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Comparative 1-Year Outcomes of Invasive *Staphylococcus aureus* Infections Among Persons With and Without Drug Use: An Observational Cohort Study

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Background. Persons who use drugs (PWUD) face substantial risk of *Staphylococcus aureus* infections. Limited data exist describing clinical and substance use characteristics of PWUD with invasive *S. aureus* infections or comparing treatment and mortality outcomes in PWUD vs non-PWUD. These are needed to inform optimal care for this marginalized population.

Methods. We identified adults hospitalized from 2013 to 2018 at 2 medical centers in San Francisco with *S. aureus* bacteremia or *International Classification of Diseases*-coded diagnoses of endocarditis, epidural abscess, or vertebral osteomyelitis with compatible culture. In addition to demographic and clinical characteristic comparison, we constructed multivariate Cox proportional hazards models for 1-year infection-related readmission and mortality, adjusted for age, race/ethnicity, housing, comorbidities, and methicillin-resistant *S. aureus* (MRSA).

Results. Of 963 hospitalizations for *S. aureus* infections in 946 patients, 372 of 963 (39%) occurred in PWUD. Among PWUD, heroin (198/372 [53%]) and methamphetamine use (185/372 [50%]) were common. Among 214 individuals using opioids, 98 of 214 (46%) did not receive methadone or buprenorphine. PWUD had lower antibiotic completion than non-PWUD (70% vs 87%; $P < .001$). While drug use was not associated with increased mortality, 1-year readmission for ongoing or recurrent infection was double in PWUD vs non-PWUD (28% vs 14%; adjusted hazard ratio [aHR], 2.0 [95% confidence interval {CI}: 1.3–2.9]). MRSA was independently associated with 1-year readmission for infection (aHR, 1.5 [95% CI: 1.1–2.2]).

Conclusions. Compared to non-PWUD, PWUD with invasive *S. aureus* infections had lower rates of antibiotic completion and twice the risk of infection persistence/recurrence at 1 year. Among PWUD, both opioid and stimulant use were common. Models for combined treatment of substance use disorders and infections, particularly MRSA, are needed.

Keywords. *Staphylococcus aureus*; methicillin-resistant *Staphylococcus aureus*; bacteremia; substance-related disorders; patient readmission.

In step with soaring rates of drug use and overdose in recent years [1, 2], hospitalizations for serious bacterial infections associated with drug use have increased by a factor of 2–10 in the past decade [3–5]. *Staphylococcus aureus* infections occur commonly in people who use drugs (PWUD) [6, 7] and confer substantial morbidity and mortality [8]. On average, PWUD hospitalized for these infections are younger, have fewer chronic medical conditions, and have higher rates of homelessness than persons not using drugs (non-PWUD) [9–12]. However, detailed comparative outcome data on *S. aureus* bacteremia and other invasive infections in PWUD vs non-PWUD are limited.

So, while there are increasing numbers of invasive *S. aureus* infections among PWUD, there are comparatively few data defining outcomes among PWUD.

In this study, we sought to (1) characterize clinical and substance use characteristics of PWUD with invasive *S. aureus* infections, and (2) assess rates of antibiotic treatment completion, hospital readmission for ongoing or recurrent infection, and mortality of PWUD vs non-PWUD.

METHODS

Study Design, Setting, and Participants

We conducted a retrospective cohort study of patients hospitalized from 2013 to 2018 at San Francisco General Hospital, a 226-bed public county hospital/trauma center, and University of California, San Francisco Medical Center, a 600-bed tertiary care/referral hospital.

We identified all hospitalizations of adults (age ≥ 18 years) during which (1) *S. aureus* was isolated via blood cultures or culture of another sterile site (tissue, abscess, fluid, or bone) and (2) an *International Classification of Diseases, Ninth or Tenth*

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Revision (ICD) diagnosis code compatible with invasive *S. aureus* infection (bacteremia, endocarditis, epidural abscess, and/or vertebral osteomyelitis; [Supplementary Appendix 1](#)) was documented. Given the possibility of incomplete or inaccurate ICD coding, we also included hospitalizations in which *S. aureus* was isolated in ≥ 1 blood culture but lacked a compatible ICD code. For all hospitalizations, we conducted structured medical record reviews and excluded hospitalizations where *S. aureus* was either designated a contaminant and not treated, or did not involve a *S. aureus* infection of interest. This yielded an analysis set of hospitalizations of adults with *S. aureus* bacteremia, endocarditis, epidural abscess, and/or vertebral osteomyelitis from 2013 to 2018 (see [Supplementary Appendix 2](#) for modified Consolidated Standards of Reporting Trials [CONSORT] diagram). A priori power calculation indicated that a sample size of 729 would be adequate to detect a 10% difference in readmission rates between groups with 80% power and $\alpha = .05$.

Chart Review/Definitions

Four authors (A. A., M. A., S. L., J. D.) performed structured medical records review, with a subset of medical records jointly reviewed to ensure standardization of data extraction. We defined PWUD as persons with any nonprescribed substance use noted in hospital notes by the primary admitting team, infectious disease consultants, or social workers. We excluded cannabis, alcohol, and tobacco use from the PWUD definition. Type of drug, administration route, and timing of use were also recorded. We specified a priori our primary outcomes of antibiotic treatment completion, hospital readmission for infection persistence or recurrence, and death. Using local electronic medical record (EMR) data as well as available regional EMR data, we ascertained antibiotic treatment completion, as well as readmission for ongoing or recurrent *S. aureus* infection within 30 days and at 1 year. Antibiotic treatment was considered incomplete if noted as such in the EMR or if no subsequent records referencing treatment could be located in any health system. We ascertained mortality by medical record review and by cross-comparison to the California state death registry. Deaths occurring out of state were not ascertained.

Statistical Analysis

Demographic and clinical characteristics of PWUD and non-PWUD were summarized using median and interquartile range (IQR) for continuous variables and count and percentage for categorical variables. These characteristics were compared between groups using Wilcoxon rank-sum tests for continuous variables and χ^2 tests for categorical variables. Clinical outcomes and hospital treatments were similarly compared between groups.

To compare survival distributions for both recurrence of readmission for infection within 1 year of discharge and all-cause mortality (measured from hospital admission to 1 year

postdischarge), we examined univariate associations with time to each of the 2 outcomes individually for our primary predictor, drug use, and all variables considered to be potential confounders (including age, race, housing status, medical comorbidities, and methicillin-resistant *S. aureus* [MRSA] vs methicillin-susceptible *S. aureus* [MSSA]) using Cox proportional hazards models. We then created multivariable Cox proportional hazards models including variables that attained statistical significance in univariate analyses and had a plausible explanation for acting as confounders. We considered time origin for all-cause mortality to be time of admission to the hospital, in order to account for in-hospital deaths. For time to recurrence, however, those who died in-hospital were excluded, since they were incapable of experiencing a recurrence, and time origin was considered to be date of discharge. For mortality analyses, patients were censored at 1 year postdischarge if known to be alive at that time; if mortality 1-year postdischarge was unknown, they were censored at last time seen and known to be alive. For time to recurrence analyses, patients were censored at time of death (if death occurred before recurrence), at 1 year postdischarge (if known to be alive and recurrence-free at that point), and at last time seen and known to be recurrence-free (if data were otherwise unavailable). To account for the possibility that deaths among the study population represented competing risks for recurrence rather than censoring events, we also performed a sensitivity analysis using treating death as a competing risk, and calculated a sub-hazard ratio (HR) for infection persistence/recurrence. Finally, we performed a subgroup analysis evaluating 1-year mortality in PWUD who did vs did not complete antibiotic treatment.

Ethics Statement

The study protocol was approved by the University of California, San Francisco Committee on Human Subjects Research.

RESULTS

Demographics and Clinical Characteristics of PWUD and Non-PWUD with *S. aureus* Infections

We identified 1011 hospitalizations from 2013 to 2018 for *S. aureus* infections, and via structured medical record reviews identified 963 hospitalizations for invasive *S. aureus* infections that occurred in 946 unique individuals. Of these, 372 of 963 (39%) were among PWUD ([Table 1](#)). Compared to non-PWUD, PWUD were younger (median age, 50 vs 60 years; $P < .001$), more frequently experiencing homelessness (37% vs 5%; $P < .001$), had fewer chronic health conditions (median Charlson comorbidity index, 2 vs 4; $P < .001$), and had a higher prevalence of human immunodeficiency virus infection (18% vs 4%; $P < .001$). Of PWUD, 258 of 372 (69%) reported injection drug use and 264 of 372 (71%) reported drug use within the last month. PWUD reported opioid use ($n = 214$ [58%]), methamphetamine use ($n = 185$

Table 1. Demographic, Clinical, Substance Use, and *Staphylococcus aureus* Infection Characteristics Among Persons Who Use Drugs (PWUD) and Non-PWUD Individuals Hospitalized for Invasive Disease

Characteristic	PWUD (n = 372)	No History of Drug Use (Non-PWUD) (n = 591)	P Value ^a
Demographic			
Age, y, median (IQR)	50 (40–57)	60 (50–71)	<.001 ^b
Male sex	264 (71)	407 (69)	.49
Race/ethnicity			<.001
White	218 (59)	251 (43)	
Black/African American	76 (20)	79 (13)	
Hispanic/Latinx	47 (13)	88 (15)	
Asian/Pacific Islander	8 (2)	128 (22)	
Other	23 (6)	45 (8)	
Experiencing homelessness	136 (37)	27 (5)	<.001
Clinical			
Charlson comorbidity score, median (IQR)	2 (0–4)	4 (2–7)	<.001 ^b
HIV positive	68 (18)	22 (4)	<.001
Immunosuppressed ^c	77 (21)	165 (28)	.01
History of hepatitis C infection	177 (48)	15 (3)	<.001
Any mental health condition	129 (35)	148 (25)	.001
Substance use			
Injection route described	258 (69)	...	
Recent drug use (<1 mo)	264 (71)	...	
Drug type			
Heroin	198 (53)	...	
Any opioid	214 (58)	...	
Cocaine	139 (37)	...	
Methamphetamine	185 (50)	...	
Opioid and stimulant	145 (39)	...	
Other	17 (5)	...	
Risky alcohol use/AUD ^d	73 (20)	69 (12)	.002
<i>S. aureus</i> infection type			
MRSA infection	180 (48)	183 (31)	<.001
Type of infection			
Bacteremia	275 (74)	514 (87)	<.001
Endocarditis	76 (20)	70 (12)	<.001
Vertebral osteomyelitis	104 (28)	76 (13)	<.001
Epidural abscess	92 (25)	66 (11)	<.001
Two or more of the above	175 (47)	142 (24)	<.001
Pitt bacteremia score, median (IQR)	1 (0–2)	1 (0–2)	.56 ^b
Duration of bacteremia, d, median (IQR) ^e	3 (2–5)	2 (2–4)	<.01 ^b
ICU admission during hospital course	145 (39)	265 (45)	.001

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AUD, alcohol use disorder; HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; PWUD, people who use drugs.

^aP values were calculated using χ^2 test unless otherwise indicated.

^bP value calculated using Wilcoxon rank-sum test.

^cImmunosuppressed defined as those with HIV, chronic exposure to daily prednisone ≥ 10 mg, biologic agents or disease-modifying anti-rheumatic drugs, hematologic malignancy, or chemotherapy.

^dDiagnosed with AUD or noted to consume more than 3 or 4 alcoholic drinks daily in women and men, respectively.

^eAmong those with bacteremia.

[50%]), and concomitant opioid and stimulant use (n = 145 [39%]) (Table 1).

Among PWUD, 48% of infections were caused by MRSA, compared to 31% in non-PWUD ($P < .001$). PWUD had higher rates of deep-seated *S. aureus* infection compared to non-PWUD: 20% vs 12% had endocarditis ($P < .001$), 28% vs 13% had vertebral osteomyelitis ($P < .001$), and 25% vs 11% had epidural abscess ($P < .001$), respectively (Table 1).

Care Delivery

Planned parenteral antibiotic treatment duration for bacteremia, endocarditis, vertebral osteomyelitis, and epidural abscess followed established guidelines and did not differ between PWUD and non-PWUD groups (Table 2). Of patients without preexisting central venous access, fewer PWUD than non-PWUD received a peripherally inserted central catheter (PICC) for parenteral antibiotic treatment (65% vs 84%; $P < .001$).

Table 2. Care Delivery During Hospitalizations of Persons Who Use Drugs (PWUD) and Non-PWUD

Characteristic	PWUD (n = 372)	Non-PWUD (n = 591)	PValue
Planned parenteral antibiotic treatment			
Bacteremia alone, median weeks (IQR)	4 (2–6)	4 (2–6)	.59 ^a
Endocarditis, median weeks (IQR)	6 (6–6)	6 (6–6)	.35 ^a
Vertebral osteomyelitis, median weeks (IQR)	6 (6–6)	6 (6–6)	.63 ^a
Epidural abscess, median weeks (IQR)	6 (6–6)	6 (6–6)	.43 ^a
Inpatient medications for OUD (persons reporting opioid use, n = 214)			
New start methadone ≤40 mg	36 (17)	...	
New start methadone >40 mg	11 (5)	...	
New start buprenorphine	6 (3)	...	
Prior methadone or buprenorphine continued	63 (29)	...	
No inpatient treatment for OUD	98 (46)	...	
Discharge planning			
PICC placed ^b	202/309 (65)	334/400 (84)	<.001 ^c
Discharge setting			<.001 ^c
Remained inpatient for antibiotic course	65 (18)	64 (11)	
Skilled nursing facility	157 (42)	194 (33)	
Home	48 (13)	208 (35)	
Patient-directed discharge from hospital	46 (12)	7 (1)	
Other ^d	24 (6)	23 (4)	
Died or transitioned to hospice in the hospital	31 (8)	95 (16)	
Patient-directed discharge ("AMA") any time during antibiotic course ^e	80 (24)	12 (2)	<.001 ^c

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AMA, against medical advice; IQR, interquartile range; OUD, opioid use disorder; PICC, peripherally inserted central catheter.

^aP value calculated using Wilcoxon rank-sum test.

^bNot including those with preexisting central access, those who died, or those who transitioned to hospice in the hospital.

^cP value calculated using χ^2 test.

^dIncludes transfer back to referring hospital, discharge to medical respite (recuperative services for homeless persons), etc.

^eDenominator in those who survived to hospital discharge, not on hospice: n = 340 in PWUD, n = 496 in non-PWUD.

Among PWUD reporting opioid use, 98 of 214 (46%) did not receive opioid use disorder or opioid withdrawal treatment in the hospital. Furthermore, only 53 of 214 (25%) had new medications for opioid use disorder (MOUD) started while hospitalized (Table 2). Most PWUD who did not die or transition to hospice in the hospital were discharged to a skilled nursing facility (157/340 [46%]) or remained in the hospital until their planned or patient-directed discharge (112/340 [33%]). Non-PWUD who did not die or transition to hospice in the hospital more often completed their antibiotic treatment at home (208/496 [42%]) or at a skilled nursing facility (194/496 [39%]). Almost 1 in 4 episodes of *S. aureus* infection care among PWUD involved a

patient-directed discharge (ie, against medical advice, 24%), compared to only 2% of episodes of care in non-PWUD (Table 2; $P < .001$).

Treatment Completion, Readmission, and Mortality

Table 3 shows unadjusted primary and secondary outcomes. Of persons surviving to hospital discharge, 70% of PWUD vs 87% of non-PWUD completed antibiotic treatment ($P < .001$). At 1 year following hospital discharge, 28% of PWUD were readmitted to the hospital for ongoing or recurrent *S. aureus* infection vs 14% in non-PWUD ($P < .001$). Overall 1-year all-cause mortality was 18% in PWUD vs 30% in non-PWUD ($P < .001$).

Table 3. Clinical Outcomes of *Staphylococcus aureus* Infections

Outcome	PWUD (n = 340) ^a	Non-PWUD (n = 496) ^a	PValue ^b
Completed antibiotic treatment	239/340 (70%)	430/496 (87%)	<.001
30-day hospital readmission due to ongoing or recurrent <i>Staphylococcus aureus</i> infection	72/340 (21%)	54/496 (11%)	<.001
1-year hospital readmission for ongoing or recurrent <i>S. aureus</i> infection	95/340 (28%)	67/496 (14%)	<.001
1-year mortality	67/372 (18%)	175/591 (30%)	<.001

Abbreviation: PWUD, persons who use drugs.

^aDenominator consists of those who survived to hospital discharge, not on hospice.

^bP values calculated using χ^2 tests.

One-year survival without hospital readmission for *S. aureus* infection persistence or recurrence in PWUD vs non-PWUD is shown in [Figure 1](#). PWUD had a 2-fold increased hazard of readmission for infection (adjusted HR [aHR], 2.00 [95% confidence interval {CI}: 1.36 – 2.94]; $P < .001$; [Table 4](#)). Patients with MRSA also had an independently increased hazard of readmission for infection (HR, 1.54 [95% CI: 1.12–2.12]; $P = .01$). Neither age, race, housing, nor medical comorbidities conferred excess hazard for readmission ([Table 4](#)). Results of analyses treating death without recurrence as a competing risk yielded results consistent with those in which subjects who died without recurrence were censored.

Time-to-event analysis focused on all-cause mortality in PWUD vs non-PWUD is shown in [Supplementary Figure 2](#) ([Supplementary Appendix 3](#)). In this adjusted Cox proportional hazards model for mortality, drug use was not associated with increased hazard of 1-year mortality (aHR, 0.82 [95% CI: .59–1.15]; [Supplementary Appendix 4](#)), and only degree of comorbid illness was independently associated with increased hazard of death (aHR, 1.20 [95% CI: 1.14–1.26]; [Supplementary Appendix 4](#)).

In the subgroup of PWUD who survived to hospital discharge, we compared individuals who completed antibiotic therapy vs those who did not complete therapy. Unadjusted 1-year mortality following discharge among PWUD who did not complete antibiotic treatment was 27.6% (95% CI: 18.6%–39.9%) compared to 11.5% (95% CI: 2.9%–38.6%) in PWUD who successfully completed antibiotic treatment.

DISCUSSION

In this large cohort of patients hospitalized for invasive *S. aureus* infections at academic and public hospitals, we found that PWUD, compared to non-PWUD, had double the risk of readmission for infection persistence or recurrence 1 year after hospital discharge. MRSA infection was also independently associated with decreased readmission-free survival. Additionally, PWUD had markedly decreased antibiotic treatment completion and experienced differences in care delivery. Among PWUD, opioid and stimulant use were common, though substance use disorder treatment rates were low.

In this comparative outcomes study, we found that PWUD hospitalized with invasive *S. aureus* infections had double the hazard of hospital readmissions for ongoing or persistent infection compared to non-PWUD, though with no meaningful difference in mortality between groups. This finding of more frequent hospital readmissions coupled with comparable or lower rates of mortality among PWUD vs non-PWUD are consistent with prior studies on drug use–associated endocarditis [10, 11, 13]. The higher rate of infection persistence and recurrence we found did not appear to be due to prescription of inadequate antibiotic treatment regimens: in our study, we found no difference in planned antibiotic durations in PWUD vs non-PWUD. This is similar to findings of a smaller recent study evaluating quality metrics in care for PWUD with *S. aureus* bacteremia [14]. However, higher infection recurrence in our cohort did appear to be associated with higher frequency of antibiotic treatment interruptions and incomplete regimens.

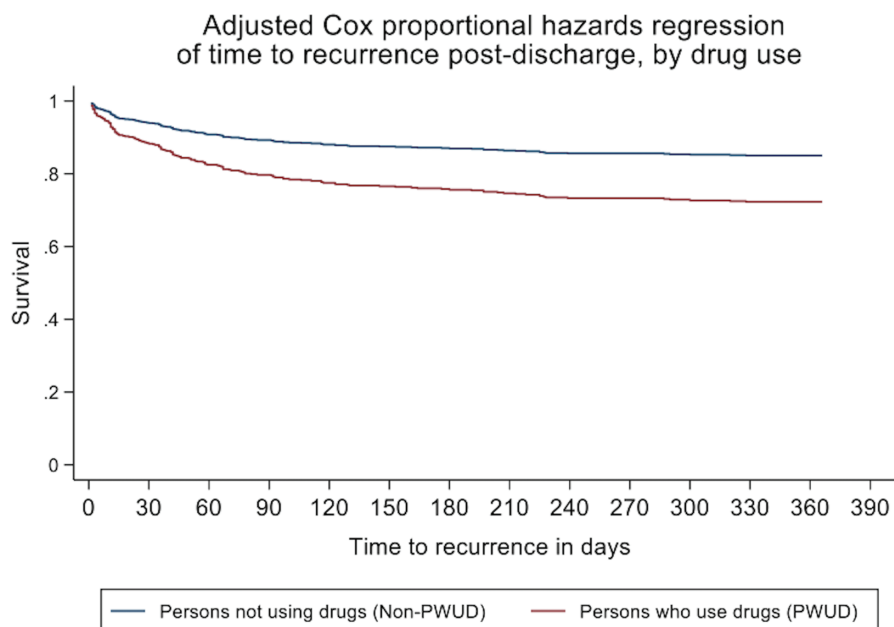


Figure 1. Infection-related readmission-free survival in persons who use drugs (PWUD) vs non-PWUD: Cox proportional hazards regression. One-year survival without hospital readmission for *Staphylococcus aureus* infection persistence or recurrence in PWUD (red) vs non-PWUD (blue) demonstrates early and persistent increase in hazard of infection-related hospital readmission among PWUD (adjusted hazard ratio, 2.00 [95% confidence interval: 1.36 – 2.94]; $P < .001$).

Table 4. Factors Associated With Hospital Readmission for *Staphylococcus aureus* Infection Persistence or Recurrence Within 1 Year of Hospital Discharge

Characteristic	Univariate Analysis			Multivariable Analysis		
	HR	(95% CI)	P Value	HR	(95% CI)	P Value
Drug use	2.30	(1.68–3.15)	<.001	2.00	(1.36–2.94)	<.001
Age	0.88	(.80–.97)	.01	0.94	(.82–1.08)	.37
Sex	0.94	(.67–1.32)	.74	1.00	(.71–1.40)	.99
Race/ethnicity						
White	Ref	
Black	1.03	(.67–1.57)	.90	0.97	(.63–1.49)	.89
Hispanic/Latinx	0.57	(.33–.99)	.05	0.66	(.38–1.15)	.14
Asian/Pacific Islander	1.00	(.63–1.60)	1.00	1.67	(.99–2.80)	.05
Native American	3.02	(1.11–8.23)	.03	2.48	(.91–6.81)	.08
Other	0.62	(.27–1.43)	.27	0.72	(.31–1.65)	.44
Experiencing homelessness	1.83	(1.29–2.61)	.001	1.24	(.83–1.83)	.29
Charlson comorbidity score	0.94	(.88–.99)	.03	1.01	(.94–1.08)	.86
HIV	0.79	(.64–.97)	.03	0.89	(.71–1.12)	.33
Any immunosuppression	1.02	(.71–1.46)	.92	
Any mental health condition	1.10	(.78–1.53)	.59	
MRSA	1.72	(1.26–3.24)	.001	1.54	(1.12–2.12)	.01
Duration of bacteremia	1.00	(.99–1.00)	.80	
Received surgical procedure	0.96	(.70–1.31)	.81	

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MRSA, methicillin-resistant *Staphylococcus aureus*.

In our study, PWUD—who were overall younger and healthier though with more prevalent mental health conditions—were more likely to experience interrupted treatment, leading to ongoing need for treatment or to chronic infection or reinfection. The lower mortality observed among PWUD is consistent with known factors including younger age and fewer advanced medical comorbidities [10, 13].

The toll of *S. aureus* antibiotic treatment noncompletion is high and associated with increased healthcare costs [15, 16]. More research is needed to understand infection-related outcomes when antibiotics are delivered to PWUD via alternate methods such as oral antibiotic regimens [17], long-acting injectable lipoglycopeptide antibiotic regimens [18], and out-of-facility supported models. Likewise, more research is needed on integrating substance use disorder and infection treatment to create models of care that best fit patients' needs.

Our study identified 2 care delivery-related factors that may contribute to higher rates of treatment noncompletion among PWUD. First, PWUD were less frequently offered antibiotics via PICC. In tandem, PWUD were less frequently discharged home; their therapy was more often delivered in the hospital. Together, these findings are consistent with existing literature showing that many physicians and home care providers have reservations about offering outpatient parenteral antibiotic therapy (OPAT) for PWUD [19, 20]. While there have been reports of infections related to PICC lines in OPAT patients [21] that underscore the importance of reliable PICC care during therapy, increasing literature supports the overall safety and effectiveness of home-based OPAT for PWUD [22–25]. This

emphasizes the importance of providing patient-centered care to PWUD and non-PWUD alike. Our concomitant finding that PWUD had far higher rates of patient-directed discharges (ie, against medical advice) reflects the challenges of prolonged hospitalizations.

Another important difference in care delivery for PWUD was the infrequent provision of opioid use disorder treatment. Similar to previous reports on inpatient care for PWUD, we found that among patients using opioids but not previously on MOUD, these medications were infrequently prescribed. This is a known contributor to patient-directed discharges and other poor health outcomes [10, 26, 27]. Additionally, we found that, of patients initiated on methadone, most received lower doses more appropriate for physiologic withdrawal rather than MOUD treatment doses. This may have contributed to patient-directed discharges and antibiotic treatment noncompletion [27]. Importantly, these pharmacotherapy-based quality metrics do not incorporate the pervasive stigma and undertreated pain that PWUD face in acute care settings [28]. They also leave unaddressed the high prevalence in our sample of patients using stimulants, for whom limited pharmacologic treatments exist.

While substantial national attention has focused on the opioid epidemic given rates of opioid overdose [2] and opioid-related infections [3, 29], we found that stimulants, particularly methamphetamine, were involved in more than half of invasive *S. aureus* infections among PWUD. Patterns of drug use in the United States are distinctly regional. Data describing injection drug use (IDU)-related bacterial infections in Maine [10] and North Carolina [30] have noted

prevalence of stimulant use to be only 9%–20%. However, consistent with our California data, a recent report from Florida described a 43% prevalence of stimulant use among patients hospitalized for IDU-related infections [31]. Many mechanisms likely contribute to stimulant-related infections. Methamphetamine use likely raises infection risk via bacterial inoculation of sterile tissue sites during injection drug use, via diminished innate and cellular immunity leading to increased susceptibility to *S. aureus* infection [32, 33], and via increased skin picking behavior. More research including PWUD is needed to elucidate these factors and their relative magnitudes.

For patients with stimulant use disorders, there is a limited evidence base for both pharmacotherapy and behavioral treatments (contingency management, cognitive behavioral therapy) in acute care settings, representing an important treatment gap. Given the rising level of use of both opioids and stimulants nationally (ie, the “fourth wave” of the opioid epidemic) [34, 35], infections related to stimulant use may rise in coming years. Therefore, it is crucial to gain a better understanding of infection pathophysiology and develop interventions to co-deliver therapy for stimulant use disorders and infections.

Finally, in addition to drug use, we also found that MRSA infection was independently associated with increased risk of hospital readmission for infection persistence or recurrence. Compared to MSSA infections, MRSA infections have been associated with poorer outcomes [36, 37], though there is debate about whether this is due to varying efficacy of anti-staphylococcal β -lactams and glycopeptides [38, 39], pathogen-related factors [40, 41], host factors, or confounders such as comorbid illnesses such as cancer and renal failure [36, 42, 43]. Our finding that MRSA infection was associated with increased readmission for infection is concordant with a 2014 study of >90 000 US patients with *S. aureus* bacteremia that found that MRSA infection raised the hazard of both infection-related readmissions, as well as in-hospital mortality. In that study, ICD-coded “drug abuse” was also associated with increased readmission rates [15]; however, only 10.5% of patients had an ICD code for drug abuse, suggesting that PWUD may have been underestimated. The challenge of ascertaining drug use by ICD codes alone is significant [44]. Last, given PWUD have higher rates of MRSA colonization and infection [7, 45, 46], our findings of lower antibiotic completion among PWUD as well as decreased readmission-free survival associated with both drug use and MRSA both suggest that incomplete MRSA treatments in PWUD may be particularly harmful.

Our study has several important limitations. First, our study population was comprised of patients hospitalized at a county and academic medical center in an urban West coast location. As such, our sample may overrepresent patients with homelessness and other socioeconomic hardship, stimulant use, and

chronic illness. However, as stimulant use rises nationally, our results may be generalizable to more urban locations [34, 35]. Second, the accuracy of substance use histories documented in EMRs is challenging to assess. While data collected directly from patient interviews would be optimal, the medical record review methods we used have been shown to be more accurate than administrative coding data in recording comorbidities [47, 48]. Finally, it is possible that our retrospective medical record review–based study design may have underestimated or overestimated both treatment completion and mortality among PWUD. However, our medical record review method included use of our EMR’s CareEverywhere feature, allowing us to incorporate clinical follow-up data from regional medical centers. Additionally, we determined mortality not just from participants’ EMRs but also from the California death registry, thereby increasing accuracy.

To our knowledge, our study is among the largest retrospective cohort studies to date evaluating comparative outcomes among PWUD and non-PWUD hospitalized with invasive *S. aureus* infections. Among PWUD, we found low provision of substance use disorder treatment along with high rates of antibiotic treatment noncompletion and hospital readmission for infection, particularly those with MRSA infection. Given rising rates of serious bacterial infections among PWUD, our findings represent an urgent call to innovate, test, and implement more effective, patient-centered models for co-treatment of *S. aureus* infections and substance use disorders.

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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