Outcomes of Partial Oral Antibiotic Treatment for Complicated *S. aureus* Bacteremia in People Who Inject Drugs

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Running Title: Partial Oral Abx for IDU-S. aureus bacteremia

Abstract:

Background: *Staphylococcus aureus* represents the leading cause of complicated bloodstream infections among persons who inject drugs (PWID). Standard of care (SOC) intravenous (IV) antibiotics result in high rates of treatment success, but are not feasible for some PWID. Transition to oral antibiotics may represent an alternative treatment option.

Methods: We evaluated all adult patients with a history of injection drug use hospitalized from 1/2016 through 12/2021 with complicated *S. aureus* bloodstream infections, including infective endocarditis, epidural abscess, vertebral osteomyelitis, and septic arthritis. Patients were compared by antibiotic treatment (SOC IV antibiotics, incomplete IV therapy, or transition from initial IV to partial oral) using the primary composite endpoint of death or readmission due to microbiologic failure within 90 days of discharge.

Results: Patients who received oral antibiotics after an incomplete IV antibiotic course were significantly less likely to experience microbiologic failure or death than patients discharged without oral antibiotics ($p<0.001$). There was no significant difference in microbiologic failure rates when comparing patients who were discharged on partial oral antibiotics after receiving at least 10 days of IV antibiotics to SOC regimens ($P>0.9$).

Conclusion: Discharge of PWID with partially treated complicated *S. aureus* bacteremias without oral antibiotics results in high rates of morbidity and should be avoided. For PWID hospitalized with complicated *S. aureus* bacteremias who have received at least 10 days of effective IV antibiotic therapy after clearance of bacteremia, transition to oral antibiotics with outpatient support represents a potential alternative if the patient does not desire SOC IV antibiotic therapy.

Keywords: Substance abuse, opioid use disorder, endocarditis, osteomyelitis, *Staphylococcus aureus*,

Introduction:

Staphylococcus aureus is the most common pathogen in serious injection drug use related infections such as infective endocarditis, osteomyelitis, epidural abscess, and septic arthritis [1-3]. The current standard of care for complicated *S. aureus* bacteremia is prolonged courses of intravenous (IV) antibiotics for four to six weeks [4, 5]. However, a 4-6-week course of antibiotics for persons who inject drugs (PWID) can be challenging [6-8]. PWID are frequently considered ineligible for outpatient parenteral antibiotic therapy (OPAT), [9] and often choose to leave the hospital or skilled nursing facilities prior to completing a multi-week course of IV antibiotic therapy as inpatients [10, 11]. Transition to oral antibiotic regimens may represent an attractive treatment strategy.

The consensus surrounding IV-only therapy for invasive *S. aureus* infections has recently come under increased scrutiny following the publication of several large randomized controlled trials of bacteremia, osteomyelitis, and infective endocarditis [12-14]. Iversen et. al demonstrated that transition to oral antibiotics is safe and effective for patients with infective endocarditis – however their study notably did not identify any methicillin resistant *S. aureus* (MRSA) infections and only included five PWID [14]. A quasi-experimental study evaluating transition to high dose oral trimethoprim-sulfamethoxazole (TMP-SMX) yielded similar results while including a number of MRSA infections [15]. Li et. al demonstrated that transition to oral antibiotics is safe and effective for patients with osteomyelitis – however this study excluded patients with any associated bacteremia [13]. Taken together, these studies suggest that oral step-down therapy may be reasonable for some invasive infections after initial IV antibiotic therapy has stabilized the patient and cleared their bacteremia. However, there is limited data on partial oral antibiotic treatment for many of the more complex clinical syndromes associated with *S. aureus* bacteremia in PWID.

PWID represent a unique population in infectious diseases. Clinicians must assess anticipated antibiotic adherence, feasibility of outpatient monitoring, potential drug-drug interactions with medications for opioid use disorder, and access to outpatient follow-up care. The aim of this retrospective cohort study was to compare the effectiveness of standard of care (SOC) IV antibiotic regimens to incomplete IV antibiotic therapy or transition to partial oral antibiotic therapy for PWID with complicated *S. aureus* bloodstream infections.

Methods:

Study Design and Patient Population

We completed a retrospective cohort analysis of patients admitted to Barnes Jewish Hospital (BJH) in St. Louis, Missouri, with *S. aureus* bloodstream infections and a history of active or recent injection drug use (IDU). Patients were identified from microbiology blood culture results that were positive for *S. aureus* from 1/2016 - 12/2021, and all charts were reviewed for IDU history as described previously [16]. Patients were included if they had at least 1 positive blood culture for *S. aureus*, a history of active or recent IDU on chart review, evidence of either infective endocarditis, septic arthritis, epidural abscess, and/or vertebral osteomyelitis, as diagnosed in infectious diseases (ID) consult notes, and if they survived to hospital discharge. Patients were excluded if they died during the index hospitalization, were discharged on OPAT, or had a left ventricular assist device. Only index hospitalizations for *S. aureus* bloodstream infections were included (Figure 1). For patients with multiple hospitalizations for *S. aureus* bloodstream infections over the five-year study period, only the earliest hospitalization with a *S. aureus* bloodstream infection was included for each discrete clinical episode that were at least 90 days apart.

Data Collection

Patient demographics, substance use history, infection type, care characteristics, and outcomes were reviewed in the electronic medical record. Patient comorbidities were captured using the Elixhauser comorbidity index [17]. Duration of bacteremia was defined as the number of days between the first positive blood culture and the last positive blood culture (inclusive of both the first and last date). Prolonged bacteremia was defined as five or greater days of documented *S. aureus* bacteremia prior to sustained negative blood cultures. Physicians (L.R.M., M.J.D., N.L.C., N.S.N., S.L., S.S.) performed manual chart review of ID consult notes, echocardiography reports, imaging, and microbiology data to identify type of clinical syndrome. Patients were divided into 3 antibiotic treatment strategy groups;

- Strategy A) "SOC": standard of care IV antibiotics – patients who completed a SOC IV antibiotic regimen during their inpatient admission as recommended by ID consult notes;
- Strategy B) "incomplete IV": incomplete IV antibiotic therapy – patients who left the hospital prior to completing IV antibiotic therapy and did not receive any oral antibiotics on discharge; and
- Strategy C) "partial oral": transition to partial oral antibiotic therapy – patients who left the hospital on oral antibiotics either through a patient directed discharge or against medical advice discharge prior to completing a SOC IV antibiotic regimen.

The planned antibiotic duration was determined by chart review of infectious disease consultation notes and discharge summaries. The date of effective IV antibiotic therapy used to calculate duration of antibiotics prior to discharge was determined as the date of both source control (i.e. laminectomy, joint washout, or heart valve replacement surgery if applicable) and/or blood culture negativity, whichever was achieved later. Physicians reviewed discharge prescriptions and post-discharge clinic follow-up notes to identify the type of oral antibiotics prescribed. The majority of patients in strategy C (partial oral) participated in a previously published post-discharge support program which focused on antibiotic adherence and substance use disorder care by providing patient's with access to health coaches, case management, close ID clinic follow-up, and free antibiotics for uninsured patients [18]. Patient-reported antibiotic adherence for PWID on oral antibiotics who participated in this program was abstracted from the chart where available. All subsequent admissions within 90 days after discharge were reviewed by two study physicians to identify if death or readmission was related to microbiologic failure. If there was no consensus, a third physician reviewed the case and readmission was discussed as a group to determine if it met criteria for the primary outcome.

The primary outcome was microbiological treatment failure at 90 days. This endpoint was defined as a composite readmission within 90 days of discharge that was related to the initial *S. aureus* infection with either ongoing infection without any significant change, or development of new clinical worsening including isolation of *S. aureus* from any sterile site, or death during a subsequent hospital stay associated with microbiologic failure. Common reasons for readmissions which were not considered to represent microbiologic failure included non-fatal drug overdose, noninfectious medical issues like gun-shot wounds, normal spontaneous vaginal delivery, suicidal ideation, complications of diabetes, or readmissions for new infectious complications from IDU with a different pathogen.

Statistical Analysis

Descriptive analysis was performed using the baseline characteristics, as well as the primary and secondary outcomes. Categorical variables were summarized as percentages and continuous variables as the median and interquartile range (IQR). Group comparisons were investigated using the Kruskal-Wallis test for continuous variables and the chi-square test (or variants thereof) for categorical variables. Uni-

and multivariable logistic regression analysis was used to determine the factors associated with treatment failure with the appropriate outcome as the dependent variable. We included all the explicative variables that were clinically relevant or that have been previously associated with poor outcomes in the univariable analysis; demographics, comorbidities, health insurance status, type of infection, MRSA versus MSSA, prolonged bacteremia, addiction medicine consultation, medications for opioid use disorder (MOUD), and antibiotic treatment group. Those variables significant at the 10% level in univariable analyses were included in the multivariable models with forwards selection and backwards deletion used to determine the most parsimonious model. Inverse probability weights were included in the models to adjust for baseline covariate imbalance between the respective patient groups.

All analyses were performed using SAS (version 9.4; SAS Institute Inc.) and R version 4.1.1 (R foundation for Statistical Computing, Vienna, Austria). P values <0.05 were considered statistically significant with pairwise comparisons were not corrected for multiple testing (unless stated otherwise).

Subgroup Analysis

We performed a subgroup analysis comprised of patients who had completed at least 10 days of IV antibiotic therapy after clearance of bacteremia and source control, similar to the minimum duration recommended in the POET trial [14].

Patient Consent Statement

The Washington University School of Medicine Human Research Protection Office (HRPO) approved this study under IRB 202110099. Informed consent was not required for this study according to the HRPO regulations given its minimal risk and retrospective observational study design.

Results:

Patient demographics and infection characteristics are presented in Table 1. Substance use characteristics and MRSA prevalence at baseline were not significantly different between groups. Groups differed in rates of infective endocarditis (p=0.007), and the Elixhauser comorbidity score (p=0.004), both of which were highest in strategy A (SOC). Duration of bacteremia differed across all groups with a marginally shorter mean duration seen among patients in strategy B (incomplete IV) (p=0.03), however, there was no significant difference in pairwise comparisons between patients in strategy A (SOC) or strategy C (partial oral) for either prolonged bacteremia (A vs C: 44/122 (36.1%) vs 25/69 (36.2%), p>0.9) or duration of bacteremia (median 3 days, IQR 1-6 for both Strategy A and C p=0.9). The loss to follow-up rate was lowest in strategy C (partial oral), likely influenced by the concurrent implementation of a post-discharge support program at our institution [18].

In terms of primary endpoint among patients who had cleared bacteremia prior to discharge, patients in strategy B were the most likely across all groups to experience microbiologic failure or death within 90 days post-discharge (p<0.001). In contrast, strategies A (SOC) and C (partial oral) had comparable levels of the primary outcome (A vs C: 13/122 (10.7%) vs 9/69 (13.0%), p=0.6). The median duration of oral antibiotics prescribed in strategy C (partial oral) was 21 days (IQR 9-33). Evidence on using partial oral antibiotics for MRSA bacteremia is very limited, thus we further analyzed if there was any influence of MRSA vs MSSA infection on primary outcome rates in patients receiving strategy C (partial oral). While the data was not adequately powered to study this outcome, we observed no significant difference whether partial oral antibiotics were used to treat MRSA (4/32 (12.5%)) or MSSA (5/37 (13.5%), p>0.9).

Duration of IV antibiotics received prior to discharge was associated with a duration-dependent effect on infection outcome (Figure 2). Discharge prior to clearance of bacteremia universally resulted in microbiologic failure for patients discharged without antibiotics, and results remained poor even for patients discharged with oral antibiotics, with 2 out of 4 patients readmitted for microbiologic failure. However, in the subgroup of patients who received at least 10 days of IV antibiotics prior to transition to oral antibiotics, outcomes were not significantly different between strategy C (partial oral) and strategy A (SOC) (Figure 2). In terms of time from discharge to failure, Figure 3 shows the Nelson-Aalen cumulative hazard ratio for all patients (Figure 3A), patients who cleared their bacteremia prior to discharge (Figure 3B) and patients who were discharged after a minimum of 10 days of effective IV antibiotic therapy after clearance of bacteremia and source control (Figure 3C). In all cases, patients discharged without oral antibiotics had the highest rate of microbiologic failure.

Excluding those who did not clear their bacteremia prior to discharge, the only strong independent predictors of an increased risk of microbiologic failure in multivariable models were being in strategy B (incomplete IV therapy) (adjusted odds ratio (aOR) 7.9 compared to strategy A, 95% confidence interval [CI] (2.9, 21.6), p<0.001, Table 2) and paraplegia (aOR 7.8, (2.1, 28.6), p=0.002).

When evaluating patients who left the hospital prior to completion of IV antibiotics (strategies B and C), there was a significantly higher risk of microbiologic failure associated with strategy B (incomplete IV) compared with strategy C (partial oral), and this difference persisted in inverse probability weighted (IPW) models adjusted for baseline covariate imbalance (aOR 6.7 [1.9, 25.8], p=0.005, Table 3, Figure 4). There was no significant difference in outcomes between strategy A (SOC) and strategy C (partial oral) (IPW aOR 1.3 (0.4, 3.7), p=0.7).

Subgroup analyses

Our subgroup analysis found that patients in strategy C (partial oral) who had received at least 10 days of effective IV antibiotic therapy vs. strategy A (SOC) had similar results (Figure 4).

Antibiotics used, along with patient self-reported antibiotic adherence data obtained through chart review, are shown in Table 4. While the sample size was not powered to compare different treatment regimens, no specific treatment regimens resulted in a noticeably higher failure rate. Self-reported antibiotic adherence could be assessed in 53 out of 73 patients discharged on partial oral antibiotic therapy, while 20 patients (31.5%) had incomplete data on antibiotic adherence. There was a higher but non-significantly different rate of self-reported antibiotic non-compliance in patients who were prescribed dual oral antibiotic therapy (p=0.7).

Discussion:

Our data suggests that when faced with a patient who no longer wishes to receive SOC IV antibiotics for treatment of their complicated *S. aureus* infection, providing a transition to oral antibiotics with a hospital-based outpatient antibiotics support program, significantly reduces the risk of microbiologic failure or death compared to discharge without any additional antibiotic treatment. For patients discharged on partial oral antibiotics, success rates were highest when patients received at least 10 days of IV antibiotic therapy after clearance of bacteremia, similar to durations study participants received in the POET trial [14]. The observed rate of microbiologic failure in both patients who received SOC IV antibiotic therapy and those receiving partial oral antibiotic therapy after at least 10 days of IV antibiotics is consistent with rates described in the broader population [19-21]. This data suggests that oral antibiotics may represent an effective treatment for complicated *S. aureus* bacteremias in PWID with endocarditis, epidural abscess, vertebral osteomyelitis or septic arthritis, who have had adequate source

control, and received at least ten days of IV antibiotics after clearance of bacteremia. These findings are consistent with other literature that shows partial oral antibiotics are effective in smaller cohorts of IDU-associated endocarditis [22]. However, our cohort represents an important addition to the literature as it includes a significant proportion of infections secondary to MRSA.

The choice of oral antibiotic regimens in PWID with invasive *S. aureus* infections often presents unique challenges compared with the treatment of other populations. Factors confounding their care include high rates of unstable housing [23], low health literacy rates [24], and low rates of health insurance [25]. Identifying optimal antibiotic therapy regimens for this population may require balancing the need for medication adherence against the existing evidence on antibiotic treatment options. For example, oral antibiotic treatment options used previously for infective endocarditis [14] have relied heavily on adjunctive rifampin which may not be feasible for many PWID who may be on methadone, or receiving direct acting antivirals for hepatitis C treatment. Similarly, many of the previously proposed endocarditis regimens required dosing three or four times a day [14] which may be more challenging in populations with limited health literacy [26]. In contrast, the OVIVA trial [13] included several antibiotic regimens with once or twice daily dosing with a single antibiotic which may prove easier for many PWID to achieve optimal antibiotic adherence. While not powered to assess individual regimens, our data suggests that several oral antibiotic regimens with twice daily dosing including doxycycline, linezolid, cefadroxil, and TMP-SMX may be potential options for patients in whom pill burden and medication non-adherence is a significant concern.

The increasing movement for OPAT programs to support PWID will enhance patient access to SOC IV antibiotic treatment, and represents an important advancement in infectious diseases care for PWID [27-29]. However, it is likely that even at institutions with expanded access to OPAT, not all PWID may be eligible, either due to physician perceived barriers, lack of safe and stable housing, lack of health insurance, or limited access to outpatient follow-up [30, 31]. For some patients there may also be benefits to avoiding the complexities of OPAT. Multi-disciplinary conferences for coordinating prolonged antibiotic therapy for PWID, allow for both patients and providers to identify patient-centered antibiotic treatment options [32]. Physicians caring for PWID who decline SOC IV antibiotic treatment and desire to leave the hospital prior to completion of IV antibiotics, should engage patients in shared decision making about the risks and benefits of partial oral antibiotic therapy. Key aspects of this discussion include the consistent adherence needed while on oral antibiotics, the importance of completing the full duration of oral antibiotic therapy, and following up in post-discharge clinic visits.

PWID discharged on oral antibiotics for complicated *S. aureus* bacteremia should receive multidisciplinary care during both the hospitalization and immediate post-discharge time period. In our experience, many PWID struggle with navigating the healthcare system, and outpatient support is required to ensure that patients both initiate and tolerate antibiotic prescriptions. Outreach by health-care team members can help address any cost issues for antibiotics, while also trouble-shooting common side effects such as nausea that might otherwise result in premature cessation of antibiotics. These simple interventions along with close clinic follow-up are essential to help minimize subsequent treatment failures.

This study has several important limitations. This was a single-center, retrospective study performed at an academic institution with access to addiction medicine physicians over a time-period where there was an increasing emphasis on multidisciplinary care including outpatient support for patients discharged on oral antibiotics; this may not be available at all institutions. There also was a higher loss to follow-up in

patients discharged without oral antibiotics, which may lead to an underestimation of risk of death in that cohort. Additionally, we have excluded any patients that died prior to discharge, potentially favoring SOC IV antibiotics, and have used the date of discharge as a standard starting point for calculating a 90-day follow-up period which may lead to immortal time bias. Methodologically, we attempted to adjust for baseline covariate imbalance by fitting models including inverse probability weights, but this cannot overcome underlying systematic unmeasured confounding between the groups. Lastly, patients in this cohort were immunocompetent, and younger than the average aged patient with non-PWID associated *S. aureus* infections, and many of the *S. aureus* strains causing infections in this cohort have been previously identified as having fewer virulence factors and supra-antigenic toxins than what is often seen in non-PWID associated *S. aureus* infections [16].

Conclusion:

The SOC for *S. aureus* bacteremias complicated by septic arthritis, vertebral osteomyelitis, epidural abscess or infective endocarditis, is a multi-week course of IV antibiotics [4, 5]. We firmly believe that SOC regimens should continue to be offered to all PWID with complicated *S. aureus* bacteremias. However, we recognize that for many patients this option is not desired or feasible and would significantly reduce their quality of life. Our data suggest that incomplete antibiotic therapy should be avoided at all costs, and that transition to oral antibiotics should be offered to PWID who decline SOC IV antibiotics, with the best outcomes observed in patients who are able to complete at least 10 days of effective in-house IV antibiotic therapy after clearance of bacteremia. These findings should be incorporated into treatment guidelines to caution against discharging PWID with partially treated infections without offering them outpatient oral antibiotic therapy.

NOTES

Author contributions. L.M. and JAW. conceptualized and designed the study. AA and JAW conducted the statistical analysis. L.R.M., M.J.D., N.L.C., N.S.N., S.L., S.S performed all chart review. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the writing and critical revision of the report. All authors contributed to the data acquisition, data analysis, or data interpretation and reviewed and approved the final version.

Patient consent: This study was approved and granted a waiver of consent by the Washington University Institutional Review Board before any research activities were performed.

Funding: This work was also supported by the National Institutes of Health under grant numbers [KL2TR002346, K23DE029514]. AA was partially supported for this work by the Swiss National Science Foundation grant number CRSK-3_190977/1.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Potential conflicts of interest. All authors: No reported conflicts of interest. MDJ reports grants from CDC Epicenters (U54CK000609), NIH/NIDCR (K23DE029514), NIH/NIDA (R21DA053710), NIH/NIDCR (X01DE030402, X01DE030403, X01DE031119), NIH/NCATS (R21TR003410), and Pew Charitable Trusts; payment for lecture from American Hospital Association and Hektoen Institute for Medical Research (paid to author); payment for expert witness from Fisher Rushmer, Rouse Frets Write Gross, and Stanton Barton (paid to author); support for attending meetings and/or travel from Pew Charitable Trusts (Harnessing Health Systems to Expand and Enhance Antibiotic Stewardship in Outpatient Settings); and DSMB member for Duvelisib for treatment of COVID-19 (unpaid participation). AA reports paid work for University Children's Hospital Basel. JM reports the following grants or contracts unrelated to this work: PI, Swiss National Science Foundation, "Understanding the drivers of surgical site infections" (paid to institution in Switzerland); Sub-PI, CDC Prevention Epicenters Grant, "The Impact of An Existing Anesthesia Control Tower (ACT) Intervention to Improve Intraoperative Care on Infectious Outcomes" (paid to Washington University School of Medicine); Site PI (PI Philip Polgreen, U of Iowa), NCATS R21, "Determining the acceptability and feasibility of mobile-health approaches to gather clinical information from patients at home following hospital discharge (paid to Washington University School of Medicine). JM also reports consulting fees (payments <$10,000 per year to author) for work as consultant on the topic of catheter associated urinary tract infection surveillance for the Swiss National Center of Infection Control; role as Board Member for Swiss National Center for Infection Control (paid to institution in Switzerland) and role as Steering Committee Member for National Center for Antibiotic Resistance, Switzerland (unpaid); and other financial or non-financial interests as Co-PI (PI: Thomas Kessler, U of Zurich), Swiss National Science Foundation, Engineered Bacteriophages as Antibiotic Alternatives for Treating Catheter-Associated Urinary Tract Infections (CAUTIs) (unpaid).

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FIGURE LEGENDS

Figure 1. Flow-chart for development of retrospective cohort. Abbreviations: IV, intravenous; LVAD, left ventricular assist device; OPAT, outpatient parenteral antibiotic therapy; SOC, standard of care

Figure 2. Rates of microbiologic failure within 90 days after discharge by duration of effective IV antibiotic therapy received prior to discharge.
*Days of IV antibiotic therapy received after clearance of bacteremia and source control. Confidence intervals are 95% Clopper=Pearson confidence intervals. Pvalues determined by Fisher's exact test, not corrected for multiple testing. Abbreviations: IV, intravenous; SOC, standard of care

Figure 3. Nelson-Aalen cumulative hazard plot by antibiotic treatment group of (A) all patients, (B) patients who achieved clearance of bacteremia prior to discharge, and (C) patients who received at least 10 days of effective IV antibiotic treatment after clearance of bacteremia and/or source control prior to discharge.

Figure 4. Forest plot of estimates from logistic regression analyses of subgroups. Abbreviations: ABX, antibiotics; adj. adjusted; IPW, inverse probability weighted model; uni. Univariable

Table 1. Demographics of PWID admitted for complicated *S. aureus* bacteremia, by antibiotic treatment group

n (%) median [IQR]	**All patients n=238**	**Characteristics of patients who were discharged following clearance of *S. aureus* bacteremia grouped by antibiotic treatment strategy n=227**			**A vs B vs C p-value**
		Strategy A Completed Inpatient IV [Standard of Care] n=122	**Strategy B Partial IV, no oral antibiotics [Incomplete Therapy] n=36**	**Strategy C Partial IV, partial oral antibiotics [Partial Oral] n=69**	
Age (years)	35 [31, 42]	35 [30, 42]	32 [30, 40]	37 [32, 44]	0.03
Male gender	126 (52.9)	62 (50.8)	24 (66.7)	36 (52.2)	0.2
White	171 (71.8)	85 (69.7)	24 (66.7)	55 (79.7)	0.2
Unstable housing	48 (20.2)	19 (15.6)	7 (19.4)	22 (31.9)	0.03
Insurance – self-pay	77 (32.4)	29 (23.8)	16 (44.4)	25 (36.2)	0.03
Substance Use Characteristics*					
Injection Opioid Use	218 (91.6)	114 (93.4)	31 (86.1)	62 (89.9)	0.4
Injection Methamphetamine Use	84 (35.3)	43 (35.2)	15 (41.7)	22 (31.9)	0.6
Injection Cocaine	38 (16.0)	16 (13.1)	9 (25.0)	11 (15.9)	0.2
Comorbidities					
Hepatitis C infection	157 (66.0)	77 (63.1)	29 (80.6)	45 (65.2)	0.1
Number of Elixhauser Comorbidities	6 [4, 8]	7 [5, 9]	5 [3, 6]	5 [4, 8]	0.002
Type of clinical syndrome caused by *S. aureus* bacteremia**					
Infective Endocarditis	154 (64.7)	90 (73.8)	22 (61.1)	36 (52.1)	0.007
Epidural abscess	35 (14.7)	16 (13.1)	5 (11.6)	14 (20.3)	0.4
Septic arthritis	56 (23.5)	25 (20.5)	10 (27.8)	20 (29.0)	0.2
Vertebral Osteomyelitis	46 (19.3)	18 (14.8)	9 (25.0)	16 (23.2)	0.2
S. aureus bacteremia characteristics					
Prolonged Bacteremia (5+ Days)	77 (32.4)	44 (36.1)	6 (16.7)	25 (36.2)	0.08
Duration of Bacteremia (days)	3 [1, 6]	3 [1, 6]	2 [1, 3]	3 [1, 6]	0.03
Methicillin Resistant S. aureus	99 (41.6)	48 (39.3%)	18 (41.7%)	32 (46.4%)	0.6

Inpatient Care Received					
Duration of IV abx prior to discharge (days)	34 [14, 42]	42 [42, 42]	15 [4, 27]	18 [7, 32]	<0.001
Length of stay (days)	39 [17, 48]	47 [43, 52]	18 [5, 31]	26 [8, 35]	-
% IV antibiotic course completed in the hospital	100 [38, 100]	100% [100, 100]	37% [11, 71]	46% [17, 76]	-
Addiction medicine consultation	145 (60.9)	81 (66.4)	14 (38.9)	48 (69.6)	0.001
Medications for Opioid Use Disorder					0.004
none	98 (41.2)	40 (32.8)	24 (66.7)	25 (36.2)	
buprenorphine	79 (33.2)	47 (38.5)	4 (11.1)	37 (39.1)	
methadone	61 (25.6)	35 (28.7)	8 (22.2)	17 (24.6)	
Lost to Care	31 (13.0)	18 (14.8)	8 (22.2)	5 (7.2)	0.09
Primary Endpoint – Composite outcome microbiologic failure or death within 90 days of discharge	38 (16.7)	**13 (10.7)**	**16 (44.4)**	**9 (13.0)**	**<0.001**
Secondary Endpoint - All Cause Readmission within 90 days of discharge	47 (19.7)	38 (31.1%)	19 (52.8%)	18 (26.1%)	0.02

Abbreviations: Abx, antibiotics; IV, intravenous; *Patients may report more than one type of substance use; **Patients may present with multiple concurrent serious injection related infections

Table 2. Variables associated with primary outcome among PWID with complicated *S. aureus* bacteremia

	univariable			multivariable		
Variable	OR	95% CI	p value	OR	95% CI	p value
Patient Demographics*						
Insurance						
Managed Care	1.0	Reference		1		
Medicaid			NS	(reference)		NS
Medicare	3.9	(0.8, 18.8)	0.09		(1.1, 33.0)	0.04
Self Pay			NS	5.9		NS
Inpatient Care						
OUD treatment						
None	1					
Buprenorphine	(reference)	(0.2, 1.0)	0.04			NS
Methadone	0.4		NS			
Addiction Medicine consult	0.4	(0.2, 0.8)	0.01			NS
Duration of IV antibiotics before Discharge:						
Bacteremic at discharge	4.5	(1.0, 20.8)	0.05			
1-9 Days effective IV abx	0.1	(0.02, 0.5)	0.01			
10+ Days effective IV abx	0.1	(0.01, 0.3)	<0.001			
Completed Inpatient IV abx	0.03	(0.01, 0.1)	<0.001			
Elixhauser Comorbidities*						
Fluid and electrolyte disorders	0.5	(0.2, 0.9)	0.03	0.4	(0.2, 1.0)	0.06
Paraplegia	6.9	(2.3, 20.5)	<0.001	7.8	(2.1, 28.6)	0.002
Infection Characteristics*						
Septic arthritis	2.4	(1.2, 5.1)	0.02	2.3	(1.0, 5.4)	0.06
Antibiotic treatment group						
Completed inpatient IV	1.0 (Reference)			1.0 (reference)		
Partial IV, partial oral	1.3	(0.5, 3.1)	0.6	-	-	NS
Partial IV, no oral	6.7	(2.8, 16.0)	<0.001	7.9	(2.9, 21.6)	<0.001

*Only variables that were statistically significant in univariate analysis are listed; statistical significance is included at the 5% level.

Table 3. Inverse propensity weighting comparisons of primary endpoint (microbiologic failure at 90 days) by antibiotics strategy

Comparison groups	A Completed Inpatient IV [Gold standard]	B Partial IV, no oral	C Partial IV, partial oral	p-value
Comparing microbiologic failure at 90 days between patients who discharged before completing IV antibiotics (strategy B vs C) - Inverse probability weighted		16 (44.4) [N = 36] aOR 6.7 (1.9, 25.8)	9 (13.0) [N=69] 1 (reference)	0.001 0.005
Comparing microbiologic failure at 90 days between patients who completed standard of care (strategy A) vs partial oral antibiotics (strategy C) - Inverse probability weighted	13 (10.7) [N=122] 1 (reference)		9 (13.0) [N=69] aOR 1.3 (0.4, 3.7)	0.8 0.7
Subgroup analysis: Including only those with >=10 days effective IV antibiotic therapy prior to discharge				
Comparing microbiologic failure at 90 days between patients who discharged before completing IV antibiotics (strategy B vs C) - Inverse probability weighted		9 (40.9) [N=22] aOR 5.4 (1.2, 24.0)	5 (10.9) [N=46] 1 (reference)	0.004 0.03
Comparing microbiologic failure at 90 days between patients who completed standard of care (strategy A) vs partial oral antibiotics (strategy C) - Inverse probability weighted	13 (10.7) [N=122] 1 (reference)		5 (10.9) [N=46] aOR 1.1 (0.3, 3.9)	0.9 0.9

Table 4.

Table of type of oral antibiotics used

		Self-reported Adherence Abstracted from Medical Record through Chart Review		
Antibiotic Class and dosing	Primary outcome (Microbiologic failure at 90 days)	Self-reported Adherence	Self-reported Non-Adherence	No adherence data available
Beta-lactams*	0/8 (0%)	6	1	1
Clindamycin 450 mg QID	1/3 (33%)	2	0	1
Doxycycline 100 mg BID	6/37 (16%)	23	5	9
Ciprofloxacin 750 mg BID	0/2 (0%)	1	0	1
Linezolid 600 mg BID	3/15 (20%)	9	2	4
Rifampin** 450 mg BID	1/3 (33%)	1	1	1
TMP-SMX 2 DS BID	4/26 (15%)	15	4	7
Comparison of dual vs single antibiotic class therapy				
Single Agent therapy	7/52 (13%)	33	3	16
Dual Agent therapy***	4/21 (19%)	12	5	4

*Includes amoxicillin-clavulanate 875 mg BID, cephalexin 500 mg QID, cefadroxil 1,000 mg BID, and dicloxacillin 1,000 mg QID

**Rifampin was never used as single agent therapy

**Patients who received dual agent therapy are listed for both categories

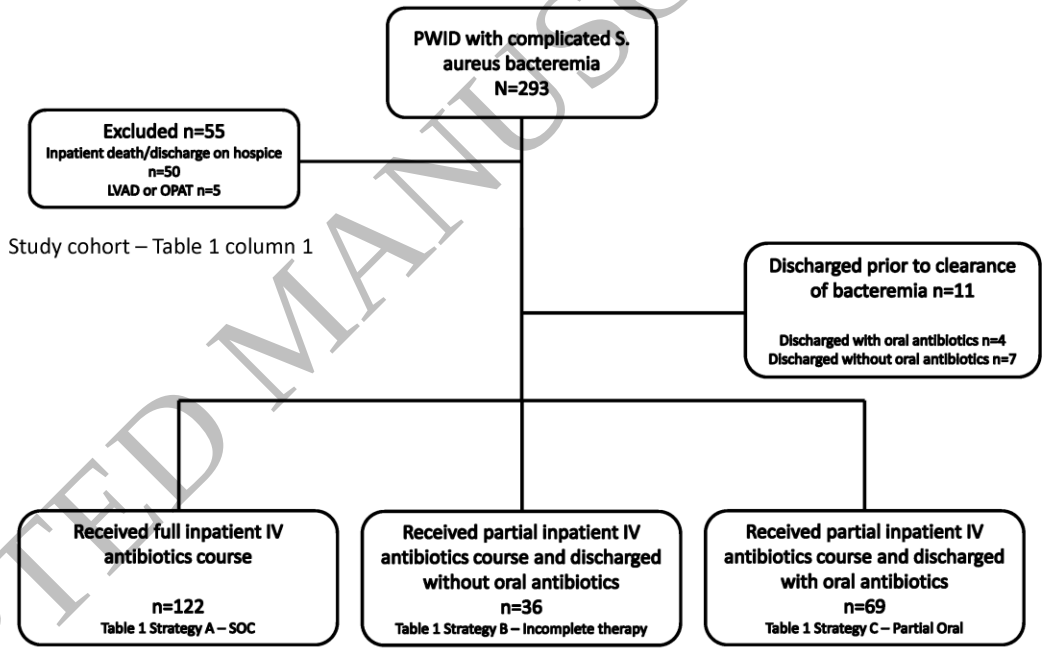

Figure 1
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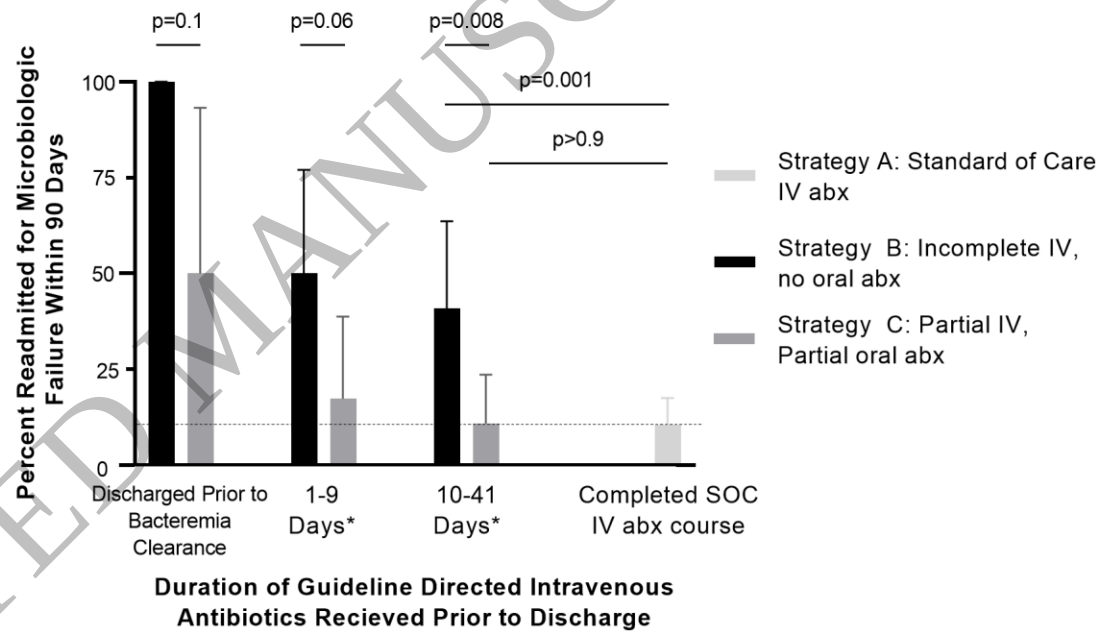

Figure 2
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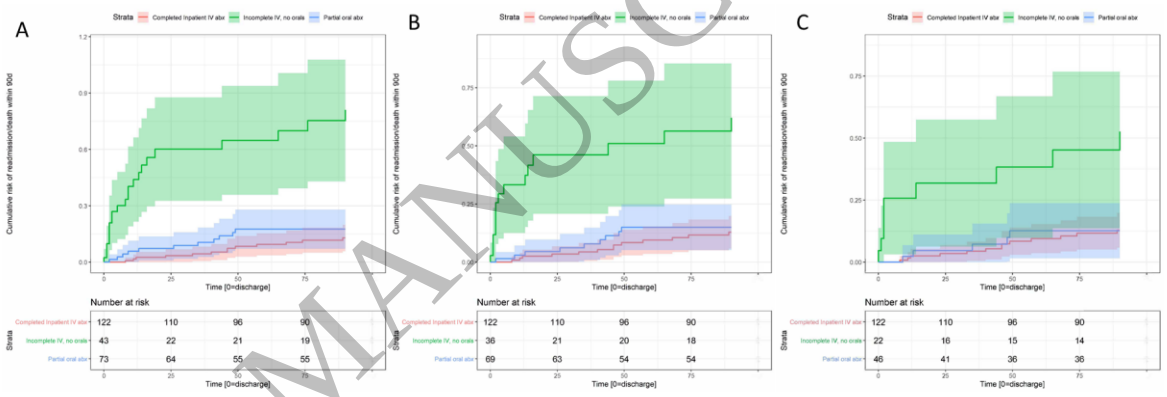

Figure 3
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