

## Original Article

# The Cost of Self-Reported Penicillin Allergy: A Systematic Review

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**What is already known about this topic?** Many patients who self-report a penicillin (PCN) allergy are not truly allergic to PCN and may receive an antibiotic regimen that is suboptimal for their condition.

**What does this article add to our knowledge?** This systematic review shows that most studies involving PCN allergy focus on inpatient drug therapy optimization and show that inpatient costs are higher on average in the presence of a PCN allergy label.

**How does this study impact current management guidelines?** Future cost-effectiveness studies of PCN allergy testing should evaluate relationships between PCN allergy testing/delabeling and long-term clinical and economic outcomes.

**BACKGROUND:** Patients who report a penicillin (PCN) allergy receive suboptimal antibiotic therapy compared with patients not reporting an allergy. However, a majority of patients who report PCN allergy are not truly allergic on confirmatory testing. Ruling out PCN allergy by testing may improve clinical and economic outcomes for patients with reported allergies requiring antibiotic therapy.

**OBJECTIVE:** The objective of this study was to summarize clinical and economic outcomes associated with PCN allergy and provide recommendations for future cost-effectiveness analyses for PCN allergy testing.

**METHODS:** A literature search was conducted using SCOPUS, EMBASE, and PubMed, including all articles published any date through April 25, 2017 (PROSPERO Registration number 42017064112). A total of 1518 abstracts were found during the initial search with 96 duplicates, for a total of 1422 articles for screening. Thirty articles were included for qualitative synthesis and full data extraction.

**RESULTS:** The majority of the studies included had an observational design focusing on inpatient admissions. The most frequently measured outcome in the context of PCN allergy was optimizing antibiotic therapy. Patients with PCN allergy were found to have direct drug costs during inpatient admission ranging from no difference to an additional \$609/patient compared with patients without PCN allergy. Outpatient prescription costs were estimated from \$14 to \$193/patient higher for PCN allergic patients. Total inpatient costs were less for patients without PCN allergy with average savings from \$1145 to \$4254/patient.

**CONCLUSIONS:** Evaluations of clinical and economic outcomes of PCN allergy are primarily observational and focus on inpatient populations. Long-term relationships between PCN allergy and clinical and economic outcomes are unknown. © 2018 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2018;■:■-■)

**Key words:** Penicillin allergy;  $\beta$ -Lactam; Outcomes; Cost

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Approximately 10% to 20% of patients report a penicillin (PCN) allergy when presenting in a clinical setting, which influences antibiotic treatment selections and health outcomes.<sup>1-3</sup> Reported antibiotic allergies have been associated with suboptimal antibiotic therapy, increased antimicrobial resistance, increased length of stay, increased antibiotic-related adverse events, increased rates of *Clostridium difficile* infection, intensive care unit admission, death, and increased treatment cost.<sup>3,4</sup> Antibiotic regimens deviate from the standard of care in approximately 35% of patients who report a PCN allergy.<sup>3</sup> The costs of suboptimal antibiotic therapy due to reported PCN allergy are likely significant, reaching far beyond the actual differences in antibiotic costs. Cost-effectiveness analyses conducted to evaluate interventions to confirm true PCN allergy and delabel patients without an allergic response to  $\beta$ -lactam antibiotics may

*Abbreviations used**PCN- Penicillin**PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-Analyses*

need to consider a wide range of current and future costs potentially avoided.

This article summarizes published data on clinical and economic outcomes associated with PCN allergy. We also provide recommendations for future cost-effectiveness analyses conducted to evaluate the benefit of confirmatory PCN allergy testing.

## METHODS

Our systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and the full protocol is registered with PROSPERO (Registration number 42017064112).<sup>5</sup> A literature search was conducted using SCOPUS, EMBASE, and PubMed, including studies published through April 25, 2017. The search terms included (“penicillin” AND “allergy”) AND (“costs” OR “cost-of-illness” OR “economics” OR “cost effectiveness”), and results were limited to peer-reviewed publications in English. Titles and abstracts were screened by multiple reviewers for relevance to infectious diseases where penicillin allergy was reported. Abstracts were divided among 3 teams of 2 authors for screening. After abstract review, discrepancies between the 2 reviewers were assessed with a full second screening requirement if the discrepancy rate exceeded 20%.

After abstract and title screening, full-text articles were assessed for eligibility for inclusion. Three authors reviewed all full-text articles, and disagreements regarding inclusion were discussed until full agreement was reached. Risk of bias was assessed by considering study rigor, type of analysis used, and population as described in the results. Data extraction included the following variables: Authors, Article Title, Journal Title, Year Published, Type of Study, Population, Outcomes Identified in Study, and Any Costs Identified in Study. A narrative synthesis of the findings was structured around the target population characteristics, type of outcome, and type of costs identified. For cost comparisons where studies identified a specific dollar amount, all costs reported were adjusted to 2017 costs based on the consumer price index for inflation.<sup>6</sup>

## RESULTS

A total of 1518 abstracts were found during the initial search with 96 duplicates, for a total of 1422 articles for screening. An additional 1347 articles were removed during abstract screening because of lack of relevance or study type. Reviewer agreement for inclusion during screening was 92.3% (1315/1422). Two separate authors conducted a second review to serve as a tiebreaker for the 107 disagreements, of which 21% (22/107) were included in the full text review for a total of 75 articles. An additional 45 articles were excluded after full text review because of lack of relevance, study type, not a full manuscript, or inappropriate comparators or outcomes assessed. A total of 30 articles were included for qualitative synthesis, and a full data extraction table (Table E1) is available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org).<sup>4,7-35</sup> The full results of the search strategy are provided in a PRISMA flow chart (Figure 1).<sup>5</sup>

Of the articles included for analysis, 22 studies were considered observational (cross-sectional, cohort, case-control), 6 studies were

interventional (pre-post design only), 1 study involved mixed methods, and 1 article was a literature review. Eighty percent of the studies focused only on inpatient admissions (24/30), whereas 10% (3/30) used outpatient data and 10% (3/10) considered both inpatient and outpatient care (Table I).

Table II summarizes the most frequent outcomes measured, including any outcomes measured by more than 1 study. The most frequently used outcome measure in the context of PCN allergy was optimizing antibiotic therapy for the admission of interest. Examples of outcomes less frequently used include aztreonam utilization and predictive values of PCN skin testing services. Appropriate antibiotic therapy was determined differently across studies depending on the population, disease state, or other factors. Some authors measured whether or not a switch occurred without assessing a qualitative judgment on appropriateness of therapy.<sup>7,9,12,19-21,25</sup> Adverse events were measured as both a reaction to the skin test intervention and potential adverse reactions to antibiotics given post-PCN allergy testing.<sup>13,22,27,28,31,33</sup>

Table III summarizes the most frequent costs identified in the context of PCN allergy. The direct cost of antibiotic treatment during a single inpatient admission was the most frequently measured outcome. Cost savings directly from switching antibiotic therapy were reported in different ways, but most frequently as a total program cost savings or as per patient savings. Jones and Bland<sup>7</sup> estimated \$314/patient savings from calculating the difference in the acquisition costs of the initial antibiotic and the post-testing therapy multiplied by the total number of days of therapy. Cost savings from antibiotic therapy changes ranged from no savings to as high as \$609/patient. Satta et al<sup>21</sup> used a similar approach focusing on drug acquisition cost differences at a hospital in the United Kingdom to estimate a savings of £89.29/patient. King et al<sup>11</sup> derived a \$297/patient cost savings in 37 patients with a negative skin test based on the cost savings in antibiotic use after factoring in the increased cost of applying the test to total 50 patients. Drug cost savings for a specific institution on an annual basis were calculated by multiple authors with the assumption that decreased prescribing of more expensive antibiotics, such as aztreonam, would result from PCN allergy testing.<sup>9,10,13,20</sup>

Other direct medical costs included costs of subsequent readmissions, hospital length of stay, additional costs associated with intravenous antibiotics versus oral, increased cost due to transfer to a higher level of care, or costs of outpatient antibiotic prescriptions. Total potential cost savings of delabeling in the inpatient setting were driven by length of stay reductions ranging from \$1145 to \$4254/patient.<sup>26</sup> Perencevich et al<sup>31</sup> reviewed 38 patients who tested negative for PCN allergy over a 2-year period and found that 86% of the readmissions requiring antibiotic therapy received at least one  $\beta$ -lactam demonstrating the potential for downstream cost savings with skin testing, but the study did not quantify these savings. Charneski et al<sup>23</sup> found associations with PCN allergy labels and increased hospital length of stay, higher levels of care, number of antibiotics received during stay, and death during hospitalization in a large cohort of 11,872 adult admissions. Macy and Contreras<sup>18</sup> found an increase in total number of hospital days and increased prevalence of multidrug resistant organisms in 51,582 PCN allergic cases matched with nonallergic controls.

## DISCUSSION

Most studies evaluating the impact of reported PCN allergies focus on antibiotic optimization based on PCN allergy testing

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