Patients with infective endocarditis and history of injection drug use –a register-based study of a 10-year period

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Abstract

Background: Patients with injection drug use (IDU) have increased risk of developing infective endocarditis (IE), however data of these patients are scarce and need to be explored further. This study aims to describe the clinical characteristics and outcomes among patients with IDU-IE.

Methods: Data of adults with IDU-IE and non-IDU-IE, treated between 2008-2017 at the Karolinska University Hospital in Stockholm were obtained from the Swedish National Registry of Infective Endocarditis. Clinical characteristics, microbiological results, treatment durations, results from echocardiography and in-hospital mortality were compared between the groups.

Results: In total, 165 (32%) of the included patients had IDU-IE. Patients with IDU-IE were younger than the patients with non-IDU-IE (mean age IDU-IE: 41.6 years; non-IDU-IE: 64.3 years; P<0.01). No difference in distribution of genders was observed, 33% women in both groups. History of previous IE (n=49, 30%) and vascular phenomena (n=101, 61%), were more common among patients with IDU-IE while prosthetic heart valves (n=83, 23%) and known valvular disease (n=78, 22%) were more common among patients with non-IDU-IE (P<0.05). Aetiology of *Staphylococcus aureus* (n=121, 73%) and tricuspid (n=91, 55%) or pulmonary valve (n=7, 4%) vegetations were more common among IDU-IE (P<0.05). The overall incidence of IDU-IE decreased during the study period, while the incidence of definite IE increased (P<0.01).

Conclusions: Patients with IDU-IE were younger, frequently presenting with right-sided vegetations and *S. aureus* aetiology, and were less frequently treated with surgery. Patients with IDU-IE had higher prevalence of vascular phenomena and history of previous IE, aspects that are important for improved management of this population.

Background

The incidence of infective endocarditis (IE), one of the infectious diseases with the highest morbidity and mortality, is increasing [1-4]. One factor contributing to the increase of IE is the increasing incidence of injection drug use (IDU) [1-3]. People with IDU are at 100-fold increased risk of developing IE compared with the general population [1].

There are several mechanisms that can explain the increased risk of IE among patients with IDU: direct injury from injected substances, poor hygiene during injection, contaminated injection equipment, and physiological factors associated with IDU such as vasospasm and cardiac damage have also been described [2, 3, 5, 6]. IDU-related IE (IDU-IE) more often present as right-sided, rather than left-sided. The exposure from injected substances causing endothelial damage has been reported as the mechanism behind the right-sided manifestations, which most often present as tricuspid valve vegetations [3, 6, 7].

Despite the known relationship between increasing IDU and increasing incidences of IE, relatively few studies have explored the outcomes in the population of IDU-IE. Previous studies have reported persistent and recurrent IE, increased duration of hospital stay, persistent IDU, and poor adherence and compliance

in the IDU-IE patient group [8, 9]. Further studies of clinical characteristics and outcomes among the patients with IDU-IE are needed and might provide a basis for optimized care and prevention of readmissions in this population.

This study aimed to present the clinical characteristics and outcomes among the patients with IDU and definite IE admitted to a university hospital in Stockholm between 2008 and 2017 and further to highlight differences between this patient group and patients with IE without IDU, referred to as non-IDU-IE.

Methods

Study setting

This study is based on data from patients with IDU and IE, admitted to the Karolinska University Hospital in Stockholm, Sweden. The hospital has a special ward for drug addicts with infectious diseases, with an uptake area covering Stockholm County Council with approximately 1.9 million adult (18 years and above) inhabitants. The ward is operated by infectious diseases consultants and addiction psychiatrists. This contributes to the relatively high prevalence of patients with IDU among patients admitted to the hospital with IE, which was presented in a previous study [10]. According to guidelines, most of the patients with IE at the hospital are discussed within an endocarditis team, comprising specialists in infectious diseases, cardiology, clinical physiology and thoracic surgery [11]. The majority of the ECHO investigations were conducted at the Department of Clinical Physiology, a unit specialized in cardiovascular imaging.

Study design

This study is registry-based on data from the Swedish National Registry of Infective Endocarditis (SRIE). The SRIE is a national registry established in 1995, covering data from patients treated for possible or definite IE (ICD codes I33.0, I33.9, I38.9, and I39.8) in all Swedish departments for infectious diseases, with an estimated coverage of 70–80% [12]. Data of patients with definite IE, treated at the Karolinska University Hospital in Stockholm, between 1 January 2008 and 31 December 2017 were obtained from the SRIE. Patients aged 18 years and above with registered history of IDU were selected for further analysis and compared with patients with non-IDU-IE. Age, gender, date of admission, clinical characteristics, congenital heart disease, co-morbidities, results from blood cultures and cultures or polymerase chain reaction (PCR) amplification from material sampled during cardiac surgery, results from ECHO investigations (transthoracic echocardiography: TTE and transesophageal echocardiography: TEE), antibiotic treatment durations, and in-hospital mortality were obtained from the SRIE. Coagulase-negative staphylococci (CoNS) were grouped including *Staphylococcus lugdunensis* and *Staphylococcus epidermidis*. The review of data from the registry was performed by one person (AD) and discussed with a specialist in infectious diseases (KW). All methods were performed in accordance with the relevant guidelines and regulations.

Statistical methods

Continuous variables were described as means and standard deviations (SDs) or median and 25th and 75th percentiles and categorical variables as proportions (percentages). Mann-Whitney's test was used for comparisons of continuous variables. For comparisons of categorical variables, chi-squared test was conducted for values ³ 5 and the two-sided Fisher's exact test for values < 5. Multivariable linear and logistic regression models were used to analyse duration of antibiotic treatment and in-hospital mortality. Variations over time were analysed using linear regression. In all analyses, P-values < 0.05 (two-tailed) were considered statistically significant. Analyses were performed using STATA software (version 15.1 Stata Corp., College Station, Texas, USA).

Results

In total, 522 patients were registered with definite IE at the Karolinska University Hospital between 2008 and 2017, of these 165 (32%) had history of IDU. The clinical characteristics of the patients with IDU-IE and non-IDU-IE are presented in Table 1. About two thirds of the included patients with IDU-IE were male (110 patients, 67%), which was the same percentage as non-IDU-IE patients. Mean age among the patients with IDU-IE was 41.6 years, which was mean 22.7 years younger than patients with non-IDU-IE (P < 0.01). A majority of the patients with IDU-IE (101 patients, 61%) presented with vascular phenomena, which was more common than among patients with non-IDU-IE (Table 1). More specifically, spondylitis and pulmonary septic emboli were more common among IDU-IE compared with patients with non-IDU-IE (spondylitis n = 25, 15% vs n = 30, 9%; P = 0.02, pulmonary septic emboli n = 55, 33% vs n = 11, 3%; P < 0.01). Further, history of previous IE was more common among the patients with IDU-IE, while prosthetic heart valves, known valvular disease, cardiovascular implantable electronic device (CIED)-associated IE were more common among patients with non-IDU-IE (Table 1). The incidence of definite IE registered at the Karolinska University Hospital increased during the study period from 2.52 (2008) to 4.21 cases (2017) per 100,000 adult (18 years and older) inhabitants in Stockholm county (P < 0.01). Contrasting, there was an overall decrease in incidence of IDU-IE registered at the hospital between 2008 and 2017 (P < 0.01), however, an initial increase between 2008 and 2011 was seen from 0.58 to 1.34 cases per 100,000 adult inhabitants (P < 0.01, Fig 1), but from 2012 to 2017, there was a decrease in incidence from 1.14 to 0.89 cases per 100,000 adult inhabitants in Stockholm county (P < 0.01, Fig 1). Further, the rate of patients with IDU-IE were lower during the winter compared to the other seasons (P = 0.01, Fig 2).

Table 1. Characteristics of the patients with IDU-IE and non-IDU-IE admitted between 2008-2017

Clinical characteristics	IDU-IE (n=165 (%))	Non-IDU IE (n=357 (%))	P value
Women	55 (33)	119 (33)	1.00
Men	110 (67)	238 (67)	1.00
Age, mean (± SD); median (25th and 75th percentiles)	41.6 (11.9); 44 (31, 50)	64.3 (16.4); 67 (56, 76)	**< 0.01**
Predisposing factors			
Bicuspid aortic valve	0 (0)	20 (6)	**<0.01**
Prosthetic valve	12 (7)	83 (23)	**< 0.01**
CIED	2 (1)	38 (11)	**< 0.01**
Rheumatic heart disease	0 (0)	2 (1)	1.00
Congenital heart disease	0 (0)	8 (2)	0.06
History of IE	49 (30)	34 (10)	**< 0.01**
Known valvular disease	3 (2)	78 (22)	**< 0.01**
Heart failure before or under IE treatment	19 (12)	45 (13)	0.72
Patients fulfilling Duke's major criteria			
Blood culture positive for IE	144 (87)	304 (85)	0.78
Imaging positive for IE*	165 (100)	287 (80)	**< 0.01**
Patients fulfilling Duke's minor criteria			
Fever	150 (91)	304 (85)	0.07
Vascular phenomena	101 (61)	120 (34)	**< 0.01**
New heart murmur	20 (12)	63 (18)	0.11
Immunological phenomenon	2 (1)	19 (5)	**0.03**
Other microbiological evidence	3 (2)	14 (4)	0.29

*In total, 101 (61%) of the IDU-IE patients underwent transthoracic echocardiography and 137 (83%) patients underwent transoesophageal echocardiography during hospital stay. Significant P values are marked in bold font. Abbreviations: CIED, cardiovascular implantable electronic device; IDU, injection drug use; IE, infective endocarditis; n, number of patients; SD, standard deviation.

Of the included patients with IDU-IE, 157 (95%) had positive blood cultures. One of the patients that had negative blood culture had positive polymerase chain reaction (PCR) from heart valve surgery (methicillin susceptible *Staphylococcus aureus* - MSSA) (Table 2 and Table 3). Aetiology of *S. aureus* was significantly more common among patients with IDU-IE compared with patients with non-IDU-IE (n = 121, 73% among patients with IDU-IE, P < 0.01). Of the patients with IDU-IE, 94%, compared with 80% of the patients with non-IDU-IE (P < 0.01), had findings consistent with IE during examination with echocardiography (ECHO), the most common manifestation was tricuspid valve vegetation (91 patients, 55%), followed by mitral valve vegetation (47 patients, 28%) and aortic valve vegetation (33 patients, 20%) (Table 4). A significantly higher prevalence of tricuspid and pulmonary valve vegetations was seen among the patients with IDU-IE compared with the non-IDU-IE patients who had higher prevalence of

aortic- and mitral valve vegetations as well as abscess and CIED-associated IE (Table 4). Multiple valve vegetations were equally common among patients with IDU-IE (n = 27 (16%)) and non-IDU-IE (n = 46 (13%), P = 0.29).

Table 2. Aetiology obtained from blood- and valve culture among patients with IDU-IE.

Blood culture results* (n (%))	**144 (87)**
Staphylococcus aureus (MSSA)	110 (67)
Enterococcus faecalis	14 (8)
Viridans group streptococci	9 (5)
S. aureus (MRSA)	3 (2)
Bacillus cereus	3 (2)
CoNS	2 (1)
Group A streptococci	1 (1)
Group G streptococci	1 (1)
Klebsiella spp	1 (1)
Unspecified funghi**	1 (1)
Polymicrobial blood cultures	**13 (8)**
MSSA and *E. faecalis*	4 (2)
E. faecalis and unspecified funghi	1 (1)
MSSA and aerobic gramnegative stave	1 (1)
MSSA and candida	1 (1)
MSSA and group G streptococci	1 (1)
MSSA and MRSA	1 (1)
MSSA and unspecified funghi	1 (1)
MSSA and viridans group streptococci	1 (1)
Viridans group streptococci and CoNS	1 (1)
Blood culture negative	**8 (5)**
Bacteria in valve culture from cardiac surgery	**9 (5)**
Staphylococcus aureus (MSSA)	5 (3)
Unspecified funghi	2 (1)
CoNS	1 (1)
Enterococcus faecalis	1 (1)

* Single bacteria in blood culture. ** None had Candida albicans. All patients with positive valve culture had positive blood culture. Of all patients with positive valve culture, one had bacteria that differed between blood culture (MSSA) and valve culture (unspecified funghi). Among the patients with non-IDU-IE, 12 patients (3%) had more than one bacterium in blood cultures. Abbreviations: CoNS, coagulase negative staphylococci; E, enterococcus; IDU, injection drug use; IE, infective endocarditis; MRSA, methicillin resistant *Staphylococcus aureus*; MSSA, methicillin susceptible *Staphylococcus aureus*; n, number of patients; PCR, polymerase chain reaction; S, staphylococcus; spp, species.

Table 3. Aetiology obtained from valve PCR among patients with IDU-IE.

Bacteria in valve PCR from cardiac surgery (n (%))	**19 (12)**
Staphylococcus aureus (MSSA)	15 (9)
CoNS	2 (1)
Enterococcus faecalis	2 (1)

One patient had positive valve PCR (MSSA) and negative blood culture, all other patients with positive valve PCR had positive blood cultures. Among the patients with positive valve PCR had positive blood cultures, the bacteria found in blood culture were the same as those found in valve PCR. Abbreviations: CoNS, coagulase negative staphylococci; IDU, injection drug use; IE, infective endocarditis; MSSA, methicillin susceptible *Staphylococcus aureus*; n, number of patients; PCR, polymerase chain reaction.

Table 4. Manifestations detected by ECHO among patients with IDU-IE

All manifestations	**IDU-IE (n=165 (100%))**	**Non-IDU-IE (n=287 (80%))**	**P value**
Aortic valve vegetation	33 (20)	171 (48)	**< 0.01**
Mitral valve vegetation	47 (28)	162 (45)	**< 0.01**
Tricuspid valve vegetation	91 (55)	23 (6)	**< 0.01**
Pulmonary valve vegetation	7 (4)	2 (1)	**< 0.01**
CIED-associated IE	1 (1)	25 (7)	**< 0.01**
Abscess	4 (2)	27 (8)	**0.03**
Multiple valve vegetations			
Aortic and mitral valve vegetation	11 (7)	31 (9)	0.43
Aortic and tricuspid valve vegetation	5 (3)	3 (1)	
Aortic and pulmonary valve vegetation	1 (1)	0 (0)	
Mitral and tricuspid valve vegetation	5 (3)	5 (1)	
Mitral and pulmonary valve vegetation	1 (1)	0 (0)	
Tricuspid and pulmonary valve vegetation	4 (2)	1 (0)	
CIED and tricuspid valve vegetation	0 (0)	6 (2)	

Among the patients listed with, for instance, aortic valve vegetation, some patients had vegetations also on other valves and thus were listed also under the topic “multiple valve vegetations”. Significant P values are marked in bold font. Abbreviations: CIED, cardiovascular implantable electronic device; ECHO, echocardiography; IDU, injection drug use, IE, infective endocarditis.

Significantly less of the IDU-IE patients was treated with surgery; 27 (16%), compared with 121 (34%) among the non-IDU-IE patients (P < 0.01). The rate of patients with IDU-IE treated with surgery did not change significantly during the study period (P = 0.06). The most common single valve surgery performed in the IDU-IE group were biological aortic valve replacement (n = 6) followed by biological tricuspid valve replacement (n = 5), and one removal of tricuspid valve vegetation. Eight surgical procedures included more than one prosthetic or mechanical valve replacement of which 5 cases

included tricuspid valve replacement. Among the patients with IDU-IE treated with surgery, none were re-operated during hospital stay nor during follow-up (up to 6 months). One patient with IDU-IE caused by *E faecalis,* that was not treated with surgery during hospital stay was operated during follow-up due to prosthetic (mechanical) mitral valve dehiscence, that was inserted 14 years prior to the IE diagnosis. Among the patients with IDU-IE treated with surgery, one died during hospital stay but none died during follow-up after discharge from hospital. In-hospital mortality was equal among the patients treated with surgery and the patients not treated with surgery, both in the IDU-IE group (1 (4%) of the 27 patients treated with surgery died during hospital stay and 6 (5%) of the 132 patients not treated with surgery died during hospital stay, P = 1.00) and in the non-IDU-IE group (12 (10%) of the 121 patients treated with surgery died during hospital stay and 15 (6%) of the 236 patients not treated with surgery died during hospital stay, P = 0.23).

In-hospital mortality, defined as death during hospital stay, was equally common among patients with IDU-IE (n = 7 (4%)), and those with non-IDU-IE (non-IDU-IE n = 27 (8%), P < 0.15). However, among patients with *S. aureus* aetiology, in-hospital mortality was higher among patients with non-IDU-IE compared with the patients with IDU-IE (n = 18 (15%) and n = 5 (4%), respectively, P = 0.01). In the IDU-IE group, 80 (70%) of the patients with *S. aureus* aetiology had right-sided IE, and 35 (30%) had left sided IE. In the non-IDU-IE group, 20 (18%) of the patients with *S. aureus* aetiology had right-sided IE, and 95 (83%) had left sided IE. Hence, of the patients with *S. aureus* aetiology, right sided IE was more common in the IDU-IE group (OR 10.74; P < 0.01). In the IDU-IE group, 3 (4%) of the patients with *S. aureus* aetiology and right-sided IE died during hospital stay, which was equal to the in-hospital mortality among the left-sided IE (n = 2 (6%); OR 0.64; P = 0.64). In the non-IDU-IE group, 2 (10%) of the patients with *S. aureus* aetiology and right-sided IE died during hospital stay, which was equal to the in-hospital mortality among the left-sided IE (n = 14 (15%); OR 0.63; P = 0.73).

The duration of hospital stay was equally long among patients with non-IDU-IE (median 32, mean 40.8 days, SD 148.9) compared with patients with IDU-IE (median 32, mean days 35.5, SD 15.9, P = 0.65 for comparison of the mean and P = 1.00 for comparison of the median). Patients with left-sided IDU-IE caused by *S aureus* had significantly longer antibiotic treatment durations compared to patients with *S aureus* and right-sided IDU-IE (mean 35.88 days versus 30.04 days, P < 0.01, Table 5).

Table 5. Antibiotic treatment duration among patients with IDU-IE, comparing left- and right-sided IE.

	Both left- and right-sided IDU-IE	Left-sided IDU-IE	Right-sided IDU-IE	P value
All patients with IDU-IE	32.42 (30.30, 34.54)	34.53 (30.87, 38.18)	30.80 (27.74, 33.86)	0.12
Staphylococcus aureus aetiology	32.14 (29.56, 34.72)	35.88 (30.79, 40.97)	30.04 (26.49, 33.59)	**<0.01**
Non-Staphylococcus aureus aetiology	30.27 (29.03, 37.51) [a]	32.68 (27.90, 37.46)	34.57 (28.19, 40.96)	0.634

All values are presented in mean days (95% confidence intervals). P values between the comparisons of left- and right-sided IDU-IE, significant P values are marked in bold font. [a] No difference in treatment duration mean among S. aureus positive patients and non S. aureus patients (P = 0.63). Abbreviations: IDU, injection drug use; IE, infective endocarditis; S, staphylococcus.

Discussion

People with IDU have an increased risk of developing IE. The estimate of people with IDU who had IE is between 1.5% and 20% [1, 13-15]. It is of great importance to address this population, as they tend to have worse outcomes than people with non-IDU-IE in terms of higher mortality after valve replacement and increased frequency of repeat endocarditis, [16, 17] the latter confirmed in our study. History of previous IE was more common in this patient group, however a lower extent of the patients with IDU-IE had prosthetic heart valves and known valvular disease compared with those with non-IDU-IE. The rate of patients with positive ECHO was higher among patients with IDU-IE compared with non-IDU-IE, which could possibly be explained by the higher rate of right-sided valve vegetations in the IDU-IE group, which can be easier to identify also with TTE. Another reason could be the younger age and less comorbidity in the IDU-IE group compared with the non-IDU-IE group, which could have contributed to more frequent use of TEE in this group, which has higher sensitivity and specificity for IE, compared with TTE.

The patients with IDU-IE were younger than the patients with non-IDU-IE (mean difference 22.7 years). Supportive to our results, previous studies of IDU-IE present younger populations compared to patients with non-IDU-IE [2, 3, 8, 13]. The population of patients with IE is known to have a domination of male gender, the ratio of male to female patients are commonly presented as 3:1 or 2:1 [13, 18, 19]. However, Wurcel et al., presented a prevalence of female gender of 40.9% among IDU-IE and even higher in the age group of 15-34-year-old patients with IDU-IE [3]. The population of IDU-IE patients in our study had the same rate of female patients in the age group 15-34 years as in that study. This finding suggest that the demographics of patients with IDU-IE are shifting towards a population of younger, female patients compared with previously reported demographics of the IDU-IE population [3, 13].

Previous studies have described an increasing incidence IE in general, and of of IDU-IE specifically [1, 8]. In our study, the incidence of definite IE registered at the Karolinska University Hospital increased during the study period, but the incidence varied among the patients with IDU-IE. There was an increase in incidence of IDU-IE registered at the hospital between 2008 and 2011 but from 2011 to 2017, there was an overall decrease. Further, the rate of patients with IDU-IE were lower during the winter compared to the other seasons, which according to our knowledge, has not been presented before. The decrease in incidence of IDU-IE after 2011 might be explained by the syringe exchange programme that was implemented in Stockholm around that time.

S. aureus was the most common aetiology among the patients with IDU-IE, and significantly more common compared with patients with non-IDU-IE. This finding is supported by previous studies that have shown *S. aureus* was the most common aetiology among IDU-IE [1, 16, 20]. The high prevalence of *S. aureus* among the IDU-IE may explain the higher prevalence of vascular phenomena such as spondylitis and pulmonary septic emboli among the IDU-IE compared with the non-IDU-IE, findings that are supported by Lassen et al [20]. In our study, patients with *S. aureus* aetiology and non-IDU-IE had higher in-hospital mortality compared with the patients with *S. aureus* aetiology and IDU-IE. Further, left-sided IE was more common among the patients with *S. aureus* aetiology and non-IDU-IE. Previous studies of patients with IE have presented higher in-hospital mortality among patients with *S. aureus* aetiology and left-sided IE, compared with right-sided IE [21, 22]. This might have explained that the patients with IDU-IE positive for *S aureus* with left-sided IE had significantly longer antibiotic treatment durations compared to those positive for *S aureus* with right-sided IE.

In this study, patients with IDU-IE were less treated with surgery compared to patients with non-IDU-IE. The rate of patients with IDU-IE treated with surgery did not change significantly during the study period. Moreover, the in-hospital mortality was equal among patients treated with surgery and those not treated with surgery, both in the IDU-IE and the non-IDU-IE group. However, a previous study presented that IDU-IE was associated with a higher hazard of death or reoperation between 90 and 180 days after first surgery, and that reoperation were less common among non-IDU-IE [9]. Such increased risk in the IDU-IE population should be taken into account for the management of these patients.

In our study, the in-hospital mortality was equal among patients with IDU-IE and non-IDU-IE, although the relatively low absolute numbers of patients could explain the absence of a significant difference. However, supportive to our results are two studies from the U.S., one that showed hospital mortality did not differ between IDU-IE and non-IDU-IE patients and one that presented less hospital mortality among IDU-IE [1, 8]. On the contrary, both studies presented a longer duration of hospital stay among IDU-IE which was not the case in this study [1, 8]. This could possibly be explained by the higher prevalence of Methicillin resistant *S. aureus* (n = 3,799, 13.8% and n = 19, 39.6% respectively) among IDU-IE in those studies from the U.S. compared to only 3.2 % in our study.

A larger extent of the patients with IDU-IE in this study had history of previous IE (30%), compared with the patients with non-IDU-IE. This has been described before [1, 8, 16]. Lassen et al., described 29% of the patients with IDU-IE had recurrence during follow-up [20]. Relapse of IDU has been described as a major risk factor of reinfection in patients with IDU-IE. This increases the risks of potential need for surgical treatment, and death [23]. Hence, treatment of addiction is crucial in patients with IDU-IE [23]. Further, a Swedish study of 7603 patients with IE presented significantly higher long term mortality (1-5 years) among patients IE, especially among patients with IDU-IE, compared to the general population (standardized mortality ratio of 2.2 among patients with IE and 19.1 among patients with IDU-IE) [24].

Declarations

Ethics approval and consent to participate

The study was approved by the Regional Ethics Review Board, Stockholm, Sweden (diary number K 2018-6018). Informed consents were given from the patients. None of the patients were dead when included for registration in the SRIE, hence no written informed consent from the legally authorized representatives/next of kin of patients were obtained. Data obtained from the SRIE were anonymized and did not include any personal data.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study were taken from the SRIE, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not available publicly. However, data are available from the first author upon reasonable request and with permission of the SRIE.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

A.D. and K.W. designed the study. A.D. analyzed the data and A.D. and K.W. interpreted it. A.D. was a major contributor in writing the manuscript, both authors revised it. Both authors read and approved the final manuscript.

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Figures

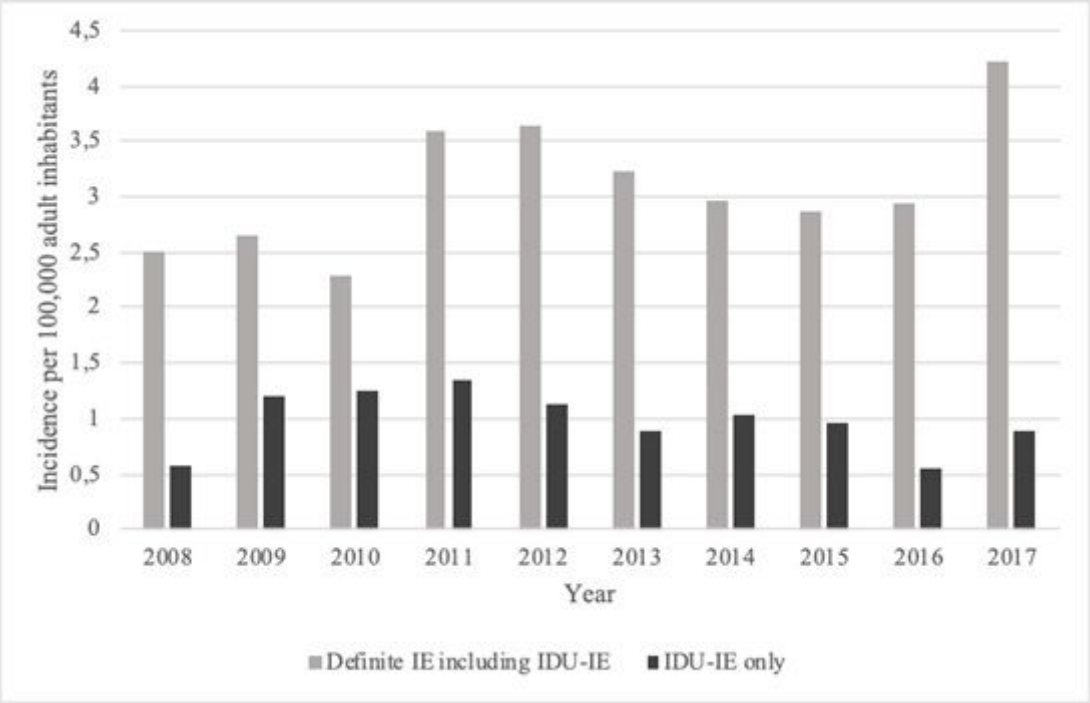

Figure 1

Incidences of definite IE and IDU-IE admitted between 2008 and 2017. Incidences are presented in number of cases per 100,000 adult inhabitants in Stockholm county each year. Abbreviations: IDU, injection drug use; IE, infective endocarditis.

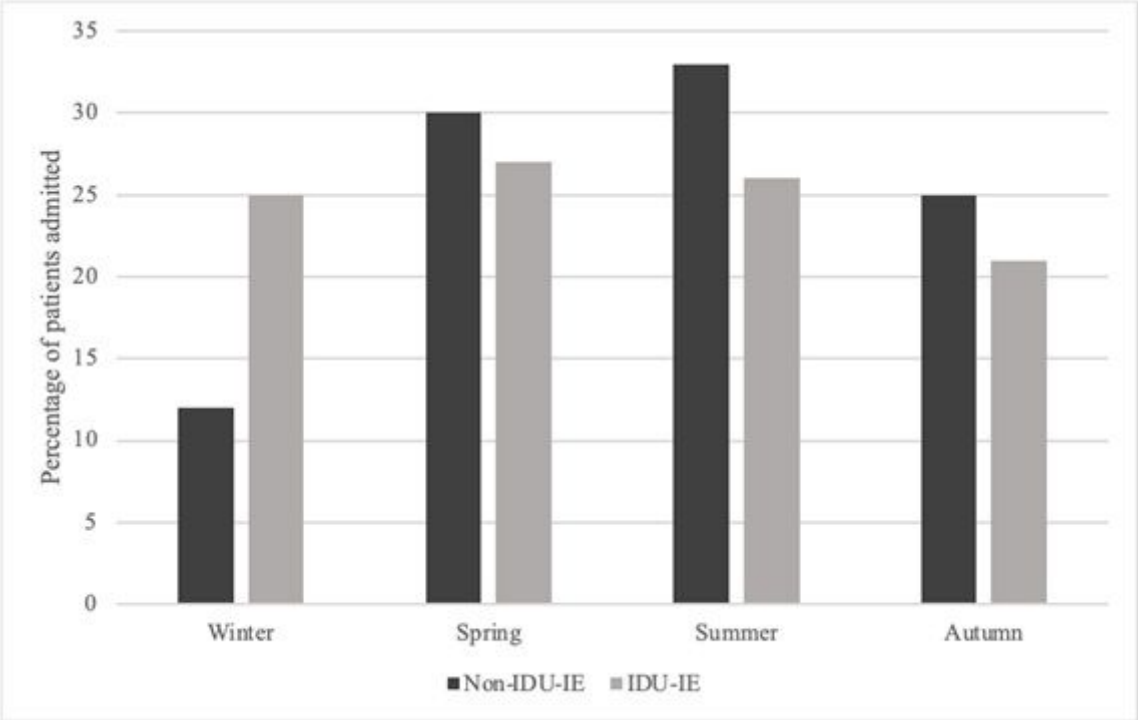

Figure 2

Seasonal variations of patients with IDU-IE and the patients with non-IDU-IE admitted between 2008-2017. Abbreviations: IDU, injection drug use; IE, infective endocarditis.