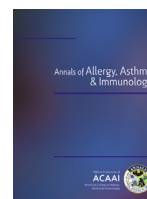




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Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy

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ABSTRACT

Background: Self-reported penicillin allergy infrequently reflects an inability to tolerate penicillins. Inpatients reporting penicillin allergy receive alternative antibiotics that might be broader spectrum, more toxic, or less effective.

Objective: To develop and assess a clinical guideline for the general inpatient provider that directs taking a history and prescribing antibiotics for patients with penicillin or cephalosporin allergy.

Methods: A guideline was implemented to assist providers with assessing allergy history and prescribing antibiotics for patients with reported penicillin or cephalosporin allergy. The guideline used a standard 2-step graded challenge or test dose. A quasi-experimental study was performed to assess safety, feasibility, and impact on antibiotic use by comparing treatment 21 months before guideline implementation with 12 months after guideline implementation.

Results: Significantly more test doses to β -lactam antibiotics were performed monthly after vs before guideline implementation (median 14.5, interquartile range 13–16.25, vs 2, interquartile range 1–3.25, $P < .001$). Seven adverse drug reactions occurred during guideline-driven test doses, with no significant difference in rate (3.9% vs 6.1%, $P = .44$) or severity ($P > .5$) between periods. Guideline-driven test doses decreased alternative antimicrobial therapy after the test dose, including vancomycin (68.3% vs 37.2%, $P < .001$), aztreonam (11.5% vs 0.5%, $P < .001$), aminoglycosides (6.0% vs 1.1%, $P = .004$), and fluoroquinolones (15.3% vs 3.3%, $P < .001$).

Conclusion: The implementation of an inpatient antibiotic prescribing guideline for patients with penicillin or cephalosporin allergy was associated with an almost 7-fold increase in the number of test doses to β -lactams without increased adverse drug reactions. Patients assessed with guideline-driven test doses were observed to have significantly decreased alternative antibiotic exposure.

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Introduction

Penicillin allergy is reported by 10% of the population and up to 15% of inpatients.^{1–5} A reported penicillin allergy is associated with increased use of alternative antibiotics, including vancomycin, clindamycin, fluoroquinolones, aminoglycosides, and aztreonam.^{2,3,6–8} These antibiotics are often more costly,^{9–12} less effective in certain clinical circumstances,^{13–15} more toxic,¹⁶ and broader spectrum, which potentially unnecessarily increases patients' risk of infection with resistant pathogens, such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* species, and *Clostridium difficile* colitis.^{5,17–19}

A reported allergy to penicillin infrequently reflects the inability to tolerate penicillins. After formal allergy evaluation, including penicillin skin testing, 90% to 99% of patients with reported allergy can tolerate penicillins.^{4,6,11,20–22} This large discrepancy between reported penicillin allergy and true allergy is due in part to the original misclassification of the reaction and the waning natural history of type I IgE-mediated penicillin allergy.^{23,24} Therefore, most patients with reported penicillin allergy are unnecessarily avoiding penicillin and related β -lactams antibiotics, such as cephalosporins.^{2,10,25–27} Even in the presence of true Gell and Coombs²⁸ type I hypersensitivity reaction to penicillin, many β -lactam antibiotics, including later-generation cephalosporins, can be safely administered by initiating therapy under observation with a small dose called a *graded challenge* or *test dose procedure*.^{1,25,26,29–32} The test dose, a limited-step graded challenge, is important to the evaluation of adverse drug reactions (ADRs).^{33–36}

Prior studies have evaluated the use of penicillin skin testing in the emergency, perioperative, and intensive care unit settings, with results demonstrating that skin testing can lead to decreased use of vancomycin and fluoroquinolones and increased use of cephalosporins.^{6,7,11,20} However, inpatient use of penicillin skin testing can predominantly shift antibiotic use toward the later-generation cephalosporins,⁴ which are safe for use in the absence of preceding skin testing with a test dose.^{25,26,31} Moreover, although skin testing is a procedure that might be costly or challenging for hospitals to widely implement, the test dose requires fewer inpatient resources.

To address the large discrepancy between reported and true penicillin allergy among inpatients, the authors developed a clinical guideline for inpatient providers that uses allergy history to determine which β -lactam antibiotics can be administered to patients with a history of penicillin or cephalosporin allergy with a full dose, a test dose, or only with preceding penicillin skin testing. Then, they evaluated this guideline's safety, feasibility, and impact on consultations and antibiotic usage.

Methods

Clinical Guideline

The guideline, developed by allergy and immunology (AI), infectious diseases (ID), and pharmacy services at Massachusetts General Hospital (MGH), assisted providers in taking a drug allergy history and prescribing antibiotics to patients with a history of penicillin or cephalosporin allergy (Fig 1 and eMethods). The guideline also provided a standardized method for primary teams to perform test doses of β -lactams on the general medical floor and indicated when AI and/or ID consultation was needed. Before guideline implementation, AI consultation was a requirement for all test doses at MGH; all test doses were given on the general medical floors by a standardized 2-step procedure since 2008.³³ After guideline implementation, test doses of β -lactam antibiotics did not require consultation. The guideline was implemented in all adult inpatient areas on April 1, 2013.

Educational Intervention

After training members of the AI, ID, and pharmacy services, brief, targeted educational presentations were delivered to 15 different groups of general inpatient providers throughout the hospital from April 3, 2013 through May 15, 2013. The presentations introduced the clinical guideline, showed providers how to navigate the guideline electronically, and communicated antibiotic stewardship goals and key concepts about penicillin allergy using interactive clinical vignettes. Instruction on taking an allergy history was provided, with emphasis on improved characterization

of rashes (urticaria vs delayed maculopapular rash vs severe cutaneous adverse reactions). After each presentation, laminated cards with figures from the clinical guideline were distributed to staff and posted in hospital workrooms. The full guideline was available electronically to all staff. After the initial educational rollout, additional educational sessions included training of the first-year AI and ID fellows (July 2014), noon conference with pediatrics residents (September 2014), and a case-based discussion of penicillin allergy with internal medicine residents (October 2014). Because of house staff turnover, additional annual education and training was necessary.

Study Design Overview

A quasi-experimental study was conducted to evaluate the hospital-wide clinical guideline (Figure 1) 21 months before implementation vs 12 months after implementation. Historical data before 21 months before implementation were not included because of the variable availability of penicillin skin testing reagents nationally and at MGH at that time. Use of the clinical guideline could result in (1) use of an alternative antibiotic; (2) use of a β -lactam antibiotic at its full dose; (3) use of a β -lactam antibiotic initiating therapy with a test dose; or (4) a consultation by AI and, if appropriate, penicillin skin testing/test dosing. Patients and providers who used the guideline for a test dose (option 3 or 4) were assessed. After identification of test doses through the electronic medication administration record, manual chart review of the electronic health record (EHR) was performed by a board-certified internist and allergist and immunologist (K.G.B.).

This study was approved by the institutional review board of Partners Human Research Committee. Written informed consent was obtained before skin testing.

Demographic and Clinical Characteristics

Information on the patient's age, sex, and drug allergy history was collected from the EHR. A patient's history of allergy to penicillin or cephalosporin antibiotics and the reported reaction were obtained from the EHR through a centralized allergy repository (Partners Enterprise Allergy Repository).³⁷

Primary Outcomes

Primary outcomes were the number and frequency of test doses of β -lactam antibiotics and resulting ADRs in the 2 periods. Test doses were identified using the electronic medication administration record, and EHR review was performed for confirmation. Test doses reviewed in the 2 periods included those performed with and without preceding penicillin skin testing. Total doses of β -lactam antibiotics dispensed at MGH before and after guideline implementation were determined using the pharmacy data system (Sunquest, Sunquest Information Systems, Tucson, Arizona).

Specific other data on the test dose included timing of test dose and infectious details. Test dose timing was calculated as an integer value between the date of admission and the date of test dose. Infections treated were identified by review of the admission note and discharge summary. The ID consultation notes also were reviewed, when applicable. Culture data were obtained from the microbiology record. Therapy was classified as culture-driven if there were relevant culture data prior to the date and time of test dose. Otherwise, therapy was classified as empiric.

The ADR frequency and severity were determined through EHR review. Patients discharged on the test dose antibiotic were classified as having no ADR. For patients not discharged on the antibiotic for which a test dose was performed, the EHR was reviewed for evidence of tolerance or reaction to the drug. When an ADR was suspected, the clinical team was contacted for details regarding reaction timing, symptoms, and treatment. The ADR details were



Figure 1. Penicillin allergy pathway in the hospital-wide clinical guideline for antibiotic prescription in patients with penicillin allergy. The pathway details which antibiotics can be used for patients with different penicillin allergy histories. Patient reactions are categorized as type II to IV HSR (serum sickness, Stevens–Johnson syndrome or toxic epidermal necrolysis, AIN, DRESS, hemolytic anemia) for which cross-reactivity data are limited; type I; IgE-mediated allergy (anaphylaxis, angioedema, wheezing, bronchospasm, hypotension, urticaria) or unknown reaction; mild reaction (delayed morbilliform or maculopapular eruption or electronic medical record or medical chart discrepancy with patient interview). The pathway directs the use of a limited-step graded challenge, or test dose, on the general medical floors. When the pathway advises consultation by the allergy and immunology service, penicillin skin testing is recommended before using the specified antibiotics. The complete internal guideline is available in the Supplementary Text. AIN, acute interstitial nephritis; DRESS, drug rash eosinophilia and systemic symptoms; EMR, electronic medical record; HSR, hypersensitivity reaction; ID, infectious diseases; IgE, immunoglobulin E; PCN, penicillin.

reviewed independently and graded by 2 allergists (K.G.B. and A.B.) according to previously used grading scales.^{33,38}

Secondary Outcomes

Secondary outcomes included the use of consultation services by AI and ID, change in antimicrobial therapy resulting from test doses after guideline implementation, and general usability and adherence to the guideline.

Consultation services were determined by the presence or absence of a consultation note by AI or ID in the EHR before the date and time of the test dose. The AI notes were reviewed for indication and the results of penicillin skin testing, if applicable.

The total number of AI inpatient consultations before and after guideline implementation was determined from the AI consultation log, which included all non-chemotherapy desensitization consultations and has been maintained by 1 administrator since November 1, 2011. The total ID inpatient consultations before and after

guideline implementation were reviewed using billing data from PatientKeeper 8.1.1 (PatientKeeper Inc, Waltham, Massachusetts).

Antimicrobial therapy was determined from the electronic medication administration record by considering therapy as a prescribed course of an antibiotic (eg, drug was not written as “x1,” “STAT,” or “PRN”) on the day before the test dose and the day after the test dose. If more than 2 antimicrobials were being coadministered, then primary and secondary therapy was determined by considering drugs that typically cover gram-positive and gram-negative organisms. Cephalosporins were grouped by generation for analysis. Piperacillin plus tazobactam was considered separately because of its broad activity.

The authors documented which inpatient service ordered the test dose and the type of ordering provider (house staff, attending physician, nurse practitioner, or physician’s assistant). Guideline adherence was determined by EHR order for the test dose procedure. Test doses were determined not to adhere to the guideline if documentation was not available to support the clinical decision making.

Table 1Demographic and allergy histories of patients receiving test doses of β -lactam antibiotics before vs after guideline implementation

Variable	Before implementation, July 1, 2011–March 31, 2013 (n = 49)	After implementation, April 1, 2013–March 31, 2014 (n = 183)
Age (y), mean (SD)	58.7 (16)	59.9 (20)
Women, n (%)	27 (55)	98 (54)
Primary penicillin allergy, n (%)	43 (88)	160 (88)
Reported reaction, n (%)		
Rash	17 (35)	54 (30)
Hives	12 (25)	41 (22)
Unknown	1 (2)	28 (15)
Angioedema or swelling	5 (10)	23 (13)
Anaphylaxis	6 (12)	8 (4)
Bronchospasm or shortness of breath	2 (4)	8 (4)
Gastrointestinal upset	0 (0)	6 (3)
Itching	2 (4)	4 (2)
Patient denies history, listed in medical record	0 (0)	4 (2)
Prior evidence of tolerated penicillin	0 (0)	2 (1)
Positive test reaction	2 (4)	1 (0.5)
Fever	0 (0)	1 (0.5)
Flushing	0 (0)	1 (0.5)
Serum sickness	1 (2)	1 (0.5)
Myalgia	1 (2)	0 (0)
Primary cephalosporin allergy, n (%) ^a	12 (25)	38 (21)
Specific cephalosporin that caused reaction (generation), n (%)		
Cephalexin (first)	2 (4)	12 (7)
Cefepime (fourth)	2 (4)	7 (4)
Unknown	3 (6)	6 (3)
Cefazolin (first)	0 (0)	3 (2)
Cefaclor (second)	1 (2)	3 (2)
Ceftriaxone (third)	4 (8)	2 (1)
Cefuroxime (second)	0 (0)	2 (1)
Cefixime (third)	0 (0)	1 (0.5)
Cefadroxil (first)	0 (0)	1 (0.5)
Cefoxitin (second)	0 (0)	1 (0.5)
Reported reaction, n (%) ^b		
Rash	6 (12)	18 (10)
Hives	2 (4)	8 (4)
Angioedema or swelling	0 (0)	5 (3)
Unknown	3 (6)	4 (2)
Itching	0 (0)	4 (2)
Anaphylaxis	1 (2)	2 (1)
Gastrointestinal upset	0 (0)	2 (1)
Bronchospasm	0 (0)	1 (0.5)
Flushing	0 (0)	1 (0.5)
Mental status change	0 (0)	1 (0.5)

^aSix patients before guideline implementation and 15 patients after implementation had penicillin and cephalosporin allergy.^bRecord might contain more than 1 description or reaction of a clinical feature of drug allergy history.

Statistical Analysis

Demographic data were reported as mean with SD or median with interquartile range (IQR). The Student *t* test was used for comparison of means and Wilcoxon test for comparison of medians. The Wilcoxon rank-sum or Fisher exact test was used to compare independent groups. The McNemar test was used to compare paired binary data, such as antibiotics before and after a test dose. Two-sided *P* values less than .05 were considered significant. All statistical analyses were conducted in SAS 9.3 (SAS Institute, Cary, North Carolina).

Results

Demographic and Clinical Characteristics

Demographic characteristics of patients who received a test dose before vs after guideline implementation were similar (Table 1). Of patients with penicillin and cephalosporin allergy, the

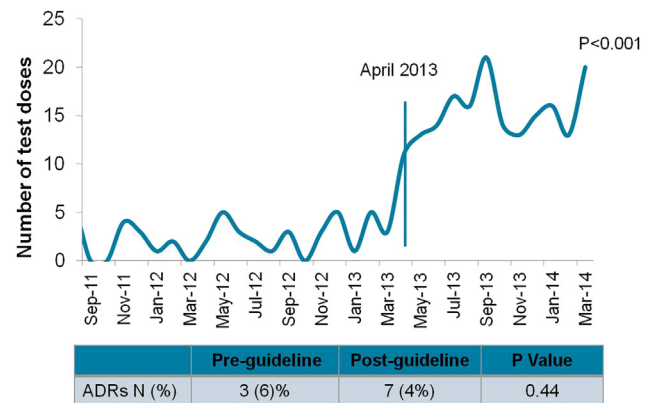


Figure 2. Impact of clinical guideline on test dose usage and adverse drug reactions (ADRs) to β -lactam antibiotics. Adoption of the clinical guideline was associated with a significant increase in test doses ($P < .001$) without a significant change in the rate of adverse drug reactions ($P = .44$).

most commonly reported reactions were rash and hives. More patients after guideline implementation had an allergy history documented as unknown compared with before implementation (15% vs 2%, $P = .013$).

Guideline Impact on Test Doses and Adverse Drug Reactions

Before guideline implementation, 49 test doses of β -lactam antibiotics were identified with a median of 2 (IQR 1–3.25, range 0–5) test doses per month (Fig 2). After implementation, 183 test doses of β -lactam antibiotics were identified, with a median of 14.5 (IQR 13–16.25, range 11–20) test doses per month. Adoption of the clinical guideline was associated with a significant increase in the number of test doses of β -lactam antibiotics after implementation ($P < .001$; Fig 2).

Before implementation, test doses were performed a median of 4 days (IQR 2–8, range 0–32) into the patient's hospitalization (Table 2). After implementation, test doses were performed a median of 2 days (IQR 1–5, range 0–44) into the patient's hospitalization, which was significantly earlier in a patient's hospitalization than test doses before implementation ($P = .002$).

A significantly smaller proportion of test doses after implementation were to penicillins compared with test doses before implementation (20% vs 57%, $P < .001$). A significantly larger proportion of test doses were to cephalosporins after vs before implementation (76% vs 33%, $P < .001$). After implementation, the most common cephalosporin test doses were to cefepime ($n = 61$, 33%), ceftriaxone ($n = 50$, 27%), and cefazolin ($n = 16$, 9%).

Among test doses before implementation ($n = 49$), 6 (12%) were performed for empiric antimicrobial treatment and 42 (86%) were performed for culture-driven antimicrobial treatment (Table 2, eTable 1). Among test doses after implementation ($n = 183$), 93 (51%) were performed for empiric antimicrobial treatment and 87 (48%) were performed for culture-driven antimicrobial treatment. Compared with test doses before implementation, test doses after implementation were used significantly more for empiric treatment ($P < .001$). The most common empiric use after implementation was for pneumonia (31%; eTable 1).

There was no significant difference in ADR rate before vs after guideline implementation (4% vs 6%, $P = .44$; Fig 2, Table 3). All 3 ADRs before implementation were determined to be immune mediated, with 2 categorized as grade 1 (cutaneous signs only) and 1 categorized as grade 2 (measurable, but not life-threatening symptoms). Treatment of these ADRs included antihistamines (100%), steroids (67%), and epinephrine (33%). The patient who received epinephrine was a 68-year-old woman with underlying

Table 2

Test doses before vs after guideline implementation

	Before implementation, July 1, 2011–March 31, 2013	After implementation, April 1, 2013–March 31, 2014	P value
Test doses, n (% β -lactam doses)	49 (0.24)	183 (0.83)	<.001
Days from admission until test dose			
Median (IQR)	4 (2–8)	2 (1–5)	.002
Test dose antibiotics, n (%)			
Penicillins	28 (57)	36 (20)	<.001
Cephalosporins	16 (33)	139 (76)	<.001
Carbapenems	5 (10)	8 (4)	.155
Infection history, n (%)			
Empiric treatment	6 (12)	93 (51)	<.001
Culture-driven treatment	42 (86)	87 (48)	
Unknown	1 (2)	3 (2)	

Abbreviation: IQR, interquartile range.

idiopathic angioedema and a history of urticaria to penicillin and ampicillin. She received a test dose of meropenem and developed immediate lip and tongue swelling with the first full dose.

After implementation, 7 ADRs were identified: 5 (71%) were determined to be immune mediated, 1 (14%) not immune mediated, and 1 (14%) unknown. Six ADRs (86%) were grade 1 and 1 (14%) was grade 2. Treatment included antihistamines (100%) and steroids (29%). No patients experienced an ADR requiring epinephrine after guideline implementation. ADR severity and treatment did not differ significantly before vs after guideline implementation (Table 3).

Guideline's Impact on Consultation Services

Before implementation, all patients were consulted by AI as required by the policy at that time compared with 25 of 183 patients (14%) after guideline implementation ($P < .001$). When AI was consulted, penicillin skin testing was indicated in a larger proportion of patients after vs before guideline implementation (76% vs 55%, $P = .084$). Overall hospital consultations for AI did not significantly change due to guideline implementation (median AI consultations per month, 19 [IQR 18–20] before implementation vs 16 [IQR 13–18.50] after implementation, $P = .141$).

Before implementation, 41 of 49 patients (91%) were consulted by ID compared with 87 of 183 (49%, $P < .001$) after implementation. Overall, median monthly ID consultations showed a nonsignificant increase from 354 (IQR 332–396) to 373 (IQR 358–417) after guideline adoption ($P = .21$).

Guideline's Impact on Antimicrobial Therapy

Test doses after guideline implementation resulted in significantly more patients on penicillins (19% vs 2%, $P < .001$) and cephalosporins of the first (10% vs 0.6%, $P < .001$), third (30% vs 5%, $P < .001$), and fourth (32% vs 7%, $P < .001$) generations (Table 4). Of patients switched to a penicillin ($n = 33$), 79% had primary penicillin allergy. After the test dose, significantly fewer patients were on vancomycin (37% vs 68%, $P < .001$), aminoglycosides (1% vs 6%, $P = .004$), aztreonam (0.6% vs 12%, $P < .001$), and fluoroquinolones (3% vs 15%, $P < .001$).

Guideline Usage and Appropriateness

After implementation, test doses according to the guideline were largely ordered by clinicians in internal medicine and its specialties ($n = 125$, 68%), with the largest groups being general internal medicine ($n = 99$, 54%), oncology ($n = 19$, 10%), and cardiology ($n = 7$, 4%). Surgical specialties performed 43 (24%) test

Table 3

Adverse drug reactions before vs after guideline implementation

	Before implementation, July 1, 2011–March 31, 2013	After implementation, April 1, 2013–March 31, 2014	P value
Adverse drug reactions, n (%)	3 (6)	7 (4)	.44
Classification of reaction, n (%)			
Immune mediated	3 (100)	5 (71)	>.5
Not immune mediated	0 (0)	1 (14)	
Unknown or unclear	0 (0)	1 (14)	
Timing of reaction, n (%)			
Immediate	2 (67)	6 (86)	>.5
Delayed	1 (33)	1 (14)	
Grading of reaction, n (%) ^a			
Grade 1	2 (67)	6 (86)	>.5
Grade 2	1 (33)	1 (14)	
Grade 3	0 (0)	0 (0)	
Grade 4	0 (0)	0 (0)	
Treatment, n (%)			
Antihistamines	3 (100)	7 (100)	.44
Corticosteroids	2 (67)	2 (29)	.154
Epinephrine	1 (33)	0 (0)	.21

^aGrade 1, presence of cutaneous signs; grade 2, presence of measurable but non-life-threatening symptoms, including angioedema, arterial hypotension, cough, or difficulty in mechanical ventilation; grade 3, presence of life-threatening reactions, including cardiovascular collapse, tachycardia or bradycardia, arrhythmias, or severe bronchospasm; grade 4, circulatory failure, cardiac arrest, or respiratory arrest.^{33,38}

doses, including general surgery ($n = 38$, 21%), oral and maxillo-facial surgery ($n = 3$, 2%), and urology ($n = 2$, 1%). The provider ordering the test dose was most commonly a house officer ($n = 131$, 72%). Other providers ordering test doses included nurse practitioners ($n = 24$, 13%), attending hospitalist physicians ($n = 24$, 13%), and physician assistants ($n = 4$, 2%).

Overall, 167 of 183 (91%) test doses were determined to adhere to the clinical guideline; nonadherent test doses did not follow the appropriate recommendations for a given allergy history or the clinician failed to document the allergy history. None of the non-adherent test doses resulted in an ADR.

Discussion

Implementation of a novel clinical guideline for prescribing antibiotics to patients with a history of penicillin or cephalosporin allergy that used a standardized 2-step test dose procedure was temporally associated with a significant (>7-fold) increase in the number of test doses of β -lactam antibiotics, without an increase in ADR frequency, type, or severity. Compared with test doses before implementation, test doses after implementation occurred earlier in the patients' hospitalization and increasingly for empiric therapy. Furthermore, the guideline-driven test doses were performed by all types of inpatient providers without increasing subspecialty consultations by AI or ID. Test doses after implementation helped improve antimicrobial management, resulting in less vancomycin, aminoglycoside, aztreonam, and fluoroquinolone use. To the authors' knowledge, this report is the first to describe a successful hospital-wide clinical guideline for general inpatient providers to guide β -lactam antibiotic use for infectious treatment of inpatients with a history of penicillin or cephalosporin allergy.

Although there have been advances in the understanding of allergy to β -lactam antibiotics, understanding drug and penicillin allergy remains challenging for inpatient providers and allergists alike.^{29,39–41} General inpatient providers have limited education and knowledge about drug and penicillin allergy but are interested in tools to help them safely and appropriately care for patients with β -lactam allergies.⁴⁰ Existing clinical guides and tools do not account for the specific generation or side chain of the cephalosporin

Table 4

Test doses improved antimicrobial therapy after guideline adoption (n = 183)

Antibiotic or class of antibiotic, n (%)	Before test dose	After test dose	P value ^a
Penicillins ^b	3 (2)	35 (19)	<.001
Piperacillin–tazobactam	4 (2)	2 (1)	>.5
Cephalosporins ^c			
First generation	1 (0.6)	18 (10)	<.001
Third generation	9 (5)	54 (30)	<.001
Fourth generation	12 (7)	58 (32)	<.001
Aztreonam	21 (12)	1 (0.6)	<.001
Carbapenems	18 (10)	11 (6)	.21
Clindamycin	3 (2)	2 (1)	>.5
Daptomycin	2 (1)	2 (1)	>.5
Fluoroquinolone	28 (15)	6 (3)	<.001
Gentamycin	11 (6)	2 (1)	.004
Linezolid	7 (4)	4 (2)	.45
Vancomycin	125 (68)	68 (37)	<.001

^aBy McNemar test.^bOther than piperacillin plus tazobactam, which was considered separately owing to its broad coverage.^cNo patients were treated with second-generation cephalosporins.

or they define the need for penicillin skin testing based solely on skin testing availability.^{1,30} The authors used a clinical guideline that advised general inpatient providers on how to take an allergy history and used the type of hypersensitivity reaction the patient experienced to prescribe antibiotics to patients with allergies to penicillin or cephalosporins. The guideline, and associated educational sessions, changed prescribing practice, with 183 test doses of β -lactam antibiotics performed on inpatients in 1 year by providers from all specialties and types of training. The test doses performed were as safe as those previously guided by AI specialists before guideline implementation, and more than 90% of test doses could be verified to have followed the guideline. Although the test doses that did not adhere to guideline did not result in an ADR, these were considered “near misses” and informed future educational sessions to improve patient safety.

Despite the common reporting of penicillin allergy by inpatients and the recognized need to perform antimicrobial stewardship,^{42–44} few studies have proposed generalizable inpatient solutions to this problem, and those that have used routine penicillin skin testing.^{4,11,45,46} Past studies found that penicillin skin testing can decrease use of broad-spectrum antibiotics and potentially decrease the cost of therapy.^{4,20,46} However, among inpatients, the shift in antimicrobial therapy realized was predominantly toward the use of later-generation cephalosporins,⁴ which are safe for use by test dose without preceding skin testing, even in confirmed IgE-mediated penicillin allergy.^{25,26,31,32} A similar increase in later-generation cephalosporins was observed, with the guideline often used to treat penicillin-allergic patients with ceftriaxone or cefepime by test dose, without preceding penicillin skin testing or AI consultation. This could reflect the choice of standard antibiotic regimens for common infections, such as later-generation cephalosporins in the treatment of pneumonia, which was the most common infection treated empirically after guideline implementation. Alternatively, after guideline implementation, patients had significantly more “unknown” allergy histories, which presented providers with the option of directly using a third- or fourth-generation cephalosporin with a test dose.

By implementing a guideline that considers allergy history in addition to the desired antibiotic treatment, the authors targeted hospital resources, such as use of procedures and consultations, appropriately. Because the negative predictive value of a penicillin skin test is not 100%, even after a negative penicillin skin test result, patients should receive a penicillin or amoxicillin test dose challenge under observation to fully assess the drug allergy.^{1,22,30} Because the guideline ADR rate was similar to the rate in the AI

literature after skin testing,^{4,6,7,21,22} implementation of the guideline could have saved 164 inpatient penicillin skin tests without incurring any additional costs. The cost of 164 skin tests performed by AI, using Medicare reimbursement, would total approximately US \$60,000 in 2014 (testing \$35,793.00, AI consultations \$23,914.48). In addition, test doses after guideline implementation were performed in the hospital approximately 2 days earlier than before implementation, allowing for more expeditious antibiotic narrowing or delivery of appropriate therapy, which could have affected another cost difference, namely length of stay. However, the present analysis was limited to this specific inpatient admission and does not account for the subsequent benefits of a negative penicillin skin test result, including improved prescription for all subsequent hospital admissions and outpatient encounters.

Limitations of the study include the inability to control for confounders. Thus, the authors cannot establish a causal relation between the guideline implementation and the reported outcomes. However, to improve the study design, multiple measurements from before the intervention were included and hospital trends, such as overall β -lactam antibiotic usage and hospital-wide AI and ID consultations, were examined. Although almost 200 test doses after guideline implementation were evaluated, more data are needed to conclusively prove the guideline’s safety, particularly with regard to penicillin test doses administered to patients reporting penicillin allergy without preceding skin testing. Another limitation was the ability to track only when the guideline was used for performing a test dose. The authors could not know how often the guideline directed providers to choose an alternative drug or full-dose antibiotic. This report describes the experience of a single tertiary care referral center in Boston, Massachusetts with availability of AI consultation and penicillin skin testing. The experience and resources at this institution might not be similar to those at other institutions. However, the guideline could be tailored to hospitals with different resources using outpatient allergy referrals at patient discharge.

This report describes the successful adoption and results of a novel and targeted approach to inpatients with penicillin and cephalosporin allergy. The guideline changed practice through the safe use of test doses. Importantly, in this era of antimicrobial resistance, test doses narrowed therapy in a patient population at risk for health care-associated infections.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2015.05.011>.

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eMethods

Evidence Supporting the Guideline Structure and the Complete Guideline Used at the Massachusetts General Hospital since April, 2013

Crucial evidence to support the penicillin pathway structure includes the type of allergy or hypersensitivity reaction (HSR)¹ that can inform which drugs should be avoided, used with a test dose, or used with a full dose. The algorithm begins with patient-friendly language to help a provider take an allergy history. For example, instead of asking about “angioedema,” the provider asks whether there is “swelling of the tongue, mouth, lips, or eyes.” Providers ultimately need to assign the patient’s reaction into 1 of 3 broad reaction categories.

On the far left, all type II to IV HSRs are included, with the exception of delayed maculopapular rash. These HSRs are uncommon and predominantly include organ involvement or severe cutaneous signs, such as mucosal lesions or skin desquamation. For patients with a penicillin reaction included in this group, using alternative agents is suggested because of very limited data on rechallenge and cross-reactivity. However, if there is a compelling infectious indication for use of a penicillin or cephalosporin drug, consultation by AI and ID is advised because there are some circumstances in which benefits might outweigh risks, as supported by limited safety data.^{2,3}

The middle category includes patients with a history of reactions that might be mediated by IgE or type I HSRs, such as anaphylaxis, hypotension, bronchospasm, angioedema, and urticaria. Unknown reactions are included here—as long as there are no warning signs of a severe type II to IV HSR—to be cautious. In the authors’ experience, even for unknown reactions, patients can determine whether there are warning signs of a severe cutaneous adverse reaction or organ involvement. For these patients, the authors advise test doses to third- or fourth-generation cephalosporins, allow for the use of alternative agents or aztreonam, and advise consultation by the AI service—because of the need for skin testing—for use of a penicillin or first- or second-generation cephalosporin.⁴

The category on the far right includes minor reactions and mild cutaneous reactions, such as the common maculopapular rash. For these patients, the authors recommend the use of a third- or fourth-generation cephalosporin or carbapenems by full dose or a penicillin or first- or second-generation cephalosporin by test dose. Maculopapular rash is included here because of cross-reactivity data in vitro and in vivo^{5–7}; providers are encouraged to assume a rash is urticaria if the allergy history cannot determine whether the rash is a delayed, maculopapular rash. Also included in this category are medical record discrepancies with patient history. When considering patients with mild reactions to penicillin, the authors determined these patients would be at low risk for a test dose to a penicillin or first- or second-generation cephalosporin. Although prior data suggest that approximately one third of patients with vague allergy histories can exhibit a positive skin test reaction to penicillin, penicillin skin testing has a variable and imperfect positive predictive value (eg, there is a possibility of false-positive results) and there are strong data supporting that true penicillin allergy among inpatients is rare.^{4,8–11}

In the penicillin allergy pathway, cephalosporins are grouped by generation in the guideline—rather than by similar vs dissimilar side chains (R groups)—for ease of use for the general inpatient provider. Although there have been emerging data supporting the safety of most cephalosporins, including first- and second-generation cephalosporins, in patients reporting penicillin allergy,^{12–18} retrospective studies could be subject to selection bias that limits their applicability in a prospective, hospital-wide guideline for all reported penicillin-allergic patients with allergy histories ranging from mild to severe.

The pathway for cephalosporin allergy is similar to the penicillin allergy pathway but uses side-chain similarity for cross-reactivity.^{15–18}

Supplementary References

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eTable 1Types of infections in patients receiving test doses to β -lactam antibiotics before vs after guideline implementation

	Before implementation, July 1, 2011–March 31, 2013 (n = 49)	After implementation, April 1, 2013–March 31, 2014 (n = 183)
Empiric treatment, n (%)	6 (12)	93 (51)
Pneumonia	1 (17)	29 (31)
Fever	1 (17)	19 (20)
Cellulitis	2 (33)	12 (13)
Sepsis	1 (17)	7 (8)
UTI	0 (0)	5 (5)
Intraabdominal infection	0 (0)	5 (5)
Bone or joint infection	1 (17)	5 (5)
Meningitis or encephalitis	0 (0)	4 (4)
Wound infection	0 (0)	4 (4)
Abscess	0 (0)	2 (2)
STD	0 (0)	1 (1)
Tick-borne illness	0 (0)	1 (1)
Sinusitis	0 (0)	1 (1)
Culture-driven treatment, n (%)	42 (86)	87 (48)
Bacteremia	12 (29)	24 (28)
Pneumonia	4 (10)	14 (16)
UTI	3 (7)	14 (16)
Bone or joint infection	9 (21)	13 (15)
Wound infection	2 (5)	9 (10)
Intraabdominal infection	3 (7)	5 (6)
Cellulitis	1 (2)	4 (5)
Endocarditis	6 (14)	2 (2)
Tick-borne illness	0 (0)	1 (1)
Sexually transmitted disease	2 (5)	1 (1)
Meningitis or encephalitis	1 (2)	0 (0)
Unknown, n (%)	1 (2)	3 (2)

Abbreviations: STD, sexually transmitted disease; UTI, urinary tract infection.