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ARTICLE

Outcome for invasive *Staphylococcus aureus* infections

G. Jacobsson · E. Gustafsson · R. Andersson

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Abstract We report a survey of invasive *Staphylococcus aureus* (ISA) infections concerning outcome variables such as mortality, recurrence and residual symptoms. A prospective, population-based study of all cases of ISA was conducted in the catchment area of Skaraborg Hospital (population 255,109) in western Sweden during the period from 1st March 2003 to 28th February 2005. One hundred and fifty-seven patients were included. Recurrences were seen in 13 cases (9.3%). Thirty patients (19.1%) died during the first 28 days. Mortality rates for complicated bacteraemia and severe sepsis were 32% and 54%, respectively. Older patients (>65 years of age), patients with concomitant heart disease and patients with endovascular infections all suffered higher mortality. Line-associated infections had a higher recurrence rate. Residual symptoms were common, with 34% of the living patients reporting incomplete recovery. Accessory gene regulator (agr) type within the bacteria did not affect disease presentation. We conclude that ISA infections are of major medical importance, with high rates of mortality (19.1%), recurrence (9.3%) and residual functional impairment (34%).

G. Jacobsson (✉)
Department of Infectious Diseases, Skaraborg Hospital,
541 85 Skövde, Sweden
e-mail: gunnar.jacobsson@vgregion.se

E. Gustafsson
School of Life Sciences, University of Skövde,
541 28 Skövde, Sweden

R. Andersson
Research and Development Centre, Skaraborg Hospital,
541 85 Skövde, Sweden

Introduction

Staphylococcus aureus (SA) is a major cause of serious invasive infections. It is among the most common significant blood culture isolate in hospitalised patients and the second most common community-acquired isolate [1, 2]. The burden of staphylococcal infections on medical services is high, and different specialities face different disease expressions. There is only one population-based study prospectively examining the total spectrum of invasive infections caused by SA [3]. However, this study does not report on recurrence and residual symptoms. Hospital-based studies on bacteraemia covering mostly mortality, and sometimes also recurrence, dominate the literature [4, 5]. Residual symptoms are seldom reported, and long-term outcome is only retrospectively studied [6]. There exists no population-based study on invasive *Staphylococcus aureus* (ISA) infections covering recurrence and residuals symptoms.

Several epidemic and pandemic methicillin-resistant SA (MRSA) clones are spreading both in hospitals and in the community, generating new clinical syndromes [7]. The acquisition of genes mediating antibiotics resistance can further favour epidemic spread by promoting the acquisition of additional virulence factors [8]. Virulence factors are regulated globally by gene regulators, such as the accessory gene regulator (agr) and staphylococcal accessory regulator (sar), and there is an emerging interest to examine these factors in the clinical setting [9]. Some workers speculate whether there is a relationship between agr and the development of further antibiotics resistance, such as glycopeptide resistance [10]. Hitherto, there are few publications on agr and clinical SA disease [11, 12].

We have previously [13] examined the epidemiology and risk factors for ISA infections. The purpose of our present

study was to report on the major outcome variables, such as mortality, recurrence and residual symptoms. We also examined the possible impact of virulence regulator (agr) on disease presentation.

Materials and methods

Patient population and study protocol

As we have described earlier [13], all cases of ISA in the healthcare region of Skaraborg Hospital were prospectively collected from 1st March 2003 to 28th February 2005. Patients with relapses were included several times. The microbiology laboratory notified the study physician in charge, who included the patients fulfilling the inclusion criteria. In the protocol, we registered the patients' medical history, clinical findings and laboratory results at the time of diagnosis. The same procedure was repeated at the end of the antibiotics treatment and one month later.

Definitions

ISA infection was defined by the isolation of SA from an otherwise sterile site, i.e. blood, synovial fluid, cerebrospinal fluid, pleural fluid, bone, or from deep-seated abscesses. Bacteraemia was defined as the presence of at least one positive blood culture for SA. All positive blood cultures were categorised as true or contaminant by evaluating the clinical history, physical findings, clinical course and response to treatment. Community-acquired infections were those associated with the first positive culture within 48 h of admission. Healthcare-related infections were those occurring in patients residing in a nursing home or receiving healthcare at home. If the first positive culture was obtained after more than 48 h after admission, the case was classified as nosocomial. A diagnosis was assigned on the basis of clinical, radiological and microbiological information. We could not ascertain the infection-caused mortality; the mortality numbers indicated present the total mortality.

Recurrence was defined as a new episode of ISA infection occurring more than 4 weeks after the time of the first diagnosis and after the antibiotics therapy was finished.

Adequate empirical antibiotics therapy

Adequate empirical antibiotics therapy was defined in bacteraemia cases as parenteral antibiotics to which the bacterium was susceptible, according to the disk diffusion method (Oxoid). In non-bacteraemia cases, adequate empirical therapy was defined as parenteral or oral antibiotics to which the bacteria was susceptible. Examples of non-adequate antibiotics were ceftazidim, penicillin G, ciprofloxacin and trimethoprim/sulfamethoxazol.

Severe sepsis

We defined severe sepsis according to the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference [14]. All patients with sepsis, fulfilling either hypotension, hypoperfusion or organ dysfunction, were assigned as severe sepsis.

Complicated bacteraemia

Complicated bacteraemia was considered if bacteraemia presented with a secondary focus, such as endocarditis, spondylitis, osteomyelitis, arthritis, deep-seated abscess or pneumonia. Line-associated infections were not registered as complicated bacteraemia, and not either urinary tract infection, soft-tissue infection with no metastatic seeding or bacteraemia without focus.

Typing of agr groups by PCR

To screen the isolates for agr groups I, II, II and IV, the primers of Peacock et al. [15] were used with polymerase chain reaction (PCR). Each strain was analysed using all primer pairs. Sequenced strains, used as positive controls, were included in each run. The final concentration of the PCR mixture was 5 ng DNA template, 1× reaction buffer, 2 mM Cl_2, 100 pmol of forward and reverse primers, 0.2 mM deoxynucleoside triphosphate mix and 2.5 U of Taq polymerase (New England BioLabs). The PCR thermal cycling programme was initial denaturation of 94°C for 5 min, 35 cycles of 94°C for 1 min, 55.8°C for 1 min and 72°C for 1 min, and a final extension of 72°C for 10 min.

Statistics

The data were analysed using SPSS (version 11.5). Differences in proportions were compared using Fisher's exact test, and quantitative variables were analysed with Student's *t*-test. The non-parametric test (Mann-Whitney) was used for variables that were not normally distributed. Confidence intervals for odds ratios (OR) were calculated by the use of logistic regression. Variables found to be significant in a univariate analysis of mortality were included in the multivariable logistic regression analysis. Two variables ("At least one episode earlier and "Age") were included for other reasons than their significant contribution to the prediction of death within 28 days. Two variables ("Bacteraemia" and "Arthritis") found to be significant in the univariate analysis were not included in the multivariable logistic regression analysis because of technical reasons

(no deaths in a category variable). Based on the significant variables in the logistic regression analysis plus the variable "Age," a compound quantitative predictor of the probability of death was constructed and evaluated in a 1−specificity−sensitivity curve (relative operating characteristic [ROC] curve).

Results

We have described the epidemiology and risk factors for ISA in a previous report on the same patient cohort [13]. We included 157 patients, mean age 65 years, ranging from newborn to 97 years of age. Fifty-eight percent were men. Recurrences were seen in 13 cases. Thirty patients (19.1%) died during the first 28 days. During the total follow-up time, 41 patients (26.1%) died. The annual population mortality due to ISA (28-day mortality) is, thus, 5.9/100,000. The median follow-up time was 73 days (range 39–425 days). Patients stayed in hospital for a median of 13 days (range 1–150 days), and were on antibiotics treatment for a median of 25 days (range 0–398 days), of which, 10 days were with parenteral therapy.

Diagnosis, bacteraemia, complicated bacteraemia, severe sepsis, mortality and agr group

Diagnosis, bacteraemia, complicated bacteraemia, severe sepsis, mortality and agr groups of the patient cohort are shown in Table 1. We present the main diagnosis for each episode of ISA, and complicated bacteraemia is considered, which represents bacteraemia with a secondary focus. In 55 (32%) episodes, complicated bacteraemia occurred, which represents 40% of the bacteraemic cases.

Endovascular infections with endocarditis are described as a separate entity. For a thorough definition of each diagnosis, see Jacobsson et al. [13]. The vast majority of the patients had bacteraemia and 30% suffered from severe sepsis. The highest mortality was seen in patients with endocarditis, respiratory infection and bacteraemia without focus. There was no significant difference in agr groups between the different diagnosis groups.

Predictive factors for mortality

The predictive laboratory and physiological parameters for mortality (at 28 days) are presented in Table 2.

Table 1 Diagnosis, bacteraemia, complicated bacteraemia, severe sepsis, mortality and agr group in 170 episodes of invasive *Staphylococcus aureus* (ISA) infection

Diagnosis	Diagnosis, *n* (%)	Bacteraemia, *n* (%)	Complicated bacteraemia, *n* (%)	Severe sepsis, *n* (%)	Mortality at 28 days, *n* (%)	agr group, *n* (%)			
						I	II	III	IV
Soft-tissue infection	32 (19)	29 (91)	8 (25)	8 (25)	5 (16)	12 (38)	8 (25)	9 (28)	3 (9)
Bacteraemia without focus	32 (19)	32 (100)	0 (0)	14 (44)	10 (31)	13 (41)	7 (22)	11 (34)	1 (3)
Arthritis	24 (14)	12 (50)	12 (50)	0	0	6 (25)	5 (21)	10 (42)	3 (12)
Line-associated infection	23 (14)	23 (100)	1 (4)	2 (9)	1 (4)	9 (39)	5 (22)	9 (39)	0
Osteomyelitis other than vertebral	13 (8)	6 (46)	5 (38)	1 (8)	0	5 (38)	(4 (31)	4 (31)	0
Endovascular infection[a]	12 (7)	11 (92)	11 (92)	11 (92)	6 (50)	5 (42)	3 (25)	2 (17)	1
Urinary tract infection	10 (6)	10 (100)	1 (10)	1 (10)	1 (10)	3 (30)	3 (30)	3 (30)	1
Respiratory infection	8 (5)	6 (75)	6 (75)	6 (75)	4 (50)	1 (12)	3 (38)	4 (50)	0
Vertebral osteomyelitis	7 (4)	7 (100)	7 (100)	5 (71)	2 (29)	3 (43)	1 (14)	3 (43)	0
Intraabdominal infection	7 (4)	4 (57)	3 (43)	3 (43)	1 (14)	5 (71)	2 (29)	0	0
Meningitis	1 (1)	0	0	0	0	0	0	1	0
Epidural abscess	1 (1)	1 (100)	1 (100)	0	0	0	1	0	0
Total	170	141 (83)	55 (32)	51 (30)	[b]30 (19.1)	62 (37)	42 (25)	56 (33)	9 (5)

[a] Ten patients with endocarditis, one patient with septic thromboflebitis, one patient with infected femoral arterial graft
[b] Recurrences (n=13) were not included in the analysis

Table 2 Laboratory and physiological predictive factors at presentation for 28-day mortality among patients with ISA infection

Parameter	Median value, non-survivors (range)	Median value, survivors (range)	*P* (Mann-Whitney)
CRP (C-reactive protein) (mg/L)	226 (447)	152 (385)	0.015
SR (sedimentation rate) (mm)	64 (92)	68 (104)	0.407
Albumin (g/L)	27 (28)	29 (25)	0.023
Haemoglobin concentration (g/L)	108 (68)	120 (111)	0.145
Leucocyte count ($\times 10^9$/L)	17.5 (30.8)	14.1 (40.9)	0.080
Trombocyte count ($\times 10^9$/L)	199 (504)	250 (783)	0.117
Creatinin (μmol/L)	142 (895)	91 (722)	<0.001
Blood pressure systolic (mmHg)	110 (117)	132 (130)	0.002
Blood pressure diastolic (mmHg)	70 (58)	73 (90)	0.026

In a univariate analysis, age and heart disease were predictive factors for mortality (Table 3). Other known risk factors for the acquisition of ISA infections, such as diabetes mellitus, haemodialysis and rheumatoid arthritis, were not associated with higher mortality. Community-acquired infections were not associated with a higher mortality than healthcare-associated infections and nosocomial infections. Bacteraemia, complicated bacteraemia and severe sepsis caused a high mortality. Among specific diagnoses, endovascular infection, bacteraemia without focus and respiratory infection were associated with higher mortality. Arthritis patients and patients with osteomyelitis had lower mortality. Among treatment characteristics, patients with adequate empirical antibiotics therapy had suffered a higher mortality than patients not receiving adequate empirical therapy.

A stepwise logistic regression analysis was performed (Table 4). The only significant independent variables were severe sepsis and systolic blood pressure. Based on this analysis, we could present a predictor for a quantitative risk estimation of the mortality. The predictor consists of age, severe sepsis and systolic blood pressure: 0.0491×Age +3.2468×Severe sepsis−0.0264×Systolic blood pressure. The area under the curve of an ROC curve of this predictor is 0.92, which is considered as an outstanding predictor according to Hosmer and Lemeshov [16]. In Fig. 1, we

Table 3 Predictive factors for death (at 28 days) among patients with ISA infection

Factor	Fatality rate		OR (95% CI)	*P*
	With factor (%)	Without factor (%)		
Patient characteristics				
Male sex	19/92 (21)	11/65 (17)	1.28 (0.56–2.91)	0.710
Age >65 years	25/92 (27)	5/65 (8)	4.48 (1.1–12.43)	0.003
Heart vitium	8/15 (54)	21/136 (15)	6.26 (2.05–19.10)	0.004
Coronary disease	12/34 (35)	18/105 (14)	2.64 (1.11–6.28)	0.052
Alcohol abuse	5/11 (46)	25/135 (18)	3.67 (1.04–12.98)	0.098
Infection characteristics				
Community-acquired infection	11/80 (14)	19/77 (25)	0.49 (0.21–1.11)	0.134
Healthcare-associated infection	7/28 (25)	23/129 (18)	1.54 (0.58–4.04)	0.529
Nosocomial infection	12/49 (24)	18/108 (17)	1.62 (0.71–3.70)	0.348
Bacteraemia	30/131 (23)	0/26 (0)		0.005
Severe sepsis	27/50 (54)	3/107 (3)	40.70 (11.37–145.69)	<0.001
Complicated bacteraemia	17/53 (32)	13/104 (12)	3.29 (1.46–7.50)	0.007
Bacteraemia without focus	10/32 (31)	20/125 (16)	2.39 (0.98–5.80)	0.096
Arthritis	0/23 (0)	30/134 (22)		0.010
Endovascular infection	6/11 (54)	24/146 (16)	6.10 (1.72–21.61)	0.014
Osteomyelitis other than spondylitis	0/15 (0)	30/142 (21)		0.070
Respiratory infection	4/9 (44)	26/146 (18)	3.69 (0.93–14.70)	0.143
Treatment characteristics				
Other initial department than infectious disease	25/127 (20)	5/29 (17)	1.18 (0.41–3.39)	>0.900
Adequate empirical antibiotics therapy	28/132 (21)	0/15 (0)		0.070
Antibiotics therapy within 24 h	23/116 (20)	3/18 (17)	1.24 (0.33–4.63)	>0.900

Recurrences were not included in the analysis (i.e. only the last episode was included if a patient had several episodes)

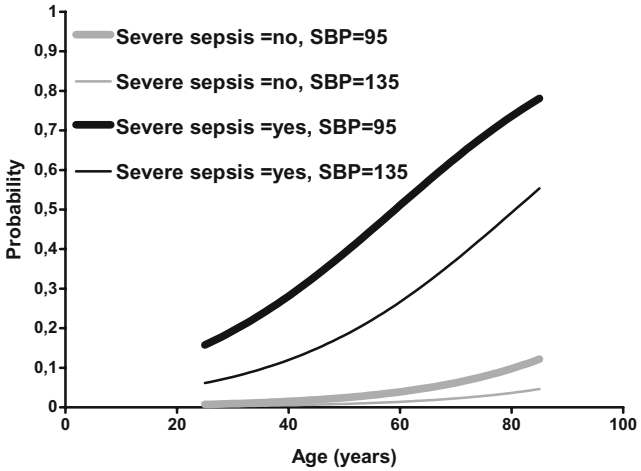

Fig. 1 Probability of death within 28 days. The probability curves were calculated from the multivariable regression model. They show the probability of death within 28 days for four combinations of the variables severe sepsis and systolic blood pressure (SBP) at different ages

show different examples of curves of the probability of death (28 days) as a function of the variables age, severe sepsis and systolic blood pressure.

Recurrences

We observed 13 recurrences in our study cohort (see Table 5). Because of our design, patients included early in the study period had a longer follow-up time for recurrence, therefore, we could have underestimated the true recurrence rate. We could not identify any specific antibiotics treatment associated with recurrence. Line-associated infections were associated with recurrence, although not significantly. Of five infected intravenous lines with recurrence, three were not replaced, one was replaced the same day as the diagnosis of bacteraemia and one was replaced one week after the diagnosis when the patient was still on parenteral antibiotics therapy.

The other specific diagnoses were not associated with recurrence. Three arthritis patients relapsed, two with prosthesis of the hip joint, which was not replaced, and one with arthritis of the hand, which was not surgically drained. Two patients with bacteraemia without focus relapsed, one patient where we could not identify any primary focus and one patient with a massive total body erytrodermia, which persisted, and we could not ascertain a single skin focus but obtained repeatedly positive cultures from various parts of the skin. Among two patients with soft-tissue infection, one was not surgically drained and the same focus persisted. One patient with urinary tract infection relapsed without any obvious eradicable focus. The presence of foreign materials was associated with recurrence, as seen in the patient characteristics.

Residual symptoms

The follow-up time continued 6 months after the end of the study period. One month after the antibiotics therapy ceased, 41 patients had died. Four patients were still on antibiotics therapy. There was a report of residual symptoms in 44 (34%) cases. As opposed to predictive factors for death, severe sepsis was not associated with worse outcome in the surviving patients. To note, non-bacteraemia patients and patients with complicated bacteraemia suffered functional impairment more often. We could also discern specific diagnosis with higher rates of sequels: patients with arthritis and osteomyelitis. Hospital-acquired infections caused significantly less frequent residual symptoms. Concomitant illnesses were not associated with impairment, and high age was associated with the development of sequels. Non-adequate antibiotics therapy did not turn out in a univariate analysis as a cause of impairment, but both the longer duration of symptoms and delays in antibiotics therapy were seen in patients with impairment (Table 6).

Summary of mortality, recurrence and residual symptoms

In Table 7, we relate the infections characteristics to the mortality, recurrence and residual symptoms.

Table 4 Multivariable logistic regression analysis for mortality (at 28 days)

Variable	β	SE	*P*-value	OR	95% CI
Constant	−3.6415	2.3389			
At least one previous episode	−0.4649	1.4225	0.7439	0.63	0.04–10.21
Age	0.0491	0.0262	0.0613	1.05	0.998–1.11
Severe sepsis	3.2468	0.8057	0.0001	25.71	5.30–124.70
Systolic blood pressure	−0.0264	0.0109	0.0160	0.97	0.95–0.995

Two factors are presented for other reasons than being significant. With the variable "At least one episode earlier," we gain better applicability from including all episodes, and the variable "Age" is of fundamental interest. The β coefficient, which we use in the quantitative risk estimation of death, was calculated by using the logistic regression method

Table 5 Recurrences among patients with ISA infection

Factor	Recurrence, *n* (%) or mean±SD		OR or mean difference (95% CI)	*P*
	With factor	Without factor		
Patients characteristics				
Prosthesis of joint	4/13 (31)	8/119 (7)	6.17 (1.55–24.49)	0.037
Renal disease	6/34 (18)	7/106 (7)	3.03 (0.94–9.75)	0.123
Diabetes mellitus	4/38 (11)	9/99 (9)	1.18 (0.34–4.07)	>0.900
Infection characteristics				
Line-associated infection	5/23 (22)	8/117 (7)	3.78 (1.11–12.87)	0.080
Bacteraemia	11/111 (10)	2/29 (7)	1.48 (0.31–7.10)	>0.900
Complicated bacteraemia	2/38 (5)	11/102 (11)	0.46 (0.10–2.18)	0.518
Severe sepsis	1/24 (4)	12/116 (10)	0.38 (0.05–3.04)	0.613
Community-acquired infection	4/73 (5)	9/67 (13)	0.37 (0.11–1.28)	0.183
Healthcare associated infection	4/25 (16)	9/115 (8)	2.24 (0.63–7.97)	0.361
Hospital-acquired infection	5/42 (12)	8/98 (8)	1.52 (0.47–4.95)	0.682
Treatment characteristics				
Antibiotics therapy not within 24 h	2/17 (12)	8/101 (8)	1.55 (0.30–8.01)	0.877
Non-adequate empirical antibiotics therapy	0/15 (0)	13/117 (11)		0.384
Duration of antibiotics therapy (≤14 days)	2/16 (12)	11/113 (10)	1.32 (0.27–6.61)	>0.900

The median time for recurrence was 76 days, with a minimum of 29 days and a maximum of 422 days, and an interquartile range of 42–274 days. The median follow-up time was 347 days; 14 patients had a shorter follow-up time for recurrence than 90 days
In the analysis, we excluded the patients who died within 4 weeks, 30 patients, thus, leaving a remaining 140 eligible patients. We observed 13 recurrences in total, i.e. a recurrence rate of 9.3%

Table 6 Residual symptoms in patients with ISA infection at the follow-up one month after the antibiotics therapy

Factor	Impairment, *n* (%)		OR or mean difference (95% CI)	*P*
	With factor	Without factor		
Patient characteristics				
Men	22/74 (30)	22/52 (42)	0.58 (0.27–1.21)	0.205
Children (≤18 years)	1/12 (8)	43/114 (38)	0.15 (0.02–1.20)	0.072
Heart vitium	3/8 (38)	40/114 (35)	1.11 (0.25–4.89)	>0.900
Coronary disease	11/21 (52)	33/105 (31)	2.40 (0.93–6.21)	0.116
Malignancy	9/22 (41)	34/98 (35)	1.30 (0.51–3.36)	0.752
Diabetes	13/35 (37)	30/89 (34)	1.16 (0.51–2.62)	0.872
Infection characteristics				
Bacteraemia	30/100 (30)	14/26 (54)	0.37 (0.15–0.89)	0.044
Complicated bacteraemia	19/35 (54)	25/91 (27)	3.14 (1.40–7.049	0.010
Severe sepsis or septic chock	9/21 (43)	35/105 (33)	1.50 (0.58–3.90)	0.552
Soft-tissue infection	18/37 (49)	26/89 (29)	2.30 (1.04–5.06)	0.062
Arthritis	15/25 (60)	29/101 (29)	3.72 (1.50–9.24)	0.008
Urinary tract infection	0/8 (0)	44/108 (41)		0.038
Bacteraemia without focus	1/19 (5)	43/107 (40)	0.08 (0.01–0.64)	0.004
Osteomyelitis other than vertebral	9/13 (69)	35/113 (31)	5.01 (1.45–17.39)	0.017
Line-associated infection	4/22 (18)	40/104 (38)	0.36 (0.11–1.13)	0.109
Community-acquired infection	26/67 (39)	18/59 (31)	1.44 (0.69–3.03)	0.431
Healthcare-associated infection	10/21 (48)	34/105 (32)	1.90 (0.73–4.90)	0.278
Hospital-acquired infection	8/38 (21)	36/88 (41)	0.39 (0.16–0.94)	0.048
Treatment characteristics				
Antibiotics within 24 h	27/92 (29)	9/15 (60)	0.28 (0.09–0.85)	0.046
Adequate empirical antibiotics therapy	39/108 (36)	3/13 (23)	1.88 (0.49–7.26)	0.545

In 44 episodes, the patients suffered from residual symptoms: amputation (6), girdlestone operation of the hip (1), reduced function of a limb or a joint (12), reduced ability to walk (2), paraparesis (1), reduced eyesight (1), unhealed fracture (1), heart failure (1), renal failure (1), unhealed wound (2), pain (3), still on antibiotics therapy (4), recurrence (4), sick-listed (5)

Table 7 Infections characteristics of ISA and the risk for mortality, recurrence and residual symptoms

Diagnosis	Mortality	Recurrence	Residual symptoms
Soft-tissue infection	N	N	N
Bacteraemia without focus	N	N	O
Arthritis	O	N	W
Line-associated infection	N	N	N
Osteomyelitis other than vertebral	O	N	W
Endovascular infection	W	N	N
Urinary tract infection	N	N	O
Respiratory infection	N	N	N
Vertebral osteomyelitis	N	N	N
Intraabdominal infection	N	N	N
Bacteraemia	W	N	O
Complicated bacteraemia	W	N	W
Severe sepsis	W	N	N
Community-acquired infection	N	N	N
Healthcare-associated infection	N	N	N
Nosocomial infection	N	N	O

O=better outcome
X=worse outcome
N=neutral outcome

Discussion

This investigation is one of few population-based studies prospectively addressing ISA diseases, and the only study which examines major outcome variables, such as mortality, recurrence and residual symptoms, beyond the hospitalisation time [3, 17]. To include all invasive cases and not just bacteraemia cases is of great advantage. It is a well-known clinical experience that a blood culture could be false-negative, and, for example, one of our patients suffered from both meningitis and endocarditis with negative blood cultures. In our definition of invasive infection, there needed to be a culture from a normally sterile local or a sterile culture taken from a deep-seated infection. For this reason, complicated skin and soft-tissue infection with only wound cultures are excluded in our study. ISA patients are cared for at many different departments, and the willingness and routines to order blood cultures varies among clinicians. Retrospective studies of bacteraemia will fail to detect a substantial number of serious *S. aureus* cases.

Laupland et al. [3] reported an in-hospital mortality of 19% in a population-based study of ISA (annual mortality of 4.9/100,000), which is comparable to our figure of 19.1% (5.9/100,000). In a retrospective study of bacteraemia in an 800-bed primary and tertiary care centre for adult patients [18], the overall hospital mortality was 20%.

Among specific diagnoses, we found the highest mortality in patients with bacteraemia without known source, patients with respiratory infections and patients with endovascular infections, which is in agreement with others [3, 19]. Only 40 of the patients in our study were examined with either transthoracic or transoesophageal echocardiography (34% of the bacteraemia cases), so we could have underestimated the rate of endocarditis. Higher rates of endocarditis than ours (6%) have been reported [20] and echocardiography has been proposed as a standard examination method in the early evaluation of patients with *Staphylococcus aureus* bacteraemia (SAB) [21, 22]. Hence, the routine care of ISA with bacteraemia can be improved, and echocardiography should be part of the standard assessment of patients with ISA infection and bacteraemia.

Patients with bacteraemia, complicated bacteraemia and severe sepsis all suffered higher mortality. Only severe sepsis and systolic blood pressure were independent factors for mortality in the multivariable regression model. This highlights the importance of the initial assessment and care of ISA patients.

Metastatic infections occurred in 39% of the bacteraemia cases (55/141). This is a higher figure than that previously reported. Mitchell and Howden [23] reported estimates of between 14% and 31%, and Khatib et al. [24] noted only 9.4%.

We could not discern any difference in mortality between cases with community-acquired infections, cases with healthcare-associated infections and cases with nosocomial infections. Still, patients with bacteraemia without focus and endovascular infections are often community-acquired, and others [14] report higher mortality figures for patients with community-acquired infections. Age over 65 years and concomitant heart disease are associated with increased mortality, in accordance with other studies [3]. We could not prove any treatment characteristic which affects mortality, apart from the surprising result that patients with adequate empirical antibiotics therapy had higher mortality. However, others [3] have detected the same striking result. An explanation for this may be that patients with poorer prognosis presented with more severe clinical findings and were more likely to be treated empirically with broad-spectrum antibiotics. Fowler et al. [25] reported successful outcomes of 44% and 42% of patients with SAB and endocarditis, respectively, in a clinical trial concerning daptomycin versus vancomycin or antistaphylococcal penicillin together with low-dose gentamicin. We could not evaluate if treatment with a betalactame antibiotic or a glycopeptide antibiotic affects the outcome

because we had too few patients with the latter regime. It is a well-known fact that vancomycin therapy clears bacteraemia less effectively than betalactames [24]. Several workers have documented the beneficial effect of early antibiotics therapy [26, 27]. Lodise et al. [27] demonstrated that delaying therapy for >44.75 h substantially increased the risk of infection-related mortality in patients with hospital-acquired SAB. Others studies [18] have, like us, failed to demonstrate the effect of antibiotics therapy within 24 h on mortality, as we did. Roghmann [28] failed to find a relationship between survival and the administration of effective antibiotics therapy within 48 h after SAB onset.

Some researchers have pointed out the beneficial effect on the mortality of an infectious disease consultant [18, 19]. The practice in our hospital is that every ISA with bacteraemia is reported to an infectious consultant, so we could not examine this hypothesis. Initial care in a department other than the infectious department did not affect mortality. A limitation of our study is the small study size, and, hence, a low power to detect factors associated with mortality. We cannot rule out the importance of factors other than age and heart disease, for example, diabetes mellitus, haemodialysis and rheumatoid arthritis, as contributors to mortality. This is also true for the mode of acquisition of infection and therapy-related factors.

Hogevik et al. [29] found the same virulence factors in isolates from superficial skin infections as in isolates from endocarditis patients with *S. aureus*. Instead, it may be useful to examine virulence gene regulators, both the function and the type. agr is one of the major virulence gene regulators in SA. Since it is believed [30] that the different agr groups interfere with each other, it would be advantageous for therapeutic and prophylactic measures if a certain agr group could be linked to a certain disease entity or to mortality. Sakoulas et al. [10] have demonstrated a connection between agr group II and glycopeptide resistance. It is not custom to type SA isolates according to agr group and there are few studies on agr group and clinical disease. In our study, the frequency of agr groups was not different in different disease entities, as shown in Table 1, and was also not correlated to the mortality. Jarraud et al. [11] found an association between the type of disease and agr group for toxin-mediated diseases and endocarditis. However, the relevant factor was the phylogenetic group to which the agr group belonged, which does not imply a direct role for the agr group in the type of human disease, which is in accordance with our result. Ben Ayed et al. [12] examined MRSA isolates and found a relationship between agr group III and non-invasive infections, and agr group I with invasive infections, especially bacteraemia. Since we only included invasive infections, we could not examine this connection.

We registered 13 recurrences, but we did not have the opportunity to decide if these were relapses or reinfections. According to Chang et al. [5], the majority of recurrences are relapses with the same strain. Four patients with prostheses of a joint (hip) relapsed, but we could only document a prosthesis infection in two of these cases. However, permanent foreign bodies are a known risk factor for recurrence. Patients with line-associated infections have a high relapse rate if the intravenous line is not replaced [5]. In three of five cases with recurrent line-associated infections, the intravenous line was not replaced.

Some researchers report higher relapse rates with shorter antibiotics therapy [31], but others do not [5, 32]. We did not find any differences in relapse rate among patients with shorter antibiotics therapy than 14 days compared to those with therapy exceeding 14 days. There was no difference among bacteraemia cases versus non-bacteraemia cases regarding the relapse rate in our study. There has been no previous study on relapse rates among ISA infections. For example, Laupland et al. [3] did not include relapses in their population-based study of ISA.

Sequelae or functional impairment are not reported in large, both retrospective and prospective, surveys on both SAB and ISA [3, 6]. Davis [33] report a high rate of morbidity and long-term functional impairment for bone and joint infections; 40–50% of patients with septic arthritis have residual joint dysfunction. This burden of post-infectious sequelae occurs in a population already affected by many concomitant diseases, and a population of high age. The interest in the medical community is mostly concentrated on bacteraemia and endocarditis, and, for example, bone and joint infections receive less attention. Davis [33] report on a PubMed search for "*Staphylococcus aureus*" covering the years 2000–2005. He found 28 clinical trials (16 randomised, controlled) relating to bloodstream infections but only 12 (three randomised, controlled) relating to osteomyelitis or septic arthritis.

We documented a high rate of residual symptoms; in 44 episodes of 129 (170 episodes minus the 41 cases in which the patient died), the residual symptoms rate was 34%. This was the short-term follow-up, but many of the sequels were irreversible. Age and infection characteristics affected the risk of recovery, with the older population being at a higher risk.

If the patients survived bacteraemia and severe sepsis, there was little risk of sequelae, unless no secondary focus was present. Patients with complicated bacteraemia had a high rate of residual symptoms. This was also true for patients with bacteraemic soft-tissue infections, patients with arthritis and patients with osteomyelitis. We document the lower rate for residual symptoms for nosocomial infections, and this is in accordance with the observation that both the symptom time before diagnosis and delay in antibiotics therapy affected the risk of incomplete recovery.

As presented in Table 7, common for the control of mortality, recurrence and residual symptoms is the focus for identification and eradication. Others [34, 35] have noted this relation regarding mortality and recurrence. This is the first prospective study on ISA infections to identify risk factors for sequelae.

There are several limitations to our study. We report only methicillin-sensitive *S. aureus* (MSSA) cases, but this may possibly be a strength. MRSA cannot be a confounding factor in our study.

The follow-up time ended one month after the antibiotics treatment finished, so we could not analyse the one-year outcome of the patients. Fätkenheuer et al. [6] reported a crude one-year mortality of 38%, but this was a retrospective study of bacteraemia and no data regarding recurrence or sequel was presented. The follow-up time of recurrences was not uniform, so we could have underestimated the rate of relapses.

The notification of antibiotics treatment was only registered in days, and we could not evaluate the delay of treatment in hours.

In this study, we have presented a thorough account of all clinical aspects of ISA infections concerning mortality (19.1%), recurrence (9.3%) and residual symptoms (34%). We also present new frequency data on agr groups in different clinical presentations of ISA.

There is a need to further characterise the host defence against SA. We intend to examine the antibody production against both the SA and human leukocyte antigen (HLA) haplotypes among our patients.

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