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Three Separate Clinical Entities of Infective Endocarditis—A Population-Based Study From Southern Finland 2013–2017

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Background. Health care–associated infective endocarditis (HAIE) and intravenous drug use–related IE (IDUIE) have emerged as major groups in infective endocarditis (IE). We studied their role and clinical picture in a population-based survey.

Methods. A population-based retrospective study including all adult patients diagnosed with definite or possible IE in Southern Finland in 2013–2017. IE episodes were classified according to the mode of acquisition into 3 groups: community-acquired IE (CAIE), HAIE, and IDUIE.

Results. Total of 313 episodes arising from 291 patients were included. Incidence of IE was 6.48/100 000 person-years. CAIE accounted for 38%, HAIE 31%, and IDUIE 31% of IE episodes. Patients in the IDUIE group were younger, and they more frequently had right-sided IE (56.7% vs 5.0%; $P < .001$) and *S. aureus* as etiology (74.2% vs 17.6%; $P < .001$) compared with the CAIE group. In-hospital (15.1% vs 9.3%; $P = .200$) and cumulative 1-year case fatality rates (18.5% vs 17.5%; $P = .855$) were similar in CAIE and IDUIE. Patients with HAIE had more comorbidities, prosthetic valve involvement (29.9% vs 10.9%; $P = .001$), enterococcal etiology (20.6% vs 5.9%; $P = .002$), and higher in-hospital (27.8% vs 15.1%; $P = .024$) and cumulative 1-year case fatality rates (43.3% vs 18.5%; $P < .001$) than patients with CAIE. *Staphylococcus aureus* caused one-fifth of IE episodes in both groups.

Conclusions. Our study indicates that in areas where injection drug use is common IDUIE should be regarded as a major risk group for IE, along with HAIE, and not seen as part of CAIE. Three different risk groups, CAIE, HAIE, and IDUIE, with variable characteristics and outcome should be recognized in IE.

Keywords. bacterial endocarditis; drug abuse; health care–associated; injection drug use; *Staphylococcus aureus*.

Classic risk factors for infective endocarditis (IE), like rheumatic fever, have decreased in high-income countries, but the incidence of IE has not decreased [1–3]. Health care–associated IE (HAIE) has become a major and more frequent clinical entity of IE [4–7]. Incidence of IE is increasing in the elderly [8]. In areas where injection drug use is prevalent, cases among people who inject drugs (PWID) constitute an increasing group of individuals with IE [9]. Injection drug use–related IE (IDUIE) differs from other risk groups due to the younger age of patients, fewer comorbidities, more common right-sided infection, and better short-term prognosis related to these factors [9–11]. IDUIE, however, is associated with poor compliance, higher risk for recurrent infection, and need for concomitant addiction treatment, which may affect long-term outcome [10–13]. The changes in the risk groups have resulted in alterations in the microbial spectrum of IE, and *Staphylococcus aureus* has become the most common pathogen [2, 3].

The prevalence of injection drug use varies with geographical region, and hence the proportion of IDUIE may vary greatly between studies [7–9, 14]. Studies on IDUIE have compared IDUIE with non-IDUIE, which usually also includes both community-acquired IE (CAIE) and HAIE cases [11, 13]. Therefore, the clinical picture of IDUIE in comparison with CAIE (in non–drug users) may be somewhat obscure. Injection drug use is a growing problem in many countries, as has recently been reported in studies from the United States [9, 11]. In Finland, injection drug use has been common and has been reported to be increasing [15, 16].

In the present work, we studied the proportion and clinical characteristics of IDUIE as a potentially increasing and separate risk group, in addition to CAIE and HAIE, in a population-based study in Southern Finland.

METHODS

Study Design and Population

The study design was an observational retrospective population-based cohort study including all adult patients (aged ≥18 years) residing in the Helsinki University Hospital Area in Southern Finland who were diagnosed with IE between 2013 and 2017. IE patients were mainly treated at

Helsinki University Hospital, but patients from all other hospitals that treated IE patients (2 Helsinki city hospitals) were included as well. The study hospitals are responsible for the treatment of acute, severe infections requiring hospitalization (such as IE) and have the only emergency departments in the area. Therefore, the possibility that patients would be treated in other hospitals or in the private sector was minimal, and these hospitals were not included. The study area consisted of 6 municipalities with an adult population of 0.993 million in 2017 (approximately one-fifth of the whole adult population in Finland), mainly in urban setting. The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) was low, only 5% of all *Staphylococcus aureus* bacteremias in the year 2017 [17].

Patients were identified from hospital registers using the ICD-10 codes for IE: I33, I38, and I39. The medical records of each identified patient were reviewed, and patients fulfilling the criteria for definite or possible IE according to the modified Duke criteria were included [18]. Patients residing outside the study region, those with an IE diagnosis outside the study period, and those rejected by the modified Duke criteria were excluded. Patient selection is described in more detail in Supplementary Figure 1. Data on demographics, clinical variables, diagnostic procedures, microbiology, radiology, antibiotic treatment, and outcome were retrieved from electronic medical patient records. The research board at the Inflammation Center, Helsinki University Hospital, and also the city of Helsinki approved the study protocol, and given the retrospective nature of this study, informed consent was not required.

Case Definitions

IE was defined as definite or possible according to the modified Duke criteria [18]. A relapse of IE was defined as an IE episode occurring within 6 months after the initial episode with the same causative agent. Re-infection was defined as an episode of IE occurring 6 months after a previous IE episode or as an IE episode within 6 months but not fulfilling the definition for relapse, consistent with a previous study [12]. Patients with pacemaker infection confined to a generator without any evidence of lead or endocardial involvement and those with aortic prosthetic infections without evidence of valve involvement were excluded. Operative treatment for IE was defined as an operation during antibiotic treatment. Location of IE was determined on the basis of findings on echocardiogram, other imaging studies, surgery, or in a few cases according to clinical picture. Septic embolus and a deep focus of infection were defined as a focus of infection (noncardiac) found in imaging studies or clinically that was compatible with IE.

IE episodes were categorized according to the mode of acquisition as follows: (1) community-acquired IE, (2) health care–associated IE, and (3) intravenous drug use–related IE. These categories were mutually exclusive.

IE was defined as HAIE according to following criteria: (1) onset of IE >48 hours after admission to the hospital or within 6 months after discharge from hospitalization for ≥2 days; (2) IE developed within 6 months after a significant invasive procedure performed during hospitalization or in an ambulatory setting; (3) extensive out-of-hospital contact with health care, defined as receipt of wound care or intravenous treatment within 1 month before onset of IE; or (4) residence in a nursing home or similar facility [4, 19, 20]. IE occurring in a prosthetic valve within 12 months after the operation was defined as early-onset prosthetic valve endocarditis (PVE) and was classified as HAIE. Patients with a recent (within 1 month) history of intravenous drug use were classified as having IDUIE even if health care association was present. Patients without a health care association and with no history of injection drug use were classified into the CAIE group. IE occurring after dental procedures was considered CAIE if no other health care association was present [4].

The medical records of each patient were reviewed for 1 year after the IE episode. Every IE patient is not routinely followed up for 6 months according to local practice, and some patients may be lost from scheduled follow-up. However, if a patient were to present with a relapse of infection, they would be treated in the study hospitals, and blood culture results would have been observed from the laboratory system as our laboratory is the only one where blood cultures are processed in the study area. Data on mortality were retrieved from the Digital and Population Data Services Agency, which contains basic information (eg, date of death, if applicable) of all residents in Finland. Each resident in Finland has a unique 10-digit personal identification number, and with this number a person can be reliably identified from registries and hospital medical records.

Statistical Analysis

The results are presented as percentages (which were calculated using the total number of IE episodes as the denominator), followed by number of IE episodes, unless otherwise specified. Categorical variables were summarized using numbers and percentages and continuous variables using median, interquartile range (IQR), and range. Differences between the groups were compared using the chi-square test for categorical variables and the Mann-Whitney *U* test for continuous variables. Multinomial logistic regression was used to test the association of demographics, patient characteristics, affected valves, microbiology, complications, treatment, and outcome of IE episodes according to the mode of acquisition. Odds ratios (ORs) with 95% CIs were calculated to compare the CAIE group with the HAIE and IDUIE groups. Comparison of continuous variables between 3 groups was done using the Kruskal-Wallis test. Poisson regression was used to calculate the 95% CIs for incidence rates and to examine the change in incidence rates over the study period. A *P* value <.05 was considered statistically

significant. Statistical analysis was conducted using SPSS, version 25.0 (IBM corp., Armonk, NY, USA).

RESULTS

Characteristics of the Study Cohort

The study cohort consists of 313 episodes of IE occurring in 291 patients. Seventy-nine percent (n = 247) of IE episodes were classified as definite and the rest as possible according to the modified Duke criteria [18]. Patient characteristics are presented in Table 1 and microbial etiology in Table 2. Of note, *Staphylococcus aureus* was responsible for 36.1% of all IE episodes and streptococci for 31%, with viridans group streptococci being the most common among them. Enterococci accounted for 9.9% of cases. Prosthetic valve was affected in 16.3%, and 40.9% of patients had a known underlying cardiac risk factor of IE. Surgery was performed in 23% of cases. The in-hospital case fatality rate was 17.3%, and the cumulative 1-year case fatality rate was 25.9% among all episodes.

Incidence and Mode of Acquisition

Community-acquired cases accounted for 38.0% (n = 119) of IE episodes, health care–associated cases for 31.0% (n = 97), and intravenous drug use–related cases for 31.0% (n = 97). The incidence of IE was 6.48/100 000 person-years (95% CI, 5.80–7.24). The incidence was highest (7.96/100 000 person-years) during the last study year, 2017. However, differences in incidence between the study years were not statistically significant. The incidence by mode of acquisition was 2.46/100 000 (95% CI, 2.06–2.95) for CAIE, 2.01 (95% CI, 1.65–2.45) for HAIE, and 2.01 (95% CI, 1.65–2.45) for IDUIE for the total adult population.

Patients in the CAIE group were older (64 [IQR, 52–75] years) as compared with the IDUIE group (35 [IQR, 29–38] years; *P* < .001). Patients in the HAIE group (69 [IQR, 58–77] years; *P* = .365) did not differ from the CAIE group in age. Distribution of IE cases by age and mode of acquisition is shown in Figure 1.

While more than 70% of patients in the CAIE and HAIE groups were male, the male predominance was lower in the IDUIE group (59.8%) (Table 3). Patients in the CAIE group had less diabetes, chronic kidney disease, and immunosuppressive treatment compared with the HAIE group (Table 3). Having a known preexisting cardiac condition was more frequent in the CAIE group compared with the IDUIE group, but a history of a previous episode of IE was less frequent (Table 3).

Valves Affected

Prosthetic valve endocarditis (PVE) was almost 3 times more common in HAIE than in CAIE, but otherwise there were no differences in the affected valves between these 2 groups (Table 3). One-third of PVEs in the HAIE group were early onset (ie, occurred within 12 months after operation). Only 5% of IE

Table 1. Characteristics of the Population-Based Study Cohort Including 313 Episodes of Infective Endocarditis

Characteristics	No. (%)
Age, median (IQR), y	55 (36–71)
Male gender	215 (68.7)
Known preexisting cardiac risk factor	128 (40.9)
History of previous IE	47 (15.0)
Diabetes	45 (14.4)
Chronic kidney disease	34 (10.9)
Dialysis	22 (7.0)
Immunosuppressive treatment	17 (5.4)
Liver cirrhosis	9 (2.9)
TEE performed[a]	180 (57.5)
Prosthetic valve[b]	51 (16.3)
Aortic valve alone affected	126 (40.3)
Mitral valve alone affected	99 (31.6)
Tricuspid valve alone affected	63 (20.1)
Left-sided IE	236 (75.4)
Right-sided IE[c]	66 (21.1)
Bilateral	11 (3.5)
Septic complication or deep focus[d]	162 (51.8)
Cerebral complication[e]	45 (14.4)
Septic complication or deep focus, other than cerebral	145 (46.3)
ICU admission[f]	29 (9.3)
IMCU or CCU admission[g]	94 (33.1)
Heart failure needing mechanical or noninvasive ventilation	46 (14.7)
Duration of IV antimicrobial treatment, median (IQR), d	35.5 (29–44.8)
Surgical treatment	72 (23.0)
Time to surgical treatment, median (IQR), d	14 (7.3–34.8)
Relapse[h]	9 (3.6)
In-hospital case fatality rate	54 (17.3)
One-year cumulate case fatality rate	81 (25.9)

Number (% of all IE episodes [n = 313]), unless otherwise indicated.

Abbreviations: CCU, cardiac care unit; ICU, intensive care unit; IE, infective endocarditis; IMCU, intermediate care unit; IQR, interquartile range; IV, intravenous; TEE, transesophageal echocardiogram.

[a]Transthoracic echocardiogram performed in every case.

[b]Biological valves in 39, mechanical valves in 7, mitral valvuloplasty in 2, and transcatheter aortic valve implant in 3.

[c]Including 2 IE episodes in which pulmonary valve alone was affected and 1 episode in which pulmonary and tricuspid valves were affected.

[d]A focus of infection (other than cardiac) related to IE and verified by imaging studies or clinically.

[e]Radiologically verified infarct or hemorrhage.

[f]Postoperative ICU admission not included.

[g]Of those who were not admitted to the ICU (n = 284).

[h]Of those who survived the initial episode (n = 259).

episodes affected only right-sided valves in the CAIE and HAIE groups. IDUIE differed regarding the affected valves. PVE was equally common in CAIE and IDUIE, whereas right-sided IE constituted 56.7% of all cases in IDUIE and left-sided IE was significantly less common as compared with CAIE (Table 3). Bilateral IE was more common in IDUIE than in CAIE.

Etiology of IE

The etiology of IE was determined in 91.4% (n = 286) of episodes (Table 2). Blood cultures were positive in 87.5% (n = 274)

Table 2. Microbial Etiology of Infective Endocarditis (n = 313) During 2013–2017 in a Population-Based Survey

Microorganisms	No.	(%)
Staphylococcus aureus	113	(36.1)
Methicillin-susceptible	106	(33.9)
Methicillin-resistant[a]	7	(2.2)
Coagulase-negative staphylococci	13	(4.2)
Staphylococcus lugdunensis	3	(1.0)
Viridans group streptococci[b]	67	(21.4)
Streptococcus anginosus	4	(1.3)
Beta-hemolytic streptococci	25	(8.0)
Group A	2	(0.6)
Group B	8	(2.6)
Group C or G[c]	11	(3.5)
Group D	4	(1.3)
Other streptococci[d]	2	(0.6)
Enteroccus spp.	31	(9.9)
Enterococcus faecalis	27	(8.6)
Enterococcus faecium	4	(1.3)
Granulicatella adiacens	2	(0.6)
Lactobacillus spp.	3	(1.0)
Bacillus cereus	2	(0.6)
Bartonella quintana	6	(1.9)
Coxiella burnetii	1	(0.3)
Tropheryma whipplei	1	(0.3)
Candida spp.[e]	3	(1.0)
Other[f]	10	(3.2)
Polymicrobial[g]	3[5]	(1.0)
Unknown	27	(8.6)

Percentages counted of all IE episodes (n = 313).

[a]In 1 episode, both methicillin-resistant and -susceptible strains in blood cultures.

[b]*Str. mitis/oralis* 10, *Str. mitis* 5, *Str. oralis* 1, *Str. mutans* 6, *Str. sanguinis* 6, *Str. parasanguinis* 1, *Str. gordonii* 4, not specified 34; *Str. anginosus* considered separately due to different clinical picture and treatment recommendations.

[c]Group G 8, Group C 2, Group C/G 1.

[d]Alfa-hemolytic streptococci 1, *Streptococcus pneumoniae* 1.

[e]*Candida glabrata* 2, *Candida tropicalis* 1.

[f]*Abiotrophia* spp. 1, *Aerococcus urinae* 1, anaerobic gram-positive cocci 1, *Burkholderia pseudomallei* 1, *Gemella* spp. 1, *Escherichia coli* 2, *Erysipelothrix rhusiopathiae* 1, *Klebsiella pneumoniae* 1, *Moraxella nonliquefaciens* 1.

[g]*Pseudomonas aeruginosa,* viridans group streptococci and coagulase-negative staphylococci in blood cultures in 1; *Aggregatibacter aphrophilus* and *Staphylococcus epidermidis* in 1; *Enterococcus faecalis* and *Staphylococcus epidermidis* in 1.

of episodes. Of the blood culture–negative cases (n = 39), the etiology was identified in 30.8% (n = 12) as follows: polymerase chain reaction (PCR) from resected valve (n = 4), PCR and culture from resected valve (n = 1), PCR from resected valve combined with serology (n = 2), bacterial culture from a deep infection focus or septic embolus (n = 3), PCR from a thrombotic mass in the artery supplemented with serology (n = 1), and serology alone (n = 1). In 8.6% (n = 27) of IE cases, the etiology remained unknown.

Staphylococcus aureus caused IE equally in the CAIE and HAIE groups (17.6% vs 20.6%; *P* = .580) but accounted for 74.2% of all cases in IDUIE (*P* < .001 vs CAIE) (Table 3). Seven episodes (6.2% of all *S.* aureus IE episodes) were caused by methicillin-resistant *S. aureus,* and all but 1 occurred in the

IDUIE group. Viridians group streptococci were responsible for IE more frequently in the CAIE group (37.8%) than HAIE (16.5%; *P* = .001) or IDUIE (6.2%, *P* < .001). *Enterococcus* spp. were uncommon in CAIE (5.9%) and IDUIE (4.1%), but in HAIE they accounted for 20.6% of all cases (*P* = .002 vs CAIE). Vancomycin-resistant strains of *Enterococcus* spp. were not found.

Complications of IE

There was no difference in cerebral complications between CAIE and HAIE or CAIE and IDUIE (Table 4). Whereas septic emboli in other sites were found in roughly one-third of cases in CAIE and HAIE, they occurred in three-quarters of IDUIE (*P* < .001 vs CAIE). No differences between the groups were found in intensive care unit, intermediate care unit, or cardiac care unit admissions, or in the need for mechanical or noninvasive ventilation due to heart failure (Table 4).

Relapses and Re-infections

In the study cohort, 273 patients had only 1 episode during the study period. Fourteen patients had 2 episodes during the study period, and 4 patients had 3 episodes. Fifty percent (n = 9) of the second IE episodes belonged to the IDUIE group, 28% (n = 5) to the HAIE group and 22% (n = 4) to the CAIE group. All 4 third episodes belonged to the IDUIE group. Relapse occurred in 3.5% (n = 9) of patients with IE episodes who survived the first IE episode (n = 259), and two-thirds of them occurred in IDUIE patients.

Treatment and Outcome

The median duration of intravenous antibiotic treatment was the same in the CAIE, HAIE, and IDUIE groups (Table 4). Valve surgery was performed more frequently in the CAIE group (30.3%) than in the IDUIE group (16.5%, *P* = .020). The median time to operation did not differ between the study groups (Table 4). The in-hospital case fatality rate was lower in CAIE (15.1%) than in HAIE (27.8%, *P* = .024). Although a trend toward higher in-hospital case fatality rate was observed in CAIE compared with IDUIE (9.3%), it was not statistically significant (*P* = .200). The 1-year case fatality rate was higher in HAIE (43.3%), compared with CAIE (18.5%, *P* < .001), but did not differ between CAIE (18.5%) and IDUIE (17.5%).

Cohort of First IE Episodes Only

We performed an additional analysis where only the first episode for each patient (n = 291) during the study period was included. In this analysis, 39.5% (n = 115) of IE episodes were CAIE, 31.6% (n = 92) CAIE, and 28.9% (n = 84) IDUIE. A comparison of CAIE with HAIE and IDUIE in this subgroup is presented in Supplementary Table 1. All previously presented statistically significant differences between the groups remained significant also in this analysis, but history of previous IE and
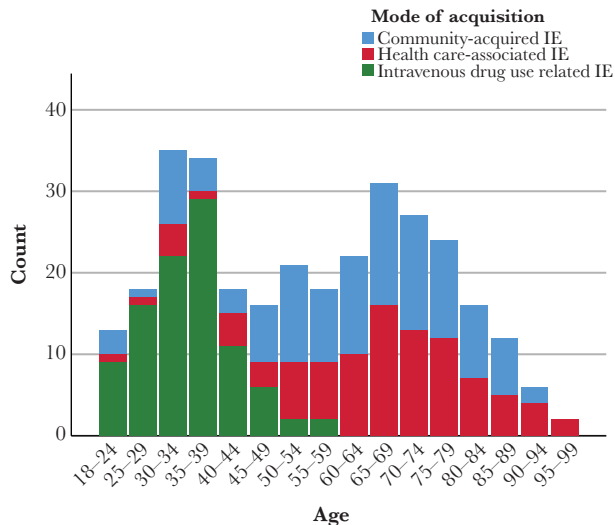
Figure 1. Number of infective endocarditis (IE) episodes by age and mode of acquisition in a population-based cohort of 313 IE episodes.

proportion of males became nonsignificant. In this analysis, proportion of patients aged >60 years was significantly higher in the HAIE group than compared with CAIE, but no difference in median age between these groups was found.

DISCUSSION

In the present population-based study, we observed that IE occurred in 3 different modes of acquisition in almost equal proportions, as 38% of IE episodes were community-acquired, 31% health care–associated, and 31% related to intravenous drug use. This finding was possible after differentiating IDUIE from CAIE in an area with presumably high intravenous drug use. IDUIE was predominantly caused by *Staphylococcus aureus* and affected right-sided valves. In-hospital and cumulative 1-year case fatality rates did not differ between CAIE and IDUIE. HAIE was associated with underlying diseases and prosthetic valves and accounted for more than two-thirds of all enterococcal IE episodes. HAIE had significantly poorer prognoses as compared with CAIE.

The incidence of IE in our study was 6.48 per 100 000 person-years. This is comparable to a recent population-based registry study from the country of Finland, which found occurrence of IE hospital admissions to be 6.33 per 100 000 person-years [21]. We observed that when counted across the whole adult population, the incidence of CAIE was 2.46 and the incidence rates of HAIE and IDUIE were both 2.01 per 100 000 person-years. An Australian population-based study reported the annual incidence of HAIE to be only 1.5/100 000 [22]. The definition of

Table 3. Comparison of Demographics, Affected Valves, and Microbiology of Infective Endocarditis (n = 313) During 2013–2017 in a Population-Based Survey Grouped According to the Mode of Acquisition

	CAIE (n = 119)		HAIE (n = 97)		IDUIE (n = 97)		CAIE vs HAIE		CAIE vs IDUIE	
	No.	%	No.	%	No.	%	OR (95% CI)	P Value	OR (95% CI)	P Value
Demographics and risk factors of IE										
Age ≥60 y	71	59.7	69	71.1	0	0	0.60 (0.34–1.06)	.080		<.001[a]
Male gender	87	73.1	70	72.2	58	59.8	1.05 (0.58–1.91)	.877	1.83 (1.03–3.24)	.039
Known cardiac risk factor	63	52.9	50	51.5	15	15.5	1.06 (0.62–1.81)	.838	6.15 (3.19–11.87)	<.001
Diabetes	10	8.4	32	33	3	3.1	0.19 (0.09–0.40)	<.001	2.88 (0.77–10.75)	.117
History of previous IE	9	7.6	14	14.4	24	24.7	0.49 (0.20–1.18)	.109	0.25 (0.11–0.57)	.001
Chronic kidney disease[b]	4	3.4	30	30.9	0	0	0.08 (0.03–0.23)	<.001		.129[a]
Immunosuppressive therapy	3	2.5	14	14.4	0	0	0.15 (0.04–0.55)	.004		.254[a]
Location of IE[c]										
TEE done	80	67.2	58	59.2	42	43.3	1.38 (0.79–2.41)	.259	2.69 (1.54–4.68)	<.001
Prosthetic valve	13	10.9	29	29.9	9	9.3	0.29 (0.14–0.59)	.001	1.20 (0.49–2.94)	.691
Aortic valve alone	55	46.2	56	57.7	15	15.5	0.63 (0.37–1.08)	.093	4.70 (2.43–9.07)	<.001
Mitral valve alone	52	43.7	30	30.9	17	17.5	1.73 (0.99–3.04)	.055	3.65 (1.93–6.90)	<.001
Left-sided IE	112	94.1	90	92.8	34	35.1	1.24 (0.42–3.68)	.692	29.65 (12.42–70.77)	<.001
Tricuspid valve alone	6	5.0	4	4.1	53	54.6	1.24 (0.34–4.51)	.750	0.04 (0.02–0.11)	<.001
Right-sided IE	6	5.0	5	5.2	55	56.7	0.98 (0.29–3.30)	.970	0.04 (0.02–0.10)	<.001
Bilateral IE	1	0.8	2	2.1	8	8.2	0.40 (0.04–4.51)	.460	0.09 (0.01–0.77)	.027
Causative agent of IE										
Staphylococcus aureus	21	17.6	20	20.6	72	74.2	0.83 (0.42–1.63)	.580	0.07 (0.04–0.14)	<.001
Viridans group streptococci	45	37.8	16	16.5	6	6.2	3.08 (1.60–5.91)	.001	9.22 (3.73–22.81)	<.001
Enterococcus spp.	7	5.9	20	20.6	4	4.1	0.24 (0.10–0.60)	.002	1.45 (0.41–5.12)	.561

Data are presented as number (%) unless otherwise indicated.

Abbreviations: CAIE, community-acquired IE; HAIE, health care–associated IE; IDUIE, injection drug use–related IE; IE, infective endocarditis; OR, odds ratio.

[a]The Fisher exact test was used; OR could not be calculated due to 0 values.

[b]Twenty-two patients were on dialysis and classified as HAIE by definition.

[c]Based on either imaging studies or clinical features.

Table 4. Comparison of Complications, Treatment, and Outcome of Infective Endocarditis (n = 313) During 2013–2017 in a Population-Based Survey Grouped According to the Mode of Acquisition

	CAIE (n = 119)		HAIE (n = 97)		IDUIE (n = 97)		CAIE vs HAIE		CAIE vs IDUIE	
	No.	%	No.	%	No.	%	OR (95% CI)	P Value	OR (95% CI)	P Value
Complication of IE										
Cerebral complication	22	*18.5*	11	*11.3*	12	*12.4*	1.77 (0.81–3.87)	.150	1.61 (0.75–3.44)	.222
Septic emboli[a] (other than CNS)	35	*29.4*	35	*36.1*	75	*77.3*	0.74 (0.42–1.31)	.298	0.12 (0.07–0.23)	<.001
Septic emboli[b] to lungs	12	*10.1*	13	*13.4*	53	*54.6*	0.73 (0.31–1.67)	.450	0.09 (0.05–0.19)	<.001
ICU admission	7	*5.9*	9	*9.3*	13	*13.4*	0.61 (0.22–1.71)	.347	0.40 (0.15–1.06)	.065
IMCU or CCU admission[c]	35	*31.3*	22	*25.0*	37	*44.0*	1.36 (0.73–2.55)	.332	0.58 (0.32–1.04)	.067
Heart failure needing NIV/MV	18	*15.1*	15	*15.5*	13	*13.4*	0.97 (0.46–2.05)	.945	1.15 (0.53–2.49)	.719
Treatment										
Operative treatment	36	*30.3*	20	*20.6*	16	*16.5*	1.67 (0.89–3.13)	.110	2.20 (1.13–4.26)	.020
Days to operation,[d] median (IQR)	17.5	7.3–35.8	13.5	7–39	11	8.3–30.8				
Duration of IV antimicrobials[e]	33	28.8–45.3	39	29–47	35	29–43				
Outcome										
In-hospital case fatality rate	18	*15.1*	27	*27.8*	9	*9.3*	0.46 (0.24–0.90)	.024	1.74 (0.75–4.08)	.200
One-year case fatality rate	22	*18.5*	42	*43.3*	17	*17.5*	0.30 (0.16–0.55)	<.001	1.07 (0.53–2.15)	.855
Relapse of IE (n = 259)[f]	2	*2.0*	1	*1.4*	6	*6.8*	1.39 (0.12–15.68)	.788	0.28 (0.05–1.41)	.121

Data are presented as number (%) unless otherwise indicated.

Abbreviations: CA-IE, community-acquired IE; CCU, cardiac care unit; CNS, central nervous system; HA-IE, health care–associated IE; ICU, intensive care unit; IDU-IE, injection drug use-related IE; IE, infective endocarditis; IMCU, intermediate care unit; IQR, interquartile range; IV, intravenous; MV, mechanical ventilation; NIV, noninvasive ventilation; OR, odds ratio.

[a]Includes also other focus of infection related to IE.

[b]Includes also lung abscess or lung infection related to IE.

[c]Including patients who did not require ICU admission (n = 284).

[d]Expressed as median (IQR); no difference between groups (.771, Kruskal-Wallis test).

[e]Expressed as median (IQR); no difference between groups (.282, Kruskal-Wallis test); data missing in one case (n = 312).

[f]Including those who survived the initial episode (n = 259).

HAIE in the Australian study was relatively narrow (eg, it did not include in-patient nosocomial cases).

A key finding in this study is that nearly one-third of IE episodes were IDUIE. A population-based study from another region in Finland reported a significant increase in IDUIE earlier in 1980–2004, which accounted for 20% of all cases during the last 5-year period [23]. A national registry-based study from the United States, where the opioid epidemic is prevalent, found an increase in the proportion of IDUIE from 15% to 29% between 2010 and 2015 [11]. A study from Western Norway reported a 23.5% proportion of IDUIE [24]. These studies illustrate the increasing proportion of IDUIE in all IE cases in many Western countries. In contrast, population-based studies from Spain and France have reported proportions of IDUIE <10%, with stable or decreasing incidence [14, 25]. These data point out the need to be cautious when extrapolating data from different regions as geographical variation of injection drug use and concomitant IDUIE may significantly affect the results. This was illustrated in a recent study from the United States that showed variation of IDUIE proportions in different parts of the United States [9]. One explanation for our high IDUIE occurrence is the reported rising drug abuse in Finland and more common intravenous drug use due to common amphetamine use [17]. It was estimated that in 2012 in our study region 5600–10 300 persons abused

amphetamine and/or opioids [16]. Assuming that this group of people constitutes the population at risk for IDUIE, the annual incidence of IE in that group would be as high as 1.9–3.5 cases per 1000. This would mean roughly 100-fold higher annual incidence than that of CAIE in the general population.

The present study confirms most of the clinical characteristics of IDUIE observed in other recent studies. *S. aureus* was responsible for three-quarters of IE episodes, and right-sided valve involvement was found in more than half of the cases [10, 11, 26]. Interestingly, PVE was equally common in IDUIE and CAIE. Septic emboli were significantly more common in IDUIE than in CAIE, which is probably related to more common *S. aureus* etiology in IDUIE. IDUIE was not associated with lower risk for cerebral complications, ICU admission, or heart failure compared with CAIE. In IDUIE group more frequent right-sided and bilateral involvement, more patients with a history of previous IE and a higher proportion of *S. aureus* were observed compared with CAIE, which is in accordance with a recent study [13]. Although Leahey and colleagues reported more frequent surgery rates for IDUIE than non-IDUIE [13], this finding was not supported by our study (CAIE 30.0% vs IDUIE 16.5%; *P* = .002). The reason for this might be the tertiary care setting and the higher proportion of left-sided IE in their study [13]; left-sided IE necessitates operative treatment more frequently compared with right-sided involvement [26].

Indeed, in our study patients with left-sided IE were more frequently operatively treated compared with those with right-sided IE (26.7% vs 7.6%; P = .001). Of note, in the present study transesophageal echocardiogram (TEE) was performed in less than half of the IDUIE cases and significantly more seldom in IDUIE than CAIE; thus the bilateral valve involvement in this group may be underestimated.

One third of all IE episodes, and almost half of the IE episodes with non-drug users, belonged to HAIE group. Only one-fourth of cases were HAIE in a population-based study [7], and one-third in a large multinational study where PVE and PWID were excluded [5]. Interestingly, in a population-based study between 1998 and 2013 from New York State and California, nearly half of all IE episodes were HAIE [27]. Together with our data, this indicates that HAIE has become a more important entity among all IE cases.

HAIE differed from CAIE in several aspects. HAIE patients had more comorbidity than CAIE patients, as described in earlier studies [4, 6, 7, 22]. However, we found no difference in age between these 2 groups, whereas a population-based study from France reported that non-drug-using patients with HAIE tend to be older than non-drug-using patients with CAIE [7]. When compared with most studies, the exclusion of IDUIE from CAIE in our study may explain the lack of age difference between HAIE and CAIE. PVE was more common in the HAIE group than in the CAIE group and accounted for almost one-third of all HAIE cases. PVE accounted for 13% of HAIE in an Australian study [22] and 25% of HAIE in a French study [7], and in the Australian study PVE occurred in equal proportions in CAIE and HAIE.

Staphylococcus aureus and *Enterococcus* spp. were equally common causative agents of HAIE, and both accounted for one-fifth of HAIE cases. In other studies, *S. aureus* has been reported to be the cause of HAIE more frequently than enterococci [4, 7]. Similar to our observation, equal proportions of *S. aureus* in HAIE and CAIE were reported in a population-based setting [22], whereas in other studies *S. aureus* has been reported to be more common in HAIE than in CAIE [4, 7]. More frequent enterococcal etiology in HAIE compared with CAIE has previously been reported, similar to our findings [4, 22], but also equal shares have been reported [7]. Reported proportions of enterococcal etiology in HAIE have ranged from 11% to 23% [4, 7].

Although HAIE cases had no more cerebral or septic complications and no more ICU treatment or surgery, the outcome in the HAIE group was significantly poorer than in CAIE. The in-hospital case fatality rate for HAIE was 27.8%, and cumulative 1-year mortality was as high as 43.3%. Higher mortality in HAIE compared with CAIE has also been reported previously [4, 6, 7]. The increasing occurrence and poor outcome call for studies to find improved treatment and prevention for HAIE.

The present study confirms the observation of *S. aureus* as the leading causative microorganism of IE at the population level, followed by viridans group streptococci and *Enterococcus* spp., with proportions similar to what has been reported elsewhere [3, 7]. Viridans group streptococci were responsible for IE more frequently in the CAIE group (38%) than in the HAIE group (17%). In fact, viridans group streptococci were the leading causative agents in the CAIE group, which is in line with other studies [4, 6, 7]. *Enterococcus* spp. have been reported in increasing and higher proportions than in our study [24, 28]. Interestingly, we observed 6 cases due to *Bartonella quintana,* which has been reported to be rare in Northern Europe [29].

The strength of this study is its population-based design. patients treated in referral centers [8]. This may lead to selection bias toward more complicated cases [30]. Another strength is detailed information on microbiology and very few missing values. In 91.4% of IE episodes, etiology was resolved, and blood cultures were positive in 87.5% of cases. In contrast, in a recent large multinational study, one-fifth of blood cultures were negative [28], and in a large Spanish study, microbiological information was missing in one-third of the cases [14].

The retrospective nature of this study is its major limitation. Details on patient history before hospitalization rely on data initially recorded by treating physicians and might be inaccurate. Also, follow-up data on relapse of IE might have been inaccurate if a patient had moved outside the study region during the following 6 months, but we believe this number to be very low. Virtually all patients with IE in the study region were included, as long as we were able to recognize them using ICD-10 codes. As we separated IDUIE, we might have missed some HAIE cases among IDUIE, but this risk has been reported to be low in other studies [11, 31]. It should be noted that the definition of HAIE in the present study was broad and included also IE episodes with hospitalization within the previous 6 months, as proposed by Ben-Ami et al. [20], instead of 3 months [3]. Residence in a nursing home or a similar facility was included in the definition of HAIE in our study, similar to other studies [3, 10] but not all [4, 7]. Four patients were placed in the HAIE category solely on the basis of the nursing home residence (or similar facility) criterion in our study. Further categorization of HAIE into nosocomial and non-nosocomial was not within the scope of this study. The clinical characteristics and outcomes of these 2 entities have been reported to be similar [5]. History of intravenous drug use was based on patient self-report. Data on which intravenous drugs were abused were not collected, which is a limitation. We included also cases of possible IE episodes in order to capture all IE episodes treated in our facilities. This approach and the relatively high proportion of possible IE episodes might, however, confer some degree of diagnostic uncertainty. The frequency of TEEs performed

was relatively low in our study, which may partly explain the high number of possible IE cases. However, it might reflect clinical practice, where transthoracic echocardiogram (TTE) findings are not always confirmed by TEE. This might especially apply to IDUIE with right-sided involvement as TEE has less additional value to TTE in detecting right-sided involvement of IE, and the high number of IDUIE might hence explain the relatively low frequency of TEE in our study.

CONCLUSION

Our study indicates that in areas with common intravenous drug use IDUIE should be regarded as one of the main risk groups of endocarditis and not as a part of CAIE. In such areas, IDUIE should be recognized to be responsible for a significant proportion of resource use, morbidity, and mortality in IE. Three different risk groups, CAIE, HAIE, and IDUIE, with variable characteristics and outcomes, should be recognized in IE.

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