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Original Article

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Prevalence of Right- and Left-Sided Endocarditis Among Intravenous Drug Use Patients at a Large Academic Medical Center

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Abstract

Background: Left-sided infective endocarditis (IE) is increasingly being recognized among intravenous drug use (IVDU) patients. We sought to assess the trends and risk factors that contribute to left-sided IE in this high-risk population at University of Kentucky.

Methods: A retrospective chart review of patients with the diagnosis of both IE and IVDU admitted at University of Kentucky was carried out from January 1, 2015 to December 31, 2019. Baseline characteristics, trends of endocarditis and clinical outcomes (mortality and in-hospital interventions) were recorded.

Results: A total of 197 patients were admitted for management of endocarditis. One hundred and fourteen (57.9%) had right-sided endocarditis, 25 (12.7%) had combined left-sided and right-sided endocarditis, and 58 (29.4%) had left-sided endocarditis. *Staphylococcus aureus* was the most common pathogen. Mortality and inpatient surgical interventions were higher among patients with left-sided endocarditis. Patent foramen ovale (PFO) was the most common shunt found (3.1%), followed by atrial septal defect (ASD, 2.4%) with PFO being significantly more common among patients with left-sided endocarditis.

Conclusion: Right-sided endocarditis continues to be predominant among IVDU patients and *Staphylococcus aureus* was the most common organism involved. Patients with evidence of left-sided disease were found to have significantly more PFO, needed more inpatient valvular surgeries, and had higher all-cause mortality. Further studies are needed to assess if PFO or ASD can increase the risk of acquiring left-sided endocarditis in IVDU.

Keywords: Kentucky; Trends; Infective endocarditis; Mortality; IVDU

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Introduction

Intravenous drug use (IVDU) is a known risk factor for infective endocarditis (IE) and is an established minor criterion for the Modified Duke criteria [1]. IVDU results in access of bacteria into the venous system. The tricuspid and pulmonic valves are exposed along the pathway and are the common structures to get infected. IE has significant in-hospital mortality ranging 15-20% [2]. Infective material in the blood stream should be eliminated by the pulmonary macrophages and other immune systems, yet, left-sided IE (those involving mitral and/or aortic valves) is not uncommon. Previous research suggests that IVDU patients with left-sided IE tend to be younger, have more frequent multi-valve involvement, *Staphylococcus aureus* infections, previous IE, and experience more strokes [3]. This study was set out to see the common denominators for patients with left-sided IE, and hopefully help clinicians identify potential risk factors for IVDU patients to develop left-sided and/or mixed (right and left), as opposed to right-sided IE.

Materials and Methods

We reviewed charts for patients in Sunrise Clinical Medical software used at Albert B. Chandler Hospital and Good Samaritan Hospital at University of Kentucky who were admitted between January 1, 2015 to December 31, 2019 with the diagnosis of both IE and IVDU. We collected data including baseline characteristics, types of substance use, underlying medical conditions, vital signs and laboratory results at the time of admission. Further data regarding microbiology data, echocardiographic parameters involving risk stratification and prognostication of IE, and surgical or procedural outcomes (especially percutaneous aspiration debulking of vegetation through Angiovac) were also observed. Echocardiographic parameters in this study included number and severity of valves infected, left ventricular ejection fraction (LVEF), tricuspid valve regurgitation maximum velocity (TRVmax), presence of left-to-right shunts (atrial and ventricular septal defects (ASD, VSD), patent foramen ovale (PFO), and patent ductus arteriosus (PDA)), and presence of valve perforation. We divided patients into three groups: patients with isolated right-sided IE (only tricuspid and/or pulmonic valves involved; designated

group 1), combined right- and left-sided IE (tricuspid and/or pulmonic valves plus mitral and/or aortic valves involved; designated group 2), and isolated left-sided IE (only mitral and/or aortic valves involved; designated group 3).

Baseline characteristics and outcomes were stratified and compared. For categorical variables, frequencies, and column percentages (%) were reported and P-values were calculated using Chi-square and Fisher's exact tests, as appropriate. Continuous variables were assessed for normality using histograms. Normally distributed continuous variables were reported using means and standard deviations (SDs) and P-values were calculated using two-sample *t*-tests and one-way analysis of variance (ANOVA) assuming unequal variances; otherwise, medians and first/third quartiles (Q1, Q3) were reported and P-values were calculated using Mann-Whitney U and Kruskal-Wallis tests.

Statistical significance was set at $P < 0.05$ and all tests were two-sided. Missing observations were excluded on an analysis-by-analysis basis. All analyses were done in R programming language, v.4.1.1.

Ethical issues

All procedures of the present study were conducted in compliance with the Helsinki Declaration for research on human beings. The study was approved by the Institutional Review Board at University of Kentucky.

Results

We collected data from a total of 455 patient encounters. Two-hundred and fifty-eight were excluded due to either incomplete data availability, duplicate, or erroneous encounters. Among the 197 patients, 84 (42.6%) were male and 113 (57.4%) were female with mean age of 35.1 years old. One-hundred and fourteen (57.9%) belonged to group 1, 25 (12.7%) were in group 2, and 58 (29.4%) were included in group 3.

The baseline characteristics are displayed in Table 1. Of note, patients in group 3 had significantly more diagnoses of diabetes and ischemic heart disease than groups 1 and 2. Group 1 had significantly more diagnosis of hypertension than the other two groups. No patients had previous valvular interventions before being enrolled in the study. Tobacco smoking was the most common substance use found in the study (84.8%), followed by opioids (73.1%), amphetamine (43%), cannabinoids (21.1%), and cocaine (9.6%), respectively. This hierarchy seems to be the same in all patient groups.

The results in bacteriology and echocardiographic parameters are depicted in Table 2. Overall, 162 (82.2%) had bacteremia with mean duration of 4.2 days. *Staphylococcus aureus* was the most common organism involved, with 47 (25.8%) being methicillin-susceptible strain, and 70 (38.5%) being methicillin-resistant strain. Streptococcus and Enterococcus were found more in group 3. Echocardiographic parameters were collected from transthoracic echocardiogram (TTE, 78.7%) without bubbles used (91.1%). Almost all of the encounters were native valve infection (80.6%) with tricuspid valve being the most commonly affected (68.5%), followed by mitral valve (23.4%) and aortic valve (22.3%). Pulmonic valve was involved in only 6.6% of the patients. The mean LVEF was 51.2% and mean TRVmax was 2.8 m/s. The different severity of valvular abnormalities is displayed in Table 2. Valvular perforation was found in 18.3% of the patients, more in groups 2 and 3. No VSD or PDA was found. PFO was the most common shunt found (3.1%), followed by ASD (2.4%) with PFO being found to be significantly more common in groups 2 and 3. When combined patients with any left-sided endocarditis and compared to group 1, they were also found to have significantly more PFOs (odds ratio (OR) 3.5, $P = 0.046$).

Surgical and interventional outcomes are outlined in Table 3. Overall, 23.1% received valve surgeries while inpatient, and 9.3% underwent percutaneous aspiration debulking of vegetations with Angiovac while inpatient. Valve surgeries were done in higher percentage of patients in groups 2 and 3. When combined patients in groups 2 and 3 together, valve surgeries were done in higher percentage of patients than group 1 while inpatient (OR 4.3, $P < 0.001$). Since all percutaneous aspiration debulking with Angiovac was done for tricuspid valve vegetations, they were either in group 1 or 2. All-cause mortality was significantly different between groups, more in groups 2 and 3 than in group 1. When combined groups 2 and 3, they were found to have significantly higher all-cause mortality rate than group 1 (OR 10.2, $P < 0.001$).

Discussion

According to Pennsylvania Office of Rural Health, as of 2020, Kentucky was considered the top 20 in States with the Biggest Drug Problems, with Missouri being the highest on the list. According to the Substance Abuse and Mental Health Services Administration (SAMHSA), 25,428 people were admitted to Kentucky drug and alcohol rehab programs in 2010. About 66.9% of those admitted were men and 33.1% were women. Opiates (not including heroin) comprised 28.2% of admissions as the most abused substance by those admitted to Kentucky drug treatment centers, followed by alcohol and then marijuana, 18.8% and 16.7% consecutively. University of Kentucky (Albert B. Chandler and Good Samaritan Hospitals) serves as the tertiary referral center for patients in most counties from central, to Northern, Southern, and Eastern part of the state of Kentucky and can potentially represent patient population in the state.

It has been well established that IE in the general population occurs most frequently on the left side of the heart, affecting either the mitral or aortic valves. Conversely, the majority of right-sided endocarditis involves the tricuspid valve and occurs among IVDU. The proposed pathogenesis of the predilection was hypothesized to be from endothelial damage, relationship of infecting organism and valvular location, bacterial "load" and localization of valve lesion, and host immune status and localization of valve lesion [4]. The pathophysiology of left-sided IE in IVDU patients, in contrast, is unclear. Persistent bacteremia and the presence of right-to-left shunts

Table 1. Baseline Characteristics

N (%)	Group 1 (N = 114)	Group 2 (N = 25)	Group 3 (N = 58)	Overall (N = 197)	P-value
Age (years), mean (SD)	33.2 (8.0)	36 (7.6)	38.6 (9.8)	35.1 (8.8)	0.002*
Sex					< 0.001*
Male	34 (29.8)	15 (60.0)	35 (60.3)	84 (42.6)	
Female	80 (70.2)	10 (40.0)	23 (39.7)	113 (57.4)	
Race					0.097
Black/AA	3 (2.6)	1 (4.0)	0 (0.0)	4 (2.0)	
Caucasian	111 (97.4)	23 (92.0)	57 (98.3)	191 (97.0)	
Refused/unreported	0 (0.0)	1 (4.0)	1 (1.7)	2 (1.0)	
Medical conditions					
Diabetes mellitus	3 (3.3)	3 (13.0)	8 (14.0)	13 (7.7)	0.010*
Hypertension	31 (27.2)	13 (52.0)	28 (48.3)	72 (36.5)	0.006*
Dyslipidemia	5 (4.4)	2 (8.0)	8 (13.8)	15 (7.6)	0.085
HIV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Ischemic heart disease	5 (4.4)	6 (24.0)	13 (22.4)	24 (12.2)	< 0.001*
Procedures					
Valvular interventions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	N/A
CIEDs	29 (25.4)	13 (52.0)	29 (50.0)	71 (36.0)	0.001*
Substance use					
Tobacco	92 (86.8)	18 (78.3)	46 (83.6)	156 (84.8)	0.487
Opioid	90 (78.9)	14 (56.0)	40 (69.0)	144 (73.1)	0.045*
Amphetamine	49 (43.0)	7 (28.0)	20 (34.5)	76 (38.6)	0.283
Cocaine	11 (9.6)	1 (4.4)	5 (8.6)	18 (9.1)	1.000
Cannabinoids	24 (21.1)	4 (16.0)	13 (22.4)	41 (20.8)	0.800
Last drug use (days)	108.6 (395.3)	11.0 (14.1)	35.9 (92.0)	82.3 (323.1)	0.238
Labs					
Hemoglobin (g/dL)	9.9 (2.3)	9.7 (2.4)	10.3 (2.1)	10.0 (2.2)	0.385
WBC ($\times 10^9$/L)	13.1 (6.5)	12.0 (5.0)	14.0 (6.4)	13.2 (6.3)	0.305
Creatinine (mg/dL)	1.0 (0.9)	1.0 (0.5)	1.1 (1.1)	1.0 (1.0)	0.978
HbA1c (%)	5.9 (2.0)	6.3 (2.5)	5.6 (0.8)	5.8 (1.6)	0.477
AST (U/L)	36.4 (37.8)	46.4 (37.5)	46.9 (58.3)	41.0 (45.2)	0.298
ALT (U/L)	31.1 (62.4)	45.4 (53.3)	50.0 (119.2)	38.9 (83.3)	0.339
CRP (µg/mL)	27.1 (59.2)	20.5 (28.3)	18.5 (45.8)	24.1 (53.1)	0.663
ESR (mm/h)	60.6 (27.3)	62.0 (41.9)	68.0 (33.0)	62.6 (30.6)	0.785
Vitals					
Temperature (°C)	37.1 (0.7)	37.0 (1.1)	37.1 (0.8)	37.1 (0.8)	0.959
SBP (mm Hg)	114.9 (18.9)	119.7 (16.5)	123.6 (23.9)	118.1 (20.5)	0.050*
DBP (mm Hg)	70.9 (11.0)	70.9 (11.0)	73.8 (18.0)	72.5 (15.6)	0.669
HR (bpm)	104.1 (19.4)	109.6 (16.1)	97.5 (18.2)	102.8 (19.0)	0.010*
SpO_2 (%)	96.9 (2.3)	96.0 (2.8)	96.7 (3.5)	97.6 (2.8)	0.343

Data are presented as means and standard deviations (SDs) in parentheses or numbers with percentage in parentheses. *Significant P-values. ALT: alanine transaminase; AST: aspartate aminotransferase; CIEDs: cardiac implantable electrical devices; CRP: C-reactive protein; DBP: diastolic blood pressure; ESR: erythrocyte sedimentation rate; HIV: human immunodeficiency virus; HR: heart rate; SBP: systolic blood pressure; WBC: white blood cell.

Table 2. Bacteriology and Echocardiographic Parameters

	Group 1 (N = 114)	Group 2 (N = 25)	Group 3 (N = 58)	Overall (N = 197)	P-value
Bacteremia	92 (80.7)	24 (96.0)	46 (79.3)	162 (82.2)	0.137
Days with bacteremia	4.2 (3.5)	4.9 (2.3)	4.0 (4.0)	4.2 (3.5)	0.592
Bacteria, N (%)					0.002*
MSSA	32 (30.8)	6 (25.0)	9 (16.7)	47 (25.8)	
MRSA	45 (43.3)	12 (50.0)	13 (24.1)	70 (38.5)	
Streptococci	4 (3.8)	0 (0.0)	10 (18.6)	14 (7.6)	
E. faecalis	2 (1.9)	3 (12.5)	7 (13.0)	12 (6.6)	
Pseudomonas spp.	0 (0.0)	1 (4.2)	2 (3.8)	3 (1.6)	
Others	7 (6.7)	2 (8.3)	4 (7.4)	13 (7.1)	
Polymicrobial	2 (1.9)	0 (0.0)	2 (3.7)	4 (2.2)	
Culture-negative	3 (2.9)	0 (0.0)	0 (0.0)	3 (1.6)	
Echo					0.011*
TTE	98 (86.0)	16 (67.0)	41 (70.7)	155 (78.7)	
TEE	16 (14.0)	9 (36.0)	17 (29.3)	42 (21.3)	
With bubbles	6 (5.4)	3 (12.5)	8 (14.0)	17 (8.9)	0.117
Valve types					0.164
Native	95 (84.1)	20 (80.0)	43 (74.1)	158 (80.6)	
Bioprosthetic	18 (15.9)	1 (16.0)	14 (24.1)	36 (18.4)	
Mechanical	0 (0.0)	1 (4.0)	1 (1.7)	2 (1.0)	
Valve involvement					
Tricuspid	111 (97.4)	24 (96.0)	0 (0.0)	135 (68.5)	< 0.001*
Pulmonic	9 (7.9)	4 (16.0)	0 (0.0)	13 (6.6)	0.009*
Mitral	0 (0.0)	18 (72.0)	28 (48.3)	46 (23.4)	< 0.001*
Aortic	0 (0.0)	11 (44.0)	33 (56.9)	44 (22.3)	< 0.001*
LVEF (%), mean (SD)	53.0 (12.1)	46.4 (17.9)	49.6 (14.7)	51.2 (13.8)	0.125
TRVmax (m/s)	2.7 (0.5)	2.9 (0.5)	3.1 (1.3)	2.8 (0.8)	0.098
Tricuspid abnormalities					
TS					0.497
Trivial-mild	0 (0.0)	0 (0.0)	1 (1.7)	1 (0.5)	
Moderate	4 (3.6)	0 (0.0)	0 (0.0)	4 (2.1)	
Severe	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.5)	
TR					< 0.001*
Trivial-mild	31 (27.4)	10 (40.0)	23 (39.6)	64 (32.7)	
Moderate	35 (31.0)	3 (12.0)	8 (13.8)	46 (23.5)	
Severe	41 (36.3)	10 (40.0)	1 (1.7)	52 (26.5)	
Pulmonic abnormalities					
PS					1.000
Trivial-mild	2 (1.8)	0 (0.0)	0 (0.0)	2 (1.0)	
Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
PR					0.697
Trivial-mild	37 (33.0)	5 (20.0)	19 (32.8)	61 (31.3)	
Moderate	1 (0.9)	0 (0.0)	1 (1.7)	2 (1.0)	

Table 2. Bacteriology and Echocardiographic Parameters - (continued)

	Group 1 (N = 114)	Group 2 (N = 25)	Group 3 (N = 58)	Overall (N = 197)	P-value
Severe	2 (1.8)	0 (0.0)	0 (0.0)	2 (1.0)	
Mitral abnormalities					
MS					0.086
Trivial-mild	0 (0.0)	1 (4.0)	1 (1.7)	2 (1.0)	
Moderate	0 (0.0)	0 (0.0)	1 (1.7)	1 (0.5)	
Severe	0 (0.0)	0 (0.0)	1 (1.7)	1 (0.5)	
MR					< 0.001*
Trivial-mild	51 (45.2)	12 (48.0)	16 (28.5)	79 (40.7)	
Moderate	2 (1.8)	3 (12.0)	12 (21.4)	17 (8.8)	
Severe	0 (0.0)	3 (12.0)	12 (21.4)	15 (7.7)	
Aortic abnormalities					
AS					0.073
Trivial-mild	0 (0.0)	0 (0.0)	4 (6.9)	4 (2.0)	
Moderate	1 (0.9)	0 (0.0)	1 (1.7)	2 (1.0)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
AR					< 0.001*
Trivial-mild	2 (1.8)	2 (8.0)	7 (12.0)	11 (5.7)	
Moderate	1 (0.9)	2 (8.0)	5 (8.6)	8 (4.1)	
Severe	0 (0.0)	8 (32.0)	19 (32.8)	27 (13.8)	
Valve perforation	10 (9.0)	11 (47.8)	14 (24.6)	35 (18.3)	< 0.001*
Shunts					
ASD	2 (2.8)	0 (0)	1 (2.6)	3 (2.4)	1.000
PFO	5 (7.1)	5 (31.2)	6 (16.7)	16 (3.1)	0.021*
VSD	0 (0)	0 (0)	0 (0)	0 (0)	N/A
PDA	0 (0)	0 (0)	0 (0)	0 (0)	N/A

*Significant P-values. MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; TEE: transesophageal echocardiography; TTE: transthoracic echocardiogram; LVEF: left ventricular ejection fraction; SD: standard deviation; TRVmax: tricuspid valve regurgitation maximum velocity; TS: tricuspid stenosis; TR: tricuspid regurgitation; PS: pulmonary stenosis; PR: pulmonary regurgitation; AS: aortic stenosis; AR: aortic regurgitation; MS: mitral stenosis; MR: mitral regurgitation; ASD: atrial septal defect; PFO: patent foramen ovale; VSD: ventricular septal defect; PDA: patent ductus arteriosus.

have been suggested as the possible mechanism of the development of left-sided IE in said patients, but the data are so far not robust. PFO, in particular, was found in this patient population in previous case reports [5].

We found in this study that patients with right-sided valvular infection were predominant and mostly affected by *Staphylococcus aureus*, similar to prior study around the same time frame in North Carolina [3], with similar patterns of mitral valves being involved more than aortic valves. Patients with left-sided involvement in this study were found to have significantly more PFO. This was also proved to be true with analyses among three groups of patients and also between patients with right-sided endocarditis versus the combination of groups 2 and 3.

Patients with left-sided endocarditis in this study received more inpatient valvular surgeries with statistical significance similar to previous study [6], and had higher all-cause mor-

Table 3. Inpatient Surgical and Interventional Outcomes

	Group 1 (N = 114)	Group 2 (N = 25)	Group 3 (N = 58)	Overall (N = 197)	P-value
Valve surgeries	14 (12.4)	9 (37.5)	22 (37.9)	45 (23.1)	< 0.001*
Angiovac	16 (14.3)	2 (8.3)	0 (0)	18 (9.3)	0.002*
All-cause mortality	3 (2.6)	4 (30.8)	15 (25.9)	21 (10.7)	< 0.001*

*Significant P-values.

tality rate similar to previous studies [6, 7]. The difference in mortality carries over with the combination of groups 2 and 3 versus group 1.

Primary treatment of IE is targeted antibiotic therapy for at least 6 weeks; however, in certain cases, the intravenous antibiotics are not sufficient and surgical intervention is required. The indications for the surgical management of IE generally include fungal endocarditis, persistent bacteremia for more than 7 days despite appropriate antibiotic therapy, heart failure due to valve regurgitation, large-sized vegetation > 2 cm, or recurrent septic emboli despite medical treatment [1].

Right-sided endocarditis has better outcomes compared to left-sided IE or right and left-sided combined IE owing to reduced mortality and fewer post-operative complications [8]. This can be attributed to increased perivalvular abscess formation, higher occurrence of septic shock, renal failure and need for emergent surgeries in left-sided IE compared to the right [9]. Left-sided IE was also associated with higher rates of heart failure and systemic embolization [10].

In high-risk surgical patients, percutaneous aspiration system using a veno-venous bypass circuit to debulk tricuspid valve vegetations has now become common, with Angiovac system (by AngioDynamics, Latham, NY) being used in our institution. Benefits of percutaneous aspiration debulking include rapid clearance of bacteremia, and can be preferred over surgery by preventing sternotomy, complications of surgery and risk of reinfection with relapse in IVDU, and its utility in critically ill patients who are not surgical candidates. In a meta-analysis, Angiovac system assisted debulking of tricuspid endocarditis resulted in > 50% vegetation reduction achieved in 90%, and bacteremia clearance achieved in 82.5% of patients [11]. In addition to debulking of tricuspid valve, with use of transeptal approach and use of sentinel cerebral protection device, debulking of mitral valve and aortic valve IE has been successfully attempted [12].

Limitations

According to analyses of October 2016 and August 2019, Medicare claims data and determined of the 170 Alcohol & Drug Abuse hospitalizations at UK Healthcare - Albert B. Chandler Hospital, 49 were readmitted which was a readmission rate of 28.82% [13]. We also saw the same pattern of frequent discharges against medical advice and readmissions in IVDU patients. That leaves a challenge in data gathering from different encounters of the same patients and excluding the duplicate data points and determination of the episodes of IE. In this study, there were a significant amount of data points that were excluded solely due to readmissions of the same patients with the same diagnoses, and some of them carried incomplete data for analyses. We set out to analyze all encounters between the 5-year time described in Methods, but quite a few of those were excluded for said reason. We did our due diligence to try to encompass as many patients during that time without counting the readmissions but may affect the outcome in differences and the statistical significances. This was a retrospective study, and data collection was limited from 2015 to 2019, after approval of the study by the IRB in 2021; however, since then the primary offending organisms may have changed.

The investigators notice the underuse of bubble studies in the diagnosis of patients with suspected IE in this population. Since intracardiac shunts, especially PFO sometimes can be invisible with routine TTEs, this can be missed without bubbles, and may have affected the incidence of PFO found in those studies. In this study, more patients had right-sided IE, and patients with left-sided IE represented the smallest group with relatively small sample size. Future larger studies might be able to include more patients especially in the latter group to make clearer differences between groups and more significant statistical analyses.

Conclusion

In this retrospective cohort study of IVDU patients admitted to University of Kentucky during the 5-year interval, right-sided endocarditis was predominant and *Staphylococcus aureus* was the most common causative organism. Right-sided endocarditis patients underwent successful percutaneous aspiration debulking of vegetations. Patients with evidence of left-sided endocarditis were found to have significantly more PFO, needed more inpatient valvular surgeries, and had higher all-cause mortality. Further studies are needed to assess if PFO or ASD can increase the risk of acquiring left-sided endocarditis in IVDU.

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Conflict of Interest

None to declare.

Informed Consent

None to declare.

Author Contributions

Data collection: KJ, SA, MV. Drafting of manuscript: KJ, AA, SA. Statistical analysis: KH. Manuscript revision: MV, AA, HA. Final approval: KJ, MV, HA, AA, KH, SA.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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