Low Use of Outpatient Parenteral Antimicrobial Therapy for Drug Use-Associated Infective Endocarditis in an Urban Hospital System

Ashley G. Ceniceros,[1] Nupur Shridhar,[2] Melissa Fazzari,[3] Uriel Felsen,[1] and Aaron D. Fox[4]

[1]Division of Infectious Diseases, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA, [2]Albert Einstein College of Medicine, Bronx, New York, USA, [3]Department of Epidemiology & Population Health (Biostatistics), Albert Einstein College of Medicine, Bronx, New York, USA, [4]Division of General Internal Medicine, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA

Background. The opioid crisis in the United States has led to increasing hospitalizations for drug use-associated infective endocarditis (DUA-IE). Outpatient parenteral antimicrobial therapy (OPAT), the preferred modality for intravenous antibiotics for infective endocarditis, has demonstrated similar outcomes among patients with DUA-IE versus non-DUA-IE, but current studies suffer selection bias. The utilization of OPAT for DUA-IE more generally is not well studied.

Methods. This retrospective cohort study compared OPAT use for DUA-IE versus non-DUA-IE in adults hospitalized between January 1, 2015 and September 1, 2019 at 3 urban hospitals. We used multivariable regression analysis to assess the association between DUA-IE and discharge with OPAT, adjusting for clinically significant covariables.

Results. The cohort included 518 patients (126 DUA-IE, 392 non-DUA-IE). Compared to those with non-DUA-IE, DUA-IE patients were younger (53.0 vs 68.2 years, $P < .001$) and more commonly undomiciled (9.5% vs 0.3%, $P < .01$). Patients with DUA-IE had a significantly lower odds of discharge with OPAT than non-DUA-IE patients (adjusted odds ratio [aOR] = 0.20; 95% confidence interval [CI], 0.10–0.39). Odds of discharge with OPAT remained lower for patients with DUA-IE after excluding undomiciled patients (aOR = 0.22; 95% CI, 0.11–0.43) and those with patient-directed discharges (aOR = 0.27; 95% CI, 0.14–0.52).

Conclusions. Significantly fewer patients with DUA-IE were discharged with OPAT compared to those with non-DUA-IE, and undomiciled patients or patient-directed discharges did not fully account for this difference. Efforts to increase OPAT utilization among patients with DUA-IE could have important benefits for patients and the healthcare system.

Keywords. endocarditis; OPAT; opioid use disorder; substance use disorder.

The United States' 3-decade long opioid crisis has unfolded in 3 phases with increasing opioid analgesic use and misuse beginning in the 1990s leading to greater heroin use after 2007 and skyrocketing rates of overdoses from synthetic opioids (eg, fentanyl) after 2013 [1]. An estimated 800 000 Americans—and potentially more than 4 million—use heroin and/or synthetic opioids; 40%–70% of heroin users report having injected in the past year [2, 3]. As medical and public health systems have struggled to reduce opioid use and overdose deaths, another crisis has unfolded with increasing hospitalizations for drug use-associated infective endocarditis (DUA-IE) [4].

Injection drug use is a well documented risk factor for infective endocarditis (IE). Between 2005 and 2014, hospitalizations for DUA-IE increased from 6.3% to 11.6% of all IE hospitalizations and may account for one fifth of all deaths among people who inject drugs [5, 6]. Patients with DUA-IE often present with tricuspid valve disease due to invasive *Staphylococcal aureus*, and rates of methicillin-resistant *S aureus* infection more than doubled between 2011 and 2016 [7, 8]. Compared to patients with nondrug use-associated IE (non-DUA-IE), patients with DUA-IE have longer hospitalizations and more readmissions [9].

Treating IE requires prolonged parenteral antimicrobial therapy [10]. Outpatient parenteral antimicrobial therapy (OPAT), the administration of intravenous (IV) antimicrobials in at least 2 doses on different days without intervening hospitalization, is the standard of care for patients who require prolonged antimicrobials. When compared with prolonged inpatient antimicrobial therapy, OPAT benefits include decreased length of stay, increased patient satisfaction, and decreased treatment costs [11–13]. However, due to a paucity of evidence, there are currently no guidelines regarding the delivery of antimicrobial therapy for DUA-IE [14]. Studies have

reported similar cure and complication rates when OPAT is used for serious DUA infections, including IE, compared with serious non-DUA infections [15–18]. However, patients receiving OPAT in these studies are likely a highly selected group, whereas utilization of OPAT for DUA-IE more generally is not well studied. Outpatient parenteral antimicrobial therapy seems promising for treating serious infections, including DUA-IE, but additional research is necessary to understand appropriate OPAT utilization. Differences in OPAT utilization for DUA-IE and non-DUA-IE, in the absence of compelling contraindications, would raise the potential for an unethical disparity in care for patients who inject drugs.

The objective of this study was to compare OPAT use among patients with DUA-IE to patients with non-DUA-IE within a large urban hospital system. We hypothesized that OPAT would be used less often for DUA-IE than non-DUA-IE. We also investigated sociodemographic and clinical characteristics associated with OPAT use to identify modifiable factors that may contribute to OPAT underutilization. These data may inform efforts locally and within other hospital systems to improve the quality of care for patients with DUA-IE.

METHODS

Setting and Participants
We performed a retrospective cohort study of adults hospitalized with IE at an urban academic medical center between January 1, 2015 and September 1, 2019. The academic medical center has 3 adult hospitals and 1 children's hospital in the Bronx, New York. The Bronx is New York City's poorest borough with 28.6% of its residents living below the federal poverty line [19]. In 2018, the Bronx had the highest rate of overdose deaths (34.1 per 100 000 residents) compared with other New York City boroughs [20].

In July 2015, the medical center's Division of Infectious Diseases instituted an OPAT program, utilizing an Infectious Diseases Society of America (IDSA) recommended bundle. The program includes discussion of risks and benefits of therapy via the infectious disease consultant, outpatient care coordination, and patient and family education, and it is available at the 3 adult hospitals [21]. There are no specific guidelines for using OPAT in DUA-IE or requirement for evaluation by the addiction psychiatry consult service. There is currently no standard of care for linkage to addiction services on discharge.

We included patients who were ≥18 years old, admitted with an *International Classification of Disease, Ninth Revision* (ICD-9)*, Clinical Modification* or ICD-10 code consistent with IE and received IE treatment (see Supplementary Tables). We excluded patients who were admitted to the children's hospital, which did not have access to the OPAT program. We also excluded those who underwent cardiothoracic (CT) surgery during their hospitalization. This population was excluded due to an interaction between those who underwent CT surgery and the main independent variable, leading to statistically different posthospital dispositions for this population of patients. The Institutional Review Board of the medical center approved the study.

Patient Consent Statement
Due to the retrospective nature of this work, we received a waiver of written consent. This work has been approved by the Albert Einstein College of Medicine Institutional Review Board.

Data Collection
We extracted data from the medical center's electronic health record using healthcare surveillance software (Clinical Looking Glass [CLG]; Emerging Health Information Technology, Yonkers, NY). One author (A.G.C.) individually reviewed medical records from each hospitalization for additional data that could not be electronically queried. All data collected via medical record review were confirmed by a second author (N.S.). Data were managed using REDCap electronic data capture tools hosted by Albert Einstein College of Medicine [22, 23].

Drug Use-Associated Endocarditis
The main independent variable was whether IE was DUA (yes/no). The variable was defined based on a previously published algorithm using ICD-9 or ICD-10 codes for substance use or hepatitis C (see Supplementary Tables) [24]. Because chronic diseases are not consistently coded during admissions, we included codes used concurrent with or in the 6 months preceding the IE admission.

Outpatient Parenteral Antimicrobial Therapy
The primary outcome was discharge disposition: discharge with OPAT versus discharge without OPAT. Outpatient parenteral antimicrobial therapy was defined as a documented plan to discharge an individual home to receive IV antimicrobials. Non-OPAT dispositions included the following: discharged for IV antimicrobial administration at a skilled nursing facility, IV antimicrobials finished while hospitalized, discharged with oral antimicrobials, patient-directed discharge (documented discharge "against medical advice" or "elopement"), discharged to hospice, expired, or transferred to a different acute care hospital.

Other Variables
Patient demographics included age, sex, race/ethnicity, and type of insurance. We collected housing status from social work documentation in the medical record and categorized the status as domiciled, undomiciled, or unknown if the note did not specify current living arrangements. The Charlson Comorbidity Index, a score predicting 10-year survival in patients based on age and comorbidities, was calculated for

each patient based on ICD-9 or ICD-10 codes in the 5 years preceding the admission [25]. We recorded IE clinical characteristics including valves affected and major and minor Duke criteria.

We collected additional information regarding the hospitalization that may have affected OPAT use, including year of admission, length of stay, and intensive care unit (ICU) admission. Length of stay was dichotomized as <14 days or ≥14 days. We chose this point, which is halfway to the shortest recommended treatment duration for IE of 4 weeks, because providers could have reasonably determined whether to discharge with OPAT or complete antibiotics in an alternate matter. We recorded documentation of ICU admission to account for severity of illness.

We also recorded drug use characteristics among patients with DUA-IE. We recorded the type of drug used based on ICD-9 and -10 codes and confirmed this use via chart review. We also recorded whether the patient was enrolled in methadone or buprenorphine/naloxone treatment at admission based on chart review.

Statistical Analysis

We compared demographic, clinical, and hospitalization characteristics between patients with DUA-IE versus non-DUA-IE. Categorical variables were analyzed with the χ^2 and Fisher exact tests, and continuous variables were evaluated using the t test or Mann-Whitney U test; 2-tailed $P < .05$ were considered statistically significant. We used multivariable logistic regression to assess the association between DUA-IE and discharge with OPAT. The model was adjusted for clinically significant covariates that were decided a priori: age, sex, race, insurance, year of admission, length of stay, Charlson Comorbidity Index, and admission to the medical ICU. All covariates listed were assessed for interactions with the exposure of interest and were not significant.

We conducted additional sensitivity analyses to investigate factors that may affect an individual's ability to receive OPAT. One model excluded undomiciled patients, a second model excluded patient-directed discharges, and a third model excluded both groups. We also examined separate categories of participants with DUA-IE who did and did not receive medication for opioid use disorder (MOUD).

The primary analysis defined DUA-IE based on the presence of any DUA or hepatitis C ICD-9 and -10 codes rather than documented injection drug use. To address possible misclassification, we performed a sensitivity analysis with the exposure defined as endocarditis plus documented injection drug use. A final sensitivity analysis included only patients meeting Duke criteria for definite or possible IE. Assumptions for each statistical method were evaluated and addressed. All statistics were performed with Stata, version 16.1 (StataCorp, College Station, TX).

RESULTS

Between January 1, 2015 and September 1, 2019, 1014 patients were admitted with an ICD-9 or ICD-10 code for IE. Of those patients, 350 were excluded because endocarditis was not diagnosed nor treatment recommended, and 2 were excluded because they were admitted to the children's hospital. In addition, we excluded 144 patients who underwent CT surgery during the admission. After exclusions, 518 patients were included in the primary analysis, 126 (24.3%) of whom had DUA-IE (Figure 1). Baseline demographic, clinical, and hospitalization characteristics are detailed in Table 1. Age, race, and housing status differed significantly between groups. Patients with DUA-IE (vs non-DUA-IE) were younger (53.0 vs 68.2 years, $P < .001$) and more commonly Hispanic (41.3% vs 26.8%, $P < .01$), undomiciled (9.5% vs 0.3%, $P < .01$), and human immunodeficiency virus positive (13.5% vs 2.8%, $P < .001$). Proportions of those with diabetes, hypertension, and end-stage renal disease were similar between groups.

Endocarditis Clinical Characteristics

Patients with DUA-IE (vs non-DUA-IE) were more often diagnosed with a tricuspid valve vegetation (23.8% vs 5.4%, $P < .001$) and less often with mitral valve vegetations (23.0% vs 36.7%, $P < .01$). Presumed endocarditis in the absence of vegetations on echocardiography was similar between groups (38.9 vs 38.0%, $P = .86$).

Substance Use Characteristics

Injection drug use was documented in 61.1% of patients with DUA-IE. The most frequently documented drug type was opioids (69.1%). Among patients classified as having DUA-IE, 12.7% lacked medical record documentation of drug use type. Among patients using opioids (n = 87), 3 reported treatment with buprenorphine/naloxone and 20 reported treatment with methadone.

Discharge Disposition

Patients with DUA-IE (vs non-DUA-IE) were less often discharged with OPAT (11.9% vs 28.1%, $P < .001$) (Table 2). Drug use-associated IE (vs non-DUA-IE) patients more commonly completed the course of antimicrobials while inpatient (15.9% vs 6.6%, $P < .01$) or had a patient-directed discharge (17.5% vs 1.8%, $P < .001$). The proportion of patients discharged to skilled nursing facilities to complete treatment was similar between groups (27.0% vs 33.4%, $P = .18$).

Primary Analysis and Sensitivity Analyses

As detailed in Table 3, patients with DUA-IE (vs non-DUA-IE) had significantly lower odds of being discharged with OPAT (adjusted odds ratio [aOR] = 0.20; 95% confidence interval [CI], 0.10–0.39), accounting for age, sex, race/ethnicity, insurance, year of admission, length of stay, Charlson Comorbidity
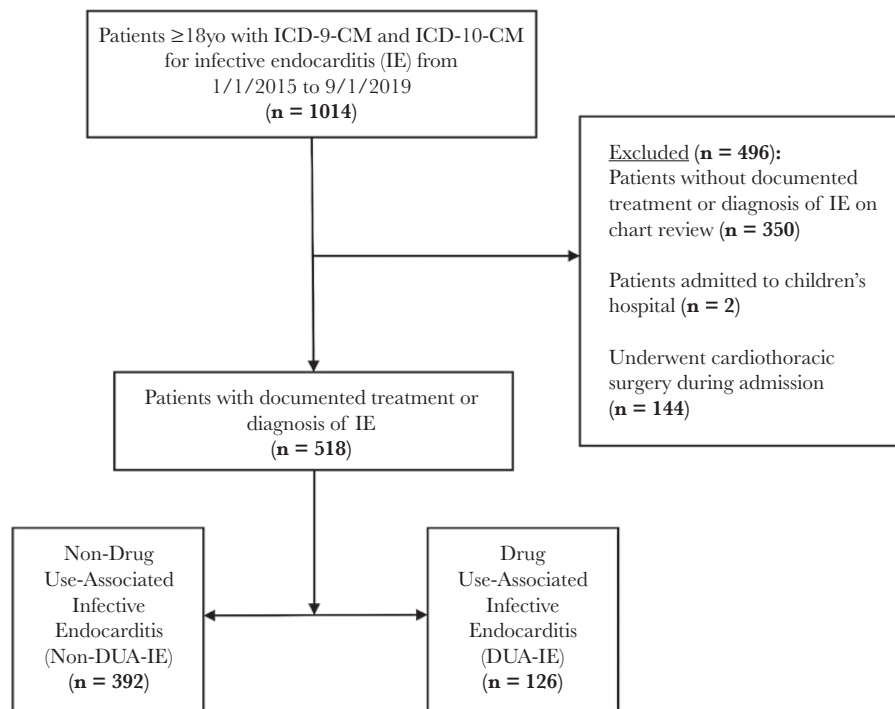
Figure 1. Flow diagram of study population. DUA-IE, drug use-associated infective endocarditis; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICD-10-CM, ICD *Tenth Revision, Clinical Modification.*

Index, and ICU admission. In the second model, in which we examined separate categories of participants with DUA-IE who did and did not receive MOUD, patients who received MOUD had a 0.61 aOR (95% CI, 0.22–1.67) of discharge with OPAT versus non-DUA-IE, whereas the odds of discharge with OPAT without receipt of MOUD were 0.12 aOR (95% CI, 0.05–0.29) versus non-DUA-IE (see Supplementary Tables). Results of sensitivity analyses did not substantially alter the inferences of the primary analyses. When we removed the undomiciled patients (n = 13), patients with DUA-IE had lower odds of being discharged with OPAT (aOR = 0.22; 95% CI, 0.11–0.43). Likewise, when we removed patient-directed discharges (n = 29), the odds of patients with DUA-IE discharged with OPAT remained low (aOR = 0.27; 95% CI, 0.14–0.52) (Table 4). Our models utilizing a definition of DUA-IE that required documentation of injection drug use or defined IE based on Duke criteria demonstrated similar statistically significant associations between DUA-IE and lower odds of discharge with OPAT (aOR = 0.12, 95% CI = 0.05–0.30 and aOR = 0.13, 95% CI = 0.05–0.32, respectively) (see Supplementary Tables).

DISCUSSION

This retrospective cohort study demonstrates low OPAT use among patients with DUA-IE at a large academic medical center. Although there were significant differences among group demographics, insurance, and clinical comorbidities, our analysis demonstrated that these variations were insufficient to explain differences in OPAT use between patients with DUA-IE and non-DUA-IE. Furthermore, we found that patients with DUA-IE more often completed the entire antimicrobial course as inpatients. We conducted multiple sensitivity analyses to address other potential reasons for differences in OPAT use, but using strict definitions of DUA-IE and excluding patients who were undomiciled or experienced patient-directed discharges did not change our findings.

Our study is the first to examine differences in OPAT use among patients with DUA-IE and non-DUA-IE. Two studies examined patients who were hospitalized for DUA infections, including IE, and found that they were less likely to be discharged home (45.3% vs 63.1%, *P* < .001 and 10.7% vs 25.8% *P* < .001, respectively) and more likely to have patient-directed discharges (defined as discharge against medical advice) (19.1% vs 2.6%, *P* < .001, 4.8% vs 1.8% *P* < .001, respectively) than those with non-DUA-infections [26, 27]. However, these studies did not examine OPAT use.

We did not explicitly examine clinicians' reasons for recommending OPAT or another disposition; however, other data regarding clinicians' attitudes toward OPAT use in DUA-IE are informative. Clinicians express uncertainty about discharging patients who use drugs with OPAT. In a survey of infectious disease physicians, 78% reported treating patients who use drugs, but 65% reported "rarely" or "never" recommending OPAT for these patients [28]. A survey of hospital physicians reported that only 29% would consider OPAT in patients who

Table 1. Characteristics of Nondrug Use-Associated Infective Endocarditis and Drug Use-Associated Infective Endocarditis Admissions, January 2015–September 2019

Patient Characteristics	Non-DUA-IE, n = 392 (75.7%)	DUA-IE, n = 126 (24.3%)	P Value[a]
Mean age, years (SD)	68.2 (15.6)	53.0 (15.7)	**<.001**
Sex, male (%)	224 (57.1)	76 (60.3)	.53
Race/ethnicity (%)			**.02**
White, non-Hispanic	127 (32.4)	33 (20.2)	.19
Black, non-Hispanic	109 (27.8)	27 (21.4)	.16
Hispanic	105 (26.8)	52 (41.3)	**<.01**
Other/declined	51 (13.0)	14 (11.1)	.31
Insurance (%)			.62
Public	325 (82.9)	102 (81.0)	
Private	67 (17.1)	24 (19.1)	
Housing Status (%)			**<.001**
Domiciled	377 (96.2)	107 (84.9)	**<.001**
Undomiciled	1 (0.3)	12 (9.5)	**<.001**
Unknown	14 (3.6)	7 (5.6)	.33
Median Charlson comorbidity index (IQR)	6 (4.8)	5 (3–8)	.11
Admission to Intensive Care Unit (%)			
Length of Stay			
≥14 days (%)	223 (56.9)	70 (55.6)	.79
Median LOS (IQR)	15.5 (10–26)	16 (8–29)	.65
Year of Admission[b] (%)			.77
2015–2016	173 (44.1)	50 (39.7)	
2017–2019	219 (55.9)	76 (60.3)	
Diabetes (%)	168 (42.9)	46 (36.5)	.21
Hypertension (%)	75 (19.1)	34 (27.0)	.06
End-stage renal disease (%)	74 (18.9)	16 (12.7)	.11
HIV (%)	11 (2.8)	17 (13.5)	**<.001**
Duke Criteria Classifications (%)			**.03**
Definitive infective endocarditis	216 (55.1)	83 (65.9)	**.03**
Possible infective endocarditis	153 (39.0)	33 (26.2)	**<.01**
Rejected infective endocarditis	23 (5.9)	10 (7.9)	.41
Microbiology (%)			**.02**
Methicillin-sensitive *Staphylococcus aureus*	69 (17.6)	37 (29.4)	**<.01**
Methicillin-resistant *S aureus*	57 (14.5)	22 (17.5)	.43
Coagulase-negative *Staphylococcus* sp	28 (7.1)	14 (11.1)	.16
Streptococcus sp	58 (14.8)	16 (12.7)	.56
Enterococcus sp	46 (11.7)	8 (6.4)	.09
Other	32 (8.2)	6 (4.8)	.20
Negative cultures	102 (26.0)	23 (18.3)	.08
Valves[c] (%)			
No vegetation seen	149 (38.0)	49 (38.9)	.86
Mitral valve	144 (36.7)	29 (23.0)	**<.01**
Aortic valve	76 (19.4)	18 (14.3)	.20
Tricuspid valve	21 (5.4)	30 (23.8)	**<.001**
Pulmonary valve	14 (3.8)	2 (1.6)	.26
Substance Use Among DUA-IE[c], n = 126 (24.3%)			
Opioids		87 (69.1)	
Cocaine		42 (33.3)	
Marijuana		13 (10.3)	
Alcohol		17 (13.5)	
Amphetamines		3 (2.4)	
Benzodiazepines		1 (0.8)	
Unknown[d]		16 (12.7)	
Documented injection drug use[e]		77 (61.1)	
Use of buprenorphine/naloxone at admission		3 (2.4)	
Use of methadone at admission		20 (15.9)	
Addiction psychiatry consult ordered		19 (15.1)	

Values that are considered statistically significant are indicated in bold.

Abbreviations: DUA-IE, drug use-associated infective endocarditis; HIV, human immunodeficiency virus; IQR, interquartile range; LOS, length of stay; SD, standard deviation.

[a]P values calculated using the χ^2 test for categorical variables and Wilcoxon rank-sum test for nonnormally distributed continuous variables.

[b]January 1, 2015–December 31, 2016 and January 1, 2017–September 1, 2019.

[c]More than 1 category may be reported, based on *International Classification of Diseases, Ninth Revision* (ICD-9) and ICD *Tenth Revision* (ICD-10) codes and confirmed on chart review.

[d]Patients with "Unknown" substance use were captured via ICD-9 and -10 codes, but no substance was listed in text on chart review.

[e]Seventy-six documented opioid use, 1 documented amphetamine use.

Table 2. Disposition Characteristics of Nondrug Use-Associated Infective Endocarditis and Drug Use-Associated Infective Endocarditis Admissions, January 2015–September 2019

Disposition Characteristics	Non-DUA-IE, n = 392 (75.7%)	DUA-IE, n = 126 (24.3%)	P Value*
Outpatient parenteral antimicrobial therapy (%)	110 (28.1)	15 (11.9)	**<.001**
Intravenous antimicrobials administered at a skilled nursing facility (%)	131 (33.4)	34 (27.0)	.18
Intravenous antimicrobials finished while inpatient (%)	26 (6.6)	20 (15.9)	**<.01**
Discharged with oral antimicrobials (%)	4 (1.0)	2 (1.6)	.60
Patient-directed discharge (%)	7 (1.8)	22 (17.5)	**<.001**
Hospice (%)	14 (3.6)	1 (0.8)	.40
Expired (%)	96 (24.5)	28 (22.2)	.60
Transferred (%)	4 (1.0)	4 (3.2)	.09

Values that are considered statistically significant are indicated in bold.

Abbreviations: DUA-IE, drug use-associated infective endocarditis.

*P values calculated using the χ^2 test for categorical variables and Wilcoxon rank-sum test for nonnormally distributed continuous variables.

use drugs and cited socioeconomic barriers, such as unstable housing, and the potential for misusing the catheter as reasons for limiting OPAT use [29]. However, our findings demonstrated lower OPAT utilization even among those with stable housing. In addition, recent studies have shown comparable OPAT complication rates between patients who use drugs and patients who do not use drugs [30]. Future research should examine why clinicians are using OPAT less frequently with DUA-IE than non-DUA-IE. Additional safety data may be necessary to assuage clinicians' concerns about catheter misuse.

These findings have several implications relating to patient satisfaction, hospital costs, and potential treatment outcomes. Completing treatment inpatient requires prolonged hospitalizations that can place patients at elevated risk for hospital-acquired complications including hospital-acquired infections and deconditioning [31, 32]. In addition to these risks, patients with DUA-IE also report experiencing stigma and discrimination, inadequate withdrawal treatment, and delays in care

during hospitalization, which may prompt patient-directed discharges [33, 34]. These discharges are associated with increased rehospitalization and mortality compared with planned discharges [35]. Offering OPAT to patients with DUA-IE may prevent prolonged hospitalizations or unplanned discharges, which, in turn, could improve patient satisfaction and clinical outcomes.

Increasing the number of patients with DUA-IE discharged with OPAT will require multifaceted solutions. Our results suggest that patients with DUA-IE, if offered MOUD, had increased odds of discharge with OPAT than if not offered MOUD (vs non-DUA-IE). Emerging evidence also supports combining medications for opioid use disorder with OPAT in the setting of DUA-IE. Integrating antimicrobial therapy with addiction treatment can assure that both needs are met. A clinic providing OPAT and buprenorphine treatment demonstrated dramatically decreased length of hospital stay compared with usual care and led to successful antimicrobial completion for all patients

Table 3. Univariate and Multivariable Analysis of Discharge With OPAT Versus No OPAT in Patients With Infective Endocarditis

Patient Characteristics	OPAT, n = 125 (24.1%)	No OPAT, n = 393 (75.9%)	Unadjusted Odds Ratio (95% CI)	P Value	Adjusted Odds Ratio[a] (95% CI)	P Value
DUA-IE[a] (%)	15 (12.0)	111 (28.2)	0.35 (0.19–0.62)	**<.01**	0.20 (0.10–0.39)	**<.001**
Mean age, years (SD)	62.7 (17.1)	65.1 (16.8)	0.99 (0.54–1.20)	.17	0.98 (0.96–0.99)	**<.01**
Sex, male (%)	78 (62.4)	222 (56.5)	1.28 (0.85–1.93)	.24	1.15 (0.73–1.80)	.54
Race (%)						
White, non-Hispanic	33 (26.4)	127 (32.3)	Reference		Reference	
Black, non-Hispanic	33 (26.4)	103 (26.2)	1.23 (0.71–2.13)	.45	1.19 (0.65–2.19)	.57
Hispanic	46 (36.8)	111 (28.2)	1.59 (0.95–2.67)	.08	2.10 (1.19–3.70)	**.01**
Other/declined	13 (10.4)	52 (13.2)	0.96 (0.47–1.97)	.92	0.91 (0.42–1.98)	.81
Insurance, Public (%)	94 (75.2)	333 (84.7)	0.55 (0.33–0.89)	.02	0.51 (0.29–0.89)	**.02**
Year of admission, 2017–2019 (%)	75 (60)	220 (56.0)	1.18 (0.78–1.78)	.43	1.41 (0.90–2.23)	.14
Length of stay, ≥14 days (%)	50 (40)	243 (61)	0.41 (0.27–0.62)	**<.001**	0.39 (0.25–0.61)	**<.001**
Median Charlson Comorbidity Index (IQR)	5 (3–8)	6 (4–8)	0.97 (0.91–1.03)	.27	1.01 (0.94–1.08)	.83
Admission to ICU (%)	8 (6.4)	79 (20.1)	0.27 (0.13–0.58)	**<.01**	0.24 (0.11–0.54)	**<.001**

Values that are considered statistically significant are indicated in bold.

Abbreviations: CI, confidence interval; DUA-IE, drug use-associated infective endocarditis; ICU, intensive care unit; IQR, interquartile range; OPAT, outpatient parenteral antimicrobial therapy; SD, standard deviation.

[a]Adjusted for age, sex, race/ethnicity, insurance, year of admission, length of stay, Charlson Comorbidity Index, and ICU admission.

Table 4. Multivariable Sensitivity Analysis of Discharge With OPAT Versus No OPAT in Domiciled Patients and Patients Without Patient-Directed Discharges

Patient Characteristics	Analysis Without Undomiciled Patients (n = 505)		Analysis Without Patient-Directed Discharges (n = 489)		Analysis Without Undomiciled Patients and Patient-Directed Discharges (n = 480)	
	OPAT aOR[a] (95% CI)	P Value	OPAT, aOR (95% CI)	P Value	OPAT, aOR (95% CI)	P Value
DUA-IE[a]	0.22 (0.11–0.43)	**<.001**	0.27 (0.14–0.52)	**<.001**	0.28 (0.14–0.55)	**<.001**
Mean age, years	0.98 (0.96–0.99)	**<.01**	0.97 (0.95–0.98)	**<.001**	0.97 (0.95–0.98)	**<.001**
Sex, male	1.16 (0.74–1.83)	.52	1.19 (0.75–1.88)	.52	1.19 (0.75–1.89)	.46
Race/ethnicity						
White, non-Hispanic	Reference		Reference		Reference	
Black, non-Hispanic	1.14 (0.62–2.12)	.66	1.13 (0.60–2.11)	.37	1.08 (0.58–2.04)	.80
Hispanic	2.10 (1.19–3.73)	**.01**	2.32 (1.30–4.17)	**<.01**	2.29 (1.27–4.13)	**<.01**
Other/declined	0.90 (0.41–1.97)	.78	0.95 (0.43–2.13)	.91	0.93 (0.41–2.08)	.86
Insurance, Public	0.50 (0.29–0.88)	**.02**	0.53 (0.30–0.94)	**.03**	0.52 (0.29–0.93)	**.03**
Year of admission, 2017–2019	1.42 (0.90–2.24)	.15	1.48 (0.92–2.35)	.10	1.47 (0.92–2.34)	.11
Length of stay, ≥14 days	0.39 (0.25–0.61)	**<.001**	0.30 (0.19–0.48)	**<.001**	0.31 (0.20–0.50)	**<.001**
Median Charlson Comorbidity Index	1.00 (0.94–1.07)	.96	1.01 (0.95–1.08)	.71	1.01 (0.94–1.08)	.78
Admission to ICU	0.24 (0.11–0.52)	**<.001**	0.19 (0.09–0.44)	**<.01**	0.19 (0.08–0.44)	**<.001**

Values that are considered statistically significant are indicated in bold.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; DUA-IE, drug use-associated infective endocarditis; ICU, intensive care unit; IQR, interquartile range; OPAT, outpatient parenteral antimicrobial therapy.

[a]Adjusted for age, sex, race/ethnicity, insurance, year of admission, length of stay, Charlson comorbidity index, and ICU admission.

studied [36]. Another group created tailored OPAT protocols incorporating a patient risk assessment by addiction medicine specialists. The group reported 100% completion of antimicrobial therapy and no reported overdoses or central line complications among those selected to receive OPAT [18]. Furthermore, some groups have reported success with OPAT in DUA-IE by adding a tamper-proof sticker to catheters or even without added programing [37, 38]. In addition to these interventions, research and clinical efforts to improve inpatient withdrawal treatment and reduce provider stigma may prevent patient-directed discharges, increasing eligibility for OPAT. Finally, few reports have been published on the use of long-acting injectable antimicrobials in patients with DUA infections, and further prospective studies may increase their use for appropriate patients with DUA-IE [39].

Our study has several limitations. All 3 hospital sites were part of a single urban, academic medical center so our findings may not be generalizable to other geographic areas. In addition, no ICD-9 or ICD-10 codes currently exist for DUA infections; therefore, we risked misclassification between groups. To minimize this risk, we used diagnosis codes that have been validated in previous studies. We also performed sensitivity analyses based on chart review of patients with documented injection drug use, and our findings were not significantly altered (see Supplementary Tables). Due to limitations in data collection, our analysis did not include provider characteristics, which may be important in determining what treatment the patient is offered. Oral antibiotics were infrequently used in our study, but oral regimens are increasingly being used as an alternative to OPAT. For the subpopulation of patients with IE who would

qualify for oral antibiotics, however, it will be important to ensure that new standards are equitably applied among those with and without DUA-IE [40]. Outpatient parenteral antimicrobial therapy use was also low among patients with non-DUA-IE at our medical center; however, recent findings from another cohort study reported similar OPAT use for IE in the general population [41].

CONCLUSION

Outpatient parenteral antimicrobial therapy utilization was lower among patients with DUA-IE compared to patients with non-DUA-IE admitted to an urban academic medical center. Unstable housing, unplanned discharges, or misclassification were unlikely to account for the significant difference between groups. Other research has demonstrated promising outcomes for OPAT use in DUA-IE; therefore, efforts to increase OPAT utilization could have broad benefits for patients and the healthcare system.

References

1. Ciccarone D. The triple wave epidemic: supply and demand drivers of the US opioid overdose crisis. Int J Drug Policy **2019**; 71:183–8.
2. Midgette G, Davenport S, Caulkins JP, Kilmer B. What America's Users Spend on Illegal Drugs, 2006–2016. Santa Monica, CA: RAND Corporation, **2019**.
3. Behrends CN, Paone D, Nolan ML, et al. Estimated impact of supervised injection facilities on overdose fatalities and healthcare costs in New York City. J Subst Abuse Treat **2019**; 106:79–88.
4. Wurcel AG, Anderson JE, Chui KK, et al. Increasing infectious endocarditis admissions among young people who inject drugs. Open Forum Infect Dis **2016**; 3:ofw157.
5. Mori M, Brown KJ, Bin Mahmood SU, Geirsson A, et al. Trends in infective endocarditis hospitalizations, characteristics, and valve operations in patients with opioid use disorders in the United States: 2005–2014. J Am Heart Assoc **2020**; 9:e012465.
6. Barocas JA, Eftekhari Yazdi G, Savinkina A, et al. Long-term infective endocarditis mortality associated with injection opioid use in the United States: a modeling study. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa1346
7. Jackson KAB, Brooks MK, Asher JT, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections among persons who inject drugs–six sites, 2005–2016. MMWR Morb Mortal Wkly Rep **2018**; 67:625–8.
8. Colville T, Sharma V, Albouaini K. Infective endocarditis in intravenous drug users: a review article. Postgrad Med J **2016**; 92:105–11.
9. Kadri AN, Wilner B, Hernandez AV, et al. Geographic trends, patient characteristics, and outcomes of infective endocarditis associated with drug abuse in the United States from 2002 to 2016. J Am Heart Assoc **2019**; 8:e012969.
10. Baddour LM, Wilson WR, Bayer AS, et al.; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American heart association. Circulation **2015**; 132:1435–86.
11. MacKenzie M, Rae N, Nathwani D. Outcomes from global adult outpatient parenteral antimicrobial therapy programmes: a review of the last decade. Int J Antimicrob Agents **2014**; 43:7–16.
12. Mitchell ED, Czoski Murray C, Meads D, et al. Clinical and cost-effectiveness, safety and acceptability of community intravenous antibiotic service models: CIVAS systematic review. BMJ Open **2017**; 7:e013560.
13. Chapman AL, Dixon S, Andrews D, et al. Clinical efficacy and cost-effectiveness of outpatient parenteral antibiotic therapy (OPAT): a UK perspective. J Antimicrob Chemother **2009**; 64:1316–24.
14. Norris AH, Shrestha NK, Allison GM, et al. 2018 Infectious Diseases Society of America clinical practice guideline for the management of outpatient parenteral antimicrobial therapy. Clin Infect Dis **2019**; 68:e1–35.
15. Beieler A, Magaret A, Zhou Y, et al. Outpatient parenteral antimicrobial therapy in vulnerable populations– people who inject drugs and the homeless. J Hosp Med **2019**; 14:105–9.
16. D'Couto HT, Robbins GK, Ard KL, et al. Outcomes according to discharge location for persons who inject drugs receiving outpatient parenteral antimicrobial therapy. Open Forum Infect Dis **2018**; 5:ofy056.
17. O'Callaghan K, Tapp S, Hajkowicz K, et al. Outcomes of patients with a history of injecting drug use and receipt of outpatient antimicrobial therapy. Eur J Clin Microbiol Infect Dis **2019**; 38:575–80.
18. Price CN, Solomon DA, Johnson JA, et al. Feasibility and safety of outpatient parenteral antimicrobial therapy in conjunction with addiction treatment for people who inject drugs. J Infect Dis **2020**; 222:S494–8.
19. New York State Department of Health. Socio-economic status and general health indicators–Bronx County. Available at: https://www.health.ny.gov/ statistics/ chac/chai/docs/ses_58.htm. Accessed 9 July 2020.
20. Nolan ML, Tuazon E, Blachman-Forshay J, Paone D. Epi data brief: unintential drug poisoning (Overdose) deaths in New York City, 2000 to 2017. Available at: https://www1.nyc.gov/assets/doh/downloads/pdf/epi/databrief104.pdf. Accessed 9 July 2020.
21. Madaline T, Nori P, Mowrey W, et al. Bundle in the Bronx: impact of a transition-of-care outpatient parenteral antibiotic therapy bundle on all-cause 30-day hospital readmissions. Open Forum Infect Dis **2017**; 4:ofx097.
22. Harris PA, Taylor R, Minor BL, et al.; REDCap Consortium. The REDCap consortium: building an international community of software platform partners. J Biomed Inform **2019**; 95:103208.
23. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform **2009**; 42:377–81.
24. Ball LJ, Sherazi A, Laczko D, et al. Validation of an algorithm to identify infective endocarditis in people who inject drugs. Med Care **2018**; 56:e70–5.
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
26. Kim JH, Fine DR, Li L, et al. Disparities in United States hospitalizations for serious infections in patients with and without opioid use disorder: a nationwide observational study. PLoS Med **2020**; 17:e1003247.
27. Rudasill SE, Sanaiha Y, Mardock AL, et al. Clinical outcomes of infective endocarditis in injection drug users. J Am Coll Cardiol **2019**; 73:559–70.
28. Rapoport AB, Fischer LS, Santibanez S, et al. Infectious diseases physicians' perspectives regarding injection drug use and related infections, United States, 2017. Open Forum Infect Dis **2018**; 5:ofy132.
29. Fanucchi L, Leedy N, Li J, Thornton AC. Perceptions and practices of physicians regarding outpatient parenteral antibiotic therapy in persons who inject drugs. J Hosp Med **2016**; 11:581–2.
30. Suzuki J, Johnson J, Montgomery M, et al. Outpatient parenteral antimicrobial therapy among people who inject drugs: a review of the literature. Open Forum Infect Dis **2018**; 5:ofy194.
31. Wong JG, Chen MI, Win MK, et al. Length of stay an important mediator of hospital-acquired methicillin-resistant *Staphylococcus aureus*. Epidemiol Infect **2016**; 144:1248–56.
32. Brown CJ, Redden DT, Flood KL, Allman RM. The underrecognized epidemic of low mobility during hospitalization of older adults. J Am Geriatr Soc **2009**; 57:1660–5.
33. Bearnot B, Mitton JA, Hayden M, Park ER. Experiences of care among individuals with opioid use disorder-associated endocarditis and their healthcare providers: Results from a qualitative study. J Subst Abuse Treat **2019**; 102:16–22.
34. Ti L, Ti L. Leaving the hospital against medical advice among people who use illicit drugs: a systematic review. Am J Public Health **2015**; 105:e53–9.
35. Southern WN, Nahvi S, Arnsten JH. Increased risk of mortality and readmission among patients discharged against medical advice. Am J Med **2012**; 125:594–602.
36. Fanucchi LC, Walsh SL, Thornton AC, et al. Outpatient parenteral antimicrobial therapy plus buprenorphine for opioid use disorder and severe injection-related infections. Clin Infect Dis **2019**. doi:10.1093/cid/ciz654
37. Ho J, Archuleta S, Sulaiman Z, Fisher D. Safe and successful treatment of intravenous drug users with a peripherally inserted central catheter in an outpatient parenteral antibiotic treatment service. J Antimicrob Chemother **2010**; 65:2641–4.
38. Dobson PM, Loewenthal MR, Schneider K, Lai K. Comparing injecting drug users with others receiving outpatient parenteral antibiotic therapy. Open Forum Infect Dis **2017**; 4:ofx183.
39. Bork JT, Heil EL, Berry S, et al. Dalbavancin use in vulnerable patients receiving outpatient parenteral antibiotic therapy for invasive Gram-positive infections. Infect Dis Ther **2019**; 8:171–84.
40. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med **2019**; 380:415–24.
41. Pericas JM, Llopis J, Gonzalez-Ramallo V, et al. Outpatient parenteral antibiotic treatment (OPAT) for infective endocarditis: a prospective cohort study from the GAMES cohort. Clin Infect Dis **2019**. doi:10.1093/cid/ciz030