Incidence of Imipenem Hypersensitivity Reactions in Febrile Neutropenic Bone Marrow Transplant Patients with a History of Penicillin Allergy

The purpose of this retrospective study was to assess cross-hypersensitivity between imipenem/cilastatin and penicillin in patients with reported penicillin allergies. Medical records of febrile neutropenic, penicillin-allergic bone marrow transplant recipients who received imipenem/cilastatin treatment were retrospectively reviewed. The findings of this study indicate the incidence of cross-reactivity between imipenem/cilastatin and penicillin among patients with a history of penicillin allergy may be lower than previously reported.

Patients frequently report drug allergies to β-lactam antibiotics, especially penicillin. Many patients believe that they are allergic to penicillin when, in fact, true allergy does not exist. They may have mistaken an adverse event that occurred while taking a prescription of penicillin (i.e., nausea) as penicillin allergy. Moreover, some patients may have been told by others that they were allergic to penicillin but cannot remember the specifics of the reported allergic reaction and, in fact, may not be truly allergic. Another possibility is that the patient had developed a rash when given an older and less pure formulation of penicillin in the past and that the newer formulations of penicillin will not elicit the same response. However, there are many patients who are truly allergic to penicillin, for whom administering penicillin may be life threatening.

Neutropenic bone marrow transplant patients often require empirical broad-spectrum antimicrobial therapy, typically with β-lactam antibiotics. For these patients, a self-reported history of penicillin allergy can complicate the selection of empirical antibiotics. Carbapenems, such as imipenem, are broad-spectrum antibiotics ideally suited to such empirical therapy. However, carbapenems are β-lactam antibiotics that are similar in chemical structure to penicillin. Therefore, the use of imipenem/cilastatin in a truly penicillin-allergic patient is associated with a risk for allergic cross-reactivity with imipenem/cilastatin.

There are few data describing the incidence of imipenem/cilastatin allergy among penicillin-allergic patients. One study reported a 47% incidence of cross-reactivity that was based solely on the subject’s reactivity to both penicillin and imipenem/cilastatin skin tests [1]. Clinically, administering a skin test to assess hypersensitivity to either imipenem/cilastatin or penicillin typically is not routine; rather, antibiotic selection is often based solely on self-reported allergies. Therefore, the purpose of this retrospective, medical record review was to determine the incidence of imipenem/cilastatin allergy among those patients with self-reported penicillin allergies who had received systemic intravenous therapy with imipenem/cilastatin.

Bone marrow transplant patients with penicillin allergies in their medical record who had received ≥1 iv administered dose of imipenem/cilastatin (Primaxin; Merck, West Point, PA) from January 1996 through August 1998 were included in this analysis. Allergies to penicillin were subclassified as either self-reported or documented. Self-reported penicillin allergy was defined as preexisting penicillin allergy reported by the patient or recorded in the patient’s medical record, in which documentation or confirmation of true penicillin allergy could not be found in reviewing the patient’s medical record. Documented penicillin allergy was defined as penicillin allergy documented or witnessed by health care personnel at this institution during the admission reviewed that may or may not have been previously reported by the patient or in the patient’s medical record.

Allergies to imipenem/cilastatin were identified by documentation of either imipenem/cilastatin allergy in the medical record made during the admission reviewed or allergic reaction (i.e., rash, eosinophilia, angioedema, etc.) in the medical chart that was temporally related to imipenem/cilastatin administration and that was identified by study personnel during medical record review. Imipenem/cilastatin allergies were further subclassified as definite, likely, possible, or unknown, on the basis of the following 4 criteria: documentation or lack of documentation 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 and/or other antibiotics in relation to the other 3 above-mentioned criteria (table 1).

Table 1. Classifications of imipenem (Imi) allergies in a study of hypersensitivity reactions in febrile neutropenic bone marrow transplant patients with a history of penicillin allergy.

<table>
<thead>
<tr>
<th>Documentationa</th>
<th>Documentation or no documentationa</th>
<th>No documentationa</th>
<th>No documentationa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolutionb</td>
<td>Resolutionb</td>
<td>Persistenceb</td>
<td>Resolutionb</td>
</tr>
<tr>
<td>OPC, no</td>
<td>OPC, yes</td>
<td>OPC, yes</td>
<td>OPC, yes</td>
</tr>
<tr>
<td>Imi stopped</td>
<td>Imi stopped</td>
<td>Imi stopped</td>
<td>Multiple antibiotics stopped</td>
</tr>
</tbody>
</table>

NOTE: OPC, other possible causes exist (e.g., concurrent medications).

*Diagnosis of Imi allergy made in the medical record.

b Adverse reactions to Imi (i.e., rash).
(grams), total duration (days), and number of doses administered. Signs and symptoms of allergic reaction were also collected.

Medical records for 82 patients were initially identified as eligible for review. Records for 7 of these patients were unavailable, and 12 patients were not administered imipenem/cilastatin after it was prescribed. The remaining 63 patients were included in the analysis. Fifty-seven patients were classified as having self-reported penicillin allergies, and 6 were classified as having documented penicillin allergies, according to study definitions. None of the 63 patients had documentation of a penicillin skin test being administered. Six patients were classified by study definition as having imipenem/cilastatin allergies. The overall incidence of imipenem/cilastatin allergy among 63 patients with documented or self-reported penicillin allergy was 9.5% (6/63 patients; table 2). The incidence of imipenem/cilastatin allergy among patients classified as having self-reported and documented penicillin allergies was 7% (4/57 patients) and 33% (2/6 patients), respectively.

Of the 6 patients with imipenem/cilastatin allergies, 1 was classified as having definite imipenem/cilastatin allergy (a self-reported penicillin-allergic patient), and 3 were classified as having likely imipenem/cilastatin allergies (1 with self-reported penicillin allergy and 2 with documented penicillin allergies). The remaining 2 patients were classified as having possible imipenem/cilastatin allergies (both with self-reported penicillin allergies). All 6 of the imipenem/cilastatin allergies manifested as rashes, and 1 also manifested as acute renal failure, in addition to a rash. Both patients with documented penicillin allergies who were identified as having likely imipenem/cilastatin allergies had received penicillin immediately before the initiation of imipenem/cilastatin treatment, and their rashes persisted during imipenem/cilastatin therapy. The patient who developed acute renal failure was 1 of the 2 patients with documented penicillin allergies. This patient developed acute renal failure shortly after the initiation of penicillin treatment, which was switched to imipenem/cilastatin. The renal function of this patient did not improve during the 3 days during which imipenem/cilastatin was administered.

Patient demographics, data on the dose and duration of imipenem/cilastatin, antibiotic histories, allergic symptoms, and other drug allergies are presented in table 3. Patients with imipenem/cilastatin allergies received fewer doses of imipenem/cilastatin, on average, and had a shorter duration of therapy than did patients without imipenem/cilastatin allergies. There were no obvious differences in the antibiotic histories or drug allergies between the imipenem/cilastatin–allergic and nonallergic groups.

Determining whether patients who report penicillin allergies are truly penicillin allergic is a significant dilemma for health care providers. The simplest solution to this dilemma is to withhold penicillin and administer an antibiotic from a different chemical class. However, all β-lactam agents are structurally related to penicillin; thus, patients who are truly penicillin allergic are at risk for cross-reactivity to this broad class of antibiotics. Penicillin allergies can, therefore, complicate therapy for patients requiring treatment with any β-lactam antibiotic.

The penicillin skin test (Pre-Pen; Schwarz Pharma, Mequon, WI) contains only the major antigenic determinants (MADs) of penicillin and can be a useful tool for assessing accelerated reactions (i.e., reactions occurring within 1–72 hours of administration) to penicillin [2, 3]. However, Pre-Pen does not reliably predict the occurrence of immediate (IgE-mediated) or late reactions to penicillin (i.e., exanthematous reactions, positive results of Coombs’ test, or granulocytopenia) that are due to the minor antigenic determinants (mADs) [2, 3]. For this reason, it is recommended that practitioners administer an mAD penicillin skin test, in addition to Pre-Pen, to assess for penicillin hypersensitivity [2, 3]. Unfortunately, there are currently no commercial skin test formulations available that contain mADs. Therefore, it is currently recommended to use a solution of penicillin G administered intradermally to test for hypersensitivity to mADs of penicillin [3].

Saxton et al. [1] used imipenem/cilastatin and penicillin skin tests to assess hypersensitivity to the respective agents. In their study, they gave 40 patients with reported penicillin allergies

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**Table 2.** Incidences of penicillin and imipenem allergies among febrile neutropenic bone marrow transplant patients with a history of penicillin allergy.

<table>
<thead>
<tr>
<th>Imipenem allergy</th>
<th>Overall (n = 63)</th>
<th>Self-reported (n = 57)</th>
<th>Documented (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Likely</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Possible</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total (%)</td>
<td>6 (9.5)</td>
<td>4 (7)</td>
<td>2 (33)</td>
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penicillin skin tests (containing both MADs and mADs), and 48% (19) had positive reactions to both tests. The 19 subjects who reacted to the penicillin skin tests were then administered an imipenem/cilastatin skin test, and 47% (9) of the subjects had positive reactions. The investigators concluded that there was a 47% (9/19) incidence of cross-reactivity between imipenem/cilastatin and penicillin, which, by definition of cross-reactivity to skin tests, is accurate. However, the incidence of imipenem/cilastatin hypersensitivity among patients with reported penicillin allergies, which is more clinically relevant, was much lower. Only 1 of the 20 subjects with reported penicillin allergies and negative penicillin skin tests reacted to the imipenem/cilastatin skin test, and, as previously stated, there were 9 subjects with both positive imipenem/cilastatin and penicillin skin tests. Therefore, the true incidence of hypersensitivity to imipenem/cilastatin (both positive and negative penicillin skin tests) among patients with reported penicillin allergies was 25% (10/40).

Saxon et al. [1] also noted that ~80% of imipenem/cilastatin–penicillin cross-reactivities occurred with penicillin G (an mAD) given intradermally. Only 44% (4/9) of imipenem/cilastatin–penicillin cross-reactivities were demonstrated when the MAD penicillin skin test or Pre-Pen was used by itself, whereas 78% (7/9) of imipenem/cilastatin–penicillin cross-reactivities occurred when penicillin G was given intradermally. Moreover, they also tested mADs of imipenem/cilastatin by skin testing, but the parent drug (imipenem/cilastatin) accounted for 78% of the imipenem/cilastatin–penicillin cross-reactivities. Of note, most cross-reactivities determined by skin testing would be missed if only the MADs of penicillin (i.e., Pre-Pen) were used to determine penicillin hypersensitivity. The clinical significance of an imipenem/cilastatin skin test to assess imipenem/cilastatin hypersensitivity is unknown; thus, the primary limitation of the study by Saxon et al. [1] was that imipenem/cilastatin hypersensitivity was determined solely by skin tests, and no patients received systemic therapy.

Conversely, in the current retrospective analysis, an imipenem/cilastatin skin test was not used as a marker for imipenem/cilastatin allergy, and every patient received ≥1 iv dose of imipenem/cilastatin. The incidence of imipenem/cilastatin hypersensitivity among patients with self-reported penicillin allergies was considerably lower than that reported elsewhere [1–3]. Therefore, the incidence of imipenem/cilastatin hypersensitivity among patients with reported penicillin allergies may actually be similar to that reported for other β-lactam antibiotics such as cephalosporins (≈10%) [3].

The current study has certain limitations because of its retrospective design. Interpretation of data collected retrospectively is difficult because it relies on proper documentation and completeness of the patient’s medical record. Furthermore, determination of a temporal relationship between allergic manifestations and imipenem/cilastatin administration is difficult. Despite adherence to study definitions, the present study may have overestimated cross-reactivities in patients with documented penicillin allergies. All patients with documented penicillin allergies received penicillin at the time of the admission reviewed and developed allergic reactions immediately before the initiation of imipenem/cilastatin treatment. Two of these patients were subsequently classified as having imipenem/cilastatin allergies.

Moreover, none of the patients in the current study was given either an MAD or mAD penicillin skin test; therefore, the true incidence of penicillin allergy could not be determined. Although this is a scientific limitation, our study is still clinically relevant, despite the absence of data on skin tests, because skin testing is rarely performed in the clinical setting. A prospective trial to determine the incidence of imipenem/cilastatin allergy among patients with a history of penicillin allergy (who are subjected to penicillin skin testing) and imipenem/cilastatin therapy would more accurately define the incidence of cross-hypersensitivity between those drugs.

Results from this retrospective study demonstrate a markedly lower incidence of imipenem/cilastatin hypersensitivity among patients with self-reported penicillin allergies than that previously reported. However, because imipenem/cilastatin is structurally related to penicillin (both contain a β-lactam ring), caution should be used when administering imipenem/cilastatin to a penicillin-allergic patient. Of note, no patients in the current study reported anaphylactic reactions to penicillin. For such patients, imipenem/cilastatin therapy should be avoided until data are available that clearly demonstrate that these patients are not at risk for cross-hypersensitivity.

The incidence of cross-hypersensitivity between penicillin and imipenem/cilastatin may be lower than that previously reported. Indeed, the incidence of imipenem/cilastatin hypersensitivity among penicillin-allergic patients was 9.5% in the current retrospective analysis, which is similar to that reported for other β-lactam agents. However, imipenem/cilastatin hypersensitivity more likely occurred in those patients with a history of true penicillin allergy that could be documented in the patient’s medical record. In addition, the use of imipenem/cilastatin is not recommended for patients with a history of anaphylactic reactions to penicillin.

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References