



# Outcome of methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia: impact of diabetes

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Received: 2 May 2019 / Accepted: 23 July 2019 / Published online: 5 August 2019  
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## Abstract

The aim of this study was to describe the epidemiology of methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia in a diabetic and a non-diabetic population of the University Hospital of Charleroi and to analyze medical outcomes, including risk of metastatic infection and mortality. Descriptive and multivariable analyses were performed using MedCalc 18.9 (MedCalc Software bvba, Ostend, Belgium). A total of 248 patients with MSSA bacteremia were identified between 1st January 2012 and 28th June 2017 out of which 32.7% were diabetic. Within the diabetic patients, we observed more prolonged hospital duration of stay ( $p=0.034$ ), more secondary bacteremia of cutaneous sources (including cellulitis, diabetic foot and ulcer) ( $p=0.037$ ), and more metastatic infection ( $p=0.002$ ). The overall 30-day mortality was 24.2% with no difference between the two groups. With a logistic regression analysis, it was demonstrated that age  $\geq 60$  years (odds ratio (OR), 2.20 (95% CI, 1.03–4.67)) and Charlson Comorbidity Index (CCI)  $\geq 3$  (OR, 2.95 (95% CI, 1.51–5.79)) were the only independent risk factors of mortality, while removal of the primary site of infection was a protective factor (OR, 0.27 (95% CI, 0.12–0.62)). Risk of developing metastatic infection was increased with diabetes (OR, 2.08 (95% CI, 1.12–3.90)), while early empirical antibiotic therapy (OR, 0.38 (95% CI, 0.20–0.71)) decreased this risk. Diabetes was not associated with increased 30-day mortality after MSSA bacteremia. However, diabetes increased significantly the risk of metastatic infection. An aggressive treatment of MSSA bacteremia seems crucial to improve the outcome of diabetic patients.

**Keywords** Methicillin-sensitive *Staphylococcus aureus* bacteremia · Diabetes mellitus · Mortality

## Introduction

*Staphylococcus aureus* is a major cause of bacteremia, with a 30-day mortality of 20 to 40% [1–4]. Five percent of the Belgian population suffer from diabetes, which can increase susceptibility to *Staphylococcus aureus* bacteremia because of coexisting comorbidities and complications, tissue hyperglycemia, and decreased oxygenation, which generally lead to reduced immunity [5, 6].

Data regarding the prognostic factors of MSSA (methicillin-sensitive *Staphylococcus aureus*) bacteremia are

conflicting, and to our knowledge, only few studies have investigated the impact of diabetes as a primary objective. Therefore, we conducted a retrospective observational study to describe the epidemiology of MSSA bacteremia in both diabetic and non-diabetic patients, and we investigated the impact of diabetes on the outcome and mortality of MSSA bacteremia.

## Materials and methods

### Study population

The study included all patients hospitalized between 1st January 2012 and 28th June 2017 in the University Hospital of Charleroi (Belgium) with a first episode of bacteremia with methicillin-sensitive *Staphylococcus aureus*. This multisite hospital has 1321 beds, including 44 ICU beds, with approximately 125 000 admissions per year. We limited inclusions to

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patients aged  $\geq 15$  years, hospitalized with complete medical records available, and who received a treatment.

Patients were identified in the database of microbiology laboratory with Infectio.Global® 3.0.1 (partner4lab, Nancy, France) and bacteremia characteristics were retrospectively collected.

## Definitions

We defined an episode of MSSA bacteremia as a bacteremia in a patient who has had at least one MSSA-positive blood culture. Bacteremia was considered as community-acquired (CA) if it occurred  $\leq 2$  days after admission and as nosocomial thereafter [7].

Patients with community-acquired MSSA bacteremia and healthcare contact within 30 days of the current admission were sub-classified as healthcare-associated MSSA bacteremia (e.g., hospitalization, surgery, dialysis).

Source of bacteremia was determined according to the definitions of the National Surveillance Program for Hospital Infection (NSIH) [8]. Secondary bacteremia was sub-classified as cutaneous, postoperative wound, pulmonary, urinary, or joint-related. In our study, we defined diabetes as the presence of antidiabetic drugs on admission (oral antidiabetics and/or subcutaneous insulin), or new-onset diabetes defined according to usual biological criteria. The level of glycemic control was ascertained using the most recent glycated hemoglobin A1c (HbA1c) measurement within 1 year of the current hospitalization [1].

We used the Charlson Comorbidity Index (CCI) to identify the severity of previous comorbidity, which is a validated comorbidity scoring system [1, 9, 10]. We removed the diabetes from the CCI and designated the index as a modified CCI (m-CCI), according to Smit [1]. Level of comorbidity was defined as “high” if m-CCI was  $\geq 3$  [1].

We defined severe presentation as ICU admission, high APACHE II score, and/or lactatemia  $\geq 2$  mmol/L. Early empirical treatment was defined as an antibiotic therapy started before the result of the blood cultures, whether adapted to the antibiotic susceptibility test or not. Final treatment was considered as adequate when the antibiotic treatment included at least 14 days of intravenous treatment and was appropriate for the antibiotic susceptibility test.

Success was defined as negative blood culture and/or no sign of infection within 7 days of initiation of antibiotic therapy.

Bacteremia was considered as persistent when blood cultures remain positive after 48 h of appropriate antibiotic therapy.

We assessed all-cause 30-day mortality, intra-hospital mortality and bacteremia-related mortality.

## Statistical analyses

Continuous variables were described using mean  $\pm$  SD or median (interquartile range (IQR)) as appropriate. Discrete variables were reported using absolute values and percentages. Comparisons between two independent groups were performed using Student's *t* tests (or Welch's test for unequal variances) or the Mann-Whitney *U* tests as appropriate. Comparisons between proportions were assessed using chi-squared tests or exact Fisher's tests as appropriate. Binary logistical regression analysis was performed to assess the relationship between binary outcomes and exposure variables using a stepwise approach. A *p* value  $< 0.05$  was considered as statistically significant. All calculations were performed with IBM® SPSS® Statistics 22.0 and MedCalc® 18.6 (MedCalc Software bvba, Ostend, Belgium).

## Results

Demographic data and characteristics of MSSA bacteremia are summarized and compared between diabetic and non-diabetic patients in Table 1. From 2012 to 2017, after withdrawal of multiple episodes and relapses, we identified 248 patients with first episode of MSSA bacteremia, of whom 81 (32.7%) had diabetes. Median HbA1c level was 7.1% (54 mmol/mol) (IQR, 6.5–7.9).

12.5% of patients were sent to the hospital after being examined by a general practitioner and 16.5% by a hospital clinician and 46% were admitted by the emergency department (25% was unknown—data not shown). We identified 70% of secondary bacteremia, whereas 50% of them were from soft-tissue infections such as cellulitis, diabetic foot, or ulcer.

Management and outcomes of MSSA bacteremia are represented in Table 2. Eradicable foci were removed in a majority of diabetic patients, by catheter removal or by surgery. Amputation was performed in more diabetic than non-diabetic patients (27.3% vs 3.7%; *p* = 0.008). We observed no difference between the 2 groups of patients in other type of surgeries (e.g., debridement, cardiac surgery, device removal) (data not shown).

The 30-day mortality is 24.2% with no statically significant difference between the two groups.

Table 3 shows the multivariate analysis of 30-day mortality. An age  $\geq 60$  years and a m-CCI  $\geq 3$  increase the 30-day mortality risk. Neither diabetes nor HbA1c levels significantly influence 30-day mortality. The analysis was also conducted for attributable mortality and hospital mortality, showing identical results (data not shown). Table 4 presents the results of the multivariate analysis of factors influencing the risk of metastatic infection. Unlike mortality, age does not influence the risk of metastatic infection. Diabetes doubles the risk of metastatic infection (OR, 2.08 (1.12–3.90)); thus, the HbA1c level does not increase it.

**Table 1** Demographic data and characteristics of MSSA bacteremia

	Total <i>n</i> = 248 <i>n</i> (%)	Patients with diabetes <i>n</i> = 87 <i>n</i> (%)	Patients without diabetes <i>n</i> = 161 <i>n</i> (%)	<i>p</i> value
Age (median)	67 (57–79)	69 (59–79)	66 (54–79)	NS
≥ 60 years	170 (68.5)	65 (74.7)	105 (65.2)	NS
Male sex	158 (63.7)	60 (69)	98 (60.9)	NS
Length of hospitalization, median (IQR) (days)	22 (13–39)	26 (15–41)	21 (10–36)	NS
Length of hospitalization ≥ 15 days	176 (71)	69 (79.3)	107 (66.5)	0.034
Comorbid conditions				
Diabetes mellitus	87 (32.7)	87 (32.7)	NA	
With Insulin		52 (59.8)		
With oral antidiabetic drug		35 (40.2)		
De novo		3 (3.4)		
Ischemic heart disease	76 (30.6)	39 (44.8)	37 (23)	0.0004
High blood pressure	133 (53.6)	55 (63.2)	78 (48.4)	0.026
Vascular peripheral disease	34 (13.7)	24 (27.6)	10 (6.2)	< 0.0001
COPD	49 (19.8)	17 (19.5)	32 (19.9)	NS
Renal insufficiency	62 (25)	34 (39.1)	28 (17.4)	0.0002
Dialysis ( <i>n</i> = 62)	30 (12.1)	16 (18.4)	14 (8.7)	0.026
IV drug	11 (4.4)	0 (0)	11 (6.8)	0.009
Cirrhosis	27 (10.9)	8 (9.2)	19 (11.8)	NS
m-CCI, median (IQR)	1.5 (0–4)	3 (1–5)	1 (0–3)	< 0.0001
m-CCI median ≥ 3	122 (49.2)	63 (72.4)	59 (36.6)	< 0.0001
Community acquired	170 (68.5)	63 (72.4)	107 (66.5)	NS
Including healthcare associated	58 (23.4)	20 (23)	38 (23.6)	NS
Nosocomial acquired	78 (31.5)	24 (27.6)	54 (33.5)	NS
ICU admission	88 (35.5)	30 (34.5)	58 (36)	NS
APACHE II Score <sup>1</sup> , median, (IQR)	19 (15–24)	19 (15–23)	19 (14–24)	NS
Lactate ≥ 2 mmol/L	46 (79)	18 (66.7)	28 (54.9)	NS
Primary bacteremia	74 (29.8)	26 (29.9)	48 (29.8)	NS
Primary	36 (48.6)	11 (42.3)	25 (52.1)	NS
Catheter associated	38 (51.4)	15 (57.7)	23 (47.9)	NS
Secondary bacteremia	174 (70.2)	61 (70.1)	113 (70.2)	NS
Multiple sources	4 (2.3)	2 (3.3)	2 (1.8)	NS
Soft-tissue	87 (50)	38 (62.3)	49 (43.4)	0.037
Postoperative wound	21 (12.1)	3 (4.9)	18 (15.9)	0.034
Pulmonary	42 (24.1)	9 (14.7)	33 (29.2)	NS
Urinary	11 (6.3)	4 (6.6)	7 (6.2)	NS
Osteoarticular	9 (5.2)	5 (8.2)	4 (3.5)	NS

Statistically significant at the level alpha 0.05

NS, not significant; IQR, interquartile range; NA, not applicable; COPD, chronic obstructive pulmonary disease; IV, intravenous; m-CCI, modified Charlson's Comorbidity Index; APACHE II, Acute and Physiology Chronic Health Care Evaluation II

<sup>1</sup> Calculated on 86 (34.7%) patients

## Discussion

Our study including 248 episodes of MSSA bacteremia was conducted in the town of Charleroi, one of the most deprived strata of the region of Hainaut (Belgium) [11]. The rate of unemployment in the Hainaut in general (15.6%) and particularly

in the area of the hospital (20.3%) is above the national mean (9.3%) and the mean annual income is also lower in the Hainaut (26 530€) than in Belgium in general (31 655€) [11]. This socio-economic situation (which is known to impact patient's infection risk [12]) could explain that our patients are younger than patients included in other similar studies [7, 13–15] and that we

**Table 2** Management and outcomes of MSSA bacteremia

	Total <i>n</i> = 248 (%)	Patients with diabetes <i>n</i> = 87 (%)	Patients without diabetes <i>n</i> = 161 (%)	<i>p</i> value
Empirical therapy started	152 (61.3)	56 (64.4)	96 (59.6)	NS
Adequate treatment <sup>1</sup>	124 (56.1)	46 (63)	78 (52.7)	NS
Removal of eradicable foci	80 (32.3)	35 (40.2)	45 (28)	0.049
Catheter removal	31 (38.7)	15 (42.9)	18 (40)	NS
Surgery	49 (61.3)	22 (62.8)	27 (16.8)	NS
Amputation <sup>2</sup>	7 (14.3)	6 (27.3)	1 (3.7)	0.008
Surgical debridement <sup>2</sup>	42 (85.7)	16 (72.7)	26 (96.3)	NS
Success	124 (50)	37 (42.5)	87 (54)	NS
Persistent infection	30 (12.1)	11 (12.6)	19 (11.8)	NS
Metastatic infection	64 (25.8)	30 (34.5)	34 (21.1)	0.002
Endocarditis	14 (21.9)	3 (10)	11 (32.4)	NS
Spondylodiscitis	18 (28.1)	9 (30)	9 (26.5)	NS
Thrombophlebitis	5 (7.8)	0 (0)	5 (14.7)	NS
Osteoarticular infections	30 (46.9)	17 (56.7)	13 (38.2)	0.008
30-day mortality	60 (24.2)	18 (20.7)	42 (26.1)	NS

Statistically significant at the level alpha 0.05

NS, not significant

<sup>1</sup> Data on 221 patients

<sup>2</sup> Percentages calculated on the whole samples of diabetic and non-diabetic patients

have 32.7% of diabetic patients, about 10% more than the fraction reported in other studies (23 to 30%) [7–10].

The polypathological profile of patients with diabetes could explain the proportion of long hospital stays for these patients and the fact that around 30% of episodes are nosocomial [7, 8, 13, 16, 17].

In our study, nosocomial acquired infection has no influence on 30-day mortality. Kaeck et al. showed that the nosocomial bacteremia is associated independently with a better prognosis (OR 0.4 (0.2–0.7)), and that the main reason for the better outcome is the earlier detection of bacteremia in hospital than in the community [3].

We observe 70% of secondary bacteremia and more than 30% of cutaneous source of infection, which is higher than other results found in literature (respectively 26 to 50–60% and 9.3 to 20%) [8, 14–16, 18–21]. Patients could have poorly treated cutaneous infections sources, in a context of precarious hygiene, and could have only come to hospital when the symptomatology was severe.

Interestingly, patients with diabetes did not have significantly higher ICU admission rates, APACHE II Score, or lactatemia, a marker of septic shock. These data show that diabetic patients do not have a more severe clinical presentation of MSSA bacteremia.

The rate of metastatic infection is significantly higher in our diabetic population, as reported by Kanafani et al. [9]. Diabetes promotes infection and therefore metastatic spread by altering immune defenses in hyperglycemic environment

and by breaking the skin barrier, via diabetic foot ulcers and vascular disorder [1, 19]. Osteoarticular complications are well described in diabetic patients, with a 4-fold higher risk of osteomyelitis than in the non-diabetic patients [21].

We only found one study about the prognostic factors of metastatic infection, and it contradicts our findings. According to Fowler et al., neither diabetes nor empirical antibiotic therapy influences the risk of complications [17]. Our data suggests that early empirical antibiotic therapy protects from developing metastatic infection.

Removal of the original source of infection reduces the risk of death to 30 days. In our study, aggressive surgical treatment (such as amputation or surgical debridement of all devitalized tissues) is crucial in decreasing mortality.

Thirty-day mortality is 24.2% and attributable mortality 17.7%; these data are consistent with those found in literature [3, 15, 16]. However, compared with a Belgian study of 2007 and with Fowler et al., we observe a much lower attributable mortality (respectively 17.7% vs 32% and 17.7% vs 28%) [13, 17]. This difference in our study could be explained by the initial presentation of our patients directly in a hospital center (46% of patients arrived from the emergency department and 16.5% from a specialist consult) and not from general practitioner (which represents 12.5% of patients in our cohort), but also by the inclusion of MRSA bacteremia in the 2 other studies. In our study, age  $\geq$  60 years doubles the risk of 30-day mortality, which is well described in the literature [2, 10, 20].

**Table 3** Logistic regression of 30-day mortality explained by different variables ( $n = 60$ )

Variables	<i>p</i>	OR (CI)	<i>n</i> (%)
Age $\geq 60$ years	0.04	2.20 (1.03–4.67)	49 (81.7)
Diabetes	NS	0.52 (0.25–1.06)	18 (30)
m-CCI $\geq 3$	0.002	2.95 (1.51–5.79)	40 (66.7)
Removal of eradicable foci	0.002	0.27 (0.12–0.62)	8 (13.3)

Statistically significant at the level alpha 0.05

OR, odds ratio; CI, confidence interval; NS, not significant

Mortality is not higher in diabetic patients [15, 16, 18]. Unlike our finding, other studies show a significant difference in mortality in diabetic patients, including Kanafani et al. (22.1% vs 11.4%) [9, 20]. Moreover, diabetes is not an independent prognostic factor for mortality in the general population [2, 22]. But Mylotte et al. describe a 2.5 times greater risk of death at 30 days in diabetic patients (OR 2.4 (1.2–4.7)) [20], which is confirmed by Hansen et al. in 2017 (OR 1.61 (1.00–2.57)) [4].

In our study, the absence of correlation between diabetes and mortality may come from the fact that the patients, often for financial reasons, diabetic or not, attend hospital emergency departments from the outset, resulting in rapid intravenous antibiotic therapy. Moreover, in this impoverished population, diabetic patients are more medicalized than non-diabetic patients (e.g., free consultations organized for the diabetic patients by the Belgian health insurance system), which is proven by the relatively low level of HbA1c in our diabetics patients.

Our study might have some limitations. We have not identified all the characteristics of diabetes, such as the duration of disease, the differentiation between type 1 and type 2, and the associated complications. However, Smit et al. showed in 2016 that none of these characteristics influence the prognosis of MSSA bacteremia [15].

We focused on the clinical aspect of MSSA bacteremia and did not collect microbiological data regarding MSSA such as the detailed antibiotic susceptibility test or the presence of

**Table 4** Logistic regression of metastatic infection explained by different variables ( $n = 64$ )

Variables	<i>p</i>	OR (CI)	<i>n</i> (%)
Removal of eradicable foci	0.003	2.68 (1.41–5.08)	
Diabetes	0.023	2.08 (1.12–3.90)	30 (46.9)
Empiric antibiotic	0.003	0.38 (0.20–0.71)	
Primary source (including catheter)	0.03	0.44 (0.21–0.92)	14 (21.9)

Statistically significant at the level alpha 0.05

OR, odds ratio; CI, confidence interval

some virulence factors. The retrospective and monocentric characteristics of our study are also a weakness, but it is a long-term study (over 5 years) including a large number of episodes of MSSA bacteremia.

## Conclusion

Our study of 258 episodes of *Staphylococcus aureus* methicillin-sensitive bacteremia at the University Hospital of Charleroi (Belgium) demonstrated that diabetic patients had statistically more cutaneous secondary bacteremia and a more frequent prolonged ( $\geq 15$  days) hospital stay and developed more metastatic infection than non-diabetic patients, although those diabetic patients did not have more severe clinical presentations upon admission.

Diabetes did not appear to be an independent predictor of mortality; however, this could be explained by the free access to the hospital emergency department and with the free consultations provided to the diabetic patients by the Belgian healthcare insurance system, which enabled rapid diagnosis of infection and provided intravenous antibiotic therapy. Our study also highlighted that 30-day mortality risk factors are age  $\geq 60$  years and presence of comorbidities, shown by a m-CCI  $\geq 3$ . In contrast, removal of the original source of infection reduced the risk of mortality. MSSA bacteremia was associated with an increased risk of metastatic infection in patients with diabetes.

Finally, our study showed that early initiation of empirical antibiotic therapy and eradication of the site of infection seemed capital to reduce mortality and metastatic infection complications.

## Compliance with ethical standards

**Conflict of interest** The authors declare that there is no conflict of interest.

**Ethical approval** The study was approved by the ethic committee of the University Hospital of Charleroi on 27th September 2017 (CCB: B325201733405).

**Informed consent** There was no informed consent because the author conducted a retrospective study with de-identified data.

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