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Tackling Inpatient Penicillin Allergies: Tools for Antimicrobial Stewardship

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Abbreviations: SOC, standard of care; ST, penicillin skin testing; APP, computerized guideline application with decision support; BWH, Brigham and Women's Hospital; OR, odds ratio; CI, confidence interval; IQR, interquartile range.

Clinical Implications

Improved antibiotic choice among medical inpatients reporting prior penicillin allergy was achieved using a computerized guideline, which resulted in an overall significant increased odds of penicillin or cephalosporin use compared to standard of care (aOR 1.8 [95% CI 1.1, 2.9]).

Capsule Summary

This study uses quasi-experimental analysis to assess the impact of two distinct approaches, penicillin skin testing and a computerized guideline with decision support, implemented to improve antibiotic choice in medical inpatients with reported penicillin allergy.

ABSTRACT

Background: Reported penicillin allergy rarely reflects penicillin intolerance. Failure to address inpatient penicillin allergies results in more broad-spectrum antibiotic use, treatment failures, and adverse drug events.

Objective: We aimed to determine the optimal approach to penicillin allergies among medical inpatients.

Methods: We evaluated internal medicine inpatients reporting penicillin allergy in three periods: (1) standard of care (SOC), (2) penicillin skin testing (ST), and (3) computerized guideline application with decision support (APP). The primary outcome was use of a penicillin or cephalosporin, comparing interventions to SOC using multivariable logistic regression.

Results: There were 625 patients: SOC 148, ST 278, and APP 199. Of 278 ST patients, 179 (64%) were skin test eligible; 43 (24%) received testing and none were allergic. In the APP period, there were 292 unique website views; 112 users (38%) completed clinical decision support. While ST period patients did not have an increased odds of penicillin or cephalosporin use overall (aOR 1.3 [95% CI 0.8, 2.0]), we observed a significant increased odds of penicillin or cephalosporin use overall in the APP period (aOR 1.8 [95% CI 1.1, 2.9]), and in a per protocol analysis of the skin tested subset (aOR 5.7 [95% CI 2.6, 12.5]).

Conclusions: Both the computerized guideline with decision support and penicillin skin testing – when completed – increased use of penicillin and cephalosporin antibiotics among inpatients reporting penicillin allergy. While the skin tested subset showed an almost 6-fold impact, the computerized guideline significantly increased penicillin or cephalosporin use overall nearly 2-fold and was readily implemented.

INTRODUCTION

Penicillin allergy is reported in up to 15% of inpatients and is associated with increased use of alternative antibiotics, including vancomycin, clindamycin, aminoglycosides, and aztreonam.¹⁻⁴ Compared to beta-lactam antibiotics, these drugs are less effective in some clinical circumstances,⁵⁻⁸ more toxic,^{4,9} more costly,^{10,11} and generally cover a broader antimicrobial spectrum. When a beta-lactam antibiotic is the preferred inpatient antibiotic, but not administered due to alleged allergy, patients experience more treatment failures and adverse events.^{4,8} Patients reporting penicillin allergy have increased odds of antibiotic resistant organisms, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*.¹²

Despite a reported penicillin allergy, more than 95% of patients evaluated for such allergy are found penicillin and cephalosporin tolerant.^{10,12-16} Therefore, active attention to clarifying old and inaccurate penicillin allergies is supported by various U.S. guidelines and agencies as an important feature of antimicrobial stewardship.¹⁷⁻²⁰ Because the optimal approach to the evaluation and management of inpatient penicillin allergy is unknown, yet impacts a substantial number of patients per year, we implemented and assessed two healthcare delivery system innovations to improve antibiotic choice among medical inpatients reporting a history of penicillin allergy.

METHODS

Design Overview

We conducted a quasi-experimental study evaluating prospectively identified cohorts of internal medicine inpatients at the Brigham and Women's Hospital (BWH). We sequentially evaluated three strategies: (1) BWH standard of care (SOC); (2) history-appropriate penicillin skin testing (ST), a process-based innovation; and (3) a computerized guideline application with clinical decision support, a technology-based innovation (APP). We compared antibiotic use in the intervention periods to the SOC period. This study was approved by the Partners Human Research Committee.

Study Population

A daily electronic tracker identified medical inpatients with a history of penicillin allergy prescribed one or more doses of any antimicrobial in all periods (Fig 1). Patient readmissions and patients not meriting treatment of a presumed infection were excluded. The latter exclusion comprised patients who did not receive therapeutic antibiotics in the first seven days of hospitalization, and those who received < 48 hours of antibiotic therapy, accounting for both discharge antibiotics and amended dosing frequency associated with renal dosing.²¹

Study Periods

BWH Standard of Care (SOC)

SOC was the comparison period when no active intervention was performed. SOC patient data were collected from June 9, 2014 through November 5, 2014. As an academic, tertiary care facility, BWH has an antibiotic stewardship program that restricts some broad-

spectrum and costly antibiotics (e.g., linezolid, daptomycin). BWH also has a drug allergy program with inpatient Allergy/Immunology consultation and 24-hour on-call services. During SOC, all penicillin skin testing and test dose challenge²² procedures were performed only when referred by the primary team and deemed appropriate after Allergy/Immunology consultation (eMethods 1, Fig E1a).

Penicillin Skin Testing (ST)

The ST period began November 12, 2014, and continued through June 30, 2015. During the ST period, all tracker-identified patients were screened by the care redesign team for skin test eligibility. Patients ineligible for skin testing included patients with penicillin intolerances (e.g., gastrointestinal upset), patients taking medications that interfered with skin testing (e.g., antihistamines), and patients with multiple beta-lactam allergies, penicillin anaphylaxis in the last five years, or a type II-IV hypersensitivity reaction²³ to penicillin. Skin testing was routinely intended for all skin test eligible patients, but required permission from the primary team, coordination of skin testing using a moonlighting pool of allergy trainees and nurses, and patient consent (eMethods 1, Fig E1b). Patients with both negative penicillin skin testing and tolerance of an oral amoxicillin test dose were deemed not allergic. The primary medical team and the patients were updated regarding changes in allergy status.

Computerized Guideline Application with Clinical Decision Support (APP)

After a five month study break due to a hospital-wide electronic health record conversion,²⁴ the APP period ran from November 20, 2015 through June 13, 2016 (Fig E1c). A clinical pathway that guided beta-lactam antibiotic use in patients with listed penicillin allergy

was previously developed, implemented, and assessed at an academic hospital affiliate (eMethods 2).^{5,25-27} The guideline empowered inpatient providers to group allergic reactions into hypersensitivity type, then recommended if and how specific beta-lactam antibiotics be used (i.e., very low risk: full doses; low risk: test doses; medium to high risk: Allergy/Immunology consultation; serious type II-IV hypersensitivity reactions: avoidance).

The previously studied pathway was adapted into a computerized guideline,^{28,29} a mobile-friendly website with optional clinical decision support, functionally similar to a smartphone application (eMethods 3). Due to the coincident electronic health record conversion at BWH, the computerized guideline was not integrated into the electronic health record, but remained a distinct clinical workflow. The guideline was accessible at any BWH desktop computer or mobile device on the secure intranet. Providers could access the pathway figures directly from the website and/or login to use clinical decision support. After decision support computed the patient's likely allergic reaction type, it stratified the reaction into a risk category and displayed recommendations for further action (Fig E2). The website housed additional educational information and provider videos.

Data Collection

All patient data were collected from the electronic health record, with duplicative entry, initially by research assistants (NP, AEN), followed by internal medicine housestaff. Data were entered and maintained using Research Electronic Data Capture hosted at Partners HealthCare.³⁰

Demographic Characteristics

Collected patient data included age, sex, race, admission date, discharge date, admission diagnosis, allergy history, intensive care unit stay and duration time, Infectious Diseases consultation, Allergy/Immunology consultation, history of colonization or infection with methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus*, renal disease, and overall length of stay. Two board-certified internists and allergists/immunologists (KGB, PGW) determined which admission diagnoses were related to an infection as well as which penicillin allergies were intolerances.

Intervention Uptake

In the ST period, we determined the frequency with which eligible patients completed skin testing. In the APP period, we tracked usage through reports from Google Analytics Solutions (website views) and clinical decision support responses.

Outcomes

The primary outcome was use of formulary unrestricted penicillins or cephalosporins (Table E2). Penicillin and cephalosporin use was identified through inpatient antibiotic administrations. Secondary outcomes included the proportion of patients discharged on a penicillin or cephalosporin antibiotic, inpatient use of alternative antibiotics, and resultant adverse drug reactions.

Penicillins and cephalosporins on BWH formulary were included; cephalosporins were grouped by generation for analysis. Because of the intent to improve antibiotic choice, we excluded penicillins and cephalosporins historically restricted by BWH's antibiotic stewardship

program, including piperacillin-tazobactam, ceftaroline, ceftolozane-tazobactam, and ceftazidime-avibactam. Alternative antibiotics included drugs that are potentially more toxic, less effective, more costly, and/or more broad-spectrum: vancomycin, clindamycin, daptomycin, linezolid, carbapenems, aztreonam, and aminoglycosides.

Balance Measure

We analyzed macrolide antibiotic utilization as a balance measure, given its use would not be expected to change as a result of interventions related to penicillin allergy evaluation.

Statistical Analysis

Study period duration and sample size were estimated in advance (eMethods 4). Pair-wise study group comparisons were specified *a priori*. While the primary analysis between periods was an intention-to-treat analysis, we performed an additional secondary (per protocol) analysis for the ST period (ST-PP) to estimate the potential impact of this strategy if it were fully implemented. Demographic data were reported as medians with quartiles or as frequencies with percentages. Fisher's exact tests were used to compare study groups for binary variables, and Wilcoxon rank sum tests were used for continuous variables. Racial differences among study groups were tested using the Freeman-Halton test. Logistic regression was used to test group differences, with unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CI) presented. Selection of variables to include in multivariable models involved prior knowledge of association with outcome, and imbalance across the study duration. Nominal p-values were reported in this context of three *a priori* non-independent pair-wise group comparisons,

218 considering 5% two-sided alpha. Statistical analyses were conducted using SAS 9.4 (SAS
219 Institute Inc., Cary, NC, USA).

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RESULTS

Cohort Characteristics

Of 1,000 medicine inpatients with a reported penicillin allergy prescribed one or more antibiotic dose, there were 780 unique patients and 625 unique patients admitted with a presumed infection across three periods: SOC 148, ST 278, and APP 199 (Fig 1).

Patient characteristics were largely balanced across periods, with a few exceptions (Table I). Compared to the SOC period, there were fewer females in the subset of patients skin tested (i.e., skin test per protocol analysis [ST-PP]), more patients with an admission diagnosis of infection in the ST and APP periods, more frequent Allergy/Immunology consultation in the ST period and in the ST-PP analysis, more frequent methicillin-resistant *Staphylococcus aureus* colonization in the ST and APP periods, and more reported cephalosporin allergies in the ST and APP periods.

Intervention Uptake

Among 278 patients in the ST period, 179 (64%) were skin test eligible. Of 43 (24%) patients skin tested, none were allergic (Fig 2). There were 2,802 webpage views in the APP period, with 292 unique page views lasting 26 seconds on average (Table E1). There were 112 unique users who completed decision support.

Primary Outcome, Inpatient Penicillin or Cephalosporin Use

Of 148 patients in the SOC period, 56 (38%) were treated with a penicillin or cephalosporin (Table II). Of 278 patients in ST period, 116 (42%) were treated with a penicillin or cephalosporin antibiotic. Of 43 ST-PP patients, 31 (72%) of patients were treated with a penicillin or cephalosporin antibiotic. Of 199 patients in the APP period, 99 (50%) were treated with a penicillin or cephalosporin antibiotic; treated patients received the penicillins and/or cephalosporins after negative penicillin skin testing (n=5, 5%) or directly with a test dose or full dose challenge (n=94, 95%).

In univariable analyses compared to SOC, penicillin or cephalosporin use was similar in the ST period overall ($p=0.44$), but greater in the ST-PP analysis ($p<0.001$) and overall in the APP period ($p=0.03$). In the multivariable logistic regression model, patients in the ST period did not have a significant increased odds of receiving a penicillin or cephalosporin (aOR 1.3 [95% CI 0.8, 2.0], Table III). ST-PP patients had increased odds of receiving a penicillin or cephalosporin, with an adjusted OR 5.7 [95% CI 2.6, 12.5]. APP period patients had increased odds of receiving a penicillin or cephalosporin, with an adjusted OR 1.8 [95% CI 1.1, 2.9].

Secondary Outcomes

Although a similar proportion of patients in the ST period used a penicillin or cephalosporin on discharge compared to the SOC period, a greater frequency of ST-PP patients received a penicillin or cephalosporin on discharge compared to SOC (26% vs 16%, $p=0.18$, Table II). In the multivariable model, there was an increased odds of a penicillin or cephalosporin used for discharge treatment for ST-PP patients, compared to SOC (OR 2.5 [95% CI 1.04, 6.2], Table III). In both univariable and multivariable analyses, the frequency of

discharge use of a penicillin or cephalosporin was similar in the APP period, compared to SOC (Tables II and III).

Overall frequency of alternative antibiotic use was largely similar across periods (Tables II and III, Bottom).

There were no adverse drug reactions identified in SOC or ST periods. One patient in the APP period with history of penicillin allergy developed erythema and pruritus to amoxicillin after a negative penicillin skin test.

Balance Measure

The frequency of inpatient macrolide antibiotic use was unchanged by the interventions, compared to SOC (10%), for all comparisons (ST 10%, $p=0.89$; ST-PP 2%, $p=0.10$; APP 12%, $p=0.67$).

DISCUSSION

In this study of two antibiotic stewardship innovations designed to safely increase use of favorable beta-lactam antibiotics in medical inpatients reporting penicillin allergy, we found that the allergy history-driven computerized guideline as well as completed penicillin skin testing significantly increased penicillin or cephalosporin antibiotic use. While skin testing period patients did not have increased odds of penicillin or cephalosporin use, patients in the computerized guideline period had a significant almost 2-fold increased odds of receiving a penicillin or cephalosporin antibiotic. Completed skin testing, in the per protocol analysis, had an almost 6-fold increased odds of receiving a penicillin or cephalosporin antibiotic.

Among inpatients treated for infections, 5-25% report an allergy to penicillin.^{1,4,7,16,31} Although up to 3 in 4 patients with alleged penicillin allergy warrant inpatient treatment with a beta-lactam antibiotic,⁴ only half were receiving these antibiotics in the baseline SOC period. We implemented interventions that were associated with increased use of favorable penicillins and cephalosporins, reflecting improved antibiotic choice and stewardship. Since the impact of over-reporting penicillin allergy is felt beyond antibiotic utilization to resultant readmissions,³¹ treatment failures,⁸ and adverse events,⁴ safely increasing the use of penicillin and cephalosporin antibiotics in this patient population is a crucial first step towards improved quality of care and reduced cost.³²

We did not observe a significant impact of the interventions on the frequency of discharge use of penicillins or cephalosporins in the primary analyses, or inpatient use of alternative antibiotics. The former may be explained by providers' choice for outpatient therapy placing more emphasis on medication convenience. Yet, we observed that patients who completed skin testing in the per protocol analysis had an increased odds of penicillin or

cephalosporin use at discharge, which may indicate that skin test negative patients have improved antibiotic use beyond their hospitalization. It was not surprising that neither intervention had a significant impact on use of alternative antibiotics, since medical inpatients with infections are often given empiric treatment that includes the alternative antibiotics.

Prior studies addressing over-reported penicillin allergies have demonstrated the utility of penicillin skin testing in emergency, intensive care, and perioperative patients.^{10,13,33} Fewer skin testing studies are reported among highly selected inpatient subsets.^{16,34-36} Alternative approaches to address inpatient penicillin allergies have included consultation by allergy specialists^{34,37} and guidelines/clinical pathways.^{26,38} By implementing and assessing both a skin testing approach and guideline approach in sequential cohorts at the same institution, we were able to determine the overall hospital policy level impact of these interventions.

While completed penicillin skin testing was effective at improving inpatient antibiotic choice, 36% of patients were ineligible for testing, consistent with prior estimates that deemed 4-59% of inpatients skin test ineligible.^{16,39,40} One modifiable reason that patients in the ST period overall may not have experienced a significant increase in penicillin and cephalosporin use was an inability to coordinate testing for 58 skin test eligible patients. However, we skin tested 16% of all patients reporting penicillin allergy on antibiotics in this period, and 24% of those who were skin test eligible, largely comparable to the 19% yield achieved through the use of a designated pharmacist performing skin testing in a prior study.³⁶ Still, more patients would have had testing completed, and overall findings may have differed, had we hired an on-site skin testing clinician.

Despite challenges associated with coincidental innovation at the time of electronic health record conversion,⁴¹⁻⁴⁴ there were almost 300 unique webpage views of the computerized

guideline, and 112 providers completed decision support. Given the computerized guideline's overall positive impact on antibiotic use, reliance on new technology over new human capital, and relative ease of implementation, the computerized guideline and decision support tool have great potential to improve the care of inpatients with reported penicillin allergy. This conclusion is further strengthened by our knowledge of the intervention's limited electronic health record integration and basic user interface during the study period.^{45,46} Further, the computerized guideline and decision support tool can provide guidance when hospitals do not have access to allergists or penicillin skin testing, or when patients are otherwise ineligible or unwilling to complete a skin test.

Innovations in healthcare delivery substantially change care, while quality improvement targets incremental change.⁴⁷ The interventions implemented challenged the *status quo* by introducing a new process (i.e., skin testing) and a new technology (i.e., computerized guideline) to change the care of inpatients labeled penicillin-allergic. Healthcare systems are ill-equipped to address penicillin allergy because general clinicians have poor drug allergy knowledge,²⁵ there are inadequate numbers of allergy specialists to perform these evaluations,^{48,49} and less than 15% of U.S. hospitals have the skin testing reagent on formulary.⁵⁰ Thus, healthcare delivery innovations are needed with investments in infrastructure, technology, and/or human resources. These investments may contain elements of the computerized guideline, which was easy to implement and relatively inexpensive. Hospitals will likely need processes for performing penicillin skin testing and test dose challenges, even without access to allergy specialists.

While the hospital policy perspective of this study afforded us a realistic view of the overall impact of our interventions, the analysis underestimates the potential impact because of incomplete uptake. Using a per protocol analysis for the penicillin skin testing period provided

additional insight, but is subject to selection bias towards patients who would most clearly benefit from the penicillin skin test. While a per protocol analysis may have been similarly favorable for patients whose providers used the computerized guideline, these data were not available. Although cohorts were identified prospectively, data were gathered retrospectively, potentially resulting in missing or misclassification information; for example, we could not identify mild adverse reactions, if they were not included in the electronic health record. Data were also gathered in two different electronic health record systems, however, variables were collected by medicine-trained chart verifiers comfortable with both systems. We acknowledge that our quasi-experimental design limits our ability to demonstrate causality, but we included the macrolide balance measure to provide reassurance against unmeasured confounders or secular trends. This study assessed antibiotic outcomes within patients' incident admission only, and did not capture important longitudinal outcomes, such as clarity of allergy status/documentation or types of antibiotics (i.e., beta-lactams or alternatives) used after discharge or in future hospitalizations. Finally, internal medicine patients may not be similar to other types of inpatients (e.g., surgical, obstetric), and results may differ in hospitals whose patients, resources, and/or personnel differ from those of BWH.

In summary, we implemented and assessed two interventions in the care of hospitalized medical patients with reported penicillin allergy. Although barriers to completing skin testing routinely in medical patients made skin testing impractical and without an overall impact on antibiotic use, skin tested patients had almost 6-fold odds of increased penicillin and cephalosporin use. The computerized guideline had an overall positive, almost 2-fold impact, with a feasible implementation and long-term strategy for greater technology integration.

FIGURE LEGENDS

Fig 1. This flow chart demonstrates patient cohort identification. The care redesign team was notified prospectively if patients met initial criteria, including (1) internal medicine inpatient, (2) reported penicillin allergy, and (3) prescribed one or more antibiotic doses. From this cohort, we excluded readmissions and patients whose admission was not for treatment of an infection. Of 625 patients meeting these criteria, 148 were admitted in the standard of care period, 278 were admitted in the penicillin skin testing period, and 199 were admitted in the computerized guideline period.

Fig 2. This flow chart includes all penicillin skin testing period patients. Of 278 patients in the skin testing period, 179 patients were eligible for skin testing. Of the 179 patients for whom skin testing was intended, 43 patients completed penicillin skin testing, and none were allergic.

394 TABLES

Table I. Cohort characteristics of medicine patients with reported penicillin allergy, requiring antibiotics over three periods (n= 625).

	Standard of Care (n=148)	Penicillin Skin Testing				Computerized Guideline/APP (n=199)	
		All (n=278)	p value*	Per Protocol (n=43)	p value*	No (%)	p value*
	No (%)	No (%)		No (%)			
Age (Med, IQR)	64 [48,79]	68 [54, 80]	0.09	71 [52, 77]	0.66	65 [52, 76]	0.96
Female sex	97 (66)	173 (62)	0.53	21 (49)	0.05	128 (64)	0.82
Race			0.14		0.01		0.72
White	109 (77)	183(69)		25 (61)		143 (73)	
Black	23 (16)	46 (17)		6 (15)		36 (18)	
Hispanic	6 (4)	26 (10)		7 (17)		10 (5)	
Other	3 (2)	11 (4)		3 (7)		8 (4)	
Admission diagnosis of infection	72 (49)	163 (59)	0.05	25 (58)	0.30	124 (62)	0.01
Reported penicillin allergy history [†]							
Rash or hives	79 (53)	149 (54)	>0.99	28 (65)	0.22	108 (54)	0.91
Angioedema [‡]	17 (11)	27 (10)	0.62	11 (26)	0.03	14 (7)	0.18
Anaphylaxis	12 (8)	22 (8)	>0.99	4 (9)	0.76	17 (9)	>0.99
Shortness of breath [‡]	2 (1)	7 (3)	0.73	2 (5)	0.22	6 (3)	0.49
Unknown history	26 (18)	65 (23)	0.17	6 (14)	0.65	35 (18)	>0.99
Intolerance only	11 (7)	15 (5)	0.40	1 (2)	0.30	16 (8)	>0.99
ICU Stay > 24 hours	23 (16)	37 (13)	0.56	3 (7)	0.21	27 (14)	0.64
Infectious Diseases consultation	43 (29)	78 (28)	0.82	11 (26)	0.71	55 (28)	0.81
Allergy/Immunology consultation	6 (4)	21 (8)	0.21	6 (14)	0.03	8 (4)	>0.99
Penicillin skin test performed**	2 (1)	43 (16)	<0.001	43 (100)	<0.001	5 (3)	0.70
Resistant organism history							
MRSA colonization	9 (6)	36 (13)	0.03	1 (2)	0.46	32 (16)	0.004
VRE colonization	9 (6)	25 (9)	0.35	1 (2)	0.46	15 (8)	0.67
Renal disease	45 (30)	96 (35)	0.45	13 (30)	>0.99	74 (37)	0.21
Other reported antibiotic allergies							
Cephalosporins	1 (0.7)	42 (15)	<0.001	3 (7)	0.04	35 (18)	<0.001
Sulfonamides	30 (20)	70 (25)	0.28	8 (19)	>0.99	54 (27)	0.16
Fluoroquinolones	21 (14)	28 (10)	0.21	3 (7)	0.30	31 (16)	0.76

Table I (cont.)

Vancomycin	7 (5)	14 (5)	>0.99	0 (0)	0.35	12 (6)	0.64
Macrolides	18 (12)	26 (9)	0.40	3 (7)	0.42	20 (10)	0.60
Length of stay	5 [3,8]	5 [3,8]	0.61	5 [4,8]	0.91	5 [3,9]	0.61

* Fisher's exact test or Wilcoxon Rank Sum test between innovations and standard of care.

† Records may contain more than one description or reaction of clinical feature of drug allergy history.

‡ Includes swelling.

§ Includes bronchospasm.

** Median time from patient admission to penicillin skin test was 2.0 days [IQR 1.0, 3.0 days] in the Skin Testing period and 3.0 days [IQR 2.0, 4.0 days] in the Computerized Guideline/APP period. Neither median times were significantly different from the median time in the Standard of Care period (2.0 days [IQR 1.0, 3.0 days], $p=0.80$ and $p=0.48$ respectively).

Abbreviations: ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*

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Table II: The impact of interventions on antibiotic use over three periods.

	Standard of Care (n=148)		Penicillin Skin Testing				Computerized Guideline/APP (n=199)	
	No (%)	No (%)	All (n=278)	p value*	Per Protocol (n=43)	p value*	No (%)	p value*
Penicillin and cephalosporin antibiotics [†]								
Inpatient use								
Penicillins or cephalosporins	56 (38) [‡]	116 (42) [§]	0.47		31 (72)	<0.001	99 (50) [¶]	0.03
Penicillins	7 (5)	14 (5)	>0.99		6 (14)	0.08	11 (6)	0.81
Cephalosporins (1 st or 2 nd)	6 (4)	12 (4)	>0.99		5(12)	0.07	13 (7)	0.35
Cephalosporins (3 rd or 4 th)	47 (32)	102 (37)	0.34		27 (63)	<0.001	86 (43)	0.03
Discharge Use								
Penicillins or cephalosporins	24 (16)	33 (12)	0.23		11 (26)	0.18	34 (17)	0.88
Penicillins	5 (3)	9 (3)	>0.99		5 (12)	0.05	7 (4)	>0.99
Cephalosporins (1 st or 2 nd)	5 (3)	8 (3)	0.77		3 (7)	0.38	9 (5)	0.78
Cephalosporins (3 rd or 4 th)	15 (10)	16 (6)	0.12		3 (7)	0.77	18 (9)	0.85
Alternative antibiotics ^{**}								
Inpatient use	74 (50)	148 (53)	0.54		26 (60)	0.30	109 (55)	0.39

* Fisher's exact test p values compare the intervention periods to the standard of care period.

[†] Excludes piperacillin-tazobactam, ceftaroline, ceftolozane-tazobactam and ceftazidime-avibactam (see methods).

[‡] Penicillin or cephalosporin-treated patients received a median of 5.5 [IQR 3.0, 10.5] doses.

[§] Penicillin or cephalosporin-treated patients received a median of 5.0 [IQR 2.0, 7.0] doses.

^{||} Penicillin or cephalosporin-treated patients received a median of 5.0 [IQR 2.0, 11.0] doses.

[¶] Penicillin or cephalosporin-treated patients received a median of 6.0 [IQR 2.0, 8.0] doses.

^{**} Includes vancomycin, clindamycin, aztreonam, daptomycin, linezolid, carbapenems, and aminoglycosides (see methods).

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Table III. The impact of innovations on use of penicillin or cephalosporin antibiotics in unadjusted and adjusted analyses.

	Unadjusted Analysis*			Adjusted Analysis*		
	Skin Testing	Skin Testing Per Protocol	Computerized Guideline/APP	Skin Testing	Skin Testing Per Protocol [‡]	Computerized Guideline/APP [‡]
Inpatient Penicillin or Cephalosporin	1.2 [0.8, 1.8]	4.2 [2.0, 8.9][‡]	1.6 [1.1, 2.5][§]	1.3 [0.8, 2.0]	5.7 [2.6, 12.5][‡]	1.8 [1.1, 2.9][¶]
Discharge Use Penicillin or Cephalosporin	0.7 [0.4, 1.2]	1.8 [0.8, 4.0]	1.1 [0.6, 1.9]	0.7 [0.4, 1.3]	2.5 [1.04, 6.2]**	1.0 [0.6, 1.9]
Inpatient Use of Alternative Antibiotics	1.1 [0.8, 1.7]	1.5 [0.8, 3.1]	1.2 [0.8, 1.9]	1.1 [0.7, 1.7]	1.8 [0.9, 3.8]	1.0 [0.7, 1.7]

* Data presented as OR [95% CI]

[†] Adjusts for frequency of methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus* colonization, an infection as the admission diagnosis, length of stay, concomitant cephalosporin allergy, penicillin intolerance, and Allergy/Immunology consultation.

[‡] Adjusts for frequency of methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus* colonization, an infection as the admission diagnosis, length of stay, concomitant cephalosporin allergy, and penicillin intolerance.

[¶] **p<0.001; [§] p=0.03; [¶] p=0.02; **p=0.04**

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Drs. Kimberly Blumenthal and Shelley Hurwitz had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Conflicts of interest: None

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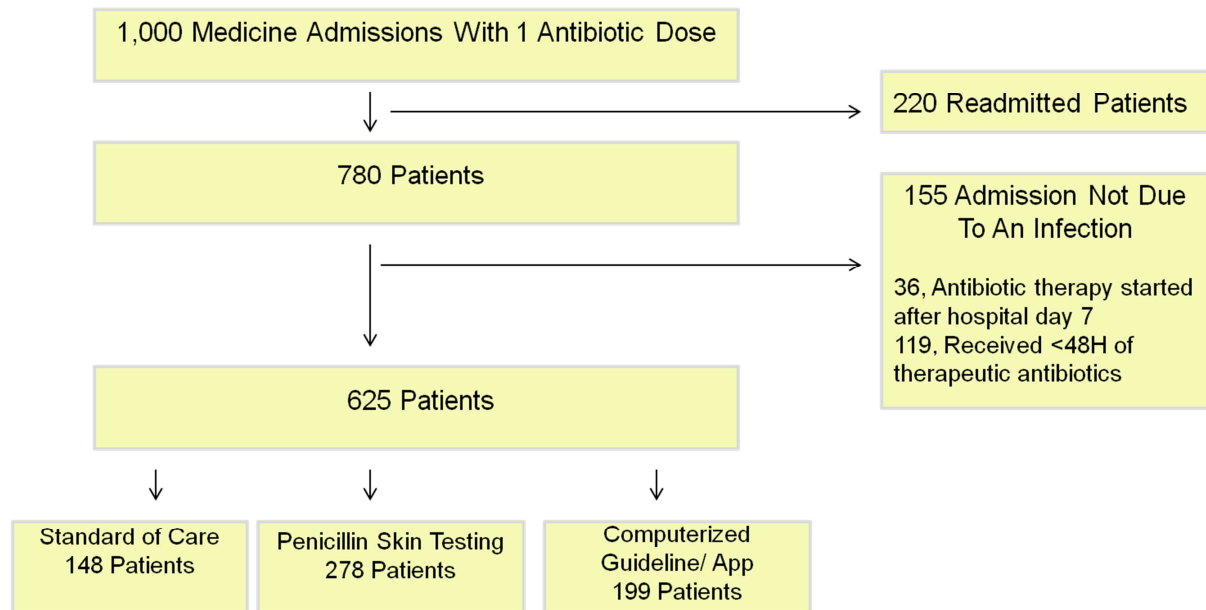
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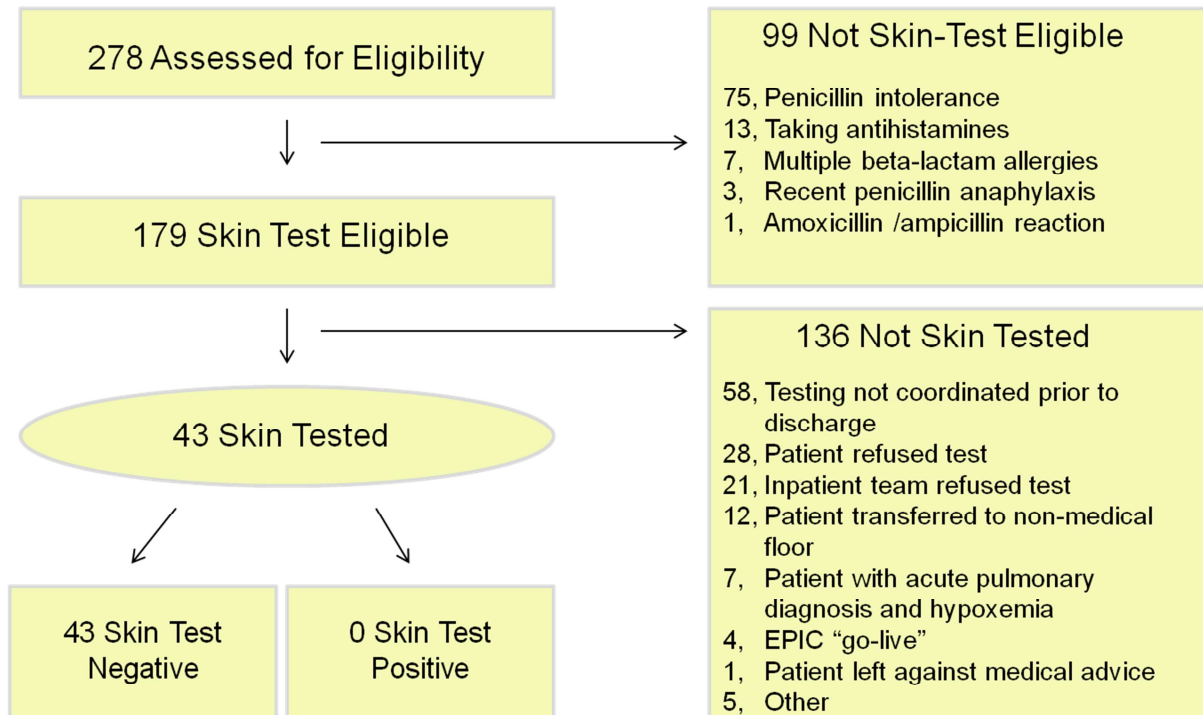


Fig E1. Study periods evaluated for medical inpatients with reported penicillin allergies: (a) Standard of Care, (b) Penicillin Skin Testing, (c) Computerized Guideline Application with Clinical Decision Support.

This figure displays the evaluation and treatment course for patients with penicillin allergy hospitalized for a presumed infection in each of the three periods. The relative frequencies with which paths are taken are indicated by the weight of arrows (i.e., heavier weight indicates more patients would take that path). Positive and negative downstream outcomes are shown at the far right.

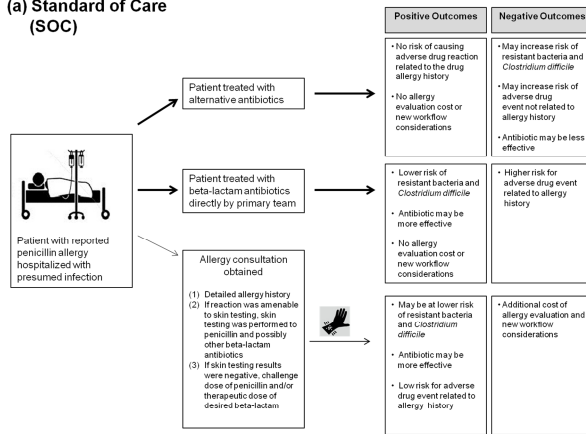
Fig E2. Example clinical decision support offered by the computerized guideline application.

The computerized guideline application contained optional clinical decision support for taking a drug allergy history. After answering questions from the patient's allergy history, the decision support would group immunologic reactions into one of three reaction categories from the penicillin hypersensitivity pathway. In this example, the patient's allergy history was suspicious for a serum sickness like reaction to penicillin, a type III hypersensitivity reaction.

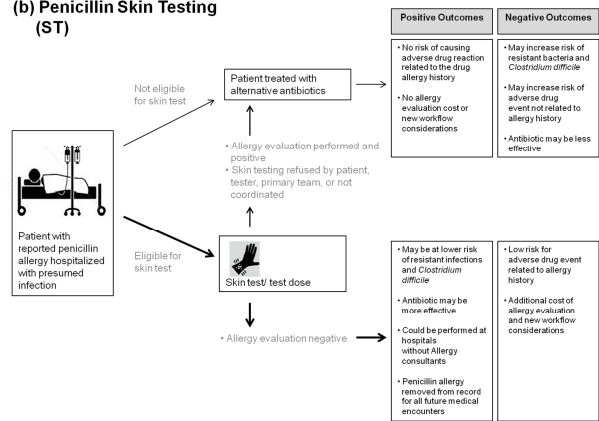
Fig E3. Disseminated posters and pocket cards in the computerized guideline application period.

Educational posters were hung in work rooms, emailed to clinicians, and dispensed as laminated pocket cards. One poster focused on accessing and using the computerized guideline application while the other displayed the penicillin hypersensitivity pathway.

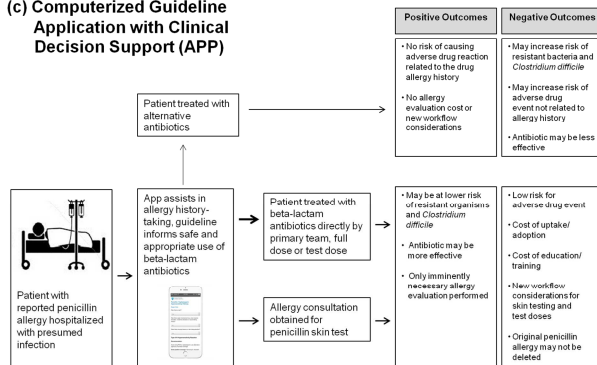
(a) Standard of Care (SOC)



(b) Penicillin Skin Testing (ST)



(c) Computerized Guideline Application with Clinical Decision Support (APP)



Allergy to:

Penicillin

Was the reaction unknown?

No

Was there a rash?

Yes

Was there organ involvement (e.g. liver enzyme elevation, creatinine elevation or acute kidney injury)?

No

Were there mucosal lesions or skin desquamation?

No

Were there joint pains, fever, or myalgias?

Yes

Assessment

Possible serum sickness reaction

Type II-IV Hypersensitivity Reaction



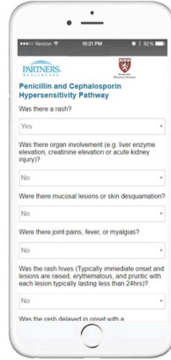
BRIGHAM AND
WOMEN'S HOSPITAL

Guideline for Prescribing Antibiotics to Inpatients with Penicillin Allergy

Why use it? The purpose of this guideline is to provide allergy history-taking support and antibiotic prescribing recommendations for patients reporting penicillin allergy.

How do I access the guideline?

- **Via your smartphone or tablet:**
 - ✓ Connect to Partners wifi (phswifi3).
 - You will not be able to access the app via unsecured wifi (phspiguest).¹
 - ✓ Access the app at <http://id.partners.org/allergy>.
 - You will be prompted for your Partners username and password.
- **Via a Partners PC:** just go to <http://id.partners.org/allergy>



What's the evidence base? This decision support tool and guideline, based on a pathway that has been used successfully hospital-wide at MGH since 2013,^{2,4} is supported by drug allergy literature and the practice parameters created by the American Academy of Allergy, Asthma and Immunology.⁵

What if I still have questions?

Please watch the educational videos at <https://id.partners.org/allergy/videos/>, contact us at phsallergypathway@partners.org, or involve Infectious Disease and/or Allergy/Immunology consultation services.

¹ For instructions on accessing phswifi3, see <http://id.partners.org/phswifi3>.

² Blumenthal KG, Shenozy ES, Hurwitz S, Vaughn CA, Hooper DC, Banerji A. Effect of a drug allergy educational program and antibiotic prescribing guideline on inpatient clinical providers' antibiotic prescribing knowledge. *J Allergy Clin Immunol Pract*. 2014; 2(4):407-13.

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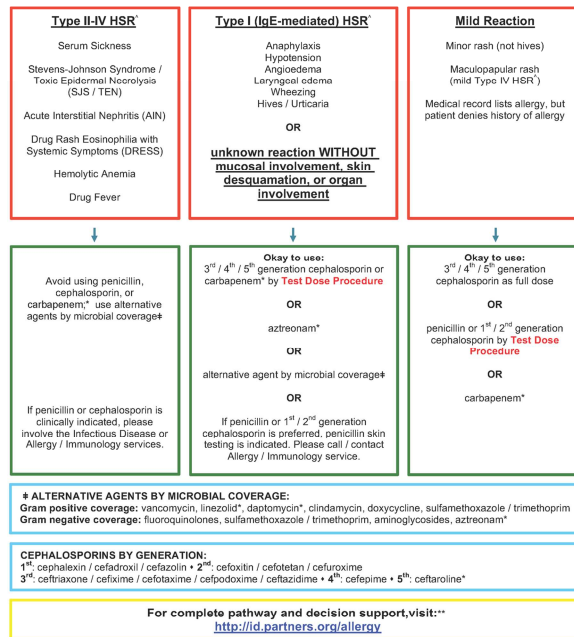
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BRIGHAM AND
WOMEN'S HOSPITAL



Penicillin / Cephalosporin Hypersensitivity Pathway



* HSR: Hypersensitivity Reaction

* Infectious Disease approval required

** Access from Partners PC or while connected through secure Partners wifi (not phspiguest)

Tackling Inpatient Penicillin Allergies: Tools for Antimicrobial Stewardship

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Keywords: stewardship, skin test, test dose, decision support, computerized guideline

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Supplementary online content: eMethods; Table E1; Fig E1-E3

ONLINE REPOSITORY MATERIAL

Supplementary Methods

1. Standard procedure for penicillin skin testing and test doses in all periods

Penicillin skin testing was performed using Pre-Pen® (ALK-Abello) and dilutions of Penicillin G (10,000 units/ml for epicutaneous and intradermal testing). Penicillin mixing and dilutions were performed by the central inpatient pharmacy. Prior to penicillin skin testing, written informed consent was obtained from the patient, or a designated health care proxy. All skin testing was performed by an Allergy/Immunology physician, registered nurse, or nurse practitioner. All negative penicillin skin tests were followed with a single oral observed challenge dose (i.e. test dose) of amoxicillin 250 mg. Although not an adult therapeutic dose, Amoxicillin 250 mg is adequate for provoking an IgE-Mediated reaction and is the standard protocol used by Brigham and Women's Hospital Allergy/Immunology.

Computerized guideline-recommended test doses to beta-lactam antibiotics without preceding skin testing followed a two-step protocol.¹ Guided by our prior studies,^{1,2} the initial dose was 1/10 of an intravenous antibiotic dose or 1/4 of an oral antibiotic dose. The second dose, administered 30 minutes later, comprised the remaining part of the therapeutic dose (i.e., 9/10 of the intravenous dose or 3/4 of the oral dose). All test doses were performed on the general medical floor, during weekday, daytime hours with one-to-one nursing for the duration of the procedure. Nurses assessed patients every 30 minutes for the duration of the challenge (i.e., 90 minutes). Guideline-recommended full dose challenges to beta-lactam antibiotics without preceding skin testing were ordered regularly, without any specific administration or observation instructions.

2. Evidence supporting the structure of the clinical pathway/guideline

Evidence supportive of the clinical guideline structure have been previously described.² The guideline uses the hypersensitivity reaction type³ to inform which drugs should be avoided, which can be used initiating with a test dose, and which can be initiated with a full dose. Providers assign the patient's reaction into one of three reaction categories that have corresponding risk stratification: (1) Type II-IV reaction, (2) Type I reaction, or (3) Mild reaction (Fig E3). Guideline implementation was previously associated with increased test dose challenges of beta-lactam antibiotics and improved first-line antibiotic therapy in methicillin-sensitive *Staphylococcus aureus* bacteremia.^{2,4-7}

3. Development and testing of computerized guideline/app

The previously studied guideline was adapted into a mobile-friendly intranet site maintained behind the Partners HealthCare firewall. The clinical decision support functionality of the website was developed by an allergist/immunologist and quality and safety leader (KGB, Fig E2), and revised based on input from allergists, infectious diseases experts, and pharmacists in Partners HealthCare System. In addition to housing links to the PDF versions of the pathway, the website included links to educational videos (offered through Vidscrip services⁸) and national data supporting penicillin allergy evaluation. Computerized guideline users could access the pathway figures directly if they were comfortable with allergy history-taking, or they could complete clinical decision support to aid in the allergy history-taking.

Prior to implementation, the clinical decision support functionality of the app was tested by 16 providers from across Partners HealthCare, and subsequently revised based on cumulative

feedback, though limitations on speed, design/user experience, and electronic health record integration persisted.

With the start of the computerized guideline period, laminated pocket cards and posters with pathway figures and website instructions were delivered to internal medicine floors for clinical providers (Fig E3).

4. Determination of innovation period length and statistical power

For 80% power to detect an increase of 15% in the use of penicillin or cephalosporin antibiotics, we required 750 total inpatients (standard of care 150, penicillin skin testing 300, computerized guideline 300), with 30% penicillin or cephalosporin use expected in the standard of care period using 2.5% alpha. With approximately 60 patients per month meeting the electronic trigger criteria, we anticipated intervention period lengths of 3-5 months in duration. Given anticipated exclusions for readmissions and patients not treated for a presumptive infection, we terminated enrollment when we reached a cohort of 1,000 medicine inpatients.

102 **Table E1. Computerized guideline and clinical decision support usage**

Characteristic	Number
Total webpage views	2,802
Unique page views	292
Average time on page (seconds)	26
Total users completed decision support	112
Allergy assessment identified from decision support	
Low risk	
Benign delayed maculopapular rash	5
EHR discrepancy	2
Medium to High Risk	
Urticaria	21
Unknown reaction	15
Angioedema	10
Unspecified rash	6
Anaphylaxis	5
Recent or severe delayed maculopapular rash	2
Use Alternative Antibiotics	
Stevens-Johnson, toxic epidermal necrolysis or exfoliative dermatitis	21
Drug rash eosinophilia and systemic symptoms or acute interstitial nephritis	10
Serum-sickness like reaction	3
Other	

Table E1. Continued

Cephalosporin allergy pathway requested*	9
Call Allergy/Immunology	3
Identifiable users completed decision support	55
Internal medicine resident	18
Internal medicine attending	15
Subspecialty fellow	12
Registered nurse	4
Pharmacist	4
Nurse practitioner	2
* Academic affiliate guideline included a corollary approach to cephalosporin allergy that was not implemented at the Brigham and Women's Hospital.	
<i>Abbreviations:</i> EHR: electronic health record	

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Table E2. Formulary restriction of beta-lactams at the Brigham and Women's Hospital

Beta-Lactam Class	Formulary Unrestricted	Formulary Restricted*
Penicillins	Amoxicillin [†] Amoxicillin-Clavulanic Acid Dicloxacillin Penicillin V potassium [†] Ampicillin Ampicillin-Sulbactam Nafcillin Penicillin G Potassium IV	Piperacillin-Tazobactam [‡] Ticarcillin-Clavulanic Acid [‡]
Cephalosporins	Cefixime [†] Cefpodoxime [†] Cephalexin [†] Cefazolin Ceftazidime Cefepime Cefotaxime Cefoxitin Ceftriaxone Cefuroxime Cefotetan	Ceftaroline Ceftolozane-Tazobactam Ceftazidime-Avibactam
Carbapenems		Meropenem Ertapenem Imipenem-Cilastatin
*In the proximal 5 years; [†] Oral ; [‡] Formulary unrestricted 2012; [‡] Removed from market 2015		

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