

Influence of Reported Penicillin Allergy on Mortality in MSSA Bacteremia

Nicholas A. Turner,¹ Rebekah Moehring,¹ Christina Sarubbi,² Rebekah H. Wrenn,² Richard H. Drew,¹ Coleen K. Cunningham,³ Vance G. Fowler,^{1,4} and Deverick J. Anderson¹

¹Division of Infectious Diseases, Department of Medicine, Duke University School of Medicine, Durham, North Carolina; ²Department of Pharmacy, Duke University Hospital, Durham, North Carolina; ³Division of Infectious Diseases, Department of Pediatrics, Duke University Medical Center, Durham, North Carolina; ⁴Duke Clinical Research Institute, Durham, North Carolina

Background. Penicillin allergy frequently impacts antibiotic choice. As beta-lactams are superior to vancomycin in treating methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia, we examined the effect of reported penicillin allergy on clinical outcomes in patients with MSSA bacteremia.

Methods. In this retrospective cohort study of adults with MSSA bacteremia admitted to a large tertiary care hospital, outcomes were examined according to reported penicillin allergy. Primary outcomes included 30-day and 90-day mortality rates. Multivariable regression models were developed to quantify the effect of reported penicillin allergy on mortality while adjusting for potential confounders.

Results. From 2010 to 2015, 318 patients with MSSA bacteremia were identified. Reported penicillin allergy had no significant effect on adjusted 30-day mortality (odds ratio [OR], 0.73; 95% confidence interval [CI], 0.29–1.84; $P = .51$). Patients with reported penicillin allergy were more likely to receive vancomycin (38% vs 11%, $P < .01$), but a large number received cefazolin regardless of reported allergy (29 of 66, 44%). Mortality rates were highest among nonallergic patients receiving vancomycin (22.6% vs 7.4% for those receiving beta-lactams regardless of reported allergy, $P < .01$). In multivariable analysis, beta-lactam receipt was most strongly associated with survival (OR, 0.26; 95% CI, 0.12–0.54).

Conclusions. Reported penicillin allergy had no significant effect on 30- or 90-day mortality. Non-penicillin-allergic patients receiving vancomycin for treatment of MSSA bacteremia had the highest mortality rates overall. Receipt of a beta-lactam was the strongest predictor of survival. These results underscore the importance of correct classification of patients with penicillin allergy and appropriate treatment with a beta-lactam when tolerated.

Keywords. bacteremia; methicillin-susceptible *Staphylococcus aureus*; penicillin allergy.

Staphylococcus aureus is a leading cause of bacteremia, infective endocarditis, and device-related infection [1]. Mortality rates for *S. aureus* bacteremia range from 10% to 50%, influenced in part by site of infection and choice of treatment [2, 3]. While vancomycin remains the preferred therapy for methicillin-resistant *S. aureus* (MRSA), beta-lactams are strongly associated with superior outcomes in methicillin-sensitive *S. aureus* (MSSA) bacteremia [4].

Up to 10% of inpatients report beta-lactam allergies, frequently limiting appropriate treatment options for MSSA bacteremia [5, 6]. While prior studies have evaluated the treatment of patients with a reported penicillin allergy and outcomes of various

antibiotic regimens, to our knowledge none have examined the influence of a reported penicillin allergy on MSSA bacteremia outcomes directly. We hypothesized that reported penicillin allergy might adversely impact survival in MSSA bacteremia by influencing treatment. Therefore, we performed this retrospective cohort study to quantify the effect of reported penicillin allergy on relevant clinical outcomes in adults with MSSA bacteremia.

METHODS

We retrospectively identified all adults with MSSA bacteremia admitted to Duke University Hospital (Durham, NC) from January 1, 2010, to December 31, 2015. MSSA bacteremia was defined as 1 or more blood cultures positive for *S. aureus* that was susceptible to oxacillin per Clinical Laboratory and Standards Institute guidelines (minimum inhibitory concentration ≤ 2 $\mu\text{g/mL}$). We excluded patients with polymicrobial bacteremia, those who died before final culture and susceptibility results were available, and those who elected not to pursue treatment (eg, pursued hospice care or left against medical advice). Our study was approved by the Institutional Review Board of the Duke University Health System.

Received 10 January 2018; editorial decision 11 February 2018; accepted 16 February 2018.

Correspondence: N. A. Turner, MD, Duke Box 102359, Durham, NC 27710 (nick.turner@dm.duke.edu).

Open Forum Infectious Diseases®

© The Author(s) 2018. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
DOI: 10.1093/ofid/ofy042

Data collected retrospectively included each patient's demographic characteristics, sequential organ failure assessment (SOFA) score on the first day positive blood cultures were obtained, comorbid conditions, Charlson comorbidity index, reported drug allergies as of the day of admission, antibiotics received, duration of therapy, and serum vancomycin trough concentrations when available. Reported drug allergies were obtained directly from the electronic medical record, as recorded by the admitting physician, along with a description of the drug reaction when available. The source of infection was recorded from either an infectious disease consult note or the relevant discharge summary. Of note, our hospital implemented a policy for mandatory infectious diseases consultation for *S. aureus* bacteremia during the latter half of the study period, 2013–2016.

We analyzed 2 factors for association with clinical outcomes. Reported penicillin allergy was obtained from each patient's list of drug allergies documented within their admission history and physical. Definitive antibiotic choice was defined as the antibiotic prescribed once susceptibility results were known. Patients who expired before antibiotic susceptibility results were available were excluded from analysis. This was done to minimize the risk of bias toward worse outcomes with vancomycin given that nearly all patients received vancomycin as part of initial empiric therapy. Sensitivity analysis showed no significant effect upon including or excluding these patients (data not shown).

The primary end points included death at 30 days and death at 90 days. Secondary outcomes included time to clearance of blood cultures (defined as the number of days from first positive to first confirmed negative blood cultures), recurrence of bacteremia by 90 days, and incidence of adverse drug events. We used standard descriptive statistics. Comparisons between categorical variables were conducted using either the Fisher exact or χ^2 where appropriate. Comparisons between continuous variables were conducted using *t* tests. All tests were 2-sided; *P* values were considered significant if $<.05$. Outcomes of interest were examined first according to reported penicillin allergy, as this was our primary question. We next analyzed the data according to treatment choice as we hypothesized that reported penicillin allergy might influence outcomes indirectly by altering treatment choice.

Mortality outcomes were also evaluated using multivariable logistic regression. We constructed a stepwise regression model to adjust for confounders. All variables with $P < .2$ were included initially, with backwards elimination to remove confounders with a $<10\%$ effect on mortality. We did not include receipt of a beta-lactam in the multivariate model estimating the effect of reported penicillin allergy, as we considered this factor a potential mediator of the effect of penicillin allergy on mortality. We used the statistical platform R version 3.4.1 (available at <https://www.r-project.org/>) for all analyses.

RESULTS

Six hundred eighty-seven patients had *S. aureus* bacteremia during the study period. Exclusion of those with methicillin-resistant *Staphylococcus aureus* (MRSA) infection, polymicrobial infection, or those choosing not to pursue treatment left 335 patients. Of these 335 patients with MSSA bacteremia, 17 expired before susceptibility results were known and before definitive therapy could be chosen. These 17 were excluded from analysis, leaving 318 subjects with MSSA bacteremia in our final cohort. The majority of patients were male ($n = 203$, 64%), and the mean age was 58 (± 16) years. The majority of patients received a beta-lactam antibiotic ($n = 243$, 76%). A large number of patients reported a penicillin allergy ($n = 66$, 21%). Among patients reporting penicillin allergy, the most common reactions reported were rash ($n = 19$, 27%) and hives ($n = 15$, 21%). A complete description of the reaction was not available for 15 (21%) cases. Reported penicillin reactions are summarized in Table 1. Twenty-nine (44%) reportedly penicillin-allergic patients still received cefazolin. Adverse drug events were too infrequent for analysis. Only a single incidence of suspected drug rash was noted in a patient with reported penicillin allergy who received a beta-lactam, along with 2 episodes of acute renal injury attributed to antibiotics. No episodes of anaphylaxis were noted.

The group with reported penicillin allergy was different than the nonallergic group by sex and some comorbidities (Table 2), but the 2 groups were similar in terms of overall Charlson comorbidity index and sequential organ failure assessment (SOFA) scores. There was a trend toward higher frequency of catheter infections in non-penicillin-allergic patients and a higher frequency of endovascular or soft tissue infection in penicillin-allergic patients (Table 3), though only the latter 2 reached statistical significance. Mortality rates were not significantly different between penicillin-allergic and non-penicillin-allergic patients at 30 days (10.6% vs 11.9%, $P = .99$) or 90 days (13.6% vs 18.3%, $P = .47$) in univariate analysis. Penicillin-allergic patients were slower to clear blood cultures (6.2 days vs 4.1 days, $P < .01$) and more likely to suffer recurrence within 90 days (7% vs 1.5%, $P = .02$).

Table 1. Reported Reactions to Penicillin

Reported Reaction to Penicillin	No. (%)
Rash	19 (27)
Hives	15 (21)
Swelling/angioedema	8 (11)
Anaphylaxis	5 (7)
Interstitial nephritis	5 (7)
Dyspnea	3 (4)
Gastro-intestinal upset	1 (1)
Unspecified	15 (21)

Table 2. Demographics and Comorbidities for 318 Patients With MSSA Bacteremia According to Penicillin Allergy

Characteristics	Allergy History		P
	Nonallergic (n = 252), No. (%)	Penicillin-Allergic (n = 66), No. (%)	
Demographics			
Age, mean (SD), y	56.6 (15)	60.9 (18)	.05
Male	169 (67)	34 (51)	.02
Comorbidities			
Myocardial infarction	56 (22)	24 (36)	.03
Heart failure	101 (40)	38 (58)	.01
Vascular disease	51 (20)	27 (41)	<.01
Cerebrovascular disease	80 (32)	34 (52)	<.01
Dementia	9 (3)	2 (3)	.99
Pulmonary	90 (36)	27 (41)	.47
Connective tissue disease	30 (12)	9 (14)	.68
Peptic ulcer disease	27 (11)	10 (15)	.38
Liver disease	25 (10)	5 (8)	.64
Diabetes	128 (51)	40 (60)	.17
Diabetes with complications	71 (28)	24 (36)	.22
Paraplegia	15 (6)	2 (3)	.54
Renal disease	133 (53)	46 (69)	.02
Cancer	77 (31)	12 (18)	.05
Metastatic cancer	39 (16)	4 (6)	.07
Severe liver disease	24 (10)	2 (3)	.13
HIV	7 (3)	1 (2)	.99
Charlson comorbidity index, mean (SD)	5.6 (3)	6.2 (3)	.23
SOFA score, mean (SD)	3.1 (3)	3.3 (3)	.58

Abbreviation: MSSA, methicillin-susceptible *Staphylococcus aureus*.

When analyzed according to choice of definitive treatment, patients receiving vancomycin were more likely to have penicillin allergy, underlying diabetes, or renal disease, and they carried slightly higher mean SOFA scores (3.7 vs 2.9, $P = .04$) and Charlson comorbidity indices (6.6 vs 5.5, $P = .03$) (Table 4). Compared with patients treated with beta-lactam antibiotics, patients treated with vancomycin had higher mortality rates at 30 days (22.6% vs 7.4%, $P = .002$) and 90 days (26.4% vs 13.6%, $P = .036$) on univariate analysis. Patients who received beta-lactam antibiotics were more likely to have had an infectious diseases (ID) consultation than those receiving vancomycin, though the difference was not statistically significant (65% vs 53%, $P = .12$). Mortality rates were lower overall for patients receiving an ID consultation (8.7% vs 16.3% at 30 days, $P = .04$; 13.9% vs 22.8% at 90 days, $P = .05$). The initiation of mandatory ID consultation did not impact this finding (data not shown).

We next created a multivariable logistic regression model to quantify the effect of reported penicillin allergy on mortality outcomes while accounting for potential confounders. Our initial models included age >65 years, sex, SOFA score, cancer, heart failure, kidney disease, skin/soft tissue source of infection, osteoarticular source of infection, penicillin allergy, and ID consultation. Both the 30- and 90-day models achieved

c-statistics >0.8. Severity of illness represented by the SOFA score was the strongest independent predictor of 30-day mortality in our adjusted model (Table 5). The following factors were independently associated with 90-day mortality in our adjusted model: age >65 years, SOFA score, and congestive heart failure. Reported penicillin allergy had no significant effect on mortality at 30 or 90 days.

Considering that a significant proportion of patients with reported penicillin allergy still received cefazolin (44%, $n = 29$), we recreated the multivariable models to assess the effect of receiving a beta-lactam antibiotic on 30- and 90-day mortality (Table 6). Receipt of a beta-lactam was strongly protective against mortality at 30 and 90 days.

Thirty-day mortality outcomes were stratified according to both penicillin allergy and definitive antibiotic choice in Figure 1. No significant difference was noted in univariate analysis comparing mortality rates for penicillin-allergic or non-penicillin-allergic patients based on the definitive treatment received. We conducted additional analysis of these subgroups to test for possible interaction between reported penicillin allergy and receipt of a beta-lactam (Table 7). As predicted in our model, receipt of a beta-lactam was protective irrespective of penicillin allergy whereas vancomycin use was associated with higher rates of 30-day mortality. An interaction term was not significant in our final model but allowed us to calculate adjusted odds

Table 3. Site of Infection, Treatment, and Outcomes for 318 Patients With MSSA Bacteremia According to Penicillin Allergy

Characteristics	Allergy History		P
	Nonallergic (n = 252), No. (%)	Penicillin-Allergic (n = 66), No. (%)	
Site of infection			
Catheter	41 (16)	5 (8)	.08
Pneumonia	18 (7)	4 (6)	.99
Endovascular	47 (19)	21 (32)	.03
Osteoarticular	43 (17)	11 (17)	.99
Soft tissue	50 (20)	21 (31)	.05
Unknown	63 (25)	14 (21)	.62
Treatment			
Vancomycin	28 (11)	25 (38)	<.01
Cefazolin	98 (39)	29 (44)	.58
Nafcillin	113 (45)	3 (5)	<.01
Other	13 (5)	9 (14)	.04
Vancomycin trough, mean (SD)	16.1 (7)	16 (6)	.97
Duration, mean (SD), wk	4.3 (2)	4.7 (2)	.25
ID consultation	146 (58)	49 (74)	.02
Outcomes			
Time to clearance, mean (SD), d	4.1 (4)	6.2 (6)	<.01
30-d mortality (%)	30 (11.9)	7 (10.6)	.99
90-d mortality (%)	46 (18.3)	9 (13.6)	.47
90-d recurrence (%)	4 (1.5)	5 (7.0)	.02

Abbreviation: MSSA, methicillin-susceptible *Staphylococcus aureus*.

Table 4. Demographics, Clinical Features, Site of Infection, and Outcomes for 296 Patients With MSSA Bacteremia Treated With Either Vancomycin or a Beta-Lactam

Characteristics	Definitive Antibiotic Choice		P
	Vancomycin (n = 53), No. (%)	Beta-lactam (n = 243), No. (%)	
Demographics			
Age, mean (SD), y	55.5 (17)	58.0 (16)	.35
Male	31 (58)	161 (66)	.34
SOFA, mean (SD)	3.7 (3.1)	2.9 (2.5)	.04
CCml, mean (SD)	6.6 (3)	5.5 (3)	.03
Penicillin allergic	25 (47)	32 (13)	<.01
Site of infection			
Catheter	9 (17)	35 (14)	.67
Pneumonia	6 (11)	15 (6)	.23
Endovascular	12 (23)	53 (22)	.86
Osteoarticular	4 (8)	49 (20)	.03
Soft tissue	11 (21)	55 (23)	.86
Unknown	14 (26)	53 (22)	.47
Treatment			
Vancomycin trough, mean (SD)	18.0 (6.1)	15.3 (6.6)	.10
Duration, mean (SD), wk	4.3 (1.8)	4.5 (1.8)	.57
ID consultation	28 (53)	159 (65)	.12
Outcomes			
Time to clearance, mean (SD), d	5.0 (5.3)	4.4 (4.2)	.47
30-d mortality (%)	12 (22.6)	18 (7.4)	<.01
90-d mortality (%)	14 (26.4)	33 (13.6)	.04
90-d recurrence (%)	5 (9.4)	3 (1.2)	<.01

Abbreviation: CCml, Charlson co-morbidity index; MSSA, methicillin-susceptible *Staphylococcus aureus*; SOFA, sequential organ failure assessment.

ratios for these subgroups. The single largest predictor of mortality was receipt of vancomycin among non-penicillin-allergic patients (odds ratio, 4.6; 95% confidence interval, 2.16–9.84; $P < .001$ compared with the subgroup who received a beta-lactam and had no penicillin allergy).

Table 5. Logistic Regression Model to Quantify Effect of Penicillin Allergy on 30-Day and 90-Day Mortality Rates in Patients With MSSA Bacteremia While Adjusting for Confounders

Variable	Odds Ratio (95% CI)	PValue
30-d mortality model		
Penicillin allergy	0.73 (0.29–1.84)	.51
SOFA score	1.32 (1.17–1.49)	<.01
Age > 65 y	1.91 (0.91–3.98)	.09
90-d mortality model		
Penicillin allergy	0.60 (0.15–1.40)	.23
SOFA score	1.32 (1.17–1.48)	<.01
Age > 65 y	1.94 (1.01–3.78)	.05
CHF	1.96 (1.03–3.75)	.04
Cancer	2.28 (1.15–4.50)	.02

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MSSA, methicillin-susceptible *Staphylococcus aureus*; SOFA, sequential organ failure assessment.

Table 6. Logistic Regression Model to Quantify Effect of Beta-Lactam Receipt on 30-Day and 90-Day Mortality Rates in Patients With MSSA Bacteremia While Adjusting for Confounders

Variable	Odds Ratio (95% CI)	PValue
30-d mortality model		
Beta-lactam	0.26 (0.12–0.54)	<.01
SOFA score	1.30 (1.14–1.47)	<.01
Age > 65 y	2.03 (0.96–4.30)	.06
90-d mortality model		
Beta-lactam	0.41 (0.21–0.81)	.01
SOFA score	1.30 (1.16–1.46)	<.01
Age > 65 y	1.88 (0.97–3.64)	.06
CHF	1.94 (1.01–3.72)	.05
Cancer	2.48 (1.26–4.90)	.01

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MSSA, methicillin-susceptible *Staphylococcus aureus*; SOFA, sequential organ failure assessment.

Recognizing the known limitations of patient-reported drug allergy and the high prevalence of reported penicillin allergy (21%) in our cohort, we conducted a sensitivity analysis using a more stringent definition of penicillin allergy to assure against misclassification bias. According to the more stringent definition, only patients reporting anaphylaxis, hives, dyspnea, or angioedema/swelling were considered allergic. With the more stringent definition, incidence of penicillin allergy in our cohort fell to 9.2%—in agreement with previously reported prevalence rates [5, 6]. On sensitivity analysis, our modeled effect measures remained unchanged (data not shown).

We conducted a post hoc comparison between nafcillin and cefazolin given prior hypothetical concerns for inferior outcomes with cefazolin in deep-seated infections (Table 8) [7, 8]. Despite patients receiving cefazolin having higher SOFA scores (3.5 vs 2.2, $P \leq .01$) and higher Charlson comorbidity indices (6.5 vs 4.5, $P \leq .01$), we found no significant difference in 30-day (8.6% for nafcillin vs 6.3% for cefazolin, $P = .63$) or 90-day (12.9% vs 14.2%, $P = .85$) mortality rates. A higher incidence of renal disease in patients receiving cefazolin (65% vs 42%, $P < .01$) may explain the trend toward higher SOFA and

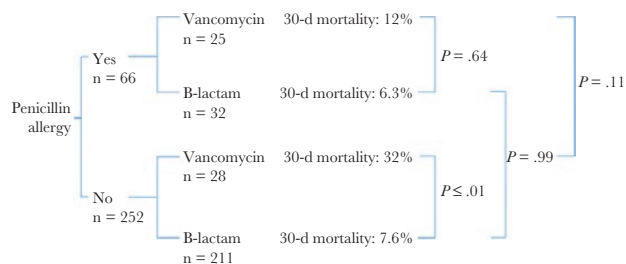


Figure 1. Comparison of 30-day mortality rates for patients with methicillin-susceptible *Staphylococcus aureus* bacteremia according to penicillin allergy and definitive treatment. Note that some patients were treated with neither vancomycin nor a beta-lactam (eg, some received daptomycin, ceftaroline, linezolid and are not shown).

Table 7. Assessment for Interaction Between Penicillin Allergy and Receipt of a Beta-Lactam With Regards to 30-Day Mortality

Subgroups	Adjusted Odds Ratio (95% CI)	PValue
Nonallergic, treated with beta-lactam	1.0	NA
Allergic, treated with beta-lactam	0.36 (0.09–1.41)	.09
Nonallergic, treated with vancomycin	4.61 (2.16–9.84)	<.01
Allergic, treated with vancomycin	2.19 (0.88–5.46)	.14

Abbreviation: CI, confidence interval.

Charlson comorbidity indices, as renal failure is a component of both scores.

DISCUSSION

While prior studies have assessed the effects of different antibiotics on outcomes in MSSA bacteremia, few have examined the effect of reported penicillin allergy [7]. In this retrospective cohort study, reported penicillin allergy did not significantly impact 30- or 90-day mortality rates. While the overall prevalence of reported penicillin allergy was higher than previously reported, many of these reactions were either undocumented or involved a nonspecific rash. Nearly half of penicillin-allergic patients were still safely treated with cefazolin—consistent with either over-reporting of allergy or the low incidence rate for cross-reactivity with cefazolin in particular [8]. Patients receiving beta-lactams consistently had the lowest mortality

rates (7.4%), regardless of reported allergy history, even after we applied a more stringent allergy definition. This suggests that reported penicillin allergy was not an accurate marker for clinically relevant reactions concerning enough to avoid cephalosporins. The most striking mortality gap is the 4-fold greater mortality rate for nonallergic patients receiving vancomycin instead of a beta-lactam. Multivariable modeling also confirmed receipt of a beta-lactam as the single strongest predictor of survival, regardless of reported allergy history or adjustment for more stringent criteria defining penicillin allergy. These data highlight 2 crucial points for improving outcomes in MSSA bacteremia. First, a reported penicillin allergy only matters if it prevents a patient from receiving a beta-lactam. Second, while clearly over-reported, penicillin allergy is not the only reason that patients are missing out on optimal therapy.

The superiority of beta-lactams over vancomycin in treating MSSA bacteremia is consistent with several prior studies [9–19]. In our study, vancomycin use was associated with a 3-fold higher mortality rate at 30 days ($P = .002$) and a 2-fold higher mortality rate at 90 days ($P = .036$). Others have separately examined the influence of reported penicillin allergy on treatment choice—concluding that penicillin allergy was associated with an increased likelihood of receiving vancomycin by nearly 3-fold, in close agreement with the 3.3-fold increase we found [7].

With such a stark difference in mortality rates, and clear evidence that patients with a reported penicillin allergy can still achieve superior outcomes if they receive another beta-lactam, our data suggest that every effort should be made to ensure that patients with MSSA bacteremia receive a beta-lactam. These efforts take several forms. Simple interventions such as an enhanced drug allergy history may reveal that patients can safely tolerate cephalosporins, as was the case for 44% of our penicillin-allergic cohort. In prior studies of patients with reported allergies, nearly 50% of patients could be transitioned to a beta-lactam based on more detailed drug history alone [20, 21]. When uncertainty persists, penicillin skin testing can be used to determine whether penicillin antibiotics can be given safely [22–28]. Formal testing confirms 5% or less of reported penicillin allergies—permitting still more patients to receive preferred therapy [5]. While all of these interventions are being actively applied and studied presently (including at our own institution), the question of how to manage the remaining patients with true penicillin allergy remains. A 2- to 3-fold increase in mortality seems unacceptable for second-line therapy of a treatable disease (in this case, use of vancomycin). It may be time to consider desensitization as a preferred next step in the management of MSSA bacteremia for the truly allergic patients. Certainly the precedent exists when other medications are felt to be crucial to outcomes (eg, penicillin desensitization for neuro-syphilis or aspirin desensitization for coronary artery disease). As far as we are aware, no studies have examined this strategy to date.

Table 8. Demographics, Clinical Features, and Outcomes for 243 Patients With MSSA Bacteremia Receiving Either Cefazolin or Nafcillin

Characteristics	Definitive Antibiotic Choice		PValue
	Cefazolin (n = 127), No. (%)	Nafcillin (n = 116), No. (%)	
Demographics			
Age, mean (SD), y	59.3 (15)	56.5 (16)	.18
Male	82 (65)	79 (68)	.59
SOFA, mean (SD)	3.5 (2.6)	2.2 (2.3)	<.01
CCmI, mean (SD)	6.5 (3)	4.5 (3)	<.01
Site of infection			
Catheter	24 (19)	11 (10)	.04
Pneumonia	9 (7)	6 (5)	.60
Endovascular	34 (27)	19 (16)	.06
Osteoarticular	21 (17)	28 (24)	.15
Soft tissue	24 (19)	31 (27)	.17
Unknown	25 (20)	28 (24)	.44
Outcomes			
Time to clearance, mean (SD)	4.5 (5)	4.2 (3)	.55
30-d mortality (%)	8 (6.3)	10 (8.6)	.63
90-d mortality (%)	18 (14.2)	15 (12.9)	.85

Abbreviations: CCmI, Charlson co-morbidity index; SOFA, sequential organ failure assessment.

Until desensitization can be fully evaluated as a treatment for MSSA bacteremia in penicillin-allergic patients, cefazolin often becomes the default beta-lactam in the subset of patients allergic to penicillin but tolerant of cephalosporins. The use of cefazolin carries with it some concerns based on a few case reports describing treatment failures, particularly in deep-seated MSSA infections, theoretically attributed to an inoculum effect [29, 30]. To add to the body of evidence addressing these concerns, we also conducted a post hoc subanalysis comparing outcomes between nafcillin and cefazolin and found no significant difference in 30- or 90-day mortality rates, despite patients receiving cefazolin having higher mean SOFA and Charlson comorbidity scores. Cefazolin's ability to achieve similar outcomes despite predictors usually associated with higher mortality is both reassuring and consistent with prior evidence [13, 14]. Indeed, the recently published literature suggests that outcomes with cefazolin are comparable to outcomes with nafcillin but with fewer adverse effects [31].

Outside of the issues surrounding treatment of penicillin-allergic patients, the remaining nonallergic patients who received vancomycin (nearly 10% in our study) pose a distinct challenge worthy of further study as well. Vancomycin might be chosen for a variety of other reasons—including persistent knowledge gaps among providers regarding vancomycin's efficacy in MSSA bacteremia, concern for alternate sources of infection or other pathogens, or the impression of convenient dosing (eg, infrequent dosing or dosing with dialysis). Investigating the reasons for vancomycin use other than true drug allergy might help target quality improvement or antimicrobial stewardship efforts and prevent the use of a less efficacious drug in this population as well.

Our study carries several limitations. First, penicillin allergy was determined based on documentation in the history and physical, which has known problems with measurement error [32, 33]. While the prevalence of penicillin allergy was high, a significant proportion of reactions were either unspecified or nonspecific—consistent with likely over-reporting of penicillin allergy. We conducted a sensitivity analysis using a more stringent allergy definition to assess for misclassification bias, with no alteration in any of our primary effect measures. Irrespective of accuracy, reported drug allergy remains clinically relevant given that treatment decisions are typically made based on the treating physician's assessment. Second, we did not have sufficient numbers to adequately assess adverse drug events. Third, any comparisons with vancomycin must be considered with the caveat that vancomycin troughs were not available for many patients, particularly after discharge, and thus we are unable to assure therapeutic levels for the duration of treatment. Finally, given the diversity of infections included, we were unable to include an assessment of source control as another factor potentially influencing mortality. We hope to incorporate these additional factors in our ongoing and future research.

In summary, reported penicillin drug allergy did not equate with increased mortality in MSSA bacteremia in our cohort. We believe this is because nearly half of the labeled “allergic” group still received a beta-lactam. Receipt of a beta-lactam, including the use of cefazolin in many patients with reported penicillin allergy, was the single strongest predictor of survival. Conversely, patients receiving vancomycin—whether due to a drug allergy history or other reasons—suffered 2- to 3-fold higher mortality rates. In particular, patients who received vancomycin without a drug allergy had the highest mortality risk. Further investigation is needed to understand why some non-allergic patients still receive vancomycin. These data highlight 2 crucial points for improving outcomes in MSSA bacteremia. First, penicillin allergy only matters if it prevents a patient from receiving a beta-lactam. Second, penicillin allergy is not the only reason that patients are missing out on optimal therapy. Future efforts should include improvement of allergy assessment and documentation, de-labeling patients based on reactions unconcerning for true allergy, and perhaps even desensitization for truly penicillin-allergic patients.

Acknowledgments

Financial support. This work was supported by the Duke University Stead Research Grant. Nicholas Turner, MD, is supported by a fellowship grant from the Antibiotic Resistance Leadership Group.

Potential conflicts of interest. Dr. Drew reports royalties from UpToDate, honorarium from the American Society of Microbiology, honorarium from Cidara, and honorarium from CustomID outside the submitted work. Dr. Fowler reports grants from National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), MedImmune, Cerexa/Forest/Actavis/Allergan, Pfizer, Advanced Liquid Logics, Theravance, Novartis, Cubist/Merck, Medical Biosurfaces, Locust, Affinergy, Contrafect, Karius, Genentech; consultancies with Pfizer, Novartis, Galderma, Novadigm, Durata, Debiopharm, Genentech, Achaogen, Affinium, Medicines Co., Cerexa, Tetraphase, Trius, MedImmune, Bayer, Theravance, Cubist, Basilea, Affinergy, Janssen, xBiotech; contrafact personal fees from Green Cross, Cubist, Cerexa, Durata, Theravance, Debiopharm; and royalties from UpToDate; and has a patent Sepsis Diagnostics pending. Dr. Anderson reports grants from the CDC during the conduct of the study; grants from NIH/NIAID Antimicrobial Resistance Leadership Group and personal fees from UpToDate outside the submitted work. Dr. Moehring reports grants or grants pending from the CDC and AHRQ and royalties from UpToDate outside the submitted work. Drs Cunningham Sarubbi and Wrenn report no conflicts of interest. Dr. Turner reports no additional conflicts of interest beyond the Antibiotic Resistance Leadership Group and internal grants disclosed in the funding above. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Tong SY, Davis JS, Eichenberger E, et al. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev* 2015; 28:603–61.
2. De Rosa FG, Corcione S, Motta I, et al. Risk factors for mortality in patients with *Staphylococcus aureus* bloodstream infection. *J Chemother* 2016; 28:187–90.
3. Braquet P, Alla F, Cornu C, et al; VIRSTA-AEPEI study group. Factors associated with 12 week case-fatality in *Staphylococcus aureus* bacteraemia: a prospective cohort study. *Clin Microbiol Infect* 2016; 22:948.e1–7.
4. Wong D, Wong T, Romney M, Leung V. Comparative effectiveness of β -lactam versus vancomycin empiric therapy in patients with methicillin-susceptible

- Staphylococcus aureus* (MSSA) bacteremia. *Ann Clin Microbiol Antimicrob* **2016**; 15:27.
5. Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. *Curr Allergy Asthma Rep* **2014**; 14:476.
 6. Solensky R. Hypersensitivity reactions to beta-lactam antibiotics. *Clin Rev Allergy Immunol* **2003**; 24:201–20.
 7. Blumenthal KG, Shenoy ES, Huang M, et al. The impact of reporting a prior penicillin allergy on the treatment of methicillin-sensitive *Staphylococcus aureus* bacteremia. *PLoS One* **2016**; 11:e0159406.
 8. Zagursky RJ, Pichichero ME. Cross-reactivity in β -lactam allergy. *J Allergy Clin Immunol Pract* **2018**; 6:72–81.e1.
 9. Stryjewski ME, Szczech LA, Benjamin DK Jr, et al. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. *Clin Infect Dis* **2007**; 44:190–6.
 10. Small PM, Chambers HF. Vancomycin for *Staphylococcus aureus* endocarditis in intravenous drug users. *Antimicrob Agents Chemother* **1990**; 34:1227–31.
 11. González C, Rubio M, Romero-Vivas J, et al. Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. *Clin Infect Dis* **1999**; 29:1171–7.
 12. Loubet P, Burdet C, Vindrios W, et al. Cefazolin versus anti-*Staphylococcal penicillins* for treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia: a narrative review. *Clin Micro Infect* **2018**; 24:125–32.
 13. Li J, Echevarria KL, Hughes DW, et al. Comparison of cefazolin versus oxacillin for treatment of complicated bacteremia caused by methicillin-susceptible *Staphylococcus aureus*. *Antimicrob Agents Chemother* **2014**; 58:5117–24.
 14. Schweizer ML, Furuno JP, Harris AD, et al. Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible *Staphylococcus aureus* bacteremia. *BMC Infect Dis* **2011**; 11:279.
 15. Wong D, Wong T, Romney M, Leung V. Comparison of outcomes in patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia who are treated with β -lactam vs vancomycin empiric therapy: a retrospective cohort study. *BMC Infect Dis* **2016**; 16:224.
 16. Paul M, Zemer-Wassercug N, Talker O, et al. Are all beta-lactams similarly effective in the treatment of methicillin-sensitive *Staphylococcus aureus* bacteraemia? *Clin Microbiol Infect* **2011**; 17:1581–6.
 17. Kim SH, Kim KH, Kim HB, et al. Outcome of vancomycin treatment in patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother* **2008**; 52:192–7.
 18. Chang FY, Peacock JE Jr, Musher DM, et al. *Staphylococcus aureus* bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. *Medicine (Baltimore)* **2003**; 82:333–9.
 19. McDaniel JS, Roghmann MC, Perencevich EN, et al. Comparative effectiveness of cefazolin versus nafcillin or oxacillin for treatment of methicillin-susceptible *Staphylococcus aureus* infections complicated by bacteremia: a nationwide cohort study. *Clin Infect Dis* **2017**; 65:100–6.
 20. Leis JA, Palmay L, Ho G, et al. Point-of-care beta-lactam allergy skin testing by antimicrobial stewardship programs: a pragmatic multicenter prospective evaluation. *Clin Inf Dis* **2017**; doi: 10.1093/cid/cix512.
 21. Bourke J, Pavlos R, James I, Phillips E. Improving the effectiveness of penicillin allergy de-labeling. *J Allergy Clin Immunol Pract* **2015**; 3:365–34.e1.
 22. Trubiano JA, Adkinson NF, Phillips EJ. Penicillin allergy is not necessarily forever. *JAMA* **2017**; 318:82–3.
 23. Rimawi RH, Cook PP, Gooch M, et al. The impact of penicillin skin testing on clinical practice and antimicrobial stewardship. *J Hosp Med* **2013**; 8:341–5.
 24. King EA, Challa S, Curtin P, Bielory L. Penicillin skin testing in hospitalized patients with β -lactam allergies: effect on antibiotic selection and cost. *Ann Allergy Asthma Immunol* **2016**; 117:67–71.
 25. del Real GA, Rose ME, Ramirez-Atamoros MT, et al. Penicillin skin testing in patients with a history of beta-lactam allergy. *Ann Allergy Asthma Immunol* **2007**; 98:355–9.
 26. Arroliga ME, Radojicic C, Gordon SM, et al. A prospective observational study of the effect of penicillin skin testing on antibiotic use in the intensive care unit. *Infect Control Hosp Epidemiol* **2003**; 24:347–50.
 27. Sacco KA, Bates A, Brigham TJ, et al. Clinical outcomes following inpatient penicillin allergy testing: a systematic review and meta-analysis. *Allergy* **2017**; 72:1288–96.
 28. Trubiano JA, Beekmann SE, Worth LJ, et al. Improving antimicrobial stewardship by antibiotic allergy delabeling: evaluation of knowledge, attitude, and practices throughout the emerging infections network. *Open Forum Infect Dis* **2016**; 3:ofw153.
 29. Quinn EL, Pohlod D, Madhavan T, et al. Clinical experiences with cefazolin and other cephalosporins in bacterial endocarditis. *J Infect Dis* **1973**; 128:S386–9.
 30. Nannini EC, Singh KV, Murray BE. Relapse of type A beta-lactamase-producing *Staphylococcus aureus* native valve endocarditis during cefazolin therapy: revisiting the issue. *Clin Infect Dis* **2003**; 37:1194–8.
 31. Lee S, Song KH, Jung SI, et al. Comparative outcomes of cefazolin versus nafcillin for methicillin-susceptible *Staphylococcus aureus* bacteremia: a prospective multicenter cohort study in Korea. *Clin Microbiol Infect* **2017**; doi:10.1016/j.cmi.2017.07.001.
 32. Preston SL, Briceland LL, Lesar TS. Accuracy of penicillin allergy reporting. *Am J Hosp Pharm* **1994**; 51:79–84.
 33. Miller LE, Knoderer CA, Cox EG, Kleiman MB. Assessment of the validity of reported antibiotic allergic reactions in pediatric patients. *Pharmacotherapy* **2011**; 31:736–41.