Diabetes and risk of community-acquired *Staphylococcus aureus* bacteremia: a population-based case–control study

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Abstract

Objective: Patients with diabetes may experience higher risk of *Staphylococcus aureus* bacteremia (SAB) than patients without diabetes due to decreased immunity or coexisting morbidities. We investigated the risk of community-acquired (CA) SAB in persons with and without diabetes.

Design: Using population-based medical databases, we conducted a case–control study of all adults with first-time CA-SAB and matched population controls in Northern Denmark, 2000–2011.

Methods: Based on conditional logistic regression, we computed odds ratios (ORs) of CA-SAB according to diabetes. We further assessed whether the risk of CA-SAB differed according to various diabetes-related characteristics (e.g. duration of diabetes, glycemic control, and presence of diabetes complications).

Results: We identified 2638 patients with incident CA-SAB, of whom 713 (27.0%) had diabetes, and 26 379 matched population controls (2495 or 9.5% with diabetes). Individuals with diabetes had a substantially increased risk of CA-SAB compared with population controls (adjusted OR=2.8 (95% confidence interval (CI): 2.5–3.1)). Duration of diabetes of ≥10 years and poor glycemic control conferred higher risk estimates, with an adjusted OR=2.3 (95% CI: 1.9–2.7) for diabetes with HbA1c < 7% (< 53 mmol/mol) and an adjusted OR=5.7 (95% CI: 4.2–7.7) for diabetes with HbA1c ≥ 9% (≥ 75 mmol/mol). The risk of CA-SAB was particularly high in patient with diabetes complications: adjusted OR=5.5 (95% CI: 4.2–7.2) with presence of microvascular complications and OR=7.0 (95% CI: 5.4–9.0) with combined macro- and microvascular complications.

Conclusions: Diabetes is associated with a substantially increased risk of CA-SAB, particularly in patients with diabetes of long duration, poor glycemic control, and diabetes complications.

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Introduction

Staphylococcus aureus remains a leading cause of bacteremia associated with a 30-day mortality of 20–40% (1, 2). Diabetes is an increasingly common disease with detrimental effects on almost all organ systems and patients' quality of life (3, 4). Patients with diabetes may have increased susceptibility to *S. aureus* bacteremia (SAB) for a number of reasons including tissue hyperglycemia and decreased oxygenation, and generally reduced immunity (5, 6). High age, coexisting morbidities and diabetes complications may further increase the risk of SAB (6).

In previous studies of SAB, diabetes has been noted as an underlying disease in 20–32% of patients (7, 8, 9, 10). Nevertheless, few clinical data exist concerning the association between diabetes and SAB, and to our knowledge, no prior study has investigated diabetes as a risk factor for SAB as the main exposure. In previous studies, patients with diabetes have been identified using non-validated methods, and diabetes has been treated as one entity disregarding the duration of disease, quality of glycemic control, and presence of diabetes complications

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(11, 12, 13, 14). In addition, the majority of former studies has been based on small and selected study populations ($n < 250$) (11, 13, 14).

Detailed information on the association between diabetes and SAB may extend our understanding of risk factors for SAB and help to optimize preventive measures for the growing group of persons with diabetes. Therefore, we conducted a population-based case-control study to investigate whether diabetes is associated with an increased risk of community-acquired SAB (CA-SAB). In addition, we ascertained the risk of CA-SAB according to various characteristics of patients with diabetes (*e.g.* diabetes type, duration of diabetes, and presence of diabetes complications), and we explored whether the risk of CA-SAB differed according to sex, age, and level of comorbidity.

Methods

Setting

This case-control study was conducted in Northern Denmark (catchment population ~1.8 million inhabitants) between January 1 2000 and December 31 2011 using population-based medical databases with routinely recorded data. Denmark has a tax-supported healthcare system providing free and unrestricted access to medical care for the entire Danish population. All Danish citizens are assigned a unique identification number (the civil registration number) upon birth or immigration, which allows unambiguous electronic linkage across the data sources (15, 16).

Patients with *S. aureus* bacteremia

Patients hospitalized with CA-SAB were identified in the databases of four regional departments of clinical microbiology from 1995 onwards (information on blood culture practice and susceptibility testing is provided in the [Supplementary Material 1](#), see section on [supplementary data](#) given at the end of this article). We restricted inclusion to patients ≥ 15 years with presence of ≥ 1 positive blood cultures with *S. aureus* as the sole isolate. Compared to the general population, patients with previous SAB are at increased risk of reinfection with SAB (17). Therefore, we only included patients with incident SAB, defined as no prior SAB diagnosis within at least 5 years of the current admission.

CA-SAB was defined as SAB in patients, in whom one or more positive blood cultures had been obtained within the first 2 days of admission. If the positive blood culture

had been obtained >2 days after admission, the infection was considered to be hospital-acquired, and the patient was excluded. The subset of CA-SAB patients with recent contacts to healthcare before the current admission was further classified as healthcare-associated SAB (HCA-SAB) if one or more of the following criteria were fulfilled: ≥ 1 hospital admission, ≥ 1 contacts to hospital outpatient surgical clinics, ≥ 1 contacts to clinics of hematology, oncology or nephrology, all within a 30-day window of the current admission.

Information on recent healthcare contacts was provided by the Danish National Patient Registry (DNPR) (18). The DNPR has tracked all admissions to Danish hospitals since 1977 and all visits to hospital outpatient clinics since 1995. Each record includes the dates of hospital admission and discharge, up to 20 discharge diagnoses, and information on surgical procedures.

Selection of population controls

The Danish Civil Registration System (DCRS), which is updated daily, keeps records on sex, age, residence, marital status, and vital status for all Danish residents (15, 16). We used this registry to randomly select 10 population controls for each SAB case on the date the first positive blood culture was drawn, matching by age, sex, and residence. Each control was assigned an index date identical to the SAB admission date for the matched case. We utilized the risk set sampling technique (19), *i.e.* eligible population controls had to be alive and at risk of a first hospitalization with SAB on the date the corresponding case was admitted.

Patients with diabetes

For both cases and controls, we identified patients with diabetes using a previously validated algorithm (20) that incorporates three databases: the DNPR, the LABKA Database (21), and The Aarhus University Prescription Database (AUPD) (22). Patients with a discharge or outpatient diagnosis of diabetes registered at any time before the index date were identified in the DNPR. The LABKA database (CSC Scandihealth, Denmark) holds laboratory test results from patients in Northern Denmark for the entire study period, including the exact time of blood sample collection (21). Using this database, we identified patients with a glycosylated hemoglobin A1c (HbA1c) level of 6.5% (48 mmol/mol) or more measured at any time predating the index date. The AUPD contains

information on all filled prescriptions in the study area in accordance with the anatomical therapeutic classification (ATC) (22). This database permitted identification of patients with at least one recorded prescription for any antidiabetic drug at any time before the index date (diagnostic, laboratory, and ATC codes are provided in the [Supplementary Material 2](#)). Patients with diabetes diagnosed before age 30 years, using insulin monotherapy, and with no history of oral anti diabetes medication were classified as type 1 diabetes. The remaining patients with diabetes were classified as type 2 diabetes.

Characteristics of patients with diabetes

We computed the duration of diabetes as the time elapsed between the first record of diabetes in any of the three registers and the date the first positive blood culture was sampled. To assess the level of preadmission glycemic control, we obtained data on all HbA1c measurements within 12 months of the index date. One or more HbA1c measurements were available for 515 (72%) of the 713 cases with CA-SAB, and 1819 (73%) of the 2495 controls with diabetes. The most recent HbA1c measurement before the index date was used in our analyses. Based on in- or outpatient contacts registered in the DNPR, we obtained data on the presence of macrovascular-, and microvascular complications, including in the latter indication of diabetes-associated renal disease in previous laboratory tests (defined by two separate dates with urinary albumin tests above the cut-off for microalbuminuria). Using the DNPR, we also identified patients with diabetes with conditions related to diabetic foot ulcers (i.e. neuropathy and/or peripheral atherosclerosis or vascular disease) and diabetes patients with previous lower-extremity ulcer diagnoses or ulcer-related procedures, as described previously (23). Preadmission renal function was ascertained using the most recent creatinine measurement from a general practitioner or an outpatient hospital clinic 1 year to 7 days before the index date (available for 78% of patients). We computed estimated glomerular filtration rates (eGFR) applying the four-variable version of the Modification of Diet in Renal Disease equation (24) (equation provided in the [Supplementary Material 2](#)).

Demographics, comorbidity, and medication

Using the DNPR (18), we retrieved all diagnoses recorded up to 10 years before the index date to identify previous morbidity included in the Charlson Comorbidity Index (CCI). The CCI is a validated scoring system for ascertaining

patients' comorbid conditions in epidemiological studies and covers both the number and severity of 19 major disease categories (25, 26). Because diabetes constituted the exposure variable of interest, we removed this condition from the CCI and designated the index as a modified CCI (m-CCI). We classified patients as having a low (score = 0), an intermediate (score = 1–2), or a high comorbidity level (score > 2). Data on a number of comorbid conditions not included in the CCI, including hypertension, dialysis (within 30 days of the index date), osteoporosis, and conditions related to alcohol and drug abuse were also collated. Using the AUPD, we retrieved information on prescriptions filled before the index date: Any previous use of antihypertensive treatment, statins, anticoagulants, and use of immunosuppressive or antibiotic drugs within 30 days of the index date (laboratory, diagnostic, and ATC codes are provided in the [Supplementary Material 2](#)).

Statistical analysis

Characteristics of patients with and without diabetes were described in a contingency table. We used conditional logistic regression to compute crude and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) as a measure of relative risks of SAB among patients with and without diabetes. Diabetes exposure was further categorized by diabetes type, duration of diabetes (< 3, ≥ 3 – < 6, ≥ 6 – < 10, ≥ 10 years), level of glycemic control (HbA1c < 7% (< 53 mmol/mol), ≥ 7 – < 8% (≥ 53 – < 64 mmol/mol), ≥ 8 – < 9% (≥ 64 – < 75 mmol/mol), ≥ 9% (≥ 75 mmol/mol), unknown), diabetes complications (absent, microvascular, macrovascular, combined micro- and macrovascular, conditions related to diabetic foot ulcers, and previous lower-extremity ulcer diagnosis), and renal function before admission (eGFR (mL/min/1.73 m²) > 90, 60–90, < 60, unknown). We adjusted for m-CCI score, alcohol-related conditions, marital status, any statin used predating the index date, and use of antibiotics within 30 days of the index date. To examine whether the risk of SAB differed among subsets of diabetes patients, we performed conventional logistic regression with additional adjustment for the matching factors and stratified the results by sex, age group (15–39, 40–59, 60–79, 80+ years), and m-CCI level (0, 1–2, > 2). We conducted all analyses using Stata 11.2 for Windows (Statacorp). According to Danish legislation, individual informed consent is not required for registry-based studies. The project was approved by the Danish Data Protection Agency (ref. no. 2012-41-0942).

Results

Descriptive data

During 2000–2011, we identified 2638 patients with incident CA-SAB and 26 379 population controls. The subset of all CA-SAB patients with recent preadmission contacts to the healthcare system (HCA-SAB) constituted 42%. MRSA was rarely observed (0.5%). Characteristics of cases and controls are given in Table 1. The median age of cases and controls was 69 years (interquartile range (IQR), 56–79), and 61% were males. CA-SAB patients were much more likely than population controls to have a history of hospital-diagnosed comorbidity, in particular congestive heart failure (13% vs 4%), peripheral vascular disease (12% vs 3%), cancer (20% vs 7%), and renal disease (17% vs 1%). Cases were also more likely to have filled prescriptions for antibiotics, angiotensin-converting-enzyme inhibitors, beta blockers, and acetylsalicylic acid.

Risk of *S. aureus* bacteremia

A total of 713 (27.0%) CA-SAB patients had diabetes, compared with 2495 (9.5%) among population controls (Table 2). The unadjusted OR for incident CA-SAB in patients with diabetes compared with persons without diabetes was 3.7 (95% CI: 3.4–4.1), and the adjusted OR was 2.8 (2.5–3.1) (Table 2). The adjusted OR for CA-SAB was 7.2 (95% CI: 3.9–13.0) in patients with type 1 diabetes compared with 2.7 (95% CI: 2.4–3.0) in patients with type 2 diabetes.

Compared with individuals without diabetes and persons with shorter duration of diabetes, patients with ≥ 10 years of diabetes history experienced markedly increased the risk of CA-SAB (adjusted OR=3.8 (95% CI: 3.2–4.6)). The risk of CA-SAB rose gradually with successive increases in HbA1c levels. Compared with individuals without diabetes, the adjusted OR was 2.3 (95% CI: 1.9–2.7) for patients with diabetes and an HbA1c level $< 7\%$ (< 53 mmol/mol), 3.2 (95% CI: 2.3–4.5) for patients with diabetes and HbA1c level ≥ 8 to $< 9\%$ (≥ 64 to < 75 mmol/mol), and 5.7 (95% CI: 4.2–7.7) for patients with diabetes and an HbA1c level $\geq 9\%$ (≥ 75 mmol/mol). Diabetes complications influenced the risk of CA-SAB, as compared with persons without diabetes. Thus, the adjusted OR was 2.3 (95% CI: 2.0–2.7) in patients with diabetes and no complications, 5.5 (95% CI: 4.2–7.2) in patients with microvascular complications, 2.7 (95% CI: 2.2–3.3) in patients with macrovascular complications, and 7.0 (95% CI: 5.4–9.0) in persons

with combined macro- and micro-vascular complications. Increased risk of CA-SAB was also evident among patients with diabetes and conditions related to diabetes foot ulcers (adjusted OR=4.9 (95% CI: 3.7–6.6)), and patients with diabetes and a previous lower-extremity ulcer or ulcer-related procedure (adjusted OR=6.9 (95% CI: 5.4–8.8)). Decreased renal function also influenced the risk of CA-SAB with an adjusted OR of 4.2 (95% CI: 3.5–5.1) in patients with diabetes and an eGFR < 60 mL/min/1.73 m² compared with persons without diabetes.

Table 3 presents ORs according to diabetes stratified by age, sex, and comorbidity level. Female patients with diabetes appeared to experience a slightly increased risk of CA-SAB compared with males (adjusted ORs 3.2 (95% CI: 2.6–3.8) and 2.5 (95% CI: 2.2–2.9) respectively). The relative risk of CA-SAB decreased with advancing age and increasing level of comorbidity (Table 3).

Discussion

In this large population-based case–control study, diabetes was strongly associated with an increased risk of CA-SAB. Compared with patients without diabetes, the excess risk of CA-SAB was most pronounced among patients with type 1 diabetes, patients with ≥ 10 years of diabetes history, patients with poor glycemic control, and patients with diabetes complications, in particular microvascular disease. In addition, the relative impact of diabetes was most pronounced in younger patients and in patients without coexisting morbidities.

Our results extend the limited existing knowledge on the risk of CA-SAB in patients with diabetes (11, 12, 13, 14). In an Italian case–control study of 165 patients with SAB, Bassetti *et al.* (11) observed an OR of 6.21 (1.62–23.77) from diabetes in multivariate analysis. In a Canadian surveillance cohort study (12) including 1508 SAB patients, the authors reported a substantial risk of SAB associated with diabetes (relative risk (RR)=10.6 (95% CI: 9.3–11.9)). In two prior studies (13, 14), the investigators assessed diabetes as a risk factor for invasive *S. aureus* infections, defined as the isolation of *S. aureus* from blood, cerebrospinal fluid, pleural or synovial fluid, or aseptically obtained deep-tissue aspirates or surgical-tissue samples. In a Swedish cohort study of 168 patients, Jacobsson *et al.* (14) observed a RR of 8.2 (95% CI: 6–12) for invasive *S. aureus* infections in patients with diabetes as compared with patients without. This was supported by results from a Canadian study cohort (13) ($n=264$), where

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Table 1 Characteristics of cases with incident, community-acquired *Staphylococcus aureus* bacteremia and population controls, Northern Denmark, 2000–2011.

	Cases	Controls
Numbers (%)	2638 (9.1%)	26 379 (90.9)
Diabetes		
Absent	1925 (73.0)	23 884 (90.5)
Present	713 (27.0)	2495 (9.5)
Age, median (IQR)	69.0 (56.2–79.3)	69.0 (56.3–79.3)
≥15–39 years	233 (8.9)	2340 (8.9)
40–59 years	605 (22.9)	6009 (22.8)
60–79 years	1182 (44.8)	11 838 (44.9)
≥80 years	618 (23.4)	6192 (23.5)
Sex		
Men	1616 (61.3)	16 159 (61.3)
Women	1022 (38.7)	10 220 (38.7)
Marital status		
Married	1270 (48.1)	15 059 (57.1)
Divorced or widowed	886 (33.6)	7742 (29.4)
Never married	482 (18.3)	3578 (13.56)
Selected comorbid conditions		
Former myocardial infarction	220 (8.3)	1037 (3.93)
Congestive heart failure	348 (13.2)	960 (3.6)
Peripheral vascular disease	328 (12.4)	889 (3.4)
Chronic pulmonary disease	363 (13.8)	1491 (5.7)
Moderate to severe renal disease	436 (16.5)	290 (1.1)
Any solid cancer	515 (19.5)	1778 (6.7)
Hypertension	651 (24.7)	3016 (11.4)
Dialysis within 30 days of the index date	251 (9.5)	21 (0.1)
Conditions related to alcohol abuse	235 (8.9)	398 (1.5)
Conditions related to drug abuse	73 (2.8)	49 (0.2)
Modified Charlson Comorbidity Index score		
Low (0)	810 (30.7)	19 035 (72.2)
Intermediate (1–2)	1012 (38.4)	6067 (23.0)
High (>2)	816 (30.9)	1277 (4.8)
Medication use before the index date		
Immunosuppressive therapy ^a	28 (1.1)	54 (0.2)
Systemic antibiotic therapy ^a	536 (20.3)	1252 (4.8)
ACE inhibitors ^b	1086 (41.2)	6768 (25.7)
Beta blockers ^b	1035 (39.2)	6470 (24.5)
Acetylsalicylic acid ^b	1121 (42.5)	7771 (29.5)
Statins ^b	625 (23.7)	4633 (17.6)
Renal function before admission ^c		
eGFR >90 mL/min/1.73 m ²	369 (14.0)	2115 (8.0)
eGFR 60–90 mL/min/1.73 m ²	605 (22.9)	6312 (23.9)
eGFR < 60 mL/min/1.73 m ²	802 (30.4)	3328 (12.6)
eGFR ^b missing	862 (32.7)	14 624 (55.4)

Patients with type 1 diabetes = 5.9%.

^aAny use within 30 days of the index date; ^bAny previous use before the index date; ^cMeasured within 1 year to 7 days before the index date. IQR, interquartile range; MRSA, methicillin resistant *Staphylococcus aureus*.

ACE inhibitors, angiotensin-converting-enzyme inhibitors; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein.

the investigators observed a considerable risk of invasive *S. aureus* infections in patients with diabetes (RR=7.0 (95% CI: 5.0–9.7)).

Nevertheless, some limitations should be taken into account in the interpretation of these previous results: Small and selected study populations (11, 13, 14), limited numbers of patients with diabetes (11, 13, 14),

incomparability of characteristics of cases and controls (11), or insufficient adjustment for concurrent comorbid conditions (12) could partly explain the observations. Furthermore, in contrast to our study, none of the previous studies assessed whether the risk of SAB differed according to characteristics of patients with diabetes or according to age, sex, and comorbidity level.

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Table 2 Crude and adjusted odds ratios (ORs) for community-acquired *Staphylococcus aureus* bacteremia associated with diabetes. Data are presented as *n* (%).

Exposure	Cases	Population controls	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)
Diabetes				
Absent	1925 (73.0)	23 884 (90.5)	1.0 (ref.)	1.0 (ref.)
Present	713 (27.0)	2495 (9.5)	3.7 (3.4–4.1)	2.8 (2.5–3.1)
Diabetes type				
Diabetes absent	1925 (73.0)	23 884 (90.5)	1.0 (ref.)	1.0 (ref.)
Type 1	40 (1.5)	29 (0.1)	16.5 (10.0–27.1)	7.2 (3.9–13.0)
Type 2	673 (25.5)	2466 (9.4)	3.6 (3.2–3.9)	2.7 (2.4–3.0)
Duration of diabetes				
Diabetes absent	1925 (73.0)	23 884	1.0 (ref.)	1.0 (ref.)
<3 years	176 (6.7)	766 (2.9)	3.0 (2.5–3.6)	2.5 (2.0–3.0)
≥3 to <6 years	144 (5.5)	596 (2.3)	3.1 (2.6–3.8)	2.6 (2.1–3.2)
≥6 to 10 years	123 (4.7)	532 (2.0)	3.1 (2.5–3.8)	2.1 (1.7–2.7)
≥10 years	270 (10.2)	601 (2.3)	5.9 (5.0–6.9)	3.8 (3.2–4.6)
HbA1c				
Diabetes absent	1925 (73.0)	23 884 (90.5)	1.0 (ref.)	1.0 (ref.)
<7% (<53 mmol/mol)	245 (9.3)	1029 (3.9)	3.1 (2.7–3.7)	2.3 (1.9–2.7)
≥7 to <8% (≥53 to <64 mmol/mol)	100 (3.8)	454 (1.7)	2.9 (2.3–3.6)	2.2 (1.7–2.9)
≥8 to <9% (≥64 to <75 mmol/mol)	69 (2.6)	169 (0.6)	5.2 (3.9–6.9)	3.2 (2.3–4.5)
≥9% (≥75 mmol/mol)	101 (3.8)	167 (0.6)	7.8 (6.0–10.0)	5.7 (4.2–7.7)
HbA1c unknown	198 (7.5)	676 (2.6)	3.8 (3.2–4.5)	3.0 (2.4–3.6)
Diabetes complications				
Diabetes absent	1925 (73.0)	23 884 (90.5)	1.0 (ref.)	1.0 (ref.)
No complications	248 (9.4)	1301 (4.9)	2.5 (2.1–2.9)	2.3 (2.0–2.7)
Microvascular only	105 (4.0)	268 (1.0)	5.0 (4.0–6.4)	5.5 (4.2–7.2)
Macrovascular only	205 (7.8)	722 (2.7)	3.9 (3.3–4.6)	2.7 (2.2–3.3)
Macro- and micro-vascular	155 (5.9)	204 (0.8)	10.1 (8.1–12.6)	7.0 (5.4–9.0)
Conditions related to diabetic foot ulcers ^b	154 (5.8)	188 (0.7)	11.1 (8.9–13.9)	4.9 (3.7–6.6)
Previous lower-extremity ulcer ^c	244 (9.3)	242 (0.9)	13.2 (10.9–15.9)	6.9 (5.4–8.8)
Renal function before the index date				
Diabetes absent	1925 (73.0)	23 884 (90.5)	1.0 (ref.)	1.0 (ref.)
eGFR >90	90 (3.4)	364 (1.4)	3.2 (2.5–4.0)	2.2 (1.7–3.0)
eGFR 60–90	155 (5.9)	906 (3.4)	2.3 (1.9–2.7)	1.8 (1.4–2.2)
eGFR <60	311 (11.8)	686 (2.6)	6.1 (5.3–7.1)	4.2 (3.5–5.1)
eGFR missing	157 (6.0)	539 (2.0)	3.7 (3.1–4.5)	3.8 (3.0–4.7)

^aAdjusted for: conditions included in the modified Charlson Comorbidity Index (excluding the morbidity in question), marital status, alcohol-related conditions, any statin use predating the index date, and antibiotic therapy within 30 days of the index date; ^bPatients with diabetes and a previous diagnosis of neuropathy and/or peripheral vascular disease; ^cPatients with diabetes and a previous lower-extremity ulcer diagnosis or ulcer-related procedure.

CI, confidence interval; HbA1c, Hemoglobin A1c; eGFR, estimated glomerular filtration rate (mL/min/1.73 m²).

A number of different pathophysiological mechanisms may explain the observed increased risk of CA-SAB associated with diabetes. Diabetes and SAB share several risk factors including high age and comorbidity (6). Adjusting for comorbid conditions attenuated the association between diabetes and CA-SAB, suggesting that part of the risk associated with diabetes is conveyed by the burden of multiple morbidities and concomitant general frailty.

In our study, the excess risk of SAB was particularly evident in patients with diabetes complications. Decreased skin barriers may allow staphylococci access to adjoining tissues (27) or, at the most severe end of the

spectrum, the blood stream (1, 2). Our findings of high ORs associated with diabetic foot ulcers may support this mechanism. Moreover, renal disease is a well-known risk factor for SAB (28), which may be of particularly importance in patients with concomitant diabetes, as indicated by the OR of 4.2 (95% CI: 3.5–5.1) observed in patients with an eGFR <60 mL/min/1.73 m².

Still, patients with diabetes may most likely experience increased susceptibility to CA-SAB for reasons other than concomitant morbidities including diabetes complications. Neutrophilic leukocytes constitute the primary cellular defense against *S. aureus* infections, yet chemotaxis, adhesion, and intracellular killing are impaired

Table 3 Crude and adjusted odds ratios (ORs) for community-acquired *Staphylococcus aureus* bacteremia associated with diabetes according to sex, age, and level of comorbidity.

	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)
Diabetes absent	1.0 (ref.)	1.0 (ref.)
Sex		
Male	3.7 (3.2–4.1)	2.5 (2.2–2.9)
Female	3.9 (3.3–4.6)	3.2 (2.6–3.8)
Age		
15–39 years	11.9 (6.6–21.3)	4.0 (1.6–9.7)
40–59 years	6.2 (4.9–7.7)	5.7 (4.1–8.0)
60–79 years	3.6 (3.1–4.1)	2.6 (2.2–3.1)
80+ years	2.7 (2.2–3.2)	2.3 (1.8–2.8)
Modified Charlson Comorbidity Index score		
Low (0)	3.2 (2.7–4.0)	3.5 (2.8–4.3)
Intermediate (1–2)	2.2 (1.9–2.5)	2.5 (2.1–3.0)
High (>2)	2.0 (1.6–2.4)	2.2 (1.7–2.7)

^aAdjusted for: conditions included in the modified Charlson Comorbidity Index (except when stratified by this variable), age and gender (when stratified by comorbidity level), alcohol-related conditions, marital status, any statin use predating the index date, and antibiotic therapy within 30 days of the index date.

in patients with diabetes (5, 6, 29). Furthermore, the impaired immunological response in patients with diabetes has been shown to be affected by the level of glycemic control (30, 31), which is in accordance with our observations of gradual increases in CA-SAB risk with successive increases in HbA1c levels.

The main strengths of our study include its considerable size, well-defined study population, and the use of routinely recorded clinical data. We excluded patients with hospital-acquired SAB, which reduces confounding from major invasive procedures and concurrent diseases. In contrast to previous studies (11, 12, 13, 14), patients with diabetes were identified using a validated algorithm (20). Furthermore, we refined our analyses of diabetes as a risk factor for SAB by incorporating detailed information on various characteristics of patients with diabetes.

Limitations include the possibility that physicians may be more likely to admit patients with diabetes on suspicion of infection compared with patients without diabetes. Such surveillance bias would prompt an overestimation of the relative risk associated with SAB. However, previous studies from our setting (32, 33) assessing the risk of pneumococcal bacteremia and pneumonia, respectively, demonstrated that preadmission antibiotic treatment, microbiological results, levels of inflammatory markers on admission, and proportion of patients with at least one blood culture were comparable among patients

with and without diabetes. This suggests that there was no substantial bias associated with the management of patients with diabetes. Although our ascertainment of diabetes was based on three separate population-based registries, some persons with diabetes may have been missed, which would bias our results toward unity. Diabetic foot ulcers were not coded consistently with unique diagnostic codes during the study period. Thus, we used conditions related to foot ulcers and previous lower-extremity ulcer diagnoses, which might represent somewhat crude proxies. Nevertheless, both variables indicated a substantially increased risk of CA-SAB associated with diabetic foot ulcers, and we find it unlikely that misclassification alone could explain risk estimates of this magnitude. Finally, we lacked data to adjust for smoking and body mass index, which constitute a considerable limitation of the study. Still, these factors may be partly accounted for by the adjustment for lifestyle-related comorbidities in our analyses.

The low prevalence of MRSA in the study area ensured a clean focus on MSSA, but our results may not be directly applicable to settings with higher MRSA prevalence. Still, the results from our study may most likely be generalizable to other healthcare systems with equal access to healthcare and prescription medication including anti diabetes therapy.

In conclusion, persons with diabetes experienced an almost threefold increased risk of CA-SAB compared with persons without diabetes. Long diabetes duration, suboptimal glycemic control, and diabetes complications including renal disease further increased the risk of CA-SAB. These results emphasize the importance of improved preventive care for patients with diabetes, including optimized glycemic control, and particularly good infection surveillance among patients with long duration of diabetes and complications.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-15-0023>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

J S designed the study and performed data management, analysis, and manuscript preparation. M S, H C S, and H N contributed to the study concept and preparation, data interpretation, and manuscript review. T F provided statistical guidance. R W T contributed to study concept and design, critical analysis of the data, and manuscript review.

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