

The effect of preoperative penicillin allergy testing on perioperative non- β -lactam antibiotic use: A systematic review and meta-analysis

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ABSTRACT

Background: The majority of patients for elective surgery and with a history of penicillin allergy are placed on alternative prophylactic antibiotic therapies, which have been associated with the emergence of multidrug-resistant pathogens and increased morbidity and mortality rates. However, self-reporting of penicillin allergy alone may overestimate the prevalence of penicillin allergy in the population.

Objective: To assess the effects of preoperative antibiotic allergy testing protocols in reducing the use of non- β -lactam antibiotics.

Methods: We searched medical literature data bases through July of 2018. Two reviewers independently extracted data from published studies and assessed the risk of bias in cohort studies by using the Newcastle-Ottawa Scale. We collected information related to study design, methodology, demographics, interventions, and outcomes. We pooled odds ratios for the rate of prescribing non- β -lactam antibiotics by using a fixed-effects model.

Results: Of 905 citations screened for eligibility, nine studies met inclusion criteria for qualitative analysis. Studies reported that the rates of non- β -lactam use after preoperative skin testing ranged from 6 to 30%. In addition, four of the nine studies had sufficient control data to be included in a meta-analysis. These four studies found that preoperative testing protocols significantly decreased the rates of prescribing non- β -lactam antibiotics compared with usual care (odds ratio 3.64 [95% confidence interval, 2.67–4.98]; $p < 0.0001$). Seven studies reported on adverse drug reactions after preoperative skin testing and found that the rate of such reactions was rare.

Conclusion: Preoperative antibiotic allergy testing protocols seemed to be a safe and effective tool in reducing the use of non- β -lactam antibiotics during surgery.

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Surgical-site infections are a significant complication for patients and are associated with significant morbidity and mortality.¹ For the past 3 decades, it has been the standard of care to provide patients who undergo elective surgery with prophylactic antibiotic therapy to prevent perioperative infections²; the World Health Organization's surgical checklist³ also includes prophylactic antibiotics. For clean and many clean-contaminated procedures, the predominant organisms that cause surgical-site infections are skin flora, including *Staphylococcus aureus*. The current guidelines rec-

ommend using the narrowest spectrum antimicrobial agent for surgical prophylaxis.

First- or second-generation cephalosporins are recommended for many procedures, including cardiac procedures, elective craniotomies, orthopedic procedures, vascular procedures, and hernia repair.⁴ However, 11 to 15% of patients admitted on a hospital self-report of a history of an allergic reaction to penicillin,^{5,6} so alternative antibiotics must be considered in these populations.⁷ Many of these patients receive non- β -lactam antibiotics, such as vancomycin, clindamycin, or fluoroquinolones, because of concerns that these patients could develop a severe reaction to penicillin. However, the use of broader-spectrum antibiotics is associated with multidrug-resistant pathogens, which result in increased morbidity and mortality.^{8,9} These antibiotics also have a higher risk of adverse reactions. For example, clindamycin carries a U.S. Food and Drug Administration black box warning regarding an increased rate of *Clostridioides difficile* infection, and levofloxacin carries a U.S. Food and Drug Administration black box warning regarding the risk of tendon, muscle, and nerve injury.¹⁰

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The use of non- β -lactam antibiotics can also lead to increased costs for hospitals and patients.^{11,12} For example, one cost-effectiveness analysis of surgical prophylaxis strategies for patients with a history of penicillin allergy determined that, when vancomycin is given indiscriminately to all the patients with a penicillin allergy, the incremental cost per anaphylactic event avoided was \$159,204.¹² Therefore, transitioning more patients from vancomycin to cefazolin when clinically indicated can lead to cost savings. Several studies demonstrated that, when relying on self-reporting to identify patients with an antibiotic allergy, self-reporting is often inaccurate and not reliable in predicting which patients will develop an allergic reaction to the drug.^{13,14} Furthermore, patients with an allergy to penicillin tend to lose their sensitivity over time.¹⁵

Although the current standard test for confirming penicillin allergy is an oral challenge dose, what constitutes a challenge dose reaction is not clearly defined.¹⁶ Penicillin skin testing is a safe and reliable method for determining whether a person is at risk of an immediate systemic allergic reaction. Skin testing results for penicillin has a reaction rate between 0.0% and 0.1%, with no serious reactions if performed properly.^{17–19} Giving β -lactams to patients with a reported penicillin allergy who have a negative skin testing result is generally found to be safe. The negative predictive value of penicillin skin testing is reported to be >99%,^{20–22} although a cohort study did find that 3% of the patients with negative penicillin skin testing results later developed a new allergy when given a therapeutic course.²³

Current antibiotic stewardship guidelines published by the Infectious Disease Society of America⁸ recommend antibiotic allergy testing as a strategy to reduce the inappropriate use of broad-spectrum antibiotics. To date, however, preoperative testing, although simple and effective, is not widely used.²⁴ The implementation of this strategy in a hospital setting may be an important tool in combating the emergence of multidrug-resistant pathogens. The purpose of this systematic review and meta-analysis was to evaluate the evidence for the safety and efficacy of preoperative penicillin allergy testing in reducing the use of alternative antibiotics when compared with usual care of acceptance of reported or previously recorded allergies in patients who were underwent planned surgery.

METHODS

Review Protocol

Before conducting the review, we wrote a protocol that outlined our approach to the identification and selection of studies that addressed the question of the efficacy of penicillin allergy testing in the preoperative environment. We used standard methodology from the

Cochrane Handbook²⁵ for the analysis and followed recommended guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement²⁶ for the reporting of methods and findings.

Study Eligibility Criteria

We defined prespecified criteria for this review to determine study eligibility. We included (1) randomized controlled trials, prospective and retrospective cohort studies, before-after studies, and quality improvement studies that compared the impact of (2) protocols or pathways that included penicillin or cephalosporin allergy skin testing versus (3) usual care on (4) the use of alternative antibiotics and repeated adverse drug reactions in (5) persons scheduled for surgery who reported a history of penicillin or cephalosporin allergy.

Outcome Measures

The primary outcome measure was the use of alternative antibiotics, such as clindamycin, fluoroquinolones, and vancomycin. The use of alternative broad-spectrum antibiotics has been associated with the emergence of multidrug-resistant pathogens, which can increase morbidity and mortality.^{8,9} Therefore, a decrease in the rates of use of these alternative antibiotics would be a measure of success. The secondary outcome measure was the rates of adverse drug reactions to antibiotics. There is a possibility that an allergy test could result in a false-negative result, and the patient, therefore, could experience an adverse reaction as a result of exposure to the antibiotic. This secondary outcome was used as a balancing measure to determine the potential harm of testing.

Search Methods

We conducted a systematic review of the literature of studies published from 1950 to 2016 by using Medline (U.S. National Library of Medicine, Bethesda, Maryland), Cumulative Index to Nursing and Allied Health Literature (EBSCO Publishing, Ipswich, Massachusetts), Embase (Elsevier, Amsterdam, Netherlands), and the Cochrane Library (John Wiley & Sons, Hoboken, New Jersey). To locate potentially relevant studies in Medline, we used exploded medical subject headings terms and keywords to generate sets for the following themes: antibiotics (penicillin and cephalosporin), drug hypersensitivity, preoperative skin testing, and surgery. We then used the Boolean term “and” to find the intersection of these themes. This basic approach was modified as necessary to search each electronic data base. Our search did not use any limits. We manually reviewed all references of the relevant articles. We checked the U.S. National Library of Medicine

clinical trials Web site for ongoing studies. Finally, we reviewed abstracts of scientific meetings for Infectious Diseases Society of America (2011–2015) and the American Academy of Allergy, Immunology & Asthma (2013–2015), and discussed potentially relevant studies with content experts at our local institution.

Study Selection

Three reviewers (CR, GB, and MG) independently screened the titles and abstracts of studies identified by our search to determine if they met the inclusion criteria. We obtained the full text of those studies that we could not fully determine inclusion and exclusion criteria solely based on the title and abstract. A full-text review was performed independently and in duplicate by two reviewers (CR and GB). We resolved any disagreements by group discussion and consensus.

Data Collection

Two reviewers (CR and GB) independently and separately extracted data, unblinded, from published studies that met our inclusion criteria. Discrepancies were adjudicated independently by a third reviewer (MG). We collected information related to study design and methodology, subject demographics, interventions, and outcomes. In the case of missing data, we attempted to contact the authors for the data.^{27,28} We excluded studies from relevant quantitative analysis if efforts to obtain missing data were unsuccessful.^{27,29–32} We were able to obtain missing data from the authors of one study; these unpublished data were included in our quantitative analysis.²⁸

Assessment of Methodological Quality

The risk of bias for studies was assessed by two reviewers (DB and PH) independently by using an eight-item modified version of the Newcastle-Ottawa Scale,³³ which we created for this study. The Newcastle-Ottawa Scale is a 10-item tool designed to assess observational studies on a variety of domains, including the selection of cohorts, cohort comparability, and assessment of outcomes. Discrepancies were adjudicated independently by a third reviewer (MG).

Analysis

Four studies provided sufficient data to be included in our meta-analysis.^{24,28,34,35} Specifically, from these four studies, we abstracted the odds ratios and 95% confidence intervals associated with the use of a non- β -lactam alternative for preoperative surgical prophylaxis for the allergy skin testing group compared with the control group. In RevMan 5.3 (John Wiley & Sons, Hoboken, New Jersey), we pooled our findings by using both a fixed- and a random-effects model for analysis. Because we found that there was no statisti-

cally significant heterogeneity across the pooled studies, we believed that it was appropriate to present the results by using a fixed-effects model.²⁵ We used a cutoff of an I^2 value of $<50\%$ to determine the absence of significant heterogeneity.

In addition to the aforementioned meta-analysis, we also summarized the rates of non- β -lactam use across the nine studies included in our review by using a qualitative approach.^{24,27–32,34,35} We described the range of rates in the studies and provided an overall summary statement of the key conclusions of the studies. Similarly, because none of the nine studies in our review provided sufficient data for meta-analysis of adverse drug events, we also summarized the rates of adverse drug events by using a qualitative approach, by describing the range of rates in the studies, and by providing an overall summary statement of the key conclusions of the studies.

We were unable to formally assess for publication bias because our review was limited to nine studies.^{24,27–32,34,35} The Cochrane Library recommends that a funnel plot analysis should not be conducted if <10 studies report on the outcome because the analysis will yield biased results.²⁵ However, we performed an informal analysis by ranking studies by sample size and by evaluating whether there seemed to be a lack of smaller studies with negative or nonsignificant findings that would indicate publication bias.

RESULTS

Description of Studies

As shown in Fig. 1, our initial search of the online data bases, review of conference abstracts, and discussion with content experts identified 905 potentially eligible citations. After initial screening by title and abstract, we excluded 869 citations. After more-detailed full-text evaluation, we identified nine studies that fulfilled the inclusion criteria.^{24,27–32,34,35} Of the nine included studies, all were either cohort, before-after, or quality improvement studies. Four studies included sufficient control data to be included in a meta-analysis. All the studies were published in peer-reviewed journals from 1990 to 2017. Eight of the nine were performed in the United States,^{24,27–30,32,34,35} the remaining study was conducted in France.³¹ Study characteristics are shown in Table 1.

Methodological Quality of Included Studies

Overall, we found that the methodological quality of the included studies was variable (Table 2). Only five of our studies contained a nonexposed control; none of the studies controlled based on age, race, or gender.^{24,27,28,34,35} The studies that lacked a distinct control group instead used historical controls from previous studies. Based on our risk of bias assess-

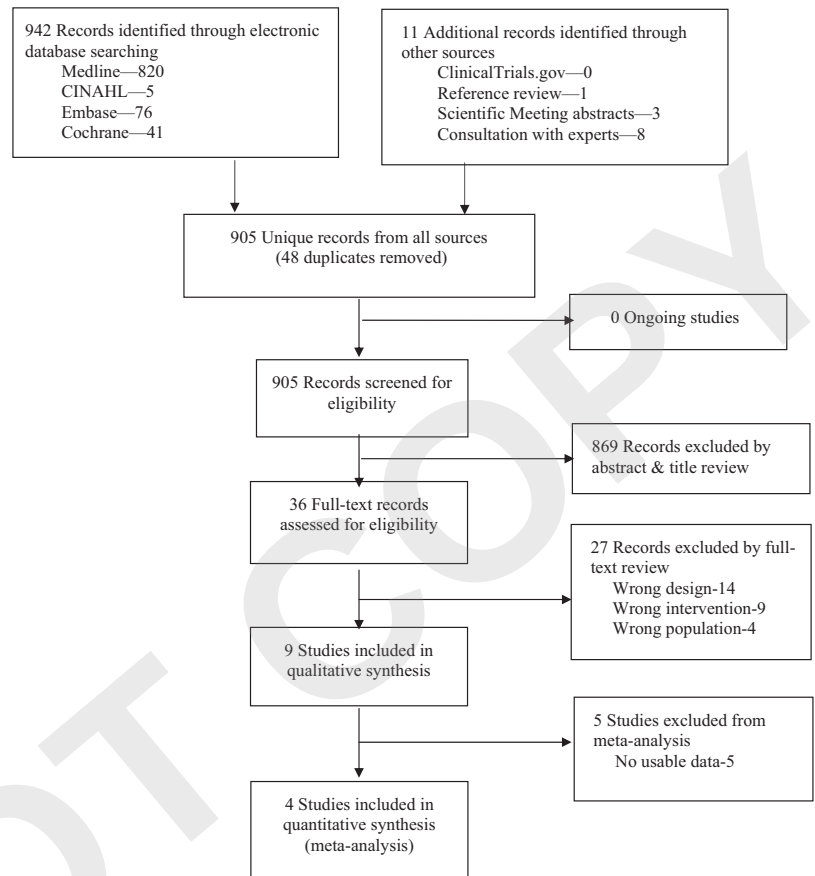


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of citations reviewed and included in the systematic review.

ment, five studies had a low risk of bias scores.^{24,28,32,34,35} All the studies had an adequate period of follow-up to observe the outcome, and attrition was uniformly low.

Risk of Publication Bias

Our informal analysis of publication bias did not indicate a lack of smaller studies with negative or nonsignificant findings. Therefore, we believe that there was minimal risk of publication bias.

Primary Outcome: Rates of Non- β -Lactam Antibiotic Use

Of the nine included studies, only five studies compared the rates of non- β -lactam antibiotic use in patients who received allergy skin testing with those patients who received usual care.^{24,27,28,34,35} All of these studies showed a decrease in the rate of non- β -lactam antibiotic use with allergy skin testing compared with usual care. The results were also statistically significant in four of the studies (Table 3). Furthermore, in the four studies that had enough usable data for a meta-analysis^{24,28,34,35} (Fig. 2), allergy skin testing led to a significant reduction in the rate of non- β -lactam antibiotic use compared with usual care (odds ratio 3.64 [95% confidence interval, 2.76–4.98]; $p < 0.0001$). Because

the meta-analysis was limited to four studies, we were unable to perform any meaningful sensitivity analyses.

The rates of non- β -lactam use in those studies without a comparison group^{29–32} were also comparable with the rates seen in our quantitative analysis (Table 4). Four studies looked specifically at the rates of vancomycin usage,^{29,30,34,35} with rates that ranged from 9 to 18%, whereas five studies looked at all non- β -lactam antibiotics,^{24,27,28,32,35} which included clindamycin, levofloxacin, and vancomycin, with rates that ranged from 6 to 30%. Presumably, without allergy testing, all of those patients would have received a non- β -lactam antibiotic; however, there were insufficient data available to draw a definitive conclusion. In an informal assessment of heterogeneity of these studies, it seemed that, although the technique of allergy skin testing was similar among the studies, there was variation in how patients were chosen and referred for testing, which indicated that heterogeneity may be a concern.

Secondary Outcome: Adverse Drug Events

Seven of the nine identified studies reported rates of adverse drug events seen.^{24,28,30–32,34,35} Overall, the rates were low, which ranged from 0% in three studies^{24,28,32} up to 4% in one study,³¹ as presented in Table 5. In general, the adverse drug events were minor and

Table 1 Characteristics of included studies

Study, Y	Study Design	Location	Subjects, no. (I:C)	Average Age, y (I:C)	Gender, no. (% male)	Surgery Type	Allergy	Broad-Spectrum Antibiotic Evaluated
Cook <i>et al.</i> , ²⁹ 2014	Quality improvement	Minnesota	276	61.7	132 (48)	Cardiac	Penicillin, cephalosporin	Vancomycin
Frigas <i>et al.</i> , ²⁴ 2008	Retrospective cohort	Minnesota	411 (365:46)	60:66	164 (45): 20 (43)*	Orthopedic, urologic, neurologic, cardiac, other	Penicillin	Vancomycin and other non- β - lactams
Harris <i>et al.</i> , ³² 1999	Quality improvement	Maryland	16	N/R	N/R	N/R	Penicillin	Non- β -lactams
Hennrikus <i>et al.</i> , ³⁰ 1990	Quality improvement	California	50	32.4	34 (68)	Orthopedic	Penicillin	Vancomycin
Li <i>et al.</i> , ³⁴ 2000	Before-after, with historical controls	Minnesota	60	62	29 (48)	Orthopedics	Penicillin, cephalosporin	Vancomycin
McDanel <i>et al.</i> , ²⁸ 2017	Retrospective cohort	Iowa	161	64	57 (35)	Orthopedics	Cephalosporin	Vancomycin and other non- β - lactams
Park <i>et al.</i> , ³⁵ 2006	Before-after, with concurrent and historical controls	Minnesota	1111 (1030:81)	60	457 (41)	Orthopedic, urologic, neurologic	Penicillin, cephalosporin	Non- β lactams, vancomycin
Pongdee <i>et al.</i> , ²⁷ 2014	Before-after, with historical controls	Florida	384	N/R	N/R	Surgery, nonspecified	Penicillin	Non- β -lactams
Promelle <i>et al.</i> , ³¹ 2015	Quality improvement	France	48	72	11 (23)	Cataract	Penicillin	No antibiotics

I = Intervention Group; C = Control Group; N/R = Not Reported.

*this value is broken down by intervention and control group respectively (I (%):C(%)).

Table 2 Risk of bias assessments for included cohort studies by using the Newcastle-Ottawa Scale

Study, Y	Selection*				Outcome§			Total Score
	1	2	3	4	5	6	7	
Cook <i>et al.</i> , ²⁹ 2014			×	×	×	×		4
Frigas <i>et al.</i> , ²⁴ 2008	×	×	×	×	×	×	×	7
Harris <i>et al.</i> , ³² 1999	×		×	×	×	×	×	6
Hennrikus <i>et al.</i> , ³⁰ 1990			×	×	×	×		4
Li <i>et al.</i> , ³⁴ 2000	×	×	×	×	×	×	×	7
McDanel <i>et al.</i> , ²⁸ 2017	×	×	×	×	×	×		6
Park <i>et al.</i> , ³⁵ 2006	×	×	×	×	×	×	×	7
Pongdee <i>et al.</i> , ²⁷ 2014		×	×	×	×	×		5
Promelle <i>et al.</i> , ³¹ 2015	×		×	×	×	×		5

*(1) Representativeness of the exposed cohort: “×” if truly or somewhat representative of the average patient with reported antibiotic allergy who underwent surgery; (2) selection of the nonexposed cohort: “×” if drawn from the same community as the exposed cohort; (3) ascertainment of exposure: “×” if a secure record; and (4) absence of outcome at baseline: “×” if demonstration that outcome of interest was not present at the start of the study.

§(5) Assessment of outcomes: “×” if independent blind assessment or record linkage; (6) length of follow-up: “×” if follow-up is long enough for outcomes to occur; and (7) adequacy of follow-up of cohorts: “×” if all the subjects completed follow-up or the subjects lost to follow-up were unlikely to introduce bias (a small number lost to follow-up).

The Newcastle-Ottawa scale also includes an assessment of Comparability. However, none of the included studies controlled for age, gender, race or other additional risk factors.

no life-threatening reactions, *e.g.*, anaphylaxis, were observed.

DISCUSSION

This review indicated that preoperative allergy consultation and skin testing for patients who reported a history of β -lactam allergy were associated with a reduction in non- β -lactam antibiotic usage during surgery. In addition, this review also indicated that this practice was safe, with an overall low rate of adverse drug reactions. The findings of this review had important implications. Reduction in non- β -lactam antibiotic usage may help to prevent overuse of broad-spectrum antibiotics and the potential development of antibiotic resistance.⁹ Use of cefazolin in place of other antibiotics, such as vancomycin or levofloxacin, may also result in cost savings. The use of allergy testing in other settings has shown cost savings by switching patients to β -lactam therapy.^{11,36} However, these potential benefits must be weighed against the overall costs of implementing allergy testing in the preoperative setting, which has not been fully elucidated. Our review was unable to comment on the costs of running a preoperative clinic with allergy consultation and skin testing, nor could we speak to whether or not such a strategy was cost-effective.

There also are alternatives to penicillin skin testing that should be considered: oral challenge dose or in-depth allergy consultation.^{37,38} Detailed allergy histories, often performed by an allergist or an infectious disease consultant, have been used to try to determine

if a patient's self-reported β -lactam allergy is valid. However, patient histories may not always provide enough useful information to determine whether the use of a β -lactam is appropriate. The use of penicillin skin testing, particularly for these patients, may help identify a larger group of patients for whom perioperative β -lactams are appropriate.¹⁴

Overall, the finding across the included studies were fairly consistent. All the studies that directly compared antibiotic usage rates demonstrated that the implementation of preoperative allergy consultation and skin testing lowered the rates of non- β -lactam usage.^{24,27,28,34,35} In addition, in the studies that looked at adverse drug reactions, the rate of such reactions were rare or nonexistent.^{24,28,30,31,34,35} Given that we were only able to perform a quantitative review on four studies,^{24,28,34,35} completeness of the evidence, however, was a concern. Although results from additional studies that include comparison groups would have strengthened our findings, we believe that these results were unlikely to change the finding that preoperative antibiotic allergy testing would lower rates of non- β -lactam antibiotics.

Reassuringly, the studies included in the review covered many different surgeries, including orthopedic, neurologic, and cardiac surgeries, which make up many of the non-urgent and elective surgeries performed in the United States. This indicated that our findings could apply to many types of surgeries. However, most of the studies occurred at large academic medical centers, so the findings may be less generaliz-

Table 3 Reduction in non- β -lactam antibiotic use*

Study, Y	Total Sample Size	Outcome Measure Reported	Intervention, no./total no. (allergy testing)	Comparison (either Difference Between Groups historical or concurrent control), no./total no.	Study Arm Favored	Statistical Significance (p-value)
Frigas <i>et al.</i> , ²⁴ 2008	411	Reduction in non- β -lactam use	111/365 (30% rate of non- β -lactam use)	28/46 (61% rate of non- β -lactam use)	50% reduction in non- β -lactam use	Allergy testing <0.001
Li <i>et al.</i> , ³⁴ 2000	187	Reduction in vancomycin use	6/60 (10% rate of vancomycin use)	38/127 (30% rate of vancomycin use)	22% reduction in vancomycin use	Allergy testing <0.05
McDanel <i>et al.</i> , ²⁸ 2017	247	Reduction in β -lactam use	16/135 (12% rate of non- β -lactam use)	31/112 (28% rate of non- β -lactam use)	16% reduction in non- β -lactam use	Allergy testing <0.05
Park <i>et al.</i> , ³⁵ 2006	1111	Reduction in vancomycin and non- β -lactam use	125/1030 (12% rate of vancomycin use); 234/1030 (23% rate of non- β -lactam use)	24/81 (30% rate of vancomycin use); 42/81 (52% rate of non- β -lactam use)	30% reduction in vancomycin use compared with historical controls (not the concurrent controls)	Allergy testing <0.01
Pongdee <i>et al.</i> , ²⁷ 2014	384	Reduction in non- β -lactam use	24/384 (6% rate of non- β -lactam use)	Not included	54% reduction in vancomycin; 40% reduction in levofloxacin; 22% reduction in clindamycin	Allergy testing Not applicable

*Qualitative summary: Allergy testing was favored over no allergy testing in all five studies, with four studies reporting statistical significance.

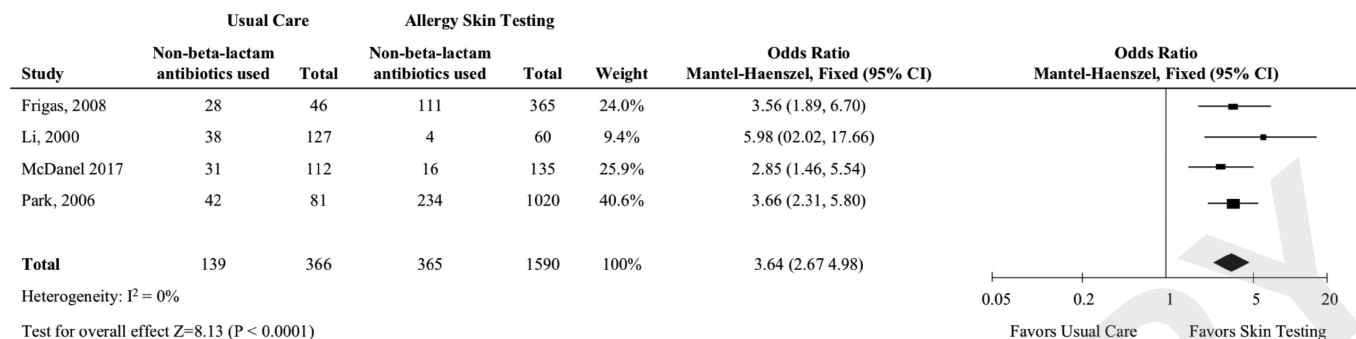


Figure 2. Graphic representation of meta-analysis of preoperative penicillin allergy testing to decrease the non- β -lactam antibiotic use compared with usual care.

Table 4 Rates of non- β -lactam antibiotic use*

Study, Y	Total Sample Size	Outcome Measure Reported	Rate Reported, no./total no. (%)
Cook <i>et al.</i> , ²⁹ 2014	276	Use of Vancomycin	24/276 (9)
Frigas <i>et al.</i> , ²⁴ 2008	411	Use of β -lactam alternative	111/365 (30)
Harris <i>et al.</i> , ³² 1999	16	Use of β -lactam alternative	3/16 (19)
Hennrikus <i>et al.</i> , ³⁰ 1990	50	Use of Vancomycin	9/50 (18)
Li <i>et al.</i> , ³⁴ 2000	187	Use of Vancomycin	6/60 (10)
McDanel <i>et al.</i> , ²⁸ 2017	247	Use of β -lactam alternative	16/135 (12)
Park <i>et al.</i> , ³⁵ 2006	1111	Use of Vancomycin	125/1030 (12)
	1111	Use of β -lactam alternative	234/1030 (23)
Pongdee <i>et al.</i> , ²⁷ 2014	384	Use of β -lactam alternative	24/384 (6)
Promelle <i>et al.</i> , ³¹ 2015	48	Use of cefuroxime alternative	8/48 (17)

*Qualitative summary: Rates of non- β -lactam antibiotic use ranged from 6 to 30%, whereas the rates of vancomycin use ranged from 9 to 18%.

Table 5 Incidence of adverse drug reactions*

Study, Y	Total Sample Size	Outcome Measure Reported	Rates Reported, no./total no. (%)
Frigas <i>et al.</i> , ²⁴ 2008	411	Adverse drug reaction	0/365 (0)
Harris <i>et al.</i> , ³² 1999	16	Adverse drug reaction	0/16 (0)
Hennrikus <i>et al.</i> , ³⁰ 1990	50	Adverse drug reaction	1/50 (2)
Li <i>et al.</i> , ³⁴ 2000	60	Immediate reaction or hives	1/60 (2)
McDanel <i>et al.</i> , ²⁸ 2017	247	Adverse drug reaction	0/135 (0)
Park <i>et al.</i> , ³⁵ 2006	1111	Adverse drug reaction	5/1030 (0.5)
Promelle <i>et al.</i> , ³¹ 2015	48	Localized reaction	2/48 (4)

*Qualitative summary: The rates of adverse drug reactions were low, ranging from 0 to 4%.

able to smaller institutions and community settings. Also, four of the nine included studies occurred at the same institution.^{24,29,34,35} Only one study occurred outside of the United States,³¹ which raised a potential concern for the international applicability of preoperative allergy testing.

Another important concern regarding the quality of the evidence featured in this review was that no randomized controlled trials were available to be included. As such,

our analysis was limited to cohort, before-after, and quality improvement studies, which have more potential for bias and confounding.^{24,27–32,34,35} Because only four of the nine studies provided enough information to be included in a meta-analysis, it was possible that we may have either over- or underestimated the effect of preoperative allergy testing in reducing the rates of non- β -lactam antibiotic use. It was generally assumed that, had the patients not undergone allergy testing, they would

have been given non- β -lactam antibiotics more often. However, without data from comparison groups, the magnitude of the change could not be assessed. We were also unable to generate a summary estimate to assess the rates of adverse drug reactions.

CONCLUSION

Although our review had several limitations, we believe that our findings supported the implementation of preoperative allergy testing for patients for elective surgical who reported a history of β -lactam allergy. We demonstrated a significant decrease in non- β -lactam use in our quantitative analysis, and the rates of non- β -lactam use also favored preoperative allergy testing in our qualitative analysis. In addition, the intervention was generally safe and associated with a low rate of adverse drug reactions. Given the significant concerns about increasing antibiotic resistance⁹ and the risk of *Clostridioides difficile* infection from broad-spectrum antibiotics, implementing this protocol in practice could help with antibiotics stewardship efforts. It may be more feasible to implement these protocols at large surgical centers and academic medical centers because these institutions will have access to allergists and resources needed to incorporate allergy testing in preoperative clinics.

Although this review showed that preoperative allergy testing was safe and effective, it is important to highlight that the evidence was based solely on cohort and before-after studies. Ideally, additional research on this topic would involve randomized controlled trials. In addition to the rate of non- β -lactam antibiotic use, future studies should also evaluate adverse drug reactions as well as other adverse effects from antibiotics, e.g., rates of *C. difficile* infection. This will help to further address the benefits and harms that could occur through widespread adoption of allergy testing. Although the use of penicillin skin testing indicated substantial cost savings,^{11,12,36} additional cost-benefit analyses are necessary to fully understand how implementing preoperative allergy skin testing compares with other methods of allergy testing, such as administering a challenge dose or obtaining a detailed allergy history.

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