MAJOR ARTICLE

A Systematic Review: Can One Prescribe Carbapenems to Patients With IgE-Mediated Allergy to Penicillins or Cephalosporins?

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Background. Cross-reactivity between penicillins or cephalosporins and carbapenems is anticipated as all have a beta lactam ring. However, the true incidence of immunoglobulin (Ig)E-mediated cross-reactivity is not known.

Methods. A systematic review was conducted to collect and combine all published data on children and adults reported to have a clinical history of IgE-mediated hypersensitivity to a penicillin and/or cephalosporin who were subsequently given a carbapenem. Reactions were classified as proven, suspected, or possible IgE-mediated and non–IgE-mediated.

Results. Ten studies and 12 case reports describing 854 participants fit the study criteria. For patients with previous proven, suspected, or possible IgE-mediated penicillin reactions (N = 838), the incidence of any type of suspected hypersensitivity reaction to a carbapenem was 36/838 (4.3%; 95% confidence interval [CI], 3.1%–5.9%) and the incidence of proven (1/838), suspected (0/838), or possible (19/838) IgE-mediated reactions was 20/838 (2.4%; 95% CI, 1.6%–3.7%). Of the subset of patients with positive penicillin skin tests (n = 295), only 1 had a hypersensitivity reaction (0.3%; 95% CI, .06%–1.9%), and this was a possible IgE-mediated reaction. For patients with previous proven, suspected, or possible IgE-mediated cephalosporin reactions (N = 12), the incidence of any type of hypersensitivity reaction to a carbapenem was 3/12 (25%); this included 2 non–IgE-mediated reactions and 1 possible IgE-mediated reaction.

Conclusions. The cross-reactivity between penicillins and carbapenems for IgE-mediated reactions is very low, but caution is still advised. Cross-reactivity rates may be higher between cephalosporins and carbapenems; however, minimal data are available.

Keywords. drug allergy; cross-reactivity; carbapenem; penicillin; cephalosporin.

Penicillins or cephalosporins can cause any of the 4 types of Gell and Coombs immunologic hypersensitivity reactions, although immunoglobulin (Ig)E-mediated reactions (type I) and delayed cutaneous reactions (mostly type IV) are most commonly encountered. IgE-mediated reactions are of particular concern as they can be life threatening. This type of reaction presents with various combinations of pruritus, flushing, urticaria, angioedema, wheezing, laryngeal edema, abdominal distress with emesis or diarrhea, and hypotension. Recurrence risk with reexposure to the same drug is not known but is thought to be substantial; subsequent reactions are often more severe than was the initial reaction.

Patients with IgE-mediated allergy to penicillins or cephalosporins may react to the beta lactam ring structure that is common to all penicillins, cephalosporins, monobactams, and carbapenems or to the R-group side chains that distinguish different penicillins or cephalosporins from one another. In the United States, most penicillin-allergic patients are thought to be sensitive to the beta lactam core, and so one would anticipate cross-reactivity with other beta lactams. In contrast, where amoxicillin constitutes 90% of antibiotic use in certain southern European countries, up to one-third of patients appear to react to the R-group side chain [1].

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The rate of cross-reactivity of penicillins with cephalosporins was originally reported to be about 10%. However, the true rate with newer cephalosporins appears to be much lower; an incidence of approximately 1% was recently reported in a literature review [2]. Some have suggested that the incidence of cross-reactivity between penicillins and carbapenems may be even lower [3]. Very little has been published on the cross-reactivity rate between cephalosporins and carbapenems. Not unexpectedly, a recent study has demonstrated that many allergists, internists, pediatricians, and family physicians are unclear as to whether patients with penicillin allergy can be prescribed cephalosporins or carbapenems [3].

Our primary objective in this systematic review was to determine if carbapenems can be safely prescribed for patients who have had presumed IgE-mediated reactions to penicillins or cephalosporins. Because patients with IgE-mediated reactions to 1 antibiotic are more likely than controls to have allergies to any other antibiotic, one would anticipate some cross-reactivity. Our hypothesis was that although there would be some cross-reactivity, the rate of life-threatening events upon challenge with a carbapenem would be <1%.

METHODS

The systematic review protocol was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [4].

Inclusion Criteria

Any article that described the outcome when 1 or more patients of any age with a history of symptoms compatible with IgE-mediated allergy to any penicillin or cephalosporin subsequently receiving a minimum of 1 dose of any carbapenem was included in the study. No language or publication date restrictions were imposed, and all study designs were included.

Exclusion Criteria

Reports of patients who had only a positive skin test to a penicillin or cephalosporin but presumably were never given a penicillin or cephalosporin were excluded, as the positive predictive value of penicillin skin tests for IgE-mediated reactions is low [5]. Carbapenem skin testing alone was not considered to be administration of a carbapenem. Articles that did not specify the class of beta lactam that resulted in the original suspected IgE-mediated reaction were excluded.

Definitions

A reaction was considered to be proven IgE mediated if the patient had a serious allergic reaction (defined as those that resulted in hypotension, wheezing, angioedema, laryngeal edema, hospitalization, or death) with onset of symptoms within 4 hours of drug administration. A reaction was considered to be a suspected IgE-mediated reaction if the patient developed pruritus, flushing, an urticarial rash, or edema within 4 hours of drug administration and the author attributed the symptoms to the drug. A possible IgE-mediated reaction was considered when symptoms were not well described or when symptoms of a serious allergic reaction were documented to start more than 4 hours after drug administration yet the author considered them to be IgE mediated. For example, patient-reported reactions with few details provided were considered to be possible IgE-mediated reactions. However, maculopapular rashes or gastrointestinal reactions alone were considered to be non–IgE-mediated, even if the authors considered them to be IgE mediated. Results of skin tests for penicillins, cephalosporins, or carbapenems were recorded when provided. However, as mentioned previously, positive skin tests alone were not considered to be proof of IgE-mediated reactions.

Search Strategy

The search was performed in May 2013 and included Ovid MEDLINE (1946–present), PubMed (inception–present), Embase (1974–present), Scopus (inception–present), and the Cochrane Library (inception–present). The following terms were searched and combined with variations of "hypersensitivity" and "cross reactions" and finally with "penicillin" and "cephalosporin": "carbapenem," "thienamycin," "imipenem," "meropenem," "ertapenem," "doripenem," "eripenem," "primaxin," "doribax," "invanz," "panipenem," "biapenem," "merrem," "meronem," and "faropenem" (Supplementary Appendix 1). The references within articles that met the inclusion criteria were hand searched for additional articles. Hand searches were also performed for articles that cited those that met the inclusion criteria. Also, 2 authors were personally contacted to obtain clarification regarding their studies.

Process of Study Selection and Data Collection

Two investigators (G. D. and B. K.) independently reviewed the titles and abstracts from the search and obtained the required data from studies that met the inclusion criteria. The 2 investigators then reached consensus on which articles met the inclusion criteria and confirmed the data. Any inability to reach a consensus was reconciled by discussion with the third investigator (J. L. R.).

Data Collection

Data extracted from each article that met the inclusion criteria included the following: evidence of allergy to a penicillin and/or a cephalosporin, with subsequent classification as proven, suspected, or possible IgE-mediated reaction using the definitions above; results of penicillin or cephalosporin skin testing if performed; the country where the study took place; the age of the

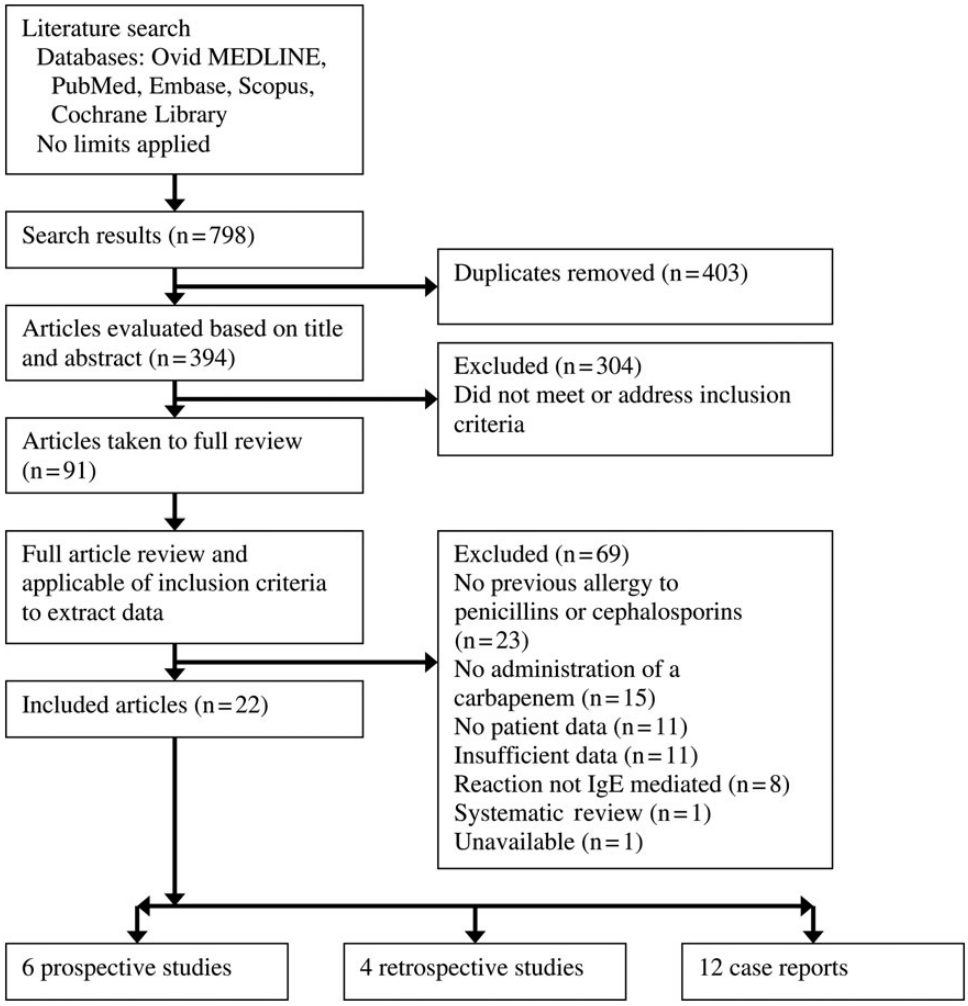

Figure 1. Flow chart of methodology for studies chosen for the review. Abbreviation: Ig, immunoglobulin.

patient(s); the number of patients who met the inclusion criteria; the type of carbapenem administered; the number of patients with any kind of hypersensitivity reaction attributed to carbapenems; and classification of IgE-mediated reactions to carbapenems as proven, suspected, or possible using the definitions above.

Data Analysis

Studies were combined where feasible to report the types of reactions to carbapenems in patients with possible, suspected, and proven IgE-mediated reactions to penicillins and to cephalosporins. If patients had a previous IgE-mediated reaction of different severity to both a penicillin and a cephalosporin, they were classified as having the more severe reaction. For the subset of patients who had skin test results reported for penicillins or cephalosporins, reactions to carbapenems were compared for those with positive vs negative tests. Ideally, one would determine risk factors for reactions to carbapenems (eg, gender, age, severity of symptoms upon exposure to penicillins or cephalosporins). However, given anticipated significant study heterogeneity, this was not thought to be practical.

Risk of Bias Across Individual Studies

Due to safety concerns, 4 patients who would have otherwise met the eligibility criteria for the current systematic review were not given a carbapenem as they had a positive carbapenem skin test. This could artificially decrease our reported cross-reactivity incidence, and those patients were not included in the review.

Assumptions Made

Patients were stratified according to proven, suspected, or possible IgE-mediated reaction to penicillins, cephalosporins, or both within each study if specific details were provided. In

Table 1. Case Series of Children or Adults With Previous Immunoglobulin E-Mediated Reactions to Penicillins or Cephalosporins Subsequently Given Carbapenems

Source	Study Design	Class of Drug Causing Previous Reaction	Number of Patients Meeting Inclusion Criteria	Age Range (Years)	Classification of Penicillin/ Cephalosporin Reaction	Carbapenem Administered
Atanasković-Marković et al (2008) [9]	Prospective	Penicillin	107	4–13	Proven IgE-mediated	Meropenem
Atanasković-Marković et al (2009) [7]	Prospective	Penicillin	123	4–13	Proven IgE-mediated	Imipenem
Cunha et al (2008) [11]	Prospective	Penicillin	110	28–94	51 proven and 59 possible IgE-mediated	Meropenem
Patriarca et al (1999) [6]	Prospective	Penicillin	9	17–63	4 possible, 2 suspected, and 3 proven IgE-mediated	Imipenem
Romano et al (2006) [8]	Prospective	Penicillin	110	45.56 ± 15.66	Proven IgE-mediated	Imipenem
Romano et al (2007) [10]	Prospective	Penicillin	103	14–83	Proven IgE-mediated	Meropenem
Lager et al (2009) [12]	Retrospective	Penicillin	94	>18	7 proven, 32 suspected, and 55 possible IgE-mediated	Imipenem, meropenem or ertapenem
McConnell et al (2000) [13]	Retrospective	Penicillin	63	20–74	Possible IgE-mediated	Imipenem
Prescott et al (2004) [14]	Retrospective	Penicillin	100	2–86	Possible IgE-mediated	Imipenem or meropenem
Sodhi et al (2004) [15]	Retrospective	Penicillin	163	32–91	10 proven and 153 possible IgE-mediated	Imipenem or meropenem

Abbreviation: Ig, immunoglobulin.

each category, the age range of those in the entire study was applied since the exact ages of patients in each category were not available.

RESULTS

The search provided 798 citations. After discarding duplicates, 395 items remained, of which 91 were potentially relevant for review in full, with the exception of 1 that could not be obtained and 1 that was in Italian but did not appear to be relevant from the abstract. Six prospective studies, 4 retrospective studies, and 12 case reports met the eligibility criteria for the review (Figure 1). No items based on references from the eligible articles were added to the systematic review, nor were supplementary items added based on review of citations of included articles.

Study Characteristics

The 6 prospective studies were published in English and all examined the cross-reactivity between penicillins and carbapenems (Table 1). Three used imipenem [6–8] and 3 meropenem [9–11]. Five of the 6 studies looked at patients with previous IgE-mediated hypersensitivity reactions specifically, while 1 study aimed to include patients with previous cell-mediated reactions [6]. The latter study, however, described 9 patients who met our study definition of IgE-mediated reactions, and these 9 patients were included. The age range was not reported for 1 study, and the author did not reply when these data were requested [8].

The 4 retrospective studies were published in English and also examined the cross-reactivity between penicillins and carbapenems (Table 1) [12–15].

Of the 12 case reports, 10 were published in English, 1 in Spanish [16], and 1 in French [17]. Five of the case reports described patients with previous reactions to penicillins [18–22], 3 to cephalosporins [17, 23, 24], and 4 to both penicillins and cephalosporins [16, 25–27].

Participants

The total number of potential participants in the studies was 1006. Four were excluded as they were not given a carbapenem due to a positive carbapenem skin reaction, including 1 patient from the Romano et al imipenem study (who was also in the meropenem study) [8, 10] and 1 patient reported in each of the Atanasković-Marković et al studies [7, 9]. Another 148 patients were excluded as they were described in more than 1 study (81 duplicate patients arose from the 2 Atanasković-Marković et al studies [7, 9] and 67 from the 2 Romano et al studies [8, 10]). The remaining 854 constituted 838 patients

Table 2. Reactions to Carbapenems in Children and Adults With Previous Immunoglobulin E-Mediated Reactions to Penicillins

Reference	Evidence for Allergy	Skin Test	Country	Age of Population (Years)	N	Type of Carbapenem	Number With Proven IgE-Mediated Reactions to Carbapenem	Number With Suspected IgE-Mediated Reactions to Carbapenem	Number With Possible IgE-Mediated Reactions to Carbapenem	Number With Non–IgE-Mediated Reactions to Carbapenem	Total Number With Reactions to Carbapenem
Atanasković-Marković et al (2009, 2008) [7, 9]	Proven IgE-mediated	Positive	Serbia	3–14	81	Imipenem and meropenem	0	0	0	0	0
Cunha et al (2008) [11]	Proven IgE-mediated	NR	United States	28–94	51	Meropenem	0	0	0	0	0
Atanasković-Marković et al (2009) [7]	Proven IgE-mediated	Positive	Serbia	3–14	42	Imipenem	0	0	0	0	0
Atanasković-Marković et al (2008) [9]	Proven IgE-mediated	Positive	Serbia	3–14	26	Meropenem	0	0	0	0	0
Sodhi et al (2004) [15]	Proven IgE-mediated	NR	United States	32–91	10	Imipenem or meropenem	0	0	0	1	1
Lager et al (2009) [12]	Proven IgE-mediated	NR	United States	>18	7	Imipenem, meropenem, or ertapenem	0	0	0	0	0
Patriarca et al (1999) [6]	Proven IgE-mediated	Negative	Italy	23–60	3	Imipenem	0	0	0	0	0
Gorman et al (2003) [18]	Proven IgE-mediated	Positive	Canada	40	1[a]	Imipenem	0	0	1	0	1
Romano et al (2007) [10]	Suspected IgE-mediated	Positive	Italy	14–83	35	Meropenem	0	0	0	0	0
Romano et al (2006, 2007) [8, 10]	Suspected IgE-mediated	Positive	Italy	NR	68	Imipenem and meropenem	0	0	0	0	0
Romano et al (2006) [8]	Suspected IgE-mediated	Positive	Italy	44.56 ± 15.66	42	Imipenem	0	0	0	0	0
Lager et al (2009) [12]	Suspected IgE-mediated	NR	United States	>18	32	Imipenem, meropenem, or ertapenem	0	0	1	0	1
Patriarca et al (1999) [6]	Suspected IgE-mediated	Negative	Italy	27 and 29	2	Imipenem	0	0	0	0	0

Table 2 continued.

Reference	Evidence for Allergy	Skin Test	Country	Age of Population (Years)	N	Type of Carbapenem	Number With Proven IgE-Mediated Reactions to Carbapenem	Number With Suspected IgE-Mediated Reactions to Carbapenem	Number With Possible IgE-Mediated Reactions to Carbapenem	Number With Non–IgE-Mediated Reactions to Carbapenem	Total Number With Reactions to Carbapenem
Sodhi et al (2004) [15]	Possible IgE-mediated	NR	United States	32–91	153	Imipenem or meropenem	1	0	2	11	14
Prescott Jr et al (2004) [14]	Possible IgE-mediated	NR	United States	2–86	100	Imipenem or meropenem	0	0	8	3	11
McConnell et al (2000) [13]	Possible IgE-mediated	NR	United States	20–74	63	Imipenem	0	0	6	0	6
Cunha et al (2008) [11]	Possible IgE-mediated	NR	United States	30–92	59	Meropenem	0	0	0	0	0
Lager et al (2009) [12]	Possible IgE-mediated	NR	United States	>18	55	Imipenem, meropenem or ertapenem	0	0	1	0	0
Patriarca et al (1999) [6]	Possible IgE-mediated	Negative	Italy	17–63	4	Imipenem	0	0	0	0	0
Lambden et al (2010) [19]	Possible IgE-mediated	NR	United Kingdom	64	1	Meropenem	0	0	0	1	1
Satta et al (2012) [20]	Possible IgE-mediated	NR	United Kingdom	38	1	Ertapenem	0	0	0	0	0
Modi et al (2011) [21]	Possible IgE-mediated	NR	United States	62	1	Imipenem	0	0	0	0	0
Kushawaha et al (2009) [22]	Possible IgE-mediated	NR	United States	27	1[b]	Meropenem	0	0	0	0	0

Abbreviations: Ig, immunoglobulin; NR, not reported.

[a] Patient had previous reaction to carbapenem administration, but was successfully desensitized to tolerate the described course.

[b] Patient was initially desensitized to penicillin G, then tolerated the course of meropenem without incident, but was concurrently dosed with diphenhydramine.

Table 3. Reactions to Carbapenems in Children and Adults With Previous Immunoglobulin E-Mediated Reactions to Cephalosporins

Reference	Evidence for Allergy	Skin Test	Country	Age of Population (Years)	N	Type of Carbapenem	Number With Proven IgE-Mediated Reactions to Carbapenem	Number With Suspected IgE-Mediated Reactions to Carbapenem	Number With Possible IgE-Mediated Reactions to Carbapenem	Number With Non–IgE-Mediated Reactions to Carbapenem	Total Number With Reactions to Carbapenem
Aouam et al (2006) [23]	Suspected IgE-mediated	NR	Tunisia	18	1	Imipenem	0	0	0	0	0
Chavez et al (2010) [24]	Suspected IgE-mediated	NR	United States	17	1	Meropenem	0	0	0	1	1
Prescott Jr et al (2004) [14]	Possible IgE-mediated	NR	United States	0.08–89	9	Imipenem or meropenem	0	0	1	0	1
Barbeau et al (1991) [17]	Possible IgE-mediated	NR	France	30	1	Imipenem	0	0	0	1	1

Abbreviations: Ig, immunoglobulin; NR, not reported.

with previous penicillin reaction, 12 with previous cephalosporin reaction, and 4 with previous reactions to both a penicillin and a cephalosporin.

Cross-Reactivity Rates

For patients with previous proven, suspected, or possible IgE-mediated penicillin reactions (N = 838), the incidence of any type of reaction to a carbapenem was 36/838 (4.3%; 95% confidence interval [CI], 3.1%–5.9%) and the incidence of proven (1/838), suspected (0/838), or possible (19/838) IgE-mediated reactions was 20/838 (2.4%; 95% CI, 1.6%–3.7%). Looking only at the subset of patients with previous proven, suspected, or possible IgE-mediated penicillin reactions who had a positive skin test (N = 295), the incidence of any type of reaction to a carbapenem was 1/295 (0.3%; 95% CI, .06%–1.9%), with the 1 reaction being possibly IgE mediated (Table 2). Nine patients were documented to have a negative penicillin skin test, and all tolerated a carbapenem.

Only 12 patients had a previous IgE-mediated cephalosporin reaction, of which 10 were possible, 2 were suspected, and none were proven. Three of the 12 had reactions to cephalosporins, of which 2 were not IgE mediated and 1 was possibly IgE mediated (Table 3). Only 4 patients had previous reactions to both penicillins and cephalosporins, with 1 having a suspected IgE-mediated reaction to a carbapenems (Table 4).

Overall, the incidence of any reaction to a carbapenem after a previous history of a proven, suspected, or possible IgE-mediated reaction to a penicillin (N = 838), cephalosporin (N = 12), or both (N = 4) was 40/854 (4.7%). For those with proven IgE-mediated reactions to a penicillin (N = 221), cephalosporin (N = 0), or both (N = 0), the incidence of a proven (N = 0), suspected (N = 0), or possible (N = 1) IgE-mediated reaction to a carbapenem was 1/221 (0.5%; Table 5).

DISCUSSION

This systematic review included 838 patients with some evidence for an IgE-mediated reaction to penicillin who were subsequently given a carbapenem, of which 36 (4.3%) had a suspected hypersensitivity reaction. However, only 20 of these reactions were compatible with an IgE-mediated reaction, and only 1 was considered to be a proven IgE-mediated reaction. There is a paucity of data on the use of carbapenems in patients with IgE-mediated reactions to cephalosporins (N = 12) or to both a penicillin and a cephalosporin (N = 4). This lack of data fits with the fact that cephalosporin hypersensitivity may now be much rarer than reported in studies with older cephalosporins.

A previous systematic review published by Frumin and Gallagher in 2009 examined the cross-reactivity between penicillins or monobactams and carbapenems, demonstrating no definitive

Table 4. Reactions to Carbapenems in Children and Adults With Previous Immunoglobulin E-Mediated Reactions to Both Penicillins and Cephalosporins

Reference	Evidence for Penicillin Allergy	Evidence for Cephalosporin Allergy	Skin Test	Country	Age of Population (Years)	N	Reaction to Carbapenem
Wilson et al (2003) [25]	Suspected IgE-mediated	Possible IgE-mediated	Positive for penicillins and cephalosporins	United States	20	1[a]	Suspected IgE-mediated reaction to imipenem
de Escalante Yanguela et al (2007) [16]	Possible IgE-mediated	Possible IgE-mediated	NR	Spain	75	1	No reaction to imipenem
Wojewoda et al (2012) [26]	Possible IgE-mediated	Possible IgE-mediated	NR	United States	23	1	No reaction to imipenem or meropenem
Sawhney et al (1996) [27]	Possible IgE-mediated	Possible IgE-mediated	NR	United States	79	1	No reaction to imipenem

Abbreviations: Ig, immunoglobulin; NR, not reported.

[a] Patient was subsequently successfully desensitized to meropenem.

Table 5. Number of Reactions to Carbapenems in Children or Adults With Previous Immunoglobulin E-Mediated Reactions to Penicillins or to Cephalosporins

Type of Previous Reaction to Penicillin/ Cephalosporin	Proven IgE-Mediated Reaction to Carbapenem	Suspected IgE-Mediated Reaction to Carbapenem	Possible IgE-Mediated Reaction to Carbapenem	Total IgE-Mediated Reaction to Carbapenem	Non–IgE-Mediated Reaction to Carbapenem	Total Reaction to Carbapenem (IgE and Non–IgE-Mediated)
Proven IgE-mediated reaction to a penicillin	0/221	0/221	1/221 or 0.5%	1/221 or 0.5%	1/221 or 0.5%	2/221 or 0.9%
Suspected IgE-mediated reaction to a penicillin	0/182	0/182	1/182 or 0.5%	1/182 or 0.5%	0/182	1/182 or 0.5%
Possible IgE-mediated reaction to a penicillin	1/451 or 0.2%	0/451	17/451 or 3.8%	18/451 or 4.0%	15/451 or 3.3%	33/451 or 7.3%
Proven, suspected, or possible IgE-mediated reaction to a penicillin AND positive skin test to a penicillin	0/295	0/295	1/295 or 0.3%	1/295 or 0.3%	0/295	1/295 or 0.3%
Proven, suspected, or possible IgE-mediated reaction to a penicillin AND results of penicillin skin test not known	1/534 or 0.2%	0/534	18/534 or 3.4%	19/534 or 3.6%	16/534 or 3.0%	35/534 or 6.6%
Proven, suspected, or possible IgE-mediated reaction to a penicillin AND negative skin test to a penicillin	0/9	0/9	0/9	0/9	0/9	0/9
Proven IgE-mediated reaction to a cephalosporin	0	0	0	0	0	0
Suspected IgE-mediated reaction to a cephalosporin	0/2	0/2	0/2	0/2	1/2 or 50%	1/2 or 50%
Possible IgE-mediated reaction to a cephalosporin	0/10	0/10	1/10 or 10%	1/10 or 10%	1/10 or 10%	2/10 or 20%

Abbreviation: Ig, immunoglobulin.

cross-reactivity rate for penicillins and a negligibly low incidence for aztreonam [28]. However, that review differed from our review in that the researchers included patients with positive skin tests to penicillins with no documentation that they had ever had an IgE-mediated reaction to a penicillin. Given the relatively high rate of false-positive penicillin skin tests [29, 30], this could potentially lead to underestimation of the cross-reactivity between carbapenems and other beta lactams. The previous review reported the potential utility of carbapenem skin testing, as throughout various studies, all patients with negative carbapenems skin tests (N = 320) subsequently tolerated carbapenems [28].

One limitation of our systematic review is the highly heterogeneous patient population examined. One would assume that only a small percentage of patients exposed to carbapenems with an IgE-mediated reaction to other classes of beta lactams are reported in the literature, and it is difficult to predict if authors are more likely to report those with or without reactions to carbapenems. One would anticipate that patients challenged with carbapenems had less serious reactions to other beta lactams than did patients who were not challenged. Authors also may not have always made the correct judgment as to whether an adverse event was drug related. Authors used many different definitions for what constituted an IgE-mediated reaction. Our ability to accurately classify IgE-mediated reactions as possible, probable, or proven depended on the limited information provided by authors. There were also limitations of the individual studies included. Some included only patients with previous proven IgE-mediated reactions, while others included patients with less convincing previous reactions, such as a patient-reported history alone.

Given the low rate of cross-reactivity in previous studies, when antibiotics are required in patients with IgE-mediated reactions to penicillins, carbapenems would appear to be a reasonable option. However, one should still proceed with caution. The first dose of carbapenem should be given in a setting where anaphylaxis can be managed. One option would be to challenge with a very low dose of the carbapenem, such as 1% of the full dose. If the patient has no reaction, then 10% of the full dose could be given 1 hour later, followed by the full dose 1 hour later if the patient remains asymptomatic. The data on the cross-reactivity between cephalosporins and carbapenems are sparse, so again, a protocol with challenge doses should be strongly considered. If the patient has a reaction during the challenge, options are to formally desensitize to the carbapenem or to change to a non–beta lactam antibiotic. Although carbapenem skin tests are not well validated, a negative result appears to predict that it is likely that carbapenems will be tolerated and so may play a role in future algorithms for management of such patients [28].

Priorities for future research include prospective studies of the outcomes when larger numbers of unselected patients with IgE-mediated reactions to other beta lactams are given carbapenems and validation of carbapenem skin testing.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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