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STAPHYLOCOCCUS AUREUS BACTERAEMIA AND ENDOCARDITIS

EPIDEMIOLOGY, SHORT- AND LONG-TERM MORTALITY

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Staphylococcus aureus bacteraemia and endocarditis – epidemiology, short- and long-term mortality

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ABSTRACT

Staphylococcus aureus is a major cause of bloodstream infections and endocarditis. *S. aureus* bacteraemia (SAB) is associated with substantial morbidity and mortality, and endocarditis is a severe complication. Population-based studies on *S. aureus* bacteraemia have been sparse, and few large studies exist on *S. aureus* endocarditis (SAE).

The objective of this thesis was to study the epidemiology, characteristics, and short- and long-term outcome of *S. aureus* bacteraemia and endocarditis in Iceland and Stockholm.

In **paper I and II** we studied SAB in the entire Icelandic adult and paediatric populations. Cases were retrospectively identified at the clinical microbiological laboratories.

In adults the incidence was 24.5 /100,000 person-years during 1995-2008 (721 cases), increasing by 28% during the study period (p=0.01). The paediatric incidence was 10.9 /100,000 child-years during 1995-2011 (146 cases), decreasing by 36% during the period (p=0.001). At the same time the average annual frequency of blood cultures from children analysed at the main study site decreased by 27% (p<0.001). SAB incidence was highest in infants (<1 year), 58.8 /100,000.

The proportion of adults with nosocomial infections decreased from 56% in 1995-99 to 39% in 2005-08 (p=0.001), while community acquired SAB increased from 29% to 46% (p<0.001). Health-care associated community-onset cases were 15%. Among the paediatric cases 34% were nosocomial, 14% health-care associated, and 51% community acquired. Bone or joint infection was the focus of SAB in 40% of children, followed by intravascular catheters in 30%, and an unknown focus in 10%.

The 30-day mortality in adults was 17.1%, and decreased from 22.2% during 1995-99 to 11.4% during 2005-08 (p=0.001). The 1-year mortality was 33.0%, and decreased from 38.9% to 28.2% (p=0.06). In children the SAB-related mortality was 0.7%, 30-day mortality 1.4%, and the 1-year mortality 3.6%. These case fatality ratios are lower than those observed in most previous studies.

In **paper III** we studied SAE in adults in Stockholm, and in **paper IV** we specifically focused on SAE in people who inject drugs. Individuals treated for SAE at the Department of Infectious Diseases at the Karolinska University Hospital were retrospectively identified by diagnostic codes from medical records.

The calculated incidence of SAE in adults in Stockholm County was 1.56 /100,000 person-years during 2004-13 (245 cases), and the incidence of SAE related to intravenous drug use (IVDU) was 0.76 /100,000 person-years (120 cases). This incidence is high in comparison with other regions. The SAE incidence increased by 42% during the study period (p=0.002), and this was largely caused by a change in the incidence of the IVDU-related SAE which

increased by 91% (p=0.02). The SAE incidence among people who inject drugs in Stockholm was estimated to be 2.5 (range 1.5-6.5) per 1,000 person-years.

Thirty-day, in-hospital, and 1-year mortality rates were 6.1%, 9.0%, and 19.7%, respectively, among all SAE cases. In-hospital and 1-year mortality rates associated with IVDU-related SAE were 2.5% and 8.0%, respectively. The case fatality ratios noted are very low compared to previous reports. Age and female sex were independently associated with in-hospital mortality in a multivariate analysis, and age and left-sided disease with the 1-year mortality. Central nervous system (CNS) involvement was observed in 12% of patients, and valvular surgery was performed during hospitalisation in 15%. In left-sided SAE the strongest predictors for surgery were lower age and not being an intravenous-drug-user, and for CNS involvement lower age.

In conclusion, we found an increasing incidence of SAB and SAE in adults, probably related to a change in risk factors both for SAB and SAE, and possibly due to more liberal diagnostics. The decrease noted in SAB incidence in children was probably in part due to lower blood culture frequency and possibly a result of infection control measures introduced. The reason for the favourable short- and long-term outcomes associated with SAB and SAE in Iceland and Stockholm is not clear. It could be related to diagnosis of more early and mild cases, but other factors might also have contributed.

LIST OF SCIENTIFIC PAPERS

I. Asgeirsson H, Gudlaugsson O, Kristinsson KG, Heiddal S, Kristjansson M. ***Staphylococcus aureus*** **bacteraemia in Iceland, 1995-2008: changing incidence and mortality**. Clin Microbiol Infect 2011; 17(4):513-8.

II. Asgeirsson H, Gudlaugsson O, Kristinsson KG, Vilbergsson GR, Heiddal S, Haraldsson A, Weiland O, Kristjansson M. **Low mortality of** ***Staphylococcus aureus*** **bacteremia in Icelandic children - nationwide study on incidence and outcome**. Pediatr Infect Dis J 2014; [Epub ahead of print].

III. Asgeirsson H, Thalme A, Kristjansson M, Weiland O. **High incidence and low mortality in** ***Staphylococcus aureus*** **endocarditis – a 10-year experience**. Submitted manuscript.

IV. Asgeirsson H, Thalme A, Weiland O. ***Staphylococcus aureus*** **endocarditis in people who inject drugs – low mortality but increasing incidence**. In manuscript.

RELATED PUBLICATIONS

i. Asgeirsson H, Kristjansson M, Kristinsson KG, Gudlaugsson O. ***Staphylococcus aureus bacteraemia* – Nationwide assessment of treatment adequacy and outcome**. J Infect 2011; 62(5):339-46.

ii. Asgeirsson H, Kristjansson M, Kristinsson KG, Gudlaugsson O. **Clinical significance of *Staphylococcus aureus* bacteriuria in a nationwide study of adults with *S. aureus* bacteraemia**. J Infect 2012; 64(1):41-6.

CONTENTS

LIST OF ABBREVIATIONS

CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute
CNS	Central nervous system
HACEK	*Haemophilus spp, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*
HBV	Hepatitis B virus
HCA	Health-care associated
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICD	Implantable cardioverter defibrillator
ICU	Intensive care unit
ID	Infectious diseases
IE	Infective endocarditis
IgG	Immunoglobulin G
IQR	Interquartile range
IV	Intravenous
IVDU	Intravenous drug use
MRSA	Methicillin resistant *Staphylococcus aureus*
MSSA	Methicillin sensitive *Staphylococcus aureus*
OR	Odds ratio
PBP	Penicillin-binding protein
PWID	People who inject drugs
SAB	*S. aureus* bacteraemia
SAE	*S. aureus* endocarditis

1 INTRODUCTION

1.1 HISTORY AND BASIC MICROBIOLOGY OF *STAPHYLOCOCCUS AUREUS*

In 1880 Sir Alexander Ogston first described staphylococcal disease and its role in abscess formation and sepsis [1, 2]. In the first half of the 20th century *Staphylococcus aureus* bloodstream infections carried a mortality of over 80% [3]. Today, more than a century after its discovery, *S. aureus* remains an important human pathogen, which can cause severe morbidity and death.

S. aureus belongs to the family of Staphylococcaceae. The name *Staphylococcus* derives from the Greek words "staphyle" (bunch of grapes) and "kokkos" (granule), since in microscopy the organisms appear as cocci in clusters. After Gram-staining the bacteria colour Gram-positive. Colonies of *S. aureus* have a golden pigmentation. Hence, the species name *aureus*, which is derived from the Latin word "aurum" (gold). An important biochemical feature when distinguishing *S. aureus* from many other staphylococcal species, is its positive result in the coagulase test [4].

1.2 COLONISATION AND PATHOGENESIS OF *S. AUREUS*

S. aureus is often found as an asymptomatic coloniser on the skin and mucosal surfaces of humans. The anterior nares are considered to be the primary colonisation site, although the bacteria may also be found in other locations such as in the throat, perineum, on the skin, and in the intestine. Approximately 30-50% of healthy people carry *S. aureus* in their nose, and 10-20% are persistently colonised [4-8]. Colonised persons readily contaminate their local environments, with their hands or by airborne droplets from the nose, and can transmit the bacteria to others [8]. The hands of health-care workers have been a major source of staphylococcal transmission in hospitals [9-11]. The biology of colonisation of the skin and mucosal linings is multifactorial and incompletely understood, but colonisation is believed to precede infection [8, 12, 13].

Infection can occur when a rupture of the skin or mucosal barrier allows the bacteria to gain access to and invade adjoining tissues. Certain underlying conditions can predispose

individuals to *S. aureus* infections, such as diabetes mellitus, haemodialysis dependence, intravenous drug abuse, and certain immune defects [8, 14]. The virulence of *S. aureus* is determined by multiple bacterial factors controlling attachment (e.g. teichoic acid, fibronectin-binding protein), invasion (e.g. proteases, haemolysins) and immune evasion (e.g. protein A, leukotoxins, superantigenic toxins). In addition *S. aureus* has the ability to form protective biofilms, e.g. on prosthetic materials and heart valves. Infection is thus a result of an interaction between the *S. aureus* and the host. The infection can spread locally, or possibly gain access to the bloodstream. Hence, staphylococcal infection ranges from being localised to disseminated, and from being mild to severe, and possibly fatal [4, 14-16].

1.3 INFECTIONS CAUSED BY *S. AUREUS*

S. aureus can infect virtually any organ. *S. aureus* is a major cause of skin and soft tissue infections, bone and joint infections and endovascular infections. It is also an important but less common cause of respiratory tract infections and urinary tract infections. The presence of foreign material in the human body (e.g. intravascular catheter, suture material, urinary tract catheter, joint prosthesis, and cardiac valve prosthesis) increases the risk for infection. This seems to be a result of increased bacterial adherence to the fibronectin and fibrinogen coated surfaces of foreign material, whereas a lack of vascularisation impairs the influx of leukocytes. Skin and soft tissue infections are the most common clinical manifestation of *S. aureus* infections in all age groups. They are thought to account for approximately 90% of all infections caused by *S. aureus*. Haematogenous seeding can lead to various clinical manifestations, such as septic arthritis, osteomyelitis, epidural abscesses, and endocarditis. The condition when bacteria are found in the blood is called *S. aureus* bacteraemia (SAB) [4, 17]. *S. aureus* is a major pathogen of bloodstream infections in all age groups, both in the community and hospital settings [18-22]. SAB is a severe form of *S. aureus* infection which may be complicated by metastatic infections, endocarditis and septic shock [4, 17].

1.4 *S. AUREUS* BACTERAEMIA

1.4.1 Incidence

Population-based studies have been proposed as the best way to assess the epidemiology of serious infectious diseases since all cases within a predefined geographical area are included. Nationwide studies further diminish the likelihood of selection and referral bias [23-25]. The incidence of SAB has been assessed in a number of population-based studies [18, 26-44], but national studies only exist from Denmark and Finland [26, 29, 31, 35, 38]. The incidence in adults has been reported to be 16-41 /100,000 person-years [18, 26-44]. The paediatric incidence has seldom been reported, but has been found to be 6.5-17 /100,000 child-years [26, 27, 35-37]. The risk of getting SAB increases with age and it is less common in children than in adults. Infants and neonates are, however, most commonly affected among children [21, 26, 29, 30, 35, 36]. The temporal changes in the epidemiology of SAB have been assessed by some researchers [21, 26, 28-31, 33-35, 38, 44]. A selection of important population-based studies on SAB is shown in Table 1.

Table 1. Selected population-based studies on *S. aureus* bacteraemia

First author	Population, years	N	Total incidence /100,000	Adult incidence /100,000	Paediatric incidence /100,000	Mortality %[a]	Nosocomial acquisition %	MRSA %	Change in incidence over time
All ages									
Lyytikainen [26]	Finland, 1995-2001	5,045	14	16	6 (<15 y)	17 (children 1%)	51	<1	↑ 55%
Huggan [27]	New Zealand, 1998-2006	779	21	24	13 (<15 y)	18[b] (children 3%)	36 (51% HCA)	0.4	Fluctuating
Laupland [28]	Canada, 2000-06	1,542	20	NA	NA	25	39 (36% HCA)	11	Stable
Mejer [29]	Denmark, 1995-2008	16,330	23	NA	NA	26	57	0.8	Stable
Laupland [30]	5 countries, 2000-08	18,430	26	NA	NA	NA	39	7	Stable
Adult SAB									
Benfield [31]	Denmark, 1981-2000	18,702	-	18-31	-	22-35	57	0.3	↑ 68%
Hill [32]	New Zealand, 1996-97	424	-	41	-	19	50	5	-
Allard [33]	Canada, 1997-2005	~368[c]	-	28	-	24	60 (26% HCA)	8	↑ 34%
El Atrouni [34]	USA, 1998-2005	247	-	38	-	NA	23 (59% HCA)	32	Stable
Paper I	Iceland, 1995-2008	721	21.5[d]	24.5	-	17[e]	46 (15% HCA)	0.6	↑ 27%
Paediatric SAB									
Frederiksen [35]	Denmark, 1971-2000	2,648	-	-	8.4 (<21 y)	2.5	55	0.5[f]	↑ 83%
Hill [36]	New Zealand, 1996-98	125	-	-	16.9 (<15 y)	3.1	30	6	-
Vanderkooi [37]	Canada, 2000-06	120	-	-	6.5 (<18 y)	2.5	27 (18% HCA)	0.8	Stable
Paper II	Iceland, 1995-2011	146	21.5[d]	-	10.9 (<18 y)	1.4[g]	34 (14% HCA)	0	↓ 36%

N: number of SAB cases, MRSA: methicillin-resistant *S. aureus*, y: years, HCA: health-care associated, NA: not available, SAB: *S. aureus* bacteraemia.

a. Mortality at one month or during admission.

b. 30% 1-year mortality.

c. Mortality and mode of acquisition based on 815 cases during 1991-2005.

d. The combined incidence of adults and children during 1995-2008.

e. 33% 1-year mortality.

f. Rate in 1996-2000.

g. 3.6% 1-year mortality.

1.4.2 Mode of acquisition

A large proportion of SAB is acquired in a health-care setting. Usually 40-60% of adult cases in population-based studies have been found to be nosocomial, or hospital acquired [26-34], with even higher rates (50-70%) in institution-based reports [45-47]. Similar proportions have been seen in children, with 30-70% of SAB being nosocomial [21, 29, 35-37, 47-49]. SAB with an onset in the community can, however, be health-care associated if it is acquired in association with a health-care contact. Examples of this are individuals with chronic underlying diseases with frequent health-care contacts, and patients recently undergoing invasive procedures. Community-onset health-care associated bacteraemia has become regarded as a distinct entity, thought to share more similarities with nosocomial than with true community acquired infections regarding the antimicrobial susceptibility pattern of the pathogens and outcome [50-52]. Only a few studies on SAB have specifically identified this group of patients, and they have used somewhat different definitions. In adults, rates of 25-60% have been reported [28, 33, 34, 53], and in children 15-35% [37, 47, 54].

1.4.3 Focus

The most common focus, or source, of SAB has generally been reported to be skin and soft tissue infections and intravascular catheters. In a significant proportion of cases (10-40%) the focus cannot, however, be identified [31, 45, 53, 55]. Infective endocarditis (IE) is a serious complication or manifestation of SAB. Usually less than 15% of SAB patients are diagnosed with IE [31, 33, 45, 53, 56-58]. In a retrospective study on the treatment of Icelandic adults with SAB we found that only 3% (8/279) had an IE (echocardiography was performed in 51% of episodes) [53]. The frequency of IE diagnosed is, however, linked to how frequently echocardiographies are performed. By actively performing echocardiography up to 30% of adults with SAB have been found to have IE [59-61]. Some therefore recommend that all patients with SAB should undergo echocardiography [61, 62]. IE is, however, rare in children, where <5% of SAB cases usually are reported to have IE [35, 37, 63], although higher rates have been reported [64].

1.5 INFECTIVE ENDOCARDITIS

1.5.1 History and incidence

IE is a well-known disease since more than a century. Sir William Osler in 1885 held lectures on what he termed malignant endocarditis for the Royal College of Physicians of London where he gave a comprehensive overview of the disease [65]. Historically viridans streptococci were the most common cause of IE, but *S. aureus* today has become the leading causes of IE in many regions of the world. *S. aureus* accounts for 15-40% of all IE cases [66-72], and approximately two thirds of cases in people who inject drugs (PWID) [66, 69, 73]. Population-based studies focusing on all IE cases have generally reported *S. aureus* endocarditis (SAE) rates of 0.2-1.6 /100,000 person-years [68, 70, 74, 75]. In a recent study performed in 7 regions of France the annual incidence of SAE was 0.90 /100,000 adults, and in an Italian region 0.76 /100,000 [70, 75]. In an older Swedish study from Gothenburg performed in 1984-88 an SAE incidence of at least 1.4 /100,000 inhabitants per year was found [74].

1.5.2 Pathogenesis

The cardiac valvular endothelium is normally resistant to attachment and colonisation by bacteria. Damage to the endothelium can be caused by turbulent blood flow (from a congenital or acquired cardiac abnormality), repeated intravenous injections of solid particles (such as in intravenous drug users), or injury caused by intracardiac electrodes and catheters. Endothelial damage triggers blood coagulation with deposition of fibrin and platelets to form a sterile thrombus. Circulating microorganisms may adhere to the damaged endothelium, and subsequently proliferate and infect the valves. The bacteria become encased in the platelet/fibrin matrix, the infected coagulum is termed a vegetation. Absence of valve vasculature causes low penetration of phagocytic leukocytes into the infected tissue and the host immune response has difficulties fighting back the infection [76-78].

The mitral valve is most commonly affected in IE, followed by the aortic valve. The right-sided valves (tricuspid and pulmonic valves) are less commonly involved except in PWID. Pathogens can also adhere to the fibronectin and fibrinogen coated surfaces of prosthetic heart valves, or other prosthetic intracardiac materials such as pacemaker and implantable

cardioverter defibrillator (ICD) leads. Prosthetic valve endocarditis is a severe form of IE and is associated with poorer prognosis [66, 79].

Embolisation of a vegetation is a well-known complication of IE. Vegetations on the right-sided valves embolise to the pulmonary circulation, while left-sided vegetations embolise via the systemic circulation. This can cause septic embolies in virtually any organ. Embolies to the central nervous system (CNS) can cause severe events, such as ischemic infarction or intracranial bleeding [76, 77, 80]. The risk of CNS embolisation depends on the size and the location of the vegetation, large vegetations (>10-15 mm) and mitral valve location being associated with higher risk [81-85]. IE caused by *S. aureus* is also associated with a higher risk of embolic events than IE caused by most other pathogens [67, 82]. Other possible complications of IE are valvular dysfunction (e.g. perforation of a valve, rupture of chordae, valve obstruction, prosthetic valve dehiscence) leading to congestive heart failure, and intracardiac abscess formation possibly disrupting the heart's electrical conduction system and causing arrhythmias [76, 77, 80].

1.5.3 Diagnosis

The diagnosis of IE is based on microbiologic, echocardiographic, clinical and histopathologic findings. The diagnostic criteria currently most widely used are the modified Duke criteria (Table 2). These modifications of the original Duke criteria from 1994 were proposed in the year 2000, previously other criteria have been used [86, 87]. Transoesophageal echocardiography is generally more sensitive and specific than transthoracic echocardiography in the diagnosis of IE [88, 89].

Table 2. The modified Duke criteria for infective endocarditis [a]

Pathologic criteria

- Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolised, or an intracardiac abscess specimen; or
- Pathologic lesions: vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis.

Major criteria

- Blood culture positive for IE

Typical microorganisms consistent with IE from 2 separate blood cultures:

Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or

Community-acquired enterococci, in the absence of a primary focus; or

Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:

At least 2 positive cultures of blood samples drawn >12 hours apart; or

All of 3 or a majority of ≥ 4 separate cultures of blood (with first and last sample drawn at least 1 hour apart); or

Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titre >1:800.

- Evidence of endocardial involvement

Echocardiogram positive for IE, defined as follows:

Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or

Abscess; or

New partial dehiscence of prosthetic valve; or

New valvular regurgitation.

Minor criteria

- Predisposition: predisposing heart condition or injection drug use.
- Fever: temperature >38°C.
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions.
- Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
- Microbiological evidence: positive blood culture but does not meet a major criterion as noted above[b], or a serological evidence of active infection with organism consistent with IE.

Definition of infective endocarditis

Definite IE:

1 pathologic criterion; or

2 major criteria; or

1 major criterion and 3 minor criteria; or

5 minor criteria.

Possible IE:

1 major criterion and 1 minor criterion; or

3 minor criteria.

Rejected:

Firm alternate diagnosis explaining evidence of IE; or

Resolution of IE syndrome with antibiotic therapy for ≤ 4 days; or

No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤ 4 days; or

Does not meet criteria for possible IE.

IE: infective endocarditis, HACEK: *Haemophilus spp, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae.*

a. Based on Li, et al. **[86]**.

b. Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause IE.

1.6 OUTCOME OF *S. AUREUS* BACTERAEMIA AND ENDOCARDITIS

In the pre-antibiotic area SAB carried a mortality of over 80% [3]. Today, the case fatality ratio at one month is generally 15-25% among adults in developed countries, although rates of up to 40% are occasionally reported [26-29, 31-33, 45, 46, 90-94]. In children it is considerably lower, 1-9% [26, 27, 29, 35-37, 48, 49, 54, 95] (Table 1). Long-term mortality associated with SAB, is either due to sequelae or complications caused by the SAB, or it reflects deaths from underlying diseases. It has, however, rarely been assessed [27, 46, 96, 97]. Most of the studies on outcome in SAB have been institution-based rather than population-based. Increasing age is the most consistent and strongest predictor of mortality associated with SAB. Examples of other factors that have been associated with a detrimental outcome are presence of co-morbidities, antibiotic resistant *S. aureus* isolates, nosocomial acquisition, female sex, type and timing of the antibiotic treatment, presence of concomitant *S. aureus* bacteriuria, and having endocarditis as the source of bacteraemia [28, 53, 57, 63, 90, 98, 99].

SAE is associated with worse outcome than IE caused by most other bacterial pathogens [100]. SAE is generally associated with 20-30% in-hospital mortality [67, 100-110]. Left-sided disease is regarded to be more severe than right-sided [67, 100, 101]. A significant proportion of SAE patients (15-35%) experience symptomatic CNS complications, such as cerebral embolisation or CNS infection [67, 100-106, 108]. It should be realised that SAE is relatively infrequent in most institutions. Hence, previous studies on SAE have rarely included large number of patients [67, 100-108]. Of studies including more than 100 SAE episodes only one has focused exclusively on cases diagnosed in the 21st century. This study included patients from 39 medical centres in 16 different countries during 2000-03 [100]. Single centre studies, on the other hand, often represent a more homogenous sample than multicentre studies, with less differences in data collection, diagnostics and treatment practices. A selection of large ($\geq$ 100 cases) studies on SAE is shown in Table 3.

Table 3. Large studies on *S. aureus* endocarditis

First author	Location, years	N	IVDU	Right sided	Prosthetic valve	Nosocomial acquisition	MRSA	CNS events	Cardiac surgery	In-hospital mortality	One-year mortality
			%	%	%	%	%	%	%	%	%
Fowler [100]	16 countries, 2000-03	558	21	NA	15	23 (HCA 16%)	27	21	38	22	NA
Fernández Guerrero [101]	Spain, 1985-2006	133	47	48	15	22	6	19	27	28	NA
Hsu [102]	Taiwan, 1995-2005	123	17	27	11	17	39	17	20	26	NA
Remadi [103]	France, 1991-2001	116	6	26	17	NA	13	28	47	26	37
Miro [67]	5 countries, 1979-99	566[a]	37	44[b]	NA	24	15	21	26	20	NA
Røder [104]	Denmark, 1982-91	260[c]	(21)[d]	5	9	33	0	35	15[e]	46[e]	NA
Watanakunakorn [105]	USA, 1980-91	106	20	16	7	17	1	15	8	25	NA
Espersen [106]	Denmark, 1976-81	119[f]	9	12	3	38	0[g]	33	7[h]	35[h]	NA
Cervera [107]	Spain, 1995-2011	93[i]	12	(28)[j]	22	25 (HCA 9%)	-	11	38	40	43
Rasmussen [108]	Denmark and Sweden, 1996-2008	170[k]	7	-	24	NA	2	41	41	22	39
Paper III	Sweden, 2004-13	245	49	37	11	9 (HCA 9%)	2	12	15	9	20

N: number of SAE cases, IVDU: intravenous drug use, MRSA: methicillin-resistant *S. aureus*, CNS: central nervous system, NA: not available, HCA: health-care associated.
a. Native valve *S. aureus* endocarditis only.
b. Of 389 cases with echocardiographically defined vegetations.
c. 177 (68%) cases clinically diagnosed, 83 (32%) not clinically suspected but autopsy confirmed.
d. 103 of 485 suspected IE cases, but these were excluded from further analysis.
e. Of 177 clinically diagnosed cases. ~62% mortality of all cases (including autopsy diagnosed).
f. 54 (45%) cases clinically diagnosed, 65 (55%) not clinically suspected but autopsy confirmed.
g. According to another publication by the same authors [111].
h. Of 54 clinically diagnosed cases. 71% mortality of all cases (including autopsy diagnosed).
i. Left-sided methicillin-sensitive *S. aureus* endocarditis only.
j. 46 of 163 *S. aureus* endocarditis cases with available strains, but these were excluded from further analysis.
k. Left-sided *S. aureus* endocarditis only.

1.7 ANTIBIOTIC TREATMENT OF SAB AND SAE

S. aureus is naturally susceptible to most antibiotics. This susceptibility led to Sir Alexander Fleming's discovery of penicillin in 1928 [112, 113]. *S. aureus* has, however, high ability to become antibiotic resistant. Within a few years from the introduction of penicillin in 1941 resistance had become a significant problem, and today over 80% of *S. aureus* isolates are resistant to penicillin. Penicillin-resistance is generally caused by the bacterial production of beta-lactamases. In addition *S. aureus* early became able to develop resistance to other available antibiotics, such as erythromycin, streptomycin, and the tetracyclines [114-116]. Semi-synthetic penicillins (e.g. cloxacillin, nafcillin, and methicillin) are penicillinase-stable, and have for decades been the principal antibiotics used for the treatment of SAB. Other antibiotic classes such as the cephalosporins (e.g. cefazoline) and glycopeptides (e.g. vancomycin) have also been used [55, 113, 117]. Not long after the introduction of semi-synthetic penicillins in the middle of the 20th century, naturally occurring strains of methicillin-resistant *S. aureus* (MRSA) were reported [118]. Methicillin-resistance involves the expression of an acquired penicillin-binding protein (PBP2a) (encoded by the *mec*A gene), with reduced affinity to most betalactam antibiotics. Since then the prevalence of MRSA has steadily increased, with substantial regional differences [116, 119]. In the previously mentioned studies on SAB and SAE, MRSA rates of up to 40% have been observed [34, 102]. MRSA strains are most commonly seen in hospitals and other health-care facilities, but community acquired strains have been increasingly endemic in many parts of the world. Glycopeptides remain the most commonly used antibiotics for invasive MRSA infections, and resistance is still uncommon [62, 116, 119, 120].

Previously intravenous antibiotics for at least 4 weeks were generally recommended for treatment of SAB. Long treatment duration is thought to diminish the risk of relapses. Relapse rates of up to 18% are still being reported after SAB [53, 56, 121]. Today, intravenous treatment during 7-14 days is usually regarded as adequate for uncomplicated SAB. Two weeks intravenous duration has been recommended for right-sided endocarditis without any complications. At least 4 weeks intravenous treatment is often advocated for complicated SAB with metastatic infections, and 4-6 weeks for left-sided endocarditis [55, 79, 80, 122-125]. In our previously mentioned study on the treatment of SAB in Icelandic adults, 47% (130/279) got substantially shorter intravenous treatment than the operating recommendations suggested [53]. In the case of prosthetic valve endocarditis a combination

antibiotic treatment with rifampicin is usually recommended for at least 4-6 weeks, adding gentamicin for the first 2 weeks. Rifampicin helps eradicate bacteria attached to foreign material [79, 80, 126]. Cardiac surgery may also be a necessary part of SAE treatment.

1.8 CARDIAC SURGERY FOR *S. AUREUS* ENDOCARDITIS

In previous reports on SAE valvular surgery has been performed in 20-45% of patients during the admission (early surgery) [67, 100-104, 107; 108] (Table 3). Indications for early surgery include heart failure (as a result of valve dysfunction), uncontrolled infection (e.g. intracardiac abscess formation, enlarging vegetation, persisting fever and positive blood cultures), and prevention of embolic events (e.g. large vegetations >10-15 mm, especially on the aortic or mitral valve). The decision regarding operation needs, however, to be individualised. The objectives of surgery are total removal of all infected tissue and reconstruction of cardiac morphology, accomplished with valve repair or valve replacement. Biological or mechanical prosthesis can be used [79, 89]. Early valvular surgery for SAE has by some been associated with lower in-hospital mortality [67], while others have failed to confirm such an association [100, 103]. The most common indication for late surgery (weeks to months after completion of the antibiotic treatment for IE) is valvular insufficiency causing heart failure [79].

1.9 PEOPLE WHO INJECT DRUGS

1.9.1 Infectious complications

Intravenous drug use (IVDU) is a global health problem. The number of PWID in a given region is, however, difficult to estimate. In Stockholm County the number has been calculated to range from 1850 to 7800 [127-129] (National Board of Health and Welfare 2014 (unpublished), Martin Kåberg, MD, personal communication).

IVDU is associated with severe social problems as well as a wide range of medical complications. Infections are a major cause of morbidity and hospitalisation among PWID. These include infections caused by bacteria, fungi and viruses (e.g. HIV, and hepatitis C) [130, 131]. Skin- and soft tissue infections can result from unsterile injections, and are the

most common bacterial infections seen in PWID. Many microbes can be involved. *S. aureus* is the principal pathogen and it most often appears to originate from the drug user's own skin and nose [130, 132]. *S. aureus* colonisation has been shown to be more common among PWID than in the general population [133]. PWID sustain considerable skin and mucosal damage, IVDU is often associated with poor hygiene, and the drugs injected can have both direct and indirect effects on the host immune response [134]. Transmission of *S. aureus* strains between individuals can occur within drug-use networks [135, 136]. If the bacteria gain access to the bloodstream this can result in IE, which is an important and serious reason for hospitalisation among PWID. Despite its importance, recent studies concerning SAE in PWID are few [100, 109, 137-141].

1.9.2 Incidence of endocarditis

Reports on the incidence of IE among PWID are few and usually limited by small size or selected populations. An incidence of 3.3 /1,000 person-years among HIV-negative PWID (35 cases) and 13.8 among HIV-positive PWID (82 cases) was reported from Baltimore USA during 1988-98, where 76% of the 117 cases were caused by *S. aureus* [142]. In a smaller study from Amsterdam the IE incidence rates among HIV-negative (3 cases) and positive (14 cases) PWID were 3.9 and 24.8 /1,000 person-years respectively during 1989-93. In this study 65% of the 17 cases were caused by *S. aureus* [143]. In the population-based study on IE in Gothenburg, Sweden, 7 IVDU-related IE cases were identified over a period of 5 years (1984-88) in an estimated population of 1280 PWID, hence the annual incidence was 1.1 /1,000 person-years (all pathogens) [74]. Older reports have presented similar or lower estimates of the incidence [144, 145]. Thus, relatively little is known about the current epidemiology, clinical features, management and outcome of SAE in PWID.

2 AIMS

The overall aims of this thesis were to assess the epidemiology, clinical aspects, and outcome of SAB and SAE in Iceland and Stockholm, respectively.

More specifically the aims were as follows:

1. To evaluate the **incidence of SAB in adults** in the Icelandic population, the associated **short- and long-term fatality**, and **changes over time** during 1995-2008 (Paper I).

2. To assess the **incidence of SAB in** Icelandic **children**, and the associated **short- and long-term mortality** during 1995-2011 (Paper II).

3. To assess the **proportions of nosocomial and health-care associated SAB** in adults and children, and the isolates' **antimicrobial susceptibility** (Paper I and II).

4. To define the **focus of SAB in children** (Paper II).

5. To evaluate the **short- and long-term outcome, treatment, and clinical characteristics of SAE** patients, and **changes in incidence over time** in Stockholm, Sweden, during 2004-2013 (Paper III).

6. To study **factors associated with valvular heart surgery** and risk factors for **mortality and CNS complications** associated with SAE (Paper III).

7. To study the **incidence** and associated **short- and long-term mortality of SAE in PWID** in Stockholm, Sweden, during 2004-2013 (Paper IV).

8. To evaluate the **clinical aspects and management of SAE in PWID**, and compare with that in non-addicts (Paper IV).

3 MATERIALS AND METHODS

3.1 PAPER I AND II – *S. AUREUS* BACTERAEMIA

3.1.1 Study population

In Iceland a university hospital is located in the capital, Reykjavik, and a teaching hospital in the town of Akureyri. Both hospitals include a clinical microbiological laboratory and paediatric departments. Smaller regional hospitals send blood cultures to either of two laboratories.

At the end of the study period for adults (Dec 31st 2008) the Icelandic population ≥ 18 years of age consisted of 238,587 adults. During the period the proportion of persons ≥ 50 years of age rose from 33% to 38% of the adult population. At the end of the study period for children (Dec 31st 2011) the Icelandic population <18 years of age consisted of 79,851 children.

3.1.2 Study protocol

SAB cases occurring between January 1st 1995 and December 31st 2011 were retrospectively identified at the clinical microbiological laboratories. Adults ≥ 18 years of age with growth of *S. aureus* in a blood culture during 1995-2008 were included in Paper I. Children <18 years of age with a growth of *S. aureus* in a blood culture during 1995-2011 were included in Paper II. Information about admission and discharge dates, and microbiological data were obtained from medical records and from the laboratories. Clinical data were collected for the children and were obtained from medical records. Information about the national population and dates of death was available from Statistics Iceland.

3.1.3 Definitions

3.1.3.1 SAB episode

An episode of SAB was defined by the isolation of *S. aureus* from at least one blood culture bottle. All positive blood cultures in adults were considered to represent clinically significant SAB (Paper I). In children *S. aureus* was considered to be a contaminant and excluded if isolated from a single blood culture without a demonstrable source of infection and not judged as a being a true pathogen by the physicians treating the patient, and lacking event on follow up (Paper II). A new SAB episode was considered to be a relapse, and hence not counted as a separate episode, if it occurred within 90 days after the index bacteraemia.

Blood culturing systems used at Landspitali University Hospital were BACTEC™ (Becton Dickinson and Company, Sparks, MD, USA) in 1995, Difco ESP® (Difco Laboratories, Detroit, MI, USA) in 1996-2002 and BacT/ALERT® (bioMérieux, Marcy l'Etoile, France) during 2002-11, and at Akureyri Hospital SEPTI-CHEK™ (Becton Dickinson and Company, Sparks, MD, USA) in 1995-99, Difco ESP® in 1999-2008 and BacT/ALERT® during 2008-11. Antibiotic susceptibility testing was performed by disc diffusion tests according to the standards and definitions of the Clinical and Laboratory Standards Institute (CLSI).

3.1.3.2 Mode of acquisition

Nosocomial bacteraemia was defined as an episode for which the first positive blood culture was drawn more than two days after hospital admission. Positive culture drawn two days or less after hospital discharge with a minimum of two days stay was also defined as nosocomial. Infection occurring within the first 48 hours after birth was also classified as nosocomial.

Health-care associated bacteraemia in adults (Paper I) was defined as an episode not being nosocomial but occurring in an individual who had been admitted to hospital for more than two days in the 90 days prior to bacteraemia. Health-care associated SAB in children (Paper II) was defined as one not being nosocomial but occurring in an individual having the following risk factors: 1) admittance to hospital for two or more days 90 days prior to the SAB, 2) attendance at a specialised hospital clinic or emergency department in the 30 days prior to SAB, 3) having an intravascular catheter at the time of infection, or 4) developing

SAB directly following a procedure in another health-care setting (modifications from Friedman et al.) [50].

A community acquired bacteraemia was defined as one that was neither nosocomial nor health-care associated.

3.1.3.3 SAB focus in children

A local infection was considered to be the focus or source of SAB if localised symptoms or signs of infection were present at the time of bacteraemia as assessed by the treating physicians, often supported by microbiological and/or radiological findings, or if confirmed at autopsy.

3.1.3.4 Mortality

Thirty-day and 1-year mortality were defined as all-cause death within 30 and 365 days, respectively, from the SAB (Paper I and II). In children (Paper II) death was judged to be bacteraemia related if signs or symptoms due to SAB were persistent and/or if blood cultures were positive at the time of death, further if autopsy results confirmed *S. aureus* infection as the cause of death (modifications from Lodise et al.) [146].

3.1.4 Statistical analysis

The Pearson's chi square test, or Fisher's exact test when needed, was used for comparing categorical data. The Mann-Whitney U test was used to compare continuous data between two groups. Linear time trends in incidence and mortality rates were tested by the chi-squared trend test. Time trends in other data were evaluated by Kendall's correlation. Survival data is displayed by Kaplan-Meier curves and groups were compared by the log-rank test. The level of significance was set at 0.05. For processing the data in Paper I the IBM® SPSS® Statistics 17.0 program package was used. The data in Paper II were analysed with the JMP® 8.0.2 statistical software from SAS Institute Inc (Cary, NC, USA).

3.1.5 Ethical permits

Studies in Iceland were approved by the National Bioethics Committee and Data Protection Authority (VSNb2008030023/03-15 with an addition).

3.2 PAPER III AND IV – *S. AUREUS* ENDOCARDITIS

3.2.1 Study population

Stockholm County has some 2.2 million inhabitants (1.7 million adults ≥ 18 years). The number of PWID in the county has been estimated to be between 1850 and 7800, with an average of 4825 persons [127-129] (National Board of Health and Welfare 2014 (unpublished), Martin Kåberg, MD, personal communication). The Karolinska University Hospital serves as a tertiary referral centre for the county's entire population, providing secondary health-care to part of it. Patients with suspected or confirmed IE are usually admitted to specialised infectious diseases (ID) departments, although occasionally they may be treated by other medical specialities. The ID departments are also responsible for severely ill IE patients who require intensive care treatment, and patients who need valvular surgery are usually admitted to an ID department both before and after the operation. Approximately two thirds of ID in-patient beds and the only thoracic surgery department in the region are located at the Karolinska University Hospital. Hence, patients with suspected IE are often transferred to the hospital from smaller hospitals. Furthermore, most PWID needing admission for serious infections in Stockholm County are directly referred to and treated at a medical ward at the Karolinska University Hospital specialised for this purpose. Nearly all PWID with suspected SAE are therefore treated at our hospital.

3.2.2 Study protocol

Individuals treated for SAE at the Department of Infectious Diseases at Karolinska University Hospital between January 1st 2004 and December 31st 2013 were included. A retrospective search was done in the records of the department by diagnostic codes representing IE according to the 10th revision of International Classification of Diseases (ICD-10). Clinical and microbiological data were obtained from medical records and patients with IE caused by *S. aureus* were identified. Patients with active IVDU were specifically identified. Echocardiography reports were reviewed and the diagnosis of IE was verified according to the modified Duke criteria [86].

3.2.3 Definitions

3.2.3.1 SAE episode

An episodes of IE was defined as *definite* or *possible* according to the modified Duke criteria (Table 2) [86, 87]. IE on pacemaker or ICD leads were considered to be definite if culture of removed leads demonstrated *S. aureus* or if the modified Duke criteria were fulfilled [147-149]. IE was defined as right-sided if it only involved structures on the heart's right side (tricuspid valve, pulmonic valve, pacemaker or ICD leads). IE was defined as left-sided if the aortic or mitral valves were engaged. SAE episodes involving both the right and left side were classified as left-sided. A new episode within 90 days after completing treatment for SAE was considered to be a relapse and not counted as a separate episode. The blood culture systems used at the Karolinska were BACTEC™ (Becton Dickinson and Company, Sparks, MD, USA) during 2004-07 and BacT/ALERT® (bioMérieux, Marcy l'Etoile, France) during 2004-13.

3.2.3.2 Mode of acquisition

Nosocomial or hospital acquired SAE was defined if signs or symptoms of IE presented more than 48 hours after admission, or less than 48 hours after hospital discharge after a minimum of two days admission. Infection was also defined as nosocomial if it was related to haemodialysis. Other cases were considered to be community-onset episodes.

Health-care associated community-onset SAE was considered if at least one of the following risk factors was present: 1) admittance to hospital for two or more days 90 days prior to the SAE, 2) attendance at a specialised hospital clinic or emergency department in the 30 days prior to SAE, 3) having an intravascular catheter at the time of infection, or 4) developing SAE directly following a procedure in another health-care setting [50].

3.2.3.3 Underlying diseases and complications

IVDU was judged to be active if there was a history of IVDU in the three years before the IE or if there was evidence of drug use in the year following the SAE. CNS involvement or

complication was defined as a CNS embolisation, intracranial haemorrhage, or CNS infection. Predisposing heart disease was defined as in the original Duke criteria [87, 150].

3.2.3.4 Mortality

In-hospital mortality was defined as all-cause death while still admitted to an acute care hospital, also if the patient had been transferred from the Karolinska University Hospital to another hospital and died there. Thirty-day and 1-year mortality were defined as all-cause death within 30 days and 365 days, respectively, from the SAE.

3.2.4 Statistical analysis

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. Time trends in incidence rates were tested by the chi-squared trend test. Survival data is 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 judgment. 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.

3.2.5 Ethical permits

The studies were approved by the Ethical Review Board in Stockholm (2013/1069-31/2).

4 RESULTS AND DISCUSSIONS

4.1 PAPER I AND II – *S. AUREUS* BACTERAEMIA

Population-based studies have been proposed as the best way to assess the epidemiology of serious infectious diseases [23-25]. These two nationwide studies provide information on the epidemiology and outcome of adult and paediatric SAB in Iceland, and the changes over time.

4.1.1 Patients

In the study period 1995-2008 we identified 692 adults with 721 distinct episodes of SAB. Cases were identified from 19 hospitals and health-care institutions. The mean age at diagnosis was 62.6 years (range 18-99 years) and the male to female ratio was 1.4. During 1995-2011 a total of 140 children had 146 distinct episodes of SAB. The median age at diagnosis was 7.4 years, and the male to female ratio 1.8. An additional 15 (9%) children were identified who had a positive blood culture result that was regarded as a contamination and therefore excluded.

4.1.2 Incidence

4.1.2.1 Incidence rates

The incidence of SAB in Icelandic adults was 24.5 /100,000 person-years during 1995-2008, and the total (adult + paediatric) SAB incidence was 21.5 /100,000 person-years. Other population-based studies have reported incidence rates of 14 to 41 /100,000 person-years [18, 26-34, 38-44], most of which have included children (Table 1). The incidence of paediatric SAB was 10.9 /100,000 child-years in 1995-2011. For boys it was 13.7 and for girls 7.9 /100,000 (p=0.001). This is somewhat higher than found in other population-based studies on children [21, 26, 35, 40], although a similar or higher incidence has been reported earlier [27, 36] (Table 1).

The differences seen in the incidence rates in studies from different countries and regions can have many possible explanations. Differences in population structures, such as age distribution and co-morbidities, play a role. Variations in health-care systems and diagnostic methods also can affect the observed incidence. Our blood culture sampling frequency during 1995-2008 was similar to that reported from Finland during 1995-2001 [26]. Handling of contaminations differs between studies. Most of the adult population-based studies have included all positive blood cultures, and did not exclude suspected contaminations, while two of the population-based paediatric studies excluded probable contaminations from the analysis. In these 7-12% of blood cultures growing *S. aureus* were considered to be contaminations, compared to our 9% in Icelandic children [36, 40]. Finally, genetic and bacterial factors might possibly influence the incidence [8, 151, 152].

In adults the incidence rate increased with age, whereas in children it was highest among the youngest. The incidence rate in infants (< 1 year) was similar to that for adults >55 years of age, but for children in general it was considerably lower than in adults (Figure 1). Others have reported similar dynamics in the age distribution of SAB [29, 30], and a high incidence in neonates and infants is consistent with previous reports on SAB and paediatric bloodstream infections in general [21, 22, 26, 29, 36, 37, 48]. Most of the infections in infants were nosocomial or health-care associated and occurred in vulnerable children.

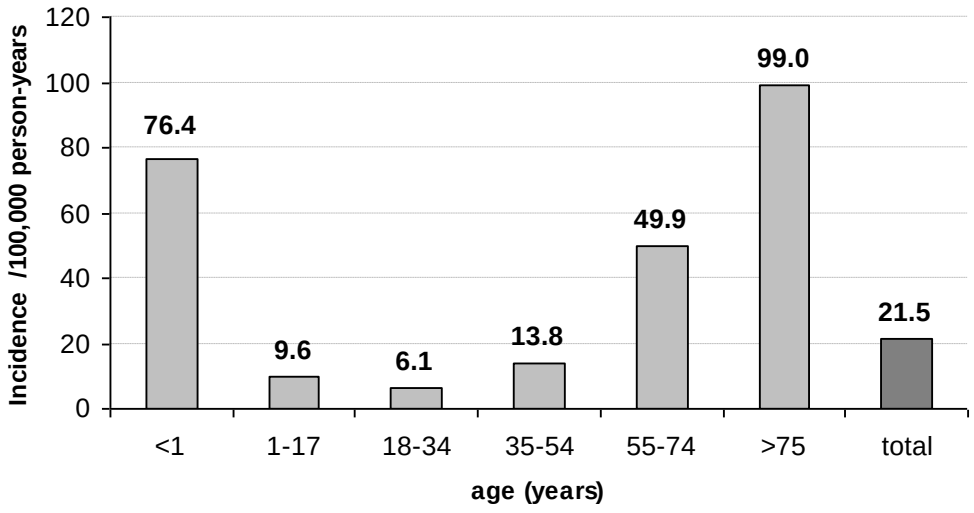

Figure 1. Age-specific incidence of paediatric and adult *Staphylococcus aureus* bacteraemia in Iceland during 1995-2008.

4.1.2.2 Changes in incidence in adults

In adults the SAB incidence rate increased by 28%, from 22.3 /100,000 person-years in 1995-99 to 28.8 in 2005-08 (p=0.01) (Table 4). A similar trend has been seen in two Nordic national studies and a Canadian study. In Denmark the incidence rose by 40% from 1981 to 2000, in Finland by 55% from 1995 to 2001, and in Quebec, Canada by 34% from 1997 to 2005 [26, 31, 33]. Other reports, including a recent multinational study have, however, found a stable incidence over time [29, 30, 34], and even a decrease has been reported [44] (Table 1).

The explanation for the increase in incidence is not clear. How frequently blood cultures are obtained might influence the observed incidence. The frequency of blood cultures analysed at the clinical microbiology laboratory at Landspitali University Hospital did not change substantially during the study period since it was 38.4 /1,000 adults per year in 1995-2001 and 39.7 in 2002-08. As our definition of SAB episodes in adults included possible contaminations, any change in the rate of contaminations could be important. Such a change is unlikely since the percentage of SAB episodes with a single positive blood culture and the proportion with polymicrobial aetiology did not change significantly with time. The noted increase in SAB incidence thus seems to be a real increase. It might be attributed to an increase in predisposing risk factors for *S. aureus* infections, with an ageing population, with higher numbers of individuals living with malignancies, more people having chronic diseases such as diabetes and obesity, and expanding use of invasive procedures and prosthetic devices [153, 154].

4.1.2.3 Changes in incidence in children

The incidence of paediatric SAB decreased by 36% during 1995-2011, from 13.1 /100,000 child-years in 1995-2003 to 8.4 in 2004-11 (p=0.001). A similar trend has not been observed in other studies on SAB in children. As opposed to this a stable or an increasing incidence of SAB has been described [35, 37]. A part of the explanation for the decreasing incidence could be the 27% reduction in the frequency of blood cultures collected in children during the period, from 19.6 /1,000 children per year during 1995-2003 to 14.3 /1,000 during 2004-11 (p<0.001). The lower frequency of blood cultures towards the end of the study period can probably be attributed to an international financial crisis beginning in 2008. It hit Iceland hard

and a consequence of the crisis was that physicians were encouraged to reduce "unnecessary" investigations. This, however, does not explain a reduction that was observed prior to 2008. A factor leading to a real decrease in SAB incidence could be the extensive infection control measures that have been applied during the period possibly reducing the risk of *S. aureus* transmission. A strict national MRSA reduction policy has been in place from 2001 focusing on screening and isolation of at risk patients along with eradication of MRSA in positive individuals ("search and destroy" policy). Furthermore, a department of infection control was established in the university hospital in 2001, promoting for example improved intravascular catheter hygiene routines and starting a hand hygiene promotional campaign in 2004, emphasising the use of alcohol hand sanitisers [155].

4.1.3 Mortality

4.1.3.1 Short-term mortality

The 30-day case fatality ratio among adults was 17.1% during 1995-2008, and the annual mortality rate (based on 30-day mortality) was calculated to be 4.3 deaths /100,000 adults. Towards the end of the study period the case fatality ratio had declined to 11.4% (in 2005-08) (Table 4). The 30-day mortality could, however, be an overestimate of mortality attributed to SAB since some patients most likely had serious underlying diseases and died of other causes. Our adult 30-day case fatality is relatively low in comparison to the 19-26% seen in most other population-based studies (Table 1) [26-28, 31-33]. Increasing age in adults was associated with higher 30-day mortality, the rate being 28% in persons ≥ 75 years of age. The mortality was 23% in nosocomial SAB, 15% in health-care associated SAB, and 10% in community acquired SAB ($p<0.001$). The mortality was similar among males (16%) and females (19%) ($p=0.27$).

In children one death could be attributed to SAB (0.7%), and the 30-day mortality was 1.4% (2 deaths). This case fatality ratio is among the lowest reported in children. In the few other population-based studies the case fatality ratio has been some 1-3.5% [26, 27, 29, 35-37], while in institution-based studies 1.5-9% [47-49, 54, 95, 156]. The annual mortality rate (based on 30-day mortality) was calculated to be 0.15 deaths /100,000 children.

Table 4. Incidence and mortality of adult *S. aureus* bacteraemia in Iceland during three different time periods

Variable	1995-99 (n = 216)	2000-04 (n = 242)	2005-08 (n = 263)	*p*-value
Incidence rate, /10^5 person-years	22.4	23.1	28.9	.01
Age				
18-34 years	3.4	6.7	8.5	
35-54 years	12.3	13.9	15.4	
55-74 years	55.7	43.3	51.1	
≥ 75 years	79.8	94.0	122.8	
Mode of acquisition				
Nosocomial	12.4	10.7	11.2	ns
Health care associated	3.5	3.0	4.3	ns
Community acquired	6.4	9.4	13.4	<.001
Case fatality at 30 days, %	22.2	18.7	11.4	.001
Case fatality at 1 year, %	38.9	32.8	28.2	.06
Mortality rate, /10^5 person-years[a]	5.0	4.3	3.3	.048

n: number of *S. aureus* bacteraemia episodes, ns: not significant.

a. Mortality rate per population was calculated based on 30-day case fatality.

4.1.3.2 One-year mortality

The 1-year case fatality ratio among adults was 33% during 1995-2008. This is relatively low compared to the 30-56% reported in previous studies [27, 46, 96, 97]. It was 41% for patients with nosocomial SAB, 36% in health-care associated SAB, and 22% in community-acquired infections ($p<0.001$). In Figure 2 the 1-year survival curves for the three different modes of acquisition (community acquired, health-care associated and nosocomial) are shown. Among patients who died within one year, 52% died during the first 30 days and 48% in the next 11 months, which is very similar to the rates noted in two other studies [27, 46]. One-year mortality may reflect deaths from underlying co-morbid conditions as well as long-term sequelae of SAB. This illustrates that it may be important not only to look at the short-term mortality of adult patients with SAB.

The 1-year mortality after SAB in children has to the authors' knowledge never been assessed before. The 1-year mortality during 1995-2011 was 3.6%. The five children who died within one year all had nosocomial infections and serious underlying diseases, whereas no children with community-onset infections died (p=0.02). The difference between short- and long-term mortality in children thus primarily seems to reflect deaths from underlying co-morbid diseases rather than the SAB per se.

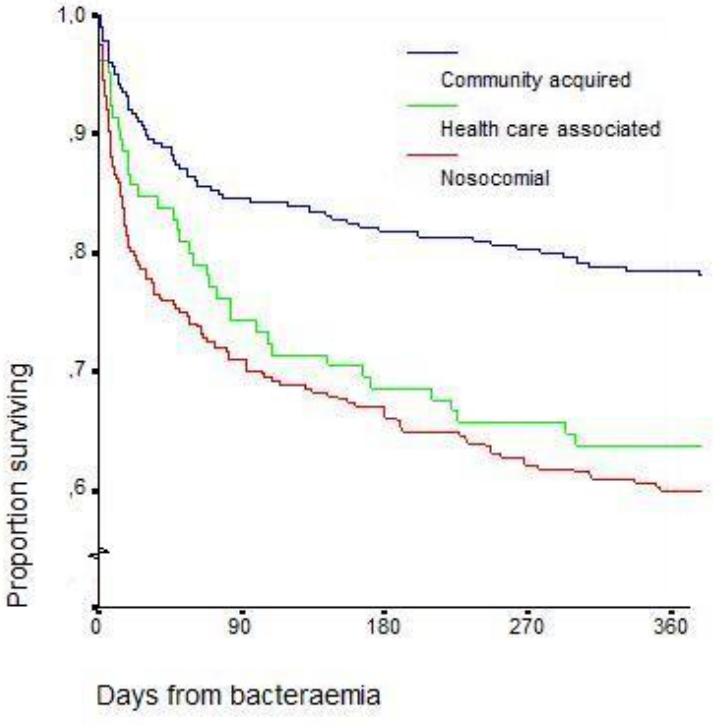

Figure 2. One-year survival curves after adult *S. aureus* bacteraemia by different modes of acquisition (p<0.001, log-rank test).

4.1.3.3 Reasons for the low mortality in Iceland

The reason for the low short- and long-term mortality among both our adults and children is not clear. It could in part reflect the low rate of antibiotic resistance. Low resistance rates generally make wider range of empiric antibiotic treatments effective, and SAB caused by MRSA has in some studies been associated with poor outcome compared to SAB caused by methicillin-sensitive *S. aureus* (MSSA) [28, 54, 99]. The relatively low proportion of nosocomial SAB in children could also play a role since nosocomial bacteraemia in some studies has been independently associated with a worse outcome [63, 99]. Furthermore, survival could possibly be related to local conditions, such as the quality of supportive care or the timing of diagnosis, or possibly to as yet unidentified bacterial or host factors [157, 158].

4.1.3.4 Changes in mortality over time

The 30-day case fatality ratio associated with adult SAB decreased during the study period, from 22.2% in 1995-99 to 11.4% in 2005-08 (p=0.001), and the 1-year mortality from 38.9% to 28.2% (p=0.06) (Table 4). In Figure 3 the 1-year survival curves for different time periods are shown. Similarly, in-hospital mortality decreased in Denmark from 1981 to 2008 (by 37% during 1981-2000, and by 22% during 1995-2008), and in a Swiss study from 1980 to 2002 (by 14%) [29, 31, 90], while other studies have not shown a change over time [26, 28]. The reason for the decreasing mortality in Iceland is not obvious. Similarly, a decreasing mortality associated with bloodstream infections in general was observed in the United States between 1979 and 2000, and has in part been thought to reflect improvements in supportive treatment [159]. It may also be speculated that increased awareness and earlier diagnosis of bacteraemia and sepsis might have contributed, and possibly changes in bacterial factors.

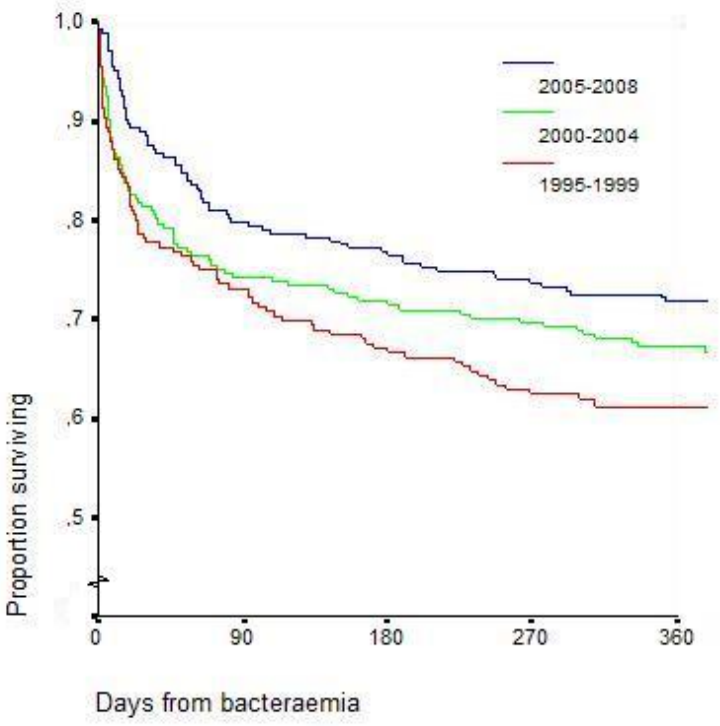

Figure 3. One-year survival curves after adult *S. aureus* bacteraemia during three different time periods (p=0.03, log-rank test).

4.1.4 Mode of acquisition

In adult SAB 46% of cases were nosocomial, 15% health-care associated, and 39% community acquired. The proportion with nosocomial infections decreased during the period, from 56% in 1995-99 to 39% in 2005-08 (p=0.001), while community acquired SAB increased from 29% to 46% (p<0.001). In children 34% of episodes were nosocomial, 14% health-care associated, and 51% community acquired. Nosocomial and health-care associated infections were most common in the youngest children (Table 5). The percentage of nosocomial infections in our adults is in the same order as that reported in most other studies (Table 1) [26-28, 30, 32]. Among children the proportion is relatively low when compared to previous studies on paediatric SAB, which have generally found nosocomial infections to account for 30-70% of cases [21, 29, 35-37, 47-49]. This could in part be due to the population-based nature of our study, since it also included cases from smaller hospitals. It is

also possible that the improved infection control measures undertaken after the year 2001 mentioned previously could have contributed to a reduced risk for *S. aureus* transmission.

A restricted definition for community-onset health-care associated SAB was used in adults since complete clinical information could not be collected for all patients. Therefore it is likely that the proportion of health-care associated SAB (15%) is an underestimation. SAB episodes in adult patients receiving ambulatory intravenous treatments or haemodialysis were considered to be health-care associated only if patients were admitted to a hospital in the 90 days prior to the SAB. In children the definition of health-care associated infections was more complete. Considering the retrospective nature of the study it is nevertheless likely that some health-care associated paediatric cases have been unidentified. Our proportion (14%) of children with health-care associated infections might therefore also be an underestimation. Most studies on adult or paediatric SAB have not included health-care associated infections as a specific entity. Rates of 25-60% have, however, been reported in adults [28, 33, 34, 53], including our study for the period 2003-08 where more complete clinical data were collected (finding 27% health-care associated episodes) [53]. Two recent paediatric studies have reported figures similar to our findings in children [21, 54]. Our findings indicate that a significant proportion of community onset SAB in adults and children is health-care associated. Future studies should try to use well defined and consistent criteria when identifying health-care associated infections [160].

4.1.5 Focus in children

In our population-based study we found the most common focus for paediatric SAB to be bone and joint infections (40%), followed by intravascular catheters (30%), and an unknown focus (10%) (Table 5). This is very similar to the proportions reported from New Zealand, but differs from that found in a study from South-Africa [36, 54]. This is also somewhat different than what we found in 279 SAB episodes in Icelandic adults where the most common focus was intravascular catheters (21%), followed by unknown focus (20%), bone and joint infections (18%) and skin infections (15%) [53]. A marked difference was seen in the distribution of SAB foci between different age groups of children (Table 5).

Table 5. Comparison of paediatric *S. aureus* bacteraemia in different age groups

Characteristics	<1 year (n=44)	1-5 years (n=24)	6-17 years (n=78)	Total (n=146)	*p*-value[a]
Male	29 (66)	16 (67)	49 (63)	94 (64)	ns
Mode of acquisition					
Nosocomial	29 (66)	10 (42)	11 (14)	50 (34)	<.001
Health-care associated	11 (25)	5 (21)	5 (6)	21 (14)	.004
Community acquired	4 (9)	9 (38)	62 (79)	75 (51)	<.001
Infection focus					
Bone and joint	2 (5)	5 (21)	52 (67)	59 (40)	<.001
Intravascular catheter	22 (50)	12 (50)	10 (13)	44 (30)	<.001
Skin and skin structure	3 (7)	1 (4)	6 (8)	10 (7)	ns
Respiratory tract	3 (7)	4 (17)	2 (3)	9 (6)	ns
Other [b]	6 (14)	0 (0)	3 (4)	9 (6)	.047
Unknown [c]	8 (18)	2 (8)	5 (6)	15 (10)	.04
Outcome					
Relapse	4 (9)	3 (13)	1 (1)	8 (5)	.03
Mortality, SAB related	1 (2.3)	0 (0)	0 (0)	1 (0.7)	ns
Mortality at 30 days	2 (4.6)	0 (0)	0 (0)	2 (1.4)	ns
Mortality at 365 days [d]	4 (9.5)	1 (4.4)	0 (0)	5 (3.6)	.007

Data are number (%) of episodes.

n: number of episodes, ns: not significant, SAB: *S. aureus* bacteraemia.

a. *p*-values derived by comparing the groups *<1 year* and *6-17 years*.

b. Urinary tract infections (2), Parotitis (2), Endocarditis (1), Deep muscle abscess (1), Intra-abdominal infection (1), Endometritis in mother (1).

c. Five of 15 had an intravascular catheter but no clear evidence of it being the source of bacteraemia (no local signs, symptoms nor positive culture).

d. Excluding six re-infections from the analysis.

4.1.6 Antibiotic resistance

Four (0.6%) cases of bacteraemia caused by MRSA were noted among our adults during 1995-2008. They all survived. This figure is much lower than in most previous studies, but similar to that in the nationwide Finnish and Danish SAB studies [26, 31, 161]. No episode caused by MRSA was identified in children. In other studies the rate has varied from 0 to25% [21, 22, 35, 36, 47-49, 54, 95]. The most likely reason for the low frequency of MRSA is the strict policy against MRSA which has been implemented in hospitals in Iceland and in the other Nordic countries and the Netherlands [162, 163]. Since nosocomial SAB today often is regarded as being caused by MRSA, our results remind us that MSSA still is an important cause of nosocomial and health-care associated SAB.

Eighteen percent of our SAB isolates obtained from adults were sensitive to penicillin, a percentage higher than that usually observed in *S. aureus* isolates [164, 165]. It is nevertheless close to the penicillin susceptibility of MSSA reported elsewhere [32, 117]. The 17% penicillin susceptibility in children is higher than generally observed in paediatric SAB, also among MSSA isolates [36, 49, 54, 95]. Resistance to erythromycin and clindamycin were noted in 4% and 1%, respectively, in adults, and 3% and 2%, respectively, in children. Although an increasing level of resistance against clindamycin and erythromycin was observed in adults (Table I, Paper I), this level is still considerably lower than generally reported [32, 164, 165]. We found no correlation between the antibiotic susceptibility of our isolates and mortality.

4.2 PAPER III AND IV – *S. AUREUS* ENDOCARDITIS

Earlier reports on SAE have rarely included many patients. These two studies from Stockholm describe a large number of individuals diagnosed with SAE during the past decade. Furthermore, since our hospital manages nearly all PWID with IE within a defined geographical area the results provide a fairly accurate overview of SAE in PWID on a population basis.

4.2.1 Patients

During 2004-13 a total of 245 SAE episodes were seen in 222 individuals, 227 (93%) were definite and 18 (7%) possible IE cases. Evidence of active IVDU was noted in 120 (49%) episodes in 101 individuals. An additional 6 episodes were seen in individuals with prior but not currently active IVDU. The valve involvement in our 245 SAE episodes is depicted in Table 6. This table further compares the valve involvement in PWID and non-addicts. Historically, IE associated with IVDU most often has been right-sided. We found that SAE related to IVDU was left-sided in 35%, which is consistent with a few other recent reports [100, 137, 139], but not all [101].

Table 6. Valve characteristics of 245 *S. aureus* endocarditis episodes

Valve characteristics	Total (n=245)	PWID (n=120)	Non-addicts (n=125)	*p*-value
Location				
Left-sided [a]	152 (62)	42 (35)	110 (89)	<.0001
Right-sided	91 (37)	77 (64)	14 (11)	<.0001
Unknown	2 (1)	1 (1)	1 (1)	ns
Valve type [b]				
Native	208 (85)	113 (94)	95 (76)	<.0001
Prosthetic	28 (11)	7 (6)	21 (17)	.007
Number of valves involved [c]				
One valve	193 (79)	86 (77)	107 (86)	.01
Two valves	30 (12)	24 (21)	6 (5)	.0003
Three valves	3 (1)	2 (2)	1 (1)	ns
Valves involved [d]				
Aortic	79 (32)	20 (17)	59 (47)	<.0001
Mitral	87 (36)	31 (26)	56 (45)	.002
Tricuspid	87 (36)	82 (68)	5 (4)	<.0001
Pulmonic	7 (3)	6 (5)	1 (1)	.04
Pacemaker/ICD leads	13 (5)	(0)	13 (10)	.0003
Other	1 (0.4)	0 (0)	1 (1)	ns
Unknown	9 (4)	8 (7)	1 (1)	.02

Data are number (%) of episodes. PWID: people who inject drugs, n: number of cases, ns: not significant, ICD: implantable cardioverter defibrillator.

a. Including 19 cases with bilateral involvement.

b. Thirteen pacemaker/ICD cases not shown. Each episode can involve >1 category.

c. Unknown in 9 episodes, solely pacemaker/ICD leads in 10.

d. Each episode can involve >1 category.

4.2.2 Incidence

4.2.2.1 Incidence rates

We found a SAE incidence of 1.56 /100,000 person-years during 2004-13 in adults in Stockholm County. The incidence of IVDU-related SAE was 0.76 /100,000 person-years. SAE in Stockholm may also be treated in smaller hospitals and occasionally by other medical specialities outside the ID Department at Karolinska University Hospital. It is, however, unlikely that many IVDU-related cases were missed because of this. In addition some IE cases may not have received a correct diagnostic code and might thus have been missed. Hence, the total SAE incidence rate presented is probably lower than the actual incidence. The noted incidence, however, is among the highest reported, since previous population-based studies on IE have generally reported rates of 0.2-1.6 /100,000 person-years [68, 70, 74, 75]. Our incidence of IVDU-related SAE is very high when compared to the aforementioned studies, which generally included few IVDU-related cases (0-7% of IE episodes) [68, 70, 74, 75].

The high SAE incidence found is probably in part due to the mostly urban population in Stockholm, leading to a high number of IVDU-related cases. Other population factors, such as variations in age distribution and co-morbidities, could also lead to differences between studies. As the diagnosis of IE is dependent on echocardiography and blood cultures, the incidence of SAE is related to how frequently these investigations are done. Thus the noted incidence could in part reflect a liberal use of diagnostic procedures and a high awareness among the medical personnel, in part due to the concentration of PWID to our hospital.

4.2.2.2 Changes in incidence over time

The incidence of SAE among adults in Stockholm County increased by 42% between the periods 2004-08 and 2009-13, from 1.28 to 1.82 /100,000 person-years (p=0.007). The incidence of SAE related to IVDU increased by 90% between the same time periods, from 0.52 to 0.99 /100,000 (p=0.0001), and accounted for most of the increase. Figure 4 depicts the incidence of SAE in Stockholm in two-year intervals. Changes in the observed incidence might reflect a change in referral practices. However, such a change is an unlikely explanation. Our hospital has treated the majority of IE patients in Stockholm during the

entire period, and 46% were referred from other hospitals during 2009-13 compared to 51% during 2004-08 (p=0.41). The increased incidence could in part be due to an ageing population with more co-morbidities, and an increasing number of PWID. In Sweden a constant increase in the number of people with heavy narcotic use was seen from 1979 to 2007 on a national level, with a 13% increase being noted between 1998 and 2007 [128]. Although no exact data on the prevalence of IVDU are available specifically for Stockholm County, the number of PWID in Stockholm has most likely also increased. An increasing number of PWID is, however, probably not the only explanation for the increased incidence of SAE related to IVDU. A marked increase in hospitalisations for IE associated to IVDU has also been reported from the United States while the at-risk population did not change [166]. Certain drugs have been claimed to be associated with higher risk to develop IE than others [166-168]. No change, however, was noted in the type of narcotic drugs used during the study period. Injection frequency probably also plays a role, but could not be assessed. Finally, a greater awareness of IE and better or more frequent utilisation of diagnostic procedures could result in an increase in the observed incidence.

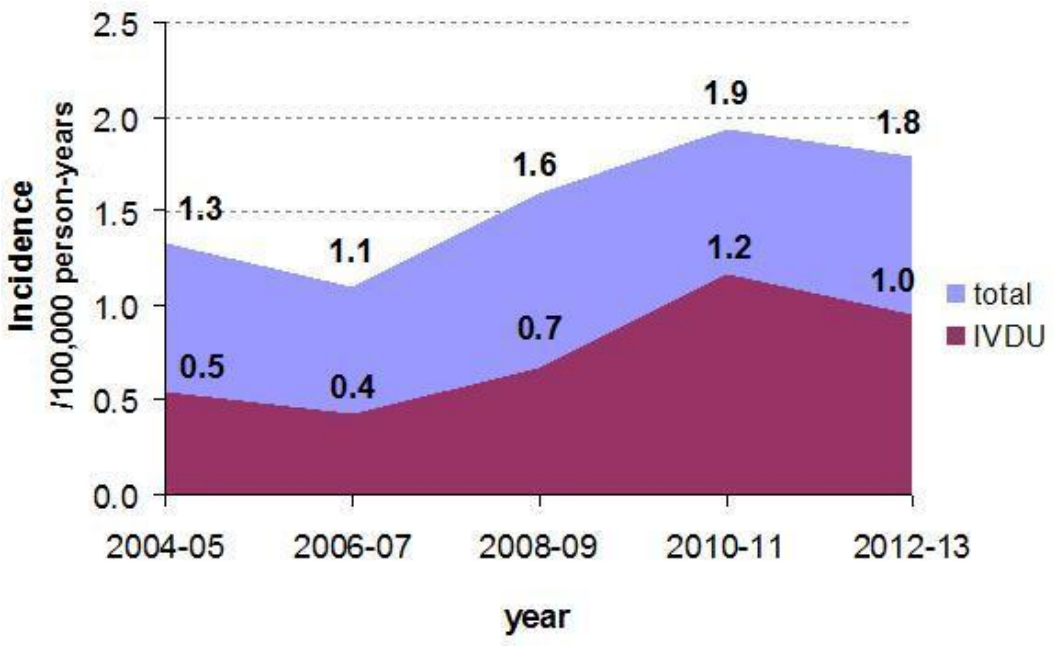

Figure 4. Incidence of *S aureus* endocarditis in Stockholm County by study years, intravenous drug use (IVDU) related (red) and total rate (blue).

4.2.2.3 Incidence in PWID

It is not easy to estimate the incidence of SAE in PWID, since the exact number of drug users in a geographical region is usually unknown. We estimated that the SAE incidence in PWID in Stockholm was 2.5 (range 1.5-6.5) per 1,000 person-years. The range is quite wide due to the uncertainty of the exact number of PWID in the county. Two previous studies have reported a similar incidence of IE among HIV negative PWID, with higher rates in HIV positive PWID [142, 143]. Others have presented somewhat lower estimates [74, 144, 145].

4.2.3 Characteristics

4.2.3.1 Valve location and IVDU

Characteristics of the 245 SAE cases are depicted in Table 7, with comparison between right- and left-sided episodes. Of our 91 cases with a right-sided SAE, 85% were seen in patients with active IVDU, and 12% were related to a pacemaker/ICD. PWID with left-sided SAE were older and more often had predisposing heart diseases than PWID with right-sided disease. Non-addicts with left-sided SAE were in turn generally older and more often had underlying diseases than PWID with left-sided SAE (Table II, Paper IV).

Table 7. Characteristics of *S. aureus* endocarditis by location

Characteristics	Left-sided (n=152)	Right-sided (n=91)	*p*-value	Total (n=245)
Age, median years	60.3	38.0	<.0001	53.4
Male sex	117 (77)	54 (59)	.004	173 (71)
Underlying conditions				
Intravenous drug use	42 (28)	77 (85)	<.0001	120 (49)
Predisposing heart disease [a]	56 (37)	6 (7)	<.0001	62 (25)
Treatment				
In-hospital cardiac surgery	37 (24)	0 (0)	<.0001	37 (15)
Days of IV treatment, median [b]	34	29	.0001	32
Days admitted, median [c]	36	30	.003	33
Outcome				
ICU-admission, non post-op	34 (22)	17 (19)	ns	51 (21)
Relapse of SAB [d]	2 (1)	5 (6)	ns	7 (3)
30-day mortality	13 (9)	2 (2)	.046	15 (6)
In-hospital mortality	20 (13)	2 (2)	.004	22 (9)
1-year mortality [e]	40 (28)	6 (7)	.0001	46 (20)

Data are number (%) of episodes unless otherwise indicated.

n: number of episodes, IV: intravenous, ICU: intensive care unit, ns: not significant, SAB: *S. aureus* bacteraemia.

a. Prosthetic valve, congenital malformations (excluding atrial septal defect), valvular dysfunction, hypertrophic cardiomyopathy.

b. Excluding 27 episodes: 22 deaths or end-of-life decisions while being treated, 5 lacking information.

c. Information missing in 11 transferred cases.

d. Excluding 15 patients who died within 30 days.

e. Excluding 8 cases with a re-infection within one year, 3 with incomplete follow-up.

4.2.3.2 Mode of acquisition

Nosocomial SAE episodes accounted for 9.4% of cases, and an additional 9.4% were related to health-care without being nosocomial. This is considerably lower than the 17-38% nosocomial episodes found in most other studies (Table 3) [67, 100-102, 104-107]. The reason for the low proportion of nosocomial infections is in part due to the high percentage of PWID in our material. We only searched for SAE cases at the ID department and did not include cases treated by other medical specialities, which could also have influenced our findings. MRSA was seen in 6 (2%) SAE episodes, one was nosocomial and five were community acquired. The proportion of MRSA strains has varied greatly (0-40%) in earlier studies from different regions [67, 100-105, 108, 110].

4.2.3.3 Underlying diseases in PWID and drugs used

Amphetamine was by 47% of the PWID reported to be the main injected drug used, followed by heroine by 43%. No correlation was seen between type of drug used and age, sex, valve involvement, surgical treatment or outcome. A HIV infection was seen in 10% of PWID, three individuals had CD4 counts <200 cells/mm^3. Hepatitis C virus (HCV) infection was present in 82% of the PWID, 23% had both HCV and hepatitis B virus (HBV), and 3% HBV only. The proportion of different narcotic drugs injected, the male to female ratio, and the percentage of individuals infected with HCV, HBV and HIV in our study was similar to that reported from the county and noted in the Stockholm needle exchange program [127, 169]. Our patients with SAE related to IVDU thus seem to be representative for PWID generally seen in Stockholm.

4.2.4 Mortality

4.2.4.1 SAE

The 30-day mortality rate was 6.1% and 9.0% died during the acute hospitalisation. This case fatality is one of the lowest ever reported in association with SAE. It is much lower than the in-hospital SAE mortality of 19-46% observed in previous large studies (Table 3) [67, 100-109, 170]. It is even lower than the 15-25% usually reported in association with *S. aureus* bacteraemia in general [26-28, 31-33, 94]. This is interesting since SAE is considered to be one of the most severe complications of SAB. More specifically the fatality was 13% in left-sided SAE and 2% in right-sided SAE (p=0.004). For those who died during the admission, the median time to death was 25.5 days (range 5-61 days) implicating that most patients survived the acute phase, but died from complications later. The 1-year mortality was 19.7%, which is in the same order as that reported from Finland during 1980-2004 [170], but considerably lower than the 35-44% reported by others [103, 107, 108, 110, 171].

4.2.4.2 SAE related to IVDU

In PWID the 30-day and in-hospital mortality was 2.5%, the same for right- and left-sided SAE. This is lower than the 8-12% found in most previous reports [100, 101, 109, 138, 139], but a similar mortality was, however, noted in two older studies [140, 141]. At 1-year the mortality rate in our PWID was 8.0%, 4.1% in right-sided and 15.4% in left-sided SAE. Even if the mortality was low, almost one quarter (23%) needed intensive care treatment. PWID with left-sided SAE had a lower short- and long-term mortality than non-addicts (Table II, Paper IV), but PWID was not independently associated with mortality. The low mortality in PWID compared to that noted in non-addicts, can in part be explained by their lower age, the lower frequency of nosocomial infections, and the lack of major co-morbidities besides the IVDU. It has also been reported that PWID with SAB have a more vigorous antibody response to many *S. aureus* antigens than non-addicts, probably due to previous exposure to the infecting strain, and that this might offer some protection and contribute to the more favourable outcome [172]. Finally, transmission of *S. aureus* strains can occur within drug-use networks [135, 136], and PWID with SAE might thus be colonised and infected with *S. aureus* strains associated with low mortality. A study looking at microbiological factors in SAE among PWID, however, did not find such an association [173].

4.2.4.3 Reasons for the low mortality in Stockholm

The reason for the low case fatality ratio associated with SAE in Stockholm is not clear. A high proportion of episodes related to IVDU probably has contributed. However, the mortality rates in non-addicts and in left-sided SAE were also lower than those generally seen. Referral bias is not likely to have had a major influence on the case fatality rate in our study. The low proportion of nosocomial and health-care associated cases could have contributed to the low mortality, since nosocomial IE by some has been associated with a worse outcome than community acquired [100, 174]. The low rate of MRSA might also have had an effect since MRSA bacteraemia sometimes has been associated with a higher mortality rate than bacteraemia caused by MSSA [63, 99]. A high awareness of IE among the medical doctors in Stockholm could have resulted in that more early and mild cases were diagnosed causing a lower mortality in our series. Also, differences in treatment practices [53, 63] or bacterial and host genetic factors might possibly have contributed [157, 158, 175].

4.2.4.4 Predictors of mortality

Factors independently associated with in-hospital mortality were higher age (OR 1.06 per year) and female sex (OR 3.0) (Table 8). At one year, independent risk factors associated with mortality were higher age (OR 1.04 per year) and left-sided SAE (OR 2.7). Figure 5 shows survival curves after SAE according to age. We have no explanations for the difference in mortality between the sexes, but a similar trend has occasionally been seen before in both SAE and in SAB [27, 29, 33, 63, 105]. It has been speculated whether differences in health-seeking behaviours between the genders and hormonal factors could play a role [29, 33, 63, 105]. Absence of surgical treatment was not associated with short- or long-term mortality. In one study a low frequency of cardiac surgery was independently associated with in-hospital mortality [67], while others have failed to find such an association [100, 103]. No difference was seen over time in the short- or long-term mortality rates.

Table 8. Factors associated with in-hospital mortality in *S. aureus* endocarditis

Variable	Univariate analysis			Multivariate analysis	
	Died (n=22)	**Survived** (n=223)	*p*-value	**Odds ratio** (95% CI) [a]	*p*-value
Age, median years (IQR)	66 (56-85)	51 (35-67)	<.0001	**1.06 (1.02-1.09)** [b]	**.0005**
Female sex	9 (41)	63 (28)	.21	**2.95 (1.06-8.16)**	**.04**
Prosthetic valve IE	5 (23)	23 (10)	.08	2.08 (0.59-6.48)	.24
Right-sided IE [c]	2 (9)	89 (40)	.004	0.37 (0.05-1.60)	.20
In-hospital cardiac surgery	5 (23)	32 (14)	.30	2.34 (0.62-8.12)	.20

Data are number (%) of episodes unless otherwise indicated.
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 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 one year increase in age.
c. Unknown side in two episodes.

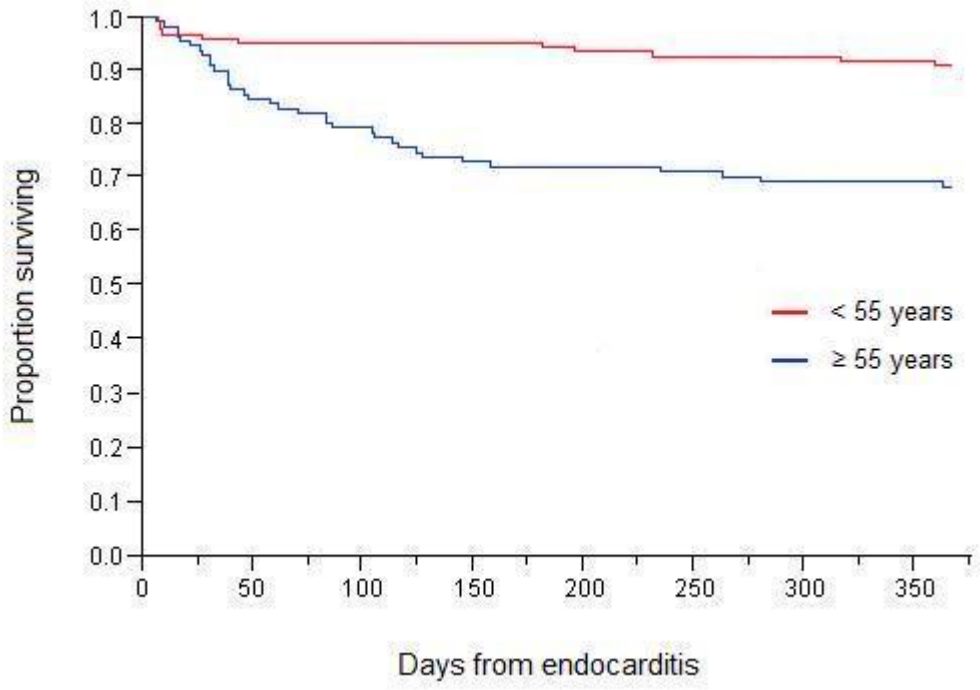

Figure 5. Survival after *S. aureus* endocarditis according to age, < or ≥ 55 years (p<0.0001, log-rank test).

4.2.5 Central nervous system complications

4.2.5.1 Rate of CNS involvement

CNS involvement in association with the SAE was observed in 30 (12%) patients. Of these 6 experienced an intracerebral bleeding and 2 had meningitis. The remainder had cerebral embolisation with neurological symptoms of various degrees. Our rate of CNS involvement is somewhat lower than 15-35% generally reported (Table 3) [67, 100, 101, 103, 105, 108]. We have already speculated that a high awareness of IE and early diagnosis could lead to low mortality. Diagnosis of more early and mild cases would probably also lead to fewer CNS complications being observed.

4.2.5.2 Predictors of CNS involvement

Factors independently associated with having a CNS involvement were lower age (OR 1.04 per year), not being an intravenous-drug-user (OR 3.8), and mitral valve involvement (OR 2.7) (Table 9). Mitral valve involvement has in previous studies on IE been found to be an independent predictor of CNS complications [81, 82]. Lower age has earlier been independently associated with increased risk of CNS events in IE in general, but the cause of this is not well understood [82, 83, 176]. It may, however, be that CNS events are simply under-diagnosed in the older population as a result of more unspecific symptoms and signs [82, 83, 176]. The reason for the independent association noted between IVDU and having a lower risk of CNS complications is unclear. Vegetation size has often been found to be a predictor of cerebral embolism [81-84]. This could, however, not be analysed due to inconsistent registration of vegetation size in our records.

Table 9. Factors associated with central nervous system involvement in left-sided *S. aureus* endocarditis

Variable	Univariate analysis			Multivariate analysis	
	CNS event (n=30)	**No CNS event** (n=122)	*p*-value	**Odds ratio** (95% CI) [a]	*p*-value
Age, median years (IQR)	54 (43-68)	62 (51-75)	.02	**0.96 (0.93-0.99)** [b]	**.007**
Mitral valve IE [c]	21 (70)	66 (54)	.11	**2.66 (1.06-7.28)**	**.04**
Intravenous drug use	9 (30)	33 (27)	.75	**0.26 (0.07-0.86)**	**.03**
Previous IE	8 (27)	16 (13)	.07	3.21 (1.00-10.43)	.05

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 one year increase in age.
c. Each episode may involve >1 valve.

4.2.6 Treatment

4.2.6.1 Cardiac surgery

Cardiac surgery was performed before discharge in 15% of our SAE patients, all had a left-sided SAE (24% operation frequency in left-sided SAE). This is lower than the 20-45% usually reported in association with SAE (Table 3) [67, 100-103, 107, 108], but similar or even lower rates have been reported during the 1980s [104, 105].

Valvular surgery was performed during the hospitalisation in only 8% of PWID (24% of the left-sided, no right-sided), compared to 22% of non-addicts (p=0.004). This is lower than the 35% observed by Fowler et al. but similar to the findings from older studies on PWID mostly from the 1980's [100, 138-140]. Interestingly, the cardiac surgery was performed earlier in PWID than in non-addicts (6 days median time to operation compared to 11 days in non-addicts, p=0.03). This indicates that PWID who were selected for surgery had a more advanced disease than non-addicts.

4.2.6.2 Predictors of cardiac surgery

In left-sided IE lower age, no active IVDU, community onset infection, multi-valvular involvement, and ICU-admission were identified by multivariate logistic regression as independent predictors for cardiac surgery (Table 10). Higher age has earlier been associated with lower operation frequency in association with IE in general [176, 177]. Admission to ICU and multi-valvular involvement are both associated with the severity of IE [178, 179], old age and nosocomial infections are usually correlated with more co-morbidities, IVDU is a risk factor to acquire a new IE, and PWID are often regarded as less compliant to treatments. This might all influence the decision to perform surgery [180-182]. No difference was seen over time in the operation frequency.

Table 10. Factors associated with early cardiac surgery for left-sided *S. aureus* endocarditis

	Univariate analysis			Multivariate analysis	
Variable	**Operated** (n=37)	**Not-operated** (n=115)	*p*-value	**Odds ratio** (95% CI) [a]	*p*-value
Age, median years (IQR)	53 (44-62)	64 (51-78)	.0005	**0.93 (0.89-0.97)** [b]	**.0001**
Nosocomial IE	2 (5)	16 (14)	.16	**0.08 (0.01-0.44)**	**.002**
Multivalvular IE	13 (35)	16 (14)	.004	**6.70 (1.80-30.23)**	**.004**
Intravenous drug use	10 (27)	32 (28)	.92	**0.06 (0.01-0.25)**	**<.0001**
ICU-admission, non post-op	16 (43)	18 (16)	.0005	**3.56 (1.37-9.45)**	**.01**

Data are number (%) of episodes unless otherwise indicated.
n: number of episodes in analysis, CI: confidence interval, IQR: interquartile range, IE: infective endocarditis, ICU: intensive care unit.
a. Odds ratios for the association between selected variables and in-hospital surgery in the multivariate analysis. Variables with odds ratios reported were included in the final multivariate logistic regression model.
b. Odds ratio presented per one year increase in age.

4.2.6.3 Antibiotic treatment

Cloxacillin was the principal treatment in 76% of the cases, followed by cephalosporins (17%) and vancomycin (5%). This reflects the low rate of MRSA isolates. The median duration of intravenous treatment with antibiotics was 32 days. In 40 non-immune-compromised patients with isolated uncomplicated right-sided SAE, without known septic emboli outside the lungs and no other deep focus or other complication, the median intravenous treatment duration was a full 29 days. The ID specialists in our institution thus do not seem to shorten the duration of antibiotic treatment in these cases, despite existing instructions and evidence which recommend this [79, 80, 183].

5 CONCLUSIONS

The incidence of S. aureus bacteraemia and endocarditis

In Iceland the incidence of SAB was similar to that in other regions, while the SAE incidence in Stockholm was high. Furthermore, an increasing incidence of adult SAB was noted during 1995 to 2008 in Iceland, and of SAE during 2004 to 2013 in Stockholm. The increase in both regions was probably related to changes in risk factors both for SAB and SAE, such as an ageing population, more people living with chronic diseases, and a rising number of PWID. It might also be that more frequent utilisation of diagnostic procedures for IE has contributed.

A decrease was, however, observed in the SAB incidence in Icelandic children from 1995 to 2011. The decrease was probably in part due to a lower blood culture frequency attributed to savings inflicted by an international financial crisis starting in 2008, but infection control measures introduced during the period might also have reduced the *S. aureus* transmission rate. The paediatric SAB incidence was considerably lower than in adults, except for in infants and neonates.

The SAE incidence in PWID in Stockholm was 2.5 per 1,000 person-years, which underlines the importance of SAE in this group. Compared to non-addicts, PWID had cardiac valvular surgery less commonly performed and a more favourable outcome.

In adults almost half of SAB cases were nosocomial, and one-third of episodes in children. A decrease in the proportion of nosocomial infections was observed in adult SAB during 1995 to 2008, possibly as a result of improved infection control measures. Health-care associated SAB and SAE were 15% and 9%, respectively. Hence, a significant proportion of community-onset SAB and SAE is health-care associated, a distinct entity which shares more similarities with nosocomial than true community acquired infections. The most common focus of SAB in children was bone and joint infections followed by intravascular catheters, which is somewhat different from that in adults. Very few MRSA isolates were seen in both Iceland and Stockholm, most likely a result of the strict MRSA reduction policies applied in both regions.

The mortality of S. aureus bacteraemia and endocarditis

A reduction was seen in the case fatality ratio associated with SAB in adults in Iceland during 1995 to 2008, to become one of the lowest reported. The case fatality noted in children was also among the lowest reported. The mortality associated with SAE in Stockholm was also very low compared to earlier studies, both in PWID and non-addicts, and CNS complications were less common. Relatively few patients needed valvular surgery for the SAE. The reason for the favourable outcome of SAB and SAE in Iceland and Stockholm, respectively, is not clear. Low rates of antibiotic resistance might have played a role. It could also be related to a high awareness and a more liberal utilisation of diagnostic procedures in these regions, leading to the diagnosis of more early and mild cases. Factors related to population demographics, co-morbidities, the treatment, or possibly unidentified bacterial or host genetic factors might also have contributed.

The 1-year mortality rate in adult SAB and SAE increased with age, and was higher in nosocomial compared to community-onset SAB. The children who died within a year from the SAB all had nosocomial infections and serious underlying co-morbidities. The long-term mortality after SAB and SAE both reflects deaths associated with underlying diseases and from the infections per se.

To conclude we found changing incidence rates over time but a favourable short- and long-term outcome associated with SAB and SAE in Iceland and Stockholm.

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