

Allergic Cross-Sensitivity Between Penicillin, Carbapenem, and Monobactam Antibiotics: What Are the Chances?

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Penicillin is the most common cause of drug-induced anaphylaxis.¹ The incidence of cross-reactivity between penicillins and other β -lactams is a topic of debate. Clinicians may be confused by the multitude of studies examining this question, the various designs of those studies, and the sometimes contradictory conclusions of the investigators. As a result, due to the fear of cross-reactivity, β -lactams are often avoided in patients with reported penicillin allergies. This results in increased healthcare costs, risk of developing bacterial resistance, use of alternative antibiotics with other potentially dangerous adverse effects,² and, additionally, the use of possibly inferior antibiotics, such as vancomycin for the treatment of serious methicillin-susceptible *Staphylococcus aureus* infections.³

Gell and Coombs described 4 classifications of immunologically mediated drug reactions (Table 1).^{4,7} There are also numerous other types of allergic reactions that do not fit these categories and are idiosyncratic. In a type 1 reaction, immunoglobulin (Ig) E antibodies for a specific drug allergen develop during initial exposure to the drug. Upon repeat exposure, within 30–60 minutes, a reac-

OBJECTIVE: To evaluate the literature on the allergic cross-reactivity between penicillin, carbapenem, and monobactam antibiotics.

DATA SOURCES: A MEDLINE search (1950–June 2008) of the English literature was performed using the search terms β -lactam, penicillin, monobactam, carbapenem, allergy, and cross-reactivity. References of review articles were also screened for inclusion.

STUDY SELECTION AND DATA EXTRACTION: All articles in English from the data source were identified. Studies whose primary goal was to evaluate drug hypersensitivity and the potential for cross-reactivity were evaluated.

DATA SYNTHESIS: Many patients have reported penicillin allergies that have not been verified by skin testing; many healthcare providers avoid the use of other β -lactam antibiotics, namely carbapenems, in these patients due to fear of the potential for immunoglobulin E-mediated allergic cross-reactivity. A wide range of cross-reactivity between penicillins and carbapenems has been reported in various studies; however, more recent prospective studies have shown the incidence of cross-reactivity between penicillin and carbapenem skin tests to be around 1%. Additionally, many prescribers freely use the monobactam aztreonam in penicillin-allergic patients, believing there is no cross-reactivity between the 2 drugs. Although data support the lack of cross-reactivity between aztreonam and penicillins, immunology and some clinical data support an interaction between ceftazidime and aztreonam due to the similarity of their side chains.

CONCLUSIONS: Although variability in cross-reactivity rates between β -lactam classes exists in the literature, the practice of avoiding carbapenems in penicillin-allergic patients should be reconsidered. With regard to monobactams, the administration of aztreonam in a patient with a ceftazidime allergy may carry an increased risk of type 1 hypersensitivity reactions and should be considered with caution. Additionally, the importance of obtaining a thorough patient history regarding the previous allergic event, proper documentation, and penicillin skin testing is reemphasized.

KEY WORDS: β -lactam, carbapenem, cross-reactivity, hypersensitivity, monobactam, penicillin.

Ann Pharmacother 2009;43:304-15.

Published Online, 3 Feb 2009, www.theannals.com, DOI 10.1345/aph.1L486

THIS ARTICLE IS APPROVED FOR CONTINUING EDUCATION CREDIT
ACPE UNIVERSAL PROGRAM NUMBER: 407-000-09-003-H01-P

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tion occurs that can be either limited to a single organ system, such as bronchospasm, or multiple organs simultaneously, causing anaphylaxis.⁶ IgE-mediated reactions include anaphylaxis, urticaria, laryngeal edema,⁸ bronchospasm, and angioedema.⁷ Reviews about the cross-reactivity between penicillin and cephalosporin allergies are common in the literature.⁷⁻¹⁵

We review the literature evaluating the cross-reactivity of penicillin allergy with that of monobactams and carbapenems. Although all 4 types of immunologic reactions have been observed with penicillin,^{5,6} the major focus of this review is on IgE-mediated type 1 reactions.

Background

PENICILLINS AND ANAPHYLAXIS

Penicillin degrades to reactive intermediates, the antigenic determinants of which vary depending on ring modifications and the point of protein attachment. These products of penicillin metabolism are termed the major and minor determinants and represent the amount of drug that is metabolized to that product, not the severity of the reaction they cause.^{5,8,14} Penicilloyl, the major penicillin determinant, accounts for 95% of penicillin metabolites. A variety of minor determinants account for the remaining amount and include unmetabolized penicillin, penicillenate, penicilloic acid, penicillanyl, penicoyl, penilloic acid, and other conjugates.^{5,8,14,15}

SPECIAL CONSIDERATIONS

Numerous considerations must be kept in mind when evaluating the available literature on the cross-reactivity between β -lactam antibiotics. The methods by which allergies are verified (ie, skin test, graded challenge, single test dose, full therapeutic courses) and the definition of allergic reaction are perhaps the 2 most important considerations. Studies that use a wide range of symptoms to define allergy may confuse clinicians who focus on IgE-mediated reactions by overestimating their incidence, but they can provide useful information on other adverse reactions that can be attributed to the antibiotic.

Of patients who report a history of penicillin allergy, 80–90% have a negative penicillin skin test response.¹ Skin testing to major and minor penicillin determinants identifies 97–99% of potential reactors,¹ and is useful in predicting IgE-mediated type 1 reactions but not the possibility of other types of hypersensitivity reactions occurring more than 24 hours after the administration of the drug.⁵ The major penicillin determinant, benzylpenicilloyl polylysine (Pre-Pen, AllerQuest, West Hartford, CT), is currently not available but is expected to be available in 2009.¹⁶ A minor determinant mixture is not commercially available, but penicillin G is an acceptable alternative.⁵ Some studies have found specific IgE antibodies directed to the penicillin side chain and suggest that the addition of other determinants may improve the sensitivity of skin testing and may play a role in the cross-reactivity between various penicillins.^{14,17-20} However, while skin tests to other penicillins, cephalosporins, carbapenems, and monobactams are used in clinical studies, the usefulness of their results is unknown, as these tests are not standardized.

An additional phenomenon that has been noted is the presence of multiple, seemingly unrelated drug allergies in some patients.^{18,19} One study found that the history of prior reactions to other medications was significantly more common in patients who had an allergic reaction to penicillin than in those who did not.¹⁹ Penicillin anaphylaxis has been noted to be more common in patients with atopy.¹⁸ Although from a mechanistic standpoint it may be important to consider whether hypersensitivity reactions to β -lactam antibiotics are indeed due to their cross-reactivity or are a coincidental allergy in a patient prone to multiple drug allergies, clinically the differentiation is less significant, since either way the patient is at an increased risk of reacting.

Carbapenems

The structural similarity between penicillin and carbapenem antibiotics is the bicyclic core, composed of a 5-membered ring attached to the β -lactam ring (Figure 1).²¹⁻²³ This commonality is generally believed to be responsible for the cross-sensitivity between these classes of antibiotics.^{8,24-26}

Table 1. Types of Hypersensitivity Reactions^{4,7}

Type	Classification	Onset	Examples
I	immunoglobulin E mediated (anaphylactic)	within 30 min–1 h	penicillin, aspirin, NSAIDs, cancer chemotherapy agents
II	cytotoxic	5–12 ⁶ / ⁷ 72 ⁷ h	transfusion reactions; quinidine, methyl dopa, or penicillin-induced hemolytic anemia
III	immune complex	3–8 ⁶ / ⁷ 72 ⁷ h	serum sickness
IV	cell mediated (delayed)	24–48 ⁶ / ⁷ 72 ⁷ h	contact dermatitis, tuberculin reaction

NSAIDs = nonsteroidal antiinflammatory drugs.

The incidence of imipenem and meropenem hypersensitivity in the general population has been estimated to be from 0.3% to 2.3%, mostly reported as rash, pruritus, or urticaria.²⁷⁻³⁰ However, there is no consensus on the rate of hypersensitivity in individuals also allergic to penicillin. To date, 7 studies have evaluated the cross-sensitivity between carbapenems and penicillins, the results of which range widely, from 0.9% to 47.4%.^{24-26,31-34} The wide variability in these results is due in part to the variety of study designs employed when researching the issue of cross-sensitivity between these drugs.

EARLY PROSPECTIVE STUDY

Saxon et al.²⁵ performed the first prospective study of the cross-reactivity between imipenem and penicillin. They evaluated 59 participants, 39 of whom reported a penicillin allergy and were skin tested for reactivity to penicillin and the major and minor penicillin determinants, then to imipenem and its metabolites. Of the 39 subjects, 19 (48.7%) had a positive skin test to penicillin or the major or minor penicillin determinant.

Of these 19 penicillin skin test–positive subjects, 9 (47.4%) had a positive skin test to imipenem or its metabolites, while only 1 (5%) of 20 penicillin skin test–negative participants reacted to imipenem. The cross-sensitivity between penicillin and imipenem in patients who reported a penicillin allergy was therefore 25.6% (10/39 patients). However, the cross-sensitivity between imipenem and those determined to be penicillin allergic via penicillin skin test was higher, at 47.4% (9/19 patients). No *p* values were reported in this study, but the difference is significant by Fisher's exact test (*p* < 0.01).²⁵ The limitations of this study include small sample size, use of a nonstandardized imipenem skin test, and the fact that imipenem was not ad-

ministered. Despite the limitations of this study, a lack of other data led to the oft-quoted cross-reactivity rate of approximately 50% between imipenem and penicillin allergies.

RETROSPECTIVE STUDIES

After the initial study by Saxon et al., a period of quiescence occurred in the study of carbapenem–penicillin cross-reactivity. However, in 2000 McConnell et al.³³ published a retrospective review that assessed the medical records of 63 febrile neutropenic bone marrow transplant patients with penicillin allergies who received at least one intravenous dose of imipenem/cilastatin. Patients were divided into those with a reported penicillin allergy and those with a documented penicillin allergy, and were deemed imipenem-allergic if there was documentation of an allergy in the medical record or allergic symptoms (eg, rash, eosinophilia, angioedema) temporally related to imipenem administration.

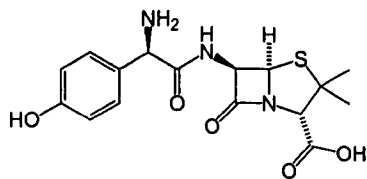
The overall incidence of imipenem cross-sensitivity among all patients was 9.5% (Table 2). The incidence of imipenem cross-sensitivity in patients with a documented penicillin allergy was 33.3% and was 7% (4/57 patients) in patients with a self-reported penicillin allergy. All of the imipenem allergies manifested as rashes. However, both patients with a documented penicillin allergy who reacted to imipenem received penicillin immediately prior to treatment with imipenem.³³

Prescott et al.²⁴ performed a retrospective review of 211 patients with and without reported penicillin allergies who received at least one intravenous dose of imipenem/cilastatin or meropenem. Patients were deemed penicillin-allergic if they had a reported or documented penicillin allergy but were excluded if their allergy was associated with

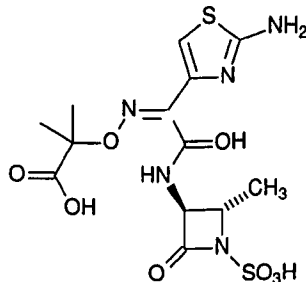
aminopenicillins, with the rationale that non-immunologic drug rashes or gastrointestinal disturbances are often reported as allergic reactions to these agents. Patients were considered to have experienced an allergic reaction to the carbapenem if one or more of the following reactions occurred: dermatologic reactions (rash or hives), fever, anaphylaxis, angioedema, hematological abnormalities (thrombocytopenia or leukopenia), eosinophilia if it led to the discontinuation of carbapenem therapy, or any other signs and symptoms thought to be allergic.

Of the 211 patients evaluated, 47.4% had a reported or documented penicillin allergy (Table 2). Similar numbers of patients were treated with imipenem/cilastatin and meropenem. There was a significantly higher incidence of carbapenem allergic reactions in patients

Amoxicillin, a penicillin



Aztreonam, a monobactam



Imipenem, a carbapenem

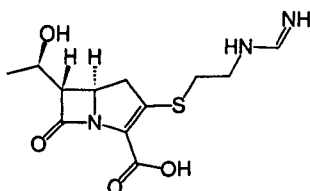


Figure 1. Examples of β -lactam antibiotics.²¹⁻²³

Table 2. Summary of Retrospective Clinical Trials of Carbapenem and Penicillin Cross-Sensitivity

Reference	Total/PCN-Allergic (N/n)	PCN Allergy Verification	PCN Allergy Reported	Reported Reaction to PCN (n)	Carbapenem Allergy Verification	Documented Reaction to Carbapenem (n)	Result of Cross-Sensitivity Between PCN and Carbapenem
McConnell (2000) ³³	63/63	documented vs reported (separated)	NR*	NR*	iv imipenem/cilastatin	6 pts. had 7 reactions rash (6); acute renal failure (1)	6/63 (9.5%) in documented or reported penicillin-allergic pts.; 2/6 (33%) in documented penicillin-allergic pts.
Prescott (2004) ²⁴	211/100	documented or reported (combined)	NR	only reported for 11 penicillin-allergic pts. who reacted to a carbapenem rash (5); unknown (4); anaphylaxis (1); hematologic (1)	iv imipenem/cilastatin or meropenem	14 pts. had 19 reactions rash (8); drug fever (3); hives (2); respiratory distress (2); neutropenia (1); anaphylaxis (1); arthralgia (1); acute renal failure (1)	11/100 (11%) and 3/111 (2.7%) in documented/reported and non-penicillin-allergic pts., respectively (p = 0.024; OR 5.2; 95% CI 1.4 to 20)
Sodhi (2004) ²⁶	266/163	reported	NR	unknown (88); rash (57); facial swelling and/or anaphylaxis (10); other (8)	iv imipenem/cilastatin or meropenem	maculopapular rash (11); drug fever and rash (1); maculopapular rash and facial edema (1); pruritus (1); other (1)	15/163 (9.2%) and 4/103 (3.9%) in reportedly penicillin-allergic and non-penicillin-allergic pts. respectively (p = 0.16)

NR = not reported; PCN = penicillin.

*None reported anaphylaxis.

with a reported penicillin allergy compared with those without, at 11% and 2.7%, respectively. There was no difference between reactions to imipenem and meropenem. Five patients in the penicillin-allergic group and none in the non-penicillin-allergic group had a carbapenem allergy that was classified as definite ($p = 0.0227$). The most common reaction was rash. After adjusting for age, sex, and prednisone use, and excluding patients with aminopenicillin allergies, this study found the odds that a patient with a reported penicillin allergy will have an allergic reaction to imipenem or meropenem 5.2 (odds ratio 5.2; 95% CI 1.4 to 20) when compared with non-penicillin-allergic patients.²⁴

A third retrospective trial evaluated 266 patients with and without reported penicillin allergies treated for at least one day with imipenem/cilastatin or meropenem.²⁶ A carbapenem allergy was defined as development of rash, hives, fever, angioedema, bronchospasm, or pruritus that resolved upon discontinuation of the carbapenem. The penicillin allergy was an unknown reaction in 54% of 163 patients who reported an allergy (Table 2). The incidence of allergic reaction to a carbapenem was 9.2% in penicillin-allergic patients and 3.9% in non-penicillin-allergic patients ($p = 0.164$). The most frequent allergic reaction was manifested as maculopapular rash.

MORE RECENT PROSPECTIVE STUDIES

More recently, Atanasković-Marković et al.³¹ and Romano et al.^{32,34} conducted 3 prospective studies to evaluate the cross-sensitivity between penicillins and carbapenems. All participants included were skin tested to the major and minor penicillin determinants, benzylpenicillin, and aminopenicillins (ampicillin and amoxicillin), and had a positive reaction to at least one reagent. Subjects were then skin tested to a carbapenem; if the skin test was negative, they were challenged with intravenous or intramuscular doses of the carbapenem. In the first hour, subjects received 1/100 of the dose, then 1/10 in the second hour, and then the full dose in the third hour.

The first study examined the use of imipenem in penicillin-allergic subjects.³² Included were 112 participants who were skin tested to penicillin determinants described above, as well as to piperacillin and imipenem. If the skin test was negative, an imipenem/cilastatin challenge was given as fractions of the therapeutic intramuscular dose of 500/500 mg.

When subjects were skin tested to penicillin reagents, 127 (43.8%) reactions were to benzylpenicillin or the major or minor determinant (Table 3). Although the number of participants who reacted to only the semisynthetic penicillins is unclear, there were a total of 163 (56.2%) reactions to these penicillins. Only one person with a positive penicillin skin test reacted to the imipenem skin test. Of the

Table 3. Summary of Prospective Clinical Trials of Carbapenem and Penicillin Cross-Sensitivity

Reference	Total/PCN-Allergic (N/n)	PCN Allergy Verification	PCN Allergy Reported (n)	Reported Reaction to PCN (n)	PCN Determinant Skin Test Positive (n)	Carbapenem Allergy Verification	Carbapenem Determinant Skin Test Positive (n)	Result of Cross-Sensitivity Between PCN and Carbapenem Skin Test
Saxon (1988) ²⁵	59/39	skin test (penicillin, major and minor penicillin determinants)	NR	NR	penicillin (11); major determinant (6); minor determinant (6)	imipenem skin test (imipenem, imipenemoyl, imipenemoate)	imipenem (7); imipenem metabolites (5)	10/39 (25.6%) in reported penicillin-allergic pts.; 9/19 (47.4%) in penicillin skin test-positive pts.
Romano (2006) ³²	112/112	skin test (major and minor determinants, benzylpenicillin, ampicillin, amoxicillin, piperacillin)	amoxicillin (66); bacampicillin (26); ampicillin (51); piperacillin (17); penicillin G (4); benzylpenicillin (5)	anaphylactic shock (89); urticaria (32); urticaria and angioedema (21); angioedema (1)	major determinant (36); minor determinant (48); benzylpenicillin (43); ampicillin (59); amoxicillin (63); piperacillin (41)	imipenem skin test, then im challenge	imipenem (1)	1/112 (0.9%) in penicillin skin-test positive pts.
Romano (2007) ³⁴	104/104	skin test (major and minor determinants, benzylpenicillin, ampicillin, amoxicillin, piperacillin)	amoxicillin (73); ampicillin (25); bacampicillin (18); piperacillin (16); benzathine-penicillin (3); benzylpenicillin (3)	anaphylactic shock (85); urticaria (29); urticaria and angioedema (24)	major determinant (27); minor determinant (35); benzylpenicillin (44); ampicillin (63); amoxicillin (63); piperacillin (44)	meropenem skin test, then iv challenge	meropenem (1)	1/104 (1%; 95% CI 0.02% to 5.2%) in penicillin skin test-positive pts.
Atanasković-Marković (2008) ³¹	128/108	skin test (major and minor determinants, benzylpenicillin, ampicillin, amoxicillin)	benzylpenicillin (60); amoxicillin (52); ampicillin (13)	urticaria (101); urticaria or angioedema (18); anaphylactic shock (9); angioedema (1)	major determinant (52); minor determinant (54); benzylpenicillin (70); ampicillin (27); amoxicillin (46)	meropenem skin test, then iv challenge	meropenem (1)	1/108 (0.9%) in penicillin skin test-positive pts.

NR = not reported; PCN = penicillin.

110 participants with a negative imipenem skin test who agreed to undergo the intramuscular imipenem challenge, none reacted to imipenem.³² The authors concluded that the cross-sensitivity is significantly lower than previously reported by Saxon et al.²⁵ and proposed that imipenem skin tests can be performed in patients who require imipenem therapy, and if the results are negative, patients can safely receive a challenge such as the one used in this study.³²

The second study assessed the use of meropenem in penicillin-allergic subjects.³⁴ One hundred four participants over the age of 13 years with histories of penicillin allergy were skin tested to penicillin determinants described above, as well as piperacillin and meropenem. The first 40 subjects received intravenous graded challenges with 3 meropenem dilutions, but subsequent subjects received 2 dilutions of 1/10 of the dose followed by the full dose 1 hour later. Sixty-nine of the subjects had also participated in the imipenem study described above.³²

When subjects were skin tested to penicillin reagents, 106 (38.4%) reactions were to benzylpenicillin or the major or minor determinant (Table 3).³⁴ The number of patients who reacted only to semisynthetic penicillins was not reported, but there were 170 (61.6%) reactions to these penicillins. Only one person with a positive penicillin skin test also reacted to the meropenem skin test. The subject who was skin test-positive to both penicillin and meropenem is the same person who was included in a previous imipenem study and had a positive skin test to imipenem.³² All 103 subjects with negative meropenem skin tests tolerated the intravenous challenge (100%; 95% CI 96.5% to 100%).³⁴ The authors concluded that the rate of cross-reactivity between penicillins and meropenem is no higher than 5.2%, the upper confidence bound. Additionally, no more than 3.5% of patients would be expected to react to a meropenem challenge after a negative meropenem skin test result.

The third study was performed in children aged 3–14 years and examined

the cross-sensitivity between penicillin and meropenem.³¹ One hundred eight children with histories of penicillin allergy were skin tested to penicillin reagents described above and meropenem. After the first 30 intravenous meropenem challenges with 3 meropenem dilutions, subjects received meropenem challenges with 2 dilutions.

When subjects were skin tested to penicillin reagents, 51 (47.2%) were positive only to the major or minor determinant and 32 (29.6%) only to a semisynthetic penicillin (Table 3). Only one person with a positive penicillin skin test reacted to the meropenem skin test, while none of the 20 control children reacted. All 107 meropenem skin test–negative subjects tolerated the intravenous meropenem challenge. The authors concluded that there is a very low rate of cross-reactivity between penicillins and meropenem, and that a meropenem skin test followed by a graded challenge can be performed in patients with penicillin allergies.³¹

DISCUSSION

The incidence of cross-sensitivity between penicillins and carbapenems from prospective studies using skin testing ranges from 0.9% to 47.4%.^{25,31,32,34} Although the 3 retrospective studies used patients with documented and/or reported penicillin allergies that were not verified by skin testing, employed a broad definition for allergic reaction, and relied on chart documentation, they were the only studies in which patients were administered full courses of therapy without a challenge first. The cross-sensitivity in these trials was between 9.2% and 11%.^{24,26,33} On the other hand, the 4 prospective studies used skin tests to penicillins and carbapenems to determine allergies,^{25,31,32,34} and the 3 more recent studies administered challenges with increasing doses of the carbapenem to carbapenem skin test–negative participants to assess tolerability.^{31,32,34} All carbapenem skin test–negative patients tolerated the carbapenem challenges.

Many differences must be noted before drawing a conclusion from the 7 studies about the safety of administering carbapenems to penicillin-allergic patients. First, it is important to keep in mind how penicillin allergies were verified. Studies that additionally skin tested to semisynthetic or aminopenicillins may have enrolled patients who are not truly penicillin-allergic, thus diluting the penicillin-allergic population studied and finding a lower rate of cross-sensitivity. Additionally, the predictive value of the carbapenem skin tests used in the prospective studies is not established, since none of the skin test–positive patients were challenged with the carbapenem. Furthermore, the cross-reactivity rate between penicillin and carbapenem skin tests varied depending on whether carbapenem metabolites were used. This may explain the difference in cross-sensitivity of 47.4% in the Saxon et al. study,²⁵ which

had a much smaller sample size and used imipenem and its metabolites, when compared with 0.9% and 1% in the more recent studies, which used only the parent carbapenem compound.^{31,32,34} It is unknown whether patients in the carbapenem skin test–negative groups in the studies of Romano et al. and Atanasković-Marković et al. may have reacted to a carbapenem metabolite skin test. However, since all carbapenem parent compound skin test–negative patients tolerated the carbapenem challenge, it is reasonable to conclude that patients with a negative carbapenem skin test to the parent compound can safely receive a carbapenem challenge.

In the case of verifying a carbapenem allergy, the most reliable predictor is a reaction to a therapeutic dose of the drug in question, which is what was done in the retrospective studies^{24,26,33} and in the 3 more recent prospective studies.^{31,32,34} However, the retrospective studies used broad definitions of allergic reactions, including patients with fever, rash, and hematologic abnormalities (leukopenia or thrombocytopenia), which can be nonimmunologic in nature and not mediated by IgE antibodies. Nonetheless, they do capture data on non-IgE-mediated potential allergic reactions that may be useful. On the other hand, the more recent prospective studies administered a full dose of imipenem or meropenem to patients with a negative skin test to the carbapenem, but did so by administering increasing amounts of the drug before the full therapeutic dose.^{31,32,34} The conclusion can be made that it appears to be safe to administer a carbapenem following this dosing regimen to patients with a negative carbapenem skin test. Although administering graded challenges differs from desensitization in that it does not alter the immune system's response to the antigen,³⁵ it is not known whether this dosing scheme needs to be used prior to every course of carbapenem therapy.

There is clearly no consensus on what the actual cross-sensitivity is between penicillins and carbapenems, or how much of the allergy can be attributed to a coincidental allergic reaction to the carbapenem that is not related to the patient also being allergic to a penicillin. The wide range of cross-sensitivity reported between penicillins and carbapenems can be attributed to the way in which penicillin and carbapenem allergies are defined and the manner in which they are verified. When the studies that verified penicillin allergy by the accepted standard (ie, skin test to the major and minor penicillin determinants) and tested for carbapenem allergy by administering a full therapeutic dose to carbapenem skin test–negative patients are examined, the cross-reactivity between skin tests appears to be around 1%, with all carbapenem skin test–negative patients tolerating the challenge.^{31,32,34} Based on these studies, a recommendation can be made to skin test to the carbapenem those patients with a penicillin allergy; if the results are negative, the carbapenem can be safely adminis-

tered at increasing amounts in the manner described above. However, administering a carbapenem skin test may not always be feasible and a carbapenem test dose or graded challenge may be considered instead.

Monobactams

IMMUNOLOGY

Aztreonam is the only monobactam available for clinical use. It is composed of a β -lactam nucleus with no adjoining ring and a side chain (Figure 1). As a result of this difference in structure, the immunology and clinical tolerance of aztreonam in penicillin-allergic patients is of interest.

The immunogenicity of aztreonam has been heavily studied. One study showed that aztreonam interactions with anti-penicillin and anti-cephalothin antibodies and anti-aztreonam antibodies' cross-reactivity with penicillin and cephalothin were negligible.^{36,37} Additionally, the serum of 3 penicillin-allergic patients, verified via skin test, showed that aztreonam was only very weakly cross-reactive with human IgE anti-penicilloyl antibody.³⁶ This study also evaluated 36 healthy men with no previous exposure to aztreonam, who received aztreonam intravenously or intramuscularly for 7 days. Their sera were examined for the presence of IgE anti-aztreonam antibodies, which were found to be absent in all patients at all time periods evaluated. Additional immunogenicity studies suggested that aztreonam antibodies were directed to the side chain rather than the β -lactam ring^{36,37}; this was further confirmed in experiments showing that monobactams with side chains different from aztreonam did not interact with antibodies against aztreonam, whereas ceftazidime, which has a side chain identical to that of aztreonam, produced complete blocking of anti-aztreonam antibodies.³⁷

These results indicate that aztreonam is weakly immunogenic and does not significantly cross-react with penicillin and cephalosporin antibodies, except ceftazidime, with which it shares a common side chain. This belief is supported by The American Academy of Allergy, Asthma and Immunology.¹

CLINICAL EVIDENCE: PROSPECTIVE TRIALS

The low immunogenicity of aztreonam has been evaluated in patients to establish its clinical relevance. Data provided by ER Squibb on adverse reactions in 3360 patients receiving multiple doses of aztreonam in Phase 1 and 2 clinical trials revealed 71 (2.1%) immunologic reactions and 7 (0.2%) type 1 reactions.³⁸ The immunology study above additionally evaluated the cross-sensitivity between penicillins and aztreonam in vivo.^{37,39} A group of 81 penicillin skin test–positive and –negative subjects were skin tested to aztreonam and its metabolites, which correspond to penicilloyl and penicilloate. Half of 40 control patients

and 29 of 41 (70.7%) penicillin skin test–positive patients had histories of prior reactions to penicillins, but none to cephalosporins. None of the 81 patients were unequivocally positive for aztreonam or its determinants (Table 4). Four of 41 penicillin skin test–positive patients showed some reactivity; however, there were difficulties in interpreting their results. The skin tests were repeated in these 4 patients, and the aztreonam skin test was negative. The results of the study failed to show evidence of cross-reactivity between penicillin and aztreonam skin tests.

The tolerance of aztreonam in cystic fibrosis patients, who frequently require therapy with β -lactam antibiotics due to continual infections with *Pseudomonas aeruginosa*,⁴⁰ was evaluated in 2 trials.^{41–44} Fifteen cystic fibrosis patients with a documented history of hypersensitivity reactions to β -lactam antibiotics were skin tested to aztreonam; if the results were negative, they were administered escalating test doses of intravenous aztreonam.^{41,42} If no reaction was present, patients received aztreonam intravenously for 14 days. All 15 patients had a negative aztreonam skin test and tolerated the intravenous challenge. None experienced a hypersensitivity reaction during the first course of therapy; however, 56 total courses of aztreonam therapy were administered to all patients for *Pseudomonas* reinfection and 2 patients developed drug fever during the third or fourth course of therapy. The authors concluded that aztreonam can be used in cystic fibrosis patients with previous severe hypersensitivity reactions to other β -lactam antibiotics if they are skin tested and receive graded challenges as outlined in their study.

Another study evaluated 21 cystic fibrosis patients with a history of generalized hypersensitivity reaction to β -lactam antibiotics.^{43,44} Patients were skin tested to the major and minor penicillin determinants and the β -lactam antibiotic responsible for their most recent allergic reaction (the primary drug). They were also skin tested to aztreonam and its metabolites. If the result was negative, patients were treated with intravenous aztreonam for 10–21 days. All patients received multiple courses of the β -lactam before the development of an allergic reaction. Skin tests were positive to at least one β -lactam reagent in 19 patients, most commonly to the primary drug (17/19 patients; Table 4). Only 1 patient was skin test–positive to aztreonam; the remaining 18 patients received intravenous aztreonam therapy, along with 2 patients who were β -lactam skin test–negative.

One patient (5%) of the 20 treated with intravenous aztreonam did not tolerate it, and an additional 3 patients were sensitized and developed hypersensitivity reactions during subsequent aztreonam exposure. One patient was sensitized to aztreonam during her first treatment and developed bronchospasm on day 9 of therapy. Three additional patients were sensitized to aztreonam and developed hypersensitivities upon reexposure, including pruritic rash,

Table 4. Summary of Prospective Aztreonam Clinical Trials

Reference	Total/ β-Lactam- Allergic (N/n)	β-Lactam Allergy Verification	β-Lactam Allergy (n)	Reaction to β-Lactam (n)	β-Lactam Skin Test- Positive (n)	Aztreonam Allergy Verification	Aztreonam Determinant Skin Test-Positive (n)	Aztreonam Reaction (n)	Result of Cross-Sensitivity Between β-Lactam and Aztreonam
Saxon (1984, 1985) ^{37,39}	111/49, 41 ^a	skin test (major and minor determinants)	NR	urticaria (16); none (12); anaphylaxis (5); exanthem (6); positive skin test (1); large local reaction (1)	41 skin test-positive pts. major penicillin determinant (36); minor penicillin determinant (25)	skin test (aztreonam, open-ring hydrolysis product of aztreonam, conjugate of the open- ring aztreonam hydrolysis product)	none	none	none had a positive aztreonam skin test
Jensen (1987, 1991) ^{41,42}	15/15	documentation	carbenicillin (NR); azlocillin (NR); piperacillin (NR); cefazolin (NR); cefazidime (NR); cefotaxime (NR)	drug fever (10); generalized urticaria (10); rash (7); ana- phylaxis (7); angioedema (3)		skin test (aztreonam) and iv therapy	none	drug fever (2); rash (1)	0% had positive aztreonam skin test; 0% developed hyper- sensitivity reaction during first course of therapy; 2/15 (13.3%) were sensitized
Moss (1991) ^{43,44}	21/21, 19 ^b	skin test (major and minor determinants, primary drug ^c)	primary drug cefazidime (6); ticarcillin (6); piperacillin (5); azlocillin (4); other drugs ^d	cutaneous: pruritus, erythema, urticaria, and/or angioedema (21) respiratory: wheezing or stridor (8); fever (2); nephritis (1); serum sickness (1)	19 skin test-positive pts. primary drug (17); minor penicillin determinant (11); major penicillin determinant (6)	skin test (aztreonam, open-ring hydrolysis product of the open- ring aztreonam hydro- lysis product) and iv therapy	5 pts. had 9 reactions* aztreonam (2); open-ring hydro- lysis product of aztreonam (2); conjugated open- ring hydrolysis product of aztreonam (5)	bronchospasm (2); pruritic rash (1); angioedema (1)	1/19 (5.3%) of β-lactam- positive skin test had positive aztreonam skin test; 4/20 (20%) sensitization in reported β-lactam allergy treated with aztreonam; 3/18 (16.7%) sensitization in β-lactam skin test-positive treated with aztreonam
Vega (1991) ⁴⁵	49/29	controlled challenge test or skin test (major and minor penicillin determinants, benzylpenicillin, ampicillin, amoxicillin, cephamandole)	amoxicillin (17); benzylpenicillin (7); ampicillin (4); cefadroxil (1)	anaphylaxis (12); anaphylactic shock (8); non- immediate exanthem (5); urticaria/angio- edema (4)	29 skin test-positive pts. amoxicillin (13); major penicillin determinant (12); benzylpenicillin (10); minor penicillin determinants (9); ampicillin (9); cephamandole (5)	skin test (aztreonam) and iv challenge	none		1/29 (3.4%) of β-lactam-allergic pts. had positive aztreonam skin test; 0% reacted to intravenous aztreonam
Martin (1992) ⁴⁶	6/6	challenge and skin test (major and minor penicillin determinants, benzylpenicillin, amoxicillin, ampicillin)	amoxicillin (4)	generalized urticaria (4); hypotension (2); pruritus (2); dys- phonia/hoarse- ness (2); facial angioedema (1); vomiting and shortness of breath (1)	4 skin test-positive pts. amoxicillin (3); ampicillin (1)	im challenge	none		0% of amoxicillin-allergic pts. reacted to benzylpenicillin, aztreonam, or cefazidime

NR = not reported.

^a49 reported penicillin allergy, 41 verified by skin test.^b21 reported penicillin allergy, 19 verified by skin test.^cPrimary drug: β-lactam antibiotic responsible for the most recent allergic reaction.^dOther drugs causing previous allergic reactions: imipenem (2), oxacillin (1), carbenicillin (1), ticarcillin and clavulanic acid (1), and cefoperazone (1).^eFive pts. were aztreonam skin test-positive: 1 prior to and 4 after intravenous aztreonam exposure.

angioedema, bronchospasm, and a positive aztreonam skin test. This study showed a 5.3% rate of cross-reactivity between positive β -lactam and aztreonam skin tests. Sensitization, however, occurred in 20% and 16.7% of cystic fibrosis patients with reported β -lactam allergy and β -lactam skin test-positive reactions, respectively, treated with intravenous aztreonam.^{43,44}

Vega et al.⁴⁵ evaluated 49 patients with and without β -lactam allergies verified by skin test or controlled challenge tests. Patients were skin tested to a variety of penicillin determinants, cephamandole, and aztreonam (Table 4). The controlled challenge test included the administration of benzylpenicillin, phenoxymethylpenicillin, and amoxicillin, with evaluation for hypersensitivity reactions between each step. Seven days after presentation of a reaction, patients received one parenteral dose of aztreonam 500 mg. None of the nonallergic patients and 1 of 29 β -lactam-allergic patients was skin test-positive to aztreonam. However, all patients, including the patient with the positive aztreonam skin test, tolerated the administration of intravenous aztreonam 500 mg. This study also examined the cross-reactivity between aztreonam and benzylpenicilloyl IgE antibodies and found none.

A final case series report described 6 amoxicillin-allergic patients who tolerated benzylpenicillin, aztreonam, and ceftazidime.⁴⁶ Patients were skin tested with benzylpenicillin, the major and minor penicillin determinants, amoxicillin, and ampicillin. If the skin test was negative, patients were given a graded challenge of benzylpenicillin and amoxicillin until a reaction was observed. Each patient was also challenged with intramuscular aztreonam and ceftazidime in increasing doses. Four patients were skin test-positive to amoxicillin or ampicillin and all patients developed hypersensitivity reactions after oral challenge with amoxicillin (Table 4). However, all patients tolerated benzylpenicillin, aztreonam, and ceftazidime.

CLINICAL EVIDENCE: CASE SERIES AND REPORTS

A retrospective review evaluated the incidence of adverse reactions, specifically skin rash, fever, and eosinophilia, with aztreonam in 22 patients, 15 of whom reported penicillin allergies.⁴⁷ Five (22.7% of all patients; 33.3% of those reportedly penicillin-allergic) patients experienced an adverse event: 3 developed a skin rash, 1 eosinophilia, and 1 drug fever. Although all of these 5 patients had reported penicillin allergies, the allergy history was not a significant predictor of an adverse event with aztreonam ($p = 0.13$).

Numerous case reports have been published describing the use of aztreonam in β -lactam-allergic patients. A 69-year-old female who failed oral penicillin desensitization received aztreonam therapy with no adverse events.⁴⁸ Another case report described a 53-year-old male with a rash to penicillin who developed an urticarial rash to both aztre-

onam and imipenem.⁴⁹ The cross-reactivity specifically between aztreonam and ceftazidime was described in a case report of a 57-year-old male with a clindamycin allergy history.⁵⁰ He developed a maculopapular eruption when treated with aztreonam and amoxicillin/clavulanate; the rash worsened when only amoxicillin/clavulanate was stopped, which required discontinuation of aztreonam. The patient was skin tested to the major and minor penicillin determinants, benzylpenicillin, amoxicillin, amoxicillin/clavulanate, cephadrine, ceftazidime, and aztreonam, the results of which were positive for ceftazidime and aztreonam only.

DISCUSSION

Immunology studies of the possible cross-reactivity between anti-penicillin and anti-cephalosporin IgE antibodies with aztreonam indicate a lack of significant interaction.^{36,37,51} They additionally suggest that aztreonam antibodies are directed at the side chain and recognize ceftazidime because of the identical side chain.^{36,37} Although valuable, immunology data alone cannot be used as the basis of clinical decisions as to whether to administer aztreonam to β -lactam-allergic patients.

An evaluation of 5 trials shows the cross-sensitivity between β -lactam antibiotics and aztreonam to be low (between 0% and 5.3%), regardless of whether or not the study used additional penicillin determinants in verifying β -lactam allergy, skin tested to aztreonam as well as its metabolites, or administered aztreonam parenterally with or without a graded challenge first.^{37,39,41-46} The cross-reactivity between penicillin and aztreonam skin tests was 3.4–5.3%.⁴³⁻⁴⁵ However, no patients showed clinical signs of hypersensitivity after receiving parenteral aztreonam,^{37,39,41-46} except cystic fibrosis patients, who became sensitized and developed allergic reactions upon reexposure to aztreonam at a later time.⁴¹⁻⁴⁴ The data from cystic fibrosis patients, however, cannot be applied to the general population. This population can develop hypersensitivity reactions after numerous exposures to the same or a possibly cross-reacting medication,⁵² which was seen in the study by Moss et al.^{43,44} It is thus difficult to assess how much can be attributed to cross-sensitivity between the β -lactam antibiotics and aztreonam versus sensitization in a patient population that has a high rate of generalized immune responsiveness.⁵³ If the reactions that patients experienced upon exposure to aztreonam were IgE-mediated type 1 hypersensitivity reactions due to cross-sensitivity, the reaction would be expected to manifest immediately.^{6,7} However, this was not the case. Additionally, the cystic fibrosis patients in the Jensen et al.^{41,42} study had documented β -lactam allergies, which were not verified by skin test, while in the Moss et al.^{43,44} study, skin testing to the primary drug to which the patient reported an allergy was performed, the

predictive value of which is not known. These patients also received graded intravenous test doses prior to the full therapeutic course,^{41,42} which brings into question the possibility that patients were desensitized to aztreonam before the first course of therapy. This may account for the lack of immediate hypersensitivity reactions observed upon initiation of aztreonam therapy. However, if the patients were indeed allergic to aztreonam, one would expect an immediate reaction upon reexposure to the drug during future courses of therapy, and this did not occur. The patients who became sensitized developed drug fever and rash, which are not IgE-mediated.⁸

The studies in non-cystic fibrosis patients show no clinical cross-reactivity between β -lactams and aztreonam. Although the Saxon et al.^{37,39} study included the most patients, it evaluated only skin tests and patients did not receive any parenteral aztreonam. The other 2 studies performed both aztreonam skin tests, and parenteral challenges with or without a graded challenge first and found no clinical cross-reactivity, even in the 1 patient who was aztreonam skin test-positive.^{45,46}

One case series evaluated patients for skin rash, fever, and eosinophilia, which are not IgE-mediated reactions and thus do not help evaluate the immediate cross-sensitivity between these 2 classes, but show that other allergic-type adverse reactions may occur.⁴⁷ The case reports are of limited value, but the report of the patient with an allergy to aztreonam and ceftazidime but not benzylpenicillin, amoxicillin, or other cephalosporins is of note.⁵⁰ This case report addresses the concern of cross-reactivity between ceftazidime and aztreonam because of the same side chain. Aside from this report, 1 of 6 (16.7%) ceftazidime-allergic cystic fibrosis patients became sensitized to aztreonam and developed angioedema and bronchospasm upon reexposure to aztreonam.^{43,44} This is the only prospective trial that reported specifically about ceftazidime-allergic patients reacting to aztreonam. There are insufficient clinical data to conclude with certainty that aztreonam cross-reacts with ceftazidime, although the concept is logical and supportive immunology data exist.^{36,37} Given the available data, the cross-reactivity between β -lactams and aztreonam is negligible, although patients with ceftazidime allergies should be administered aztreonam with extra caution.

Summary

A review of the data on the cross-reactivity between penicillins and carbapenems indicates that the potential for development of a type 1 hypersensitivity reaction in a penicillin-allergic patient is very low and the use of carbapenems should not be completely avoided. Although many people may be classified as penicillin-allergic, 80–90% of those who report an allergy do not react to skin testing for IgE reactivity. It is therefore important to obtain

a thorough patient history, determining the drug the patient received, type of reaction, time between receiving the medication and development of symptoms, other medications the person was taking at the time that may have caused the reaction, and possibly cross-reacting drugs received since the initial reaction and whether they were tolerated.

Once the presence of a past IgE-mediated reaction to penicillin is confirmed by penicillin skin test or properly documented history, the likelihood of true cross-reactivity is considered. Although an early study of cross-reactivity between penicillin and imipenem and their metabolites showed a high incidence, this result has not been replicated. More recent prospective studies show the cross-reactivity between the penicillin and carbapenem parent compound skin test to be around 1%. Although it is unknown how many patients with positive carbapenem skin test will clinically develop a type 1 hypersensitivity reaction, 1% can be considered the likely upper limit of the cross-reactivity incidence since all patients with a negative carbapenem skin test tolerated the challenge used in studies. Since it is also not known whether the dosing scheme used in trials should be employed for all penicillin-allergic patients requiring carbapenem therapy, a graded challenge or test dose can be considered for patients determined by history to have experienced an IgE-mediated reaction or positive skin test to penicillin.

Both immunologic studies and evidence from clinical trials do not show any clinical cross-reactivity between aztreonam and penicillins except the development of sensitization reactions in cystic fibrosis patients. There are, however, immunology and some clinical data that a degree of cross-reactivity may exist between ceftazidime and aztreonam due to the similarity in side chains.

The consequences of IgE-mediated allergy can be severe, and diligence is required when β -lactams are chosen as therapy in reportedly β -lactam-allergic patients. However, it is important to reemphasize that the use of alternative antibiotics in patients reporting a penicillin allergy does not come without risks. These include but are not limited to increased healthcare costs, risk of developing bacterial resistance, use of alternative antibiotics with other potentially dangerous adverse effects, and the use of possibly inferior antibiotics. Choosing antibiotics for these patients is difficult, and it is important for the clinician to consider the allergy type in question, the infection being treated, and the availability, cost, and effectiveness of alternatives, as the risk of inducing an IgE-mediated type reaction to another β -lactam is lower than many believe.

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We acknowledge Kazumi Morita PharmD for her contribution to the presentation that led to the writing of this article.

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Sensibilidad Alérgica Cruzada Entre los Antibióticos Penicilina, Carbapenemo, y Monobactama: ¿Cuáles son las Probabilidades?

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Ann Pharmacother 2009;43:304-15.

EXTRACTO

OBJETIVO: Evaluar la literatura relacionada a sensibilidad alérgica cruzada entre los antibióticos penicilina, carbapenemo, y monobactama.

FUENTES DE DATOS: Una búsqueda en MEDLINE (1950-junio 2008) de la literatura en inglés se llevó a cabo usando los términos β -lactama, penicilina, monobactama, carbapenemo, alergia, y reactividad cruzada. Las referencias de los artículos revisados fueron chequeadas para inclusión.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Todos los artículos en inglés de las fuentes de datos fueron identificados. Estudios primarios cuyo principal objetivo era evaluar la hipersensibilidad a fármacos y potencial para reactividad cruzada fueron evaluados.

SÍNTESIS DE DATOS: Muchos pacientes llevan una etiqueta de alergia a penicilina que no ha sido verificada con una prueba en la piel y muchos proveedores de salud evitan el uso de otros antibióticos β -lactama, como los carbapenemos, por miedo a una reacción alérgica cruzada potencial mediada por IgE. Existe una variedad amplia de reacciones cruzadas entre penicilinas y carbapenemos reportadas en varios estudios, sin embargo la incidencia es de 1% en las pruebas de piel entre penicilina y carbapenemos. Además, muchos prescriben libremente monobactama aztreonam en pacientes alérgicos a penicilina, creyendo que no existe reactividad cruzada entre ambas. Aunque los datos apoyan la falta de reactividad cruzada entre aztreonam y penicilinas, la inmunología y datos clínicos apoyan una interacción entre ceftazidima y aztreonam dado lo parecido de las cadenas laterales.

CONCLUSIONES: A pesar de que existe una variedad de tasas de reacciones cruzadas entre las clases de β -lactama en la literatura, la práctica de evitar el uso de carbapenemos en pacientes alérgicos a penicilina debe

ser reconsiderada. Con relación a las monobactamas, un área de precaución y riesgo alto a reacciones de hipersensibilidad tipo 1 puede incluir la administración de aztreonam en pacientes con alergia a ceftazidima. Además, la importancia de obtener un buen historial del paciente en relación a eventos alérgicos previos, documentación apropiada y pruebas en la piel con penicilina se re-enfatizan.

Traducido por Sonia I Lugo

Qu'elles Sont les Possibilités de Développer une Allergie Croisée Entre la Pénicilline, le Carbapénème, et les Antibiotiques de la Classe des Monobactames

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Ann Pharmacother 2009;43:304-15.

RÉSUMÉ

OBJECTIF: Évaluer la documentation médicale concernant les réactions allergiques croisées entre la pénicilline, le carbapénème, et les antibiotiques de la classe des monobactames.

SOURCES DE DONNÉES: Une recherche MEDLINE a été effectuée dans la documentation de langue anglaise en utilisant les termes de recherche β -lactamines, pénicilline, monobactame, carbapénème, allergie, et réaction croisée. Les références des articles de revue sur le sujet ont également été évaluées pour inclusion.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Tous les articles de langue anglaise provenant de la source de données ont été identifiés. Les principales études pour lesquelles l'objectif primaire était d'évaluer l'hyposensibilité aux médicaments et le potentiel d'allergie croisée ont été analysées.

SYNTHÈSE DES DONNÉES: Plusieurs patients traînent une mention d'allergie à la pénicilline qui n'a pas été vérifiée à l'aide d'un test cutané et plusieurs professionnels de la santé évitent d'utiliser d'autres antibiotiques du groupe des β -lactamines, nommément carbapénème, de peur de provoquer une réaction allergique croisée indirecte par les IgE. Il existe une grande variété de réaction croisée entre les pénicillines et les carbapénèmes rapportées dans différentes études, cependant l'incidence est approximativement de 1% entre les tests cutanés de pénicilline et carbapénème. De plus, plusieurs prescripteurs utilisent aisément le monobactame aztréonam chez les patients allergiques à la pénicilline, croyant qu'il n'existe aucune allergie croisée entre ces 2 médicaments. Bien que les données appuient l'absence de réaction allergique croisée entre l'aztréonam et les pénicillines, l'immunologie et quelques données cliniques soutiennent une interaction entre la ceftazidime et l'aztréonam en partie à cause de la similitude de leur chaîne latérale.

CONCLUSIONS: Bien qu'une variabilité existe entre les taux de réactions allergiques croisées entre les classes de β -lactamines dans la documentation scientifique, la pratique courante d'éviter les carbapénèmes chez les patients allergiques à la pénicilline doit être revue. En ce qui a trait aux monobactames, une zone de prudence et un risque plus élevé de réaction d'hyposensibilité de type 1 peut inclure l'administration d'aztréonam chez un patient allergique à la ceftazidime. De plus, l'importance d'obtenir un bon historique entourant les événements allergiques du patient, avec documentation appropriée et un test cutané à la pénicilline doit être accentuée à nouveau.

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