Penicillin and Beta-Lactam Hypersensitivity

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KEYWORDS

• Penicillin • Beta-lactam • Allergy • Hypersensitivity

KEY POINTS

- More than 90% of individuals with history of penicillin allergy tolerate penicillins, and skin testing is the optimal method for evaluation.
- "Penicillin allergy" is associated with antimicrobial resistance, prolonged hospitalizations, readmissions, and increased costs.
- There is minimal allergic cross-reactivity between penicillins and cephalosporins, except selective allergy to aminopenicillin R-group side chains, which greatly increase the risk of reactions to cephalosporins with identical R1 group side chains.
- There is minimal allergic cross-reactivity between penicillins and carbapenems.
- Allergy to cephalosporins is usually side-chain specific and may warrant graded challenge with cephalosporins containing dissimilar R1 or R2 group side chains.

PENICILLIN ALLERGY

Background

Drug allergy is defined as an unpredictable reaction, or type B reaction, which is mediated by immune mechanisms.[1] Penicillin allergy is the most commonly reported medication allergy.[2] Immunoglobulin (Ig)E-mediated (or type I) reactions are one type of drug allergy, and they are the focus of this review. For further information on delayed reactions, please refer Caitlin M.G. McNulty and Miguel A. Park's article, "Delayed Cutaneous Hypersensitivity Reactions to Antibiotics, Management with Desensitization," in this issue. IgE-related reactions are typically immediate, with symptoms occurring within minutes to 6 hours of last administered dose, although onset is classically within

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1 hour. IgE-related symptoms may include pruritus, flushing, urticaria, angioedema, bronchospasm, laryngeal edema, nausea, emesis, and hypotension.

Epidemiology

Penicillin allergy is self-reported by approximately 10% of patients.[3] However, following thorough evaluation, 90% or more of individuals with a history of penicillin allergy tolerate penicillins.[4–7] As a result, a history of penicillin allergy is unreliable in predicting reactions with subsequent administration of the medication. There are various reasons for this incongruity. Often, reaction histories are poorly characterized and very remote. Symptoms may simply have been a consequence of an underlying illness, such as a viral infection, or from an interaction between a penicillin antibiotic and an infectious agent. A well-characterized example of the latter is when actively infected patients with Epstein-Barr virus are treated with ampicillin and develop a morbilliform rash.[8] Another important contributor to the discrepancy is loss of penicillin sensitivity over time. Approximately 50% of penicillin-allergic patients lose their sensitivity over 5 years, and approximately 80% over 10 years.[9,10]

Based on the rate of positive penicillin skin tests, the prevalence of immediate reactions to penicillin antibiotics is decreasing over the past 2 decades.[11,12] Penicillin-induced anaphylaxis is relatively rare, with several studies suggesting a rate of approximately 0.01% to 0.04% of treated patients.[13,14] In the United States, it has been estimated that 500 to 1000 deaths per year are secondary to penicillin-induced anaphylaxis.[15]

Detriment of "Penicillin Allergy" Label

Physicians frequently choose alternative antibiotics for those labeled with "penicillin allergy."[16–22] Unfortunately, this is associated with increased antimicrobial resistance, increased *Clostridium difficile* infections, prolonged length of hospital stays, increased intensive care admissions, increased hospital readmissions, and increased mortality.[19,23–26] Beyond compromising one's health, there are significantly higher costs associated with the "penicillin allergy" label.[18–21,27] Recently, King and colleagues[27] calculated that an average of $297 per patient would be saved if patients switched from a non–beta-lactam antibiotic to a beta-lactam antibiotic. Macy and Contreras[19] reported "penicillin-allergic" patients stayed an extra 0.59 days longer than control patients, resulting in an estimated $64.6 million cost. Cost-analysis studies thus far focus on one patient encounter, but extrapolating these data to the lifetime of a patient with potential future intensive care admissions, hospital readmissions, and expensive second-line antibiotic prescriptions could result in an overwhelming financial burden for patients.

Immunochemistry

Penicillin, like most drugs, is generally too small to be immunogenic; therefore, the immune response is directed against complexes of penicillin degradation products covalently bound to self-proteins.[28–30] The allergic components of penicillin are derived from either the beta-lactam core ring structure or from a specific side chain R group (**Fig. 1**). The core beta-lactam ring structure is shared among all penicillin antibiotics, whereas the R-group side chains differentiate penicillin antibiotics from each other.

After penicillin administration, the beta-lactam ring opens spontaneously to form several breakdown products. The most prevalent of these is penicilloyl polylysine, or major allergenic determinant, which comprises 95% of the breakdown products.