup analyses to explore sources of heterogeneity, identifying variables that explained differences across studies. To minimize publication and information bias, we searched 3 different electronic bibliographic databases without applying exclusion criteria based on the date or language of publication and contacted authors whenever relevant information was missing. Relevance to clinical practice is the final strength of this study because the results could lead to the standardization of preoperative cefazolin in patients with unconfirmed penicillin allergies, thus decreasing surgical site infections.

The study also has limitations, mostly related to the methods of the included primary studies. The possibility of selection bias exists. It is likely that only a small percentage of patients with a natural penicillin allergy who get tested for and/or exposed to cefazolin are described in the literature. In addition, in many primary studies, not all patients reporting a penicillin allergy were prophylactically or therapeutically exposed to cefazolin, which may have biased our sample. Unfortunately, information was lacking on whether those patients who did not receive cefazolin tended to be different (eg, regarding the symptoms or severity of their index allergy) from those who were exposed to this drug. A possibility of information bias also exists. For example, surgery studies reporting only reactions in the surgery setting would miss delayed hypersensitivity reactions. The most significant limitation, however, is the lack of specific information about each allergic reaction because cross-reactivity is not plausible in patients who experience different physiologic reactions to each antibiotic (eg, anaphylaxis [IgE mediated] to cefazolin and contact dermatitis [T-cell mediated] to penicillin). Without individual-level data describing risk factors for medication allergies, including existing immunologic diseases and history of other medication allergies, we could not clarify cross-study differences or distinguish between probability of cross-reactivity and multiple drug hypersensitivity syndrome. Finally, the small number of patients with index cefazolin allergy limited meta-regression analyses.

Conclusions

This systematic review and meta-analysis found that cross-reactivity between penicillins and cefazolin was rare, with hypersensitivity reactions to cefazolin occurring in less than 1% of patients with unconfirmed penicillin allergy and in 3% of patients with allergy confirmation. Similar results were observed when specifically analyzing the surgical setting, with only 1 hypersensitivity reaction in each 1000 patients with unconfirmed penicillin allergy receiving cefazolin. These results suggest that most patients with a penicillin allergy history undergoing surgical prophylaxis may safely receive cefazolin. The exception may be those patients with confirmed penicillin allergy or a history of severe reactions, in whom additional care is warranted. The increased incidence of dual allergy may not be specific to cefazolin and may extend to other perioperative antibiotics. Future primary studies and systematic reviews should assess the frequency of allergic reactions to other antibiotics in surgical patients with confirmed penicillin allergy. These reassuring findings are broadly relevant to surgery because there are clear patient care consequences of avoiding cefazolin for surgical prophylaxis.

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ARTICLE INFORMATION

Accepted for Publication: December 17, 2020.

Published Online: March 17, 2021. doi:10.1001/jamasurg.2021.0021

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Concept and design: Sousa-Pinto, Blumenthal, Courtney, Jeffres.
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Statistical analysis: Sousa-Pinto, Jeffres.
Administrative, technical, or material support: Blumenthal, Mancini, Jeffres.
Supervision: Blumenthal, Jeffres.

Conflict of Interest Disclosures: Dr Blumenthal reported receiving grants from the National Institute of Allergy and Infectious Diseases and the American Academy of Allergy, Asthma, and Immunology Foundation during the conduct of the study and grants from Crico, the risk management foundation of Harvard Medical School, outside the submitted work. In addition, Dr Blumenthal has a patent for the Beta-Lactam Allergy Clinical Decision Support Tool licensed by Persistent Systems. No other disclosures were reported.

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Supplementary Online Content

Sousa-Pinto B, Blumenthal KG, Courtney L, Mancini CM, Jeffres MN. Assessment of the frequency of dual allergy to penicillins and cefazolin: a systematic review and meta-analysis. *JAMA Surg.* Published online March 17, 2021. doi:10.1001/jamasurg.2021.0021

eTable 1. Search Queries Used in the Different Electronic Bibliographic Databases

eTable 2. Characteristics of Included Cohort Studies

eTable 3. Characteristics of Case Reports Included

eTable 4. Risk of Bias of Individual Studies

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eTable 1. Search queries used in the different electronic bibliographic databases

Database	Search query
MEDLINE/ PubMed	(hypersensitivit*[Text Word] OR hypersensitivity[Text Word] OR allerg*[Text Word] OR allergy[Text Word] OR cross-reactiv*[Text Word]) AND (penicillin*[Text Word] OR amoxicillin[Text Word] OR ampicillin[Text Word] OR aminopenicillin[Text Word]) AND (cefazolin[Text Word] OR cephazolin[Text Word] OR cephazoline[Text Word] OR ancef[Text Word] OR cephalosporin*[Title/Abstract])
Web of Science	(TS=hypersensitivit* OR TS=hypersensitivity OR TS=allerg* OR TS=allergy OR TS=cross-reactiv*) AND (TS=penicillin* OR TS=amoxicillin OR TS=ampicillin OR TS=aminopenicillin) AND (TS=cefazolin OR TS=cephazolin OR TS=cephazoline OR TS=ancef OR TS=cephalosporin*)
Embase	(hypersensitiv*:ti,ab,kw OR hypersensitivity:ti,ab,kw OR allerg*:ti,ab,kw OR allergy:ti,ab,kw OR 'cross react*':ti,ab,kw OR 'cross reaction':ti,ab,kw) AND ('penicillin derivative':ti,ab,kw OR penicillin:ti,ab,kw OR amoxicillin:ti,ab,kw OR ampicillin:ti,ab,kw OR aminopenicillin:ti,ab,kw) AND (cefazolin:ti,ab,kw OR cephazolin:ti,ab,kw OR cephazoline:ti,ab,kw OR ancef:ti,ab,kw OR 'cephalosporin derivative':ti,ab,kw)

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eTable 2. Characteristics of Included Cohort Studies

Source, Country	Setting	Age group	Index HS onset	Penicillin HS diagnosis method	Cefazolin HS diagnosis method	N of assessed participants	N of participants with dual allergy (%)
Patients with index penicillin allergy and assessed for cefazolin allergy							
Ahmad et al[17] 2020, USA	Surgical	Not specified	Not specified	Self-reported	Exposure	5	0 (0)
Aihara et al[18] 1987, Japan	Outpatient	Adults, children	Delayed	Skin test, provocation test	Skin test	11	3 (27.3)
Anstey et al[19], 2019, USA	Surgical	Adults	Immediate, delayed	Self-reported	Exposure	2570	2 (0.1)
Beam et al[20] 1984, USA	Surgical	Adults	Immediate	Skin test	Skin test	2	1 (50.0)
Beltran et al[21] 2015, USA	Inpatient	Adults, children	Immediate, delayed	Self-reported	Exposure	127	1 (0.8)
Blumenthal et al[22] 2019, USA	Inpatient	Adults, children	Immediate, delayed	Self-reported	Provocation test	106	3 (2.8)
Blumenthal et al[23] 2015, USA	Inpatient	Adults	Immediate, delayed	Self-reported	Provocation test	21	1 (4.8)
Castleton et al[24] 1976, UK	Inpatient	Adults	Not specified	Self-reported	Exposure	5	0 (0)
Cook et al[25] 2014, USA	Surgical	Adults	Immediate, delayed	Skin test	Skin test	22	11 (50.0)
Desai et al[26] 2017, USA	Pregnant	Adults	Immediate, delayed	Self-reported	Exposure	1332	10 (0.8)
Desravines et al[27] 2019, USA	Pregnant	Adults	Not specified	Self-reported	Exposure	65	0 (0)
Fonacier et al[28] 2005, USA	Surgical	Adults, children	Immediate, delayed	Self-reported	Exposure	37	0 (0)
Goodman et al[29] 2001, USA	Surgical	Adults	Not specified	Self-reported	Exposure	299	1 (0.3)
Haslam et al[30] et al. 2012, Canada	Surgical	Adults	Delayed	Self-reported	Exposure	54	0 (0)
Laaouaj et al.[31] 2016, USA	Surgical	Adults	Immediate, delayed	Self-reported	Provocation test	139	6 (4.3)

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Lam et al.[46] 2020, USA	Surgical	Adults	Not specified	Self-reported	Exposure	500[a]	0 (0)
Maguire et al.[32] 2020, USA	Emergency department	Adults	Not specified	Self-reported	Provocation test	14	0 (0)
Michaud et al[33] 2017, Canada	Surgical	Adults	Delayed	Self-reported	Exposure	81	0 (0)
Novalbos et al[68] 2001, Spain	Outpatient	Adults	Immediate, delayed	Skin test, provocation test	Skin test, provocation test	41	0 (0)
Park et al.[35] 2006, USA	Surgical	Adults, children	Immediate, delayed	Self-reported	Exposure	19	1 (5.3)
Park et al[36] 2010, USA	Outpatient	Adults	Not specified	Skin test	Exposure	59	1 (1.7)
Pines et al[37] 1977, UK	Inpatient	Adults	Not specified	Self-reported	Provocation test, exposure	10	1 (10.0)
Ponvert et al[38] 2011, France	Outpatient	Children	Not specified	Skin test	Skin test	150	0 (0)
Rodriguez et al[39] 2019, Spain	Outpatient	Adults	Immediate, delayed	Skin test, *in vitro*, provocation test	Skin test	86	0 (0)
Romano et al[40] 2020, Italy	Outpatient	Adults	Immediate	Skin test, provocation test	Skin test, provocation test	131	1 (0.8)
Schlosser et al[41] 2020, USA	Surgical	Adults	Immediate, delayed	Self-reported	Exposure	38	0 (0)
Stone et al[42] 2019, USA	Surgical	Adults	Immediate, delayed	Self-reported	Exposure	28	0 (0)
Thellier et al[43] 2020, France	Obstetrics	Adults	Immediate, delayed	Self-reported	Exposure	8	0 (0)
Trubiano et al[44] 2019, Australia	Outpatient	Adults	Delayed	Skin test, *in vitro*	Skin test	12	0 (0)
Turner et al[45] 2018, USA	Inpatient	Adults	Immediate, delayed	Self-reported	Exposure	29	1 (3.4)
Patients with index cefazolin allergy and assessed for penicillin allergy							
Alves et al[47] 2015, Portugal	Surgical	Adults, children	Immediate, delayed	Provocation test	Skin test, exposure	2	0 (0)
Chng et al[48] 2016, Singapore	Outpatients	Adults, children	Immediate, delayed	Skin test	Skin test, provocation test	4	2 (50.0)

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Cook et al[25] 2014, USA	Surgical	Adults	Immediate, delayed	Skin test	Skin test	24	11 (45.8)
Farinha et al[49] 2018, Portugal	Surgical	Adults, children	Immediate	Skin test, provocation test	Skin test, exposure	3	1 (33.3)
Jimenez-Rodriguez et al[39] 2019, Spain	Outpatient, inpatient	Adults	Immediate	Skin test, *in vitro*	Skin test	3	0 (0)
Kuhlen et al[50] 2016, USA	Surgical	Adults	Immediate	Skin test, provocation test	Skin test, exposure	5	0 (0)
Laguna et al[51] 2018, Spain	Outpatient	Adults	Immediate	Skin test, *in vitro*, provocation test	Skin test, provocation test	11	0 (0)
Li et al[52] 2019, Australia	Surgical	Adults, children	Immediate	Provocation test	Skin test, exposure	40	1 (2.5)
Mota et al[69] 2018, Portugal	Surgical	Adults	Immediate	Skin test, *in vitro*, provocation test	Skin test, exposure	7	0 (0)
Pipet et al[54] 2011, France	Outpatient	Adults, children	Immediate	Skin test, provocation test	Skin test	10	1 (10.0)
Romano et al[56] 2015, Italy	Outpatient	Adults, children	Immediate	Skin test, *in vitro*	Skin test	6	0 (0)
Romano et al[55] 2010, Italy	Outpatient	Adults, children	Immediate	Skin test	Skin test	2	0 (0)
Uyttebroek et al[70] 2016, Belgium	Surgical	Not specified	Immediate	Skin test, *in vitro*, provocation test	Skin test, exposure	19	0 (0)
Warrington et al[58] 1996, Canada	Surgical	Adults	Immediate	Skin test	Skin test, exposure	4	0 (0)
Yuson et al[59] 2019, Australia	Outpatient	Adults	Immediate	Skin test, *in vitro*, provocation test	Skin test, provocation test	6	0 (0)

Abbrviations: HS, hypersensitivity; USA, United States of America; UK, United Kingdom

[a] Estimate sample size based on figure

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eTable 3. Characteristics of case reports Included

Case study	Sex	Age	Index HS onset	Penicillin HS diagnosis method	Cefazolin HS diagnosis method	Dual allergy to penicillin and cefazolin
Patients with index penicillin allergy and assessed for cefazolin allergy						
Ahmed et al[71] 2012,	Not specified	1	Delayed	Skin test	Exposure	No
Alves et al[47] 2015	F	50	Immediate	Skin test	Exposure	No
Berrocal et al[72] 2001	F	70	Immediate	Self-reported	Exposure	Yes
Castro et al[73] 1996	M	3	Delayed	Skin test, provocation test	Skin test	No
Christen et al[74] 1990	M	43	Delayed	Self-reported	Exposure	No
Eser Simsek et al[75] 2018	F	10	Immediate	Skin test, provocation test	Provocation test	No
Fitzgerald et al[76] 2016	Not specified	66	Immediate	Self-reported	Exposure	No
Freedman et al[77] 1997	F	40	Not specified	Self-reported	Exposure	No
Gonzalez-Delgado et al[78] 2006	F	7	Delayed	Skin test, patch test	Skin test, patch test	No
Ho et al[79] 2004	F	74	Delayed	*in vitro*	*in vitro* IgE	No
Jao et al[80] 2006	F	37	Not specified	Self-reported	Exposure	Yes
Kraushar et al[81] 1994	F	72	Not specified	Self-reported	Exposure	Yes
Moake et al[82] 1978	F	39	Immediate	*in vitro*	*in vitro* IgE	Yes
Nemati et al[83] 1981	M	24	Delayed	Self-reported	Exposure	Yes
Philips et al[84] 2001	Not specified	Not specified	Delayed	Skin test, patch test	Skin test	Yes
Vogt et al[85] 1998	F	46	Delayed	Self-reported	Exposure	No
Patients with index cefazolin allergy and assessed for penicillin allergy						
Almeida et al[86] 2017	F	36	Immediate	Provocation test	Skin test, *in vitro* IgE	No
Almeida et al[86] 2017	F	49	Immediate	Provocation test	Skin test, *in vitro* IgE	No
Chan et al[87] 2016	Not specified	Not specified	Immediate	Skin test	Skin test	Yes
Culp et al[88] 2017	M	44	Immediate	Skin test, *in vitro*	Exposure	No

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Gonzalo-Garijo et al[89] 2006	F	66	Not specified	Skin test, provocation test	Skin test	No
Igea et al[90] 1992	F	21	Immediate	Skin test, provocation test	Skin test, *in vitro* IgE	No
Igea et al[90] 1992	F	45	Immediate	Skin test, provocation test	Skin test, *in vitro* IgE	No
Lee et al[91] 2004	F	46	Immediate	Skin test	Skin test	No
Padial et al[92] 2008	Not specified	43	Delayed	Skin test, provocation test	Skin test, provocation test	No
Pinheiro et al[93] 2018	F	31	Delayed	Patch test	Patch test	Yes
Romano et al 2001[94]	F	44	Delayed	Skin test, patch test, *in vitro*, provocation test	Skin test, patch test, *in vitro* IgE, provocation test	No
Romeira et al[63] 2017	Not specified	Not specified	Not specified	Skin test	Skin test	No
Somech et al[95] 2009	M	12	Immediate	Skin test, provocation test	Skin test	No
Tayman et al[96] 2008	F	0	Immediate	Skin test, *in vitro*	Skin test, *in vitro* IgE	Yes
Velasco et al[97] 2009	F	63	Delayed	Skin test, patch test, *in vitro*, provocation test	Skin test, patch test, *in vitro* IgE, provocation test	No
Vieira et al[98] 2009	M	32	Immediate	Skin test, *in vitro*	Skin test	No
Weber et al[99] 1996	F	33	Immediate	Skin test, provocation test	Skin test	No
Wieczorek et al[100] 2008	F	18	Immediate	Skin test, *in vitro*, provocation test	Skin test, *in vitro* IgE	No
Yun et al[101] 2016	M	26	Immediate	Skin test	Skin test	No
Patients with index beta-lactam allergy and assessed for penicillin and cefazolin allergy						
Classen et al[102] 2015	F	24	Not specified	Skin test	Skin test, patch test	Yes
Gonzalo-Garijo et al[89] 2006	M	80	Not specified	Skin test, provocation test	Skin test	No
Rozlucka et al[103] 2019	Not specified	65	Not specified	Skin test, provocation test	Skin test, provocation test	No

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eTable 4. Risk of bias of individual studies

Study	Risk of Bias				
	Representation of the target population	Consecutive sampling	Non-response bias	Definition of the allergic reaction	Consistency of data collection/assessment
Studies assessing patients with index penicillin allergy (tested for cefazolin)					
Castleton B (1976)	🔴	🟡	🟡	🟢	🟢
Pines A (1977)	🟢	🟡	🔴	🟡	🟢
Beam TR (1984)	🔴	🟢	🟢	🟢	🟢
Aihara M (1987)	🟡	🟡	🔴	🟡	🟢
Goodman EJ (2001)	🔴	🔴	🔴	🟢	🟢
Novalbos A (2001)	🟢	🔴	🟢	🟢	🟢
Fonacier L (2005)	🟡	🔴	🔴	🟢	🟢
Park M (2006)	🟢	🔴	🔴	🟢	🟢
Park M (2010)	🟡	🔴	🔴	🟢	🟢
Ponvert C (2011)	🟢	🟢	🟢	🟢	🟢
Haslam S (2012)	🔴	🔴	🔴	🟢	🟢
Cook DJ (2014)	🔴	🔴	🔴	🟢	🟢
Beltran RJ (2015)	🟢	🔴	🔴	🟢	🟢
Blumenthal KG (2015)	🟢	🔴	🔴	🟢	🟢
Laaouaj J (2016)	🔴	🟢	🔴	🟢	🟢

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Desai SH (2017)	●	●	●	●	●
Michaud L (2017)	●	●	●	●	●
Turner NA (2018)	●	●	●	●	●
Astey K (2019)	●	●	●	●	●
Blumenthal KG (2019)	●	●	●	●	●
Desravines N (2019)	●	●	●	●	●
Jimenez-Rodriguez T (2019)	●	●	●	●	●
Schlosser KA (2019)	●	●	●	●	●
Thellier C (2019)	●	●	●	●	●
Trubiano J (2019)	●	●	●	●	●
Ahmad H (2020)	●	●	●	●	●
Lam PW (2020)	●	●	●	●	●
Maguire M (2020)	●	●	●	●	●
Romano A (2020)	●	●	●	●	●
Studies assessing patients with index cefazolin allergy (tested for penicillins)					
Warrington RJ (1996)	●	●	●	●	●
Romano A (2010)	●	●	●	●	●
Pipet A (2011)	●	●	●	●	●
Cook DJ (2014)	●	●	●	●	●
Alves C (2015)	●	●	●	●	●
Romano A (2015)	●	●	●	●	●
Chng H (2016)	●	●	●	●	●
Kuhlen JL (2016)	●	●	●	●	●
Uyttebroek AP (2016)	●	●	●	●	●
Farinha SM (2018)	●	●	●	●	●
Laguna JJ (2018)	●	●	●	●	●
Mota I (2018)	●	●	●	●	●
Jimenez-Rodriguez T (2019)	●	●	●	●	●
Li J (2019)	●	●	●	●	●
Yuson C (2019)	●	●	●	●	●

Legend: ● - Low risk of bias; ● - Unclear risk of bias; ● - High risk of bias.

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Supplementary Online Content

Sousa-Pinto B, Blumenthal KG, Courtney L, Mancini CM, Jeffres MN. Assessment of the frequency of dual allergy to penicillins and cefazolin: a systematic review and meta-analysis. *JAMA Surg.* Published online March 17, 2021. doi:10.1001/jamasurg.2021.0021

eTable 1. Search Queries Used in the Different Electronic Bibliographic Databases

eTable 2. Characteristics of Included Cohort Studies

eTable 3. Characteristics of Case Reports Included

eTable 4. Risk of Bias of Individual Studies

This supplementary material has been provided by the authors to give readers additional information about their work.

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eTable 1. Search queries used in the different electronic bibliographic databases

Database	Search query
MEDLINE/ PubMed	(hypersensitivit*[Text Word] OR hypersensitivity[Text Word] OR allerg*[Text Word] OR allergy[Text Word] OR cross-reactiv*[Text Word]) AND (penicillin*[Text Word] OR amoxicillin[Text Word] OR ampicillin[Text Word] OR aminopenicillin[Text Word]) AND (cefazolin[Text Word] OR cephazolin[Text Word] OR cephazoline[Text Word] OR ancef[Text Word] OR cephalosporin*[Title/Abstract])
Web of Science	(TS=hypersensitivit* OR TS=hypersensitivity OR TS=allerg* OR TS=allergy OR TS=cross-reactiv*) AND (TS=penicillin* OR TS=amoxicillin OR TS=ampicillin OR TS=aminopenicillin) AND (TS=cefazolin OR TS=cephazolin OR TS=cephazoline OR TS=ancef OR TS=cephalosporin*)
Embase	(hypersensitiv*:ti,ab,kw OR hypersensitivity:ti,ab,kw OR allerg*:ti,ab,kw OR allergy:ti,ab,kw OR 'cross react*':ti,ab,kw OR 'cross reaction':ti,ab,kw) AND ('penicillin derivative':ti,ab,kw OR penicillin:ti,ab,kw OR amoxicillin:ti,ab,kw OR ampicillin:ti,ab,kw OR aminopenicillin:ti,ab,kw) AND (cefazolin:ti,ab,kw OR cephazolin:ti,ab,kw OR cephazoline:ti,ab,kw OR ancef:ti,ab,kw OR 'cephalosporin derivative':ti,ab,kw)

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eTable 2. Characteristics of Included Cohort Studies

Source, Country	Setting	Age group	Index HS onset	Penicillin HS diagnosis method	Cefazolin HS diagnosis method	N of assessed participants	N of participants with dual allergy (%)
Patients with index penicillin allergy and assessed for cefazolin allergy							
Ahmad et al[17] 2020, USA	Surgical	Not specified	Not specified	Self-reported	Exposure	5	0 (0)
Aihara et al[18] 1987, Japan	Outpatient	Adults, children	Delayed	Skin test, provocation test	Skin test	11	3 (27.3)
Anstey et al[19], 2019, USA	Surgical	Adults	Immediate, delayed	Self-reported	Exposure	2570	2 (0.1)
Beam et al[20] 1984, USA	Surgical	Adults	Immediate	Skin test	Skin test	2	1 (50.0)
Beltran et al[21] 2015, USA	Inpatient	Adults, children	Immediate, delayed	Self-reported	Exposure	127	1 (0.8)
Blumenthal et al[22] 2019, USA	Inpatient	Adults, children	Immediate, delayed	Self-reported	Provocation test	106	3 (2.8)
Blumenthal et al[23] 2015, USA	Inpatient	Adults	Immediate, delayed	Self-reported	Provocation test	21	1 (4.8)
Castleton et al[24] 1976, UK	Inpatient	Adults	Not specified	Self-reported	Exposure	5	0 (0)
Cook et al[25] 2014, USA	Surgical	Adults	Immediate, delayed	Skin test	Skin test	22	11 (50.0)
Desai et al[26] 2017, USA	Pregnant	Adults	Immediate, delayed	Self-reported	Exposure	1332	10 (0.8)
Desravines et al[27] 2019, USA	Pregnant	Adults	Not specified	Self-reported	Exposure	65	0 (0)
Fonacier et al[28] 2005, USA	Surgical	Adults, children	Immediate, delayed	Self-reported	Exposure	37	0 (0)
Goodman et al[29] 2001, USA	Surgical	Adults	Not specified	Self-reported	Exposure	299	1 (0.3)
Haslam et al[30] et al. 2012, Canada	Surgical	Adults	Delayed	Self-reported	Exposure	54	0 (0)
Laaouaj et al.[31] 2016, USA	Surgical	Adults	Immediate, delayed	Self-reported	Provocation test	139	6 (4.3)

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Lam et al.[46] 2020, USA	Surgical	Adults	Not specified	Self-reported	Exposure	500[a]	0 (0)
Maguire et al.[32] 2020, USA	Emergency department	Adults	Not specified	Self-reported	Provocation test	14	0 (0)
Michaud et al[33] 2017, Canada	Surgical	Adults	Delayed	Self-reported	Exposure	81	0 (0)
Novalbos et al[68] 2001, Spain	Outpatient	Adults	Immediate, delayed	Skin test, provocation test	Skin test, provocation test	41	0 (0)
Park et al.[35] 2006, USA	Surgical	Adults, children	Immediate, delayed	Self-reported	Exposure	19	1 (5.3)
Park et al[36] 2010, USA	Outpatient	Adults	Not specified	Skin test	Exposure	59	1 (1.7)
Pines et al[37] 1977, UK	Inpatient	Adults	Not specified	Self-reported	Provocation test, exposure	10	1 (10.0)
Ponvert et al[38] 2011, France	Outpatient	Children	Not specified	Skin test	Skin test	150	0 (0)
Rodriguez et al[39] 2019, Spain	Outpatient	Adults	Immediate, delayed	Skin test, *in vitro*, provocation test	Skin test	86	0 (0)
Romano et al[40] 2020, Italy	Outpatient	Adults	Immediate	Skin test, provocation test	Skin test, provocation test	131	1 (0.8)
Schlosser et al[41] 2020, USA	Surgical	Adults	Immediate, delayed	Self-reported	Exposure	38	0 (0)
Stone et al[42] 2019, USA	Surgical	Adults	Immediate, delayed	Self-reported	Exposure	28	0 (0)
Thellier et al[43] 2020, France	Obstetrics	Adults	Immediate, delayed	Self-reported	Exposure	8	0 (0)
Trubiano et al[44] 2019, Australia	Outpatient	Adults	Delayed	Skin test, *in vitro*	Skin test	12	0 (0)
Turner et al[45] 2018, USA	Inpatient	Adults	Immediate, delayed	Self-reported	Exposure	29	1 (3.4)
Patients with index cefazolin allergy and assessed for penicillin allergy							
Alves et al[47] 2015, Portugal	Surgical	Adults, children	Immediate, delayed	Provocation test	Skin test, exposure	2	0 (0)
Chng et al[48] 2016, Singapore	Outpatients	Adults, children	Immediate, delayed	Skin test	Skin test, provocation test	4	2 (50.0)

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Cook et al[25] 2014, USA	Surgical	Adults	Immediate, delayed	Skin test	Skin test	24	11 (45.8)
Farinha et al[49] 2018, Portugal	Surgical	Adults, children	Immediate	Skin test, provocation test	Skin test, exposure	3	1 (33.3)
Jimenez-Rodriguez et al[39] 2019, Spain	Outpatient, inpatient	Adults	Immediate	Skin test, *in vitro*	Skin test	3	0 (0)
Kuhlen et al[50] 2016, USA	Surgical	Adults	Immediate	Skin test, provocation test	Skin test, exposure	5	0 (0)
Laguna et al[51] 2018, Spain	Outpatient	Adults	Immediate	Skin test, *in vitro*, provocation test	Skin test, provocation test	11	0 (0)
Li et al[52] 2019, Australia	Surgical	Adults, children	Immediate	Provocation test	Skin test, exposure	40	1 (2.5)
Mota et al[69] 2018, Portugal	Surgical	Adults	Immediate	Skin test, *in vitro*, provocation test	Skin test, exposure	7	0 (0)
Pipet et al[54] 2011, France	Outpatient	Adults, children	Immediate	Skin test, provocation test	Skin test	10	1 (10.0)
Romano et al[56] 2015, Italy	Outpatient	Adults, children	Immediate	Skin test, *in vitro*	Skin test	6	0 (0)
Romano et al[55] 2010, Italy	Outpatient	Adults, children	Immediate	Skin test	Skin test	2	0 (0)
Uyttebroek et al[70] 2016, Belgium	Surgical	Not specified	Immediate	Skin test, *in vitro*, provocation test	Skin test, exposure	19	0 (0)
Warrington et al[58] 1996, Canada	Surgical	Adults	Immediate	Skin test	Skin test, exposure	4	0 (0)
Yuson et al[59] 2019, Australia	Outpatient	Adults	Immediate	Skin test, *in vitro*, provocation test	Skin test, provocation test	6	0 (0)

Abbrviations: HS, hypersensitivity; USA, United States of America; UK, United Kingdom

[a] Estimate sample size based on figure

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eTable 3. Characteristics of case reports Included

Case study	Sex	Age	Index HS onset	Penicillin HS diagnosis method	Cefazolin HS diagnosis method	Dual allergy to penicillin and cefazolin
Patients with index penicillin allergy and assessed for cefazolin allergy						
Ahmed et al[71] 2012,	Not specified	1	Delayed	Skin test	Exposure	No
Alves et al[47] 2015	F	50	Immediate	Skin test	Exposure	No
Berrocal et al[72] 2001	F	70	Immediate	Self-reported	Exposure	Yes
Castro et al[73] 1996	M	3	Delayed	Skin test, provocation test	Skin test	No
Christen et al[74] 1990	M	43	Delayed	Self-reported	Exposure	No
Eser Simsek et al[75] 2018	F	10	Immediate	Skin test, provocation test	Provocation test	No
Fitzgerald et al[76] 2016	Not specified	66	Immediate	Self-reported	Exposure	No
Freedman et al[77] 1997	F	40	Not specified	Self-reported	Exposure	No
Gonzalez-Delgado et al[78] 2006	F	7	Delayed	Skin test, patch test	Skin test, patch test	No
Ho et al[79] 2004	F	74	Delayed	*in vitro*	*in vitro* IgE	No
Jao et al[80] 2006	F	37	Not specified	Self-reported	Exposure	Yes
Kraushar et al[81] 1994	F	72	Not specified	Self-reported	Exposure	Yes
Moake et al[82] 1978	F	39	Immediate	*in vitro*	*in vitro* IgE	Yes
Nemati et al[83] 1981	M	24	Delayed	Self-reported	Exposure	Yes
Philips et al[84] 2001	Not specified	Not specified	Delayed	Skin test, patch test	Skin test	Yes
Vogt et al[85] 1998	F	46	Delayed	Self-reported	Exposure	No
Patients with index cefazolin allergy and assessed for penicillin allergy						
Almeida et al[86] 2017	F	36	Immediate	Provocation test	Skin test, *in vitro* IgE	No
Almeida et al[86] 2017	F	49	Immediate	Provocation test	Skin test, *in vitro* IgE	No
Chan et al[87] 2016	Not specified	Not specified	Immediate	Skin test	Skin test	Yes
Culp et al[88] 2017	M	44	Immediate	Skin test, *in vitro*	Exposure	No

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Gonzalo-Garijo et al[89] 2006	F	66	Not specified	Skin test, provocation test	Skin test	No
Igea et al[90] 1992	F	21	Immediate	Skin test, provocation test	Skin test, *in vitro* IgE	No
Igea et al[90] 1992	F	45	Immediate	Skin test, provocation test	Skin test, *in vitro* IgE	No
Lee et al[91] 2004	F	46	Immediate	Skin test	Skin test	No
Padial et al[92] 2008	Not specified	43	Delayed	Skin test, provocation test	Skin test, provocation test	No
Pinheiro et al[93] 2018	F	31	Delayed	Patch test	Patch test	Yes
Romano et al 2001[94]	F	44	Delayed	Skin test, patch test, *in vitro*, provocation test	Skin test, patch test, *in vitro* IgE, provocation test	No
Romeira et al[63] 2017	Not specified	Not specified	Not specified	Skin test	Skin test	No
Somech et al[95] 2009	M	12	Immediate	Skin test, provocation test	Skin test	No
Tayman et al[96] 2008	F	0	Immediate	Skin test, *in vitro*	Skin test, *in vitro* IgE	Yes
Velasco et al[97] 2009	F	63	Delayed	Skin test, patch test, *in vitro*, provocation test	Skin test, patch test, *in vitro* IgE, provocation test	No
Vieira et al[98] 2009	M	32	Immediate	Skin test, *in vitro*	Skin test	No
Weber et al[99] 1996	F	33	Immediate	Skin test, provocation test	Skin test	No
Wieczorek et al[100] 2008	F	18	Immediate	Skin test, *in vitro*, provocation test	Skin test, *in vitro* IgE	No
Yun et al[101] 2016	M	26	Immediate	Skin test	Skin test	No
Patients with index beta-lactam allergy and assessed for penicillin and cefazolin allergy						
Classen et al[102] 2015	F	24	Not specified	Skin test	Skin test, patch test	Yes
Gonzalo-Garijo et al[89] 2006	M	80	Not specified	Skin test, provocation test	Skin test	No
Rozlucka et al[103] 2019	Not specified	65	Not specified	Skin test, provocation test	Skin test, provocation test	No

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eTable 4. Risk of bias of individual studies

Study	Risk of Bias				
	Representation of the target population	Consecutive sampling	Non-response bias	Definition of the allergic reaction	Consistency of data collection/assessment
Studies assessing patients with index penicillin allergy (tested for cefazolin)					
Castleton B (1976)	🔴	🟡	🟡	🟢	🟢
Pines A (1977)	🟢	🟡	🔴	🟡	🟢
Beam TR (1984)	🔴	🟢	🟢	🟢	🟢
Aihara M (1987)	🟡	🟡	🔴	🟡	🟢
Goodman EJ (2001)	🔴	🔴	🔴	🟢	🟢
Novalbos A (2001)	🟢	🔴	🟢	🟢	🟢
Fonacier L (2005)	🟡	🔴	🔴	🟢	🟢
Park M (2006)	🟢	🔴	🔴	🟢	🟢
Park M (2010)	🟡	🔴	🔴	🟢	🟢
Ponvert C (2011)	🟢	🟢	🟢	🟢	🟢
Haslam S (2012)	🔴	🔴	🔴	🟢	🟢
Cook DJ (2014)	🔴	🔴	🔴	🟢	🟢
Beltran RJ (2015)	🟢	🔴	🔴	🟢	🟢
Blumenthal KG (2015)	🟢	🔴	🔴	🟢	🟢
Laaouaj J (2016)	🔴	🟢	🔴	🟢	🟢

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Desai SH (2017)	●	●	●	●	●
Michaud L (2017)	●	●	●	●	●
Turner NA (2018)	●	●	●	●	●
Astey K (2019)	●	●	●	●	●
Blumenthal KG (2019)	●	●	●	●	●
Desravines N (2019)	●	●	●	●	●
Jimenez-Rodriguez T (2019)	●	●	●	●	●
Schlosser KA (2019)	●	●	●	●	●
Thellier C (2019)	●	●	●	●	●
Trubiano J (2019)	●	●	●	●	●
Ahmad H (2020)	●	●	●	●	●
Lam PW (2020)	●	●	●	●	●
Maguire M (2020)	●	●	●	●	●
Romano A (2020)	●	●	●	●	●
Studies assessing patients with index cefazolin allergy (tested for penicillins)					
Warrington RJ (1996)	●	●	●	●	●
Romano A (2010)	●	●	●	●	●
Pipet A (2011)	●	●	●	●	●
Cook DJ (2014)	●	●	●	●	●
Alves C (2015)	●	●	●	●	●
Romano A (2015)	●	●	●	●	●
Chng H (2016)	●	●	●	●	●
Kuhlen JL (2016)	●	●	●	●	●
Uyttebroek AP (2016)	●	●	●	●	●
Farinha SM (2018)	●	●	●	●	●
Laguna JJ (2018)	●	●	●	●	●
Mota I (2018)	●	●	●	●	●
Jimenez-Rodriguez T (2019)	●	●	●	●	●
Li J (2019)	●	●	●	●	●
Yuson C (2019)	●	●	●	●	●

Legend: ● - Low risk of bias; ● - Unclear risk of bias; ● - High risk of bias.

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Supplementary Online Content

Sousa-Pinto B, Blumenthal KG, Courtney L, Mancini CM, Jeffres MN. Assessment of the frequency of dual allergy to penicillins and cefazolin: a systematic review and meta-analysis. *JAMA Surg.* Published online March 17, 2021. doi:10.1001/jamasurg.2021.0021

eTable 1. Search Queries Used in the Different Electronic Bibliographic Databases

eTable 2. Characteristics of Included Cohort Studies

eTable 3. Characteristics of Case Reports Included

eTable 4. Risk of Bias of Individual Studies

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eTable 1. Search queries used in the different electronic bibliographic databases

Database	Search query
MEDLINE/ PubMed	(hypersensitivit*[Text Word] OR hypersensitivity[Text Word] OR allerg*[Text Word] OR allergy[Text Word] OR cross-reactiv*[Text Word]) AND (penicillin*[Text Word] OR amoxicillin[Text Word] OR ampicillin[Text Word] OR aminopenicillin[Text Word]) AND (cefazolin[Text Word] OR cephazolin[Text Word] OR cephazoline[Text Word] OR ancef[Text Word] OR cephalosporin*[Title/Abstract])
Web of Science	(TS=hypersensitivit* OR TS=hypersensitivity OR TS=allerg* OR TS=allergy OR TS=cross-reactiv*) AND (TS=penicillin* OR TS=amoxicillin OR TS=ampicillin OR TS=aminopenicillin) AND (TS=cefazolin OR TS=cephazolin OR TS=cephazoline OR TS=ancef OR TS=cephalosporin*)
Embase	(hypersensitiv*:ti,ab,kw OR hypersensitivity:ti,ab,kw OR allerg*:ti,ab,kw OR allergy:ti,ab,kw OR 'cross react*':ti,ab,kw OR 'cross reaction':ti,ab,kw) AND ('penicillin derivative':ti,ab,kw OR penicillin:ti,ab,kw OR amoxicillin:ti,ab,kw OR ampicillin:ti,ab,kw OR aminopenicillin:ti,ab,kw) AND (cefazolin:ti,ab,kw OR cephazolin:ti,ab,kw OR cephazoline:ti,ab,kw OR ancef:ti,ab,kw OR 'cephalosporin derivative':ti,ab,kw)

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eTable 2. Characteristics of Included Cohort Studies

Source, Country	Setting	Age group	Index HS onset	Penicillin HS diagnosis method	Cefazolin HS diagnosis method	N of assessed participants	N of participants with dual allergy (%)
Patients with index penicillin allergy and assessed for cefazolin allergy							
Ahmad et al[17] 2020, USA	Surgical	Not specified	Not specified	Self-reported	Exposure	5	0 (0)
Aihara et al[18] 1987, Japan	Outpatient	Adults, children	Delayed	Skin test, provocation test	Skin test	11	3 (27.3)
Anstey et al[19], 2019, USA	Surgical	Adults	Immediate, delayed	Self-reported	Exposure	2570	2 (0.1)
Beam et al[20] 1984, USA	Surgical	Adults	Immediate	Skin test	Skin test	2	1 (50.0)
Beltran et al[21] 2015, USA	Inpatient	Adults, children	Immediate, delayed	Self-reported	Exposure	127	1 (0.8)
Blumenthal et al[22] 2019, USA	Inpatient	Adults, children	Immediate, delayed	Self-reported	Provocation test	106	3 (2.8)
Blumenthal et al[23] 2015, USA	Inpatient	Adults	Immediate, delayed	Self-reported	Provocation test	21	1 (4.8)
Castleton et al[24] 1976, UK	Inpatient	Adults	Not specified	Self-reported	Exposure	5	0 (0)
Cook et al[25] 2014, USA	Surgical	Adults	Immediate, delayed	Skin test	Skin test	22	11 (50.0)
Desai et al[26] 2017, USA	Pregnant	Adults	Immediate, delayed	Self-reported	Exposure	1332	10 (0.8)
Desravines et al[27] 2019, USA	Pregnant	Adults	Not specified	Self-reported	Exposure	65	0 (0)
Fonacier et al[28] 2005, USA	Surgical	Adults, children	Immediate, delayed	Self-reported	Exposure	37	0 (0)
Goodman et al[29] 2001, USA	Surgical	Adults	Not specified	Self-reported	Exposure	299	1 (0.3)
Haslam et al[30] et al. 2012, Canada	Surgical	Adults	Delayed	Self-reported	Exposure	54	0 (0)
Laaouaj et al.[31] 2016, USA	Surgical	Adults	Immediate, delayed	Self-reported	Provocation test	139	6 (4.3)

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Lam et al.[46] 2020, USA	Surgical	Adults	Not specified	Self-reported	Exposure	500[a]	0 (0)
Maguire et al.[32] 2020, USA	Emergency department	Adults	Not specified	Self-reported	Provocation test	14	0 (0)
Michaud et al[33] 2017, Canada	Surgical	Adults	Delayed	Self-reported	Exposure	81	0 (0)
Novalbos et al[68] 2001, Spain	Outpatient	Adults	Immediate, delayed	Skin test, provocation test	Skin test, provocation test	41	0 (0)
Park et al.[35] 2006, USA	Surgical	Adults, children	Immediate, delayed	Self-reported	Exposure	19	1 (5.3)
Park et al[36] 2010, USA	Outpatient	Adults	Not specified	Skin test	Exposure	59	1 (1.7)
Pines et al[37] 1977, UK	Inpatient	Adults	Not specified	Self-reported	Provocation test, exposure	10	1 (10.0)
Ponvert et al[38] 2011, France	Outpatient	Children	Not specified	Skin test	Skin test	150	0 (0)
Rodriguez et al[39] 2019, Spain	Outpatient	Adults	Immediate, delayed	Skin test, *in vitro*, provocation test	Skin test	86	0 (0)
Romano et al[40] 2020, Italy	Outpatient	Adults	Immediate	Skin test, provocation test	Skin test, provocation test	131	1 (0.8)
Schlosser et al[41] 2020, USA	Surgical	Adults	Immediate, delayed	Self-reported	Exposure	38	0 (0)
Stone et al[42] 2019, USA	Surgical	Adults	Immediate, delayed	Self-reported	Exposure	28	0 (0)
Thellier et al[43] 2020, France	Obstetrics	Adults	Immediate, delayed	Self-reported	Exposure	8	0 (0)
Trubiano et al[44] 2019, Australia	Outpatient	Adults	Delayed	Skin test, *in vitro*	Skin test	12	0 (0)
Turner et al[45] 2018, USA	Inpatient	Adults	Immediate, delayed	Self-reported	Exposure	29	1 (3.4)
Patients with index cefazolin allergy and assessed for penicillin allergy							
Alves et al[47] 2015, Portugal	Surgical	Adults, children	Immediate, delayed	Provocation test	Skin test, exposure	2	0 (0)
Chng et al[48] 2016, Singapore	Outpatients	Adults, children	Immediate, delayed	Skin test	Skin test, provocation test	4	2 (50.0)

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Cook et al[25] 2014, USA	Surgical	Adults	Immediate, delayed	Skin test	Skin test	24	11 (45.8)
Farinha et al[49] 2018, Portugal	Surgical	Adults, children	Immediate	Skin test, provocation test	Skin test, exposure	3	1 (33.3)
Jimenez-Rodriguez et al[39] 2019, Spain	Outpatient, inpatient	Adults	Immediate	Skin test, *in vitro*	Skin test	3	0 (0)
Kuhlen et al[50] 2016, USA	Surgical	Adults	Immediate	Skin test, provocation test	Skin test, exposure	5	0 (0)
Laguna et al[51] 2018, Spain	Outpatient	Adults	Immediate	Skin test, *in vitro*, provocation test	Skin test, provocation test	11	0 (0)
Li et al[52] 2019, Australia	Surgical	Adults, children	Immediate	Provocation test	Skin test, exposure	40	1 (2.5)
Mota et al[69] 2018, Portugal	Surgical	Adults	Immediate	Skin test, *in vitro*, provocation test	Skin test, exposure	7	0 (0)
Pipet et al[54] 2011, France	Outpatient	Adults, children	Immediate	Skin test, provocation test	Skin test	10	1 (10.0)
Romano et al[56] 2015, Italy	Outpatient	Adults, children	Immediate	Skin test, *in vitro*	Skin test	6	0 (0)
Romano et al[55] 2010, Italy	Outpatient	Adults, children	Immediate	Skin test	Skin test	2	0 (0)
Uyttebroek et al[70] 2016, Belgium	Surgical	Not specified	Immediate	Skin test, *in vitro*, provocation test	Skin test, exposure	19	0 (0)
Warrington et al[58] 1996, Canada	Surgical	Adults	Immediate	Skin test	Skin test, exposure	4	0 (0)
Yuson et al[59] 2019, Australia	Outpatient	Adults	Immediate	Skin test, *in vitro*, provocation test	Skin test, provocation test	6	0 (0)

Abbrviations: HS, hypersensitivity; USA, United States of America; UK, United Kingdom

[a] Estimate sample size based on figure

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eTable 3. Characteristics of case reports Included

Case study	Sex	Age	Index HS onset	Penicillin HS diagnosis method	Cefazolin HS diagnosis method	Dual allergy to penicillin and cefazolin
Patients with index penicillin allergy and assessed for cefazolin allergy						
Ahmed et al[71] 2012,	Not specified	1	Delayed	Skin test	Exposure	No
Alves et al[47] 2015	F	50	Immediate	Skin test	Exposure	No
Berrocal et al[72] 2001	F	70	Immediate	Self-reported	Exposure	Yes
Castro et al[73] 1996	M	3	Delayed	Skin test, provocation test	Skin test	No
Christen et al[74] 1990	M	43	Delayed	Self-reported	Exposure	No
Eser Simsek et al[75] 2018	F	10	Immediate	Skin test, provocation test	Provocation test	No
Fitzgerald et al[76] 2016	Not specified	66	Immediate	Self-reported	Exposure	No
Freedman et al[77] 1997	F	40	Not specified	Self-reported	Exposure	No
Gonzalez-Delgado et al[78] 2006	F	7	Delayed	Skin test, patch test	Skin test, patch test	No
Ho et al[79] 2004	F	74	Delayed	*in vitro*	*in vitro* IgE	No
Jao et al[80] 2006	F	37	Not specified	Self-reported	Exposure	Yes
Kraushar et al[81] 1994	F	72	Not specified	Self-reported	Exposure	Yes
Moake et al[82] 1978	F	39	Immediate	*in vitro*	*in vitro* IgE	Yes
Nemati et al[83] 1981	M	24	Delayed	Self-reported	Exposure	Yes
Philips et al[84] 2001	Not specified	Not specified	Delayed	Skin test, patch test	Skin test	Yes
Vogt et al[85] 1998	F	46	Delayed	Self-reported	Exposure	No
Patients with index cefazolin allergy and assessed for penicillin allergy						
Almeida et al[86] 2017	F	36	Immediate	Provocation test	Skin test, *in vitro* IgE	No
Almeida et al[86] 2017	F	49	Immediate	Provocation test	Skin test, *in vitro* IgE	No
Chan et al[87] 2016	Not specified	Not specified	Immediate	Skin test	Skin test	Yes
Culp et al[88] 2017	M	44	Immediate	Skin test, *in vitro*	Exposure	No

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Gonzalo-Garijo et al[89] 2006	F	66	Not specified	Skin test, provocation test	Skin test	No
Igea et al[90] 1992	F	21	Immediate	Skin test, provocation test	Skin test, *in vitro* IgE	No
Igea et al[90] 1992	F	45	Immediate	Skin test, provocation test	Skin test, *in vitro* IgE	No
Lee et al[91] 2004	F	46	Immediate	Skin test	Skin test	No
Padial et al[92] 2008	Not specified	43	Delayed	Skin test, provocation test	Skin test, provocation test	No
Pinheiro et al[93] 2018	F	31	Delayed	Patch test	Patch test	Yes
Romano et al 2001[94]	F	44	Delayed	Skin test, patch test, *in vitro*, provocation test	Skin test, patch test, *in vitro* IgE, provocation test	No
Romeira et al[63] 2017	Not specified	Not specified	Not specified	Skin test	Skin test	No
Somech et al[95] 2009	M	12	Immediate	Skin test, provocation test	Skin test	No
Tayman et al[96] 2008	F	0	Immediate	Skin test, *in vitro*	Skin test, *in vitro* IgE	Yes
Velasco et al[97] 2009	F	63	Delayed	Skin test, patch test, *in vitro*, provocation test	Skin test, patch test, *in vitro* IgE, provocation test	No
Vieira et al[98] 2009	M	32	Immediate	Skin test, *in vitro*	Skin test	No
Weber et al[99] 1996	F	33	Immediate	Skin test, provocation test	Skin test	No
Wieczorek et al[100] 2008	F	18	Immediate	Skin test, *in vitro*, provocation test	Skin test, *in vitro* IgE	No
Yun et al[101] 2016	M	26	Immediate	Skin test	Skin test	No
Patients with index beta-lactam allergy and assessed for penicillin and cefazolin allergy						
Classen et al[102] 2015	F	24	Not specified	Skin test	Skin test, patch test	Yes
Gonzalo-Garijo et al[89] 2006	M	80	Not specified	Skin test, provocation test	Skin test	No
Rozlucka et al[103] 2019	Not specified	65	Not specified	Skin test, provocation test	Skin test, provocation test	No

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eTable 4. Risk of bias of individual studies

Study	Risk of Bias				
	Representation of the target population	Consecutive sampling	Non-response bias	Definition of the allergic reaction	Consistency of data collection/assessment
Studies assessing patients with index penicillin allergy (tested for cefazolin)					
Castleton B (1976)	🔴	🟡	🟡	🟢	🟢
Pines A (1977)	🟢	🟡	🔴	🟡	🟢
Beam TR (1984)	🔴	🟢	🟢	🟢	🟢
Aihara M (1987)	🟡	🟡	🔴	🟡	🟢
Goodman EJ (2001)	🔴	🔴	🔴	🟢	🟢
Novalbos A (2001)	🟢	🔴	🟢	🟢	🟢
Fonacier L (2005)	🟡	🔴	🔴	🟢	🟢
Park M (2006)	🟢	🔴	🔴	🟢	🟢
Park M (2010)	🟡	🔴	🔴	🟢	🟢
Ponvert C (2011)	🟢	🟢	🟢	🟢	🟢
Haslam S (2012)	🔴	🔴	🔴	🟢	🟢
Cook DJ (2014)	🔴	🔴	🔴	🟢	🟢
Beltran RJ (2015)	🟢	🔴	🔴	🟢	🟢
Blumenthal KG (2015)	🟢	🔴	🔴	🟢	🟢
Laaouaj J (2016)	🔴	🟢	🔴	🟢	🟢

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Desai SH (2017)	●	●	●	●	●
Michaud L (2017)	●	●	●	●	●
Turner NA (2018)	●	●	●	●	●
Astey K (2019)	●	●	●	●	●
Blumenthal KG (2019)	●	●	●	●	●
Desravines N (2019)	●	●	●	●	●
Jimenez-Rodriguez T (2019)	●	●	●	●	●
Schlosser KA (2019)	●	●	●	●	●
Thellier C (2019)	●	●	●	●	●
Trubiano J (2019)	●	●	●	●	●
Ahmad H (2020)	●	●	●	●	●
Lam PW (2020)	●	●	●	●	●
Maguire M (2020)	●	●	●	●	●
Romano A (2020)	●	●	●	●	●
Studies assessing patients with index cefazolin allergy (tested for penicillins)					
Warrington RJ (1996)	●	●	●	●	●
Romano A (2010)	●	●	●	●	●
Pipet A (2011)	●	●	●	●	●
Cook DJ (2014)	●	●	●	●	●
Alves C (2015)	●	●	●	●	●
Romano A (2015)	●	●	●	●	●
Chng H (2016)	●	●	●	●	●
Kuhlen JL (2016)	●	●	●	●	●
Uyttebroek AP (2016)	●	●	●	●	●
Farinha SM (2018)	●	●	●	●	●
Laguna JJ (2018)	●	●	●	●	●
Mota I (2018)	●	●	●	●	●
Jimenez-Rodriguez T (2019)	●	●	●	●	●
Li J (2019)	●	●	●	●	●
Yuson C (2019)	●	●	●	●	●

Legend: ● - Low risk of bias; ● - Unclear risk of bias; ● - High risk of bias.

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Supplementary Online Content

Sousa-Pinto B, Blumenthal KG, Courtney L, Mancini CM, Jeffres MN. Assessment of the frequency of dual allergy to penicillins and cefazolin: a systematic review and meta-analysis. *JAMA Surg.* Published online March 17, 2021. doi:10.1001/jamasurg.2021.0021

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eTable 1. Search queries used in the different electronic bibliographic databases

Database	Search query
MEDLINE/ PubMed	(hypersensitivit*[Text Word] OR hypersensitivity[Text Word] OR allerg*[Text Word] OR allergy[Text Word] OR cross-reactiv*[Text Word]) AND (penicillin*[Text Word] OR amoxicillin[Text Word] OR ampicillin[Text Word] OR aminopenicillin[Text Word]) AND (cefazolin[Text Word] OR cephazolin[Text Word] OR cephazoline[Text Word] OR ancef[Text Word] OR cephalosporin*[Title/Abstract])
Web of Science	(TS=hypersensitivit* OR TS=hypersensitivity OR TS=allerg* OR TS=allergy OR TS=cross-reactiv*) AND (TS=penicillin* OR TS=amoxicillin OR TS=ampicillin OR TS=aminopenicillin) AND (TS=cefazolin OR TS=cephazolin OR TS=cephazoline OR TS=ancef OR TS=cephalosporin*)
Embase	(hypersensitiv*:ti,ab,kw OR hypersensitivity:ti,ab,kw OR allerg*:ti,ab,kw OR allergy:ti,ab,kw OR 'cross react*':ti,ab,kw OR 'cross reaction':ti,ab,kw) AND ('penicillin derivative':ti,ab,kw OR penicillin:ti,ab,kw OR amoxicillin:ti,ab,kw OR ampicillin:ti,ab,kw OR aminopenicillin:ti,ab,kw) AND (cefazolin:ti,ab,kw OR cephazolin:ti,ab,kw OR cephazoline:ti,ab,kw OR ancef:ti,ab,kw OR 'cephalosporin derivative':ti,ab,kw)

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eTable 2. Characteristics of Included Cohort Studies

Source, Country	Setting	Age group	Index HS onset	Penicillin HS diagnosis method	Cefazolin HS diagnosis method	N of assessed participants	N of participants with dual allergy (%)
Patients with index penicillin allergy and assessed for cefazolin allergy							
Ahmad et al[17] 2020, USA	Surgical	Not specified	Not specified	Self-reported	Exposure	5	0 (0)
Aihara et al[18] 1987, Japan	Outpatient	Adults, children	Delayed	Skin test, provocation test	Skin test	11	3 (27.3)
Anstey et al[19], 2019, USA	Surgical	Adults	Immediate, delayed	Self-reported	Exposure	2570	2 (0.1)
Beam et al[20] 1984, USA	Surgical	Adults	Immediate	Skin test	Skin test	2	1 (50.0)
Beltran et al[21] 2015, USA	Inpatient	Adults, children	Immediate, delayed	Self-reported	Exposure	127	1 (0.8)
Blumenthal et al[22] 2019, USA	Inpatient	Adults, children	Immediate, delayed	Self-reported	Provocation test	106	3 (2.8)
Blumenthal et al[23] 2015, USA	Inpatient	Adults	Immediate, delayed	Self-reported	Provocation test	21	1 (4.8)
Castleton et al[24] 1976, UK	Inpatient	Adults	Not specified	Self-reported	Exposure	5	0 (0)
Cook et al[25] 2014, USA	Surgical	Adults	Immediate, delayed	Skin test	Skin test	22	11 (50.0)
Desai et al[26] 2017, USA	Pregnant	Adults	Immediate, delayed	Self-reported	Exposure	1332	10 (0.8)
Desravines et al[27] 2019, USA	Pregnant	Adults	Not specified	Self-reported	Exposure	65	0 (0)
Fonacier et al[28] 2005, USA	Surgical	Adults, children	Immediate, delayed	Self-reported	Exposure	37	0 (0)
Goodman et al[29] 2001, USA	Surgical	Adults	Not specified	Self-reported	Exposure	299	1 (0.3)
Haslam et al[30] et al. 2012, Canada	Surgical	Adults	Delayed	Self-reported	Exposure	54	0 (0)
Laaouaj et al.[31] 2016, USA	Surgical	Adults	Immediate, delayed	Self-reported	Provocation test	139	6 (4.3)

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Lam et al.[46] 2020, USA	Surgical	Adults	Not specified	Self-reported	Exposure	500[a]	0 (0)
Maguire et al.[32] 2020, USA	Emergency department	Adults	Not specified	Self-reported	Provocation test	14	0 (0)
Michaud et al[33] 2017, Canada	Surgical	Adults	Delayed	Self-reported	Exposure	81	0 (0)
Novalbos et al[68] 2001, Spain	Outpatient	Adults	Immediate, delayed	Skin test, provocation test	Skin test, provocation test	41	0 (0)
Park et al.[35] 2006, USA	Surgical	Adults, children	Immediate, delayed	Self-reported	Exposure	19	1 (5.3)
Park et al[36] 2010, USA	Outpatient	Adults	Not specified	Skin test	Exposure	59	1 (1.7)
Pines et al[37] 1977, UK	Inpatient	Adults	Not specified	Self-reported	Provocation test, exposure	10	1 (10.0)
Ponvert et al[38] 2011, France	Outpatient	Children	Not specified	Skin test	Skin test	150	0 (0)
Rodriguez et al[39] 2019, Spain	Outpatient	Adults	Immediate, delayed	Skin test, *in vitro*, provocation test	Skin test	86	0 (0)
Romano et al[40] 2020, Italy	Outpatient	Adults	Immediate	Skin test, provocation test	Skin test, provocation test	131	1 (0.8)
Schlosser et al[41] 2020, USA	Surgical	Adults	Immediate, delayed	Self-reported	Exposure	38	0 (0)
Stone et al[42] 2019, USA	Surgical	Adults	Immediate, delayed	Self-reported	Exposure	28	0 (0)
Thellier et al[43] 2020, France	Obstetrics	Adults	Immediate, delayed	Self-reported	Exposure	8	0 (0)
Trubiano et al[44] 2019, Australia	Outpatient	Adults	Delayed	Skin test, *in vitro*	Skin test	12	0 (0)
Turner et al[45] 2018, USA	Inpatient	Adults	Immediate, delayed	Self-reported	Exposure	29	1 (3.4)
Patients with index cefazolin allergy and assessed for penicillin allergy							
Alves et al[47] 2015, Portugal	Surgical	Adults, children	Immediate, delayed	Provocation test	Skin test, exposure	2	0 (0)
Chng et al[48] 2016, Singapore	Outpatients	Adults, children	Immediate, delayed	Skin test	Skin test, provocation test	4	2 (50.0)

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Cook et al[25] 2014, USA	Surgical	Adults	Immediate, delayed	Skin test	Skin test	24	11 (45.8)
Farinha et al[49] 2018, Portugal	Surgical	Adults, children	Immediate	Skin test, provocation test	Skin test, exposure	3	1 (33.3)
Jimenez-Rodriguez et al[39] 2019, Spain	Outpatient, inpatient	Adults	Immediate	Skin test, *in vitro*	Skin test	3	0 (0)
Kuhlen et al[50] 2016, USA	Surgical	Adults	Immediate	Skin test, provocation test	Skin test, exposure	5	0 (0)
Laguna et al[51] 2018, Spain	Outpatient	Adults	Immediate	Skin test, *in vitro*, provocation test	Skin test, provocation test	11	0 (0)
Li et al[52] 2019, Australia	Surgical	Adults, children	Immediate	Provocation test	Skin test, exposure	40	1 (2.5)
Mota et al[69] 2018, Portugal	Surgical	Adults	Immediate	Skin test, *in vitro*, provocation test	Skin test, exposure	7	0 (0)
Pipet et al[54] 2011, France	Outpatient	Adults, children	Immediate	Skin test, provocation test	Skin test	10	1 (10.0)
Romano et al[56] 2015, Italy	Outpatient	Adults, children	Immediate	Skin test, *in vitro*	Skin test	6	0 (0)
Romano et al[55] 2010, Italy	Outpatient	Adults, children	Immediate	Skin test	Skin test	2	0 (0)
Uyttebroek et al[70] 2016, Belgium	Surgical	Not specified	Immediate	Skin test, *in vitro*, provocation test	Skin test, exposure	19	0 (0)
Warrington et al[58] 1996, Canada	Surgical	Adults	Immediate	Skin test	Skin test, exposure	4	0 (0)
Yuson et al[59] 2019, Australia	Outpatient	Adults	Immediate	Skin test, *in vitro*, provocation test	Skin test, provocation test	6	0 (0)

Abbrviations: HS, hypersensitivity; USA, United States of America; UK, United Kingdom

[a] Estimate sample size based on figure

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eTable 3. Characteristics of case reports Included

Case study	Sex	Age	Index HS onset	Penicillin HS diagnosis method	Cefazolin HS diagnosis method	Dual allergy to penicillin and cefazolin
Patients with index penicillin allergy and assessed for cefazolin allergy						
Ahmed et al[71] 2012,	Not specified	1	Delayed	Skin test	Exposure	No
Alves et al[47] 2015	F	50	Immediate	Skin test	Exposure	No
Berrocal et al[72] 2001	F	70	Immediate	Self-reported	Exposure	Yes
Castro et al[73] 1996	M	3	Delayed	Skin test, provocation test	Skin test	No
Christen et al[74] 1990	M	43	Delayed	Self-reported	Exposure	No
Eser Simsek et al[75] 2018	F	10	Immediate	Skin test, provocation test	Provocation test	No
Fitzgerald et al[76] 2016	Not specified	66	Immediate	Self-reported	Exposure	No
Freedman et al[77] 1997	F	40	Not specified	Self-reported	Exposure	No
Gonzalez-Delgado et al[78] 2006	F	7	Delayed	Skin test, patch test	Skin test, patch test	No
Ho et al[79] 2004	F	74	Delayed	*in vitro*	*in vitro* IgE	No
Jao et al[80] 2006	F	37	Not specified	Self-reported	Exposure	Yes
Kraushar et al[81] 1994	F	72	Not specified	Self-reported	Exposure	Yes
Moake et al[82] 1978	F	39	Immediate	*in vitro*	*in vitro* IgE	Yes
Nemati et al[83] 1981	M	24	Delayed	Self-reported	Exposure	Yes
Philips et al[84] 2001	Not specified	Not specified	Delayed	Skin test, patch test	Skin test	Yes
Vogt et al[85] 1998	F	46	Delayed	Self-reported	Exposure	No
Patients with index cefazolin allergy and assessed for penicillin allergy						
Almeida et al[86] 2017	F	36	Immediate	Provocation test	Skin test, *in vitro* IgE	No
Almeida et al[86] 2017	F	49	Immediate	Provocation test	Skin test, *in vitro* IgE	No
Chan et al[87] 2016	Not specified	Not specified	Immediate	Skin test	Skin test	Yes
Culp et al[88] 2017	M	44	Immediate	Skin test, *in vitro*	Exposure	No

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Gonzalo-Garijo et al[89] 2006	F	66	Not specified	Skin test, provocation test	Skin test	No
Igea et al[90] 1992	F	21	Immediate	Skin test, provocation test	Skin test, *in vitro* IgE	No
Igea et al[90] 1992	F	45	Immediate	Skin test, provocation test	Skin test, *in vitro* IgE	No
Lee et al[91] 2004	F	46	Immediate	Skin test	Skin test	No
Padial et al[92] 2008	Not specified	43	Delayed	Skin test, provocation test	Skin test, provocation test	No
Pinheiro et al[93] 2018	F	31	Delayed	Patch test	Patch test	Yes
Romano et al 2001[94]	F	44	Delayed	Skin test, patch test, *in vitro*, provocation test	Skin test, patch test, *in vitro* IgE, provocation test	No
Romeira et al[63] 2017	Not specified	Not specified	Not specified	Skin test	Skin test	No
Somech et al[95] 2009	M	12	Immediate	Skin test, provocation test	Skin test	No
Tayman et al[96] 2008	F	0	Immediate	Skin test, *in vitro*	Skin test, *in vitro* IgE	Yes
Velasco et al[97] 2009	F	63	Delayed	Skin test, patch test, *in vitro*, provocation test	Skin test, patch test, *in vitro* IgE, provocation test	No
Vieira et al[98] 2009	M	32	Immediate	Skin test, *in vitro*	Skin test	No
Weber et al[99] 1996	F	33	Immediate	Skin test, provocation test	Skin test	No
Wieczorek et al[100] 2008	F	18	Immediate	Skin test, *in vitro*, provocation test	Skin test, *in vitro* IgE	No
Yun et al[101] 2016	M	26	Immediate	Skin test	Skin test	No
Patients with index beta-lactam allergy and assessed for penicillin and cefazolin allergy						
Classen et al[102] 2015	F	24	Not specified	Skin test	Skin test, patch test	Yes
Gonzalo-Garijo et al[89] 2006	M	80	Not specified	Skin test, provocation test	Skin test	No
Rozlucka et al[103] 2019	Not specified	65	Not specified	Skin test, provocation test	Skin test, provocation test	No

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eTable 4. Risk of bias of individual studies

Study	Risk of Bias				
	Representation of the target population	Consecutive sampling	Non-response bias	Definition of the allergic reaction	Consistency of data collection/assessment
Studies assessing patients with index penicillin allergy (tested for cefazolin)					
Castleton B (1976)	🔴	🟡	🟡	🟢	🟢
Pines A (1977)	🟢	🟡	🔴	🟡	🟢
Beam TR (1984)	🔴	🟢	🟢	🟢	🟢
Aihara M (1987)	🟡	🟡	🔴	🟡	🟢
Goodman EJ (2001)	🔴	🔴	🔴	🟢	🟢
Novalbos A (2001)	🟢	🔴	🟢	🟢	🟢
Fonacier L (2005)	🟡	🔴	🔴	🟢	🟢
Park M (2006)	🟢	🔴	🔴	🟢	🟢
Park M (2010)	🟡	🔴	🔴	🟢	🟢
Ponvert C (2011)	🟢	🟢	🟢	🟢	🟢
Haslam S (2012)	🔴	🔴	🔴	🟢	🟢
Cook DJ (2014)	🔴	🔴	🔴	🟢	🟢
Beltran RJ (2015)	🟢	🔴	🔴	🟢	🟢
Blumenthal KG (2015)	🟢	🔴	🔴	🟢	🟢
Laaouaj J (2016)	🔴	🟢	🔴	🟢	🟢

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Desai SH (2017)	●	●	●	●	●
Michaud L (2017)	●	●	●	●	●
Turner NA (2018)	●	●	●	●	●
Astey K (2019)	●	●	●	●	●
Blumenthal KG (2019)	●	●	●	●	●
Desravines N (2019)	●	●	●	●	●
Jimenez-Rodriguez T (2019)	●	●	●	●	●
Schlosser KA (2019)	●	●	●	●	●
Thellier C (2019)	●	●	●	●	●
Trubiano J (2019)	●	●	●	●	●
Ahmad H (2020)	●	●	●	●	●
Lam PW (2020)	●	●	●	●	●
Maguire M (2020)	●	●	●	●	●
Romano A (2020)	●	●	●	●	●
Studies assessing patients with index cefazolin allergy (tested for penicillins)					
Warrington RJ (1996)	●	●	●	●	●
Romano A (2010)	●	●	●	●	●
Pipet A (2011)	●	●	●	●	●
Cook DJ (2014)	●	●	●	●	●
Alves C (2015)	●	●	●	●	●
Romano A (2015)	●	●	●	●	●
Chng H (2016)	●	●	●	●	●
Kuhlen JL (2016)	●	●	●	●	●
Uyttebroek AP (2016)	●	●	●	●	●
Farinha SM (2018)	●	●	●	●	●
Laguna JJ (2018)	●	●	●	●	●
Mota I (2018)	●	●	●	●	●
Jimenez-Rodriguez T (2019)	●	●	●	●	●
Li J (2019)	●	●	●	●	●
Yuson C (2019)	●	●	●	●	●

Legend: ● - Low risk of bias; ● - Unclear risk of bias; ● - High risk of bias.

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