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Survival from methicillin-sensitive *Staphylococcus aureus* bloodstream infections over 20 years: a cohort of 1328 patients

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Summary

PURPOSE: *Staphylococcus aureus* bloodstream infections (SA BSI) are associated with substantial mortality. The rapid emergence of methicillin-resistant *S. aureus* (MRSA), known to be associated with worse outcome, may blur advances made regarding mortality attributed to SA BSI caused by methicillin-sensitive *S. aureus* (MSSA) strains. In the unusual setting of a very low MRSA prevalence institution, we investigated incidence, mortality and trends of BSI caused by MSSA over the last 20 years.

OBJECTIVE: To evaluate and demonstrate trends in incidence and mortality of MSSA BSI as well as risk factors for mortality.

METHODS: Retrospective, observational analysis of the prospective bloodstream infection cohort at the University Hospital Basel between January 1993 and December 2013. All patients with blood cultures positive for MSSA were included. All patients were analysed regarding pertinent demographic, clinical and antimicrobial treatment data. We calculated incidence, temporal trends and mortality of MSSA BSI.

RESULTS: 1328 episodes of MSSA BSI were identified, accounting for a yearly incidence ranging from 2.1 to 4.5 per 10 000 patient-days (p = 0.2 for trend). Overall mortality was 19.3% and did not improve over time. Community-acquired MSSA BSI significantly increased over time, while nosocomial cases decreased (p <0.05).

CONCLUSIONS: Mortality related to MSSA BSI remains high and unchanged over the last 20 years. Despite advances in treatment and supportive care in medicine during the last 20 years survival did not improve and, therefore, new approaches are required to lower mortality in MSSA BSI.

Key words: *bloodstream infections, Staphylococcus aureus, nosocomial infections, outcome, epidemiology*

Author contributions
All authors have contributed significantly to the work. Benedikt Wiggli and Andreas Widmer had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Introduction

More than a century after its discovery, *Staphylococcus aureus* is still one of the most important causes of infections in both inpatient and outpatient settings worldwide [1–4]. The burden of disease, and especially the mortality of *S. aureus* bloodstream infection (SA BSI), remain high despite advances in supportive care and improved treatment options over the recent years [5, 6]. Age, presence of comorbidities, shock and the source of SA BSI are strong predictors of outcome. The impact of other host factors remains largely unclear [5]. Interestingly, even though hospital- and community-acquired cases differ in their characteristics [7–9], evidence does not indicate worse outcomes for either of the two groups [5, 10].

The incidence of SA BSI has been rising during the last decades [2, 11]. This is, at least partly, explained by the emergence of methicillin-resistant *S. aureus* (MRSA) [6, 12]. But the more frequent use of intravascular devices, larger numbers of immunocompromised patients and an increased number of surgical procedures are also responsible for this phenomenon [2, 4, 13]. There is evidence that the epidemiology of methicillin-susceptible *S. aureus* (MSSA) has also changed over recent decades. In particular, there seems to be a steady increase of community-acquired cases of SA BSI in the recent years, similar to that seen in MRSA [1, 6, 8]. MRSA has been thought to be associated with a much higher mortality than MSSA [14, 15]; however, this difference may possibly be biased, as prior studies may not have taken possible confounders into account [16].

Most studies evaluating mortality and risk factors for SA BSI include MSSA and MRSA cases [5]. The high prevalence of MRSA in many countries precludes analyses regarding MSSA BSI.

Our institution reports a very low prevalence of MRSA [17, 18], similarly to acute-care hospitals in Scandinavian countries and the Netherlands. Given this unique setting, we have the opportunity to report from an almost homogenous MSSA cohort. We performed a prospective cohort study to analyse incidence and mortality of MSSA BSI occurring at the University Hospital Basel, Switzerland, over the last 20 years.

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Materials and methods

Setting and study population

The University Hospital Basel is an 855-bed primary- and tertiary-care centre for adult patients, with >34 000 admissions per year, located in the north-western region of Switzerland, a few kilometres from the borders with France and Germany. It follows the "search and destroy" policy for MRSA, and has reported a very low prevalence of MRSA [17].

We established a prospective cohort of SA BSI at the University Hospital Basel. Between January 1993 and December 2013, all consecutive patients with SA BSI were included in the study.

All patients older than 16 years with at least one positive blood culture for *S. aureus* were included. Positive blood cultures with isolation of *S. aureus* within 7 days were defined as one single episode of SA BSI. Patients with MRSA bloodstream infection were excluded.

A detailed description of methodology and data acquisition has been published elsewhere [17, 19, 20]. In brief, microbiology laboratory bloodstream infection reports were the key source of data: a daily report was sent to the Infection Control Department and data about the episodes were registered in a case report form and then transferred to a database (MS Excel). Additional sources of data were medical charts, microbiology reports and pathology reports available in the Patient Management IT program (IsMED) of University Hospital Basel, or original files if needed. Until 1999, when electronic patient records were implemented, paper charts were photocopied and stored.

We carried out an analysis of basic demographics, basic comorbidities and underlying immunocompromising conditions, predictors for severity of disease (time in hospital, intensive care unit [ICU] stay, central line, septic shock, etc.), origin of the SA BSI (nosocomial vs community-acquired), as well as source and mortality. We stratified the cohort into four equal 5-year periods (5 years being a common timeframe for analyses) and compared for trends.

Definitions

MSSA BSI was defined as at least one positive blood culture with *S. aureus* and associated systemic inflammatory response syndrome [21, 22].

Nosocomial SA BSI was defined according to Centers for Disease Control and Prevention (CDC) criteria [23].

Secondary SA BSI was defined as infection originating from an established focus, identified by the treating clinician. Primary BSI was defined as BSI without a documented source of infection [23].

Microbiological diagnosis

Blood cultures were performed by use of the BacT/ALERT blood culture system (bioMérieux, USA). *S. aureus* was identified with standard methods including evaluation of typical growth, Gram staining, catalase production and detection of clumping factor, protein A and capsular antigens (Pastorex Staph-Plus; Bio-Rad, France) [24]. Since 2012, matrix-assisted laser desorption / ionisation-time of flight (MALDI-TOF) mass spectrometry (MALDI Biotyper, Bruker Daltonik, Germany) was used for identification. If results were equivocal, additional analyses were performed, such as aurease (Rapidec Staph, bioMérieux, France) or sequencing of the 16S rRNA gene. Susceptibility testing was done according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) and from June 2011 of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Phenotypic identification of MRSA or suspicious results were confirmed by detection of penicillin-binding protein 2a (MRSA-Screen, Denka Seiken, Japan), followed by PCR for *mecA* and *femA* genes.

Primary and secondary objectives

The objectives of this study were to evaluate and demonstrate trends in incidence and mortality of MSSA BSI over the last 20 years in a setting with low MRSA incidence, as well as to establish risk factors for mortality.

Statistical analysis

The χ^2 or Fisher's exact test were used for analyses of categorical variables and the Kruskal-Wallis test was applied for analyses of continuous variables. Incidence was expressed per 10 000 patient-days and trends during the observation period were analysed using linear regression.

Uni- and multivariate Cox-regression models were performed to identify variables associated with mortality. Two separate models were used in order to avoid confounding by codependent variables. A third multivariate model was created solely to correct for confounders between year groups and mortality.

Kaplan-Meier survival-plots and the log-rank test were used to compare survival distributions between the different time periods. Mortality was expressed as in-hospital, all-cause mortality. A p-value of <0.05 was considered significant for all calculations.

All analyses were performed using SPSS version 22 software (SPSS, IBM, Inc., Chicago, IL).

Results

During the 20-year study period, 540 669 blood samples were cultured. The number of blood cultures drawn increased annually from 17 201 in 1993 to 38 029 in 2013 in absolute numbers and from 865 to 1568 per 10 000 patient-days [17].

In total, we identified 1370 episodes of SA BSI in 1239 patients. MRSA accounted for 34 episodes in 30 patients and were excluded from the analysis.

Baseline characteristics were stratified in four 5-year periods (table 1). Overall, 41% of the cases were nosocomial, with a significant decrease over time. One fifth of the patients was immunocompromised, took intravenous drugs, or had diabetes mellitus.

The main sources for MSSA BSI were, in descending order: catheter-associated infections (20%), primary/unknown (18%) focus, surgical-site infections (12%), endocarditis (11%), and skin and soft-tissue infections (10%). Stratified comparison of infection sources over time showed a steady decline of surgical-site infections and primary infections with unknown source, and a slight decrease of catheter-associated infections, whereas endocarditis remained unchanged. Skin and soft-tissue infections, on the other hand, showed a steady increase over time.

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The overall incidence of MSSA BSI per 10 000 patient-days per year varied between 2.1 and 4.5 and did not change significantly during the observation period (p = 0.2). However, there was a highly significant increase in the incidence of community-acquired MSSA BSI from 0.8 to 2.9 per 10 000 patient-days (p <0.001), with a similarly significant decrease in incidence of nosocomial MSSA BSI (p = 0.005; fig. 1).

All-cause in-hospital mortality was 19%. In the multivariate analysis of demographic factors, we identified age, ICU referral, immunosuppression, alcohol and septic shock at presentation as risk factors for mortality, whereas nosocomial infection and surgery prior to onset of BSI were protective (table 2a). In the multivariate analysis of infection sources, we identified intravascular catheter-associated sources, surgical-site infections, bones and joints, and mainly respiratory focus as risk factors for mortality (Table 2b).

Mortality rates did not change significantly during the observation period, when the 5-year intervals (p = 0.1, fig. 2) were compared, and remained nonsignificant, despite correction for possible confounders in a separate multivariate model.

Figure 1: Incidence of MSSA bloodstream infection per 10 000 patient-days from 1993 to 2013.CA = community acquired; MSSA = methicillin-sensitive *Staphylococcus aureus*; NO = nosocomial

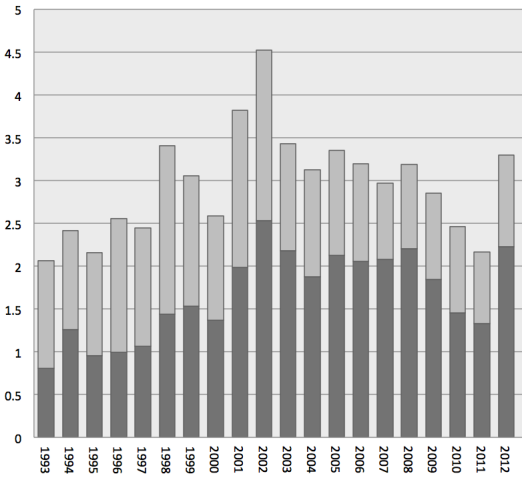

Table 1: Baseline characteristics of 1328 patients with MSSA BSI over 20 years, overall and stratified.

Variable	Overall		1993–1997		1998–2002		2003–2007		2008–2013		p for trend
	n/mean	%/SD/IQR	n/mean	%/SD/IQR	n/mean	%/SD/IQR	n/mean	%/SD/IQR	n/mean	%/SD/IQR	
Mean age at onset (y)	59	SD: 18	59	SD: 18	57	SD: 19	59	SD: 18	62	SD: 18	0.02
Male	869	65%	145	65%	217	67%	234	65%	273	65%	0.9
Median time in hospital (d)	24	IQR: 14–38	28	IQR: 17–46	26	IQR: 13–40	22	IQR: 11–34	22	IQR: 15–36	0.001
ICU stay	394	30%	85	38%	58	18%	134	37%	117	28%	<0.001
Median time in ICU (d)	3	IQR: 2–6	3	IQR: 2–6	3	IQR: 1–9	4	10B: 2–9	2	IQR: 1–4	
Intubation	209	16%	31	14%	40	12%	95	27%	43	10%	<0.001
Nosocomial BSI	545	41%	126	57%	157	49%	128	36%	134	32%	<0.001
Comorbidities											
Diabetes mellitus	278	21%	49	22%	52	16%	82	23%	95	23%	0.1
IVDU	254	19%	20	9%	56	17%	96	27%	82	19%	<0.001
Alcohol	130	10%	40	18%	21	7%	46	13%	23	5%	<0.001
Immunosuppression	272	20%	18	8%	37	11%	44	12%	173	41%	<0.001
HIV	67	5%	16	7%	20	6%	21	6%	10	2%	0.02
Number of patients with:											
Central line	637	48%	76	34%	230	71%	225	63%	106	25%	<0.001
Surgery in past 30 days	332	25%	74	33%	73	23%	92	26%	93	22%	0.03
Median duration of antibiotic therapy (d)	19	IQR: 13–38	19	IQR: 1242	16	IQR: 11–31	19	IQR: 12–34	28	IQR: 1543	<0.001
Median number of pos. blood cultures	4	IQR: 2–5	4	IQR: 2–6	4	IQR: 2–5	4	IQR: 2–6	4	IQR: 2–5	0.1
Focus											
Primary (w/o catheter)	234	18%	53	24%	77	24%	67	19%	37	9%	<0.001
Catheter–associated	268	20%	61	27%	72	22%	71	20%	64	15%	0.002
Surgical-site infection	161	12%	31	14%	68	21%	27	8%	35	8%	<0.001
Endocarditis	150	11%	24	11%	35	11%	47	13%	44	10%	0.6
Skin & soft-tissue	138	10%	NA	NA	20	6%	33	9%	85	20%	<0.001
Respiratory	101	8%	19	9%	23	7%	27	8%	32	8%	0.9
Bones and joints	94	7%	16	7%	11	3%	29	8%	38	9%	0.02
Urogenital	29	2%	6	3%	7	2%	5	1%	11	3%	
Orthopaedic implant	27	2%	NA	NA	4	1%	5	1%	18	4%	
Vascular implant/device	19	1%	NA	NA	1	<1%	6	2%	12	3%	
Other	106	8%	13	6%	6	2%	40	11%	47	11%	
Septic shock	65	5%	14	6%	17	5%	18	5%	18	4%	0.7
In-hospital mortality	258	19%	45	20%	62	19%	63	18%	88	21%	0.5

BSI = bloodstream infection; CI = confidence interval; IQR = interquartile range; ICU = intensive care unit; IVDU = intravenous drug use; HIV = human immunodeficiency virus; SD = standard deviation

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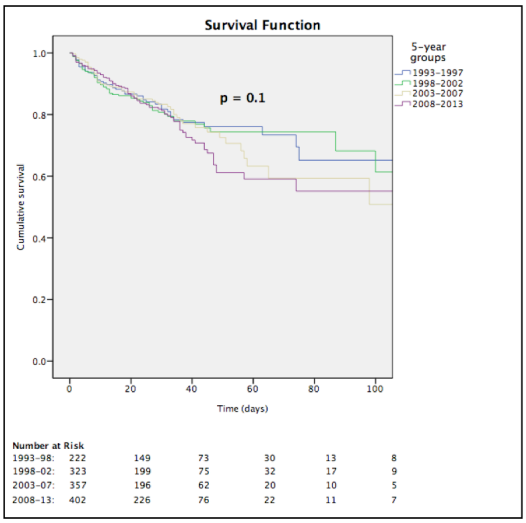
Discussion

In this large observational study, mortality related to MSSA BSI remained high and unchanged over the last 20 years. Improvements of medical care during the last two decades did not result in lower mortality and, therefore, new approaches are required to lower mortality in MSSA BSI. The incidence of community-acquired cases increased significantly.

In our cohort, we observed a mean total incidence of three MSSA BSIs per 10 000 patient-days, with no significant change over the study period. This is in contrast to a report of the European Antimicrobial Resistance Surveillance Network examining BSIs in 22 European countries, which showed a highly significant increase in the incidence of SA BSI [11]. It has to be noted that this latter report involved many countries where MRSA is endemic, which most likely explains the increasing incidence, as a growing body of evidence points to MRSA adding to the burden of disease of MSSA, rather than replacing it [12]. Another large multinational study showed no increase in overall incidence of BSI [1], supporting our results in a low MRSA incidence setting.

Figure 2: Five-year stratification of all-cause in-hospital mortality.



Our finding of a significant increase in community-acquired MSSA BSI is mirrored by several other studies [1, 25–27]. The reasons for this epidemiological shift remain elusive. The increasing availability of outpatient treatment options and virulence factors associated with community-acquired strains may be possible explanations [28]. The formation of the Infection Control Department at our institution in 1993, with the resulting implementation and improvement of several infection control measures over the last two decades [17, 26] may possibly explain the concomitant decrease in nosocomial MSSA BSIs observed over the study period.

Overall, all-cause mortality was 19% in our cohort. This is in line with previous publications [5]. We identified age, ICU referral, immunosuppression, alcohol consumption, septic shock at presentation, catheters as underlying source, and skin and soft-tissue, bone and joint, and respiratory tract foci as risk factors for mortality. Most of these predictors of mortality are confirmed by other studies [5].

Table 2: a: Uni- and multivariate analysis of demographic factors for mortality.

Variables		Survivors		Nonsurvivors		Univariate			Multivariate		
		n	%/SD	n	%/SD	HR	95% CI	p-value	HR	95% CI	p-value
Mean age (y)		58	SD 19	66	SD 16	1	1.01–1.03	<0.001	1.	1.02–1.04	<3.001
Nosocomial		440	42%	103	40%	0.7	0.5–0.9	0.004	0.7	0.5–0.9	0.005
ICU referral		291	28%	103	40%	1.	1.1–1.8	0.005	2	1.5–2.6	<0.001
Surgery in past 30 days		289	28%	43	17%	0.5	0.4–0.7	<0.001	0.4	0.3–0.6	<0.001
Comorbidities	IVDU	220	21%	28	11%	0.6	0.4–0.9	0.01	1.	0.7–1.9	0.7
	Diabetes	204	19%	69	27%	1.	1.0–1.7	0.05			
	Immunosuppression	190	18%	81	31%	2.	1.3–2.2	<0.001	2.	1.1–1.9	0.006
	HIV	59	6%	8	3%	0.7	0.3–1.3	0.26			
	Alcohol	94	9%	35	14%	2.	1.1–2.2	0.02	2.	1.03–2.2	0.03
Septic shock		31	3%	36	14%	4.	2.7–5.5	<0.001	3.	1.9–3.9	<0.001

CI = confidence interval; ICU = intensive care unit; IVDU = Intravenous drug use; HIV = human immunodeficiency virus; HR = hazard ratio; SD = standard deviation Significance level p <0.05

Table 2b: Uni- and multivariate analysis of infection foci for mortality.

Variables	Survivors		Nonsurvivors		Univariate			Multivariate		
	n	%/SD	n	%/SD	HR	95% CI	p-value	HR	95% CI	p-value
Focus primary (w/o catheter)	165	16%	56	22%	2.	1.2–2.1	0.002	1.	1.01–1.9	0.05
Catheter-associated	232	22%	36	14%	0.6	0.4–0.9	0.004	0.6	0.4–0.9	0.02
Surgical site infection	143	14%	18	7%	0.5	0.3–0.8	0.002	0.5	0.3–0.8	0.004
Endocarditis	115	11%	32	12%	0.9	0.6–1.3	0.6			
Skin & soft-tissue	112	11%	24	9%	1	0.6–1.5	0.9			
Respiratory	60	6%	41	16%	3.	2.1–4.1	<0.001	3.	1.7–3.6	<0.001
Bones & joints	83	8%	11	4%	0.5	0.3–0.9	0.02	0.5	0.3–0.9	0.03
Urogenital	23	2%	6	2%	1.	0.6–2.8	0.6			
Orthopaedic implant	25	2%	1	0.4%	0.2	0.03–1.4	0.1			
Vascular implant/device	14	1%	5	2%	1.	0.4–2.6	0.9			
Other	78	7%	28	11%	NA	NA	NA			

CI = confidence interval; HR = hazard ratio; SD = standard deviation Significance level p <0.05

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Strikingly, mortality did not improve over the last two decades of our study period, despite important advances being made in medical care during the same time. Several other studies have come to similar conclusions [27, 29, 30]. Since the pre-antibiotic era, mortality for BSI has improved dramatically, but for the last couple of decades this trend has come to a standstill.

The changing demographics of an ageing population with a larger number of comorbid conditions in combination with established risk factors could counterbalance the critical advances in medical care. However, after correcting for such confounders by multivariable analyses, mortality remained unchanged over time. Therefore, novel approaches for the management of SA BSI are needed. Several comprehensive reviews report on the lack of good quality evidence required for guidance of BSI management and point to several key questions, such as the role of echocardiography, duration of antibiotic therapy, or administration of combination therapy, that remain unanswered to date [21, 27].

Our study has several limitations. This is an observational study from a single centre, possibly limiting generalisability. However, the infectious diseases consultations (IDC) service did not change over time, the immediate reporting of the laboratory essentially remained the same as was the antimicrobial regimen with flucloxacillin. Reporting of positive blood cultures is changing from individual phone calls to automatic electronic reports, but not all hospitals can rely on such infrastructure. In addition, an observational study – in particular over a long-time period – cannot exclude confounding variables that we did not detect and control for. The laboratory methods essentially remained the same. The laboratory techniques did change from the US standards to the European standards, but these changes did not influence the results: the sensitivity to detect MRSA has increased by switching from oxacillin to cefoxitin. However, very few cases would have been missed with the low prevalence of MRSA at this institution.

As Laupland et al. have pointed out, it is important to establish the incidence of infectious diseases in order to define the respective burden. It is, however, equally important to exercise care in generalising results about the epidemiology of a selected population or single region, since there are a number of factors influencing the incidence of SA BSI in a given population [1]. As a result of the lack of follow-up data after discharge, we only were able to analyse in-hospital mortality and did not consider long-term outcomes. Further, we analysed only all-cause mortality, which may overestimate attributable mortality.

In summary, mortality related to MSSA BSI remained high and unchanged over the last 20 years. The incidence of community-acquired cases increased significantly. Improvements of medical care during the last 20 years did not result in lower mortality calling for reassessment of current treatment strategies to reduce mortality of MSSA BSI. As for the moment, rapid appropriate antibiotic treatment may be the most effective measure to improve survival, being standard of care for nowadays treatment of sepsis [31].

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Competing interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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