

MINIREVIEW

Clinical Importance of Carbapenem Hypersensitivity in Patients with Self-Reported and Documented Penicillin Allergy

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The risk of carbapenem hypersensitivity in patients with self-reported or documented penicillin allergy needs to be determined so that practitioners can make better-informed decisions regarding antibiotic therapy for this patient population. The risk of cross-reactivity between penicillin and carbapenem antibiotics initially was reported to approach 50%. Recent retrospective studies have suggested that the clinical risk of cross-hypersensitivity between these two drug classes is 9.2–11%, which is significantly lower than initially reported. Patients whose history of penicillin allergy is self-reported and is not type 1 may be at moderate risk for hypersensitivity when treated with a carbapenem antibiotic. The risk of hypersensitivity appears to be higher in patients whose penicillin allergy was documented by a health care provider, those with several antibiotic allergies, and those with a positive penicillin skin test result or a history of type 1 penicillin hypersensitivity.

Key Words: carbapenem, meropenem, imipenem-cilastatin, penicillin, allergy, hypersensitivity.

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OUTLINE

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The most common adverse effect associated with the β -lactam antibiotics is drug hypersensitivity.¹ Hypersensitivity reactions are classified as types 1–4, or as idiopathic. Type 1 hypersensitivity is mediated through immunoglobulin (Ig) E antibodies, is immediate, and most often manifests as anaphylaxis, urticaria, or hives. Types 2 and 3 are mediated through either IgG or IgM antibodies, and are more delayed than type 1. Type 2 manifests clinically as hemolytic

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anemia, cytopenia, or interstitial nephritis, and type 3 as serum sickness or drug fever. Type 4 is a delayed T-cell-mediated reaction manifested as contact dermatitis. Allergic reactions not encompassed by any of the types described are defined as idiopathic, and include eosinophilia, maculopapular rash, and Stevens-Johnson syndrome.

Carbapenem-Associated Hypersensitivity

The β -lactam antibiotics consist of the penicillins, cephalosporins, and carbapenems, and the monobactam aztreonam. Except for aztreonam, drugs in these classes are structurally related in that they possess a bicyclic core structure, the chemical entity historically believed to be most responsible for β -lactam cross-hypersensitivity (Figure 1).^{2, 3} Three carbapenem antibiotics have been approved by the United States Food and Drug Administration (FDA): imipenem-cilastatin, meropenem, and

ertapenem.⁴⁻⁶ The frequency of carbapenem-associated hypersensitivity in the general population is estimated as less than 3%.⁷⁻⁹ However, the risk of type 1 hypersensitivity in patients with a history of IgE antibodies to penicillin has been reported to approach 50%, and the package inserts for each carbapenem caution against their administration in patients with a history of penicillin hypersensitivity.^{4-6, 10}

In clinical practice, physicians must rely on a patient's self-reported allergy history or, if available, information contained in the patient's medical record. Three retrospective studies reported the clinical risk of carbapenem hypersensitivity in patients who reported or had a documented history of penicillin allergy.¹¹⁻¹³

Our objective was to determine the risk of carbapenem hypersensitivity in patients with self-reported or documented penicillin allergy, so practitioners can make better-informed decisions regarding antibiotic therapy for this patient population. Searches of MEDLINE (January 1966–June 2006) and the Cochrane Library were performed using the key terms hypersensitivity, allergy, penicillin, carbapenem, imipenem, meropenem, and ertapenem. In addition, an extensive manual review of scientific journals was performed to identify pertinent studies.

Clinical Studies

The first study to examine the potential for immune-mediated cross-reactivity between carbapenem and penicillin antibiotics was published in 1988.¹⁰ The authors estimated the frequency of cross-hypersensitivity as approximately 25% in patients reportedly allergic to penicillin and 50% in those deemed by skin testing to be truly allergic to penicillin. Initially, 40 healthy subjects with a history of penicillin allergy were enrolled in the study; many were positive for allergy based on previous skin testing.

Antihistamines and β -adrenergic drugs were avoided by all study participants for 72 hours before skin testing. Each participant was initially given a skin test with buffer and histamine controls to exclude those without an innate immune response. Subsequently, each subject was tested for reactivity to major (penicilloyl) and minor (penicillin, penicilloate, penilloate) penicillin determinants, and then to analogous imipenem reagents (imipenemoyl, imipenem, imipenemoate). A positive skin test was defined as producing a wheal at least 5 mm in diameter.

Of the 39 penicillin-allergic subjects for whom data were reported, 19 had positive penicillin skin tests: three (16%) demonstrated allergy to the major determinant, 13 (68%) to the minor determinants, and three (16%) to both major and minor determinants. Nine (47%) of the 19 subjects demonstrated a response when challenged with one or more imipenem reagents. In six of these nine, the reaction to the imipenem determinant was correlated with the reaction to an analogous penicillin minor determinant. One subject reacted to imipenem reagents but not to penicillin. Only one demonstrated reactivity on skin testing with cilastatin; this subject's penicillin and imipenem skin tests were negative. When all subjects with a reported history of

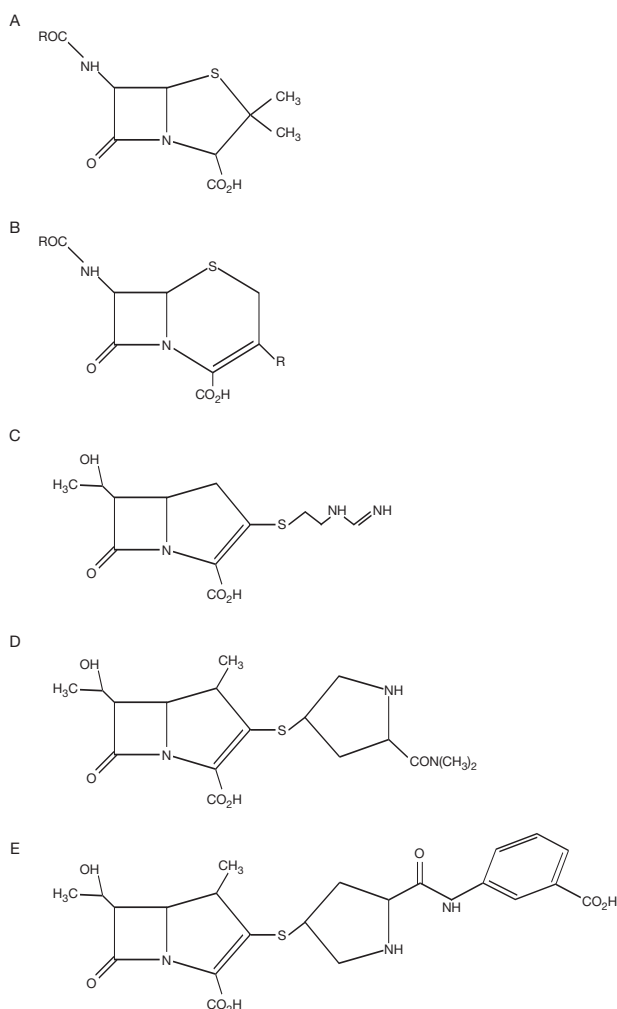


Figure 1. Structural relationships among penicillin (A), cephalosporin (B), imipenem-cilastatin (C), meropenem (D), and ertapenem (E). They each possess a bicyclic core structure, the chemical entity historically believed to be most responsible for β -lactam cross-hypersensitivity.

penicillin hypersensitivity were included in the analysis, the risk of cross-hypersensitivity was 25.6% (10 of 39 patients).

This study was well designed to estimate the cross-reactive risk in patients with documentation of a positive skin test with penicillin. The results suggest that patients with a history of penicillin allergy—particularly those deemed truly allergic as defined by *in vivo* skin testing—are at a significant risk of type 1-mediated hypersensitivity to imipenem-cilastatin. The clinical risk of type 1-mediated cross-hypersensitivity between penicillin and carbapenems cannot be discerned from this study, however, as imipenem-cilastatin was not administered in therapeutic doses by the accepted routes of administration—intravenous infusion or intramuscular injection.

Only 10–20% of patients in the general population who report a history of penicillin allergy are truly allergic based on skin testing.¹⁴ Although testing is useful in identifying patients at risk for type 1 hypersensitivity, it is not routinely performed in clinical practice. Practitioners must therefore rely on a patient's self-reported allergy history and on data readily available in the medical chart when making treatment decisions. This may be an arduous task because up to 40% of patients with self-reported antibiotic allergy describe allergic symptoms deemed nonimmunologic. In addition, as little as 4% of drug orders and 16–32% of physicians' notes contain a description of the specific nature and severity of the allergic reaction.^{15–17}

A retrospective study assessed the frequency of cross-hypersensitivity to imipenem-cilastatin in patients with a history of penicillin allergy.¹¹ The medical records of 63 bone marrow transplant recipients with fever and neutropenia and self-reported or documented penicillin allergy were reviewed. Patients had been treated with at least one intravenous dose of imipenem-cilastatin from January 1996–August 1998. Self-reported penicillin allergy was defined as reported by the patient, or recorded in the patient's medical record in which no documentation or confirmation of signs or symptoms of true penicillin allergy were found. Penicillin allergy was classified as documented if the reaction was documented or witnessed by a health care professional at the study institution during the hospital admission reviewed, even if an allergy history had been previously reported by the patient or was included in the patient's medical record.

Imipenem-cilastatin hypersensitivity reaction was identified through either documentation of a reaction in the medical record or identification of an apparent hypersensitivity reaction based on signs and symptoms. Reactions to imipenem-cilastatin were subclassified as definite, likely, possible, or unknown, based on four predetermined criteria: documentation or lack thereof in the patient's medical record, persistence or resolution of allergic symptoms, presence of other possible causes for allergic symptoms, and discontinuation of treatment with imipenem-cilastatin or other antibiotics in relation to the preceding three criteria.

Of the 63 patients included in the study, six (9.5%) were classified as having documented penicillin allergy, and 57 (90.5%) as having self-reported penicillin allergy. None had documentation of penicillin skin testing. Among the 63 patients with documented or self-reported penicillin allergy, the overall frequency of imipenem-cilastatin hypersensitivity reactions was 9.5% (six patients). Among these six patients, one reaction was considered definite, three likely, and two possible. The frequency of imipenem-cilastatin hypersensitivity reactions among the patients with documented and self-reported penicillin allergy, respectively, was 33% (two of six patients) and 7% (four of 57). Imipenem-cilastatin hypersensitivity was manifested as rash in all six patients, one of whom also developed acute renal failure.

Accurate and complete documentation in the medical record is essential for accurate differentiation between nonallergic and allergic reactions, and for facilitating establishment of a temporal relationship between carbapenem administration and the allergic manifestations. Thus, the retrospective nature of this analysis (and two subsequent retrospective analyses^{12, 13}) imposes several inherent limitations relating to difficulties in data collection. A limitation specific to this study concerns the population studied; that is, bone marrow transplant recipients with fever and neutropenia. Because these patients have inherent immunosuppression, the 9.5% risk of cross-hypersensitivity may not reflect the population as a whole. Thus, extrapolation to the general population should be performed with care.

Finally, this study reported that patients with documented penicillin allergy appear to be at greater risk for developing a hypersensitivity reaction when treated with imipenem-cilastatin than patients with self-reported penicillin allergy.

However, a definitive conclusion cannot be made based on the data presented because the data involved only six patients. In addition, the two patients in this classification who were identified as allergic to imipenem-cilastatin received penicillin immediately before the carbapenem treatment. In response to the penicillin, they developed a rash that persisted during the carbapenem treatment. The persistence of rash was depicted as imipenem-cilastatin hypersensitivity. However, this reaction may have been simply an extension of the reaction to penicillin, which may not have had sufficient time to resolve completely. Details regarding severity of the rash before and after the start of imipenem-cilastatin and regarding treatment duration were not presented.

A second retrospective analysis compared the frequency of cross-hypersensitivity associated with imipenem-cilastatin and meropenem treatment in patients with and without a history of penicillin allergy.¹² This analysis involved 211 patients: 100 with documented or reported penicillin allergy and 111 with no penicillin allergy. All had been admitted and treated with at least one intravenous dose of either imipenem-cilastatin or meropenem between January 1999 and August 2002. An equal number of patients in the two groups received each carbapenem.

Patients in the penicillin-allergic group were more likely to be allergic to cephalosporins ($p < 0.05$) and sulfa antibiotics ($p < 0.01$) than those in the nonallergic group. No between-group difference was noted in the use of corticosteroids (prednisone equivalent of ≥ 10 mg). Immunologic testing for confirmation of presumed penicillin hypersensitivity was not reported for any patient. To minimize the number of patients whose history of penicillin allergy was nonimmunologic, those whose penicillin allergy was associated with an aminopenicillin were not included in the study. After stratification, patients were excluded if they were treated with a penicillin antibiotic concurrently or within 72 hours of the start of carbapenem therapy, had undergone penicillin desensitization within 4 weeks of the start of the carbapenem, had less than 72 hours of follow-up after the first carbapenem dose, or did not receive one or more of the prescribed carbapenem doses.

A hypersensitivity reaction to the carbapenem antibiotic was defined as one or more of the following: dermatologic reaction, anaphylaxis, angioedema, fever, hematologic abnormality, or any other sign or symptom deemed allergic if it

occurred after the start of carbapenem treatment. Hypersensitivity reactions were classified as definite, likely, possible, or unknown, based on established criteria.¹¹

The frequency of carbapenem hypersensitivity was reported as 11% versus 2.7% (11 of 100 patients with vs 3 of 111 without reported penicillin allergy, $p = 0.024$).¹² Five (5%) patients in the penicillin-allergic group versus none in nonallergic group had a carbapenem hypersensitivity reaction deemed definite ($p = 0.0227$). Eight (8%) in the allergic group versus two (1.8%) in the nonallergic group had a hypersensitivity reaction defined as either definite or likely ($p = 0.0495$).

Allergies to other antibiotics, including cephalosporins, were not significant predictors of a hypersensitivity reaction. The risk of hypersensitivity in penicillin-allergic patients treated with imipenem-cilastatin and meropenem, respectively, was 12% and 10% ($p = 0.7575$). Among the 14 patients (11 penicillin-allergic, 3 nonallergic), 19 reactions were identified, 10 of which were dermatologic (rash or hives). Three reactions were manifested as drug fever, two as respiratory distress or wheezing, and one each as arthralgia, neutropenia, anaphylaxis, and acute renal failure. A dermatologic reaction accompanied the acute renal failure, arthralgia, respiratory distress (in one of two cases), and drug fever (in two of three cases). Mean time to reaction onset was 6.1 days (18 doses) and 3.7 days (11 doses), respectively, for penicillin-allergic and -nonallergic patients.

A limitation of this study is its retrospective design. A prospective evaluation would have allowed better assessment of penicillin allergy history and more accurate differentiation between allergic and nonallergic reactions to carbapenem treatment. Because the type of penicillin allergy was not reported, no association could be established between type or severity of penicillin allergy and risk of carbapenem hypersensitivity. This study, which was designed to represent the population as a whole, suggests that a clinically and statistically significant risk of hypersensitivity exists in patients with documented or reported allergy to penicillin. The risk of hypersensitivity reaction does not appear to be dependent on the selected carbapenem.

Another retrospective analysis published the same year was designed to assess the clinical safety of administering carbapenem antibiotics to patients with a history of penicillin allergy.¹³

Table 1. Overall Frequency of Carbapenem Hypersensitivity Reactions in Patients With and Without a History of Penicillin Allergy

Study Design	Self-Reported or Documented History of Penicillin Allergy		No History of Penicillin Allergy		p Value
	No. of Patients	No. (%) with Carbapenem Hypersensitivity	No. of Patients	No. (%) with Carbapenem Hypersensitivity	
Review of in vivo skin test results ¹⁰	39	10 (25.6)	NA	NA	NA
Retrospective chart review ¹¹	63	6 (9.5)	NA	NA	NA
Retrospective chart review ¹²	100	11 (11.0)	111	3 (2.7)	0.024
Retrospective chart review ¹³	163	15 (9.2)	103	4 (3.9)	0.164

NA = not applicable.

This analysis involved 266 patients: 163 with reported penicillin allergy and 103 with no penicillin allergy. All had been admitted to the hospital between 2001 and 2002 and treated with imipenem-cilastatin or meropenem for at least 1 day.

A hypersensitivity reaction to the carbapenem antibiotic was defined as the development of rash, hives, fever, angioedema, bronchospasm, or pruritis that led to withdrawal of the antibiotic followed by documented resolution of the reaction. Patients in the penicillin-allergic group were more likely to have reported allergies to sulfa and fluoroquinolone antibiotics than those in the nonallergic group ($p < 0.05$). Among the 163 patients with a reported history of penicillin allergy, 57 (35%) reported rash, 10 (6%) facial swelling and/or anaphylaxis, and 8 (5%) another, unidentified type of reaction. The type of penicillin allergy could not be determined in the remaining 88 (54%) patients.

The frequency of carbapenem hypersensitivity was reported as 9.2% versus 3.9% (15 of 163 patients with vs 4 of 103 without reported penicillin allergy, $p = 0.164$). A possible trend was observed toward an increased risk of hypersensitivity reaction in penicillin-allergic patients with allergies to several antibiotics. Most notable, of the seven patients with a history of penicillin and cephalosporin allergy, four had a hypersensitivity reaction when treated with a carbapenem, suggesting an increased risk in this subset of patients. Most reactions (14 of the 19 patients) were purely dermatologic, whereas two patients developed drug fever in addition to rash, one patient developed facial edema and lip swelling in addition to rash, and one patient developed pruritis. The type of reaction for one patient was not reported. Mean time to reaction onset was 3.6 and 5.5 days, respectively, for penicillin-allergic and -nonallergic patients.

Among the 57 patients who reported a history of rash in response to penicillin, seven (12.3%) developed a reaction to the carbapenem. Of interest, among the 10 patients with a reported history of type 1 hypersensitivity to penicillin, only one had a reaction to the carbapenem. This reaction was manifested as a maculopapular rash. Since these data are subject to the limitations of patient self-reporting, caution is still advised regarding patients with a history of type 1 penicillin allergy.

Limitations of this study are its retrospective design and inclusion and exclusion criteria. Either a prospective evaluation or better-defined inclusion and exclusion criteria would have allowed better assessment of penicillin allergy history, and thus risk of cross-hypersensitivity. The type of penicillin allergy was reported as rash in 35% of patients and could not be determined in 54% of patients.

No attempt was made in the study design to exclude patients treated with aminopenicillin formulations to which nonimmunologic reactions are often reported as allergy (e.g., nonimmunologic rashes and gastrointestinal adverse effects). Therefore, a significant proportion of patients in the penicillin-allergic group may have been nonallergic, biasing the results toward no between-group difference. Although this study did not attain a statistically significant difference between the penicillin-allergic and -nonallergic groups with respect to carbapenem hypersensitivity, this limitation must be accounted for when extrapolating the data to clinical practice.

Data evaluating the frequency of carbapenem hypersensitivity in patients with penicillin allergy are limited to skin testing and retrospective studies. The results of four studies suggest an overall frequency of carbapenem hypersensitivity of 9.2–25.6% in patients with a history of penicillin allergy (Table 1).^{10–13}

The frequency of clinical cross-hypersensitivity may be estimated by skin testing and retrospective analyses. However, a prospective evaluation that includes both immunologic testing to confirm penicillin hypersensitivity and treatment with therapeutic doses of the carbapenem by an accepted route of administration is needed to truly quantify this relationship. The risk of hypersensitivity appears to be independent of the specific carbapenem administered, although, to our knowledge, the risk of cross-hypersensitivity between ertapenem and penicillin has not yet been investigated.

Conclusion

Since most patients reporting a penicillin allergy are not truly allergic, practitioners must obtain a detailed history that includes the specific penicillin to which the patient reacted, the type and severity of the reaction, and the date the reaction occurred. This thorough history will allow practitioners to make the best-informed decisions regarding a patient's antimicrobial treatment regimen. Nevertheless, the clinical situation may remain uncertain because many patients cannot provide adequate historical information regarding their drug allergies. The decision to administer carbapenem therapy to a patient with an apparent penicillin allergy is thus left to the judgment of the practitioner.

The clinical risk of carbapenem hypersensitivity in a patient with self-reported or documented penicillin allergy has been 9–11% in retrospective studies and approached 26% in a single skin-test analysis. Carbapenems should generally be avoided in patients assumed to be at significant risk—those with a reported or documented history of type 1 penicillin hypersensitivity or positive skin tests. If a carbapenem is administered in such a patient, anaphylactic precautions should be available at bedside during administration of the first dose. In addition, certain cases may warrant carbapenem desensitization or administration of a test dose with subsequent monitoring of the patient before treatment is begun.

In patients assumed to be at moderately significant risk—those with penicillin allergy documented by a health care provider and those with allergies to several antibiotics—carbapenems should be reserved for treatment of infections involving multidrug-resistant organisms when no other therapeutic option exists. In patients assumed to be at moderate

risk—those with a self-reported history of penicillin allergy that is not type 1—a carbapenem may be administered if other treatment options are lacking and a carbapenem is deemed the most effective treatment option. When a carbapenem is administered in any patient with a suspected penicillin allergy, caution should be exercised and the patient should be closely monitored for signs and symptoms of drug hypersensitivity.

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