



## Penicillin Allergy and Cross-reactivity with other Beta-lactams.

Mohammadreza Javadi<sup>1,3</sup>, Kheirollah Gholami<sup>2</sup>, Hassan Torkamandi<sup>3</sup>, Alireza Hayatshahi<sup>1,3</sup>

<sup>1</sup> Clinical Pharmacy Department, Faculty of Pharmacy and Pharmaceutical Sciences, Tehran University of Medical Sciences, Tehran, Iran

<sup>2</sup> Faculty of Pharmacy and Pharmaceutical Sciences and Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran

<sup>3</sup> Pharmaceutical Care Department, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

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### ABSTRACT

Beta-lactams are a group of antibiotics with a broad spectrum of both Gram-negative and Gram-positive coverage. The goal of this study is to evaluate the results from studies regarding Ig-E mediated hypersensitivity to Penicillin and cross-reactivity with other beta-lactams. Review was conducted of both retrospective and prospective studies by searching in PubMed and Medline for the original and systematic review articles by using the keywords: penicillin allergy, beta-lactams and cross-reactivity. The rate of true Penicillin allergy is about 10% of reported cases by the patients. The rate of Ig-E mediated cross-reactivity between Penicillin and Cephalosporins is less than 10% for the first and second generations and less than 5% for the third and fourth generations. According to the reviewed studies, Imipenem has between 9.2% to 25.6% cross-reactivity with Penicillin. Recent studies have shown safe use of Meropenem in patients with penicillin allergy even with positive skin test. The only member of Monobactam family, Aztreonam, has no cross-reactivity with any of Penicillins, Cephalosporins (with the exception of Ceftazidime) and Carbapenems. Due to the low rate of true Penicillin allergy, the patient's self report of this adverse reaction must be justified carefully before avoiding beta-lactams. Even in the cases of true penicillin allergy, Meropenem appears to be safe, if indicated. There are also a few case reports regarding hypersensitivities to Clavulanate itself and also its cross-reactivity with Penicillin.

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### Introduction

Beta-lactams are a group of antibiotics with a broad spectrum of antibacterial activities against both gram-negative and gram-positive bacteria. Penicillins, Cephalosporins, Carbapenems and Aztreonam are members of this antibiotic family. The adverse effect profiles of the Beta-lactam antibiotics are relatively benign and they have minimal interactions with other drugs. With all these properties, Beta-lactams may be utilized in treatments of many infections. Unfortunately, due to the absence of FDA-approved penicillin tests, clinicians have to rely on patient's own reported allergy history, which may affect their decision regarding the treatment choices.

Adverse reactions to Penicillin occur in approximately

10%-20% of treatment courses. Fatal Penicillin-induced anaphylaxis occurs at the rate of 0.002% among general population. About 10% to 20% of patients report history of allergic reactions to penicillins, however about 90% of them are not hypersensitive to penicillins. Patients between ages of 20-49 are at more risks of anaphylactic reactions. Up to 80% of patients with Ig-E mediated hypersensitivity reactions to penicillins may have negative skin test in 10 years (1,2). In this article, we review the pathophysiology of penicillin allergy and studies which have evaluated the cross-reactivity of penicillins with other Beta-lactams.

### Adverse Drug Reactions and Allergy

There are two major adverse drug: Type A are predictable reactions (e.g., over dose (acetaminophen over dose and liver toxicity) and side effects (tachycardia induced by inhaled albuterol), Type B are unpredictable reactions which are generally classified as hypersensitivity

\* Corresponding Author: Dr Alireza Hayatshahi

Address: Pharmaceutical Care Department, Shariati Hospital, Kargar St., Tehran, Iran. Tel: +982184902364, Fax: +982188220025.

Email: hayatshahi@tums.ac.ir

reactions. Hypersensitivity reactions are further classified as either immune mediated reactions, which is our focus in this article or non-immune mediated reactions. The followings are the criteria for a drug reaction to be considered as an immune-mediated: reaction occurs in a small number of patients receiving the drug, reaction does not resemble the drug's pharmacologic effects, reaction occurs even with small amount of the drug, reaction occurs with drugs with similar structures, presence of eosinophilia, and reaction resolves after discontinuation of the drug (1).

### Pathophysiology of Ig-E Mediated Hypersensitivity

Reaction to Penicillin Ig-E mediated allergic reactions, also called immediate hypersensitivity reactions (Type-I hypersensitivity reactions) have an onset of as fast as a couple minutes. The major symptoms of immediate hypersensitivity reactions are urticaria, angioedema, bronchospasm, pruritis, diarrhea and anaphylaxis. Type-I hypersensitivity reactions are classified as humeral mediated reactions, however the first time a body is exposed to an immunogenic drug the T-cells, specifically T-helper-2 (TH2) cells, initiate the allergic reaction by releasing interleukine-4 and interleukine-13 (IL-4, IL-13), which activate and induce proliferation of the B-cells. The activated B-lymphocytes then produce the antigen specific Ig-E. There is a cross-link between multivalent antigen and basophils or mast cells by Ig-E specific for that antigen which leads to the degranulation of basophils and mast cells and release of inflammatory mediators (1).

Major inflammatory mediators involved in Type-I hypersensitivity reactions: Histamine, eosinophilic chemotactic factor, leukotrienes, prostaglandins, thromboxane A2, platelet activating factor, bradykinins, tumor necrosis factor-alpha, IL-4, IL-5, IL-6, and IL-13. As the result, these chemicals lead to bronchospasm, hypersecretion of mucus glands, increased capillary permeability and other inflammatory reactions. Penicillin has a small molecular weight (350 Daltons), classifying this molecule as a hapten. After spontaneous structural breakdown, major and minor determinants are formed which covalently bind to either plasma or tissue proteins. This recent process is called the haptenation process. The carbonyl group of the beta-lactam ring covalently binds to the amino group of the lysine residues of the tissue proteins or albumin. The combination of the major or minor determinants with the protein then has the ability to cross-link to the basophiles and mast cells by specific Ig-E (1, 4).

### Cross-Reactivity of Penicillin with Cephalosporins

Penicillins have a bi-cyclic nucleus including a Beta-lactam ring and a thiazolidine ring in their structures. On the other hand, Cephalosporins have the Beta-lactam ring

but instead of thiazolidine, they have dihydrothiazine ring in their bi-cyclic nucleus. The first and second generations of Cephalosporins have higher rates of cross-reactivity with penicillin. Later generations of Cephalosporins (3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup>) have decreased immunogenicity possibly due to their bulkier and more different side chains compared to earlier generations and penicillins (3, 4).

Petz performed a retrospective evaluation of 15,708 cases from clinical trials with cephalosporins (Cephaloridine, Cephalothin, Cephalexin, Cefazolin and Cefamandole), all early generations. There were 701 cases with the positive history of penicillin allergy and 15,007 cases with negative history of penicillin allergy. Fifty-seven patients were in the penicillin allergic group who also had allergic reactions to cephalosporins (8.1%), versus 285 patients with negative history of penicillin allergy who developed reactions to cephalosporins (1.9%) (5).

Dash et al., reviewed several international studies on cross-reactivity between penicillin and the 1<sup>st</sup> generation of cephalosporins. The conclusion of this study was that the rate of cross-reactivity was 7.7%. Less than 1% of patients with no penicillin allergy had reactions to cephalosporins (4).

There were a series of studies on cephalosporin allergic reactions in patients with positive penicillin skin tests on a total of 179 patients. Eight patients (4.5%) developed allergic reactions to cephalosporins. It is important to mention cephalosporins tested in these studies had side chains similar to penicillin. Also, early cephalosporin preparations had penicillin contamination, which can be considered as a confounding factor. There was also the possibility of multiple drug allergy syndrome rather than cross-reactivity (4).

### Cross-Reactivity between Penicillin and Carbapenems

Saxon et al., studied the cross-reactivity of penicillin and carbapenems on a total of 39 patients with a reported history of penicillin allergy. Nineteen of these patients had positive skin tests to penicillin and 9 patients out of those (47%) developed positive skin test to imipenem reagents. The overall rate of cross-reactivity in all 39 patients was 25.6% (10/39) (6).

Sodhi et al. also had a retrospective study on the cross-reactivity between penicillin and carbapenems on a total of 266 patients. There were 163 patients with reported penicillin allergy and 103 patients without history of penicillin allergy. Fifteen patients with penicillin allergy also developed reactions (mostly maculopapular rash) to either Meropenem or Imipenem/Cilastatin (9.2%). Four patients without history of penicillin allergy also developed allergic reactions to either Meropenem or Imipenem/Cilastatin (3.9%).  $P=0.164$ . Patients with

possible non-Ig-E mediated reactions to aminopenicillins (Amoxicillin, Ampicillin) were not excluded from this study. Also 42% of the patients with a history of penicillin allergy had reported hypersensitivity reactions to other antibiotics including fluoroquinolones, sulfa and macrolides (possible multidrug allergy), which could be a confounding factor (7).

Prescott et al., had a retrospective chart review of a total of 211 patients (100 patients with history of penicillin allergy and 111 patients without history of penicillin allergy). Patients with possible non-immunogenic hypersensitivity reactions to aminopenicillins (Amoxicillin and Ampicillin) were excluded from this study. Both Meropenem and Imipenem/Cilastatin were evaluated. This study concluded a rate of 11% cross-reactivity between penicillin and carbapenems, versus 2.7% hypersensitivity reactions in patients without history of penicillin allergy ( $P=0.024$ ). Twenty four percent of patients with a history of penicillin allergy also reported allergic reactions to cephalosporins, sulfa, fluoroquinolones and Clindamycin, which could be considered as a confounding factor since some of these patients were on these antibiotics concomitantly with carbapenems (8).

There were two recent studies on the safety of Meropenem use in patients with a history of penicillin allergy. Both studies showed minimal cross-reactivity between penicillin and Meropenem.

Atanaskovic et al., developed a prospective study on 108 children aged from 3 to 14 years. All patients had positive penicillin skin tests. A total of 107 patients received a Meropenem skin test with negative results who later received challenge doses of Meropenem with no reaction. Only 1 patient (0.9%) developed a positive skin test to Meropenem and did not receive any challenge dose of meropenem (9).

Cunha et al., performed a prospective study on the safe use of Meropenem in 110 patients with a history of penicillin allergy. Fifty-nine patients reported non-anaphylactic reactions to penicillin in the past and 51 patients reported anaphylaxis to penicillin. All patients were treated with Meropenem for a period of 1-4 weeks and none had reactions to Meropenem. This study concluded the safe use of Meropenem in patients with reported penicillin allergy; even anaphylactic reactions to penicillin (10).

Possible reasons for the results from the above studies could be the bulkier side chain in Meropenem compared to Imipenem.

### Cross-Reactivity of Aztreonam with other Beta-Lactam Antibiotics

Aztreonam is the only available Monobactam agent which has a Beta-lactam but no bi-cyclic nucleus in its structure. Both in-vitro and randomized studies showed no cross-reactivity between Aztreonam and other Beta-

lactams with the exception of Ceftazidime (11-13).

Patriarca et al. developed an observational study on 45 patients with a history of Ig-E mediated hypersensitivity reactions to beta-lactams, which was confirmed with positive skin tests to Penicillin, Amoxicillin, Imipenem and Cefaclor. All patients had negative skin tests to Aztreonam and all tolerated the challenge doses of the drug (14).

### Conclusion

From the review of the above studies, we conclude that there is up to 8% cross-reactivity between penicillin and cephalosporins. This number decreases as later generations of cephalosporins are used, due to their bulkier side chains and also possible penicillin pollution of early cephalosporins in older studies. The rate of cross-reactivity between penicillin and Imipenem/Cilastatin in the general population is reportedly from 9.2% to 25.6%, whereas the results regarding cross-reactivity between Meropenem and penicillin is more controversial. Earlier retrospective studies showed up to 11% cross-reactivity, versus almost no cross-reactivity between these agents in more recent studies. Finally, Aztreonam is considered safe in patients with the history of Ig-E mediated hypersensitivity reactions to other Beta-lactams, with the exception of Ceftazidime. One important thing to maximize the safe utilization of the Beta-lactam family would be to obtain an accurate allergy history from the patient, including the nature of the reaction, time of the reaction, and the exact Beta-lactam agent to which patient reports allergic reaction.

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