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Predictors of Nonadherence Among Patients With Infectious Complications of Substance Use Who Are Discharged on Parenteral Antimicrobial Therapy

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Background. The management of invasive infections related to substance use disorder (SUD) needing parenteral antimicrobial therapy is challenging and may have poor treatment outcomes including nonadherence and lack of completion of parenteral antimicrobial therapy.

Methods. In this retrospective cohort of 201 patients with invasive infections related to SUD, we looked at frequency and determinants of unfavorable outcomes including nonadherence.

Results. Seventy-nine percent of patients with SUD-related infection completed parenteral antibiotic therapy in skilled nursing facilities. A total of 21.5% of patient episodes had documentation of nonadherence. Nonadherence was higher in patients with active injection drug use (IDU) (28.5% versus 15% in non IDU; adjusted odds ratio [OR] 2.36; 95% confidence interval [CI], 1.1–5.5; $P = .024$), patients with active SUD in the prior year (24.5% vs 11%, $P = .047$), patients with use of more than 1 illicit substance (30.3% vs 17%, $P = .031$), as well as in people experiencing homelessness (32.8% vs 15.7% in stably housed, $P = .005$). In a multivariate model, nonadherence was significantly associated with IDU (OR, 2.38; 95% CI, 1.03–5.5) and homelessness (OR, 2.25; 95% CI, 1.01–4.8). Medication for opioid use disorder was prescribed at discharge in 68% of overall cohort and was not associated with improved outcomes for any of the above groups.

Conclusions. Nonadherence to parenteral antimicrobial therapy is high in the most vulnerable patients with unstable high-risk SUD and adverse social determinants of health.

Keywords. homelessness; injection drug use; nonadherence; parenteral antimicrobial therapy.

The opioid crisis has fueled an epidemic of overdose deaths and related infectious diseases [1]. The number of persons seeking emergency care and hospitalization related to opioid use disorder (OUD) and related conditions has steadily increased [2]. Invasive infections related to OUD and related substance use disorder (SUD) including staphylococcal bacteremia, endocarditis, and osteoarticular infections often require prolonged hospitalization and parenteral antimicrobial therapy [3, 4]

System barriers, including exclusion from traditional home outpatient parenteral antimicrobial therapy (OPAT) programs, unavailability of alternate settings for infusion and patient

factors [5] including active substance use, psychiatric comorbidities, adverse social determinants of health, and homelessness make OPAT in this population challenging. Stigma and conflict with care teams can also result in high rates of nonadherence to therapy including self-directed discharge and incomplete treatment. This may result in high rates of treatment failure or readmission [6–8]. Postacute care placement remains a challenge, and few alternative models of treatment exist to help in transition from hospitalization to postdischarge. In selected patients, people who inject drugs (PWIDs) have similar OPAT completion rates and rates of treatment failure, readmission, death, and complications compared to non-PWID. These usually involve consultation with inpatient substance use specialists and comanagement of OUD with medication for OUD (MOUD) [9–11]. The implementation of these interventions around transitions of care on a larger scale remains a challenge.

This is a retrospective analysis of patients with active SUD needing continued parenteral antimicrobial therapy postdischarge. The study analyzed discharges from 2 large academic tertiary care urban hospitals with total staffed bed capacity of 1020 located in Baltimore City, Maryland. The objective was to describe frequency and predictors of adverse outcomes of

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postdischarge parenteral antimicrobial therapy among adults who are hospitalized with infections associated with SUD.

METHODS

The OPAT program follows patients discharged from 2 academic inner city hospital campuses. Screening for OPAT appropriateness is done by an OPAT Doctor of Medicine (MD). Criteria for selection are included in the [Supplementary Appendix](#). In accordance with published guidelines, decisions on OPAT appropriateness in patients with SUD are made on a case-by-case basis depending on the patient's unique circumstances and the resources available. Patients with unstable housing or judged to be unable to maintain venous access safely were preferably discharged to complete treatment in skilled nursing facilities (SNFs). A nurse coordinator performs bedside assessment and education and provides postdischarge care coordination and tracks patients through the treatment course.

Adult patients discharged on more than 1 week of parenteral antibiotics from the 2 hospitals from October 1, 2017 to April 30, 2020 and followed through the OPAT program were screened for *International Classification of Disease, Ninth or Tenth Revision* (ICD-9 or ICD-10), *Clinical Modification* codes for substance use disorder. Patients who only had diagnoses related to alcohol and/or nicotine use were excluded ([Figure 1](#)). Patients who accessed care during the coronavirus disease surge period (May 2020 onwards) were excluded due to widespread disruptions in care plans and protocols due to pandemic surge planning at the healthcare institutions. Data abstraction was done by extraction via database query on shared list, and when not extractable as discrete variables, this was done by independent chart review of unstructured progress notes from the

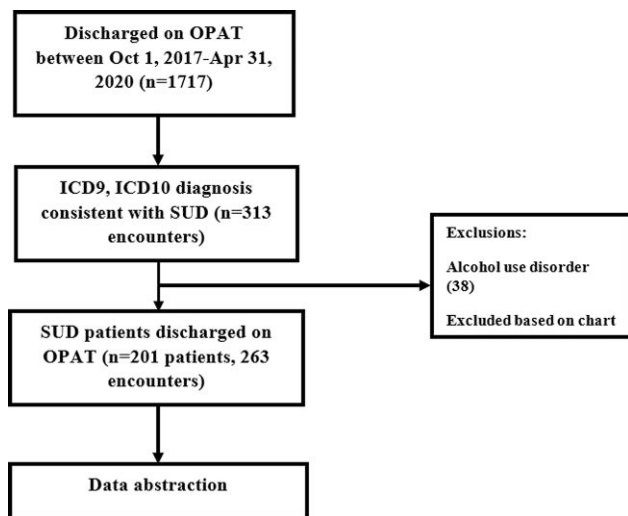


Figure 1. Study methodology. ICD9, *International Classification of Disease, Ninth Revision*; ICD10, *International Classification of Disease, Tenth Revision*; OPAT, outpatient parenteral antimicrobial therapy; SUD, substance use disorder.

chart for the episode of hospital admission. For doubtful cases, adjudication was by consensus opinion after discussion. Substance use disorder in remission was assumed if there was documentation of no illicit substance use, corroborated by negative screening urine toxicology when available, in the prior year. All others were assumed to have active SUD. Ascertainment was aided by review of contemporaneous documentation by an OPAT MD at time of determining eligibility. Unfavorable OPAT outcomes included failure of resolution of infection, adverse event-associated, drug- or line-associated, hospital readmission within 30 days of OPAT completion, death, or OPAT nonadherence. Nonadherence was defined as self-directed discharge, voluntary refusal to complete antibiotic therapy, loss to follow up, or refusal to follow up despite documentation of telephone contact being made. Every patient discharge on parenteral antimicrobial therapy was counted as an OPAT encounter, and OPAT days were counted from day of discharge to last documented day of antibiotic infusion. In instances in which multiple OPAT encounters were noted in the same patient, the first episode was counted for analysis. Data on readmission in the 30-day period postcompletion of intravenous (IV) antibiotics and death during the period of study were gathered from review of nurse coordinator notes and from review of the electronic medical record (EMR), including the Maryland State Health Information Exchange, when available. Direct variable costs of care to the hospital system for a random representative sample of this cohort spread across quartiles of length of hospital stay for the hospitalization and 30-day period after as well as for the duration of the study was calculated. This retrospective cohort study was approved by the institutional review board as exempt from review.

Data were deidentified after primary chart review and analyses were done using IBM SPSS Statistics for Windows (Version 27.0; IBM Corp., Armonk, NY). Pearson's χ^2 or Fisher exact tests were used for statistical significance testing for categorical variables. Comparisons of continuous variables were done by independent variables Mann-Whitney *U* test. Variables associated with OPAT nonadherence at $P < .20$ in univariate analysis were included in the multivariate logistic regression model using backward selection procedures. $P \leq .05$ (2-tailed) were considered statistically significant.

RESULTS

Approximately 18% (313) of our entire OPAT cohort during this period had an ICD-9 or ICD-10 diagnosis of substance use disorder. Two hundred one patients with SUD completed 263 unique courses of parenteral antibiotic therapy ([Table 1](#)). Mean patient age was 46 years (standard deviation [SD] ± 12), 52% (105) of subjects were male, and 55% (110) were White. One hundred twelve patients (55%) had documentation of coexisting psychiatric comorbidity; 35% (93) patients were

Diagnoses needing IV antibiotic therapy (n=263)

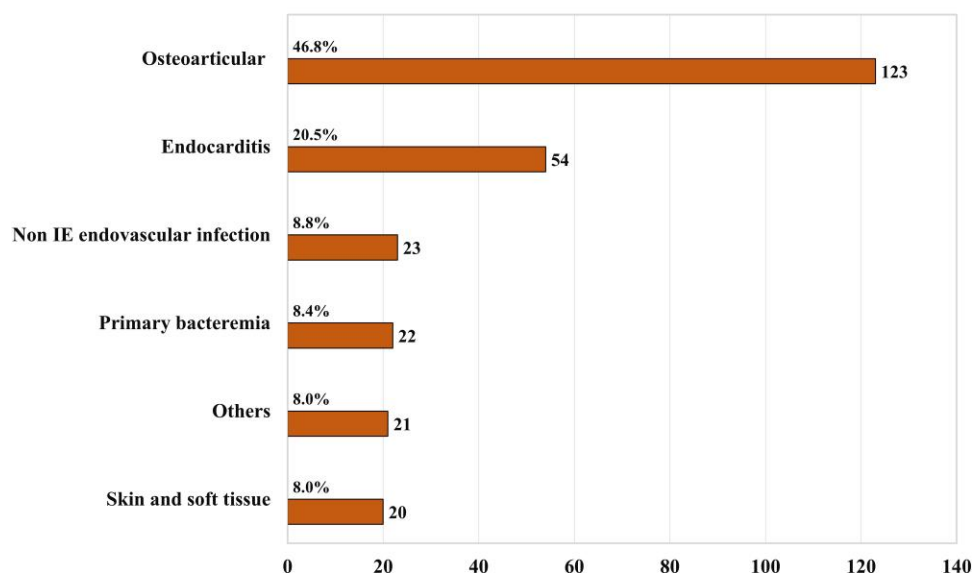


Figure 2. Infectious syndromes in substance use disorder population needing intravenous (IV) antibiotic therapy. IE, infective endocarditis.

Table 1. Demographic Characteristics

Characteristic	Patients, Number (%) [n = 201]	Adherence (%) [n = 158]	Non-adherence (%) [n = 43]	P-value	Odds ratio (95% CI)
Patient Characteristics					
Age, mean (SD), yrs	46 (12)	1. 47. (11.6)	42.1 (11.8)	.008	0.96 (.36–.99)
Male sex	105 (52%)	83 (52%)	22 (52%)	.983	...
	96 (48%)	76 (48%)	20 (48%)		
Race					
White	110 (55%)	84 (53%)	26 (62%)	.312	...
Black ^a	90 (45%)	74 (47%)	16 (38%)		...
Uninsured at hospitalization	8 (4%)	6 (4%)	2 (5%)	.674	...
Homelessness	93/263 (35%)	60/200 (30%)	33/63 (52%)	.001	2.57 (1.44–4.59)
Hepatitis C	139 (69%)	105 (66%)	34 (81%)	.063	2.19 (.95–5.05)
HIV	29 (14%)	25 (16%)	4 (9.5%)	.309	...
Mental health problem	112(55%)	73 (46%)	15 (36%)	.236	...

experiencing homelessness at the time of the hospital admission. In addition, 29 (14%) patients had human immunodeficiency virus infection and 139 (69%) were hepatitis C antibody positive.

Substance Use Disorder

One hundred fifty-five (77%) patients had documentation of active SUD within the prior year. Of these, 66 (33% of all patients) had OUD with another substance use disorder at the time of therapy. Cocaine use was most common (37%) and stimulant use was documented in <3%. Ninety-one (45%) patients had documentation of injection drug use (IDU). Prescription of MOUD before admission was documented in 111 (58%) of patients where this could be ascertained. One hundred twenty-two (61%) OPAT encounters had documentation of a consultation

by substance use services, and 133 (70%) episodes had documentation of MOUD being prescribed at discharge.

Infections

The most common infectious syndromes were osteoarticular infections (123, 47%), infective endocarditis (IE) (54, 20%), and non-IE endovascular infection (23, 9%) (Figure 2). Fifty percent (27 of 54) of patients who had endocarditis had documented left-sided IE. A clinically significant embolic stroke event occurred in 11 (40%) episodes of left-sided IE. *Staphylococcus aureus* was the primary pathogen in 164 (62%) infections, and 96 (36.5% of overall) of these infections were due to methicillin-resistant *S aureus* (MRSA). Surgical intervention was needed to control infection in 151 (57%) patient

episodes. Forty-nine patients (24%) had multiple parenteral antibiotic episodes, 78% (38) of these had 2 episodes, and the remaining had 3–4 episodes.

Median duration of OPAT originating hospitalization was 11 days (interquartile range, 7–17). Mean duration of antibiotics was 36.3 days (± 17) and 81% of patients were discharged to complete OPAT in SNFs.

Outcomes of Parenteral Antibiotic Therapy

Antibiotic therapy was completed in 162 (62%) patients encounters. Thirty-day hospital readmission was 30.5% (61 of 201). Fifty-five percent of these readmissions were related to initial infectious episode or its treatment. Adverse events occurred in 10.4% (21) of the patient encounters at a rate of 2.9/1000 OPAT days with drug adverse events occurring in 3.4% and venous catheter-related adverse events (including documentation of catheter misuse) in 7%. Cumulative rate of catheter-related adverse events was 1.9/1000 OPAT days. Catheter misuse was documented in 6 patients (0.82/1000 OPAT days). Twenty (10%) patients died during the period of study.

Direct variable costs of care to the institution for a random sample of this cohort ($n = 44$) was a median \$20 500 per hospital episode and \$23 382 including the 1-month period postdischarge. Over a two and a half year period, this sample had an average of 3.9 unique inpatient stays and 16.9 ambulatory clinical encounters with total direct variable cost of \$69 741 per patient over the study period.

Nonadherence to Outpatient Parenteral Antimicrobial Therapy

Nonadherence to OPAT, as defined above, was documented in 21.5% (43) of patients (Table 2). Mean OPAT duration of nonadherent episodes was 30.5 days ($SD = 20$) versus 37.8 days ($SD = 16.5$) where adherence was documented ($P = .015$). Nonadherence was higher in OPAT courses in IDU (28.5% vs 15% in non-IDU, $P = .024$), during active SUD versus with SUD in remission (24.5% vs 11%, $P = .047$), with use of more than 1 illicit substance (referred to as polysubstance use: 30% vs 17%, $P = .031$), as well as in people experiencing homelessness versus those stably housed (32.8% vs 15.7%, $P = .005$) (Figure 3A). Nonadherence was not associated with multisite involvement or need for surgery, being seen by SUD consult services when admitted, or being on MOUD at discharge (24% in those on MOUD vs 16% in those not on MOUD at discharge). In a multivariate model, nonadherence was significantly associated with IDU (odds ratio [OR], 2.38; 95% confidence interval [CI], 1.03–5.5) and homelessness (OR, 2.25; 95% CI, 1.01–4.8).

DISCUSSION

We present data on frequency and predictors of adverse outcomes of postdischarge parenteral antimicrobial therapy for a

large cohort of patients with substance use disorder discharged from an urban multihospital health system and followed longitudinally for a period of two and a half years. The high prevalence of SUD-related infections needing OPAT is not surprising considering that opioid abuse/dependence-related hospitalizations have steadily risen in the prior decade [4], and approximately 8% of all inpatient/outpatient events in Baltimore, Maryland, where the 2 hospitals are located, are from alcohol- and drug-related events [12].

A high proportion of patients were experiencing homelessness at the time of OPAT. The prevalence of substance use among the chronically homeless population in Baltimore is 29%–52% [13]. Homelessness increases risk of infectious conditions and presents unique challenges in management of medical problems including infections. Homeless persons who slept in a shelter have a higher risk of MRSA colonization [14], and this increases risk of MRSA skin/soft tissue infection.

Persons experiencing homelessness may have limited access to healthcare and sterile injection equipment and this may lead to increased injection risk behaviors [15] including sharing of equipment among urban PWIDs. Homelessness is also associated with increased risk of relapse to IDU after cessation [16]. This could be contributory to low adherence and higher non-completion of antibiotic therapy in the homeless SUD population in our cohort.

Substance use disorder is a relapsing, remitting condition and building up recovery capital can take time; moreover, risky behaviors that increase infection risk may continue after the acute episode. With high prevalence of adverse social factors and environmental factors, optimal preventive management should include interventions beyond medical stabilization to address the socioeconomic of homelessness and the complex psychopathology of ongoing SUD. These factors are often not addressed in context to the medical severity of the infections faced by this population. As a result, healthcare utilization for this population remains high.

People who inject drugs have been shown to have a 10-fold higher rate of nonadherence and OPAT failure [17]. In our study, besides IDU, we found active SUD within the prior year was associated with nonadherence as was use of multiple substances. This is in line with previous data on high risk of nonadherence being associated with more recent use or unstable or high-risk use [5, 6, 18]. Likewise, use of multiple drugs has been used in risk assessment tools to make recommendations for addiction support and pharmacotherapy needs for people needing IV antibiotics [19].

A high proportion of patients were on MOUD at hospital admission. This differs from and is higher than data, including from our center, presented elsewhere, because these are possibly samples from patients who have not had a premature/self-directed hospital discharge or home discharge or discharge on PO antibiotics [20]. In addition, 64% of patients received an

Table 2. Treatment Episode Details

		Sud Specific and Infection Details and Interventions				
Variable		Frequency, Number (%) [n = 201]	Adherence (%) [n = 158]	Non-adherence (%) [n = 43]	P-Value	Odds ratio (95% CI)
SUD	SUD active	155 (77.1%)	117 (74.1%)	38 (88.4%)	.047	2.66 (.98–7.23)
	Polysubstance use (PSU)	66 (32.8%)	46 (29.1%)	20 (46.5%)	.031	2.12 (1.06–4.22)
	Injection drug use (IDU)	91 (45.3%)	65 (41.1%)	26 (60.5%)	.024	2.19 (1.10–4.36)
Infection	Bacteremia present	107 (53.2%)	88 (55.7%)	19 (44.2%)	.180	0.63 (.32–1.24)
	Multisite infection	61 (30.3%)	48 (30.4%)	13 (30.2%)	.985	...
	Infective endocarditis	41 (20.4%)	36 (22.8%)	5 (11.6%)	.107	...
	Associated with stroke	12 (6%)	11 (7%)	1 (2.3%)	.468	...
	Osteoarticular infection	90 (44.8%)	68 (43%)	22 (51.2%)	.342	...
	Vertebral osteomyelitis	30 (14.9%)	22 (13.9%)	8 (18.6%)	.445	...
	Gram positive agents (%) ^b	154 (76.6%)	119 (75.3%)	35 (81.4%)	.404	...
	Staphylococcal infection	120 (69.7%)	91 (57.6%)	29 (67.4%)	.243	...
	Streptococcus	39 (19.4%)	32 (20.3%)	7 (16.3%)	.559	...
	Multiorganism infection	48(23.9%)	34 (21.5%)	14 (32.6%)	.132	...
Interventions	Duration of hospitalization, median (Q1,Q2), days (LOS)	11(7.0,17.0)	12.5(7.0,18.25)	9.0(6.0,15.0)	.028	0.96 (.91–1.002)
	Surgical intervention(SX)	115(57.2%)	94 (59.5%)	21 (48.8%)	.210	...
	Duration of OPAT, mean (SD), days	36.3 (17.5)	37.8(16.5)	30.5 (20)	.015	0.97 (.95–.99)
Discharge location	Disposition					
	Skilled nursing facility	163 (81.1%)	130 (82.3%)	33 (76.7%)	.418	...
	Home	33 (16.4%)	25 (15.8%)	8 (18.6%)		...
	Other ^c	5 (2.5%)	3 (1.9%)	2 (4.7%)		...
SUD interventions	On OUD treatment at admission (n = 190) ^d	111/190 (58.4%)	90/149 (60.4%)	21/41 (51.2%)	.291	...
	SUD consultation	122(60.7%)	94 (59.5%)	28 (65.1%)	.503	...
	OUD treatment at discharge (n = 190) ^d	133(70%)	101/149 (67.8%)	32/41 (78%)	.204	...

Abbreviations: SUD, substance use disorder; LOS, length of hospital stay; SX, surgery.

^aOne person was of race other than white or black.

^bOnly gram positive agents in cultures, and no gram negatives isolated.

^cIncludes acute rehab, antibiotics with dialysis and outpatient infusion (dalbavancin).

^dData not available on 13 encounters.

SUD consultation and 68% were prescribed MOUD at discharge, according to review of discharge documentation. Addiction medicine consultation has been shown to reduce self-directed discharge and completion rate of antibiotics [9]. In our analysis, the receipt of MOUD at discharge did not reduce nonadherence or improve completion of therapy. This high rate may have been due to documentation of continuation of prior preadmission MOUD, and rates of new initiation of MOUD were very few. This is related in major part to reluctance to start and titrate methadone while hospitalized due to Drug Enforcement Administration regulations, which prevent continuation of MOUD/methadone-initiated during hospitalization at SNFs to which the majority of patients were discharged without enrollment in an opioid treatment program [21].

Although studies have shown higher rates of completion of therapy for patients with IDU who were discharged home on parenteral antibiotics, these patients may have been perceived to be at lower risk of injection drug relapse, or nonadherence, or may have less severe or complex infections [22].

Many OPAT programs may not follow patients discharged to SNFs.

Because many unstable users may not have been initiated on MOUD during hospitalization, due to their inability to continue MOUD at a skilled nursing facility, we believe the nonadherence could be fueled by a higher rate of relapse of SUD, which can be as high as 40% according to reported literature [18].

The definition for nonadherence to OPAT has varied in the literature [6, 19], and our definition excludes noncompletion due to adverse events, relapse, readmission, or therapy failure. We understand this may still not eliminate the nonvolitional reasons of therapy nonadherence in this population. The term nonadherence may be stigmatizing to this population, but as such it indicates a breakdown in the relational autonomy framework that makes continuation of treatment unacceptable for patients.

As a result, this may be a difficult-to-reach population with unstable substance use, and interventions such as in-hospital intake into opioid treatment programs or buprenorphine

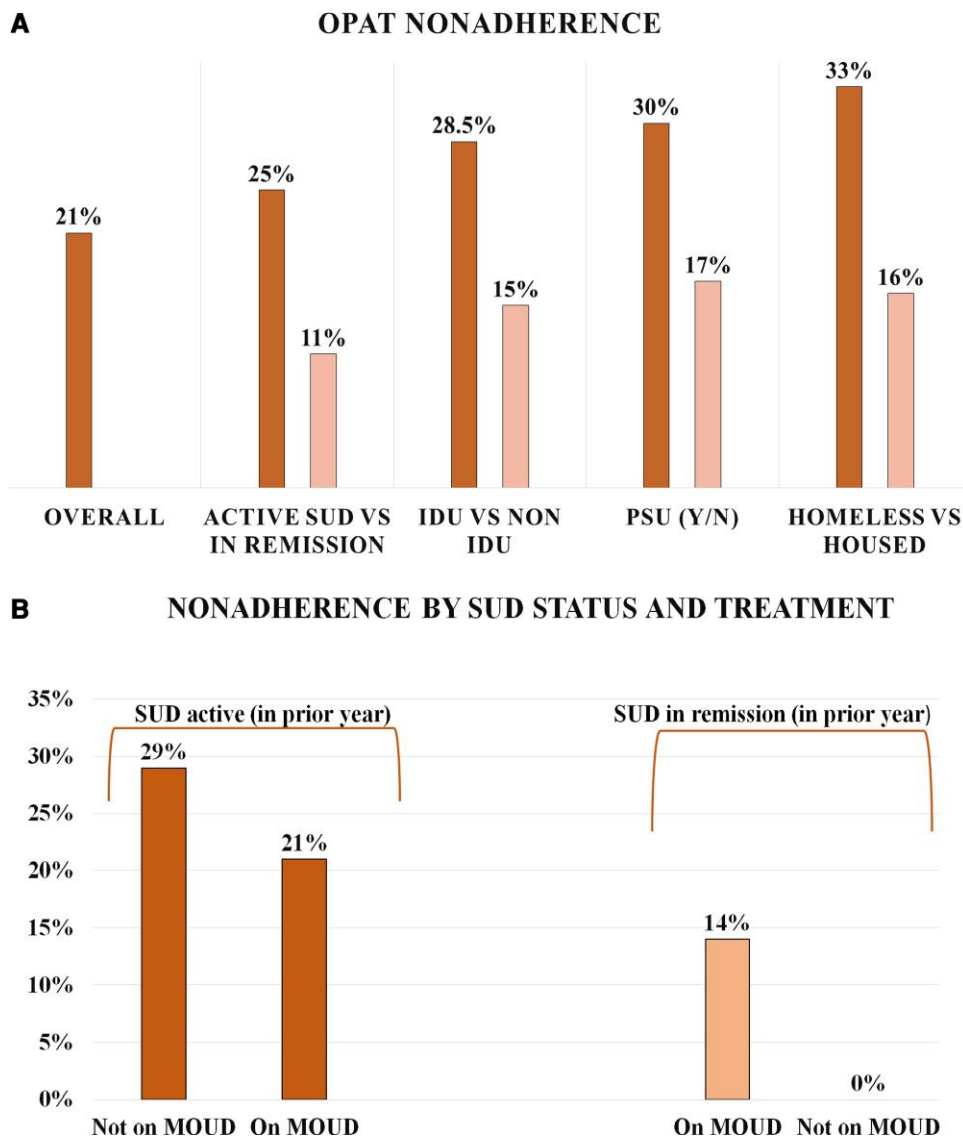


Figure 3. (A) Predictors of nonadherence to parenteral antimicrobial therapy. (B) Indicates nonadherence by substance use disorder (SUD) status and treatment with medication for opioid use disorder (MOUD) versus untreated. IDU, injection drug use; OPAT, outpatient parenteral antimicrobial therapy; PSU, polysubstance use.

microdosing with full agonists during hospitalization or at SNFs need to be considered to improve outcomes. This may also indicate the need to explore alternate locations for delivery of care, including home OPAT in selected cases or lineless, long-acting lipoglycopeptide use, which may be less disruptive and more acceptable, avoiding prolonged institutional stay and allowing outpatient titration of MOUD.

Our data are from a relatively large cohort of patients with SUD-related infections with a high complexity of presenting conditions and clinical care who were followed longitudinally, and they offer insights into determinants of poor outcomes to focus intervention. Limitations of the study include the fact that this was from a tertiary care urban location, and data may not be generalizable to other locations. Other limitations include

the retrospective nature of the study and lack of a comparator group. These patients were selected, and as such they may not represent all patients hospitalized with SUD-related infections.

Failures in documentation or coding with ICD codes may result in nonidentification of such patients. Underreporting of illicit drug use is known, using diagnosis codes for identification [23]. There are limitations to amount of data that can be abstracted from non-structured progress notes, especially with regard to descriptive variables of SUD. People may not disclose their injection drug use due to fear of stigma or transition between noninjection to injection use and vice versa, which may affect their infection risk. We believe that the contemporaneous assessment made at eligibility for individual episodes by one of the investigators (SN) makes this assessment more reliable in our cohort. In addition, we did not have access to all

records at SNFs. The model of discharge to skilled nursing facilities for provision of parenteral antibiotic therapy may not be applicable to other care locations and demands a lot of care coordination and communication between care providers and can also be associated with higher risk of loss to follow up. Deaths in this group were estimated by EMR review only, and as such the cases may be an underestimate of true mortality. In addition, definitions of variables such as active SUD or nonadherence may vary in published literature and may not necessarily be comparable to our data.

CONCLUSIONS

Our study demonstrates that among people with SUD who are hospitalized for SUD-related infections and largely complete their antimicrobial therapy in skilled nursing facilities, nonadherence to postdischarge parenteral antimicrobial therapy can occur in 21.5%. Aspects of drug use that indicate more unstable use including injection use, use of multiple substances, and active use in the prior year seemed to be associated with higher risk of nonadherence. Receipt of MOUD at discharge did not result in better outcomes. There is a need for more research in trying to optimize interventions at this critical touch point in this population with high-risk, unstable substance use.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

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Potential conflicts of interest. Shyam Kotttilil reports the following funding disclosures: Arbutus Pharmaceuticals (Investigator initiated Grant/Research Support), Gilead (Investigator initiated Grant/Research Support), Merck (Investigator initiated Grant/Research Support), Regeneron Pharmaceuticals (Advisor/Consultant), Silverback Therapeutics (Advisor/Consultant), The Liver Company (Advisor/Consultant), Yufan Biotechnologies (Advisor/Consultant).

The authors have no financial conflicts of interest relevant to the submitted manuscript to declare.

Patient consent. The protocol was reviewed by the University of Maryland, Baltimore Institutional Review Board and was determined to be exempt under 45 CFR 46.101(b) from requiring patient consent (HP-00093828).

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