

Impact of Reported β -Lactam Allergy on Management of Methicillin-Sensitive *Staphylococcus aureus* Bloodstream Infections

Journal of Pharmacy Practice
1-6
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DOI: 10.1177/0897190019841737
journals.sagepub.com/home/jpp


Michael P. Veve, PharmD^{1,2,*}, Spenser E. January, PharmD^{1,**},
Rachel M. Kenney, PharmD¹, Edward M. Zoratti, MD¹,
Marcus J. Zervos, MD¹, and Susan L. Davis, PharmD^{1,2}

Abstract

Background: Antistaphylococcal β -lactams antibiotics are the preferred treatment for methicillin-sensitive *Staphylococcus aureus* (MSSA) infections. Patient-reported β -lactam allergies may complicate antibiotic decision-making and delay optimal therapy, with potential implications on patient outcomes. **Objective:** To determine the impact of reported β -lactam allergies on the receipt of optimal therapy and outcomes for MSSA bloodstream infections (BSI). **Methods:** Retrospective, matched cohort of MSSA BSI patients with and without a reported β -lactam allergy. The primary end point was receipt of optimal therapy, defined as an antistaphylococcal β -lactam. **Results:** Two hundred twelve patients were included: 53 with reported β -lactam allergy and 159 without β -lactam allergy. Commonly reported β -lactam allergies were 26 (49%) immune-mediated reaction and 8 (15%) intolerance, with 19 (36%) having no documented reaction. Optimal antibiotics were given to 135 patients without a β -lactam allergy and 37 patients with a reported β -lactam allergy (85% vs 70%, $P = .015$). Among reported β -lactam allergy patients, those without a documented reaction were less likely to receive optimal therapy (47% vs 79%, $P = .042$). Reported β -lactam allergy was not associated with clinical response ($P = .61$) or MSSA-related mortality ($P = .83$). When adjusting for immunosuppression, variables independently associated with optimal therapy were β -lactam allergy (adjusted odds ratio [adjOR], 0.3; 95% confidence interval [CI], 0.1-0.6) and infectious diseases consultation (adjOR, 6.1; 95%CI, 2.7-13.9). Optimal antibiotic use was associated with decreased all-cause 90-day mortality (adjOR, 0.23; 95%CI, 0.09-0.54). **Conclusions:** Patients with reported β -lactam allergies, particularly those without a documented reaction, were less likely to receive optimal antibiotics for MSSA BSI. Patient outcomes may be improved with enhanced quality of allergy history and routine infectious disease consultation.

Keywords

methicillin-sensitive *Staphylococcus aureus* bloodstream infections, *Staphylococcus aureus*, beta-lactam allergy, antimicrobial stewardship

Introduction

Methicillin-sensitive *Staphylococcus aureus* (MSSA) bloodstream infections (BSI) carry significant disease burden, with an estimated contributable mortality of 23.7% and median direct medical cost of US\$11 558 per event.¹⁻⁴ Use of antistaphylococcal β -lactam antibiotics in the treatment of MSSA infections has demonstrated improved survival when compared to vancomycin, and cefazolin or nafcillin/oxacillin is considered optimal therapy in these scenarios.^{5,6} This mechanism is thought to be due to differences in host viability, microbial pathogenicity, and superior potency of anti-staphylococcal β -lactams against MSSA.⁷ The over-reporting of false β -lactam allergies leads to a prolonged time to receiving β -lactam antibiotics and may potentiate poor outcomes in patients with MSSA BSI.⁶⁻⁸ Nonsevere or falsely reported β -lactam allergies

represent an important barrier to receiving optimal therapy for MSSA BSI, but data surrounding this influence on patient outcomes are limited.⁸⁻¹⁰

¹ Henry Ford Hospital, Detroit, MI, USA

² Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, USA.

*The author is now with the Department of Clinical Pharmacy and Translational Science, University of Tennessee Health Science Center, Knoxville, TN, USA.

**The author is now with Barnes-Jewish Hospital, St Louis, MO, USA

Corresponding Author:

Michael P. Veve, Department of Clinical Pharmacy and Translational Science, University of Tennessee, Health Science Center, 1924 Alcoa Highway, Box 117, Knoxville, TN 37920, USA.
Email: mveve1@uthsc.edu

β -Lactam allergies are reported in approximately 10% of hospitalized patients, but IgE-mediated allergies are relatively rare and electronic medical record descriptions of β -lactam allergies are often lacking or incomplete.¹¹⁻¹⁴ Whereas avoidance of β -lactam therapy is a common approach in patients with a labeled β -lactam allergy,¹⁵ most literature suggests that 99% of these patients do not have a true allergy and can safely receive a β -lactam antibiotic.^{11,12}

Previous literature has demonstrated that for infections in general, patients with β -lactam allergies are more likely to receive suboptimal therapy, experience clinical failure, have an increased hospital length of stay, develop drug-resistant organisms, and have higher in-hospital mortality.^{9,16-18} Since optimal treatment of MSSA BSI is directly associated to patient outcomes, barriers to receiving optimal antibiotics are an important target for antimicrobial stewardship intervention. The objective of this study was to determine the impact of reported β -lactam allergy, including reaction type, on the receipt of optimal therapy and outcomes for MSSA BSI.

Methods

This was an institutional review board approved, retrospective, ratio-matched cohort that included hospitalized patients with MSSA BSI from January 2013 to December 2015. The study took place at 4 acute care hospitals within the Henry Ford Health-system which collectively includes over 2000 in-patient beds located throughout southeast Michigan.

Additional inclusion criteria were age ≥ 18 years and receipt of MSSA BSI treatment with at least one dose of an intravenous antibiotic. Patients were excluded if they had polymicrobial BSI, were hospice or comfort care at the time of diagnosis, or were transferred from an outside facility. Reported β -lactam allergy was defined as an allergy to a penicillin, cephalosporin, monobactam, or carbapenem agent documented within the allergy field of the electronic medical record. Immune-mediated reactions were defined as documentation of rash, hives, anaphylaxis, angioedema, or bronchospasm.⁹ Intolerances were defined as any nonimmune-mediated reaction. Matching was performed in a 1:3 ratio of patients with a reported β -lactam allergy to patients with no β -lactam allergy, using a nearest neighbor approach with respect to time (closest date of index MSSA BSI) and if at least 50% of care was managed in an intensive care unit or general ward setting.

The following data were extracted from the electronic medical record: patient demographics, select comorbid conditions, treatment, and outcomes. Immunosuppression was defined as solid organ or bone marrow transplant, acquired immune deficiency syndrome with $CD4 < 200$ cells/mm³, absolute neutrophil count < 500 cells/mm³, chronic steroids with a prednisone equivalent of 20 mg per day for at least 2 weeks, hematological disease, or receipt of chemotherapy within 30 days. Concomitant infection sites were defined according to the presence of a vegetation on echocardiography or a positive MSSA culture from another anatomical site. Blood culture susceptibilities

were performed by the clinical microbiology laboratory using the Vitek2 (bioMérieux Inc, Marcy-l'Étoile, France). All data were collected using a standardized electronic case report form.

Outcomes

The primary outcome was receipt of optimal intravenous antibiotics, defined as at least 24 hours of definitive cefazolin, nafcillin, ceftaroline, or ampicillin/sulbactam. A 24 hour cutoff was used to capture clinical intent to optimally treat MSSA. All antibiotic doses were according to institutional dosing guidelines and individualized to patient renal function. Secondary outcomes included duration of suboptimal antibiotics, clinical cure, in-hospital crude and attributable mortality, and allergy documentation practices. Suboptimal antibiotics were defined as definitive therapy with a non-antistaphylococcal penicillin or cephalosporin, or vancomycin. The duration of suboptimal antibiotic therapy was defined as the time in hours between the first microbiologically confirmed result of MSSA and the infusion start time of the first optimal antibiotic. Clinical cure was defined as resolution of signs and symptoms of MSSA BSI with no hospital readmission or death within 90 days after discharge. Mortality was determined to be attributable to MSSA BSI (ie, MSSA-related mortality) if death occurred prior to the resolution of signs and symptoms of infection or if death occurred within 7 days of MSSA BSI onset with no other known cause of death. All-cause mortality was death due to any cause within 30- or 90-days of the first positive MSSA blood culture. Adjudication of clinical cure and attributable mortality was completed by 2 co-investigators blinded to treatment and allergy status (R.M.K. and S.L.D.).

Statistical Analysis

This study was designed to determine the impact of reported β -lactam allergies on the receipt of optimal antibiotics. The sample size was calculated using the following assumptions: 2-sided α , 0.05; power $(1-\beta)$, 0.80. Using these values and an additional assumption that 95% of patients without a reported β -lactam allergy would receive optimal antibiotics, a sample size of 176 patients was calculated a priori to detect a 15% difference in the primary end point.

Bivariate analyses were performed using χ^2 or Mann-Whitney U tests where appropriate. Any clinically relevant variable found to have an association with receipt of optimal antibiotics ($P \leq .2$) was considered for inclusion to a multivariable logistic regression model. Variables were manually entered into the model to determine independent associations with the primary outcome while controlling for potential confounders, and model fit was tested using the Hosmer-Lemeshow goodness-of-fit test. A post hoc analysis of variables associated with all-cause 90-day mortality was performed using similar methodology as described above. All statistical analyses were performed using SPSS Statistics version 23.0 for Macintosh (IBM Corp, Armonk, New York).

Results

Demographics

A total of 212 patients were included: 53 with a reported β -lactam allergy and 159 without a β -lactam allergy. Baseline characteristics and infection information are listed in Table 1. Infectious disease consultations were more frequent in patients with reported β -lactam allergy than those without (89% vs 75%, $P = .04$). Source control, if applicable, was similar between groups: 14 (45%)/31 of patients with reported β -lactam allergy compared to 40 (46%)/86 without a β -lactam allergy ($P = .90$). β -lactam allergy documentation included 26 (49%) immune-mediated reactions, 8 (15%) intolerances, and 19 (36%) unspecified reactions. Allergy consultations were obtained for 7 (13%) reported β -lactam allergy patients, and β -lactam desensitization was performed in 1 (2%) patient.

Primary Outcome

Patients with a reported β -lactam allergy were less likely to receive optimal antibiotic therapy than those without a β -lactam allergy (70% vs 85%, $P = .015$). Nafcillin or cefazolin was the optimal antibiotic for 95% of patients who received any optimal antibiotics in both groups, and vancomycin was the most common nonoptimal antibiotic. Of patients with a reported β -lactam allergy who received optimal therapy, no patients developed a subsequent β -lactam-mediated reaction. When adjusting for immunosuppression in multivariable regression analyses (Table 2), reported β -lactam allergy was associated with a decreased likelihood of optimal antibiotic use (adjusted odds ratio [adjOR], 0.3; 95% confidence interval [CI], 0.1-0.6), and an infectious disease consultation was associated with an increased likelihood of optimal therapy (adjOR, 6.1; 95%CI, 2.7-13.9). Among the subgroup of reported β -lactam allergic patients, those without documentation of the nature of β -lactam allergy reaction were less likely to receive optimal therapy when compared to patients with a documented nature of allergy (47% [9/19] vs 79% [27/34], $P = .042$). There was no significant difference in the proportion of infectious diseases (ID) consultation between patients with or without a documented reaction to β -lactams ($P = .97$).

Secondary Outcomes

The median duration of suboptimal antibiotics was 44 hours (interquartile range [IQR]: 26-128) in patients with reported β -lactam allergies compared to 30 hours (IQR: 22-74) in patients with no allergy ($P = .096$). Optimal antibiotics were started within 24 hours of positive MSSA identification in 19% of the reported β -lactam allergic group and 25% in patients without β -lactam allergy ($P = .35$). Clinical response was similar between the β -lactam allergy and in patients without β -lactam allergy (76% vs 79%, $P = .61$), as was MSSA BSI-related mortality (17% vs 16%, $P = .83$) and all-cause 30-day (11% vs 10%, $P = .80$) and 90-day mortality (17% vs 16%, $P = 0.92$). Of the 117 patients eligible for infection source control, it was obtained in 22% (5/23) of patients who expired and 52% (49/

Table 1. Baseline and Infection Characteristics of Patients With Methicillin-Sensitive *Staphylococcus aureus* Bloodstream Infections.

Characteristic, n (%) or Median (IQR)	β -Lactam Allergy, n = 53	No β -Lactam Allergy, n = 159	P Value
Demographics			
Male sex	24 (45%)	91 (57%)	.08
Age, years	68 (55-80)	61 (52-72)	.2
Patient History			
MRSA infection in previous year	2 (4%)	2 (2%)	.24
Resident of long term care facility	6 (11%)	11 (7%)	.31
Hospital admission in previous 90 days	19 (35%)	53 (33%)	.74
History of injection drug use	1 (2%)	13 (8%)	.11
Comorbidities			
Chronic obstructive pulmonary disease	11 (20%)	33 (21%)	1.0
Diabetes	30 (56%)	77 (48%)	.3
Heart failure	21 (39%)	51 (32%)	.32
Dialysis dependent	12 (22%)	30 (19%)	.55
Acute kidney injury	19 (35%)	48 (30%)	.44
Immunosuppressed	5 (9%)	20 (13%)	.54
Hospital course			
Infectious disease consult	47 (89%)	120 (75%)	.04
Majority of care in intensive care unit	13 (24%)	41 (26%)	.86
Endocarditis	15 (10%)	8 (15%)	.25
Device infection	1 (2%)	8 (5%)	.33
Bone/joint infection	8 (15%)	13 (8%)	.14
Patient outcomes			
Receipt of optimal antibiotics	37 (70%)	135 (85%)	.015
Clinical response	40 (76%)	125 (79%)	.63
MSSA-related mortality	9 (17%)	25 (16%)	.83
All-cause 30-day mortality	6 (11%)	16 (10%)	.80
All-cause 90-day mortality	9 (17%)	26 (16%)	.92

Abbreviations: IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*.

94) of survivors (unadjusted odds ratio [unAdjOR], 3.9; 95%CI, 1.3-11.4). Optimal antibiotic use was associated with reduced 30-day (unAdjOR, 0.18; 95%CI, 0.07-0.45) and 90-day (unAdjOR, 0.26; 95%CI, 0.12-0.57) mortality.

When adjusting for disease type and the presence of an ID consultation, variables independently associated with all-cause 90-day mortality were patients who received optimal antibiotics (adjOR, 0.23; 95%CI, 0.09-0.54) and those with the majority of hospital stay in intensive care (adjOR, 5.3; 95%CI, 2.4-11.7; Table 3).

Discussion

This study demonstrated a significantly lower rate of optimal antibiotic use in patients with MSSA BSI with a reported

Table 2. Variables Associated With Receipt of Optimal Antibiotics.

Characteristic	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Reported β -lactam allergy	0.4 (0.2-0.9)	.02	0.3 (0.1-0.6)	.002
Immunosuppression	2.9 (0.7-13.3)	.14	2.9 (0.6-13.8)	.2
Infectious diseases consultation	4.4 (2.1-9.3)	<.001	6.1 (2.7-13.9)	<.001
Residence at long term care facility	1.7 (0.6-4.9)	.31	NT	NT
Endocarditis	1.7 (0.7-4.3)	.25	NT	NT
Documented β -lactam allergy type in EHR	4.0 (1.2-13.8)	.02	NT	NT

Abbreviations: CI, confidence interval; EHR, electronic health record; NT, not tested; OR, odds ratio.

Table 3. Variables Associated With All-Cause 90-day Mortality.

Characteristic	Unadjusted OR, (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Receipt of optimal therapy	0.26 (0.12-0.57)	<.001	0.23 (0.09-0.54)	.001
Infectious diseases consultation	0.40 (0.20-0.82)	.01	0.56 (0.23-1.3)	.2
Endocarditis	1.9 (0.71-5.4)	.19	1.9 (0.63-6.0)	.25
Majority of stay in ICU	4.8 (2.3-10.3)	<.001	5.3 (2.4-11.7)	<.001

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

β -lactam allergy when compared to patients without a reported β -lactam allergy. Additionally, the current study indicates that patients having no medical record documentation of the nature of β -lactam allergy were more likely to result in suboptimal treatment of MSSA BSI than those with a documented β -lactam allergy reaction type. This represents a critical, modifiable risk factor that should be a target for antimicrobial stewardship efforts.

Our findings are consistent with recent data that suggest reported β -lactam allergies are associated with suboptimal antibiotic use in MSSA BSI.^{8,9} Blumenthal et al performed a retrospective cohort that assessed the impact of β -lactam allergies on the receipt of optimal therapy (ie, ≥ 3 inpatient days or discharge on any first-line antistaphylococcal agents) in patients with MSSA BSI.⁹ The investigators found patients with reported β -lactam allergy were significantly less likely to receive optimal therapy than those without β -lactam allergies (47% vs 80%, $P < .001$), but allergy reaction types were not included in analyses. Turner et al performed a retrospective cohort assessing the outcomes in patients with and without β -lactam allergies and MSSA BSI and found patients with β -lactam allergies were more likely to receive definitive therapy with vancomycin ($P < .01$).¹⁰ The authors also found no difference in 30-day ($P = .99$) or 90-day ($P = .47$) all-cause mortality between groups, but receipt of a β -lactam was protective toward 30-day (adjOR, 0.26; 95% CI, 0.12-0.54) and 90-day (adjOR, 0.41; 95%CI, 0.21-0.81) mortality, which is similar to the current study. While 44% of β -lactam allergic patients still received a β -lactam, the authors concluded that a reported penicillin allergy only matters if it prevents a patient from receiving a β -lactam.

The negative economic and clinical outcomes associated with reported β -lactam allergies suggest that innovative practice models targeted to improve the quality of allergy documentation and increase access to penicillin skin testing are

needed.¹⁹ Macy and Contreras found that antibiotic allergy labels increased length of stay by 0.59 days, which was estimated to cost approximately US\$64 million over 3 years or roughly 9.5 times the cost of penicillin allergy skin testing.¹⁶ Negative effects of reported β -lactam allergies have also been demonstrated outside of MSSA BSI and are associated with increased risk of surgical site infections²⁰ and utilization of unnecessary carbapenem use in community-onset Gram-negative bacteremia.²¹ Institutional adaptations of penicillin-skin testing procedures have effectively delabeled β -lactam allergies in up to 99% of various populations.^{19,22-24} Additionally, infectious diseases consultations have been associated with increased rates of optimal antibiotic usage in *S aureus* bacteremia due to adherence to evidence-based management strategies.^{9,25} Improved allergy documentation and clarification practices in the electronic medical record, such as requiring a documented allergy reaction, can help pharmacists and providers triage clinically significant β -lactam allergies in order to avoid the use of a non- β -lactam in appropriate situations.²⁶ At our institution, pharmacists routinely clarify β -lactam allergies in patients with a documented allergy as documented in the electronic health record. This includes directly communicating with the patient to get a historical perspective of the allergy, including time of onset, drug, and reaction type. Additionally, pharmacists can clarify the likelihood of β -lactam cross-reactivity through side-chain analysis to identify situations where cephalosporins can be used.¹⁸

While this study provides additional insight on impact of β -lactam allergies on receipt of optimal therapy in MSSA BSI, a number of limitations should be addressed. Receipt of optimal antibiotics was used as the primary end point as a surrogate for clinical response and mortality. This surrogate outcome has been previously validated, demonstrating that receipt of a β -lactam leads to superior outcomes when compared to patients treated with vancomycin for MSSA BSI.⁵⁻⁷ Limitations to study design

hinder the ability to detect why non- β -lactam allergic patients had a prolonged time. The ability to detect a difference in mortality between groups was beyond the scope of this study and power calculations. This study took place within a 4-hospital health system with a well-established antimicrobial stewardship program and infectious diseases services, which could contribute to higher adherence to optimal therapy for MSSA BSI when compared to outside institutions. The institution does utilize a rapid penicillin-binding protein-2a antigen test for *S aureus* BSI that may have decreased the time to appropriate therapy. Health-system guidelines consider ceftaroline and ampicillin/sulbactam as appropriate alternatives to cefazolin or nafcillin for optimal treatment of MSSA BSI. There is little published clinical evidence for ceftaroline or ampicillin/sulbactam in the treatment of MSSA BSI; however, only 5% of the study population received either of these antibiotics.

Conclusion

Documentation of a β -lactam allergy was associated with sub-optimal antibiotic use for treatment of MSSA BSI. In this study, infectious disease consultation was associated with increased β -lactam use and reduced mortality. Allergy documentation practices were poor, and patients with no documentation of their reaction to a β -lactam were more likely to receive suboptimal therapy. Given the poor patient outcomes associated with use of a non- β -lactam in the treatment of MSSA BSI, antimicrobial stewardship interventions, including allergy clarification or penicillin skin testing procedures, are needed to improve the quality of care received by patients with MSSA BSI who report a β -lactam allergy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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