

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; β -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.¹⁻³ 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.^{3,4} Antibiotic regimens deviate from the standard of care in approximately 35% of patients who report a PCN allergy.³ 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 β -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).⁵ 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.⁶

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.^{4,7-35} The full results of the search strategy are provided in a PRISMA flow chart (Figure 1).⁵

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.^{7,9,12,19-21,25} Adverse events were measured as both a reaction to the skin test intervention and potential adverse reactions to antibiotics given post-PCN allergy testing.^{13,22,27,28,31,33}

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 Bland⁷ 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 al²¹ 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 al¹¹ 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.^{9,10,13,20}

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.²⁶ Perencevich et al³¹ 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 β -lactam demonstrating the potential for downstream cost savings with skin testing, but the study did not quantify these savings. Charneski et al²³ 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 Contreras¹⁸ 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

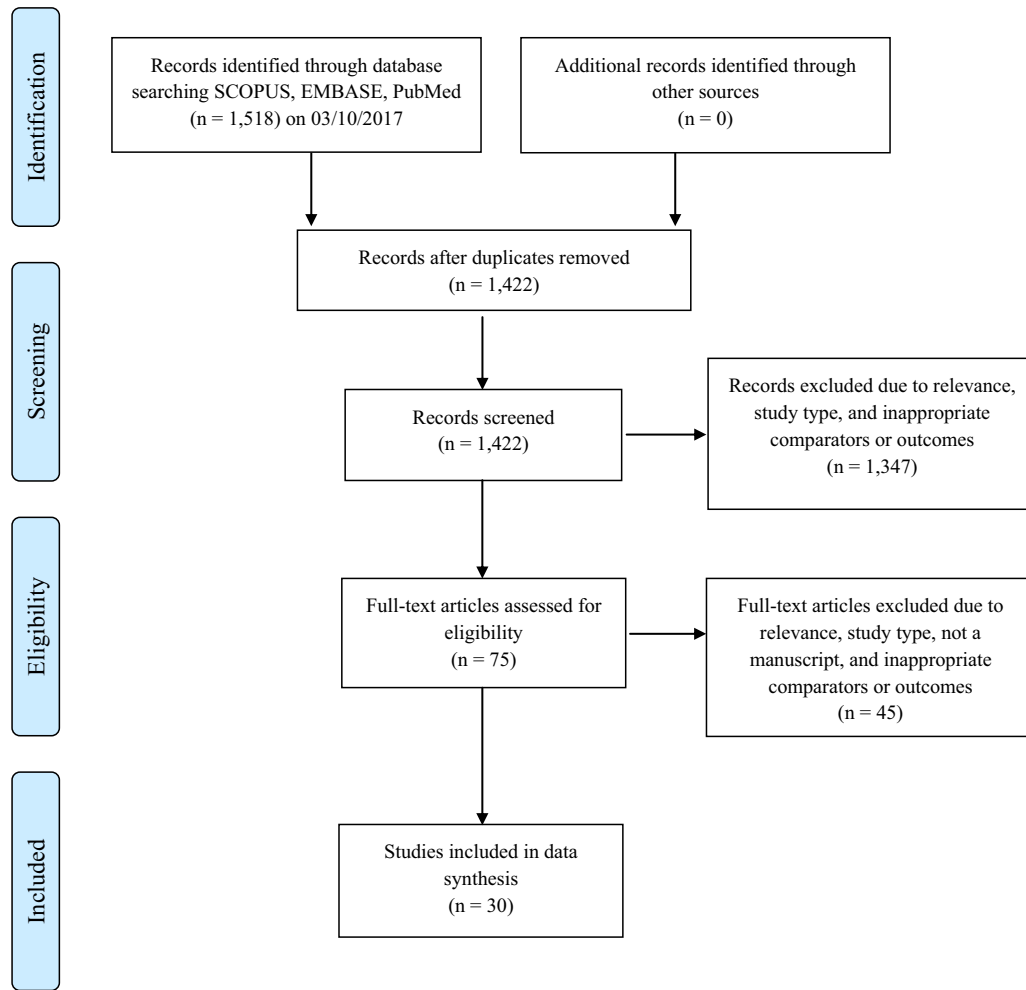


FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement flow diagram for search methods.

TABLE I. Study design and population type

	Inpatient (n = 24)	Outpatient (n = 3)	Mixed (n = 3)	Total
Observational				
Cross-sectional	4	—	—	4
Case-control	1	1	1	3
Cohort	15	—	—	15
Interventional	3	1	2	6
Other				
Mixed-methods	1	—	—	1
Literature review	1	—	—	1

and direct antibiotic costs during an inpatient admission. This optimization is aimed at improving quality, efficiency, and the cost-effective use of antibiotics in patients who may be incorrectly labeled with a PCN allergy.³⁶ From a methodological standpoint, focusing on short-term clinical and cost outcomes enables researchers with direct access to institutional data to make the case that the drug savings alone can potentially justify the additional cost to conduct PCN allergy skin testing. Macy and Contreras¹⁸ went a step further to estimate potential length

of stay savings in a retrospective case-control study of Kaiser Foundation Hospital patients in Southern California and determined that the cost savings from fewer hospital days would provide more than a 9-to-1 return on investment in PCN allergy testing. A retrospective cohort of a pilot PCN allergy testing service found significant cost savings during the first admission. More than 70% of the patients with a negative skin test who experienced a subsequent hospital admission over the following year received a β -lactam antibiotic.¹¹ Long-term observation of patients who have undergone PCN allergy testing may demonstrate the durability of this intervention in optimizing antibiotic therapy for patients far beyond the index hospitalization.

In addition, other outcomes of interest were identified in the acute care setting from a patient and health system perspective. Multiple studies considered the relationship between PCN allergy and adverse events such as reactions to medications prescribed or overall mortality during the time of admission (Table II). A prospective cohort study of 17,959 patients (1010 with a reported PCN allergy) in the Netherlands found that patients with reported PCN allergy were at a higher risk of receiving reserve antibiotics and experiencing rehospitalization, but experienced similar rates of mortality during hospitalization when compared with those without PCN allergy.¹⁴ Researchers

TABLE II. Most frequent outcomes identified in the context of penicillin allergy

Outcomes	No. of studies	Brief description
Optimizing inpatient antibiotic therapy	20 studies ^{4,7,8,10,12,14-17,19-22,24,25,27,28,31,32,35}	Switching antibiotic therapy to a more “appropriate” therapy based on various definitions
Cost	13 studies ^{4,11-13,17,19,21,25,26,30,33-35}	Cost savings from antibiotic therapy changes
Adverse events	6 studies ^{13,22,27,28,31,33}	Adverse events related to the skin test itself or adverse events from the antibiotic therapy decision post-test
Prevalence of penicillin allergy	6 studies ^{4,14,19,25,29,34}	Frequency of self-reported PCN allergy and confirmation of allergy with further consult or skin test
Readmission	6 studies ^{11,12,14,15,23,31}	Readmission rates from 30 d up to 6 mo
Length of stay	5 studies ^{9,18,23,26,29}	Average length of stay pertaining to the inpatient admission of interest
Death during inpatient admission	4 studies ^{14,15,23,29}	Mortality rate pertaining to the inpatient admission of interest
Prevalence of drug resistant organisms	2 studies ^{12,18}	Rates of multiple drug resistant organisms such as MRSA or VRE
ICU admission	2 studies ^{23,29}	Escalation of clinical condition pertaining to the inpatient admission of interest
Other outcomes mentioned	6 studies ^{9,10,13,20,30,31}	Time to discontinuation or total use of aztreonam; feasibility of skin test service; predictive value of skin testing; use of IV antibiotic; appropriate use of skin test

ICU, Intensive care unit; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; PCN, penicillin; VRE, vancomycin-resistant *Enterococcus*.

TABLE III. Most frequent costs identified in the context of penicillin allergy

Costs	No. of studies	Brief description
Antibiotic therapy cost during inpatient admission	24 studies ^{4,7-10,12,13,16,17,19-21,24,25,27-29,31,32}	Cost avoidance specific to antibiotic medications delivered during inpatient admission of interest; cost avoidance ranged from no savings to \$609/patient*
Readmission	6 studies ^{11,12,14,15,23,31}	Potential cost to the health system of future readmission
Additional cost of inpatient admission	6 studies ^{11,18,22,26,30,35}	Costs going beyond antibiotic medications to include costs of skin testing, length of stay savings, or laboratory costs; total cost savings estimated from \$1145 to \$4254 driven by shorter length of stay in the non-PCN allergy group*
Total number of antibiotics used during admission	5 studies ^{14,15,22,23,29}	Count of total number of different antibiotics used during admission of interest
IV antibiotics used during admission	3 studies ^{14,20,29}	Whether or not IV antibiotics were used during admission of interest potentially leading to higher costs related to line placement
Outpatient antibiotic costs	3 studies ^{29,33,34}	Costs specific to outpatient antibiotic medications; outpatient prescription savings reported from \$14 to \$193/patient*
ICU admission	2 studies ^{23,29}	Cost of escalation to more severe unit pertaining to the admission of interest

ICU, Intensive care unit; IV, intravenous; PCN, penicillin.

*Costs estimated in 2017 dollars after consumer price index adjustment.

evaluating a retrospective cohort of 198 Australian patients with cancer also found increased readmission rates in the PCN allergy group but no difference in mortality.¹⁵ Investigation with larger sample sizes and longer follow-up beyond the admission may be necessary to have a better understanding of any relationship between PCN allergy and an outcome like mortality.

The impact of PCN allergy on clinical or economic outcomes in the outpatient setting has been less frequently evaluated by researchers. Israeli researchers compared inpatient cases with controls and found that PCN allergic patients were likely to experience a 38% higher cost because of a more expensive medication at discharge.²⁹ A 30-year-old study of pediatric patients in a US health maintenance organization found that

children who reported PCN allergy had significantly more medical visits, more antibiotic prescriptions, and a higher average wholesale drug cost for those antibiotics when compared with a random sample of controls in the population.³⁴ Macy³³ also published a study evaluating outpatient care in the Southern California Kaiser population in patients who received confirmatory skin testing and found that the testing was associated with a decline in the total number and total cost of antibiotics used in the year after testing, but only a slight decrease in average cost per antibiotic. To our knowledge, there are no evaluations of long-term outpatient outcomes related to the effects of PCN allergy and the potential impact of delabeling patients who do not have a true allergy.

This article was limited by both the observation length and surrogate outcomes (ie, antibiotic optimization) within studies. These 2 factors limit our ability to make recommendations to use confirmatory testing based on meaningful outcomes. Another limiting factor is that several studies were conducted in other countries, thereby limiting generalizability to health care systems within the United States.

Although there are several studies that suggest potential benefit of confirmatory PCN allergy testing to help guide treatment decisions, the strength of the evidence and lack of long-term outcomes severely hampers our ability to conclusively determine a positive overall clinical and economic return on investment. In accordance with the Second Panel on Cost-Effectiveness in Health and Medicine recommendations, we recommend the use of cost-effectiveness analysis methods that include societal and health-sector perspectives capturing immediate and future outcomes and costs to evaluate the use of skin testing procedures in either inpatient or outpatient settings.³⁷ Direct medical costs should include antibiotic drug costs during inpatient admissions and long-term impact on outpatient prescribing in addition to the costs to administer the skin test and other direct medical costs related to the admitting diagnosis. In many cases, antibiotic costs make up a small proportion of the total costs of care making it extremely important to quantify the costs and benefits associated with higher quality care. In addition, we recommend engaging patients directly to understand which outcomes are meaningful to them. Many costs during hospital admission may not be directly experienced by an insured patient, but the cost of missed work or productivity losses during their hospital stay or recovery from infection may be of great importance from a patient perspective.

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.

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TABLE E1. Full description of data extracted for each study included

Authors	Year	Article title	Journal	Type of study	Patient type	Outcomes measured	Any costs identified
Jones and Bland ⁷	2017	Penicillin skin testing as an antimicrobial stewardship initiative	<i>American Journal of Health-System Pharmacy</i>	Retrospective cohort	Inpatient	Determine the efficacy of penicillin skin testing (PST) in increasing antibiotic stewardship; patients changed to β -lactam	\$315/patient saved through antibiotic acquisition savings
Blumenthal et al ⁸	2016	The impact of reporting a prior penicillin allergy on the treatment of methicillin-sensitive <i>Staphylococcus aureus</i> bacteremia	<i>PLoS ONE</i>	Retrospective cohort	Inpatient	Proportion on optimal therapy, completion of adequate therapy	No direct costs reported in dollars, only potential costs described in text due to suboptimal therapy
Estep et al ⁹	2016	Impact of an antimicrobial stewardship initiative to evaluate β -lactam allergy in patients ordered aztreonam	<i>American Journal of Health-System Pharmacy</i>	Interventional	Inpatient	Median time in hours to aztreonam discontinuation among nonanaphylactic patients, length of stay as a secondary outcome	Hospital annual savings of \$28,134 due to reduction of aztreonam use; \$414/patient savings based on 68 patients in 2016
Heil et al ¹⁰	2016	Implementation of an Infectious Disease Fellow-Managed Penicillin Allergy Skin Testing Service	<i>Open Forum InfectDis 2016</i>	Prospective cohort	Inpatient	Optimization of antibiotic selection due to PST. Optimization was considered to be changes to narrow the spectrum of activity, more effective therapy, or more cost effective therapy	Drug cost savings of approximately \$26,000/y due to PST service resulting in reduced aztreonam use; \$289/patient savings based on 90 patients in 2016
King et al ¹¹	2016	Penicillin skin testing in hospitalized patients with β -lactam allergies: effect on antibiotic selection and cost	<i>Ann Allergy Asthma Immunol 2016</i>	Retrospective cohort	Inpatient	Proportion of self-reported allergic patients with true allergy, proportion switched to β -lactam, cost savings, subsequent admissions	Drug cost savings of \$279/patient after PST service based on 37 patients in 2016
Knezevic et al ¹²	2016	The revolving door: antibiotic allergy labelling in a tertiary care centre	<i>Internal Medicine Journal</i>	Cross-sectional	Inpatient	Prevalence of antibiotic allergy label, documentation of symptoms, association of label with antibiotic choice, and hospital outcomes	Label associated with increased use of alternative antibiotics and were more likely to be readmitted within 4 wk and at 6 mo.
Staicu et al ¹³	2016	Implementation of a penicillin allergy screening tool to optimize aztreonam use	<i>American Journal of Health-System Pharmacy</i>	Interventional	Inpatient	Total aztreonam use, inappropriate aztreonam use, adverse events, antibiotic cost avoidance, and additional antibiotics given	Annual cost avoidance of \$60,000-100,000 due to reduced aztreonam use; based on 459 patients in 2016 an estimated savings of \$131-218/patient
van Dijk et al ¹⁴	2016	The High Impact of Penicillin Allergy Registration in Hospitalized Patients	<i>Journal of Allergy and Clinical Immunology: In Practice</i>	Prospective cohort	Inpatient	Risk of receiving a reserve antibiotic, death during hospitalization, rehospitalization, number and type of antibiotics prescribed during admission, and length of stay	Penicillin allergic patients had higher risk of reserve antibiotics, rehospitalization within 12 wk, and more likely to receive 2 or more types of antibiotics
Trubiano et al ¹⁵	2015	The impact of antimicrobial allergy labels on antimicrobial usage in cancer patients	<i>Antimicrobial Resistance and Infection Control</i>	Retrospective cohort	Inpatient	Readmission rate, 30-d and 60-d mortality, allergy manifestations (type A or B)	Increased antibiotic usage during admission, increased fluoroquinolone use, higher readmission rate

(continued)

TABLE E1. (Continued)

Authors	Year	Article title	Journal	Type of study	Patient type	Outcomes measured	Any costs identified
Cook et al ¹⁶	2014	Penicillin skin testing in cardiac surgery	<i>Journal of Thoracic and Cardiovascular Surgery</i>	Retrospective cohort	Inpatient	True incidence of PCN allergy, whether testing changed antibiotic use, whether skin testing reduced use of vancomycin	Reduced use of vancomycin
Li et al ¹⁷	2014	A real-time prospective evaluation of clinical pharmacoeconomic impact of diagnostic label of “penicillin allergy” in a UK teaching hospital	<i>Journal of Clinical Pathology</i>	Cross-sectional	Inpatient	Primary: total cost of antibiotics prescribed to each patient and total cost of first-line antibiotics that could have been employed; secondary: use of PCN despite self-reported PCN allergy within last year	Antibiotic costs of first-line antibiotics vs second-line through an economic model based on survey; estimated potential drug cost savings of £5,851-14,472 for 41 nonallergic patients in 2014
Macy and Contreras ¹⁸	2014	Health care use and serious infection prevalence associated with penicillin “allergy” in hospitalized patients: a cohort study	<i>Journal of Allergy and Clinical Immunology</i>	Retrospective cohort	Inpatient	Primary: total number of hospital days; secondary: antibiotics used and the prevalence rates of <i>Clostridium difficile</i> , MRSA, and VRE	Exposure to multiple abx, prevalence of <i>C. difficile</i> , MRSA and VRE, cost of care, increased hospital days, more fqs, clindamycin, and vancomycin
Picard et al ¹⁹	2013	Treatment of Patients with a History of Penicillin Allergy in a Large Tertiary-Care Academic Hospital	<i>Journal of Allergy and Clinical Immunology: In Practice</i>	Retrospective cohort	inpatient	Costs of antibiotic treatment, cost of alternative antibiotic regimen, antibiotics used, prevalence of penicillin allergy, referral to allergist on outpatient basis	Costs of treatment for patients with PCN allergy vs nonallergy, referral to allergist; estimated savings of \$15,672 for 172 patients in 2013 or \$91/patient
Rimawi et al ²⁰	2013	The impact of penicillin skin testing on clinical practice and antimicrobial stewardship	<i>Journal of Hospital Medicine</i>	Prospective cohort	Inpatient	Number of positive/negative PCN reactions, number successfully transitioned to β -lactam therapy, cost savings	Avoidance of PICC placement, laboratory costs, pharmaceutical drug calibration costs, and overall cost of therapy savings annually of \$82,000 for 146 patients
Satta et al ²¹	2013	β -Lactam allergy: clinical implications and costs	<i>Clinical and Molecular Allergy</i>	Cross-sectional	Inpatient	Compliance with hospital guidelines, total acquisition costs	Acquisition cost of PCN allergic group vs nonallergy group, estimated savings of £89.29/patient in 2013
Unger et al ²²	2013	Penicillin skin testing: potential implications for antimicrobial stewardship	<i>Pharmacotherapy</i>	Literature review	Inpatient	Type of antibiotic received, rate of allergic reactions, time to administer PCN skin test, costs for intradermal skin test/supplies	Antibiotics used, time/cost of intradermal skin test
Charneski et al ²³	2011	Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients	<i>Pharmacotherapy</i>	Retrospective cohort	Inpatient	ICU admission, number of antibiotics, readmission within 4 wk of discharge, death, rate of surgery, length of stay	Increased length of stay, ICU admission, number of antibiotics, readmission, and surgery
Frigas et al ²⁴	2008	Preoperative evaluation of patients with history of allergy to penicillin: comparison of 2 models of practice	<i>Mayo Clinic Proceedings</i>	Prospective cohort	Inpatient	Compare selection of antibiotic for perioperative prophylaxis in 2 different models of practice	Increase use of a cephalosporin and decrease vancomycin when allergy consultation and skin testing were used

Borch et al ²⁵	2006	The prevalence of suspected and challenge-verified penicillin allergy in a university hospital population	<i>Basic and Clinical Pharmacology and Toxicology</i>	Cross-sectional case-control	Inpatient	Prevalence of alleged PCN allergy and rate of true PCN allergy. Also estimated consequences of alleged PCN allergy on acquisition costs of antibiotics	Acquisition costs of antibiotic treatment in alleged PCN allergic patients; estimated savings of €159/patient in antibiotic costs in 2006
Irawati et al ²⁶	2006	Influence of penicillin allergy on antibiotic prescribing patterns and costs	<i>Journal of Pharmacy Practice and Research</i>	Prospective case-control	Inpatient	Influence of documented PCN allergy on antibiotic prescribing for patients with CAP as well as the clinical and financial consequences arising from changes to prescribing patterns	Antibiotic therapy cost based on total administration cost (acquisition, delivery, lab monitoring costs); ranges for additional drug costs in PCN allergy from \$46 to \$517 and total with LOS costs from \$972 to \$3611
Park et al ²⁷	2006	Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy	<i>Annals of Allergy, Asthma and Immunology</i>	Interventional	Mixed	Decrease vancomycin use in surgical patients with a self-reported PCN allergy	Reduction in vancomycin use for surgery prophylaxis
Arroliga et al ²⁸	2003	A prospective observational study of the effect of penicillin skin testing on antibiotic use in the intensive care unit	<i>Infection Control and Hospital Epidemiology</i>	Prospective cohort	Inpatient	Incidence of true PCN allergy, % of patient changed to β -lactam when PenST was negative, safety of test, safety of administration of β -lactam antibiotics when PenST negative	Antibiotic therapy change, cost of skin test
Sade et al ²⁹	2003	The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital	<i>Clinical and Experimental Allergy</i>	Retrospective case-control	Mixed	Hospitalization mortality, transportation to other departments, duration of hospitalization, number of abx, parental abx, doses per day, duration of treatment, price of each abx dose, price of each abx treatment	More broad spectrum antibiotics, higher mean antibiotic cost with an average of \$212/patient during hospitalization, higher antibiotic cost for continuing outpatient of approximately \$157/patient
Forrest et al ³⁰	2001	Introduction of a practice guideline for penicillin skin testing improves the appropriateness of antibiotic therapy	<i>Clinical Infectious Diseases</i>	Interventional	Inpatient	Interval between the time when patient became eligible for skin test and when the skin test was performed	No significant difference in net cost savings despite drug costs being lower
Perencevich et al ³¹	2001	Benefits of negative penicillin skin test results persist during subsequent hospital admissions	<i>Clinical Infectious Diseases</i>	Retrospective cohort	Inpatient	Subsequent antibiotic use after negative PenST, ADR during subsequent hospital admissions	Antibiotic use during subsequent readmission
Li et al ³²	2000	Reduction of vancomycin use in orthopedic patients with a history of antibiotic allergy	<i>Mayo Clinic Proceedings</i>	Interventional	Mixed	Antibiotic administration for prophylaxis, presence or absence of hypersensitivity	Antibiotic choice for prophylaxis

(continued)

TABLE E1. (Continued)

Authors	Year	Article title	Journal	Type of study	Patient type	Outcomes measured	Any costs identified
Maclaughlin et al ⁴	2000	Costs of β -lactam allergies: selection and costs of antibiotics for patients with a reported β -lactam allergy	<i>Archives of Family Medicine</i>	Retrospective review	Outpatient	Mean antibiotic cost	Mean antibiotic cost (\$26.81 for with β -lactam allergy, \$16.28 for without)
Macy ³³	1998	Elective penicillin skin testing and amoxicillin challenge: effect on outpatient antibiotic use, cost, and clinical outcomes	<i>Journal of Allergy and Clinical Immunology</i>	Interventional	Outpatient	Antibiotic use, outpatient visit rate, adverse reactions to antibiotics during the year before and after skin testing, average annual cost for antibiotics	Average annual cost for antibiotics fell if skin testing results were negative and total average costs fell for entire group for a savings of approximately \$24/patient in 1998
Kraemer et al ³⁴	1987	Increased use of medical services and antibiotics by children who claim a prior penicillin sensitivity	<i>Western Journal of Medicine</i>	Retrospective case-control	Outpatient	Number of medical visits, number of antibiotic prescriptions	Increase number of medical visits, number of antibiotic prescriptions, average cost of antibiotic prescriptions (\$4.60/mo vs \$1.75/mo); approximate annual savings of \$34/patient in 1987
Logan and Bayliff ³⁵	1997	Analysis of therapeutic options in patients reporting a penicillin or cephalosporin allergy	<i>Canadian Journal of Hospital Pharmacy</i>	Mixed method	Inpatient	Actual cost of antibiotic therapy compared with cost predicted by decision analysis model (DAM), alternative antibiotics used	Actual cost of therapy, DAM predicted cost of therapy

Abx, antibiotics; ADR, adverse drug reaction; CAP, community acquired pneumonia; fqs, fluoroquinolones; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; PCN, penicillin; PenST, penicillin skin test; PICC, peripherally inserted central catheter; VRE, vancomycin-resistant *Enterococcus*.