

# Safety of Cephalosporin, Carbapenem, and Monobactam Antibiotics in Penicillin Allergic Patients

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## ABSTRACT

Penicillin is the most common cause of drug allergies. As penicillin and other beta-lactam antibiotics share a beta-lactam ring, there are concerns about potential for cross-reactivity. These concerns served as an impetus for subsequent studies that were conducted to evaluate the therapeutic implications of beta-lactam cross-reactivity. This paper seeks to review the literature and assess the risk of cross-reactivity between beta-lactam antibiotics.

## CASE

A 17 year old with penicillin anaphylaxis presents with bacterial meningitis – which antibiotic do you choose?

## INTRODUCTION

Adverse drug reactions occur in 1% - 10% of patients treated with penicillin antibiotics and of these, 10% are reported to be allergic phenomena.<sup>1</sup> Since all beta-lactam ring-containing antibiotics (penicillins, cephalosporins, carbapenems and monobactams) are structurally related, they have the potential to share allergens that might evoke cross-reactivity. Cross-reactivity involves the ability of the immune system to recognize similarities between related medications, such that antibodies produced against allergenic determinants will react against structurally related compounds. The pertinent question is which non-penicillin beta-lactam antibiotics can be safely administered to penicillin-allergic patients?

Penicillin allergy may occur in the form of immediate or delayed hypersensitivity reactions.<sup>2</sup> Immediate reactions are usually IgE-mediated (urticaria, angioedema, anaphylaxis) while delayed hypersensitivity reactions (skin rashes, erythema multiforme) are usually T-cell mediated. These allergic reactions can be classified by immunologic mechanisms into 4 main types: Type 1 (IgE-mediated), Type 2 (antibody-mediated), Type 3 (immune-complex-mediated) and Type 4 (T lymphocyte-mediated).

Commonly, a patient's self-reported allergy history plays a pivotal role in influencing treatment choices. As such, the validity of the reported allergy is crucial. Many patients misinterpret gastrointestinal symptoms as a sign

Table 1. List of beta-lactam antibiotics

BETA-LACTAMS
Avoid other beta-lactams under the same sub-heading. There is a risk of cross-sensitivity exists between penicillins, cephalosporins and carbapenems. Use carbapenems with caution in penicillin allergy.
<b>PENICILLIN</b>
Amoxicillin
Augmentin/Co-amoxiclav (contains amoxicillin)
Benzathine penicillin
Benzylpenicillin (Pen G, CP)
Cloxacillin
Dicloxacillin
Flucloxacillin
Phenoxyethylpenicillin (Pen V)
Piperacillin (found in Tazocin)
Ticarcillin (found in timentin)
<b>CEPHALOSPORIN</b>
Cefaclor
Cefalexin
Cefazolin
Cefepime
Cefotaxime
Cefoxitin
Ceftazidime
Ceftriaxone
Cefuroxime
<b>CARBAPENEM</b>
Ertapenem
Imipenem
Meropenem
<b>MONOBACTAM</b>
Aztreonam (safe in patients with penicillin, but not ceftazidime allergy)
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of allergy. Some clinicians tend to acknowledge patients' claims without getting a detailed history of the reaction, resulting in over diagnosis of penicillin allergy.<sup>3</sup> Up to 90% of patients, who report penicillin allergy, have negative skin testing results and can subsequently tolerate an oral penicillin challenge.<sup>4</sup> Incorrect labeling of patients as being allergic to penicillin not only limits treatment options but is also associated with increased health care costs.<sup>5</sup>

The objective of this paper is to review some of the available studies that evaluate the risk of cross-reactivity in patients with penicillin allergy treated with non-penicillin beta-lactam antibiotics.

## CEPHALOSPORIN ANTIBIOTICS

Both penicillin and cephalosporin antibiotics possess a 4-member beta-lactam ring, but cephalosporins have a 6-member dihydrothiazide ring in the cephalosporin nucleus that replaces the penicillin 5-member thiazolidine ring.

A retrospective review by Petz, et al,<sup>6</sup> which looked at the use of 1st-generation cephalosporins (cephalothin, cephalexin, cefazolin), reported an 8.1% incidence rate of cephalosporin allergy in patients with penicillin allergy as compared to 1.9% in patients without penicillin allergy. Similarly, Dash, et al,<sup>7</sup> demonstrated a 7-fold increase in cross-reactivity between penicillin and 1st-generation cephalosporins (cephalexin and cephaloridine). They found that 7.7% of cases, who had penicillin allergy, were also allergic to 1st-generation cephalosporins compared with 0.8% of cases, who did not have penicillin allergy.

Later generations of cephalosporins have lower rates of cross-reactivity with penicillin than earlier generations. This is likely to be due to differing side chain profiles in the structure of newer cephalosporins, which result in reduced cross reactivity.<sup>8</sup> A meta-analysis by Pichichero, et al,<sup>9</sup> reported an increase in allergic reactions to 1st-generation cephalosporins (OR 4.8, CI 3.7 – 6.2) in patients with penicillin allergy but no increase in 2nd-generation cephalosporins (OR 1.1, CI 0.6 – 2.1) or 3rd generation cephalosporins (OR 0.5, CI 0.2 – 1.1). The relative safety of 3rd generation cephalosporins was further illustrated by another study where none of 142 patients, who had positive skin test results for penicillin allergy, experienced any allergic reactions to ceftriaxone, a 3rd generation cephalosporin.<sup>10</sup> It is also important to note that early cephalosporin formulations contained trace amounts of penicillin,<sup>11</sup> and 1st-generation cephalosporins (cephaloridine and cephalothin) have similar side chains to penicillin. These confounders may have contributed to an increased risk of cross-reactivity. A study by Novalbos, et al,<sup>12</sup> showed that none of the patients with positive penicillin skin tests, who were challenged with cephalosporins that had different side chains from the penicillin antibiotic, had an allergic reaction or experienced adverse effects.

## CARBAPENEM ANTIBIOTICS

Saxon, et al,<sup>13</sup> examined the cross-sensitivity between imipenem and penicillin in 40 patients with a reported history of penicillin allergy. Out of 20 patients who had positive IgE-mediated skin test responses to penicillin, 9 also had positive IgE-mediated skin test responses to imipenem. The clinical relevance of this high degree of skin test cross-sensitivity (9/20, 45%) between imipenem and penicillin is unclear, because studies that have given test doses of imipenem to penicillin-allergic patients have not been reported. Furthermore, the Saxon trial data was collected at a time when carbapenems were synthesized from penicillin antibiotics, which might have led to contamination and inflated rates of cross-reactivity.

More recently, a retrospective study by Sodhi, et al,<sup>14</sup> reported 9.2% of penicillin-allergic patients and 3.9% of non-penicillin-allergic patients experienced hypersensitivity reactions (predominantly a maculopapular rash) to meropenem or imipenem/cilastatin. These findings are comparable to 2 other retrospective studies that revealed a cross-reactivity incidence of 9.5% and 11% to imipenem/cilastatin.<sup>15,16</sup> Cunha, et al,<sup>17</sup> examined the safety of meropenem use in patients with a history of penicillin allergy – all 110 patients with anaphylactic (51/110, 46%) and non-anaphylactic (59/110, 54%) reactions to penicillin tolerated up to 4 weeks of meropenem without any cross-reactivity.

## MONOBACTAM ANTIBIOTICS

Aztreonam is a monobactam antibiotic with a beta-lactam ring. Unlike the rest of the beta-lactam antibiotics, which contain a bicyclic ring structure,

aztreonam's beta-lactam structure is monocyclic in nature.

There have been no reports of cross-reactivity in penicillin-allergic patients receiving aztreonam.<sup>18,19</sup> Similarly, aztreonam was found to be safe in patients with IgE-mediated responses to other beta-lactam antibiotics.<sup>20</sup> However, ceftazidime has been demonstrated in-vitro to trigger cross-reactivity with aztreonam.<sup>21,22</sup> This is a result of ceftazidime sharing side chain antigens with aztreonam.

## SUMMARY

While penicillin allergies can be life threatening, up to 90% of patients who report penicillin allergy have negative skin tests. The vast majority of these patients can be safely treated with penicillin. As such, it is of vital importance to determine the nature of the "allergic" reaction before making decisions about antibiotic treatment. Furthermore, 2nd and 3rd generation cephalosporins have lower rates of cross-reactivity in penicillin-allergic patients than 1st generation cephalosporins. In patients with IgE-mediated allergy to penicillin, cephalosporins with different side chains from penicillin can be cautiously considered. Based on results from recent studies, the true incidence of meropenem cross-reactivity may be lower than previously reported. As such, carbapenem use in penicillin-allergic patients may be considered if caution is exercised. With the exception of ceftazidime, aztreonam may be safely given to patients with a history of penicillin-allergy or IgE-mediated responses to other beta-lactams.

## RECOMMENDATIONS

If penicillin anaphylaxis is reported, it is sensible to use a non-beta-lactam antibiotic, whenever possible. If penicillin use is desirable (e.g. rheumatic fever prophylaxis, endocarditis, tertiary syphilis), referral to a clinical immunologist for review, skin testing and/or graduated penicillin challenge is prudent. A negative skin test does not always exclude past or future anaphylaxis, but the risk of anaphylaxis with the current course of treatment falls to that of the background population. For delayed hypersensitivity reactions (skin rashes), it is almost always safe to switch to another beta-lactam antibiotic (e.g. from penicillin to cephalosporin or vice versa).

In the case of the 17 year old with a life-threatening illness such as bacterial meningitis, where penicillin is the preferred option - but contraindicated because of a history of anaphylaxis - ceftriaxone given cautiously in the emergency department is a good option whilst you seek further advice.

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