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ORIGINAL ARTICLE INFECTIOUS DISEASES

Incidence and outcome of *Staphylococcus aureus* endocarditis—a 10-year single-centre northern European experience

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Abstract

Staphylococcus aureus is a leading cause of infective endocarditis. Little has been published on the outcome and epidemiology of *S. aureus* endocarditis (SAE) in the twenty-first century. Our aim was to evaluate the short-term and long-term outcome of SAE in Stockholm, Sweden, and assess its incidence over time. Patients treated for SAE from January 2004 through December 2013 were retrospectively identified at the Karolinska University Hospital. Clinical data were obtained from medical records and the diagnosis was verified according to the modified Duke criteria. Of 245 SAE cases, 152 (62%) were left-sided and 120 (49%) occurred in intravenous drug users. The calculated incidence in Stockholm County was 1.56/100 000 person-years, increasing from 1.28 in 2004–08 to 1.82/100 000 person-years in 2009–13 (p 0.002). In-hospital and 1-year mortality rates were 9.0% (22/245) and 19.5% (46/236), respectively. Age (OR 1.06 per year) and female sex (OR 3.0) were independently associated with in-hospital mortality in multivariate analysis. Involvement of the central nervous system (CNS) was observed in 30 (12%) patients, and valvular surgery was performed during hospitalization in 37 (15%). In left-sided endocarditis the strongest predictors for surgery were severe valvular insufficiency (OR 8.9), lower age (OR 1.07 per year) and no intravenous drug use (OR 10.7), and for CNS involvement lower age (OR 1.04 per year). In conclusion we noted low mortality, low CNS complication rate, and low valvular surgery frequency associated with SAE in our setting. The incidence was high and increased over time. The study provides an update on the outcome and epidemiology of SAE in the twenty-first century.
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Introduction

Staphylococcus aureus has become the leading cause of infective endocarditis (IE) in many regions of the world [1–5]. *Staphylococcus aureus* endocarditis (SAE) is associated with severe morbidity and mortality. The case fatality ratio has generally been reported to be 20–30%, central nervous system (CNS) complications are common, and cardiac valve surgery is often needed [5–10]. Earlier studies on SAE have, however, rarely included large number of patients [5–12], and few have focused on patients diagnosed in the twenty-first century [6]. Predictors of mortality in SAE have been identified [5,6,9,12], but factors associated with valvular surgery and CNS involvement have rarely been assessed specifically for SAE.

The objective of the present study was to evaluate the short-term and long-term mortality, and changes in incidence over time of SAE in Stockholm, Sweden, during 2004–13. Risk factors for mortality and CNS involvement, and factors associated with valvular heart surgery were assessed.

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Materials and methods

Study population and protocol

Stockholm County has 2.2 million inhabitants (1.7 million adults ≥18 years). The Karolinska University Hospital serves as a tertiary referral centre for the entire population, providing secondary health care to part of it. It includes the only thoracic surgery department in the region. Hence, the great majority of patients with suspected IE in Stockholm are admitted to Karolinska University Hospital.

Individuals treated for SAE at the Department of Infectious Diseases (ID) at Karolinska University Hospital from January 2004 through December 2013 were included. A retrospective search was carried out in the records of the department for diagnostic codes representing IE according to the 10th revision of International Classification of Diseases. The medical records were reviewed and microbiological data were obtained to identify cases with IE caused by *S. aureus*. Clinical data and echocardiography reports were reviewed and the diagnosis of IE was verified according to the modified Duke criteria [13]. Data on population statistics were retrieved from Statistics Sweden. The regional Ethical Review Board in Stockholm approved the study, not requiring obtaining informed consent on an individual basis because of its retrospective nature.

Definitions

An episode of IE was defined as *definite* or *possible* according to the modified Duke criteria [13]. IE was defined as right-sided if it only involved structures on the heart's right side (tricuspid valve, pulmonic valve, pacemaker or implantable-cardioverter-defibrillator leads). SAE episodes involving structures on the heart's left side, or involving both the right and left sides were classified as left-sided. A new episode within 90 days after completing treatment for SAE was considered to be a relapse and was not counted as a separate episode. Blood culture systems used were BACTEC™ (Becton Dickinson and Company, Sparks, MD, USA) during 2004–07 and BacT/ALERT® (bioMérieux, Marcy l'Etoile, France) during 2004–13.

An infection was considered nosocomial if signs or symptoms of IE presented more than 48 h after admission, or less than 48 h after hospital discharge after a minimum of 2 days hospitalization. Infection was also defined as nosocomial if related to haemodialysis. Otherwise it was considered to be a community-onset episode. A healthcare-associated community-onset infection was defined by the identification of at least one of the following risk factors: 1) admittance to hospital for two or more days in the 90 days before the SAE, 2) attendance at a specialized hospital clinic or emergency department in the 30 days before SAE, 3) having an intravascular catheter at the time of infection, or 4) developing SAE directly following a procedure in another healthcare setting (modifications from Friedman et al. [14]). CNS involvement or complication, was defined as CNS embolization, intra-cerebral haemorrhage or CNS infection. In-hospital mortality was defined as all-cause death during admittance at an acute care hospital, also if the patient had been transferred to another hospital and died there.

Statistical analysis

Description of data are given by number of observations, medians, ranges and quartiles. The Pearson's chi-square test, or Fisher's exact test when needed, were used for comparing categorical data. The Mann–Whitney *U* test was used to compare continuous data between groups. Time trend in incidence rates was tested by the chi-square trend test. Survival data are displayed by Kaplan–Meier curves and groups were compared by the log-rank test. Multivariate logistic regression was performed to calculate the contribution of different variables to mortality, CNS complications and in-hospital cardiac surgery, with the likelihood ratio test being used. Variables were considered for the models in a stepwise fashion, but the final selection of variables was also based on clinical judgement. Level of significance was set at 0.05. For processing the data the JMP®8.0.2 statistical software from SAS Institute Inc. (Cary, NC, USA) was used.

Results

Population

A total of 673 medical records containing an IE diagnosis at the Department of ID at Karolinska University Hospital were identified. In 255 episodes *S. aureus* was the aetiological pathogen. Ten episodes were excluded, five with rejected IE diagnosis by the authors, and five were relapses within 90 days of a previous SAE episode. Hence, 245 SAE episodes were seen in 222 individuals (13 had two episodes each and five had three episodes each). Of these 227 (93%) were definite IE cases and 18 (7%) were possible IE cases. Polymicrobial aetiology was present in seven (3%) cases. Echocardiography was performed in 244 (99.6%) episodes, by the trans-oesophageal route in 208 (85%) and solely trans-thoracic in 36 (15%). In 150 (61%) patients a cardiac murmur was described, new in 46 (19%, information lacking for seven patients). The valve involvement of the 245 SAE episodes is depicted in Table 1. The clinical characteristics of SAE are shown in Table 2, with a comparison between left-sided and right-sided episodes.

Incidence

During the first half of the study period 96 SAE episodes were seen and 149 in the second half. By using the whole referral

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TABLE 1. Valve characteristics of 245 *Staphylococcus aureus* endocarditis episodes

Characteristic	*n* (%)
Location	
Left-sided [a]	152 (62)
Right-sided	91 (37)
Unknown	2 (1)
Prosthetic valve IE	28 (11)
Number of valves involved [b]	
One valve	193 (79)
Two valves	30 (12)
Three valves	3 (1)
Valves involved [c]	
Aortic	79 (32)
Mitral	87 (36)
Tricuspid	87 (36)
Pulmonic	7 (3)
Pacemaker/ICD leads	13 (5)
Other	1 (0.4)
Unknown	9 (4)

Data are number (%) of episodes. ICD, implantable cardioverter defibrillator; IE, infective endocarditis.
[a]Including 19 cases with bilateral involvement.
[b]Unknown in nine episodes, solely pacemaker/ICD leads in ten patients.
[c]Total exceeds 245 as each episode can involve more than one valve.

region as a denominator the SAE incidence among adults in Stockholm County was calculated to be 1.56/100 000 person-years, increasing from 1.28 in 2004–08 to 1.82/100 000 person-years in 2009–13 (p 0.002). This translates into 47.7 SAE episodes/10 000 admissions at the Department of ID in 2004–08 and 76.3 episodes/10 000 admissions in 2009–13 (p < 0.001). Forty-nine (51%) patients were referred from other hospitals in 2009–13 compared with 68 (46%) in 2004–08 (p 0.41). No changes were observed during the period in the valvular location or mode of acquisition of SAE (data not shown).

Mortality

Fifteen (6.1%) patients died within 30 days, and 22 (9.0%) died during the acute admission (Table 2). More specifically the in-hospital mortality was 17% (19/110 episodes) among non-addicts with left-sided SAE. For those who died during the admission, the median time to death was 25.5 days (range 5–61 days). Table 3 depicts factors associated with in-hospital mortality as analysed by multivariate logistic regression. The 1-year mortality was 19.5% (46/236 episodes, excluding eight with a re-infection within 1 year and one with incomplete follow up). Independent risk factors associated with 1-year mortality were higher age (OR 1.04 per year, 95% CI 1.02–1.07, p < 0.0001) and left-sided disease (OR 2.62, 95% CI 1.05–7.53, p 0.04) (see Supplementary material, Table S1). Fig. 1 depicts survival curves after SAE according to age.

TABLE 2. Characteristics of *Staphylococcus aureus* endocarditis by location

Characteristics	Left-sided (*n* = 152)	Right-sided (*n* = 91)	p	All episodes (*n* = 245)
Age, median years (IQR)	60.3 (48–74)	38.0 (29–50)	<0.0001	53.4 (38–69)
Male sex	117 (77)	54 (59)	0.004	173 (71)
Mode of acquisition				
Nosocomial	18 (12)	4 (4)	0.05	23 (9)
Healthcare-associated	24 (16)	3 (3)	0.002	27 (11)
Community-acquired	110 (72)	84 (93)	0.0006	195 (80)
Underlying conditions				
Intravenous drug use	42 (28)	77 (85)	<0.0001	120 (49)
Predisposing heart disease [a]	56 (37)	6 (7)	<0.0001	62 (25)
Previous IE	24 (16)	18 (20)	ns	43 (18)
Pacemaker / ICD	12 (8)	11 (12)	ns	23 (9)
Haemodialysis	12 (8)	3 (3)	ns	16 (7)
Insulin-dependent diabetes mellitus	15 (10)	4 (4)	ns	20 (8)
Immunosuppression [b]	16 (11)	7 (8)	ns	24 (10)
Polymicrobial aetiology	5 (3)	2 (2)	ns	7 (3)
Methicillin resistance	4 (3)	2 (2)	ns	6 (2)
Treatment				
In-hospital cardiac surgery	37 (24)	0 (0)	<0.0001	37 (15)
Days to surgery, median (IQR)	9 (5.5–19)	—	—	9 (5.5–19)
Days admitted, median (IQR) [c]	36 (28–46)	30 (27–36)	0.003	33 (28–42)
Outcome/complications				
Severe valvular insufficiency [d]	36 (24)	16 (18)	0.26	52 (21)
Myocardial abscess [e]	18 (12)	1 (1)	0.003	19 (8)
CNS involvement	30 (20)	0 (0)	<0.0001	30 (12)
Total embolism [f]	48 (32)	63 (69)	<0.0001	111 (46)
ICU admission, non-postoperative	34 (22)	17 (19)	ns	51 (21)
Relapse of bacteraemia [g]	2 (1)	5 (6)	ns	7 (3)
30-day mortality	13 (9)	2 (2)	0.046	15 (6)
In-hospital mortality	20 (13)	2 (2)	0.004	22 (9)
1-year mortality [h]	40 (27)	6 (7)	0.0001	46 (19)

Data are number (%) of episodes unless otherwise indicated. CNS, central nervous system; ICD, implantable cardioverter defibrillator; ICU, intensive care unit; IE, infective endocarditis; IQR, interquartile range; *n*, number of episodes; ns, not significant.
[a]Prosthetic valve, congenital malformations (excluding atrial septal defect), valvular dysfunction, hypertrophic cardiomyopathy.
[b]Human immunodeficiency virus infection (13), immunosuppressive therapy (10), myelodysplastic syndrome (1), splenectomised (1).
[c]Information missing in 11 transferred cases.
[d]Grade 3 or 4 by echocardiography (on a 4-grade scale).
[e]Identified by echocardiography.
[f]Pulmonary embolism, cerebral embolism, or other systemic embolism.
[g]Excluding 15 patients who died within 30 days.
[h]Excluding eight cases with a re-infection within 1 year, one with incomplete follow up.

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TABLE 3. Factors associated with in-hospital mortality in *Staphylococcus aureus* endocarditis

	Univariate analysis			Multivariate analysis	
Variable	**Died in hospital (n = 22)**	**Survived (n = 223)**	**p**	**Odds ratio (95% CI)[a]**	**p**
Age, median years (IQR)	65.7 (56–85)	50.5 (35–67)	<0.0001	1.06 (1.02–1.09) [b]	0.0005
Female sex	9 (41)	63 (28)	0.21	2.95 (1.06–8.16)	0.04
IE in 2009–13	12 (55)	137 (61)	0.53		
Nosocomial IE	1 (5)	22 (10)	0.41		
Prosthetic valve IE	5 (23)	23 (10)	0.08	2.08 (0.59–6.48)	0.24
Right-sided IE [c]	2 (9)	89 (40)	0.004	0.37 (0.05–1.60)	0.20
Valves involved [d]					
Aortic	7 (32)	72 (33)	0.94		
Mitral	13 (59)	74 (33)	0.02		
Tricuspid	2 (9)	85 (40)	0.004		
Severe valvular insufficiency [e]	5 (23)	47 (21)	0.87		
Myocardial abscess [f]	2 (9)	17 (8)	0.81		
Underlying conditions					
Intravenous drug use	3 (14)	117 (52)	0.0005		
Predisposing heart disease [g]	7 (32)	55 (25)	0.46		
Previous IE	3 (14)	40 (18)	0.61		
Immunosuppression [h]	3 (14)	21 (9)	0.52		
Insulin-dependent diabetes	2 (1)	18 (8)	0.87		
Methicillin resistance	0 (0)	6 (3)	0.44		
Combination antibiotic therapy [i]	9 (41)	64 (29)	0.23		
In-hospital cardiac surgery	5 (23)	32 (14)	0.30	2.34 (0.62–8.12)	0.20

Data are number (%) of episodes unless otherwise indicated. IE, infective endocarditis; IQR, interquartile range; n, number of episodes in analysis.
[a]Odds ratios for the association between selected variables and in-hospital mortality in the multivariate analysis. Variables with odds ratios reported were included in the final multivariate logistic regression model.
[b]Odds ratio presented per 1-year increase in age.
[c]Unknown side in two episodes.
[d]Each episode can involve more than one valve.
[e]Grade 3 or 4 by echocardiography (on a 4-grade scale).
[f]Identified by echocardiography.
[g]Prosthetic valve, congenital malformations (excluding atrial septal defect), valvular dysfunction, hypertrophic cardiomyopathy.
[h]Human immunodeficiency virus infection (13), immunosuppressive therapy (10), myelodysplastic syndrome (1), splenectomised (1).
[i]Combination therapy including an aminoglycoside or rifampicin for ≥4 days.

CNS complications

Thirty (12%) patients had a CNS complication in association with the SAE (cerebral imaging was performed in 76 (31%) episodes). Six had intra-cerebral bleeding, two had meningitis, and the others had cerebral emboli with neurological symptoms of various degrees. Five out of 30 (17%) patients died during the admission. Factors independently associated with CNS involvement in left-sided SAE were lower age (OR 1.04 per year, 95% CI 1.01–1.07), not being an intravenous drug user (OR 3.8, 95% CI 1.2–14.2), and mitral valve involvement (OR 2.7, 95% CI 1.1–7.3) (Table 4).

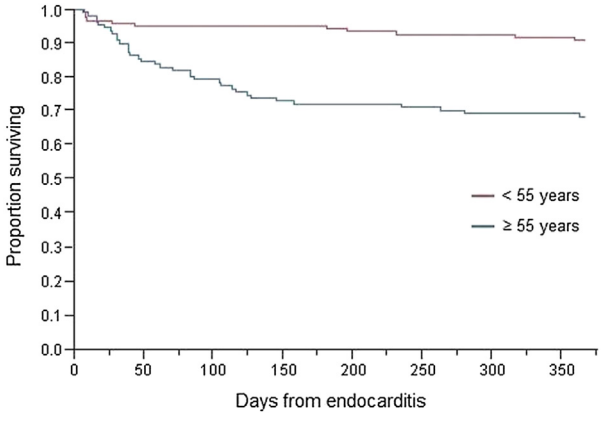

FIG. 1. Survival after *Staphylococcus aureus* endocarditis according to age, <55 or ≥55 years (p < 0.0001, log-rank test).

Treatment

Cardiac surgery was performed before hospital discharge in 37 (15%) patients. All operations were performed on patients with left-sided IE, five of which had bilateral disease and also needed tricuspid valve surgery. In left-sided IE, independent predictors of having cardiac surgery were lower age (OR 1.07 per year, 95% CI 1.03–1.12), no active IVDU (OR 10.7, 95% CI 2.6–52.2), community-onset (OR 9.3, 95% CI 1.5–115.1), severe valvular insufficiency (OR 8.9, 95% CI 3.2–26.9), myocardial abscess (OR 4.1, 95% CI 1.02–16.7), and intensive care unit admission (OR 3.1, 95% CI 1.1–9.0) (see Supplementary material, Table S2).

Cloxacillin (usually given as 3 g every 6 h) was the principal treatment in 186 (76%) episodes, second- and third-generation cephalosporins in 41 (17%), and vancomycin in 12 (5%). The median treatment duration with intravenous antibiotics was 32 days (range 7–72 days, excluding 22 deaths and five lacking information).

Discussion

This study includes a large number of SAE cases from a single northern European university clinic, with a high admission rate of patients with IVDU and a low rate of methicillin-resistant *S. aureus* strains. It highlights factors associated with mortality, CNS complications and the need for valvular surgery in SAE.

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TABLE 4. Factors associated with central nervous system complications in left-sided *Staphylococcus aureus* endocarditis

	Univariate analysis			Multivariate analysis	
Variable	**CNS event (n = 30)**	**No CNS event (n = 122)**	**p**	**Odds ratio (95% CI)** [a]	**p**
Age, median years (IQR)	53.9 (43–68)	62.3 (51–75)	0.02	0.96 (0.93–0.99) [b]	0.007
Male sex	20 (67)	97 (80)	0.13		
IE in 2009-13	17 (57)	79 (60)	0.75		
Nosocomial IE	3 (10)	15 (12)	0.73		
Prosthetic valve IE	7 (23)	19 (16)	0.31		
Valves involved [c]					
Aortic	13 (43)	66 (54)	0.29		
Mitral	21 (70)	66 (54)	0.11	2.66 (1.06–7.28)	0.04
Underlying conditions					
Intravenous drug use	9 (30)	33 (27)	0.75	0.26 (0.07–0.86)	0.03
Predisposing heart disease [d]	12 (40)	44 (36)	0.69		
Previous IE	8 (27)	16 (13)	0.07	3.21 (1.00–10.43)	0.05
Immunosuppression [e]	4 (13)	12 (10)	0.58		
Insulin-dependent diabetes	1 (3)	14 (11)	0.18		

Data are number (%) of episodes unless otherwise indicated.
CNS: central nervous system, n: number of episodes in analysis, CI: confidence interval, IQR: interquartile range, IE: infective endocarditis.
[a]Odds ratios for the association between selected variables and CNS involvement in the multivariate analysis. Variables with odds ratios reported were included in the final multivariate logistic regression model.
[b]Odds ratio presented per 1-year increase in age.
[c]Each episode can involve >1 valve.
[d]Prosthetic valve, congenital malformations (excluding atrial septal defect), valvular dysfunction, hypertrophic cardiomyopathy.
[e]Immunosuppressive therapy (10), HIV infection (6), myelodysplastic syndrome (1).

Mortality

The mortality rate in our cohort is low for studies on SAE. The 6.1% 30-day mortality and 9.0% in-hospital mortality is much lower than the in-hospital mortality of 20–46% observed in previous large studies [5–12]. It is also lower than the 15–25% usually reported in association with *S. aureus* bacteraemia in general [15,16]. The 1-year mortality rate of 20% is also considerably lower than the 35–44% found in most other reports [9,10,17,18]. The low case fatality rate in Stockholm can, to an extent, be explained by the setting and characteristics of the included SAE patients. The high proportion of patients with IVDU probably contributes, because they are generally younger and more often have the milder right-sided IE. The median age of patients in our study and the percentage with right-sided IE are, however, similar to that seen in most previous studies [5–7,9,12], and the mortality (17%) among non-addicts with left-sided disease is also relatively low. The low proportion of nosocomial and healthcare-associated cases, with low prevalence of comorbidities, may contribute because nosocomial IE has been associated by some with worse outcome than community-acquired episodes [6,19]. The low rate of methicillin-resistant *S. aureus* could also play a role because methicillin-resistant *S. aureus* bacteraemia has been associated with higher mortality than methicillin-sensitive *S. aureus* bacteraemia [16,20]. Referral bias is not likely to have had a major influence on the case fatality ratio in our study, because our hospital has treated the majority of SAE patients in Stockholm during the entire period. Finally, one may speculate that high awareness of IE among physicians could lead to a high number of early and mild cases being diagnosed. This is, however, difficult to confirm.

Age has previously been shown to be independently associated with mortality in SAE, and has been the most consistent and strongest predictor of mortality in *S. aureus* bacteraemia [5,6,16]. We have no explanation for the higher mortality in females than in males, but a similar trend has occasionally been seen, both in SAE and *S. aureus* bacteraemia [8,16,21]. More detailed data on disease severity on admission, symptom duration and timing of diagnosis and treatment are needed for such analysis.

CNS complications

We noted a lower rate (12%) of CNS involvement than the 15–35% generally reported in SAE [5–10]. A high proportion of right-sided disease and a low cerebral imaging frequency, however, can contribute to low rates of observed CNS complications. Mitral valve involvement was an independent predictor of CNS complications. This has been described in previous studies on IE in general [22,23]. Lower age has also earlier been independently associated with increased risk of CNS events in IE, as we noted among our SAE patients [22,24,25]. Less pronounced inflammatory responses, and fewer and smaller vegetations in elderly compared with younger patients have been proposed as explanations. It may, however, be that CNS events are simply under-diagnosed in the older population because of more unspecific symptoms and signs [22,24,25]. Under-diagnosis might also explain the association noted between IVDU and having a lower risk of CNS complications, but symptom duration at diagnosis or a different IE pathogenesis in this group could play a role. Vegetation size has previously been found to be a predictor of cerebral embolization [22–24], but this could not be analysed because of inconsistently registered information in our records.

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Cardiac surgery

The cardiac surgery frequency was 15% in our SAE cases, increasing to 24% among our left-sided cases. This figure is lower than the 20–45% usually reported in association with SAE [5–7,9,10,12], but despite this, a favourable outcome was observed. Similar or even lower rates of valvular surgery were, however, reported from the 1980s [8,11]. Severe valvular insufficiency and myocardial abscesses are recognized indications for surgery [26,27]. Admission to intensive care is related to disease severity, whereas higher age and nosocomial infections are in general associated with more frequent comorbidities. Furthermore, IVDU is a risk to acquiring a new IE, and drug users are often regarded as less compliant with treatments [28,29]. These factors all seem to influence the decision to perform surgery.

Incidence

The calculated SAE incidence in Stockholm County of 1.56/100 000 adult inhabitants per year can be compared with 0.2–1.6 SAE/100 000 person-years reported in previous population-based studies on IE [2,4]. As SAE in Stockholm may be treated outside the Department of ID at Karolinska University Hospital, the incidence rate presented should be regarded as a minimum and the actual incidence is likely to be somewhat higher. The high incidence observed could possibly be influenced by Stockholm being an urban area leading to a high prevalence of IVDU, or other population risk factors. The diagnosis of IE is dependent on echocardiography and blood cultures, so the high SAE incidence observed could merely, at least in part, reflect optimal diagnostic procedures and a high awareness of IE.

We found that the SAE incidence increased over time. A similar trend has been reported from the USA [1]. As no change in referral practices from other hospitals occurred during the study period this does not explain the increase in incidence. It may in part be due to changes in the at-risk population with an increasing number of people who inject drugs, more frequent invasive procedures, and an older population [30], or it might reflect a change in diagnostic capabilities and frequency.

The study has several limitations. The features and outcome of SAE in a specific urban population may not apply to populations in other settings. Second, although our department treats a majority of all SAE cases in the county, the study is based on an experience in a single centre rather than being population based. A selection and referral bias might therefore have caused an under-representation of nosocomial cases. Finally, the study is retrospective and relevant data might have been missed because they are not always documented in medical records. The large number of patients included, the high availability of medical records, and that the study was performed in a defined geographical area at a single site, on the other hand, strengthen the validity of our findings.

To conclude, in this large study on SAE in Stockholm we found a low mortality, low rate of CNS complications and a low valvular heart surgery frequency, but a high and increasing incidence over time.

Transparency declaration

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2015.04.014.

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