

Association of β -Lactam Allergy Documentation and Prophylactic Antibiotic Use in Surgery: A National Cross-Sectional Study of Hospitalized Patients

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Alternative antibiotics for surgical prophylaxis are associated with increased adverse events and surgical site infection compared to cefazolin. In a sample of perioperative inpatients from 100 hospitals in the United States, cefazolin was 9-fold less likely to be used in patients with a documented β -lactam allergy whereas clindamycin was 45-fold more likely.

Keywords. β -lactam; antibiotic; allergy; surgical prophylaxis.

Surgical site infection (SSI) is the most common adverse event affecting hospitalized surgical patients. Along with increased healthcare costs, prolonged hospital length of stay, and higher rates of hospital readmission, SSI is associated with substantial patient morbidity and mortality [1]. One of the primary strategies to prevent SSI is the perioperative administration of antibiotics. For the majority of surgical procedures, cefazolin, a first-generation cephalosporin, is preferred due to its ideal spectrum of activity, favorable pharmacokinetic and safety profiles, and proven efficacy [2].

However, approximately 10% of patients have a reported penicillin allergy and 2% have a reported cephalosporin allergy [3]. Although evidence suggests that >95% of those reporting a penicillin allergy do not have a true immunoglobulin E (IgE)-mediated allergy and that the cross-reactivity between penicillins and cefazolin is <2% due to its unique side chain [4], patients with reported β -lactam allergies will frequently receive alternative perioperative antibiotics [5]. In the setting of a confirmed β -lactam allergy, alternative agents such as vancomycin, clindamycin, gentamicin, a fluoroquinolone, or aztreonam are recommended [2]. In addition to an increased observed risk of antibiotic-related adverse events, β -lactam alternative perioperative antibiotics are associated with a 50% increased risk of developing an SSI [5].

The objective of this study was to evaluate the impact of a documented β -lactam allergy on perioperative antibiotic selection in a national sample of surgical inpatients.

METHODS

We performed a national cross-sectional study of hospitalized patients through the Acute Care Hospital Group of Vizient, Inc. A designee from the Vizient member hospitals completed an intake survey that included hospital details (eg, type of hospital, antibiotic stewardship team presence) and β -lactam allergy assessment resources (eg, access to inpatient allergy consultations, access to penicillin skin testing). The Definitive Healthcare database was used to determine geographic location, hospital location, and number of staffed beds for participating hospitals.

Participating sites then submitted de-identified clinical details for inpatients treated with any antibiotic on one day within the study period. Patient data were entered by employees who had access to patient electronic health record (EHR) and antibiotic utilization data as part of their professional duties (eg, clinical pharmacist). Patient clinical details included age, sex, race, and inpatient location. Penicillin and cephalosporin allergy histories were identified from the EHR allergy module. Colonization or infection with methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* was recorded using microbiology, "flags," and problem list data. The antibiotic indication considered in this study was surgical prophylaxis, identified by EHR review.

Statistical Analysis

The exposure of interest was a documented β -lactam allergy, defined as a documented penicillin or cephalosporin allergy in the EHR, regardless of reaction. The primary outcome was antibiotic use, considering antibiotics typically prescribed for surgical prophylaxis—cefazolin, vancomycin, fluoroquinolones,

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clindamycin, and gentamicin—and received or pending administration on the assessment day.

We examined the relation of documented β -lactam allergy to antibiotic use using generalized estimating equation models with logit link to account for clusters of patients within hospitals. In the multivariable models, we included age, sex, hospital day, number of staffed beds, geographic location, and diabetes.

We report odds ratios (ORs) with 95% confidence intervals (CIs). All P values were 2-sided with $P < .05$ considered statistically significant. Statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

There were 1632 surgical patients from 100 United States (US) hospitals included in the study (Supplementary Figure 1). All 4 US census geographic regions were represented, and most hospitals were in an urban setting (87%). Hospitals were largely short-term acute care hospitals (92%). Thirty-nine (39%) were academic medical centers. Mean number of staffed beds was 374 (standard deviation, 286). Inpatient allergy consultations were available at 37 (37%) hospitals, and inpatient penicillin skin testing was available at 29 (29%). Almost all hospitals (96%) had a formalized antibiotic stewardship program.

Of 1632 patients receiving antibiotics for surgical prophylaxis, 256 (16%) had a documented β -lactam allergy with 224 (88%) having a documented allergy to penicillin and 48 (19%) to cephalosporins. Hospital and patient characteristics

were not meaningfully different by β -lactam allergy status (Supplementary Table 1).

Cefazolin was less frequently used in patients reporting a β -lactam allergy compared to patients not reporting one (28% vs 77%; Table 1). We identified specific alternative antibiotics used more frequently in patients with a documented β -lactam allergy: vancomycin (24% vs 11%), fluoroquinolones (6% vs 2%), clindamycin (32% vs 1%), and gentamicin (11% vs 3%).

In the fully adjusted multivariable regression model, patients with a documented β -lactam allergy had lower odds of cefazolin use (adjusted OR [aOR], 0.11 [95% CI, .08–.15]) compared to those without a documented β -lactam allergy. Patients with a documented β -lactam allergy had high odds of receiving perioperative clindamycin (aOR, 45.6 [95% CI, 24.8–83.4]). They also had increased odds of receiving gentamicin (aOR, 3.90 [95% CI, 2.36–6.42]), fluoroquinolones (aOR, 3.11 [95% CI, 1.66–5.84]), and vancomycin (aOR, 2.91 [95% CI, 2.05–4.13]).

DISCUSSION

In this analysis of a national cross-sectional study of >1600 hospitalized patients receiving antibiotics for surgical prophylaxis from 100 US hospitals, patients with a documented β -lactam allergy had 9-fold lower odds of receiving first-line cefazolin and higher odds of receiving a non- β -lactam antibiotic perioperatively, including clindamycin (45-fold increased odds) and gentamicin, a fluoroquinolone, or vancomycin (~3- to 4-fold increased odds). We observed a similar prevalence of

Table 1. Antibiotic Use Among Patients With a Documented β -Lactam Allergy Compared to No Documented β -Lactam Allergy (Surgical Prophylaxis Only, N = 1632)

Antibiotic	Documented β -Lactam Allergy (n = 256)	No Documented β -Lactam Allergy (n = 1376)	Unadjusted OR (95% CI) ^a	Adjusted OR (95% CI) ^a
β-lactams				
Cefazolin	72 (28)	1064 (77)	0.11 (.08–.16)	0.11 (.08–.15)
Cephalosporins, second generation ^b	13 (5)	45 (3)	...	...
Cephalosporins, third generation ^c	5 (2)	34 (2)	...	...
Cefepime	2 (1)	4 (<1)	...	...
Other	8 (3) ^d	125 (9) ^e	...	...
β-lactam alternatives				
Clindamycin	82 (32)	15 (1)	42.8 (23.4–78.0)	45.6 (24.8–83.4)
Vancomycin	61 (24)	146 (11)	2.64 (1.88–3.69)	2.91 (2.05–4.13)
Gentamicin	27 (11)	39 (3)	4.04 (2.42–6.76)	3.90 (2.36–6.42)
Fluoroquinolones	16 (6)	30 (2)	2.99 (1.57–5.71)	3.11 (1.66–5.84)
Other	28 (11) ^f	140 (10) ^g	...	...

Abbreviations: CI, confidence interval; OR, odds ratio.

^aOdds ratios compare documented β -lactam allergy to no documented β -lactam allergy and are adjusted for age, sex, hospital day, number of staffed beds, geographic location, and diabetes. All $P < .001$.

^bSecond-generation cephalosporins included cefotetan, cefoxitin, and cefuroxime.

^cThird-generation cephalosporins included cefotaxime, ceftazidime, and ceftriaxone.

^dOther included amoxicillin (n = 2), amoxicillin-clavulanate (n = 1), cephalixin (n = 3), piperacillin-tazobactam (n = 2).

^eOther included amoxicillin (n = 4), amoxicillin-clavulanate (n = 8), ampicillin (n = 15), ampicillin-sulbactam (n = 42), ceftazidime-avibactam (n = 1), cephalixin (n = 24), penicillin G (n = 5), piperacillin-tazobactam (n = 26).

^fOther included azithromycin (n = 7), aztreonam (n = 3), doxycycline (n = 6), ertapenem (n = 1), metronidazole (n = 9), tigecycline (n = 1), and tobramycin (n = 1).

^gOther included azithromycin (n = 38), aztreonam (n = 1), clarithromycin (n = 1), dalbavancin (n = 1), daptomycin (n = 1), doxycycline (n = 17), ertapenem (n = 4), erythromycin (n = 2), linezolid (n = 1), meropenem (n = 2), metronidazole (n = 46), minocycline (n = 1), nitrofurantoin (n = 1), polymyxin B (n = 4), sulfamethoxazole-trimethoprim (n = 16), and tobramycin (n = 4).

documented penicillin (~14%) and cephalosporin (~3%) allergies in surgical inpatients as reported elsewhere [3].

The alternative antibiotics we identified as most frequently used for surgical prophylaxis in patients with a documented β -lactam allergy are associated with numerous risks including antibiotic-related adverse reactions and lower efficacy [3, 5]. Although vancomycin has broad gram-positive coverage, vancomycin is less effective at preventing methicillin-susceptible *Staphylococcus aureus* infections compared to cefazolin [3]. Additionally, the risk of vancomycin- and gentamicin-associated nephrotoxicity has been reported in patients receiving only a few doses of these antibiotics for surgical prophylaxis [6]. Since postoperative acute kidney injury is associated with increased morbidity and mortality [7], the use of these alternative agents for surgical prophylaxis should be reserved for patients truly at risk for an IgE-mediated reaction to cefazolin.

Clindamycin was the most frequently used alternative in patients with a documented β -lactam allergy. Inducible clindamycin resistance to *Staphylococcus aureus* is increasing, which potentially decreases its efficacy against this common SSI pathogen [8]. Clindamycin also carries a US Food and Drug Administration black box warning and has been associated with a nearly 3-fold increased risk of *Clostridioides difficile* infection (CDI) compared to other antibiotics, whereas penicillins and narrow-spectrum cephalosporins like cefazolin have the lowest association with CDI [6]. As even single doses of antibiotics used for surgical prophylaxis have been associated with an increased risk of CDI, appropriately evaluating β -lactam allergies to reduce unnecessary clindamycin exposure in surgical patients is essential to mitigate the threat in this population.

Our study findings highlight the importance of β -lactam allergy evaluations to routine preoperative care to ensure administration of the safest and most efficacious perioperative antibiotics. There were roughly 29 million ambulatory surgeries performed in the US in 2010, and with approximately 10% of US patients reporting a penicillin allergy, an estimated 3 million preoperative patients per year could benefit from a targeted approach to evaluate β -lactam allergies [3, 9]. Resources such as a drug allergy history tool or allergy specialist assessment [10] can improve first-line cefazolin prophylaxis [11]. One recent estimate suggests that preoperative penicillin allergy testing can increase cefazolin use from 38% to 92% (27-fold increased odds) [10]. Since allergy assessment access may be limited for inpatients, as it was in this study with only 37% of participating sites with access to inpatient allergy consultations and 29% with access to penicillin skin testing, alternative approaches may include clinical decision support tools [11] or allergy telemedicine [12].

A key limitation of this study was that our collected data were cross-sectional and retrospective. Cross-sectional data permitted us to assess antibiotics administered or ordered on 1 day only, without consideration of timing, dose, or duration of the antibiotic(s), all of which are additionally important to

safety and efficacy of SSI reduction [5]. Additionally, antibiotic appropriateness was not assessed as the type of surgical procedure was not specifically captured, nor were site-specific data on antimicrobial resistance profiles. While 95% of participating hospitals had formalized antibiotic stewardship programs, the involvement of the antimicrobial stewardship team in guiding antibiotic selection for surgical prophylaxis was unknown. This may have overstated the apparent use of alternative agents, which may have actually been first-line for some patients depending on procedure type and institution-specific guidelines. Although clinical data were entered by hospital employees retrospectively, data collection was standardized with a data entry guide, and misclassification was reduced through reliance on electronically captured data with clearly defined exposures and outcomes.

In summary, we present a large multisite US study evaluating the impact of a documented β -lactam allergy on antimicrobial selection for surgical prophylaxis. Patients with a documented β -lactam allergy of any type had significantly reduced odds of receiving the most commonly indicated perioperative antibiotic, cefazolin, and had higher odds of receiving an alternative, less effective, and potentially more toxic non- β -lactam antibiotic, especially clindamycin. This study highlights the importance of preoperative antibiotic allergy assessments to optimize selection of perioperative antibiotics for surgical prophylaxis.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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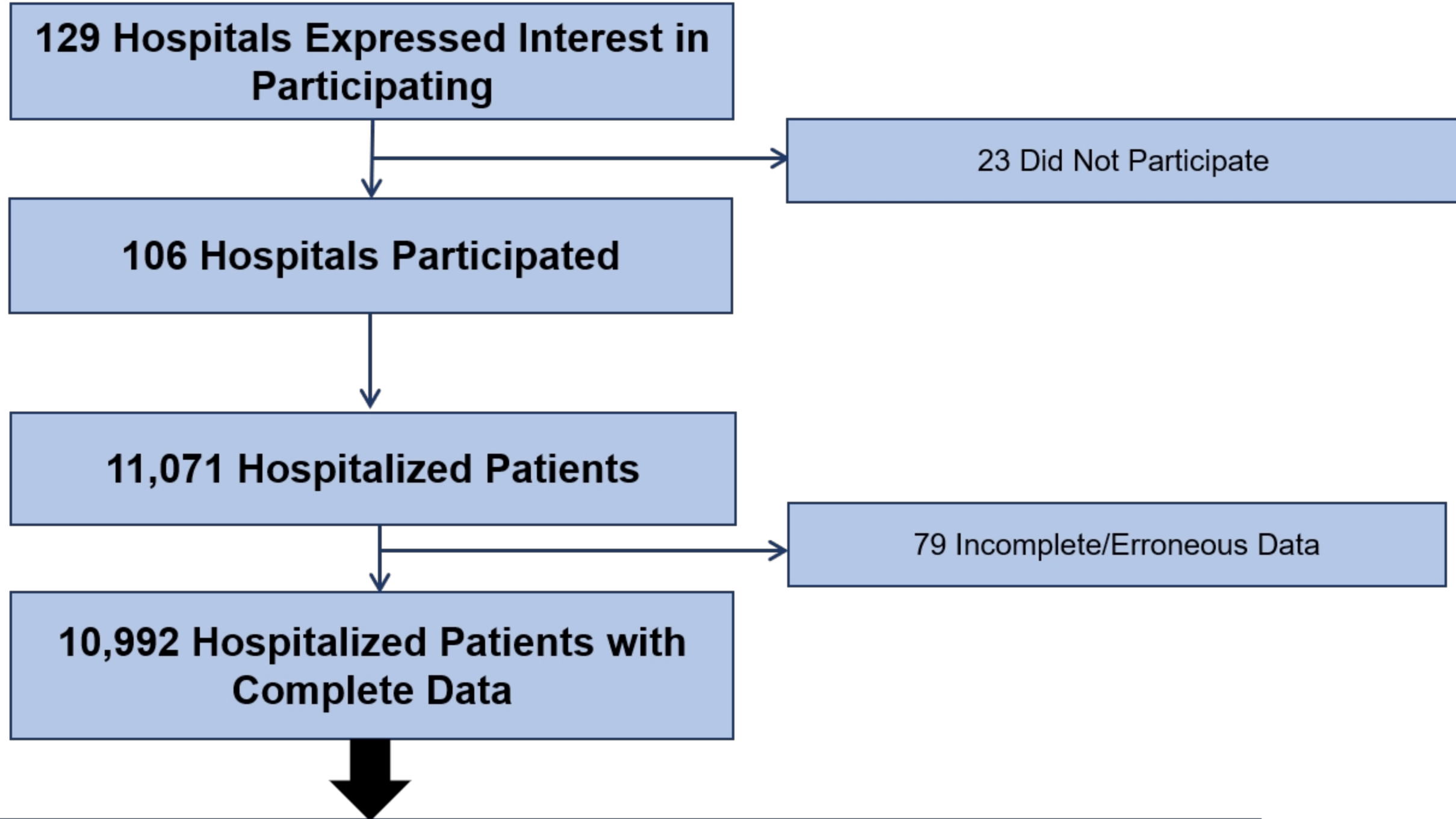
Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH), the American Academy of Allergy, Asthma and Immunology (AAAAI) Foundation, or the Massachusetts General Hospital (MGH). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. No funding for this study was received from Vizient, Inc.

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Geographic Location: Midwest 48 (48%); South 25 (25%); Northeast 16 (16%); West 11 (11%)

Urban Setting: 87 (87%)

Hospital type: Short Term Acute Care 92 (92%), Critical Access Hospital 3 (3%), Rehabilitation Hospital 3 (3%), Children’s Hospital 2 (2%)

Academic Medical Center: 39 (39%)

Mean Staffed Beds: 374 (Standard Deviation 286)

Inpatient Allergy Consultation Access: 37 (37%)

Inpatient Penicillin Skin Testing Access: 29 (29%)

Formal Antibiotic Stewardship Program: 96 (96%); with allergist 4 (4%)

Association of beta-lactam allergy documentation and prophylactic antibiotic use in surgery: A national cross-sectional study of hospitalized patients

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Supplementary Figure Legend

Supplementary Figure 1. Participating sites and patients

Supplementary Figure 1 legend. Of 129 hospitals who expressed interest in participating in this study, 106 hospitals (82%) ultimately submitted their hospital characteristics and cross-sectional patient data on 11,071 inpatients on antibiotics. After excluding 79 incomplete/erroneous patient entries (e.g., nonsensical ages or dates), and restricting patients to only those on antibiotics for surgical prophylaxis, the dataset included 1,632 hospitalized patients on antibiotics for surgical prophylaxis from 100 US hospitals.

Supplemental Table 1. Patient and Hospital Characteristics

	Documented Beta- Lactam Allergy* (n =256)	No Documented Beta- Lactam Allergy (n = 1,376)
Hospital Characteristics		
Geographic Location		
Midwest	131 (51)	710 (52)
Northeast	55 (21)	286 (21)
South	51 (20)	297 (22)
West	19 (7)	83 (6)
Urban Setting	231 (90)	1,252 (91)
Bed Size		
< 100	13 (5)	72 (5)
100-399	93 (36)	480 (35)
≥ 400	150 (59)	824 (60)
Hospital Type		
Short Term Acute Care	246 (96)	1,342 (98)
Children's	7 (3)	18 (1)
Rehabilitation	1 (<1)	11 (1)
Critical Access	2 (1)	5 (<1)
Academic Medical Center	153 (60)	747 (54)
Number of Staffed Beds (Mean, SD)	487 ± 316	499 ± 314
Inpatient Allergy Consultation Access	139 (54)	694 (50)
Inpatient Penicillin Skin Testing Access	139 (54)	694 (50)
Formal Antibiotic Stewardship Program	254 (99)	1,369 (99)
Allergist Part of Antibiotic Stewardship Program	14 (5)	75 (5)
Patient Characteristics		
Age (Mean, SD)	57 ± 18	57 ± 18
Female	162 (63)	661 (48)
Race		
White	184 (72)	979 (71)
Black	37 (14)	187 (14)
Asian	3 (1)	27 (2)
Other	32 (13)	183 (13)
Inpatient Location		
General Medical Floor	38 (15)	176 (13)
General Surgery Floor	109 (43)	545 (40)
Adult ICU	27 (11)	163 (12)
Cardiology/Telemetry	12 (5)	89 (6)
Oncology	4 (2)	27 (2)

Pediatric Floor	2 (1)	15 (1)
Pediatrics or Neonatal ICU	1 (<1)	18 (1)
Other	24 (9)	187 (14)
Renal Disease	33 (13)	144 (10)
Diabetes	57 (22)	254 (18)
MRSA Colonization/Infection	9 (4)	38 (3)
VRE Colonization/Infection	2 (1)	16 (1)
Hospital Day (Median, IQR)	1 [1, 2]	1 [1, 2]

Abbreviations: SD, standard deviation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*;

VRE, vancomycin resistant *Enterococcus*.

*224 patients (88%) with a penicillin allergy and 48 (19%) with a cephalosporin allergy.
