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Community-acquired *Staphylococcus aureus* bacteremia: Studies of risk and prognosis with special attention to diabetes mellitus and chronic heart failure

PhD thesis

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Thesis papers

I. Smit J, Søgaard M, Schønheyder HC, Nielsen H, Thomsen RW. Classification of healthcare-associated *Staphylococcus aureus* bacteremia: Influence of different definitions on prevalence, patient characteristics, and outcome. Infection Control & Hospital Epidemiology 2016; 37:208-211.

II. Smit J, Søgaard M, Schønheyder HC, Nielsen H, Frøslev T, Thomsen RW. Diabetes and risk of community-acquired *Staphylococcus aureus* bacteremia: A population-based case-control study. European Journal of Endocrinology 2016; 174:631-639.

III. Smit J, Thomsen RW, Schønheyder HC, Nielsen H, Frøslev T, Søgaard M. Outcome of community-acquired *Staphylococcus aureus* bacteraemia in patients with diabetes: A historical population-based cohort study. PLoS One 2016; 11:e0153766.

IV. Smit J, Adelborg K, Thomsen RW, Søgaard M, Schønheyder HC. Chronic heart failure and mortality in patients with community-acquired *Staphylococcus aureus* bacteremia: A population-based cohort study. BMC Infectious Diseases 2016; 16:227.

Abbreviations

aMRR: Adjusted mortality rate ratio

ATC codes: Anatomical Therapeutic Chemical classification system codes

AUPD: Aarhus University Prescription Database

CA-SAB: Community-acquired *Staphylococcus aureus* bacteremia

CCI: Charlson Comorbidity Index

CHF: Chronic heart failure

CI: Confidence interval

DCRS: Danish Civil Registration System

DNPR: Danish National Patient Registry

HA-SAB: Hospital-acquired *Staphylococcus aureus* bacteremia

Hba1c: Glycosylated hemoglobin A1c

HCA-SAB: Healthcare-associated *Staphylococcus aureus* bacteremia

ICD: Infectious disease specialist consultation

IE: Infective endocarditis

IQR: Interquartile range

LABKA: The clinical laboratory information system (LABKA) research database

m-CCI: Modified Charlson Comorbidity Index

MRR: Mortality rate ratio

MRSA: Methicillin-resistant *Staphylococcus aureus*

MSSA: Methicillin-sensitive *Staphylococcus aureus*

OR: Odds ratio

PP: Prevalence proportion

SAB: *Staphylococcus aureus* bacteremia

Contents

1. Thesis outline

Staphylococcus aureus bacteremia (SAB) is a serious clinical syndrome associated with considerable morbidity and a 30-day mortality of 20-40% in developed countries (1-3). High age and presence of chronic diseases are recognized as some of the most important risk and prognostic factors for SAB (1-2, 4-5). Due to population aging and lifestyle-related factors, the prevalences of diabetes mellitus and chronic heart failure (CHF) are rapidly increasing worldwide and in western countries in particular (6-10). Nevertheless, there is a paucity of data specifically elucidating the influence of diabetes and CHF on SAB risk and prognosis. Such information is important to extend our knowledge about the clinical course of patients with SAB and contributes to improvement of preventive measures and clinical care for patients suffering from these chronic diseases. Therefore, we used population-based registries and medical databases to investigate whether diabetes is associated with an increased risk of community-acquired SAB (CA-SAB) and whether presence of diabetes and CHF influence prognosis. SAB acquired during admission to the hospital is strongly associated with concurrent diseases and surgical procedures (11-12), which may distort the association between diabetes, CHF, and the risk and prognosis of SAB considerably. Therefore, aiming to elucidate the association between these chronic conditions and SAB in the general population, we chose to focus on CA-SAB in this thesis.

The thesis is based on four papers referred to in the text by Roman numerals (I-IV). The first paper is a methodological study portraying some of the challenges associated with the classification of SAB. Study II investigates diabetes as a risk factor for CA-SAB and the third paper ascertains the prognostic impact of diabetes in patients with CA-SAB. Finally, in the fourth study, the association between underlying CHF and CA-SAB outcome is assessed.

The introduction outlines the three central conditions SAB, diabetes, and CHF, including a review of the existing literature in relation to the aims of the thesis. The subsequent chapters include a summary of the methods used and results obtained in studies I-IV, discussion of the main results in relation to the existing literature, methodological considerations, and finally conclusion and perspectives. The last chapters provide English and Danish summaries, references, and appendices including details of the literature search strategy and full versions of studies I-IV.

2. Background

2.1 *S. aureus* bacteremia

S. aureus is both a commensal bacterium and a major human pathogen with the propensity to cause a broad spectrum of clinical disease across all age groups (1,13). *S. aureus* colonizes asymptomatically the skin and mucosa of approximately 30% of healthy persons (14-19). In addition to its frequent carriage as a commensal, *S. aureus* is a leading cause of skin and soft tissue infections (~90% of staphylococcal infections), bone and joint infections, wound infection, infective endocarditis, and infections related to medical devices (13, 20-22). In most cases, *S. aureus* infections remain localized to the affected organ, however the body´s protective mechanisms cannot always restrict the infection and staphylococci may subsequently gain entry to the bloodstream causing *S. aureus* bacteremia (the suffix ´-emia´ relates to the blood) (23).

SAB is defined as ´the isolation of *S. aureus* bacteria from one or more peripheral venous blood culture samples collected from a patient with associated relevant symptoms and signs of systemic infection´ (24). *S. aureus* is a rare contaminant as shown in prospective studies with a total of 1,809 SAB episodes of which only 27 (1.5%) were considered to represent contamination (24). Considering the serious clinical consequences associated with SAB, it is recommended that the isolation of *S. aureus* from blood cultures should always be regarded as clinically significant (24). The precondition of acquisition in the community implies that the origin of the *S. aureus* infection is rarely observed. To avoid speculative distinctions between primary and secondary foci, it is prudent to prioritize the site of infection that is the most probably source of the bloodstream infection when the first positive blood culture was drawn, based on symptoms and clinical signs, additional microbiological findings, and imaging results.

In Denmark, there is a long tradition of research on SAB. Since 1957, SAB has been surveyed on a national basis by collection of blood culture isolates. The *Staphylococcus* Laboratory at Statens Serum Institut has undertaken strain characterization and retrieval of clinical and epidemiological information on the patient level (25). Since the inception of this cohort, numerous studies have provided valuable insight into different aspects of SAB epidemiology including antibiotic resistance (26-27), clinical characteristics (28-30), incidence (31-32), and outcome (31-32). Although bacteremia with methicillin-resistant *S. aureus* (MRSA) constitutes a major challenge in many countries, bacteremia with methicillin-susceptible *S. aureus* (MSSA) represent the most common type of SAB in most parts of the world (3). In Denmark, the prevalence of MRSA bacteremia has remained uniquely low (~ 2%) during the past three decades (25, 33), though a slight increase in prevalence has been observed in recent years (2.9% in 2014) (25).

The population incidence of SAB ranges from 10 to 35 per 100,000 person years in the industrialized world (31-32, 34-36). In Denmark, the incidence of SAB increased from 18.2 per 100,000 person years to 30.5 per 100,000 person years between 1981 and 2000. Of note, annual rates increased by 6.4% for CA-SAB compared with only 2.2% for hospital-acquired SAB (HA-SAB) (32). Since 2000, the incidence of SAB in Denmark has continued to rise reaching an incidence rate of 34.9 per 100,000 person years in 2014 (25). During the past 50 years, the rates of hospital admissions, outpatient contacts, and complex invasive medical interventions have increased exponentially. Thus, increased exposure to the healthcare system may explain part of the observed increase in SAB incidence. On the other hand, the increasing incidence of SAB may also reflect demographic changes, e.g., an aging population and the increasing longevity of patients with chronic diseases due to medical progress (1). In addition, the indications for obtaining blood

cultures may have widened during the period and improvements in blood culture technology may further have influenced the incidence (37).

Once established, SAB is associated with substantial morbidity and mortality (2-3, 38-40). In the pre-antibiotic era, all-cause mortality in patients with SAB ranged between 75% and 83% (41). Although the introduction of effective antibiotics in the 1940s and 1950s radically improved SAB management, studies from different settings around the world have demonstrated that the 30-day all-cause mortality associated with SAB have plateaued at 20-35% (3, 39, 42-43). These results are corroborated by the aforementioned surveillance reports from Statens Serum Institut demonstrating an almost constant 30-day mortality of approximately 25% during the years 1998-2014 (25). SAB may also have important non-lethal outcomes including discomfort, pain, decreased functional status, long-term financial costs, and SAB recurrence (2-10% of patients) (44-46).

Clinical manifestations and management of *S. aureus* bacteremia

The presentation of SAB varies greatly and the clinical course is difficult to predict (1, 47-48). Non-specific findings of fever, hypotension, tachycardia, and leukocytosis are common, nevertheless no anamnestic features or clinical signs are considered pathognomonic of SAB (1, 47). More than 30% of patients with SAB develop more than one focus of infection (48-51), thus the full extent of *S. aureus* infection may not be obvious at presentation and the clinical picture may change several times during the course of infection. Adding to the complexity, the symptoms and findings may originate from the organ that was initially infected (e.g., a skin infection), from hematogenous or contiguous spread to another organ (e.g., infective endocarditis), or potentially from a combination of local and systemic infection (1,47).

SAB is closely associated with the clinical syndrome of sepsis which compromises physiologic, pathologic, and biochemical abnormalities elicited by the infectious process (52). During the past

two decades, sepsis has been almost synonymous with the systemic inflammatory response syndrome (SIRS) caused by confirmed or suspected infection. Sepsis with organ dysfunction or hypoperfusion was further classified as severe sepsis, which could eventually progress to septic shock (53-54). However, due to inadequate specificity and sensitivity of the SIRS criteria, updated definitions of sepsis were proposed in 2016 (55). According to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis should be defined as ´life-threatening organ dysfunction caused by a dysregulated host response to infection´. Sepsis may intensify to septic shock, defined as a subset of sepsis in which ´particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone´. Of note, since patients with evidence of organ dysfunction or hypoperfusion are encompassed by the 2016 definitions of sepsis and septic shock, the use of the term severe sepsis is no longer recommended (55). Septic shock, although definitions vary slightly between previous studies, has been demonstrated to occur in approximately 10-40% of patients with SAB (2).

Although clinical guidelines for the management of SAB are available (24, 56-58), the evidence guiding optimal treatment unfortunately remains poor. As demonstrated by a recent comprehensive review (59) assessing the clinical management of SAB, only a single study fulfilled the GRADE (grading of recommendation, assessment, development, and evaluation) criteria (60) for high-quality evidence. Despite the need for additional evidence based on well-designed studies, early identification and control of the infective focus (or foci) and appropriate antibiotic therapy are widely accepted as the two mainstays of SAB management (1, 24, 59). Although estimates vary between different clinical settings, SAB is complicated by infective endocarditis (IE) in approximately 25-38% of cases, which is often clinically indistinguishable from SAB without the presence of IE (47-48, 59). The risk of IE is highest among patients with congenital heart disease,

prosthetic heart valves, intracardiac devices, and previous episodes of IE, although ~ 50% of cases of IE develop in SAB patients with no previous history of heart valve disease (22, 47, 59). Because the presence of IE is decisive for clinical monitoring and treatment, echocardiography of all patients with SAB is recommended by most recent guidelines (59). Effective antimicrobial therapy for SAB requires careful selection of a proven agent administered with optimal frequency and sufficient dosage (24, 47, 59). The optimal duration of antibiotic therapy remains controversial, however, and continues to rest mainly on clinical traditions. Still, receipt of antibiotic therapy for less than two weeks has been associated with increased risk of relapse in patients with SAB (61-62), thus a minimum of two weeks of intravenous antibiotic treatment is recommended by the majority of current SAB guidelines (56, 58-59, 63).

Classification of *S. aureus* bacteremia

SAB can be classified in several ways, e.g., as MSSA or MRSA (1, 47) or as monomicrobial or polymicrobial (64-65). Central to this thesis, SAB is classified according to whether the infection has arisen in the community (CA-SAB) or during hospitalization (HA-SAB) (66). In 1975, McGowan et al. (67) defined community-acquired bacteremia as presence of positive blood cultures on admission or within the two first days in the hospital and hospital-acquired bacteremia as occurring on or after the third day in the hospital, and this approach was adapted in a subsequent study on bacteremia by Brenner et al. (68). Later, in 1988, Garner et al. (69) published definitions of acquisition on behalf of the Centers for Disease Control and Prevention (CDC) stating that classification of infections should be based on individual assessment using all available clinical data and not rely solely on prespecified time windows. Nevertheless, a pragmatic 48-hour cut-off between infection diagnosis and the time of hospital admission to distinguish between community and hospital acquisition has been used in most previous studies of SAB (3, 35, 39, 70-73).

Since the initial introduction of the CA and HA categories, the health care system has experienced major organizational changes and increasingly complex medical services are now being provided in the patients´ homes or in outpatient hospital clinics. Thus, it might not always be adequate to label infections simply as CA, and in 2002 a separate healthcare-associated (HCA) group was proposed by Siegman-Igra et al. (74) and by Friedman et al. (75), respectively, to extend the definition of CA bacteremia (detailed criteria are provided in Table 1). SAB is particularly often seen in patients with frequent contact to the healthcare system (1, 11-12), hence correct classification on admission is pivotal. Nevertheless, there is no international consensus on the definition of HCA bacteremia (including HCA-SAB) (76) which may influence negatively the validity of the estimates and render comparison of SAB studies difficult. Indeed, as evident from a review of the existing literature (Table 2), rather different definitions of HCA-SAB have been employed in previous studies.

Table 1. Initial definitions of healthcare-associated (HCA) bacteremia.

Study, year of publication	**HCA bacteremia criteria** *Blood culture performed within 2 days of admission and the following:*
Siegman-Igra Y, et al., 2002 (74)	1. Discharge from hospital 2 to 30 days previously *or* 2. Admission from nursing home *or* 3. Patients with long-term intravenous devices, for hemodialysis, chemotherapy or parenteral nutrition *or* 4. Chronic hemodialysis *or* 5. Invasive procedure previously or at hospital admission
Friedman D, et al., 2002 (75)	1. Received intravenous therapy at home, wound care or specialized nursing care through a healthcare agency, family or friends; or had self-administered intravenous medical therapy in the 30 days before the infection *or* 2. Attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the previous 30 days *or* 3. Were hospitalized in an acute care hospital for 2 or more days in the previous 90 days *or* 4. Resided in a nursing home or long-term care facility

Table 2. Previously used definitions of healthcare-associated (HCA) infection in studies of *S. aureus* bacteremia.

Study, year of publication	**HCA-bacteremia criteria**
Jacobsson G, et al., 2007 (77)	*Blood culture performed within 2 days of admission and:* 1. Nursing home residence *or* 2. Reception of healthcare at home
Asgeirsson H, et al., 2010 (35)	*Blood culture performed within 2 days of admission and:* 1. Hospital admission for >2 days within 90 days of the current hospitalization
Paulsen J, et al., 2015 (39)	*Blood culture performed within 2 days of admission and:* 1. Received intravenous therapy at home, wound care or specialized nursing care through a healthcare agency, family or friends, or had self-administered intravenous medical therapy in the 30 days before the infection *or* 2. Attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the previous 30 days *or* 3. Were hospitalized in an acute care hospital for ≥ 2 days in the previous 30 days *or* 4. Resided in a nursing home or long-term care facility
Yahav D, et al., 2016 (4)	*Blood culture performed within 2 days of admission and:* 1. Previous hospitalization of ≥2 days during previous 90 days *or* 2. Clinic visit during previous 30 days *or* 3. Home IV therapy or chemotherapy or wound treatment during the previous 30 days *or* 4. Patients arriving from long-term care facilities
Forsblom E, et al., 2016 (78)	1. Blood culture performed ≥48 hours after hospital *or* 2. Admission from long-term care facility *or* 3. Hemodialysis within the preceding two months

Established risk and prognostic factors for *S. aureus* bacteremia

Several factors are associated with increased risk of SAB. First of all, age is one the strongest risk factors for SAB (34-36, 79), for example the incidence of SAB is >100 per 100,000 person-years among patients aged more than 70 years (34) compared to only 4.7 per 100,000 person-years in healthier U.S. military personnel of younger age (80). Further, male gender constitutes one of the most consistent risk factors for SAB with male-to-female ratios of approximately 1.5 (35, 79-81). However, the excess risk of SAB observed among elderly and male persons may partly be

explained by more frequent contacts to the healthcare system and presence of comorbid conditions. Indeed, comorbidity is associated with markedly increased risk of SAB (1, 31, 47). As an example, a recent Danish cohort study demonstrated that patients with end-stage renal disease experienced an almost 30 times increased risk of SAB compared with population controls (82). The risk was most pronounced among patients receiving dialysis, which is corroborated by surveillance reports from the US demonstrating that the incidence of SAB is more than 100 times higher among dialysis patients compared with the healthy US population (83). According to a Danish cohort study, the risk of SAB in patients living with HIV is 24 times that of persons without HIV (84). Part of the overall increased risk among patients with HIV may, however, have been driven by a higher prevalence of injection drug abuse, which has been associated with increased risk of SAB (85-87). Finally, the presence of medical devices in general and venous catheters in particular is associated with considerable increased SAB risk (1, 88).

Several of the abovementioned risk factors for SAB also constitute important prognostic factors for SAB. Consistent across a multitude of studies, age remains the single most important prognostic factor of all-cause 30-day mortality in patients with SAB (1-3, 89). Female gender has been associated with increased mortality in previous studies (31, 90-91), yet the mechanisms underlying this association remain unclear. The place of acquisition (HA, CA, HCA) has also been investigated as a potential prognostic factor. Although a recent Norwegian cohort study (39) observed an improved outcome associated with CA-SAB, the majority of previous studies have not been able to demonstrate notable differences in 30-day mortality between patients with CA-SAB and HA-SAB, respectively (3, 31-32, 42-43, 73). Notwithstanding, some studies on bacteremia (including SAB) have suggested that patients with HCA infection are at increased risk of death as compared to patients with CA infection (92-94).

Furthermore, the prognosis of SAB varies considerably by infective focus, *viz* respiratory focus and IE are associated with high mortality, whereas osteoarticular focus and SAB related to use of intravascular access devices are associated with a better outcome (2-3, 95). Moreover, failure to identify the infective focus (89, 96) and presence of multiple foci in particular impart a poor prognosis (48, 50, 97-98). In addition to being a risk factor of SAB, presence of accumulated comorbidity also represents an important prognostic factor (31-32, 99). Although there is a paucity of in-depth data assessing the prognostic influence of specific comorbid conditions, chronic kidney disease requiring dialysis (40, 89, 100), liver cirrhosis (65, 101), cancer (2, 102), and alcohol-related conditions (31, 40) have all been suggested to be associated with poor outcome in patients with SAB. The presence of septic shock is strongly associated with poor outcome, with 30-day mortalities ranging between 38-86% (2). Still, the wide variation in outcome observed in these previous studies may partly be explained by differences in sepsis definitions and study populations (2). Finally, as touched upon in relation to the clinical management of SAB, early identification and control of the infective focus and appropriate antibiotic treatment are of importance for SAB outcome (24, 59, 103).

2.2 Diabetes

Diabetes is a major cause of morbidity and mortality on a global scale. According to reports from the International Diabetes Federation, 1 in 11 of the world´s population currently suffers from diabetes and every 6 seconds a person dies from this disease (104). Diabetes is a chronic multisystem metabolic disease resulting from insufficient insulin secretion, insulin action, or a combination of both (105-107). Due to the complex clinical presentation of diabetes and the potential presence of a mixture of phenotypes, classification of the disease is not always straightforward. Still, the American Diabetes Association recommends that diabetes is classified

into four major categories: type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types of diabetes (105). Type 1 diabetes is most commonly seen in patients aged less than 40 years and stems from autoimmune destruction of pancreatic beta cells leading to insulin deficiency. Type 2 diabetes is most frequently diagnosed in patients older than 30-40 years, but may develop at any age. It is characterized by variable degrees of insulin secretion, insulin resistance, and increased hepatic glucose production. Type 2 diabetes accounts for the vast majority (>90%) of those with diabetes (105, 108).

Owing to population ageing, increasing obesity, and inactive lifestyle, the prevalence of type 2 diabetes is on the increase globally (6-8, 104). Still, increased diagnostic activity and longer survival of patients with diabetes due to earlier diagnosis or improved anti diabetes therapy may underlie part of the observed increase in prevalence. Approximately 415 million people are afflicted by diabetes worldwide, and this is expected to increase to as many as 642 million people by 2040 (104). In line with this, approximately 320,000 Danish residents are currently living with diabetes, and the prevalence is estimated to rise by more than 20,000 patients each year (109-110). Diabetes has a negative effect on patients´ quality of life and is strongly associated with reduced life expectancy (111-112). In addition, patients with diabetes with poor glycemic control and patients with a long history of diabetes are at increased risk of a microvascular and macrovascular diabetes complications (111,113). These complications may affect multiple organ systems, thus diabetes is strongly associated with risk of ischemic heart disease (114), chronic heart failure (115), cerebrovascular disease (114), and peripheral neuropathy and peripheral arterial disease which may lead to diabetic foot ulcers (116). Moreover, diabetes is a leading cause of chronic kidney disease and blindness in the industrialized world (117). Finally, patients with diabetes are often

characterized by advanced age and concurrent chronic conditions (e.g., chronic obstructive pulmonary disease and cancer) adding further to the disease burden (111-112).

2.3 Chronic heart failure

CHF constitutes a staggering health problem affecting more than 23 million adults worldwide (9-10). In Denmark, an estimated 60,000 persons suffer from CHF leading to more than 11,000 hospital admissions annually (118). The American College of Cardiology guidelines describes heart failure as ´a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood´ (119). It is important to recognize that CHF is not a single disease but a clinical syndrome with a multitude of clinical presentations rendering its diagnosis a considerable challenge. CHF can arise from a variety of causes that may co-exist and interact with each other in an individual patient, still ischemic heart disease, hypertension, and valvular heart disease remain among the most frequent underlying causes (9-10, 119-121). In addition, there is evidence that obesity and diabetes are associated with risk of CHF independently of clinical coronary disease and hypertension (115, 122). The presence and severity of CHF is usually classified according to the New York Heart Association (NYHA) functional classification (stage I-IV) or by the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) classification system (stage A-D) (119-120). The former is based solely on exercise capacity and the symptomatic status of the diseases, whereas the latter takes into account both risk factors for CHF and documented presence of structural heart disease. Both classification schemes have, however, been demonstrated to be valuable tools for predicting prognosis in patients with CHF (119-120). Adding to the burden of CHF, the disease is often preceded and/or complicated by other cardiovascular conditions including cardiomyopathy, valvular heart disease, and atrial fibrillation (119-120). Although the mortality from CHF appears to

have declined in recent decades (9-10), the one-year all-cause mortality following diagnosis remains at 20% in Denmark (118). Additionally, CHF is associated with high rates of readmissions imposing a heavy burden on patients´ quality of life and healthcare systems (10, 123).

2.4 Diabetes, chronic heart failure, and *S. aureus* bacteremia

Diabetes may influence the risk and prognosis of CA-SAB for a number of reasons. Of chief importance, diabetes and CA-SAB share several important risk and prognostic factors counting advanced age and presence of concurrent chronic conditions. Furthermore, it may be that patients with diabetes complications are at particularly increased risk of CA-SAB. For instance, diabetic foot ulcers degrade normal skin barriers (116) which may allow staphylococci to enter the abutting tissues or ultimately the bloodstream. Moreover, diabetes is strongly associated with development of chronic kidney disease requiring dialysis (113, 117), both of which have been suggested to be associated with increased risk and poor prognosis in patients with CA-SAB (82-83).

Diabetes affects several aspects of the cellular and humoral immunity. Neutrophil leukocytes represent the most important cellular defense against *S.aureus* infections (124-125); however, chemotaxis, adhesion and intracellular killing are impaired in patients with diabetes (126-127). Furthermore, there is strong evidence indicating that diabetes is associated with chronic low-grade inflammation. Hence, increased levels of C-reactive protein and interleukin 6 have been demonstrated to precede the development of type 2 diabetes in healthy persons and increased levels of proinflammatory cytokines (including interleukin 6) are associated with manifest diabetes (128-129). In contrast, cytokine responses to an acute infectious challenge have been suggested to be blunted in patients with diabetes (130-131), thus, the impact of diabetes on cytokine responses may be envisaged to affect both the risk and outcome of CA-SAB. In line, there is evidence suggesting that patients with diabetes with serious systemic infection may be protected from severe

complications such as respiratory failure through a less active inflammatory cascade (132). On the other hand, hyperglycemia is associated with increased coagulation and subsequent risk of thrombotic events which may have a negative effect on outcome (133).
Finally, colonization with *S. aureus* may be associated with increased risk of infection including SAB (14, 134). Some previous studies have suggested that patients with diabetes are more frequently colonized with *S. aureus* than patients without (135), whereas other studies have observed no differences in prevalence of colonization associated with diabetes. (136-137). Thus, the potential role of *S. aureus* colonization for the risk and prognosis of SAB among patients with diabetes is not well understood.

In line with diabetes, CHF may also be speculated to influence the prognosis of patients with CA-SAB. As mentioned above, SAB is strongly associated with sepsis and the latter has been demonstrated to affect myocardial function negatively through various mechanisms counting maldistribution of coronary blood flow, cytokine-induced neutrophil activation and myocardial injury, and complement-triggered myocyte contractile failure. Thus, patients with sepsis may be challenged by ventricular dilatation, reduced ejection fraction, and decreased ability to mount a sufficient cardiovascular output despite the presence of increased catecholamine levels (52, 138-141. As patients with CHF are characterized by insufficient cardiac pump function at baseline, it might be speculated that these patients are particularly at risk of circulatory collapse and subsequent death when challenged by SAB. Additionally, CHF is strongly associated with advanced age and multiple morbidities which, as described previously, represent some of the most important prognostic factors for CA-SAB (2-3, 31, 89, 99).

2.5 Literature review

Searching the Medline and Embase databases from the earliest available date until September 2016, we conducted a literature review to identify and summarize existing knowledge on 1) the influence of different definitions of HCA infection on HCA-SAB prevalence, clinical characteristics, and outcome, 2) the influence of diabetes on CA-SAB risk and prognosis, and 3) the influence of CHF on outcome from CA-SAB.

No restrictions concerning language were applied and conference abstracts were also included. The entire literature review was supervised by an experienced medical librarian and we customized the search for each database using both controlled thesaurus terms and natural language terms for synonyms (the Medline and Embase search strategy details are provided in Appendix A). We assessed the title and abstract of each paper and selected all relevant studies fulfilling the PICO criteria (142), i.e. information was available on the study population, the exposure, the comparison group, and the outcome. The reference lists of all selected papers were then reviewed for additional works of relevance and we further ascertained papers indicated as relevant by Medline and Embase for each selected paper. Finally, if we through our previous work were aware of additional relevant studies not identified by the search, these were also included (n=3). The results of the literature review are summarized in Table 3.

Table 3. Summary of the literature review.

Study I: Impact of different HCA-SAB definitions on patient characteristics and outcome			
Author, year	**Design, setting, data sources, period**	**Population, expopsure, outcome**	**Results, limitations**
- Folden DV, et al. (143) - 2005	- Cross-sectional study - USA - Hospital surveillance database, microbiological results, patient charts - 2001-2003	- 100 patients with MRSA infection - Two different definitions of HCA-MRSA infection - Prevalence of CA-MRSA infection	- Proportion of HCA-MRSA infection=51% with CDC nosocomial infection criteria vs. 95% with healthcare risk factor exposure criteria - Small and selected study sample
- McCarthy NL, et al. (144) - 2010	- Cross-sectional study - USA - Microbiological results, patient charts - 2007-2008	- 352 patients with MRSA infection - Two different definitions of HCA-MRSA - Prevalence of HCA-MRSA, risk factors for HCA-MRSA	- Proportion of HCA-MRSA=54% using an epidemiological classification versus 44% using an antibiotic susceptibility phenotype rule. Age and gender did not differ notably with use of different definitions - Single-center study, epidemiological definition of HCA-MRSA unclearly described
- Sievert DM, et al. (145) - 2010	- Cross-sectional study - USA - Microbiological results, patient charts - 2004-2005	- 2,151 patients with MRSA infection - Three different definitions of HCA-MRSA - Prevalence of HCA-MRSA, demographic and clinical characteristics according to each definition	- HCA-MRSA proportion=37% using a healthcare risk factor classification, 39% using an infection-type classification, and 54% using an antibiotic susceptibility pattern classification - Single-center study, missing data
- Leung V, et al. (146) - 2013	- Cross-sectional study - Canada - Hospital database, microbiological results, patients - 2011	- 100 patients with MRSA infection - Two different look-back periods after hospitalization for identifying HCA-MRSA - Prevalence of HCA-MRSA	- Different look-back periods (4 weeks versus 12 months) did not influence the identification of HCA-MRSA (reclassification error rate=2%) - Limited and selected sample size, difference in definitions limited to varying look-back periods

- Gradel, et al. (66) - 2014	- Cohort study - Denmark - Blood culture results, population-based medical registries - 2000-2011	- 56,606 patients with bacteremia - Different time windows after hospital admission for identifying HCA bacteremia - 30-day all-cause mortality	- No difference in 30-day mortality observed for HCA bacteremia patients in relation to a 30- or 90-day time window - Not restricted to incident cases, difference in definitions limited to varying time windows

Study II: Diabetes and risk of CA-SAB			
Author, year	**Design, setting, data sources, period**	**Population, exposure, outcome**	**Results, limitations**
- Bryan CS, et al. (147) - 1985	- Cohort study - USA - Blood culture test results, patient charts - 1977-1981	- 2,978 patients with bacteremia (397 with SAB), no age restriction - Diabetes - SAB	- Number of SAB episodes per 1000 patients per year=3.0 in patients with diabetes vs. 1.2 in patients without diabetes - No distinction made between CA-SAB, HA-SAB, and HCA-SAB, not restricted to incident SAB cases, few patients with diabetes (n=46), no detailed data on diabetes exposure (e.g., diabetes duration or diabetes complications)
- Laupland KB, et al. (148) - 2003	- Cohort study - Canada - Calgary Laboratory Services Register, patient charts, Alberta Health Population Registry, regional databases - 1999-2000	- Patients with invasive *S. aureus* infection, including bacteremia, no age restriction (n=264) - Diabetes - Invasive *S. aureus* infection, in-hospital all-cause mortality	- Unadjusted RR=7.7 (95% CI, 5.0-9.7) for invasive *S. aureus* infection among patients with diabetes - Study population not restricted to patients with SAB, limited number of patients with diabetes (n=48), lack of detailed data on diabetes exposure, results not stratified according to age, gender, or other potential confounders

- Jacobsson G, et al. (77) - 2007	- Cohort study - Sweden - Patient interview, microbiological registers, The Swedish Register of Uremia Care, The Regional Diabetes Register, The Regional Cancer Registry, The Regional Rheumatoid Arthritis Registry - 2003-2005	- Patients with invasive *S. aureus* infection including bacteremia (n=168), no age restriction - Diabetes - Invasive *S. aureus* infection, recurrent infection	- Unadjusted OR=8.2 (95% CI, 6-12) for invasive *S. aureus* infection among patients with diabetes - Small study population not restricted to patients with incident infection, few patients with diabetes (n=43), no detailed data on diabetes exposure
- Laupland KB, et al. (149) - 2008	- Cohort study - Canada - Calgary Laboratory Services Register, regional clinical registers - 2000-2006	- 1,508 patients with SAB, no age restriction - Diabetes - SAB, case-fatality	- Diabetes associated with increased risk of SAB (crude IRR=10.6 (95% CI, 9.3-11.9)) - Lack of detailed data on diabetes exposure (exact number of patients with diabetes not available in the paper), insufficient adjustment for potential confounders
- Bassetti M, et al. (72) - 2011	- Combined cohort and case-control study - Italy - Patient interviews, microbiological results - 2007	- Patients with SAB aged ≥ 18 years (n=165) and controls matched 2:1 by hospital location (ward), month of admission, and length of hospital stay at the time of matching - Diabetes - SAB, 30-day all-cause mortality	- Diabetes associated with adjusted OR=6.21 (95% CI, 1.62-23.77) for CA-SAB - Small and selected study population, no data on characteristics of patients with diabetes (n=54), use of hospital controls
- Chase M, et al. (150) - 2012	- Cohort study - USA - Prospective collection of microbiological and clinical information using a standardized data collection instrument - 2005-2006	- 5,630 patients emergency department patients suspected of infection (aged ≥18 years), 68 with MRSA bacteremia - Diabetes - MRSA bacteremia	- Diabetes associated with increased risk of MRSA bacteremia (adjusted OR=2.02 (95% CI, 1.13-3.61) - Selected study population, limited number of patients with SAB, number of patients with diabetes and SAB not provided in the paper

- Hernandez C, et al. (151) - 2014	- Cohort study - Spain - Patient interviews, microbiological results, imaging results - 2005-2011	- 745 patients with bacteremia of unknown source (including SAB, n=78) in patients aged ≥18 years - Diabetes - SAB of unknown source	- Adjusted OR=1.72 (95% CI, 1.01-2.91) for SAB of unknown source among patients with diabetes - Selected study population, few patients with SAB, very few patients with diabetes (n=24)

Study III: Diabetes and outcome of CA-SAB			
Author, year	**Design, setting, data sources, period**	**Population, exposure, outcome**	**Results, limitations**
- Cluff LE, et al. (152) - 1968	- Cohort study - USA - Blood culture results, patient charts - 1952-1965	- Patients with SAB (n=185), no age restriction - Diabetes - In-hospital mortality	- In-hospital mortality=69% among patients with diabetes vs. 17% among patients with no comorbidity - Small and selected study population, few patients with diabetes (n=26), follow-up restricted to in-hospital mortality
- Cooper G, et al. (153) - 1982	- Cohort study - USA - Blood culture results, patient charts - 1977-1980	- 61 patients with SAB aged ≥18 years (27 with diabetes and 34 without) - Diabetes - Infective endocarditis, in-hospital mortality	- No difference in mortality among patients with and without diabetes (4 diabetic deaths versus 4.8 expected) - Selected study population, few patients with diabetes, insufficient control for potential confounders
- Bryan CS, et al. (147) - 1985	- Cohort study - USA - Blood culture results, patient charts - 1977-1981	- 2,978 patients with bacteremia, 397 with SAB, no age restriction - Diabetes - SAB-attributable in-hospital mortality	- In-hospital mortality=15.8% among patients with diabetes vs. 24.8% in patients without - No distinction made between CA-SAB, HA-SAB, and HCA-SAB, study not restricted to incident SAB cases, few patients with diabetes (n=46)

- Maradona JA, et al. (154) - 1992	- Cohort study - Spain - Blood culture results, prospective collection of clinical information - 1983-1989	- Patients with SAB (n=274), no age restriction - Diabetes - SAB-related in-hospital mortality	- Diabetes associated with increased in-hospital mortality among patients with CA-SAB (p=0.0540) - Small and selected study population, few patients with diabetes and CA-SAB (n=15), follow-up restricted to in-hospital mortality
- Mylotte J, et al. (42) - 2000	- Cohort study - USA - Microbiological registers, patient charts - 1995-1999	- Patients with SAB ≥18 years (n=293) - Diabetes - 30-day all-cause mortality	- adjusted OR for 30-day mortality=2.4 (95% CI, 1.2-4.7) among patients with diabetes - Small and selected study population, not restricted to incident cases, lack of detailed data on diabetes exposure (n=94)
- Hill PC, et al.(71) - 2001	- Cohort study - New Zealand - Microbiological registers, patient charts - 1996-1997	- Patients with SAB ≥18 years (n=424) - Diabetes - 30-day all-cause mortality	- RR of death within 30 days=1.5 (95% CI, 1.0-2.4) associated with diabetes - Selected study population, few patients with diabetes (n=88)
- Laupland KB, et al. (148) - 2003	- Cohort study - Canada - Calgary Laboratory Services Register, patient charts, Alberta Health Population Registry, regional databases - 1999-2000	- Patients with invasive *S. aureus* infection, including bacteremia, no age restriction (n=264) - Diabetes - In-hospital all-cause mortality	- Diabetes not associated with increased in-hospital mortality (estimate not provided in the paper) - Small study population not restricted to SAB, limited number of patients with diabetes (n=48), follow-up restricted to in-hospital mortality
- Kaech C, et al. (40) - 2006	- Cohort study - Switzerland - Blood culture results, patient charts - 1998-2002	- Patients with SAB ≥18 years (n=308) - Diabetes - In-hospital mortality	- Diabetes not associated with increased mortality (estimate not available in the paper) - Selected study population, few patients with diabetes (n=74) and no detailed data on diabetes exposure, follow-up restricted to in-hospital mortality

- Kanafani ZA, et al. (155) - 2009	- RCT (subgroup analysis) - USA - Randomization - 2002-2005	- Patients with SAB and IE ≥18 years, 86 with diabetes and 149 without diabetes - Diabetes - 6-week all-cause mortality	- Mortality at 6 weeks=22.1% for patients with diabetes vs. 11.4% among patients without diabetes - Subgroup analysis, no distinction made between CA-SAB, HA-SAB, and HCA-SAB, limited data on diabetes exposure
- Kaasch AJ, et al. (3) - 2014	- Cohort study - Multinational (Germany, Spain, United Kingdom, USA) - Prospective collection of microbiological and clinical information according to the study protocol - 2006-2011	- Patients with SAB ≥18 years (n=3,395) - Diabetes - 7-day-, 14-day-, 30-day-, 90-day mortality	- Adjusted HR for 30-day mortality=1.12 (95% CI, 0.95-1.33) among patients with diabetes - Not population-based, no detailed data on diabetes exposure (n=856)

Study IV: Chronic heart failure and outcome of CA-SAB			
Author, year	**Design, setting, data sources period**	**Population, exposure, outcome**	**Results, limitations**
- Kaech C, et al. (40) - 2006	- Cohort study - Switzerland - Blood culture results, patient charts - 1998-2002	- Patients with SAB aged ≥18 years (n=308) - CHF - In-hospital all-cause mortality, complications from SAB (e.g., infective endocarditis, renal failure, disseminated intravascular coagulation)	- Unadjusted OR for 90-day mortality=2.4 (95% CI, 1.0-5.6) among patients with CHF - Few patients with CHF (n=32), no detailed data on CHF exposure (e.g., CHF severity, CHF duration or CHF-related conditions), insufficient adjustment for comorbid conditions, follow-up restricted to in-hospital mortality

- Cuervo SI, et al. (156) - 2010	- Cohort study - Columbia - Microbiological registers, patient charts - 2001-2005	- Patients with cancer aged ≥18 years with SAB (n=267) - CHF - 90-day SAB-related death	-Adjusted HR for 90-day mortality=10.6 (95% CI, 1.8-63.7) among patients with CHF - Selected study population, very few patients with CHF (n=9), no data on functional status, misclassification of SAB-related death cannot be excluded, not population-based
- Lin SH, et al. (157) - 2010	- Cohort study - Taiwan - Microbiological registers, patient charts - 2000-2008	- Patients with persistent MRSA bacteremia aged ≥18 years (n=227) - CHF - 30-day all-cause mortality	- Adjusted OR for 30-day mortality=2.85 (95% CI, 1.44-5.65) among patients with CHF - Selected study population, limited number of patients with CHF (n=63), no detailed information on CHF exposure
- Paulsen J, et al. (39) - 2015	- Cohort study - Norway - Microbiological registers, patient charts, HUNT2 survey - 1996-2011	- Patients with SAB aged ≥ 16 years (n=373) - CHF - All-cause 30-day and 90-day mortality	- adjusted OR for 30-day mortality=2.4 (95% CI, 1.21-4.80) among patients with CHF - Few patients with CHF (n=40), no detailed data on CHF exposure, not population-based

Abbreviations: CA-SAB=community-acquired *S. aureus* bacteremia, CDC=Centers for Disease Control and Prevention, CHF=chronic heart failure, CI=confidence interval, HA-SAB=hospital-acquired *S. aureus* bacteremia, HCA=Healthcare-associated *S. aureus* bacteremia, HR=hazard ratio, IRR=incidence rate ratio, OR=odds ratio, p=p-value RCT=randomized controlled trial, RR=relative risk, SAB=*S.aureus* bacteremia.

Study I

A few previous studies have touched upon whether different definitions of HCA infection influence the prevalence, clinical characteristics, and outcome of patients with *S. aureus* infection (Table 3). In 2005, Folden et al. (143) observed an almost doubling of the HCA-MRSA infection prevalence with use of two different classification schemes. Two later studies (144-145) compared epidemiological criteria with criteria based on antimicrobial susceptibility patterns for classifying HCA-MRSA infection and obtained discrepant results. Moreover, Leung et al. (146) and Gradel et al. (66), respectively, demonstrated that the use of different time windows to define HCA infection did not notably influence the prevalence of HCA-MRSA infection (146), nor the results of prognostic models in patients with bacteremia (66). Nevertheless, all the previous studies had different primary objectives and none assessed specifically the influence of different HCA infection definitions in patients with SAB. In addition, the majority of these previous studies were limited by small and selected sample sizes (143-144, 146), which may have biased the results.

Study II

A limited number of previous studies have included diabetes among a number of other potential risk factors for SAB (Table 3). In an American cohort study, Bryan et al. (147) reported the incidence of SAB being three times higher among patients with diabetes as compared to patients without. These first results were later corroborated by two Canadian cohort studies in which Laupland et al. (148-149) found diabetes to be associated with an increased risk of invasive *S. aureus* infection and SAB in particular. In line with this, a Swedish cohort study investigating several risk factors for invasive *S. aureus* infection (including SAB) identified diabetes as one of the most important risk factors (unadjusted OR=8.2 (95% CI, 6-12)) (77). Results from an Italian case-control study (72) investigating risk factors for SAB demonstrated an increased risk of diabetes associated with CA-

SAB, and in an American cohort study comprising emergency department patients suspected of infection (150), patients with diabetes experienced a two-fold risk of MRSA bacteremia compared to patients without diabetes. Finally, in a Spanish cohort study on SAB, Hernandez et al. (151) found that diabetes was associated with SAB of unknown origin.

However, none of these studies investigated diabetes as a risk factor for SAB as the primary aim and lacked detailed information on diabetes exposure (e.g., duration of diabetes or presence of diabetes complications). Although their findings appear fairly consistent, the limitations of the individual studies are considerable, e.g., selected study populations (72, 147, 150-151), inclusion of non-incident SAB cases (147, 77), and limited numbers of patients with diabetes (n<60) (77, 147-150).

Study III

Four cohort studies were among the first to touch upon the influence of diabetes on SAB outcome (Table 3) (147, 152-154). In a cohort study on SAB, Cluff et al. (152) observed an in-hospital mortality of 17% among patients with no comorbidity compared with as high as 69% among patients with diabetes. In contrast, Cooper et al. (153) observed no difference in in-hospital mortality among patients with diabetes and without diabetes in a cohort study on SAB, and this finding was corroborated by Bryan et al. (147) who demonstrated comparable in-hospital mortality among patients with and without diabetes in a later SAB cohort study. Yet, increased in-hospital mortality was found among patients with diabetes in a later study by Maradona et al. (154). More recent studies continue to be characterized by inconsistent results. An American SAB cohort study by Mylotte et al. (42) found a 2.5-fold increased risk of 30-day mortality, which was supported by a cohort study from New Zealand (71). Moreover, in an American RCT subgroup analysis on patients with SAB and concurrent endocarditis, Kanafani et al. (155) reported an all-cause mortality at 6

weeks of 22.1% in patients with diabetes vs. 11.4% in patients without. On the other hand, in-hospital mortality did not differ in a Canadian cohort study on invasive *S. aureus* infection (148) or in a Swiss cohort study on SAB (40). These findings were corroborated by results from a cohort study by Kaasch et al. (3) who found no association between diabetes and increased 30-day mortality in patients with SAB.

Nevertheless, a number of important limitations should be taken into account in the interpretation of these prior results. The majority of the studies were conducted in tertiary care centers (40, 42, 152-155), which increases the risk of selection bias (158-159) and hampers the generalizability of the results (160-161). In addition, limited numbers of patients with SAB (40, 42, 152-155) and diabetes (40, 42, 71, 147-148, 152-155), respectively, and restriction of the follow-up to the in-hospital period (42, 147-148, 154) may have influenced the findings.

Study IV

A few previous studies have included CHF among a variety of variables in their prognostic models (Table 3) (39-40, 156-157). In a Swiss single-center SAB cohort study, Kaech et al. (40) reported a 2.5-fold increased risk of death within 90 days associated with CHF. In a later Columbian cohort study specifically investigating cancer patients with SAB, Cuervo et al. (156) observed an adjusted HR as high as 10.6 (95% CI, 1.8-63.7) for 90-day SAB-related death among patients with CHF compared to patients without. Lin et al. (157) conducted a cohort study in Taiwan on patients with persistent MRSA bacteremia suggesting that CHF was associated with increased 30-day mortality and, finally, a Norwegian cohort study assessing SAB outcome (39) demonstrated that patients with CHF were more than two times likely to die during 30 days of follow-up, compared with patients without CHF. However, CHF was only included among a variety of variables in these previous studies and none of them assessed the prognostic influence of SAB as the primary objective.

Moreover, the prior results may in part be explained by small (39-40, 156-157) and selected study populations (39-40, 156-157) including few patients with CHF (n<70), and insufficient adjustment for concomitant comorbid conditions (40) may also have influenced the results.

2.6 Limitations of the existing literature

In summary, little is known about whether differences in the definition of HCA infection influences the prevalence of HCA infection, patient characteristics, and outcome. The few previous studies on this subject had other primary objectives and none assessed specifically the impact of different definitions of HCA infection in patients with SAB. Although a number of previous studies have included diabetes among a variety of variables in their statistical models, data elucidating the association between diabetes and SAB remain sparse. Moreover, the prior studies yielded inconsistent results and the majority were restricted by selected and small sample sizes (including few patients with diabetes), insufficient confounder control, and incomplete follow-up, which may further have limited their results. Analogous with diabetes, there is a scarcity of in-depth data elucidating the influence of CHF on SAB prognosis and previous results may be influenced by selection bias rendering comparison to other settings difficult. Thus, considerable gaps in the available knowledge exist and evidence derived from population-based studies is needed.

2.7 Aims of the thesis

I. To investigate whether different definitions of healthcare-associated infection affect the proportion of patients classified as HCA-SAB, and whether the prevalence of patient characteristics and mortality reported in the HCA-SAB group vary by disparate definitions.

II. To investigate the risk of CA-SAB comparing patients with and without diabetes overall and according to characteristics of diabetes (e.g., diabetes type, duration of diabetes, and presence of diabetes complications).

III. To investigate the influence of diabetes on 30-day all-cause mortality in patients with CA-SAB overall, among patients with and without recent healthcare contacts, and according to characteristics of diabetes (in particular diabetes type, duration, and presence of diabetes complications).

IV. To investigate 90-day all-cause mortality in patients with CA-SAB comparing patients with and without CHF overall and according to presence of CHF-related conditions (e.g., cardiomyopathy and valvular heart disease), CHF severity, and duration of CHF.

3. Methods

3.1 Setting

The four studies were conducted during January 1, 2000 and December 31, 2011 in the Northern and Central Regions of Denmark, within a population of approximately 1.8 million residents. During the study period, a reform of local government merged four counties into two health regions: Central Denmark Region and North Denmark Region, collectively referred to as Northern Denmark. The study setting is served by two university hospitals and a decreasing number of regional hospitals (22 regional hospitals in 2000 versus 7 regional hospitals in 2011). Tax-supported, unfettered healthcare is available for the entire Danish population and all patients hospitalized with acute conditions are treated free of charge in these public hospitals.

3.2 Data sources

We conducted all four studies using routinely recorded data from population-based medical registries and databases. All Danish residents are given a unique 10-digit identification number (the Civil Registration Number) upon birth or immigration, which facilitates unambiguous linkage of records between the data sources (162-163) (Figure 1).

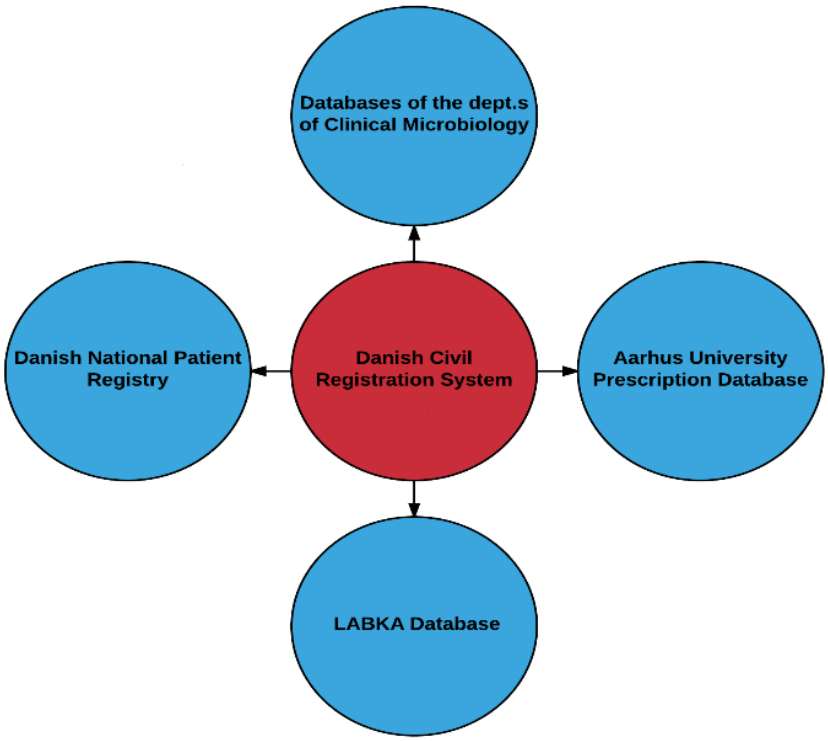


Figure 1. Data sources in studies I-IV.

3.2.1 Databases of the departments of clinical microbiology (studies I-IV)

Data on SAB were retrieved from the laboratory information systems (hereafter referred to as databases) of the departments of clinical microbiology which provided diagnostic bacteriology for the entire catchment area. During the study period, Central Denmark Region was served by three departments of clinical microbiology located in Aarhus (Aarhus University Hospital), Viborg (Regional Hospital of Viborg), and Herning (Regional Hospital West Jutland), while North Denmark Region was served by one department of clinical microbiology in Aalborg (Aalborg University Hospital). Data were obtained as part of everyday clinical practice and included the date and hour of the blood draw, number of bacterial isolates, and susceptibility to a range of antibiotics. For a small subset of blood cultures the date of receipt in the laboratory was substituted due to missing information. Blood cultures were requested by the attending physician and blood samples

were obtained by biotechnicians. Throughout the study period, the BacT/Alert blood culture system (bioMérieux, Marcy l'Etoil, France) was utilized at all hospital sites. In North Denmark Region, a standard blood culture for adults included one set with three bottles (two aerobic and one anaerobic bottle), whereas the standard for adults included two sets with two bottles each (one aerobic and one anaerobic bottle) in Central Denmark Region.

S. aureus was identified by horse plasma tube coagulase test or an equivalent commercial latex agglutination test and susceptibility testing was conducted locally by disk diffusion. All blood culture isolates were subsequently submitted to the Staphylococcal Reference Laboratory at Statens Serum Institut (Copenhagen) for national surveillance (25), definitive identification, and serotyping. Screening for methicillin resistance differed between hospital sites during 2000-2002, however from 2003 onwards, the cefoxitin disk diffusion test was used both locally and at Statens Serum Institut (164-165). Detection of the *mecA* gene cassette was conducted by in-house polymerase chain reaction (PCR) or the EVIGENE^{TM} hybridization test.

3.2.2 The Danish Civil Registration System (studies I-IV)

The Danish Civil Registration System (DCRS) was established in 1968 (162-163). This registry keeps track of demographic data (including gender, age, and marital status) and vital statistics including date of birth, changes in address, dates of immigrations and emigrations, and exact date of death. The DCRS is electronically updated daily, which ensures virtually complete patient follow-up.

3.2.3 The Danish National Patient Registry (studies I-IV)

The Danish National Patient Registry (DNPR) tracks information on all citizens admitted to Danish non-psychiatric hospitals since January 1, 1977 (166-167). From 1995 onwards, the register was

expanded to include data on emergency department visits and outpatient clinics as well. Each record includes the dates of admission and discharge, data on surgical procedures, one physician-assigned primary diagnosis and one or more optional secondary diagnoses, classified according to the International Classification of Diseases, 8th revision until the end of 1993 and the 10th revision thereafter (the 9th revision was never applied in Denmark). Since 1996, surgical procedures have been recorded with the Nordic Medico Statistical Committee Classification of Surgical Procedures codes (168). Of note, reporting to the DNPR is mandatory.

3.2.4 The LABKA database (studies II-IV)

The clinical laboratory information system (LABKA) research database is maintained by the Department of Clinical Epidemiology, Aarhus University Hospital (169). This database keeps laboratory test results using NPU codes (Nomenclature, Properties, Units) and local analysis codes for blood samples obtained during visits to general physicians and hospitals in Northern Denmark, since 1997 and 2000, respectively. In addition, the exact time of blood sample collection is recorded.

3.2.5 The Aarhus University Prescription Database (studies I-IV)

The Aarhus University Prescription Database (AUPD), also maintained by the Department of Clinical Epidemiology at Aarhus University Hospital, holds individual-level data on all reimbursable prescriptions dispensed at community pharmacies in Northern Denmark since 1998 (170). Each record logs data on the prescription redemption date and the type and quantity of medication dispensed according to the Anatomical Therapeutic Chemical (ATC) classification system.

3.3 Study designs

Using the data sources described above, we conducted a cross-sectional study (study I), a case-control study (study II), and two cohort studies (studies III and IV). The study period, 1 January 2000 and 31 December 2011, was the same for all studies. Table 4 provides an overview of the design of the four studies. According to Danish legislation, individual informed consent is not required for studies based entirely on registry data. All studies were approved by the Danish Data Protection Agency (ref. no. 2012-41-0942).

3.4 Study populations

In all four studies the population of interest was patients with SAB. Detailed information on SAB was available in the databases of the departments of clinical microbiology and we defined eligible cases as patients aged ≥15 years with one or more positive blood cultures with *S. aureus* as the only isolate. Because SAB recurrence is associated with risk and prognosis (45-46), we restricted the study population to patients with incident SAB, defined as no previous SAB diagnosis within at least five years of the current SAB episode.

SAB was defined as community-acquired if the first positive blood culture had been drawn within two days of admission and hospital-acquired (HA-SAB) if the first positive blood culture had been obtained >2 days after admission. In studies II-IV, patients with CA-SAB and healthcare contacts within 30 days of the current admission were further sub-classified as healthcare-associated SAB (HCA-SAB) if one or more of the following criteria were met: hospital admission, visit to hospital outpatient surgical clinics, visit to hospital hematology, oncology, or nephrology clinics. SAB patients admitted from nursing homes or long-term care facilities were classified as CA-SAB if they did not fulfill the HCA-SAB criteria.

In study I, a descriptive cross-sectional study, we included all patients with SAB. However, as mentioned in relation to the thesis outline, HA-SAB is associated with several factors including concurrent disease and invasive procedures, which might introduce a risk of confounding the association between diabetes, CHF and the risk and prognosis of SAB. Therefore, to reduce the risk of bias, we restricted our study population to patients with CA-SAB in studies II-IV. In study III, a case-control-study, we randomly selected 10 population controls from the DCRS on the date the first positive blood culture was drawn, matched to each CA-SAB case by age, gender, and residence. The risk set sampling technique was applied (171), requiring that the population controls had to be alive and at risk of a first CA-SAB at the time the corresponding case was diagnosed. Population controls were assigned an index date identical to that of the corresponding case.

Table 4. Overview of study designs in the four studies of the thesis.

	Study I	**Study II**	**Study III**	**Study IV**
Objectives	To investigate whether different definitions of HCA-SAB influenced the prevalence, clinical characteristics, and outcome of patients with HCA-SAB	To investigate whether diabetes is a risk factor for CA-SAB	To investigate the prognostic influence of diabetes in patients with CA-SAB	To investigate the prognostic influence of CHF in patients with CA-SAB
Data sources	Databases of the departments of clinical microbiology, DCRS, DNPR, LABKA, AUPD	Databases of the departments of clinical microbiology, DCRS, DNPR, LABKA, AUPD	Databases of the departments of clinical microbiology, DCRS, DNPR, LABKA, AUPD	Databases of the departments of clinical microbiology, DCRS, DNPR, LABKA, AUPD
Design and period	Population-based cross-sectional study, 2000-2011	Population-based case-control study, 2000-2011	Population-based cohort study, 2000-2011	Population-based cohort study, 2000-2011
Study population	4,385 adult patients with incident SAB	2,638 adult patients with incident CA-SAB and 26,379 population controls matched by age, gender, and residence	2,638 adult patients with incident CA-SAB	2,638 adult patients with incident CA-SAB
Exposure	Five different definitions of HCA-SAB	Diabetes (overall and according to characteristics of patients with diabetes)	Diabetes (overall and according to characteristics of patients with diabetes)	CHF (overall, and according to CHF-related conditions, CHF severity and CHF duration)
Outcome	Prevalence proportions of HCA-SAB, patient characteristics, and 30-day all-cause mortality according to each definition	CA-SAB	30-day all-cause mortality	90-day all-cause mortality

Covariates	Listed under outcome	Age, gender, marital status, m-CCI level, specific previous morbidity, preadmission medication use	Age, gender, marital status, m-CCI level, specific previous morbidity, preadmission medication use	Age, gender, marital status, m-CCI level, specific previous morbidity, preadmission medication use
Statistical analyses	Descriptive statistics, Kaplan-Meier estimation of 30-day mortality	Conditional and conventional logistic regression	Cox proportional hazards regression	Cox proportional hazards regression
Confounder control	n/a	Restriction, matching, multivariate adjustment, stratification	Restriction, multivariate adjustment, stratification	Restriction, multivariate adjustment, stratification

Abbreviations: AUPD=Aarhus University Prescription Database; CA-SAB=community-acquired *Staphylococcus aureus* bacteremia; CHF=chronic heart failure; DCRS=Danish Civil Registration System; DNPR=Danish National Patient Registry; HCA-SAB= healthcare-associated *Staphylococcus aureus* bacteremia; LABKA=laboratory database; m-CCI=modified Charlson Comorbidity Index; n/a=not applicable; SAB: *Staphylococcus aureus* bacteremia.

3.5 Exposures

3.5.1 HCA infection definitions (study I)

In order to classify patients as CA-SAB, HA-SAB or HCA-SAB, we collected a complete history of all patients´ hospital contacts and preadmission medication use via the DNPR and AUPD. Patients with SAB were first classified as either CA-SAB or HA-SAB. Based on our review of the literature, we then suggested five different definitions of HCA infection (the criteria are provided in Table 5) and patients were classified as HCA-SAB or ´true´ CA-SAB according to each definition. To allow comparisons among groups, we ranked the definitions in a decreasing order concerning stringency of criteria.

Table 5. Five definitions of healthcare-associated (HCA) *S. aureus* bacteremia.

	Definition	**Criteria** *Blood culture performed within 2 days of admission and the following:*
Highest level of stringency	**1.**	▪ Any hospital inpatient admission within the previous 30 days
⇣	**2.**	▪ Any hospital inpatient admission within the previous 30 days *or* ▪ Hospital outpatient clinic visit including surgery or visits to clinics of oncology, hematology or nephrology within the previous 30 days
	3.	▪ Any hospital inpatient admission within the previous 30 days *or* ▪ Any type of hospital outpatient clinic visit within the previous 30 days
	4.	▪ Any hospital inpatient admission within the past 90 days *or* ▪ Any type of hospital outpatient clinic visit within the previous 30 days
Lowest level of stringency	**5.**	▪ Any hospital inpatient admission within the past 90 days *or* ▪ Any type of hospital outpatient clinic visit within the previous 30 days *or* ▪ Antibiotic or immunosuppressive treatment 30 days prior to admission

3.5.2 Diabetes (studies II and III)

In studies II and III, patients with diabetes were identified using a previously validated method (131) incorporating two databases: the DNPR (166-167), and the AUPD (170). First, the DNPR provided information on all patients with a discharge or outpatient diagnosis of diabetes registered at any time prior to the index date. Second, the AUPD allowed for identification of patients with at least one recorded prescription for any anti diabetes drug at any time predating the index date. To further optimize the identification of patients with diabetes, we employed the LABKA database (169) to identify patients with a glycosylated hemoglobin A1c (HbA1c) level confirming diabetes ($\geq$ 6.5% (48 mmol/mol)) measured at any time before the index date. We classified patients as type 1 diabetes if they were aged up to 30 years at diagnosis and were treated with insulin as monotherapy and had no history of oral anti diabetes medication, or as type 2 diabetes (all other patients with diabetes).

We calculated the duration of diabetes as the time passed between the first record of diabetes (in any of the three registers) and the date the first positive blood culture was drawn. Data on all Hba1c measurements from the LABKA database within 12 months of the index date were obtained, which allowed us to assess the level of preadmission glycemic control (only the most recent Hba1c measurement before the index date was used in our analyses). In study 3, we further retrieved data on blood glucose levels on admission among patients with diabetes.

Using the DNPR, we collated data on the presence of macrovascular-, and microvascular complications. During the study period, no consistent or specific diagnostic codes were used for diabetic foot ulcers. Therefore, in study 2, we constructed two proxies of diabetic foot ulcers by identifying 1) patients with diabetes with conditions associated with diabetic foot ulcers (i.e., neuropathy and/or peripheral atherosclerosis or vascular disease) and 2) diabetes patients with previous lower-extremity ulcer diagnoses or ulcer-related procedures as described elsewhere (172).

Finally, we assessed the preadmission renal function of the study participants utilizing the most recent creatinine measurement from an outpatient hospital clinic or general practitioner one year to seven days prior to the index date and subsequently computed glomerular filtration rates (eGFR) using the four-variable version of the Modification of Diet in Renal Disease equation (173).

3.5.3 Chronic heart failure (study IV)

In study IV, we utilized the DNPR to identify patients diagnosed with CHF at any time before the current admission. CHF was defined as any previous hospital discharge diagnosis or outpatient diagnosis of congestive heart failure, pulmonary edema with mention of heart failure, left ventricular failure, unspecified heart failure, cardiomyopathy, or hypertensive heart disease with congestive heart failure (with or without hypertensive renal disease or renal failure). We further disaggregated patients with CHF into five subcategories of CHF-related conditions: 1) cardiomyopathy (with or without any of the following diagnoses), 2) heart valve disease (with or without any of the other diagnoses except cardiomyopathy), 3) previous myocardial infarction (with or without atrial fibrillation), 4) atrial fibrillation only, and 5) none of the above diagnoses.
The DNPR (166-167) does not include information on the severity of CHF. Therefore, as a surrogate measure of increasing CHF severity, we categorized patients according to daily dosage of filled prescriptions of loop-diuretics: non-users (no loop-diuretics), low dose (≤40 mg/day), medium dose (41-80 mg/day), high dose (81-159 mg/day), and very high dose (≥160 mg/day). We also calculated mean loop-diuretic dosages by dividing the number of dispensed tablets by a dispensing time interval of 180 days, as described previously (174-175). All data on preadmission loop-diuretic use were collated from the AUPD. Finally, duration of CHF was computed as the time passed between the first diagnosis of CHF and the date the first positive blood culture was drawn.

3.6 Outcomes

3.6.1 HCA-SAB prevalence proportions (study I)

In study I, the prevalence proportion of patients classified as HCA-SAB according to each of five HCA-definitions represented the primary outcome. Secondary outcomes were the prevalence of patient characteristics (e.g., age, gender, comorbidity) and 30-day all-cause mortality by each HCA-SAB definition.

3.6.2 CA-SAB (Study II)

In study II, the main outcome of interest was incident CA-SAB. A detailed case definition of CA-SAB is given in the section describing the study populations.

3.6.3 All-cause mortality (studies I, III-IV)

Information on vital status was obtained from the DCRS. In study I, 30-day mortality was assessed as a secondary outcome, whereas 30-day mortality constituted the primary outcome in study III. In study IV, the main outcome was 90-day mortality. Some previous studies have observed considerable additional mortality after 90 days and suggested that long-term survival should be taken into account in prognostic studies involving patients with SAB (176-178). Nevertheless, due to the acute and fulminant course of SAB, we consider it likely that the majority of deaths within up to 90 days after SAB are causally related to the infection and that the majority of additional deaths beyond 90 days are determined predominantly by the presence of coexisting morbidity. This is corroborated by results from a German cohort study on SAB (n=200) specifically ascertaining this problem. The investigators found that mortality after SAB plateaued after 90 days among patients

with little comorbidity, whereas an additional 13% of patients with severe comorbidity died after 90 days (179).

Distinguishing between death directly attributable to infection (i.e., CA-SAB) and death related to presence of preexisting morbidity is difficult and may potentially introduce bias, especially when historical data are used (178). Therefore, in studies III-IV, we decided to assess all-cause mortality only, which we consider a robust and clinically meaningful outcome.

3.7 Covariates

In all studies, we obtained information on a wide range of covariates. Demographic data were used to characterize the study populations, while other variables were included for confounder adjustment or to examine different effects across subgroups of patients.

3.7.1 Demographic data (studies I-IV)

Using the DCRS, we collected data on age, gender, and marital status on the date the first positive blood was drawn (or on the corresponding index date for controls). Unfortunately, we did not have detailed data on educational level or socioeconomic status, therefore marital status (married, divorced or widowed, never married) was utilized as a proxy and included as a factor in the stratification (study III) and in the adjustments (studies II-IV) (180).

3.7.2 Comorbidity (studies I-IV)

To assess the burden of comorbidity for each study participant and to evaluate the potential influence of preexisting disease on SAB risk and prognosis, we identified comorbid conditions included in the Charlson Comorbidity Index (CCI) (181) from all inpatient and outpatient discharge

diagnoses recorded in the DNPR. We applied a look-back period of ten years prior to (but excluding) the admission date or corresponding index date for the population controls in study II. The CCI assigns between 1 to 6 points to 19 major disease categories and has previously been validated for use with hospital discharge registry data in medical databases for the prediction of mortality (182). We computed aggregate Charlson Comorbidity Index (CCI) scores for each study participant, and defined three levels of comorbidity: low (CCI-score=0), intermediate (CCI-score=1-2), and high (CCI-score=>2). In studies II and III, diabetes represented the exposure variables, therefore we separated this condition from the CCI and the index was designated as a modified CCI (m-CCI). In line, a m-CCI excluding congestive heart failure was applied in study IV. Using the same look-back period (10 years), we also obtained data on a number of conditions not included in the CCI, counting hypertension, osteoporosis, dialysis within 30 days of the current admission/index date, and conditions related to drug or alcohol abuse.

3.7.3 Laboratory test results

In addition to the laboratory test results related to diabetes, we obtained data on plasma C-reactive protein measurements (study III) and white blood cell counts (study IV) from the LABKA database on the date the first positive blood culture was drawn. These data were used to explore potential differences in inflammatory responses to infection among exposed and unexposed patients.

3.7.4 Preadmission medication use (studies I-IV)

To characterize the study populations, and because some types of medications might influence the risk and prognosis of CA-SAB (183-185), we retrieved data on prescriptions redeemed prior to the current admission or the index date from the AUPD. In studies II-IV, we obtained information on any systemic antibiotic therapy and antineoplastic and immunomodulating agents within 30 days of

the current admission or index date. In studies II-IV, additional data were collated on any previous use of angiotensin-converting-enzyme inhibitors, beta blockers, low-dose acetylsalicylic acid, and statins.

3.8 Statistical analysis

Contingency tables with demographic data and clinical characteristics were constructed for each study, and all odds ratios (ORs) and mortality rate ratios (MRRs) were obtained with corresponding 95% confidence intervals (CIs). The potential confounding factors included in the multivariate adjustments were carefully selected a priori based on the existing knowledge on risk and prognostic factors for CA-SAB, which we consider preferable to data-driven selection processes (e.g., stepwise selection or change-in-estimate) (186). To assess potential differences in effect in subgroups of patients (effect measure modification), we conducted stratified analyses when relevant. Moreover, because the risk and prognosis of CA-SAB may differ among patients with and without recent preadmission healthcare exposure (92-94), we reran all analyses in studies II-IV restricting the study cohort alternately to patients with CA-SAB and HCA-SAB, respectively. We conducted all statistical analyses using STATA 11.2 for Windows (STATA, College Station, TX, USA).

3.8.1 Prevalence (study I)

First, we computed prevalence proportions (PPs) of patients classified as HCA-SAB by each HCA definition and presented the results graphically for comparison. Next, PPs for patient characteristics and outcomes according to each of the five HCA definitions were estimated. Finally, we compared the five HCA groups with each other and to the group including all CA-SAB patients (i.e. ´true´ CA-SAB and HCA-SAB). Thirty-day all-cause mortality was estimated using the Kaplan-Meier method.

3.8.2 Risk (study II)

Due to the matched design of study 2, we used conditional logistic regression to calculate crude and adjusted ORs of CA-SAB for persons with diabetes compared to persons without diabetes. When risk set sampling is applied, the odds ratios represent unbiased estimates of corresponding rate ratios in a similar cohort study (158). We further categorized diabetes exposure by diabetes type, duration of diabetes, the quality of the glycemic control, diabetes complications including diabetes foot ulcers, and preadmission renal function. All analyses were adjusted for marital status, m-CCI score, alcohol-related conditions, any statin use before the index date, and antibiotic treatment within 30 days of the index date. Using conventional logistic regression with additional adjustment for the matching factors, stratification was performed according to gender, age group, and m-CCI level.

3.8.3 Mortality (studies III and IV)

Time-to-event data were applied to investigate the influence of diabetes (study III) and chronic heart failure (study IV) on CA-SAB outcome, respectively. Follow-up began on the date the first positive blood culture was obtained, and all patients were followed until death, migration, or end of follow-up, whichever came first. The Kaplan-Meier method (1 – survival function) was used to compute and graphically display 30-day mortality in study III and 90-day mortality in study IV.
In study III, we used Cox proportional hazards regression to compare 30-day mortality rates for CA-SAB patients with and without diabetes as a measure of MRRs. Furthermore, we conducted stratified analyses according to gender, age category, marital status, and m-CCI level, and in a subgroup analysis restricted to patients with diabetes, we elucidated 30-day mortality by diabetes duration, the quality of glycemic control, diabetes complications, level of glucose on admission, and baseline preadmission renal function. The analyses were adjusted for age, gender, m-CCI score,

hypertension, alcohol-related conditions, marital status, and use of statins and antibiotics before admission. In the analyses assessing the influence of diabetes complications on mortality, the complication in question was excluded from the m-CCI prior to adjustment.

In study IV, a Cox proportional hazards regression model was applied to compute MRRs comparing 90-day mortality among CA-SAB patients with versus without CHF. Ninety-day mortality was further analyzed in subgroups of patients according to a number of CHF related conditions (e.g., concomitant valvular heart disease or atrial fibrillation), CHF severity (as measured by daily loop-diuretic dosage), and CHF duration. In studies III and IV, the assumption of proportional hazards in all Cox models was assessed graphically with log-minus-log plots and found appropriate.

4. Results

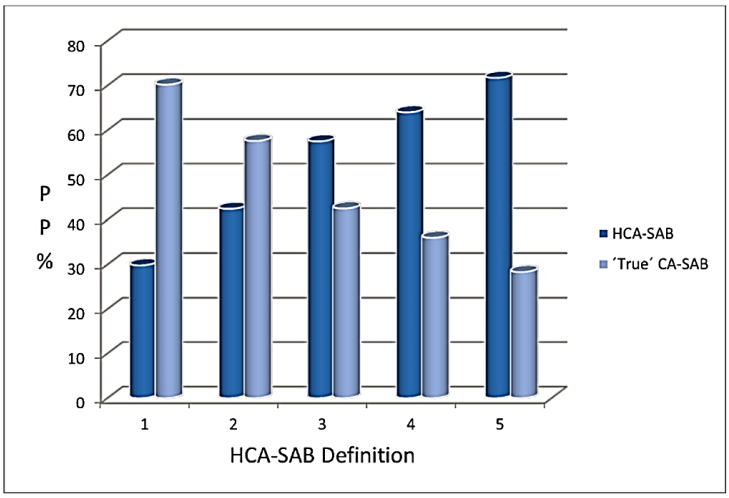
The main results of the four studies are outlined below. Further details are presented in Appendix B.

4.1 Study I

Study I included 4,385 patients hospitalized with incident SAB. Patients were most frequently male (60%), median age was 69 years (interquartile range (IQR), 57-79), and 70% had one or more conditions registered in the CCI. As little as 0.6% had MRSA bacteremia. A total of 2,638 (60.2%) were CA-SAB and 1,747 (39.8%) HA-SAB.

Figure 2 presents the proportional distribution of HCA-SAB according to each of the five definitions. The proportion of patients classified as HCA-SAB increased considerably from 29.8% of all CA-SAB episodes when the most stringent definition was applied (Def. 1) to 71.7% when using the least stringent definition (Def. 5). Correspondingly, the proportion of patients classified as ´true´ CA-SAB decreased from 70.2% with the most stringent definition (Def. 1) to 28.3% with the least stringent definition (Def 5.).

Figure 2. Prevalence proportions (PP) of patients classified as healthcare-associated (HCA) *S. aureus* bacteremia (SAB) and ´true´ community-acquired (CA) SAB by definition 1-5.



As shown in Table 5, the distribution of age, gender, and CCI score in patients with HCA-SAB varied little across the different definitions.

Table 5. Prevalence proportions of patient characteristics and 30-day mortality by definition 1-5 of healthcare-associated (HCA) *S.aureus* bacteremia (SAB).

	Definition 1	**Definition 2**	**Definition 3**	**Definition 4**	**Definition 5**
	Decreasing stringency of HCA-SAB definitions ⟶				
n (% of all CA-SAB)	787 (29.8)	1115 (42.3)	1517 (57.5)	1688 (64.0)	1892 (71.7)
Age >75 years	238 (30.2)	307 (27.5)	464 (30.6)	561 (33.2)	649 (34.3)
Male gender	454 (57.7)	663 (59.5)	914 (60.3)	1019 (60.4)	1147 (60.6)
MRSA-SAB	5 (0.6)	6 (0.5)	11 (0.7)	12 (0.7)	12 (0.6)
CCI score					
Low (0)	119 (15.1)	136 (12.2)	229 (15.1)	262 (15.5)	355 (18.8)
Intermediate (1-2)	286 (36.3)	371 (33.3)	540 (35.6)	612 (36.3)	690 (36.5)
High (≥3)	382 (48.5)	608 (54.5)	748 (49.3)	814 (48.2)	847 (44.8)
30-day mortality	195 (24.8)	252 (22.6)	344 (22.7)	406 (24.1)	468 (24.7)

CA-SAB: community-acquired SAB. MRSA-SAB: methicillin-resistant SAB. CCI: Charlson Comorbidity Index.

Contrasting patients classified initially as CA-SAB (i.e. ´true´ CA-SAB and HCA-SAB) with patients in the Def.1 group, patients with CA-SAB patients were more frequently older than 75 years (35.9% vs 30.2%), more likely to be male (61.3% vs. 57.7%), and more frequently characterized by a low CCI score (27.5% vs. 15.1%).

4.2 Study II

For study II, we included 2,638 patients with incident CA-SAB and 26,379 population controls. The median age of the study participants was 69 years (IQR, 56-79) and the majority was male (61%). Forty-two percent of all CA-SAB patients had recently been in contact with the healthcare system (HCA-SAB), and a considerably higher proportion of cases than controls (69.3% vs. 27.8%) had one or more hospital-diagnosed comorbidities.

As outlined in Table 6, diabetes was strongly associated with increased risk of CA-SAB. We observed no notable differences in risk estimates for cases with and without recent healthcare contacts, respectively.

Table 6. Unadjusted and adjusted odds ratios (ORs) for community-acquired *S. aureus* bacteremia according to presence of diabetes.

	Cases	**Controls**	**Unadjusted OR (95% CI)**	**Adjusted[1] OR (95% CI)**
Diabetes				
Absent	1,925 (73.0)	23,884 (90.5)	1.0 (ref.)	1.0 (ref.)
Present	713 (27.0)	2,495 (9.5)	3.7 (3.4-4.1)	2.8 (2.5-3.1)

[1]Adjusted for: conditions included in the modified Charlson Comorbidity Index, marital status, alcohol-related conditions, any statin use predating the index date, and antibiotic therapy within 30 days of the index date.

In analyses stratified according to characteristics of patients with diabetes, the increased risk of CA-SAB remained robust across all strata. Nevertheless, compared to patients without diabetes the risk of CA-SAB was most pronounced among patients with type 1 diabetes (aOR=7.2 (95% CI, 3.9-

13.0)), patients with ≥10 years of diabetes history (aOR=3.8 (95% CI, 3.2-4.6)), patients with a Hba1c ≥9% (aOR=5.7 (95% CI, 4.2-7.7)), and patients with diabetes complications, in particular microvascular disease (aOR=5.5 (95% CI, 4.2-7.2)).

The risk of CA-SAB appeared slightly higher among female patients compared to males (adjusted ORs 3.2 (95% CI, 2.6-3.8) vs. 2.5 (95% CI, 2.2-2.9). Furthermore, the relative impact of diabetes was most pronounced in younger patients and in patients without coexisting morbidities.

4.3 Study III

In study III, we included 2,638 patients with CA-SAB, including 713 (27.0%) with diabetes. The median age of patients with and without diabetes was comparable (71 vs. 68 years), and there were slightly more men among patients with diabetes (63.4% vs. 60.5%). Among patients with diabetes, 44% were classified as HCA-SAB compared to 42% among patients without diabetes. Patients with diabetes had considerably more comorbidity registered in the m-CCI, including CHF (23.0% vs. 9.6%), cerebrovascular disease (16.3% vs. 10.3%), and peripheral vascular disease (22.9% vs. 8.6%), as compared to patients without diabetes.

The overall 30-day cumulative mortality in patients with diabetes was 25.8% and 24.3% in patients without DM, yielding an aMRR of 1.01 (95% CI, 0.94-1.20). The corresponding estimates according to type of SAB are given in Table 7.

Table 7. Unadjusted and adjusted 30-day mortality in incident *S. aureus* bacteremia (SAB) patients with versus without diabetes.

	n	30-day mortality (95% CI)	Unadjusted MRR (95% CI)	Adjusted[2] MRR (95% CI)
All SAB				
No diabetes	1925	24.3 (22.5–26.3)	1.00 (ref.)	1.00 (ref.)
Diabetes	713	25.8 (22.8–29.2)	1.07 (0.90–1.27)	1.01 (0.84–1.20)
Type 1 diabetes	40	5.0 (1.3–18.6)	0.19 (0.47–0.75)	0.59 (0.14–2.39)
Type 2 diabetes	673	27.0 (23.9–30.6)	1.13 (0.95–1.34)	1.01 (0.85–1.21)
CA-SAB				
No diabetes	1125	24.9 (22.5–27.5)	1.00 (ref.)	1.00 (ref.)
Diabetes	398	30.4 (26.1–35.2)	1.26 (1.02–1.56)	1.13 (0.91–1.41)
HCA-SAB				
No diabetes	800	23.5 (20.7–26.6)	1.00 (ref.)	1.00 (ref.)
Diabetes	315	20.0 (15.9–24.9)	0.84 (0.63–1.11)	0.84 (0.62–1.14)

MRR: unadjusted mortality rate ratio. CA-SAB: community-acquired SAB. HCA-SAB: healthcare-associated SAB. Adjusted for: age, gender, marital status, conditions included in the modified Charlson Comorbidity Index, hypertension, alcohol-related conditions, any previous statin use prior to admission, and antibiotic therapy 30 days prior to admission.

We observed no notable differences in 30-day mortality according to gender, age group, marital status, or m-CCI level in patients with and without diabetes. Duration of diabetes did not notably influence 30-day mortality. Thus, compared with 0-3 years of diabetes duration, the aMRRs were 0.72 (95% CI, 0.47-1.12) for 3-5 years of diabetes history and 0.87 (95% CI, 0.59-1.27) for > 10

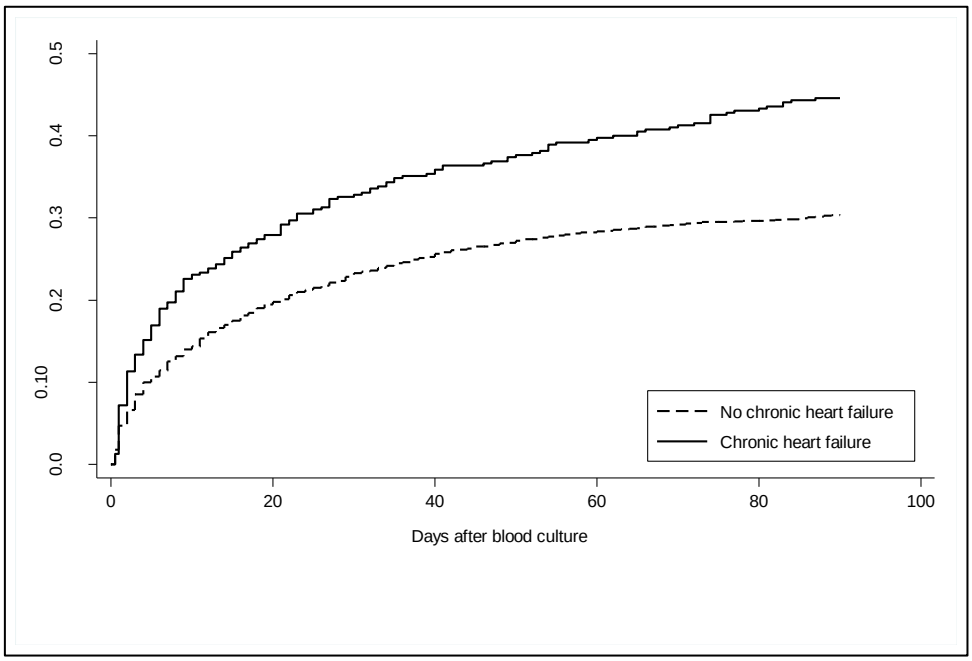
years. In line, the estimates of 30-day mortality did not differ notably according to other characteristics of patients with diabetes, including the level of glycemic control, glucose level on admission, or the presence of micro- or macrovascular complications.

4.4 Study IV

Study IV included 2,638 patients with incident CA-SAB, of whom 390 (14.8%) had CHF. The majority of patients with CHF were males (64.9% vs 60.6%) and the median age was 77 (IQR, 70-82) and 67 (IQR, 54-78) years for patients with vs. without CHF, respectively. The proportion with HCA-SAB was comparable among patients with and without CHF (48% vs. 41%). Patients with CHF had a higher prevalence of hospital-diagnosed comorbidity than patients without CHF, including diabetes (31.0% vs. 12.8%), hypertension (49.5% vs. 20.4%), and renal disease (33.3% vs. 13.6%).

Figure 3 presents Kaplan-Meier curves for 90 days of follow-up. The cumulative mortality in patients with CHF compared with patients without CHF was 44.6% *cf.* 30.4% after 90 days, corresponding to an MRR of 1.60 (95% CI, 1.36-89) and an aMRR of 1.24 (95% CI, 1.04-1.48). Restricting the study cohort alternately to patients with and without recent healthcare contacts did not influence the estimates notably.

Figure 3. Cumulative 90-day mortality in patients with incident community-acquired *S. aureus* bacteremia with versus without chronic heart failure.



Compared with patients without CHF, the excess 90-day mortality was most prominent among CHF patients with concomitant valvular disease (aMRR=1.73 (95% CI, 1.26-2.38)) and CHF patients with a daily loop-diuretic dosage greater than 160 mg/day (aMRR=1.62 (95% CI, 1.21-2.18)). In addition, CHF duration of less than three years was associated with increased mortality (aMRR=1.43 (95% CI, 1.14-1.78)), whereas longer duration of CHF was not found to be associated with a poor outcome, as compared to patients without CHF. The estimates of 90-day mortality did not differ notably across gender, age categories, or m-CCI level.

5. Discussion

5.1 Comparison with the existing literature

The following section provides a discussion of our results in relation to the existing literature (Table 3) and possible mechanisms underlying our findings are briefly touched upon.

5.1.1 Study I

To our knowledge, this is the first study to specifically investigate whether different definitions of HCA infection influences the prevalence, patient characteristics and outcome in patients with SAB. An American cross-sectional study investigating MRSA infection prevalence, reported that the prevalence of HCA-MRSA infection was 51% with use of CDC nosocomial infection criteria compared with 95% according to use of healthcare risk factor exposure criteria (e.g., recent hospitalization or residence in a long-term care facility) (143). However, the study was restricted to a limited number of patients (n=100) from a single tertiary-care center, which may have biased the findings. Two American cross-sectional studies of different size (n=352 and n=2,151, respectively) examined the prevalence of HCA- vs. CA-MRSA infections dependent on epidemiological classification criteria and antimicrobial co-resistance (144-145). Using these different classification schemes, McCarthy et al. (144) reported comparable prevalences of HCA-MRSA infections (54% vs. 44%), whereas the prevalences of HCA-MRSA differed dependent on the definition (37% vs. 54%) according to Sievert et al. (145). Still, in the study by McCarthy et al. (144), the definition of HCA-MRSA was not explicitly described, and the study by Sievert et al. (145) was limited by missing data. In a Canadian cross-sectional study of 100 patients with MRSA infection, Leung et al. (146) found no notable difference in HCA-MRSA prevalence with use of either a 4-week or 12-month look-back window (reclassification error rate=2%). A Danish cohort study of 56,606 patients

with bacteremia examined whether use of different time windows to distinguish between CA-, HCA-, and HA bacteremia influenced the results of prognostic models (66). In accordance with our results, no difference in 30-day mortality was observed for HCA patients in relation to a 30- or 90-day time window. However, the applied definitions of HCA differed only with regard to time windows and in-depth comparisons of patient characteristics according to different HCA definitions were beyond the scope of the study. In contrast to our study, infections were classified as either HCA or CA in all but one of the previous studies (66), i.e., HA infection was not considered a distinct entity and these patients were included by the HCA infection definition. In addition, the majority of the previous studies included other types of *S. aureus* infection than SAB. Thus, a direct comparison with our results may not be straightforward.

Based on our observations, we may speculate that the substantial differences in HCA-prevalence observed in previous studies of SAB is more dependent on differences in definitions of HCA infection and less so on actual discrepancies in local settings and the populations being studied.

Further, comparing patients with CA-SAB and HCA-SAB, we observed no differences in 30-day mortality. This is in contrast to results from some previous studies of bacteremia (including SAB) reporting an increased risk of death associated with HCA infection (92-94), which may be driven partly by increased colonization and infection with MRSA (187-188). Our study was conducted in a setting with very low MRSA prevalence among SAB isolates, and this might partly explain our observations.

5.1.2 Study II

To the best of our knowledge, we present the first report assessing diabetes as a risk factor for SAB as the primary aim of the study. An American cohort study (147) including 397 patients with SAB reported that the number of SAB episodes was 3.0 per 1000 patient-years in patients with diabetes

compared with 1.2 per 1000 patient-years in patients without. Nevertheless, only 46 patients with diabetes were enrolled in the study and the inclusion of non-incident cases may have inflated the results. In two previous cohort studies from Canada and Sweden (77, 148), respectively, the investigators elucidated whether diabetes was associated with increased risk of invasive *S. aureus* infection, defined as the identification of *S. aureus* from blood, cerebrospinal fluid, pleural or synovial fluid, or aseptically obtained surgical-tissue samples or deep-tissue aspirates. The Canadian study reported an unadjusted RR of 7.7 (95% CI, 5.0-9.7) for invasive *S. aureus* infection associated with diabetes (148), which was in line with the Swedish results (unadjusted OR=8.2 (95% CI, 6-12)) (77). Yet, in the Canadian study the number of patients with diabetes was determined solely on survey estimates and the use of a composite end point (invasive *S. aureus* infection) may render interpretation and direct comparison with our results difficult. An Italian combined case-control and cohort study including 165 patients with SAB reported an increased risk of diabetes associated with CA-SAB (aOR=6.21 (95% CI, 1.62-23.77)) (72) whereas, interestingly, no increased risk was observed for HA-SAB or HCA-SAB. Still, the investigators used controls sampled from hospital wards, which may not be an optimal comparison group when assessing specifically the risk of CA-SAB (189). Furthermore, an American cohort study of 5,630 emergency department patients suspected of infection identified diabetes as a risk factor for MRSA bacteremia (aOR=2.02 (95% CI, 1.13-3.61)) (150), and Hernandez et al. (151) observed an association between diabetes and SAB of unknown origin (aOR=1.72 (95% CI, 1.01-2.91)) in a Spanish cohort study including 78 patients with SAB. However, the number of patients with diabetes was not provided in the American study and only 24 patients with diabetes were included in the Spanish study, therefore the validity of these findings is difficult to assess. Finally, it should be noted that unlike our work, no previous study has provided detailed estimates of SAB risk stratified according to characteristics of patients with diabetes or according to age, gender, and comorbidity level.

Several mechanisms may underlie our findings. When we adjusted for comorbid conditions the association between diabetes and CA-SAB attenuated, which may indicate that the observed risk associated with diabetes is at least partly driven by general frailty secondary to the presence of multiple comorbidities. Also, specific diabetes complications may increase the risk of CA-SAB, which is supported by our findings of particularly high CA-SAB risk among diabetes patients with foot ulcers and patients with poor kidney function. Moreover, as described in the background section of the thesis, diabetes influences immune responses through different pathways (125-133), which can lead to generally decreased immunity and subsequent increased risk of systemic infection, yet the design of our study did not allow for investigation of these potential mechanisms. Summarizing the results from our study and previous studies, there is substantial evidence of diabetes being associated with increased risk of CA-SAB.

5.1.3 Study III

To the best of our knowledge, no previous study has investigated the prognostic influence of diabetes in patients with SAB as the primary aim. However, a number of previous studies on SAB have assessed diabetes among a variety of potential prognostic factors with highly conflicting results. In an American cohort study of 185 patients with SAB, Cluff et al. (152) observed an in-hospital mortality of 17% among patients with no comorbidity compared with 69% among patients with diabetes, which was supported by results from a Spanish cohort (n=274) (154) reporting an increased risk of SAB-related in-hospital death associated with diabetes (p=0.054). Yet, only a limited number of patients with diabetes were included in both studies (n=26 and n=44, respectively) and post-discharge follow-up was missing. In a more recent American cohort study on 293 patients with SAB, Mylotte et al. (42) observed an aOR for 30-day mortality of 2.4 (95% CI, 1.2-4.7) associated with diabetes, which was supported by results from a SAB cohort study from

New Zealand (n=424) reporting a corresponding a 30-day mortality RR of 1.5 (95% CI, 1.0-2.4) (71). However, both studies were conducted at tertiary care centers which increases the risk of selection bias (159). Moreover, the American study was not restricted to incident cases which may falsely inflate the outcome measures (160). Kanafani et al. (155) reported an all-cause mortality at 6 weeks of 22.1% in patients with diabetes vs. 11.4% in patients without in an American RCT subgroup analysis on 235 patients with SAB. However, the study population was restricted to patients with SAB and concomitant infective endocarditis which may hinder a direct comparison with our results.

In contrast, other previous studies have observed no association between diabetes and increased mortality in patients with SAB. In an American cohort of 397 patients with SAB, Cooper et al. (153) observed almost similar in-hospital mortality among patients with diabetes (n=27) and without diabetes (n=34), and an American cohort study including 397 patients with SAB reported an in-hospital mortality of 15.8% among patients with diabetes vs. 24.8% in patients without (147). Still, as both of these studies were limited by restriction to in-hospital mortality and insufficient control for concurrent comorbid conditions these results should be interpreted cautiously. In concordance, no difference in in-hospital mortality was reported in a Canadian cohort study on invasive *S. aureus* infection (n=264) (148) and in a Swiss cohort study of 308 patients with SAB (40). Yet, the exact estimates on mortality associated with diabetes were not given in these papers, and again, follow-up after discharge was not available. Finally, these findings were corroborated by results from one of the hitherto largest cohort studies on SAB (n=3,395) conducted in a multi-national setting where Kaasch et al. (3) reported an adjusted HR for 30-day all-cause mortality of 1.12 (95% CI, 0.95-1.33) associated with diabetes. In contrast to our study, none of the previous studies ascertained the impact of diabetes duration, the level of glycemic control, or presence of diabetes complications.

The mechanisms underlying our null results are not entirely clear. Comparing patients with and without diabetes, we observed no differences in the inflammatory response as measured by the plasma C-reactive protein level on admission and the distribution of important prognostic markers (including age, gender, and m-CCI level) were roughly the same. Furthermore, the majority of patients in our study were > 65 years old and suffered from multiple chronic diseases, which may suggest that the high mortality associated with CA-SAB is conveyed primarily by the accumulated burden of comorbidity, age, and gender and less so by individual comorbidities such as diabetes. In consideration of the inconsistency and limitations of previous studies, our work provides clarification and firm evidence that diabetes is not associated with increased mortality in patients with CA-SAB.

5.1.4 Study IV

Our study is, to the best of our knowledge, the first to specifically investigate CHF as a prognostic factor in patients with SAB, and our results are corroborated by the existing quite limited literature. Kaech et al. (40) reported an unadjusted OR for 90-day mortality of 2.4 (95% CI, 1.0-5.6) associated with CHF in in a study of 308 patients with SAB. Yet, the results may be inflated due to insufficient adjustment for comorbid conditions, and unfortunately, follow-up was restricted to in-hospital mortality. A Columbian cohort study by Cuervo et al. (156) observed an adjusted HR of 10.6 (95% CI, 1.8-63.7) for 90-day SAB-related mortality associated with CHF, which is markedly higher than the corresponding estimate in our study (aMRR=1.24 (95% CI, 1.04-1.48)). However, the Columbian study included only 9 patients with CHF and, as indicated by the wide CI, cautious interpretation is indeed warranted. Moreover, the study was restricted to patients with cancer and misclassification of SAB-related death may also have influenced the results. In a Taiwanese cohort study including 227 patients with persistent MRSA bacteremia, an increased 30-day mortality

associated with CHF (aOR=2.85 (95% CI, 1.44-5.65)) was observed (157). Yet, the study employed a highly selected study population hampering the external generalizeability and, again, only a limited number of patients with CHF were available for analysis (n=63). Finally, a Norwegian cohort study (n=374 patients with SAB) (39) reported an aOR for 30-day mortality of 2.4 (95% CI, 1.21-4.80) associated with CHF. In contrast to our study, the influence of CHF on SAB prognosis was not assessed according to CHF related conditions, severity of CHF, or CHF duration in this or any of the other previous studies.

The explanation for the observed increased mortality in patients with CHF in our study is most likely multifactorial. Compared to patients without CHF, patients with CHF were characterized by advanced age, a higher m-CCI score, and a higher prevalence of CHF-related conditions (e.g., valvular heart disease) which are factors that influence outcome substantially in patients with SAB (1-2, 9-10, 119). Furthermore, patients with concomitant valvular heart disease experienced the highest mortality in our study and it may be speculated that valvular heart disease can lead to pulmonary edema and circulatory collapse secondary to severe systemic infection. Nevertheless, valvular heart disease also constitutes one of the most important risk factors for infective endocarditis (22), which may have contributed to the dismal prognosis of this particular subset of patients with CHF. Yet, due to lack of access to clinical and echocardiographic data, we were unfortunately not able to investigate this potential mechanism further. In summary, our data combined with previous results provide strong evidence that CHF constitutes an important prognostic factor in patients with CA-SAB.

5.2 Methodological considerations

Systematic and random error (chance) represent important threats to the internal validity of all observational studies and must therefore be carefully considered before inferring causal associations (159). Systematic error entails selection bias, information bias, and confounding bias whereas random error refers to the statistical precision of the estimates (159). In the following, the potential influence of bias and random error will be evaluated for each study.

5.2.1 Selection bias

Selection bias is defined as a systematic error arising from the procedures to select study participants and/or from factors that influence study participation (159). The bias comes about when the association between exposure and outcome differs for study participants and non-participants. The association between exposure and outcome among non-participants is rarely known, hence selection bias must usually be inferred as opposed to being observed (159).

In a cross-sectional design **(study I)**, selection bias may occur if the study population is not representative of the background population. However, because we used routinely collected data from population-based databases within the Danish unfettered and tax-supported healthcare system, we were able to capture all patients with incident SAB in Northern Denmark, thereby considerably reducing the risk of selection bias (190). Thirty-day mortality was assessed using the daily updated and virtually complete DCRS, thus we consider loss to follow-up highly improbable.

The results of our case-control study (**study II**) could have been influenced by selection bias if the inclusion of cases and controls into the study was dependent on exposure status, i.e., diabetes. We cannot entirely rule out that contact to the healthcare system is more frequent among patients with

diabetes and physicians may be more attentive to early signs of infection in patients with versus without diabetes. Consequently, a higher proportion of CA-SAB cases could have been hospitalized among patients with diabetes and time to blood culture draw and initiation of appropriate antibiotic treatment may thus have been shorter in patients with diabetes. Such surveillance bias would inflate the risk CA-SAB associated with diabetes. Nevertheless, due to the acute and fulminant clinical presentation of CA-SAB (1, 47-48), we consider it less likely that presence or absence of diabetes should have substantially influenced the triage and clinical care of patients. In addition, previous studies from our setting on pneumococcal bacteremia and pneumonia, respectively, demonstrated no differences in microbiological results, levels of inflammatory markers on admission, antibiotic treatment, and proportion of patients with at least one blood culture taken when comparing patients with and without diabetes (131, 191).

In **studies III and IV**, selection bias would be of concern if the association between the exposure (diabetes and CHF, respectively) and the outcome (mortality) differed between study participants and non-participants, or if loss to follow-up occurred. As in study I, we ascertained vital status via the DCRS, which is virtually complete (162-163), therefore we do not consider loss to follow-up an issue.

The study populations in studies III and IV included all residents in Northern Denmark who were hospitalized with a first time episode of CA-SAB. Nevertheless, detection of CA-SAB may be influenced by admission patterns and timing of blood culture draw. Thus, we cannot preclude that a small proportion of patients with CA-SAB were not captured if some patients were hospitalized at a hospital outside of the study setting, if they had been treated with antibiotics prior to admission, or if they died before a blood culture had been obtained. If either of these factors were particularly

related to patients with diabetes or patients with CHF selection bias may have arisen and mortality would subsequently be underestimated in these patient groups. Moreover, we cannot preclude that physicians may have a lower threshold for admitting patients with diabetes and patients with CHF on suspicion on infection, which also would lead to an underestimation of mortality. Yet, in studies III and IV, the proportion of patients classified as HCA-SAB did not differ between exposed and non-exposed patients, and we saw no notable differences in levels of inflammatory markers, or the proportion of patients who had received preadmission antibiotic treatment. Although this argues against, we cannot entirely dismiss the presence of some selection bias in studies III and IV, which may have led us to underestimate mortality among CA-SAB patients with diabetes and CHF.

5.2.2 Information bias

Information bias refers to misclassification of exposure, outcome, or data on potential confounders. Non-differential misclassification arises when the probability of misclassification is the same across compared groups, and differential misclassification is introduced when the probability of being misclassified differs between the comparison groups. Non-differential misclassification of dichotomous variables will usually bias the estimate towards unity, whereas the effect of non-differential misclassification is difficult to predict (159).

We cannot entirely rule out misclassification of patients with HCA-SAB (the exposure) in **study I**. Patients with previous inpatient admissions and hospital outpatient clinic contact were identified in the DNPR which includes highly valid data on admission data (166-167). As we did not have direct access to data on chemotherapy and dialysis, contacts to outpatient hospital clinics of oncology, hematology and nephrology were utilized as proxies and this may have introduced misclassification

of some patients in previous or current treatment courses. Nevertheless, such misclassification would most likely be non-differential and thereby lead to more conservative estimates.
Further, we did not have data on nursing home residence or specialized home care, which is frequently included in definitions of HCA infection. Still, the majority of elderly people in Denmark does not live in specially adapted homes but in common housing where personal help and medical services are provided in the home by the local municipality (192). Therefore, we consider it unlikely that the addition of this factor would have considerably influenced our results. Nevertheless, we acknowledge the relevance of these exposures and consider them important for any definition of HCA infection.

In **study II**, misclassification of the exposure or confounder data could possibly have influenced the results. To identify patients with diabetes, we applied a previously validated method (131) incorporating data that were retrieved prospectively and independently of the study purpose. Moreover, information on diabetes and characteristics of patients with diabetes (e.g., diabetes duration and diabetes complications) was retrieved in the same way for cases and controls, which virtually eliminates the risk of non-response bias and recall bias. Still, we may have missed some patients with diabetes, especially if they were treated with diet and lifestyle changes alone. Nevertheless, we expect such misclassification to be evenly distributed among cases and controls (i.e., non-differential), thereby biasing the estimates towards the null.

During the study period, diabetic foot ulcers were not coded consistently with unique diagnostic codes. Thus, we constructed two separate proxy variables using data on 1) conditions related to foot ulcers and 2) previous lower-extremity ulcer diagnoses, which may have led to some misclassification. Still, both variables suggested a high risk of CA-SAB associated with diabetic

foot ulcers, and we consider it unlikely that misclassification alone could explain such high risk estimates. Furthermore, clinical data would most likely be preferable to registry data for determining the duration of diabetes and for distinguishing between type 1 and type 2 diabetes. Yet, we find it most likely that any misclassification of these factors would be non-differential, which would lead to more conservative estimates.

Data on comorbidity were obtained prior to the index date, thus information on this potential confounder was not influenced by case status. However, we obtained information on comorbidity including alcohol-related conditions using discharge diagnoses recorded in the DNPR, and misclassification of these factors due to incorrect data entry or lack of data entry of available information could potentially have biased our results. Although the PPV of the discharge diagnoses used in our study have been demonstrated to be high in the DNPR (182), the existence of some misclassification of the diagnoses in this database cannot be entirely precluded. Yet, any misclassification of comorbidity would most likely be non-differential and thus diminish the contribution of this factor to the association between diabetes and risk of CA-SAB. On the other hand, if the diagnostic coding of patients with diabetes was more complete due to surveillance bias or higher rates of hospitalizations, the misclassification of comorbidity may have been non-differential thereby overestimating or, potentially, underestimating the risk of CA-SAB associated with diabetes.

Prescription data for confounder adjustment were collated from the AUPD. Although it may vary by drug type, an estimated completeness of this database is 96% based on cross-tabulation of insulin prescriptions with hospitalization records of diabetes mellitus (170). Unfortunately, we lacked information on drug adherence, yet patient copayment is required and misclassification due to nonadherence is probably negligible.

In cohort studies (**studies III and IV)**, information bias may arise from collection of erroneous information on exposure status, outcome status, or potential confounding variables (159). The primary outcome was all-cause mortality in both studies. Information on vital status was collected from the DCRS which is updated on a daily basis and practically complete (162-163), therefore misclassification of mortality seems highly unlikely.

In **study III**, diabetes constituted the exposure of interest. As discussed in relation to study II, information on diabetes was obtained using a validated method (131) and collected prospectively and independently of our study hypothesis. Thus, we consider the introduction of differential misclassification of the exposure variable unlikely. In **study IV**, we identified patients with CHF using a range of hospital or hospital outpatient discharge diagnoses registered in the DNPR. This method for capturing patients with CHF has not been validated, thus some misclassification of CHF exposure cannot be entirely precluded. However, two recent Danish validation studies demonstrated positive predictive values for CHF in the DNPR of 81% (193) and 100 % (182), respectively. Further, any misclassification would most likely be non-differential and thus lead to underestimation of our results. CHF severity is optimally evaluated using data on the ejection fraction and by the American College of Cardiology Foundation/American Heart Association classification system or New York Heart Association Functional Class (119-120), and the use of loop-diuretic dosages may have introduced misclassification of CHF severity in our study. Hence, if some patients used loop-diuretics on other indications than CHF (e.g., concomitant chronic kidney failure), this may have diluted any differences between severe and less severe CHF. However, such misclassification may most likely be non-differential and may not explain our overall results.

In **studies III and IV**, misclassification of comorbidity and preadmission medication could also have influenced our results. Data on comorbidity was retrieved from the DNPR, and as mentioned previously some misclassification of the diagnoses in this database cannot be entirely precluded. Still, such misclassification would most likely be non-differential and thereby attenuate the influence of comorbidity on the association between the exposure (diabetes and CHF, respectively) and the outcome (mortality). On the other hand, the coding of comorbidity might be more complete among patients with diabetes or CHF due to more frequent contact to the healthcare system or surveillance bias. Such differential misclassification could potentially lead to both overestimation and underestimation of the contribution of comorbidity to the association between diabetes or CHF and mortality. As described in relation to study II, the validity of the data in the AUPD has been demonstrated to be high (170), hence we do not consider it likely that misclassification of preadmission medication has influenced the results of studies III and IV notably.

5.2.3 Confounding

Confounding is defined as a bias occurring when a measure of association between exposure and outcome is confused with or distorted by the effect of third (confounding) factor (159). By definition, a confounder is associated with the exposure and the outcome and does not constitute an intermediate link in the chain of causation between exposure and outcome (159). In contrast to selection bias and information bias, the risk of confounding can be reduced in the design phase of a study (e.g., by restriction, and matching) and in the analysis phase (e.g., by stratification and multivariate adjustment) (160). Although these methods were applied in studies I-IV, our results may still be affected by residual and unmeasured confounding. Residual confounding may stem from misclassification of the potential confounding factors or use of too crude categories of

confounders, which may lead to loss of information. Unmeasured confounding may have been introduced by confounding from known factors, which we were not able to adjust for (159).

Study I

Study I described the influence of different definitions of HCA-SAB on the outcomes HCA-SAB prevalence, patient characteristics, and mortality. As the study was a strictly descriptive study, with no statistical comparisons or examination of exposure-outcome associations, we do not consider it likely that confounding should have influenced the results of study I.

Study II

In study II, we restricted the study population to patients with CA-SAB to reduce the risk of confounding associated with HA-SAB. Further, cases and controls were matched by age, gender, and residence to prevent confounding from these factors. Finally, at the analysis level, multivariate adjustment and stratification by potential confounders were conducted.

We used the Charlson Comorbidity Index (CCI) to adjust for comorbidity. The CCI is the most extensively studied and validated comorbidity index for predicting mortality, and this also pertains to patients with SAB (31, 89, 99, 182, 194-195). Still, the index has not been validated for predicting the occurrence of subsequent diseases and may therefore not be considered optimal for adjustment of comorbidities in studies assessing risk. Yet, accumulated comorbidity constitutes one of the most important risk factors for SAB (1, 31, 47), and the CCI includes most of the single chronic diseases suggested to be associated with SAB (e.g., chronic renal disease and cancer). Residual confounding may have arisen from misclassification of the conditions included in the m-CCI due to erroneous coding or from differences in coding related to diabetes status. However, as described in relation to information bias, the discharge diagnoses included in the CCI have

previously been shown to have high positive predictive values (182). Furthermore, we consider it unlikely that coding differences due to surveillance bias alone could explain risk estimates of the magnitude observed in study II. Moreover, we chose to adjust for m-CCI level (low, intermediate, high) in lieu of individual disease categories, which might have introduced residual confounding due to improper categorization. However, rerunning the analyses while adjusting for individual disease categories left the estimates virtually unchanged.

We also adjusted for preadmission use of statins and antibiotics, however the use of other types of medications may also be associated with diabetes and risk of CA-SAB. Immunosuppressive therapy, for instance, could potentially confound the association between diabetes and CA-SAB risk (1), yet very few study participants had received this type of treatment prior to admission (0.3%). Thus, we ultimately chose to exclude this factor from the adjustment, which did not change the estimates. Furthermore, we consider medication use as a direct consequence of diabetes (e.g., insulin or metformin) to constitute a part of the exposure´s (diabetes) effect and, therefore, this factor was not considered a potential confounder.

Unfortunately, we did not have data on smoking, body mass index, and functional or nutritional status, which could potentially confound the association between diabetes and risk of CA-SAB (196). Nevertheless, we were able to adjust for several lifestyle-related comorbidities in our analyses (e.g., cardiovascular disease and chronic pulmonary disease), thereby partly accounting for these potential confounders.

Studies III and IV

As in study II, we only included patients with CA-SAB in **studies III and IV** thereby reducing the risk of confounding associated with HA-SAB. In addition, we performed stratification and multivariate adjustment for potential confounders at the analytical level.

In studies III and IV, we utilized a modified CCI (m-CCI) and we cannot entirely preclude that this might influence the index´ ability to predict mortality. Moreover, diseases not included in the m-CCI may represent a risk of confounding in studies III and IV. Yet, as previously mentioned, the CCI includes the majority of chronic diseases associated with SAB and we included alcohol-related conditions and hypertension in the adjustment. In some previous studies of SAB outcome (185, 197), the investigators adjusted for severity of SAB-related disease as measured by the Acute Physiology And Chronic Health Evaluation score, the Pitt bacteremia score, or other comparable scores (198-200, 201). However, we consider severity of disease to constitute a part of the causal pathway leading from diabetes and CHF, respectively, to mortality in patients with SAB. Therefore, this factor does not meet the definition of a potential confounder and should not be adjusted for in studies assessing SAB prognosis.

As previously mentioned, the infective focus is associated with SAB outcome (2-3, 95), however due to the historical design of our studies, data on the infective focus were not available. If the infective foci were differently distributed among patients with our without diabetes (study III) or among patients with or without CHF (study IV), this could potentially have confounded our mortality rate estimates. Moreover, we did not have data on in-hospital clinical care including antibiotic therapy, ICU admission, and surgical procedures and differences related to diabetes or CHF, respectively, could potentially have influenced our assessment of mortality. We may also speculate that if the post discharge follow-up differed among patients with or without diabetes or patients with or without CHF, this too may have played a role for our results.

As for study II, data on potential confounders such as smoking, body mass index, and functional status were not available. Furthermore, socioeconomic status is associated with SAB outcome (2,

202), but unfortunately, data on educational level and personal income were lacking. However, we adjusted for marital status although this admittedly represents a somewhat crude proxy (180). Still, as healthcare is unrestricted and free in Denmark, we do not consider it likely that differences in socioeconomic status could explain our observation in studies III and IV.

5.2.4 Precision

No amount of statistical treatment can correct for systematic error arising from the study research design, yet by increasing the sample size it is possible to improve the statistical precision of a given study (158, 160). We employed 95% CIs to evaluate the precision of the associations in studies II-IV. Rather than using significance testing (with associated p-values), we preferred to consistently report effect sizes together with uncertainty metrics (i.e., 95% CIs). Unfortunately, CIs are often used simply to judge whether it contains the null value or not, thereby converting it to a significance test. However, we believe that confidence intervals should rather be interpreted as quantitative measures indicating the magnitude of effect and degree of precision, with less attention paid to the precise location of the boundaries of the confidence interval (161, 203). Due to the considerable number of cases and outcomes in our studies, the main analyses in studies II-IV yielded statistically precise estimates, as indicated by narrow CIs. Furthermore, the estimates remained robust in most subgroup analyses in studies. We were, nevertheless, limited by sparse data on patients aged less than 40 years (studies I-IV), patients with type 1 diabetes (studies II-III), and characteristics of patients with diabetes (studies II-III).

5.2.5 External validity

External validity is the degree to which the results of a study are applicable in other settings (161). Our studies were conducted in an area with low prevalence of MRSA (0.5%). Although this facilitated a clean focus on MSSA, it might have impeded the applicability of our results to other settings with significant MRSA prevalence. Nevertheless, assuming a low risk of systematic error and taking into account the high precision of our estimates, we consider it likely that our results are generalizable to other settings and countries with similar lifestyle and free, unrestricted access to healthcare and prescription drugs including anti diabetes therapy and medications for CHF.

5.3 Main conclusions

Based on our results and the subsequent evaluation of the methodology applied in the four studies, the following main conclusions were drawn:

Study I

We demonstrated that the prevalence of patients classified as HCA-SAB varied considerably with use of different definitions of HCA infection. Of note, using the least stringent definition of HCA-SAB more than doubled the prevalence of patients classified as HCA-SAB compared with the most stringent definition. In addition, use of different definitions of HCA-SAB influenced the distribution of patient characteristics, whereas the estimates of 30-day all-cause mortality remained comparable.

Study II

We found that diabetes was a strong risk factor for CA-SAB. Compared with persons without diabetes, the influence of diabetes on CA-SAB risk was most apparent among patients with type 1 diabetes, patients with a long diabetes history, patients with inadequate glycemic control, and patients with diabetes complications in general and microvascular disease in particular. Moreover, the impact of diabetes on relative CA-SAB risk was particularly pronounced among patients aged less than 60 years and among patients with no other comorbidities.

Study III

The study provided firm evidence against an association between diabetes and 30-day all-cause mortality in patients with CA-SAB. The prognosis remained comparable among patients with and without recent preadmission healthcare contacts, respectively, and no notable differences in

mortality were demonstrated according to age, gender, marital status, or comorbidity level. Furthermore, characteristics of patients with diabetes (e.g., diabetes duration, quality of glycemic control, and diabetes complications) did not influence the 30-day mortality.

Study IV

Compared with patients without CHF, patients with CHF experienced a 24% increase in 90-day all-cause mortality. The excess risk of death was particularly pronounced in patients with CHF with concomitant valvular heart disease, patients with a short history of CHF, and patients using high daily dosages of loop-diuretics. Ninety-day mortality did not differ notably across strata of gender, age groups, and comorbidity levels.

6. Clinical implications and perspectives

This thesis highlights some of the challenges associated with the classification of SAB and extends our existing knowledge of CA-SAB with special attention to underlying diabetes and CHF. We found that the prevalence of patients classified as HCA-SAB varied substantially when different definitions of HCA infection were used. In addition to underlining the necessity for caution when designing, interpreting, and comparing studies on SAB, these results emphasize the need for an evidence-based consensus definition of HCA infection. Ideally, this should distinguish between different infectious disease syndromes and take local epidemiological and microbiological characteristics into account.

Our results further provide evidence that diabetes constitutes a considerable risk factor for CA-SAB, although this condition is not a prognostic factor. This underlines the importance of improved preventive care for patients with diabetes and particularly good infection surveillance among patients with a long history of diabetes and patients with diabetes complications. Moreover, our observations of a gradually increased risk of SAB with successive increases in HbA1c levels may help to further motivate patients and physicians to maintain an optimal Hba1c level at all times. Still, some questions remain unanswered. The exact biological mechanisms behind the increased risk of SAB continue to be unclear and should be further elucidated. In particular, as our results indicate that presence of diabetic foot ulcers is associated with very high risk of SAB, we would like to investigate this potential mechanism further using accurate clinical and microbiological data on this important diabetes complication. In addition, bacterial vaccines have proven effective in the prevention of invasive infection from *Haemophilus influenzae* type b (Hib) (204) and *Streptococcus pneumoniae* (205), yet an effective staphylococcal vaccine is still not available (206). Nevertheless, recent vaccine studies have shown promising results (207-208) and vaccination for staphylococci

might be considered as part of the preventive measures for high-risk patients with diabetes in the future.

The high mortality observed among SAB patients with CHF implies that this subset of patients may benefit from increased clinical attention. As described in relation to the background section, the association between sepsis and myocardial function is highly complex and further research is needed to investigate which specific pathophysiological mechanisms underlie the association between CHF and SAB outcome. Moreover, the potential role of heart valve disease and infective endocarditis merits further investigation, preferably in prospective clinical studies involving clinical microbiologists, cardiologists, and infectious diseases specialists.

In our studies, we observed an overall 30-day all-cause mortality of ~25% associated with CA-SAB. This is of considerable clinical and public health concern and there is a major incentive to prevent and optimize the clinical management of this clinical syndrome. In recent years, systematic infectious disease specialist consultation (IDC) has been investigated as a strategy to optimize the quality of care for patients with SAB (209-215). According to a recent systematic review and meta-analysis of 18 studies (patients with SAB=5,337), IDC was associated with improved control of the infective focus and antibiotic therapy as well as reduced risk of 30-day, 90-day mortality, and SAB relapse (216). Thus, ICD can be a promising step toward standardizing and enhancing the management of SAB and in turn facilitate improved patient outcomes. Nevertheless, further well-designed studies are warranted to validate the results and refine the specific elements of the intervention.

7. Summary

Community-acquired *Staphylococcus aureus* bacteremia (CA-SAB) is a serious infection with detrimental clinical effects. Chronic diseases constitute some of the most important risk and prognostic factors for CA-SAB. The prevalence of diabetes and chronic heart failure (CHF) is rapidly increasing on a global scale, nevertheless, there are few data available specifically elucidating the influence of these chronic conditions on CA-SAB risk and outcome.

Therefore, to extend the current knowledge, **we aimed** to I) elucidate the impact of different definitions of healthcare-associated (HCA) infection on the prevalence of HCA-SAB, patient characteristics, and mortality, II) to investigate whether diabetes is a risk factor for CA-SAB, III) to ascertain the prognostic influence of diabetes on CA-SAB outcome, and IV) to investigate the influence of CHF on mortality in patients with CA-SAB.

The thesis is based on a cross-sectional study, a case-control study, and two cohort studies, all conducted in Northern Denmark, 2000-2011. Utilizing the unique civil registration number assigned to all Danish residents, we linked data from the local departments of clinical microbiology, the Danish Civil Registration System, the Danish National Patient Registry, the LABKA database, and the Aarhus University Prescription Database.

In study I, we included 4,385 patients with SAB. The proportion of patients classified as HCA-SAB ranged between 29.8% and 71.7% across five different definitions of HCA infection. Use of different definition of HCA infection also influenced the distribution of patient characteristics, whereas estimates of 30-day mortality remained unchanged (~ 24%). **Study II** included 2,638 patients with CA-SAB and 26,379 population controls matched by age, gender, and residence. We found diabetes to be strongly associated with an increased risk of CA-SAB (adjusted odds ratio=2.8 (95% CI, 2.5-3.1)). Compared with persons without diabetes, the increased CA-SAB risk was most apparent among patients with type 1 diabetes, patients with a long diabetes history, patients with

poor glycemic control, and patients with diabetes complications. **In study III**, we included 2,638 patients with CA-SAB, of whom 713 (27.0%) had diabetes. After adjustment for potential confounders, the mortality rate ratio for patients with diabetes was 1.01 (95% CI, 0.84-1.20) after 30 days of follow-up. No notable differences in 30-day mortality were observed among patients with and without recent healthcare contacts, and the finding remained robust according to gender, age, comorbidity level, and characteristics of patients with diabetes (e.g. diabetes type and duration of diabetes). **In study IV**, CHF was associated with a 24% increase in 90-day mortality in patients with CA-SAB. The excess risk of death associated with CHF was most pronounced among patients with concomitant valvular disease and patients using very high doses of loop diuretics, as compared to patient without CHF.

In conclusion, we observed considerable variation in the proportion of patients classified as HCA-SAB when different definitions of HCA infection were applied. Diabetes was associated with a substantially increased risk of CA-SAB, whereas CA-SAB outcome was virtually unaffected by diabetes. In contrast, patients with CHF experienced increased 90-day mortality compared with patients without CHF.

8. Danish summary

Samfundserhvervet *Staphylococcus aureus* bakteriæmi (CA-SAB) er en alvorlig infektion med svære kliniske konsekvenser. Kroniske sygdomme udgør nogle af de mest betydningsfulde risiko- og prognostiske faktorer for CA-SAB. Prævalensen af diabetes og kronisk hjertesvigt (CHF) er hastigt stigende verden over, men der findes kun sparsomme data om disse kroniske tilstandes betydning for risiko og prognose for CA-SAB.

Formålet med afhandlingen var derfor at udbygge den eksisterende viden ved I) at belyse betydningen af forskellige definitioner af ´healthcare-associated´ (HCA) infektion for prævalensen af HCA-SAB, patienternes karakteristika og prognose, II) at undersøge om diabetes er en risikofaktor for CA-SAB, III) at evaluere den prognostiske betydning af diabetes hos patienter med CA-SAB, og IV) at undersøge betydningen af CHF for prognosen hos patienter med CA-SAB.

Afhandlingen bygger på et tværsnitsstudie, et case-control studie og to kohortestudier, som alle er udført i Region Nordjylland og Region Midtjylland i tidsperioden 2000-2011. Vi koblede data fra de klinisk mikrobiologiske afdelinger, CPR-registret, Landspatientregistret, Laboratoriedatabasen for Region Nordjylland og Midtjylland og Aarhus Universitets Receptdatabase ved brug af patienternes personnummer.

Studie I inkluderede 4,385 patienter med SAB. Andelen af patienter klassificeret som HCA-SAB spændte fra 29.8% til 71.7% afhængigt af definitionen. Definitionerne havde også indflydelse på fordelingen af patienternes karakteristika, hvorimod 30-dages dødeligheden ikke varierede væsentligt. **I studie II** inkluderede vi 2,638 patienter med CA-SAB og 26,379 populationskontroller, som blev matchet på alder, køn og bopæl. Vi fandt, at diabetes var associeret med en markant forhøjet risiko for CA-SAB (justeret odds ratio=2.8 (95% CI, 2.5-3.1)). Sammenholdt med patienter uden diabetes var den forøgede risiko for CA-SAB mest udtalt for patienter med type 1 diabetes, patienter med langvarig diabetes, patienter med et utilfredsstillende

Hba1c-niveau og patienter med diabetiske komplikationer. **Det tredje studie** inkluderede 2,638 patienter med CA-SAB, hvoraf 713 (27.0%) havde diabetes. Efter justering for mulige confoundere var mortalitets rate ratioen for patienter med diabetes 1.01 (95% CI, 0.84-1.20) efter 30 dages opfølgningstid. Vi fandt ingen betydelige forskelle i 30-dages dødeligheden hos patienter med og uden nylige hospitalskontakter og fundet blev ikke influeret af køn, alder, komorbiditetsniveau eller karakteristika for patienter med diabetes (fx diabetes type og diabetes varighed). **I studie IV** fandt vi, at CHF var associeret med 24% højere 90-dages dødelighed hos patienter med CA-SAB. Sammenholdt med patienter uden CHF var den relative risikoøgning for død mest udtalt hos patienter med CHF og ledsagende hjerteklapsygdom og patienter med CHF som anvendte meget høje doser af vanddrivende medicin.

Sammenfattende viser vores resultater, at selve definitionen af HCA infektion har en betydelig indflydelse på andelen af patienter, der klassificeres som HCA-SAB. Diabetes var stærkt forbundet med risiko for CA-SAB, hvorimod vi ikke fandt en sammenhæng mellem diabetes og prognose for CA-SAB. Derimod oplevede patienter med CHF højere dødelighed efter CA-SAB end patienter uden CHF.

9. References

1. Tong SYC, Davis JS, Eichenberger E, et al. *Staphylococcus aureus* infections: Epidemiology, Pathophysiology, Clinical Manifestations, and Management. Clin Microbiol Rev 2015; 28:603-661.

2. van Hal SJ, Jensen SO, Vaska VL, et al. Predictors or mortality in *Staphylococcus aureus* bacteremia. Clin Microbiol Rev 2012; 25:362-386.

3. Kaasch A, Barlow G, Edgeworth JD, et al. *Staphylococcus aureus* bloodstream infection: a pooled analysis of five prospective, observational studies. J Infect 2014; 68:242-251.

4. Yahav D, Schlesinger A, Shaked H, et al. Clinical Presentation, management and outcomes of *Staph aureus* bacteremia (SAB) in older adults. Aging Clin Exp Res 2016 (epub ahead of print).

5. McClelland RS, Fowler VG Jr., Sanders L, et al. *Staphylococcus aureus* bacteremia among elderly vs younger adults. Arch Intern Med 1999; 14:1244-1247.

6. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. BMJ Open 2016; 6:e010210.

7. Guariguata L, Whiting DR, Hambleton I, et al. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 2014; 103:161-175.

8. Whiting DR, Guariguata L, Weil C, et al. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011; 94:311-321.

9. Roger VL. Epidemiology of heart failure. Circ Res 2013;113:646-659.

10. Dunlay SM, Roger VL. Understanding the epidemic of heart failure: past, present and future. Curr Heart Fail Rep 2014;11:404-415.

11. Jensen AG, Wachmann CH, Poulsen KB, et al. Risk factors for hospital-acquired *Staphylococcus aureus* bacteremia. Arch Intern Med 1999; 159:1437-1444.

12. Mitchell BG, Collignon PJ, McCann R, et al. A major reduction in hospital-onset *Staphylococcus aureus* bacteremia in Australia – 12 years of progress: an observational study. Clin Infect Dis 2014; 59:969-975.

13. Tong SYC, Chen LF, Fowler VG. Colonization, pathogenicity, host susceptibility and therapeutics for *Staphylococcus aureus*: What is the clinical relevance? Semin Immunopathol 2012; 34:185-200.

14. Wertheim HFL, MellesDC, Vos MC, et al. The role of nasal carriage in *Staphylococcus aureus* infections. Lancet Infect Dis 2005; 5:751-762.

15. van Belkum A. Staphylococcal colonization and infection: homeostasis versus disbalance of human (innate) immunity and bacterial virulence. Curr Opin Infect Dis 2006; 19:339-344.

16. van Belkum A, Verkaik NJ, de Vogel CP, et al. Reclassification of *Staphylococcus aureus* nasal carriage types. J Infect Dis 2009; 199:1820-1826.

17. Gosbell IB, van Hal SJ. *Staphylococcus aureus* colonization: some questions answered. Lancet Infect Dis 2013; 13:380-381.

18. Coates R, Moran J, Horsburgh MJ. Staphylococci: colonizers and pathogens of human skin. Future Microbiol 2014; 9:75–91.

19. Andersen PS, Larsen LA, Fowler VG Jr., et al. Risk factors for *Staphylococcus aureus* nasal colonization in Danish middle-aged and elderly twins. Eur J Clin Microbiol Infect Dis 2013; 32:1321-1326.

20. Lowy FD. *Staphylococcus aureus* infections. N Engl J Med 1998; 339:520-532.

21. Shinefield HR, Ruff NL. Staphylococcal infections: A historical perspective. Infect Dis Clin N Am 2009; 23:1-15.

22. Hoen BH, Duval X. Infective endocarditis. N Engl J Med 2013; 368:1425-1433.

23. Lowy FD. How *Staphylococcus* adapts to its host. N Engl Med 2011; 364:1987-1990.

24. Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, et al. Clinical Management of *Staphylococcus aureus* bacteraemia. Lancet Infect Dis 2011; 11:208-222.

25. http://www.ssi.dk/~/media/Indhold/DK%20-%20dansk/Smitteberedskab/Referencelaboratorier/Stafylokoklaboratoriet/SAB%202014.ashx (Accessed September 5, 2016).

26. Westh H, Rosdahl VT, Friis H. Eryhromycin resistance in Danish *Staphylococcus aureus* hospital strains with emphasis on erythromycin consumption. APMIS 1989; 97:1121-1124.

27. Stegger M, Wirth T, Andersen PS, et al. Origin and evolution of European community-acquired methicillin-resistant *Staphylococcus aureus*. MBio 2014; e01044-14.

28. Faber V, Jessen J, Rosendal K, et al. Staphylococcal bacteraemia. Clinical and bacteriological observations in 201 cases. Br Med J 1960; 2:1832-1836.

29. Jessen O, Rosendal K, Bülow O, et al. Changing staphylococci and staphylococcal infections. A ten-year study of bacteria and cases of bacteremia. N Engl J Med 1969; 281:627-635.

30. Espersen F. Identifying the patient risk for *Staphylococcus aureus* bloodstream infections. J Chemother 1995; 7: Suppl3: 11-17.

31. Mejer N, Westh H, Schønheyder HC, et al. Stable incidence and improvement in short term mortality of *Staphylococcus aureus* bacteraemia between 1995 and 2008. BMC Infect Dis 2012; 12:260.

32. Benfield T, Espersen F, Frimodt-Møller N, et al. Increasing incidence but decreasing in-hospital mortality of adult *Staphylococcus aureus* bacteraemia between 1981 and 2000. Clin Microbiol Infect 2007; 13:257-263.

33. Westh H, Jarløv JO, Kjersem H, et al. The disappearance of multiresistent *Staphylococcus aureus* in Denmark: Changes in strains of the 83A complex between 1969 and 1989. Clin Infect Dis 1992; 14:1186-1194.

34. Laupland KB, Lyytikäinen O, Søgaard M, et al. The changing epidemiology of *Staphylococcus aureus* bloodstream infection: a multinational population-based surveillance study. Clin Microbiol Infect 2013; 19:465-471.

35. Asgeirsson H, Gudlaugsson O, Kristinsson KG, et al. *Staphylococcus aureus* bacteraemia in Iceland, 1995-2008: changing incidence and mortality. Clin Microbiol Infect 2011; 17:513-518.

36. Lyytikäinen O, Routsalainen E, Järvinen A, et al. Trends and outcome of nosocomial and community-acquired bloodstream infections due to *Staphylococcus aureus* in Finland, 1995-2001. Eur J Clin Microbiol Infect Dis 2005; 24:399-404.

37. Søgaard M, Engebjerg MC, Lundbye-Christensen S, et al. Changes in blood culture methodology have an impact on time trends of bacteraemia: a 26-year regional study. Epidemiol Infect 2011; 139:772-776.

38. Rieg S, Peyerl-Hoffmann G, de With K, et al. Mortality of *S. aureus* bacteremia and infectious diseases specialist consultation – a study of 521 patients in Germany. J Infect 2009; 59:232-239.

39. Paulsen J, Mehl A, Askim Å, et al. Epidemiology and outcome of *Staphylococcus aureus* bloodstream infection and sepsis in a Norwegian county 1996-2011: an observational study. BMC Infect Dis 2015;116.

40. Kaech C, Elzi L, Frei R, et al. Course and outcome of *Staphylococcus aureus* bacteremia: a retrospective analysis of 308 episodes in a Swiss tertiary-care centre. Clin Microbiol Infect 2006; 12:345-352.

41. Skinner D, Keefer CS. Significance of bacteremia caused by *Staphylococcus aureus*. Arch Intern Med 1941; 68:851–875.

42. Mylotte JM, Tayara A. *Staphylococcus aureus* bacteremia: predictors of 30-day mortality in a large cohort. Clin Infect Dis 2000; 31:1170-1174.

43. Turnidge JD, Kotsanas D, Munckhof W, et al. *Staphylococcus aureus* bacteraemia: a major cause of mortality in Australia and New Zealand. Med J Aust 2009; 191:368-373.

44. Dalager-Pedersen M, Thomsen RW, Schønheyder HC, et al. Functional status and quality of life after community-acquired bacteraemia: a matched cohort study. Clin Microbiol Infect 2016; 22:e1-e8.

45. Wiese L, Mejer N, Schønheyder HC, et al. A nationwide study of comorbidity and risk of reinfection after *Staphylococcus aureus* bacteraemia. J Infect 2013; 67:199-205.

46. Walker TM, Bowler ICJW, Bejon P. Risk factors for recurrence after *Staphylococcus aureus* bacteraemia. A retrospective matched case-control study. J Infect 2009; 58:411-416.

47. Bergin SP, Holland TL, Fowler VG Jr., et al. Bacteremia, sepsis, and infective endocarditis associated with *Staphylococcus aureus*. Current Topics in Microbiology and Immunology 2015 (epub ahead of print).

48. Fowler VG Jr, Olsen MK, Corey R, et al. Clinical Identifiers of complicated *Staphylococcus aureus* bacteremia. Arch Intern Med 2003; 163:2066-2072.

49. Ringberg H, Thoren A, Lilja B. Metastatic complications of *Staphylococcus aureus* septicemia. To seek is to find. Infection 2000; 28:132–136.

50. Lautenschlager S, Herzog C, Zimmerli W. Course and outcome of bacteremia due to *Staphylococcus aureus*: Evaluation of different clinical case definitions. Clin Infect Dis 1993; 16:567-573.

51. del Rio A, Cervera C. Moreno A, et al. Patients at risk of complications of *Staphylococcus aureus* bloodstream infection. Clin Infect Dis 2009; 48:S246-253.

52. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013; 369:840-851.

53. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003; 29:530+8.

54. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine Chest 1992; 101:1644+55.

55. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315:801-810.

56. Gould FK, Brindle R, Chadwick PR, et al. Guidelines (2008) for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the United Kingdom. J Antimi- crob Chemother 2009; 63:849–861.

57. Mitchell DH, Howden BP. Diagnosis and management of *Staphylococcus aureus* bacteraemia. Intern Med J 2005; 35(Suppl 2):S17–S24.

58. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis 2011; 52:e18–e55.

59. Holland TL, Arnold C, Fowler VG Jr. Clinical management of *Staphylococcus aureus* bacteremia. JAMA 2014; 312:1330-1341.

60. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336:924-926.

61. Chong YP, Moon SM, Bang KM, et al. Treatment duration for uncomplicated *Staphylococcus aureus* bacteremia to prevent relapse: analysis of a prospective observational cohort study. Antimicrob Agents Chemother 2013; 57:1150-1156.

62. Jernigan JA, Farr BM. Short-course therapy of catheter-related *Staphylococcus aureus* bacteremia: a meta-analysis. Ann Intern Med 1993; 119:304-311.

63. Gudiol F, Aguado JM, Almirante B, et al. Diagnosis and treatment of bacteremia and endocarditis due to *Staphylococcus aureus*. A clinical guideline from the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC). Enferm Infecc Microbiol Clin 2015; 33;625.e1-625.e23.

64. Roberts FJ. Definition of polymicrobial bacteremia. Rev Infect Dis 1989; 11:1029-1030.

65. Park SY, Park K, Bang KM, et al. Clinical significance and outcome of polymicrobial *Staphylococcus aureus* bacteremia. J Infect 2012; 65:119-127.

66. Gradel KO, Nielsen SL, Pedersen C, et al. No specific time window distinguishes between community-, healthcare-, and hospital-acquired bacteremia, but they are prognostically robust. Infect Control Hosp Epidemiol 2014; 35:1474-82.

67. McGowan JE Jr, Barnes MW, Finland M. Bacteremia at Boston City Hospital: occurrence and mortality during 12 selected years (1935–1972), with special reference to hospital-acquired cases. J Infect Dis 1975; 132:316–335.

68. Brenner ER, Bryan CS. Nosocomial bacteremia in perspective: a community-wide study. Infect Control 1981; 2:219–226.

69. Garner JS, Jarvis WR, Emori TG, et al. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988; 16:128–140.

70. Laupland KB, Gregson DB, Church DL. Validity of calendar day-based definitions for community-onset bloodstream infections. BMC Research Notes 2015; 8:123.

71. Hill PC, Birch M, Chambers S, et al. Prospective study of 425 cases of *Staphylococcus aureus* bacteraemia: determination of factors affecting incidence and mortality. Intern J Med 2001; 31:97-103.

72. Bassetti M, Trecarichi EM, Mesini A, et al. Risk factors and mortality of healthcare-associated and community-acquired *Staphylococcus aureus* bacteraemia. Clin Microbiol Infect 2012; 18:862-9.

73. Forsblom E, Ruotsalainen E, Mölkänen T, et al. Predisposing factors, disease progression and outcome in 430 prospectively followed patients of healthcare- and community-associated *Staphylococcus aureus* bacteraemia. J Hosp Infect 2011; 78:102-107.

74. Siegman-Igra Y, Fourer B, Orni-Wasserlauf, et al. Reappraisal of community-acquired bactermia: A proposal of a new classification for the spectrum of acquisition of bacteremia. Clin Infect Dis 2002; 34:1431-1439.

75. Friedman ND, Kaye KS, Stout JE, et al. Healthcare-associated infections in adults: A reason to the change the accepted definition if community-acquired infections. Ann Intern Med, 2002; 137:791-797.

76. Cardoso T, Almeida M, Friedman ND, et al. Classification of healthcare-associated infection: a systematic review 10 years after the first proposal. BMC Medicine 2014; 12:40.

77. Jacobsson G, Dashti S, Wahlberg T, et al. The epidemiology of and risk factors for invasive *Staphylococcus aureus* infections in western Sweden. Scan J Infect Dis 2007; 39:6-13.

78. Forsblom E, Nurmi AM, Ruotsalainen E, et al. Should all adjunctive corticosteroid therapy be avoided in the management of hemodynamically stable *Staphylococcus aureus* bacteremia? Eur J Clin Microbiol Infect Dis 2016; 35:471-479.

79. Allard C, Carignan A, Bergevin M, et al. Secular changes in incidence and mortality associated with *Staphylococcus aureus* bacteraemia in Quebec, Canada, 1991-2005. Clin Microbiol Infect 2008; 421–428.

80. Landrum ML, Neumann C, Cook C, et al. Epidemiology of *Staphylococcus aureus* blood and skin and soft tissue infections in the US military health system, 2005- 2010. JAMA 2012; 308:50–59.

81. Huggan PJ, Wells JE, Browne M, et al. Population-based epidemiology of *Staphylococcus aureus* bloodstream infection in Canterbury, New Zealand. Intern Med J 2010; 40:117–125.

82. Nielsen LH, Jensen-Fangel S, Benfield T, et al. Risk and prognosis of *Staphylococcus aureus* bacteremia among individuals with and without end-stage renal disease: a Danish population-based cohort study. BMC Infect Dis 2015; 15:6.

83. Kallen AJ, Mu Y, Bulens S, Reingold A, et al. Health care-associated invasive MRSA infections, 2005–2008. JAMA 2010; 304:641–664.

84. Larsen MV, Harboe ZB, Ladelund S, et al. Major but differential decline in the incidence of *Staphylococcus aureus* bacteraemia in HIV-infected individuals from 1995 to 2007: a nationwide cohort study. HIV Med 2012; 13:45–53.

85. Craven DE, Rixinger AI, Goularte TA, et al. Methicillin-resistant *Staphylococcus aureus* bacteremia linked to intravenous drug abusers using a “shooting gallery”. Am J Med 1986; 80:770-776.

86. Gordon RJ, Lowy FD. Bacterial infections in drug users. N Engl J Med 2005; 353:1945-1954.

87. Routsalainen E, Sammalkorpi K, Laine J, et al. Clincial manifestations and outcome in *Staphylococcus aureus* endocarditis among injection drug users and nonaddicts: a prospective study of 74 patients. BMC Infect Dis 2006; 6:137.

88. Burton DC, Edwards JR, Horan TC, et al. Methicillin-resistant *Staphylococcus aureus* central line-associated bloodstream infections in US intensive care units, 1997–2007. JAMA 2009; 301:727–736.

89. Malani PN, Rana MM, Banerjee M, et al. *Staphylococcus aureus* bloodstream infections: The association between age and mortality and functional status. J Am Geriatr Soc 2008; 56:1485-1489.

90. Smit J, López-Cortés LE, Kaasch AJ, et al. Gender differences in the outcome of comunity-acquired *Staphylococcus aureus* bacteraemia: a historical population-based cohort study. Clin Microbiol Infect 2016 (epub ahead of print).

91. Mansur N, Hazzan R, Paul M, et al. Does sex affect 30-day mortality in *Staphylococcus aureus* bacteremia? Gend Med 2012; 9:463-470.

92. Vallés J, Calbo E, Anoro E, et al. Bloodstream infections in adults: Importance of healthcare-associated infections. J Infect 2008; 56:27-34.

93. Lenz R, Leal JR, Church DL, et al. The distinct category of healthcare associated bloodstream infections. BMC Infect Dis 2012; 12:85.

94. Shorr A, Tabak YP, Killian AD, et al. Healthcare-associated bloodstream infections: A distinct entity? Insights from a large U.S. database. Crit Care Med 2006; 10:2588-95.

95. Soriano A, Martinez JA, Mensa J, et al. Pathogenic significance of methicillin resistance for patients with *Staphylococcus aureus* bacteremia. Clin. Infect Dis 2000; 30:368–373.

96. Saginur R, Suh KN. *Staphylococcus aureus* bacteraemia of uknown primary source: Where do we stand? Int J Antimicrob Agents 2008; 32:S21-25.

97. Corey GR. *Staphylococcus aureus* bloodstream infections: Definitions and treatment. Clin Infect Dis 2009; 48:s254-259.

98. Khatib R, Sharma M. Echocardiography is dispensable in uncomplicated *Staphylococcus aureus* bacteremia. Medicine (Baltimore) 2013; 92:182-188.

99. Lesens O, Methlin C, Hansmann Y, et al. Role of comorbidity in mortality related to *Staphylococcus aureus* bacteremia: A prospective study using the Charlson weighted index of comorbidity. Infect Control Hosp Epidemiol 2003; 24:890-896.

100. Kang CI, Song JH, Ko KS, et al. Clinical features and outcome of *Staphylococcus aureus* infection in elderly versus younger adult patients. Int J Infect Dis 2011; 15:e58–e62.

101. Thulstrup AM, Sørensen HT, Schønheyder HC, et al. Population-based study of the risk and short-term prognosis for bacteremia in patients with liver cirrhosis. Clin Infect Dis 2000; 31:1357-1361.

102. Braquet P, Alla F, Cornu C, et al. Factors associated with 12 week case-fatality in *Staphylococcus aureus* bacteraemia, a prospective cohort study. Clin Microbiol Infect 2016 (epub ahead of print).

103. Kern WV. Management of *Staphylococcus aureus* baceteremia and endocarditis: progresses and challenges. Curr Opin Infect Dis 2010; 23:346-358.

104. http://www.diabetesatlas.org/across-the-globe.html (accessed 7/9-2016).

105. American Diabetes Association 2. Classification and Diagnosis of Diabetes. Diabetes Care 2016; 39:S13-22.

106. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003; 26:S5-20.

107. DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988; 37:667-687.

108. http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf (accessed 07/09-2016).

109. https://sundhedsstyrelsen.dk/da/sygdom-og-behandling/kronisk-sygdom/diabetes (accessed 07/09-2016).

110. Carstensen B, Kristensen JK, Ottosen P, et al. The Danish National Diabetes Register: trends in incidence, prevalence and mortality. Diabetologia 2008; 51:2187-2196.

111. McEwen LN, Karter AJ, Waitzfelder BE, et al. Predictors of mortality over 8 years in type 2 diabetic patients: Translating Research Into Action for Diabetes (TRIAD). Diabetes Care 2012; 35:1301-1309.

112. Kelly PJ, Clarke PM, Hayes AJ, et al. Predicting mortality in people with type 2 diabetes mellitus after major complications: a study using Swedish National Diabetes Register data. Diabet Med 2014; 31:954-962.

113. Nathan DM. Long-term complications of diabetes mellitus. N Engl J Med 1993; 328:1676-1685.

114. Almdal T, Scharling H, Jensen JS, et al. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. Arch Intern Med 2004; 164:1422-1426.

115. Iribarren C, Karter AJ, Go AS, et al. Glycemic control and heart failure among adult patients with diabetes. Circulation 2001; 103:2668–2673.

116. Alexiadou K, Doupis J. Management of diabetic foot ulcers. Diabetes Ther 2012; 3:4.

117. Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. The Lancet 2009; 378:169-181.

118. http://docplayer.dk/7871991-Faktarapport-om-hjertesvigt-i-danmark-baseret-paa-indlaeggelser-indtil-aar-2011.html (accessed 07/09-2016).

119. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62:147-239.

120. Ponikowski P, Voors AA, Anker SD, et al. 2016 guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016; 18:891-975.

121. Jessup M, Brozena S. Heart failure. N Engl J Med 2003; 348:2007-2018.

122. Hubert HB, Feinleib M, McNamara PM, et al. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983; 67:968–977.

123. Alpert CM, Smith MA, Hummel SL, et al. Symptom burden in heart failure: assessment, impact on outcomes, and management. Heart Fail Rev 2016 (epub ahead of print).

124. Kumar S, Ingle H, Prasad DVR, et al. Recognition of bacterial infection by innate immune sensors. Crit Rev Microbiol 2013; 39:229-246.

125. O´Neill LA. When signaling pathways collide: Positive and negative regulation of Toll-like receptor signal transduction. Immunity 2008; 29:12-20.

126. Koh GCKW, Peacock SJ, van der Poll T, et al. The impact of diabetes on the pathogenesis of sepsis. Eur J Clin Microbiol Infect Dis 2012; 31:379-388.

127. Delamaire M, Maugendre D, Moreno M, et al. Impaired leucocyte functions in diabetic patients. Diabet Med 1997; 14:29-34.

128. Pradhan AD, Manson JE, Rifai N, et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001; 286:327-334.

129. Jain SK, Kannan K, Lim G, et al. Elevated blood interleukin-6 levels in hyperketonemic type 1 diabetic patients and secretion by acetoacetate-treated cultured U937 monocytes. Diabetes Care 2003; 26:2139-2143.

130. Esper AM, Moss M, Martin GS. The effect of diabetes mellitus on organ dysfunction with sepsis: an epidemiological study. Critical Care 2009; 13:R18.

131. Thomsen R, Hundborg HH, Lervang HH, et al. Diabetes and outcome of community- acquired pneumococcal bacteremia. Diabetes Care 2004; 27:70-76.

132. Moss M, Guidot DM, Steinberg KP, et al. Diabetic patients have a decreased incidence of acute respiratory distress syndrome. Crit Care Med 2000; 28:2187-2192.

133. Stegenga ME, van der Crabben SN, Blumer RME, et al. Hyperglycemia enhances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia. Blood 2008; 112: 82-89.

134. von Eiff C, Becker K, Machka K, et al. Nasal carriage as a source of Staphylococcus aureus bacteremia. Study Group. N Engl J Med 2001; 344:11-16.

135. Lipsky BA, Pecoraro RE, Chen MS,et al. Factors affecting staphylococcal colonization among NIDDM outpatients. Diabetes Care 1987; 10:483-486.

136. Boyko EJ, Lipsky BA, Sandoval R, et al. NIDDM and prevalence of nasal Staphylococcus aureus colonization. San Luis Valley Diabetes Study. Diabetes Care 1989; 12:189-192.

137. Mermel LA, Cartony JM, Covington P, et al. Mehicillin-resistant Staphylococcus aureus colonization at different body sites: a prospective, quantitative analysis. J Clin Microbiol 2011; 49:1119-1121.

138. Flynn A, Mani BC, Mather PJ. Sepsis-induced cardiomyopathy: a review of pathophysiologic mechanisms. Heart Fail Rev 2010; 15:605-611.

139. Maeder M, Fehr T, Rickli H, Ammann P. Sepsis-associated myocardial dysfunction. Chest 2006; 129:1349-1366.

140. Pulido JN, Afessa B, Masaki M, et al. Clinical spectrym, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock. Mayo Clin Proc 2012; 87:620-628.

141. Kakihana Y, Ito T, Nakahara M, et al. Sepsis-induced myocardial dysfunction: pathophysiology and management. J Intensive Care 2016; 4:22.

142. Richardson WS, Wilson MC, Nishikawa J, et al. The well-built clinical question: A key to evidence-based decisions. APC J Club 1995; 123:A12-13.

143. Folden DV, Machayya JA, Sahmoun AE, et al. Estimating the proportion of community-associated methicillin-resistant *Staphylococcus aureus*: two definitions used in the USA yield dramatically different estimates. J Hosp Infect 2005; 60:329-332.

144. McCarthy NL, Sullivan PS, Gaynes R, et al. Healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus* infections: A comparison of definitions. Am J Infect Control 2010; 38:600-606.

145. Sievert DM, Wilson ML, Wilkins MJ, et al. Public health surveillance for methicillin-resistant *Staphylococcus aureus*: Comparison of methods for classifying health care- and community-associated infections. Am J Public Health 2010; 100:177-1783.

146. Leung V, Lloyd-Smith E, Romney M. Classification of MRSA cases detected at the time of hospital admission: does the ´look-back´ period matter? J Hosp Infect 2013; 256-258.

147. Bryan CS, Reynolds KL, Metzger WT. Bacteremia in diabetic patients: Comparison of incidence and mortality with nondiabetic patients. Diabetes Care 1985; 8:244-249.

148. Laupland KB, Church DL, Mucenski M, et al. Population-based study of the epidemiology of and the risk factors for invasive *Staphylococcus aureus* infections. J Infect Dis 2003; 187:1452-1459.

149. Laupland KB, Ross T, Gregson DB. *Staphylococcus aureus* bloodstream infections: Risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000-2006. J Infect Dis 2008; 198:336-343.

150. Chase M, Klasco RS, Joyce NR, et al. Predictors of bacteremia in emergency department patients with suspected infection. Am J Emerg Med 2012; 30:1691-1697.

151. Hernandez C, Cobos-Trigueros N, Feher C, et al. Community-onset bacteraemia of unknown origin: clincial characteristics, epidemiology and outcome. Eur J Clin Microbiol Infect Dis 2014; 33:1973-1980.

152. Cluff LE, Reynolds RC, Page DL, et al. Staphylococcal bacteremia and altered host resistance. Ann Intern Med 1968; 69:859-873.

153. Cooper G, Platt R. *Staphylococcus aureus* bacteremia in diabetic patients. Am J Med 1982; 73:658-662.

154. Maradona JA, Carton JA, Lopéz-Alonso J, et al. Comparative study of community versus hospital-acquired *Staphylococcus aureus* bacteremia. Eur J Med 1992; 1:113-115.

155. Kanafani ZA, Kourany WM, Fowler VG Jr., et al. Clinical characteristics and outcomes of diabetic patients with *Staphylococcus aureus* bacteremia and endocarditis. Eur J Clin Microbiol Infect Dis 2009; 28:1477-1482.

156. Cuervo SI, Cortés JA, Sánchez R, et al. Risk factors for mortality caused by *Staphylococcus aureus* bacteremia in cancer patients. Enferm Infecc Microbiol Clin 2010; 28:349-354.

157. Lin SH, Liao WH, Lai CC, et al. Risk factors for mortality in patients with persistent methicillin-resistant *Staphylococcus aureus* bacteremia in a tertiary care hospital in Taiwan. J Antimicrob Chemother 2010; 65:1792-1798.

158. Rothman K, ed. Epidemiology - an introduction. 2nd ed. New York, NY.: Oxford University Press, Inc.; 2012.

159. Rothman KJ, Greenland S, Lash TL. Validity in epidemiologic studies. Modern Epidemiology 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins 2008.

160. Fletcher R, Fletcher S, Wagner E, eds. Clinical Epidemiology – The Essentials. 3rd ed. Philadelphia, Pennsylvania: Lippincott, Williams & Wilkins 1996.

161. Rothman KJ. Six persistent research misconceptions. J Gen Intern Med 2014; 29:1060-1064.

162. Pedersen CB. The Danish Civil Registration System. Scan J Public Health 2011; 39:22-25.

163. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014; 29:541-549.

164. Skov R, Smyth R, Clausen M, et al. Evaluation of a cefoxitin 30 microg disc on Iso-Sensitest agar for detection of methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother 2003; 52:204-207.

165. http://orbit.dtu.dk/files/6329669/Danmap+2010.pdf (accessed 20/9-2016).

166. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011; 39:30-33.

167. Schmidt M, Johannesdottir SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015; 7:449-490.

168. NOMESCO classification of surgical procedures. 1.15 ed. Copenhagen. Nordic Medico-Statistical Committee 2010.

169. Grann AF, Erichsen R, Nielsen AG, et al. Existing data sources for clinical epidemiology: The clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. Clin Epidemiol 2011; 1:133.

170. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol 2010; 2:273-279.

171. Wacholder S, McLaughlin JK, Silverman DT, et al. Selection of controls in case-control studies. I. Principles. Am J Epidemiol 1992; 135:1019-1028.

172. Sohn MW, Budiman-Mak E, Stuck RM, et al. Diagnostic accuracy of existing methods for identifying diabetic foot ulcers from inpatient and outpatient datasets. J Foot Ankle Res 2010; 3:27.

173. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145:247-254.

174. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. Am J Cardiol 2006; 97:1759-1764.

175. Demant MN, Gislason GH, Køber L, et al. Association of heart failure severity with risk of diabetes: a Danish nationwide cohort study. Diabetologia 2014; 57:1595-1600.

176. Hanses F, Spaeth C, Ehrenstein BP, et al. Risk factors associated with long-term prognosis of patients with *Staphylococcus aureus* bacteremia. Infection 2010; 38:465-470.

177. Yahav D, Yassin S, Shaked H, et al. Risk factors for long-term mortality of *Staphylococcus aureus* bacteremia. Eur J Clin Microbiol Infect Dis 2016; 35:785-790.

178. Gotland N, Uhre ML, Mejer N, et al. Long-term mortality and causes of death associated with *Staphylococcus aureus* bacteremia. A matched cohort study. J Infect 2016; 346-357.

179. Kaasch AJ, Rieg S, Neumann S, et al. Measuring mortality in *Staphylococcus aureus* bloodstream infections: are 3 months of follow-up enough? Infection 2011; 39:281-282.

180. Hallgren J, Fransson EI, Kåreholt I, et al. Factors associated with hospitalization risk among community living middle aged and older persons: Results from the Swedish Adoption/Twin Study of Aging (SATSA). Arch Gerontol Geriatr 2016; 66:102-108.

181. Charlson M, Pompei P, Ales KL. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chron Dis 1987; 40:373-83.

182. Thygesen SK, Christiansen CF, Christensen S, et al. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 2011;11:83.

183. Osthoff M, Sidler JA, Lakatos B, et al. Low-dose acetylsalicylic acid treatment and imoact on short-term mortality in *Staphylococcus aureus* bloodstream infection: A propensity score-matched cohort study. Crit Care Med 2016; 44:773-781.

184. Smit J, Kaasch AJ, Søgaard M, et al. Use of glucocorticoids and risk of community-acquired *Staphylococcus aureus* bacteremia: A population-based case-control study. Mayo Clin Proc 2016; 91:873-880.

185. López-Cortés LE, Gálvez-Acebal J, del Toro MD, et al. Effect of statin therapy in the outcome of bloodstream infections due to *Staphylococcus aureus*: A prospective cohort study. PLoS One 2013; 8:e82958.

186. Walter S, Tiemeier H. Variable selection: current practice in epidemiological studies. Eur J Epidemiol 2009; 24:733-736.

187. Yaw LK, Robinson JO, Ho KM. A comparison of long-term outcomes after methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* bacteraemia: an observational cohort study. Lancet Infect Dis 2014; 14:967-975.

188. Fätkenheuer G, Kaasch AJ. How deadly is methicillin-resistant *Staphylococcus aureus*. Lancet Infect Dis 2014; 14:905-907.

189. Grimes DA, Schulz KF. Compared to what? Finding controls for case-control studies. Lancet 2005; 365:1429-1433.

190. Olsen J, Basso O, Sørensen HT. What is a population-based registry? Scand J Public Health 1999; 27:78.

191. Kornum JB, Thomsen RW, Riis A, et al. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. Diabetes Care 2008; 8:1541-1545.

192. http://www.dst.dk/pukora/epub/Nyt/2012/NR668.pdf (accessed 20/9-2016).

193. Kümler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, et al. Accuracy of a heart failure diagnosis in administrative registers. Eur J Heart Fail 2008;10:658-660.

194. Pedersen G, Schønheyder HC, Sørensen HT. Source of infection and other factors associated with case fatality in community-acquired bacteremia – a Danish population-based cohort study from 1992 to 1997. Clin Microbiol Infect 2003; 9:793-802.

195. Søgaard M, Nørgaard M, Pedersen L, et al. Blood culture status and mortality among patients with suspected community-acquired bacteremia: a population-based cohort study. BMC Infect Dis 2011; 11:139.

196. Wang HE, Griffin R, Judd S, et al. Obesity and risk of sepsis: a population-based cohort study. Obesity 2013; 21:E762-769.

197. Cosgrove SE, Sakoulas G, Perecevich EN, et al. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: A meta-analysis. Clin Infect Dis 2003; 36:53-59.

198. Sharma M, Szpunar S, Khatib R. Validating severity of illness scoring systems in the prediction of outcomes in *Staphylococcus aureus* bacteremia. Am J Med Sci 2013; 346:87– 91.

199. Crowe CA, Kulstad EB, Mistry CD, et al. Comparison of severity of illness scoring systems in the prediction of hospital mortality in severe sepsis and septic shock. J Emerg Trauma Shock 2010; 3:342–347.

200. Vallés J, Palomar M, Alvárez-Lerma F, et al. Evolution over a 15-year period of clinical characteristics and outcomes of critically ill patients with community-acquired bacteremia. Crit Care Med 2013; 41:76–83.

201. Rasmussen JB, Knudsen JD, Arpi M, et al. Relative efficacy of cefuroxime versus dicloxacillin as definitive antimicrobial theraoy in methicillin-susceptible *Staphylococcus aureus* bacteraemia: a propensity-score adjusted retrospective cohort study. J Antimicrob Chemother 2011; 69:506-514.

202. Koch K, Nørgaard M, Schønheyder HC, et al. Effect of socioeconomic status in mortality after bacteremia in working-age patients. A Danish population-based cohort study. PLoS One 2013; 8:e70082.

203. Poole C. Low p-values of narrow confidence intervals: Which are more durable? Epidemiology 2001; 12:291-294.

204. Zarei AE, Almehadar HA, Redwan EM. Hib vaccines: past, present, and future perspectives. J Immunol Res 2016; 2016:7203587.

205. Mangtani P, Cutts F, Hall AJ. Efficacy of polysaccharide pneumococcal vaccine in adults in more developed countries: the state of the evidence. Lancet Infect Dis 2003; 3:71.

206. Fowler VG Jr, Proctor RA. Where does a *Staphylococcus aureus* vaccine stand? Clin Microbiol Infect 2014; 20 Suppl 5:66-75.

207. Nissen M, Marshall H, Richmond P, et al. A randomized phase I study of the safety and immunogenicity of three ascending dose levels of a 3-antigen *Staphylococcus aureus* vaccine (SA3Ag) in healthy adults. Vaccine 2015; 33:1846-1854.

208. Bagnoli F, Fontana MR, Soldaini E, et al. Vaccine composition formulated with a novel TLR7-dependent adjuvant induces high and broad protection against *Staphylococcus aureus*. Proc Natl Acad Sci U S A. 2015; 112:3680-3685.

209. Fowler VG, Sanders LL, Sexton DJ, et al. Outcome of *Staphylococcus aureus* bacteremia according to compliance with recommendations of infectious diseases specialists: Experience with 244 patients. CID 1998; 27:478-486.

210. Honda H, Krauss MJ, Jones JC, et al. The value of infectious diseases consultation in *Staphylococcus aureus* bacteremia. Am J Med 2010;123:631-637.

211. Choi SH, Cho SY, Park JH, et al. Impact of infectious-disease specialist consultations on outcomes of *Staphylococcus aureus* bacteremia in a hospital with a low volume of patients with S.aureus bacteremia. J Infect 2011; 62:181-185.

212. Forsblom E, Ruotsalainen E, Ollgren J, et al. Telephone consultation cannot replace bedside infectious disease consultation in the management of *Staphylococcus aureus* bacteremia. CID 2012; 56: 527-535.

213. López-Cortés LE, del Toro MD, Gálvez-Acebal J, et al. Impact of an evidence-based bundle intervention in the quality-of-care management and outcome of *Staphylococcus aureus* bacteremia. CID 2013; 57:1225-1233.

214. Tissot F, Calendra T, Prod´hom G, et al. Mandatory infectious diseases consultation for MRSA bacteremia is associated with reduced mortality. J Infect 2014; 226-234.

215. Bai AD, Showler A, Burry L, et al. Impact of infectious disease consultation on quality of care, mortality, and length of stay in *Staphylococcus aureus* bacteremia: Results from a large multicenter study. Clin Infect Dis 2015; 60:1451-1461.

216. Vogel M, Schmitz RPH, Hagel S, et al. Infectious disease consultation for *Staphylococcus aureus* bacteremia – a systematic review and meta-analysis. J Infect 2016; 72:19-28.

10. Appendices

The appendices contain the Medline and Embase search strategy details for studies I-IV (Appendix A) and full versions of the papers I-IV including supplementary material (Appendix B).

- **Appendix A: Medline and Embase search strategy details (studies I-IV)**

Study I: Impact of different HCA-SAB definitions on patient characteristics and outcome

Medline database

Step	Search terms	Result
1	exp Community-Acquired Infections/	11586
2	exp Cross Infection/ or exp Community-Acquired Infections/	60939
3	((healthcare or health care* or health-care*) adj2 (associat* or related*)).mp.	10023
4	exp "bacterial infections and mycoses"/	1289057
5	(infection* or bacteraemia* or bacteremia*).mp.	1583209
6	or/4-5	2158184
7	3 and 6	5093
8	2 or 7	63369
9	exp Classification/	161679
10	(classification* or definition*).mp.	374982
11	or/9-10	521589
12	8 and 11	2266

Embase database

Step	Search terms	Result
1	cross infection/ or community acquired infection/	22048
2	healthcare associated infection/	1993
3	1 or 2	23913
4	((healthcare or health care* or health-care*) adj2 (associat* or related*)).mp.	14613
5	exp infection/	2919887
6	(infection* or bacteraemia* or bacteremia*).mp.	2059944
7	5 or 6	3296491
8	4 and 7	8195
9	1 or 2 or 8	29465
10	exp disease classification/	437244
11	(classification* or definition*).mp.	783118
12	10 or 11	1056606
13	9 and 12	2059

Study II: Diabetes and risk of community-acquired *S. aureus* bacteremia and
Study III: Diabetes and outcome of community-acquired *S. aureus* bacteremia

Medline database

Step	Search terms	Result
1	exp Staphylococcal Infections/	58170
2	exp Staphylococcus aureus/	60213
3	Staphylococcus aureus.mp.	98034
4	or/1-3	125290
5	exp Bacteremia/	24507
6	Sepsis/	50011
7	(Septicemia or bacteremia or bacteraemia or sepsis or septicaemia).mp.	136446
8	(blood* adj2 infection*).mp.	12043
9	or/5-8	146638
10	exp Diabetes Mellitus/	353928
11	diabet*.mp.	552378
12	or/10-11	553954
13	4 and 9 and 12	359

Embase database

Step	Search terms	Result
1	staphylococcal bacteremia/	1391
2	exp Staphylococcus aureus/	130440
3	exp Staphylococcus infection/	41726
4	Staphylococcus aureus.mp.	152157
5	2 or 3 or 4	170428
6	exp bacteremia/	38749
7	exp sepsis/	202032
8	(Septicemia or bacteremia or bacteraemia or sepsis or septicaemia).mp.	217001
9	bloodstream infection/	7115
10	(blood* adj2 infection*).mp.	18855
11	or/6-10	257343
12	5 and 11	20573
13	1 or 12	20573
14	exp diabetes mellitus/	728982
15	diabet*.mp.	867034
16	or/14-15	871135
17	13 and 16	1079

Study IV: Chronic heart failure and outcome of community-acquired *S. aureus* bacteremia

Medline database

Step	Search terms	Result
1	exp Staphylococcal Infections/	58170
2	exp Staphylococcus aureus/	60213
3	Staphylococcus aureus.mp.	98034
4	or/1-3	125290
5	exp Bacteremia/	24507
6	Sepsis/	50011
7	(Septicemia or bacteremia or bacteraemia or sepsis or septicaemia).mp.	136446
8	(blood* adj2 infection*).mp.	12043
9	or/5-8	146638
10	exp Heart Failure/	99181
11	((heart or cardiac) adj3 (failure or insufficienc*)).mp.	173921
12	10 or 11	174774
13	4 and 9 and 12	179

Embase database

Step	Search terms	Result
1	staphylococcal bacteremia/	1391
2	exp Staphylococcus aureus/	130440
3	exp Staphylococcus infection/	41726
4	Staphylococcus aureus.mp.	152157
5	2 or 3 or 4	170428
6	exp bacteremia/	38749
7	exp sepsis/	202032
8	(Septicemia or bacteremia or bacteraemia or sepsis or septicaemia).mp.	217001
9	bloodstream infection/	7115
10	(blood* adj2 infection*).mp.	18855
11	or/6-10	257343
12	5 and 11	20573
13	1 or 12	20573
14	exp heart failure/	375756
15	((heart or cardiac) adj3 (failure or insufficienc*)).mp.	324013
16	or/14-15	420381
17	13 and 16	712

- **Appendix B: Full versions of studies I-IV including supplementary material**

Study 1

Study 2

Study 3

Study 4

Study 1

CONCISE COMMUNICATION

Classification of Healthcare-Associated *Staphylococcus aureus* Bacteremia: Influence of Different Definitions on Prevalence, Patient Characteristics, and Outcome

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We investigated whether different definitions of healthcare-associated infection influenced the prevalence, characteristics, and mortality of patients with *Staphylococcus aureus* bacteremia. With different definitions, the proportion of patients classified as having healthcare-associated *S. aureus* bacteremia varied substantially and the distribution of patient characteristics was influenced, whereas 30-day mortality remained robust.

Infect. Control Hosp. Epidemiol. 2015;00(0):1–4

Correct classification of the place of acquisition of infections is crucial for guidance of empirical antibiotic treatment and infection surveillance.[1] Traditionally, infections have been classified as community-acquired (CA) or hospital-acquired. However, owing to major increases in outpatient clinical care a separate healthcare-associated (HCA) group has been proposed in order to extend the definition of CA definitions.[2,3] Still, there is still no consensus on the definition of HCA, which may have methodologic implications for studies of infection.

Using a large cohort of patients with *Staphylococcus aureus* bacteremia (SAB), we investigated whether different definitions of HCA influenced the proportion of patients classified as HCA, and whether the prevalence of patient characteristics and mortality observed in the HCA group varied with different definitions.

METHODS

We conducted this cross-sectional study from 2000 to 2011 in Northern Denmark within a population of approximately 1.8 million inhabitants, all provided with free, tax-supported healthcare. Using the unique Civil Registration Number assigned to all Danish citizens,[4] a complete hospitalization and drug prescription history was obtained for all patients admitted with SAB.

Patients aged at least 15 years with a first hospitalization for monomicrobial SAB were identified in the databases of the regional departments of clinical microbiology. *S. aureus* was identified and tested for susceptibility by standard methods.

In order to classify patients by acquisition, we retrieved information on all in- and outpatient contacts and medication use up to 90 days before the current admission using the Danish National Patient Registry[5] and the Aarhus University Prescription Database.[6] All SAB patients were initially classified as either CA-SAB or hospital-acquired–SAB on the basis of the interval between time of admission and blood culture sampling ($\leq$2 days vs >2 days). Next, on the basis of a review of the literature,[1–3] we proposed 5 different definitions of HCA as described in Figure 1. In order to facilitate comparisons among groups, the definitions were ranked in a decreasing order with regard to stringency of criteria. Using each individual definition alternately, all patients with CA-SAB were then subcategorized as either "true" CA-SAB (ie, not fulfilling the HCA-SAB definition in question) or HCA-SAB.

We used all diagnoses recorded in the Danish National Patient Registry up to 10 years before the current admission to identify previous comorbidity included in the Charlson Comorbidity Index score.[7] Three levels of comorbidity were defined: low (0), corresponding to patients with no preexisting registered comorbidity; intermediate (1–2); and high ($\geq$3). We also obtained data on alcohol-related conditions, hypertension, and osteoporosis. Information on 30-day all-cause mortality was retrieved from the Civil Registration System,[4] which contains information on residency, vital status, and exact date of death.

Prevalence proportions of patients classified as HCA-SAB were computed according to each HCA definition. We estimated prevalence proportions for patient characteristics and outcomes according to each of the 5 HCA definitions. The 5 HCA groups were compared with each other and with the group containing all CA-SAB patients (ie, true CA-SAB and HCA-SAB). The Kaplan-Meier method was applied to ascertain 30-day all-cause mortality within groups. Statistical analyses were performed using Stata, version 11.2 (StataCorp). The project was approved by the Danish Data Protection Agency (ref. no. 2012-41-0942).

RESULTS

During the study period 4,385 patients aged at least 15 years were hospitalized with incident SAB, of which 2,638 (60.2%) were classified as CA-SAB and 1,747 (39.8%) as hospital-acquired–SAB. Methicillin-resistant SAB accounted for only 0.6% of all patients. Among patients with CA-SAB, the proportion classified as HCA-SAB ranged from 29.8% when applying the most stringent definition (def. 1, Figure 1) to 71.7% when the least stringent definition was used (def. 5).

Table 1 displays patient characteristics and outcomes according to each of the 5 definitions. The proportion of male patients classified as HCA-SAB according to the most stringent definition (def. 1) constituted 57.7% compared with 60.6% for

	Definition	Criteria *Blood culture performed within 2 days of admission and the following:*
Highest level of stringency	1.	• Any hospital inpatient admission within the previous 30 days
	2.	• Any hospital inpatient admission within the previous 30 days *or* • Hospital outpatient clinic contact including surgery or contact to clinics of oncology, hematology or nephrology within the previous 30 days
	3.	• Any hospital inpatient admission within the previous 30 days *or* • Any type of hospital outpatient clinic contact within the previous 30 days
	4.	• Any hospital inpatient admission within the past 90 days *or* • Any type of hospital outpatient clinic contact within the previous 30 days
Lowest level of stringency	5.	• Any hospital inpatient admission within the past 90 days *or* • Any type of hospital outpatient clinic contact within the previous 30 days *or* • Antibiotic or immunosuppressive therapy 30 days prior to admission

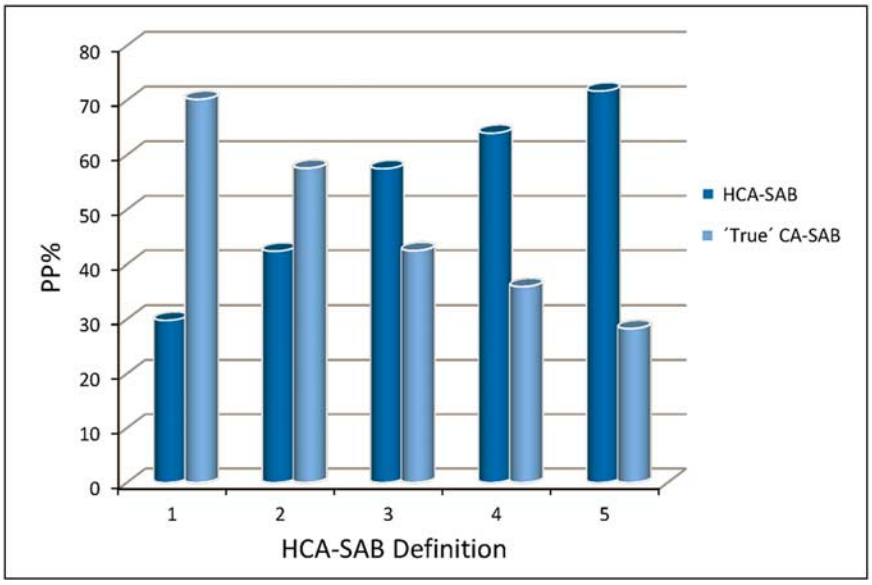

FIGURE 1. Definitions 1–5 of healthcare-associated (HCA) *Staphylococcus aureus* bacteremia (SAB) and prevalence proportion (PP) of patients classified as HCA-SAB and true community-acquired (CA) SAB according to the 5 different definitions.

patients classified using the least stringent definition (def. 5). The percentage of patients older than 75 years was 30.2% and 34.3% using def. 1 and def. 5, respectively. The proportion of patients with at least 3 conditions registered in the Charlson Comorbidity Index ranged from 48.5% for patients classified according to def. 1 to 44.8% for patients classified according to def. 5. Thirty-day all-cause mortality was 24.8% and 24.7% in patients classified according to def. 1 and def. 5, respectively.

Comparing the group including all CA-SAB patients with patients in the def. 1 group, a larger proportion of CA-SAB-patients was male (61.3% vs 57.7%), the CA-SAB patients were more often older than 75 years (35.9% vs 30.2%), but they had less comorbidity (Table 1).

DISCUSSION

In this large cross-sectional study the prevalence of patients classified as HCA-SAB varied substantially with different definitions of HCA infection. Use of different HCA-SAB definitions also influenced the distribution of patient characteristics, whereas 30-day all-cause mortality remained comparable among the 5 groups.

TABLE 1. Prevalence Proportions of Patient Characteristics and Outcome According to 5 Different Definitions of Healthcare-Associated (HCA) *Staphylococcus aureus* Bacteremia (SAB)

	Definition 1	Definition 2	Definition 3	Definition 4	Definition 5	All CA-SAB
Patient characteristics and outcomes	(Decreasing stringency of HCA-SAB definitions)					
No. (% of all CA-SAB)	787 (29.8)	1,115 (42.3)	1,517 (57.5)	1,688 (64.0)	1,892 (71.7)	2,638 (100)
Age >75 years	238 (30.2)	307 (27.5)	464 (30.6)	561 (33.2)	649 (34.3)	946 (35.9)
Male sex	454 (57.7)	663 (59.5)	914 (60.3)	1,019 (60.4)	1,147 (60.6)	1,616 (61.3)
MRSA-SAB	5 (0.6)	6 (0.5)	11 (0.7)	12 (0.7)	12 (0.6)	13 (0.5)
Comorbidity in the CCI						
Myocardial infarction	76 (9.7)	117 (10.5)	154 (10.2)	172 (10.2)	185 (9.8)	220 (8.3)
Congestive heart failure	113 (14.4)	165 (14.8)	225 (14.8)	260 (15.4)	278 (14.7)	348 (13.2)
Peripheral arterial disease	110 (14.0)	180 (16.1)	230 (15.2)	261 (15.5)	275 (14.5)	328 (12.4)
Diabetes mellitus	144 (18.3)	228 (20.4)	311 (20.5)	350 (20.7)	378 (20.0)	477 (18.1)
Any tumor	237 (30.1)	335 (30.0)	416 (27.4)	440 (26.1)	455 (24.0)	515 (19.5)
CCI score						
Low (0)	119 (15.1)	136 (12.2)	229 (15.1)	262 (15.5)	355 (18.8)	725 (27.5)
Intermediate (1–2)	286 (36.3)	371 (33.3)	540 (35.6)	612 (36.3)	690 (36.5)	941 (35.7)
High (≥3)	382 (48.5)	608 (54.5)	748 (49.3)	814 (48.2)	847 (44.8)	972 (36.8)
Comorbidity, other types						
Hypertension	226 (28.7)	367 (32.9)	466 (30.7)	517 (30.6)	546 (28.9)	651 (24.7)
Osteoporosis	55 (7.0)	66 (5.9)	92 (6.1)	107 (6.3)	121 (6.4)	146 (5.5)
Alcohol-related conditions	70 (8.9)	94 (8.4)	124 (8.2)	142 (8.4)	154 (8.1)	235 (8.9)
Preadmission medication use						
Antibiotic therapy	148 (18.8)	196 (17.6)	288 (19.0)	337 (20.0)	536 (28.3)	536 (20.3)
Immunosuppressive therapy	7 (0.9)	11 (1.0)	21 (1.4)	22 (1.3)	28 (1.5)	28 (1.1)
Length of hospital stay >14 days	364 (46.3)	526 (47.2)	759 (50.0)	847 (50.2)	959 (50.7)	1,388 (52.6)
30-day mortality	195 (24.8)	252 (22.6)	344 (22.7)	406 (24.1)	468 (24.7)	652 (24.7)

NOTE. Data are no. (%) of episodes. CA-SAB, community-acquired SAB; CCI, Charlson Comorbidity Index; MRSA-SAB, methicillin-resistant SAB.

The prevalence of HCA bacteremia, including SAB, has varied notably from 17% to 55% in previous studies,[8–10] which employed a wide span of different definitions. In our study, we observed substantial disparities in the prevalence of HCA-SAB across the 5 different definitions. These results may reflect that the wide variation in HCA bacteremia prevalence found in previous studies is affected largely by the choice of definition, and perhaps less by actual differences in local settings and study populations.

Interestingly, comparing the group containing all patients initially classified as CA-SAB (ie, true CA-SAB and HCA-SAB) with patients classified according to definitions 1–5, the variance in patient characteristics gradually became less pronounced with decreasing stringency of the HCA definition. Thus, it is possible that the use of abundantly permissive definitions may prompt an overestimation of HCA infection prevalence and a corresponding underestimation of true CA infection prevalence. In contrast to previous studies,[8–10] we observed no difference in 30-day all-cause mortality among patients with CA-SAB and HCA-SAB. HCA-SAB was previously found to be associated with an increased mortality compared with CA-SAB conveyed partly by increased colonization and infection of methicillin-resistant *S. aureus*.[8–10] Because the prevalence of methicillin-resistant SAB was very low in our study setting, this might explain our results to some extent.

The main strengths of our study include its considerable size and a population-based design; still, some limitations should be acknowledged. Contacts to outpatient hospital clinics of oncology, hematology, and nephrology were used as proxies for data on chemotherapy and dialysis. This is probably not likely to influence the overall results, yet misclassification of some patients cannot be completely ruled out. We lacked data on nursing home residence or specialized home care, which is often included in definitions of HCA infection. Taking the primary objects of our study into account, it is probably unlikely that the addition of these criteria would have substantially altered the main results. Still, we recognize the importance of these exposures and consider them relevant for any definition of HCA infection.

In conclusion, we observed substantial variation in the prevalence of patients classified as HCA-SAB when different definitions of HCA infection were used. The different definitions also influenced the distribution of patient characteristics, whereas mortality estimates remained robust. This study highlights some of the methodologic challenges associated with studies of HCA infections and emphasizes the need for caution when comparing studies using different definitions.

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REFERENCES

1. Cardoso T, Almeida M, Friedman ND, et al. Classification of healthcare-associated infection: a systematic review 10 years after the first proposal. *BMC Med* 2014;12:40.
2. Friedman ND, Kaye KS, Stout JE, et al. Healthcare-associated infections in adults: a reason to the change the accepted definition of community-acquired infections. *Ann Intern Med* 2002;137:791–797.
3. Siegman-Igra Y, Fourer B, Orni-Wasserlauf R, et al. Reappraisal of community-acquired bacteremia: a proposal of a new classification for the spectrum of acquisition of bacteremia. *Clin Infect Dis* 2002;34:1431–1439.
4. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–549.
5. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30–33.
6. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clin Epidemiol* 2010;2:273–279.
7. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987;40:373–383.
8. Vallés J, Calbo E, Anoro E, et al. Bloodstream infections in adults: importance of healthcare-associated infections. *J Infect* 2008;56:27–34.
9. Lenz R, Leal JR, Church DL, Gregson DB, Ross T, Laupland KB. The distinct category of healthcare associated bloodstream infections. *BMC Infect Dis* 2012;12:85.
10. Shorr A, Tabak YP, Killian AD, Gupta V, Liu LZ, Kollef MH. Healthcare-associated bloodstream infections: a distinct entity? Insights from a large U.S. database. *Crit Care Med* 2006;10:2588–2595.

Study 2

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 m^2) >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 ≥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 m^2 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

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%.
[a]Any use within 30 days of the index date; [b]Any previous use before the index date; [c]Measured 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.

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)

[a]Adjusted 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; [b]Patients with diabetes and a previous diagnosis of neuropathy and/or peripheral vascular disease; [c]Patients 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 m^2).

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 m^2.

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)

[a]Adjusted 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.

References

1 Kern WV. Management of *Staphylococcus aureus* bacteremia and endocarditis: progress and challenges. *Current Opinion in Infectious Diseases* 2010 **23** 346–358. (doi:10.1097/QCO.0b013e32833bcc8a)

2 Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, Kirby A, Tilley R, Török ME, Walker S, Wertheim HFL, Wilson P, Llewelyn MJ *et al*. Clinical management of Staphylococcus aureus bacteraemia. *Lancet Infectious Diseases* 2011 **11** 208–222. (doi:10.1016/S1473-3099(10)70285-1)

3 Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U & Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Research and Clinical Practice* 2014 **103** 161–175 (doi:10.1016/j.diabres.2013.11.002)

4 Whiting DR, Guariguata L, Weil C & Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Research and Clinical Practice* 2011 **94** 311–321. (doi:10.1016/j.diabres.2011.10.029)

5 Koh GCKW, Peacock SJ, van der Poll T & Wiersinga WJ. The impact of diabetes on the pathogenesis of sepsis. *European Journal of Clinical Microbiology & Infectious Diseases* 2012 **31** 379–388.

6 Thomsen RW & Mor A. Diabetes and risk of community-acquired respiratory tract infections, urinary tract infections, and bacteremia. *Open Infectious Diseases Journal* 2012 **6** 27–39. (doi:10.2174/1874279301206010027)

7 Kaasch AJ, Barlow G, Edgeworth JD, Fowler VG, Hellmich M, Hopkins S, Kern WV, Llewelyn MJ, Rieg S, Rodriguez-Baño J *et al*. *Staphylococcus aureus* bloodstream infection: a pooled analysis of five prospective, observational studies. *Journal of Infection* 2014 **68** 242–251. (doi:10.1016/j.jinf.2013.10.015)

8 Lesens O, Methlin C, Hansmann Y, Remy V, Martinot M, Bergin C, Meyer P & Christmann D. Role of comorbidity in mortality related to *Staphylococcus aureus* bacteremia: a prospective study using the Charlson Weighted Index of comorbidity. *Infection Control & Hospital Epidemiology* 2003 **24** 890–896. (doi:10.1086/iche.2003.24.issue-12)

9 Forsblom E, Ruotsalainen E, Mölkänen T, Ollgren J, Lyytikäinen O & Järvinen A. Predisposing factors, disease progression and outcome in 430 prospectively followed patients of healthcare- and community-associated *Staphylococcus aureus* bacteraemia. *Journal of Hospital Infection* 2011 **78** 102–107. (doi:10.1016/j.jhin.2011.03.010)

10 Kaech C, Elzi L, Sendi P, Frei R, Laifer G, Bassetti S & Fluckiger U. Course and outcome of Staphylococcus aureus bacteremia: a retrospective analysis of 308 episodes in a Swiss tertiary-care centre. *Clinical Microbiology and Infection* 2006 **12** 345–352. (doi:10.1111/j.1469-0691.2005.01359.x)

11 Bassetti M, Trecarichi EM, Mesini A, Spanu T, Giacobbe DR, Rossi M, Shenone E, Pascale GD, Molinari MP, Cauda R *et al*. Risk factors and mortality of healthcare-associated and community-acquired *Staphylococcus aureus* bacteraemia. *Clinical Microbiology and Infection* 2012 **18** 862–869. (doi:10.1111/j.1469-0691.2011.03679.x)

12 Laupland KB, Ross T & Gregson DB. *Staphylococcus aureus* bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000–2066. *Journal of Infectious Diseases* 2008 **198** 336–343. (doi:10.1186/s12879-014-0647-4)

13 Laupland KB, Church DL, Mucenski M, Sutherland LR & Davies HD. Population-based study of the epidemiology of and the risk factors for invasive *Staphylococcus aureus* infections. *Journal of Infectious Diseases* 2003 **187** 1452–1459. (doi:10.1086/jid.2003.187.issue-9)

14 Jacobsson G, Dashti S, Wahlberg T & Andersson R. The epidemiology of and risk factors for invasive *Staphylococcus aureus* infections in western Sweden. *Scandinavian Journal of Infectious Diseases* 2007 **39** 6–13. (doi:10.1080/00365540600810026)

15 Pedersen CB. The Danish Civil Registration System. *Scandinavian Journal of Public Health* 2011 **39** 22–25. (doi:10.1177/1403494810387965)

16 Schmidt M, Pedersen L & Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *European Journal of Epidemiology* 2014 **29** 541–549. (doi:10.1007/s10654-014-9930-3)

17 Wiese L, Mejer N, Schønheyder HC, Westh H, Jensen AG, Larsen AR, Skov R, Benfield T & Danish Staphylococcal Bacteraemia Study Group. A nationwide study of comorbidity and risk of reinfection after *Staphylococcus aureus* bacteraemia. *Journal of Infection* 2013 **67** 199–205. (doi:10.1016/j.jinf.2013.04.018)

18 Lynge E, Sandegaard JL & Rebolj M. The Danish National Patient Register. *Scandinavian Journal of Public Health* 2011 **39** 30–33. (doi:10.1177/1403494811401482)

19 Wacholder S, McLaughlin JK, Silverman DT & Mandel JS. Selection of controls in case-control studies. I. Principles. *American Journal of Epidemiology* 1992 **135** 1019–1028. (doi:10.1007/BF00050867)

20 Thomsen RW, Hundborg HH, Lervang HH, Johnsen SP, Sørensen HT & Schønheyder HC. Diabetes and outcome of community-acquired pneumococcal bacteremia. *Diabetes Care* 2004 **27** 70–76. (doi:10.1097/01.CCM.0000207345.92928.E4)

21 Grann AF, Erichsen R, Nielsen AG, Frøslev T & Thomsen RW. Existing data sources for clinical epidemiology: the clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. *Clinical Epidemiology* 2011 **1** 133.

22 Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clinical Epidemiology* 2010 **2** 273–279. (doi:10.2147/CLEP)

23 Sohn MW, Budiman-Mak E, Stuck RM, Siddiqui F & Lee TA. Diagnostic accuracy of existing methods for identifying diabetic foot ulcers from inpatient and outpatient datasets. *Journal of Foot and Ankle Research* 2010 **3** 27. (doi:10.1186/1757-1146-3-27)

24 Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F & Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Annals of Internal Medicine* 2006 **145** 247–254. (doi:10.7326/0003-4819-145-4-200608150-00004)

25 Charlson M, Pompei P & Ales KL. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases* 1987 **40** 373–383. (doi:10.1016/0895-4356(91)90008-W)

26 Thygesen SK, Christiansen CF, Christensen S, Lash TL & Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Medical Research Methodology* 2011 **11** 83. (doi:10.1186/1471-2288-11-83)

27 Otto M. How *Staphylococcus aureus* breaches our skin to cause infection. *Journal of Infectious Diseases* 2012 **205** 1483–1485. (doi:10.1093/infdis/jis248)

28 Nielsen LH, Jensen-Fangel S, Benfield T, Skov R, Jespersen B, Larsen AR, Østergaard L, Støvring H, Schønheyder HC & Søgaard OS. Risk and prognosis of *Staphylococcus aureus* bacteremia among individuals with and without end-stage renal disease: a Danish population-based cohort study. *BMC Infectious Diseases* 2015 **15** 6. (doi:10.1186/s12879-014-0740-8)

29 Schuetz P, Castro P & Shapiro NI. Diabetes and sepsis: preclinical findings and clinical relevance. *Diabetes Care* 2011 **34** 771–778. (doi:10.2337/dc10-1185)

30 Peleg AY, Weerarathna T, McCarthy JS & Davis TM. Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. *Diabetes/Metabolism Research and Reviews* 2007 **23** 3–13 (doi:10.1002/(ISSN)1520-7560)

31 Benfield T, Jensen JS & Nordestgaard BG. Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome. *Diabetologia* 2007 **50** 549–554. (doi:10.1007/s00125-006-0570-3)

32 Thomsen RW, Hundborg HH, Lervang HH, Johnsen SP, Schønheyder HC & Sørensen HT. Risk of community-acquired pneumococcal bacteremia in patients with diabetes: a population-based case-control study. *Diabetes Care* 2004 **27** 1143–1147. (doi:10.1097/01.CCM.0000207345.92928.E4)

33 Kornum JB, Thomsen RW, Riis A, Lervang HH, Schønheyder HC & Sørensen HT. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. *Diabetes Care* 2008 **8** 1541–1545. (doi:10.2337/dc08-0138)

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Supplementary Material 1

Identification and susceptibility testing of *S.aureus* isolates

Setting

During the study period a reform of local government merged four counties into two health regions: Central Denmark Region and North Denmark Region, collectively referred to as Northern Denmark. Three departments of clinical microbiology served Central Denmark Region and were situated in Aarhus (Aarhus University Hospital), Viborg (Regional Hospital of Viborg) and Herning (Regional Hospital West Jutland). North Denmark Region was served by one department of clinical microbiology at Aalborg University Hospital, Aalborg.
The total number of beds in non-psychiatric wards was 5.528 in 2000 and 4.058 in 2011.

Number of hospitals in the two health regions and their predecessors

	2000	2011
Central Denmark Region	17	5
North Denmark Region	7	4

Blood cultures

Blood cultures were ordered by the attending physician and blood samples were drawn by trained biotechnicians. The BacT/Alert system (bioMérieux, Marcy l'Etoil, France) was used throughout the study period at all hospital sites. Recommendations differed between the two health regions: In Central Denmark Region a standard blood culture for adults comprised two sets with two bottles each (one aerobic and one anaerobic bottle), whereas the standard in North Denmark Region was one set with three bottles (two aerobic and one anaerobic bottle).

Identification and susceptibility testing of *Staphylococcus aureus*

S. aureus was identified by horse plasma tube coagulase test or an equivalent commercial latex agglutination test. All blood culture isolates were referred to the Staphylococcal Reference Laboratory at Statens Serum Institut (Copenhagen) for national surveillance which included phage typing up to 2006 and *spa*-typing thereafter.

Susceptibility testing was undertaken locally by disk diffusion and confirmatory testing was performed at Statens Serum Institut. Screening for methicillin resistance varied between departments 2000-2002, but in 2003 the cefoxitin disk diffusion test was implemented both locally and at Statens Serum Institut. Detection of the *mecA* gene cassette was done by either in-house polymerase chain reaction (PCR) or the EVIGENE^{TM} hybridization test.

Methicillin resistant *S. aureus* (MRSA) became notifiable in Denmark in 2006. Due to the low prevalence of methicillin-resistance extra precautions were taken in this study by cross-referencing local data with the Danish national *S. aureus* bacteremia database at Statens Serum Institut.

Supplementary material 2

Codes for diagnoses, procedures, medication and blood tests

Formula for estimation of glomerular filtration rates (eGFR)

Preadmission comorbid conditions. Diagnoses codes are according to the 8th and 10th revision of the International Classification of Diseases, ICD-8 and ICD-10

Condition	ICD-8	ICD-10
Diabetes	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10-E14. O24 (except O24.4), G63.2, H36.0, N08.3
Myocardial infarction	410	I21-I23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50, I11.0, I13.0, I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445	I70, I71, I72, I73, I74, I77
Cerebrovascular disease	430-438	I60-I69, G45, G46
Dementia	290.09-290.19, 293.09	F00-F03, F05.1, G30
Chronic pulmonary disease	490-493, 515-518	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3

Connective tissue disease	712, 716, 734, 446, 135.99	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease	530.91, 530.98, 531-534	K22.1, K25-K28
Mild liver disease	571, 573.01, 573.04	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0
Hemiplegia	344	G81, G82
Moderate to severe renal disease	403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Any tumor	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203, 275.59	C81-C85, C88, C90, C96
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Metastatic solid tumor	195-198, 199	C76-C80
AIDS	079.83	B21-B24
Hypertension	400-404	I10-I13
Osteoporosis	723.09	M80-M82

Conditions related to alcohol abuse	291.09-291.99, 303.09-303.29, 303.91-303.99	F10, K86.0, Z72.1. T51, K29.2, G62.1, G31.2, I42.6, K70
Conditions related to drug abuse	304.09-304.99	F11-F16, F18-F19, T40
Microvacular complications:		
• Diabetic retinopathy	250.01, 249.01	H36.0, E10.3, E11.3, E12.3, E13.3, E14.3, H28.0, H33.4, H45.0
• Diabetic nephropathy	250.02, 249.02	N08.3, E10.2, E11.2, E12.2, E13.2, E14.2
• Diabetic neuropathy	250.03, 249.03	E10.4, E11.4, E14.4, G59.0, G63.2
Macrovascular complications:		
• Ischemic heart disease including atherosclerosis	410.09-414.99	I20-I25
• Stroke, transient cerebral ischemia and cerebrovascular disease	432.00-437.99	G45, I61, I63-I66, I67.2, I67.8-I67.9, I69.1, I69.3-I69.8
• Peripheral arterial disease	440.09-440.29	I70.2, I74.2-I74.5 I73.9A, I73.9B, I73.9C E10.5, E11.5
Conditions related to diabetic foot ulcers	354.01, 354.08, 354.09, 355.01, 355.09, 440.20, 440.28, 440.29, 445.00, 445.08, 445.90, 445.99	G57, G58, G62 I70.2, I74.3-I74.4, I73.9, I79.2

Lower-extremity ulcer diagnosis	707.01, 707.08, 707.09, 680.69, 680.59, 682.49, 720.13, 720.19, 720.09, 445.00, 445.09, 445.90, 997.21, 997.28, 997.29	L97, L98.4, L02.4, L03.0, L03,1, M86, R02, T87.3, T87.4, T87.5, T87.6
Lower-extremity ulcer-related procedures	850.90, 921.20, 896.20, 897.40, 898.10, 898.11, 992.20, 714.60, 714.20, 997.21, 997.28, 997.29, 805.20, 805.80, 810.55, 876.10, 840.50, 840.41, 877.00, 810.51, 808.60, 810.31	KQDB, KQDA, KQDG, UXRG30, UXRG47, UXRG50, UXAG, UXCG, UXMG, KNHK, KNHL, KNHM, KNHN, KNHQ, KNGQ, KNFQ

Procedures. Codes regarding dialysis are according to Danish Treatment codes and according to the 10th revision of the International Classification of Diseases, ICD-10.

	Danish treatment codes	**ICD-10**
Dialysis	98300, 94340, 94350 BJFD0, BJFD2	Z99.2, Z49, Z49.2, BJFD
Surgery	All surgical codes (K-codes) in the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures.	

Medication codes are according to the Anatomical Therapeutic Classification (ATC)

Type of medication	ATC codes
Antidiabetic medication:	
All antidiabetic medication	A10A, A10B
• Insulin	A10A
• Metformin	A10BA02
• Sulfonylureas	A10BB, A10BC
• Any other antidiabetic drugs	A10 without A10A, A10BA02, A10BB, A10BC
Immunosuppressive therapy	L01, L04
Systemic antibiotic therapy	J01
ACE inhibitors	C09
Beta-blockers	C07
Acetylsalicylic acid	B01AC06
Other thrombocyte function inhibitors	B01AC04, B01AC07, B01AC30
Statins or lipid lowering agents	C10AA, C10B, B04AB, C10AB, C10AC, C10AD, C10AX

Blood tests according to local analysis codes and Nomenclature for Properties and Units (NPU)-codes

Blood test	Local analysis- and NPU-codes
Creatinine	ASS00356, ASS00354, ASS00355, 11026, 1511235,1511236, 1610154, 1710301,1711807, 1811807, 1817156, 18016,1155,1311235, 1411235, 38927, 4998,

	1611807, NPU18016, NPU01807, NPU18105, NPU04998
HbA1c	AAB00091, AAA00740, AAB00061, AAB00092, 12155, NPU03835, NPU02307, NPU27300
Microalbuminuria	ASS00023, ASS00024, ASS00194, ASS00531, 1314117, 1414117, 1314118, 1414118, 1314115, 1414115, 1314114, 1414114, 10913, AAA00760, ASS00194, DNK05006, DNK05036, DNK05282, RIN00335, VEA0040, 1510913, 110723, 1513918, 1610137, 1710760, 1813919, 1815007, 1610138, 1815007, 110721, 1514935, 1610136, 1715006, 1815006, 110727, 1715036, 1817305, NPU19661, NPU19678, NPU19661, NPU19677, NPU19678, NPU19680

Formula for estimation of glomerular filtration rates (eGFR)

GFR (mL/min/1.73 m2) = 175 x (S_{cr}/88.4)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if African American) (SI units).

S_{cr} = serum creatinine.

Study 3

PLOS ONE

RESEARCH ARTICLE

Outcome of Community-Acquired *Staphylococcus aureus* Bacteraemia in Patients with Diabetes: A Historical Population-Based Cohort Study

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Data Availability Statement: The authors confirm that, for ethically approved reasons, some access restrictions apply to the data underlying the findings. Data from the registers used in the study are available for researchers who fulfill the criteria for access to confidential data. Detailed information on the application procedure for data access for researchers outside Denmark can be found at the Danish Data Protection Agency homepage (http://www.datatilsynet.dk/erhverv/tredjelande/overfoersel-til-tredjelande/). Data from the Danish National Patient Registry and the Civil Registration System

Abstract

Background

Patients with diabetes (DM) experience increased risk of *Staphylococcus aureus* bacteraemia (SAB), but the prognostic impact of diabetes in patients with SAB remain unclear. Therefore, we investigated 30-day all-cause mortality in patients with and without DM.

Methods

Population-based medical databases were used to conduct a cohort study of all adult patients with community-acquired SAB in Northern Denmark, 2000–2011. Using Cox proportional hazards regression, we computed hazard ratios as estimates of 30-day mortality rate ratios (MRRs) among patients with and without DM. We further investigated whether the prognostic impact of DM differed among patients with and without recent preadmission healthcare contacts (within 30 days of the current hospitalization) and by age, sex, marital status, level of comorbidity, and DM-related characteristics (e.g., duration of DM and presence of DM complications).

Results

Among 2638 SAB patients, 713 (27.0%) had DM. Thirty-day cumulative mortality was 25.8% in patients with DM and 24.3% in patients without DM, for an adjusted MRR (aMRR) of 1.01 (95% confidence interval (CI), 0.84–1.20). In analyses with and without recent healthcare contacts, the corresponding aMRRs were 0.84 (95% CI, 0.62–1.14) and 1.13 (95% CI, 0.91–1.41), respectively. Compared to patients without DM, the aMRR was 0.94 (95% CI, 0.74–1.20) for male patients with DM and 1.13 (95% CI, 0.87–1.47) for female patients with DM. The prognostic influence of DM on mortality did not differ notably with age, level of comorbidity, or characteristics of patients with DM.

may be obtained by applying to the Danish Health Data Authority (http://sundhedsdatastyrelsen.dk/da/forskerservice) and the Central Office of Civil Registration, Copenhagen (https://cpr.dk/cpr/site.aspx?p=194&ArticleID=4327), respectively. In order to access data from the Aarhus University Prescription Database and the LABKA database, researchers may apply to the Department of Clinical Epidemiology, at Aarhus University Hospital (www.kea.au.dk). Microbiological data can be requested from the departments of clinical microbiology at Aalborg University Hospital (http://www.aalborguh.rn.dk/Afsnit-og-ambulatorier/Klinisk-Mikrobiologisk-Afdeling) and Aarhus University Hospital (http://www.auh.dk/om-auh/afdelinger/klinisk-mikrobiologisk-afdeling/).

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Competing Interests: The authors have declared that no competing interests exist.

Conclusion

Patients with DM and community-acquired SAB did not experience higher 30-day mortality than patients without DM.

Introduction

Staphylococcus aureus is a leading cause of bacteraemia, with a 30-day mortality of 20–40% in developed countries [1–5]. Diabetes mellitus (DM) is associated with considerable morbidity and mortality, and the prevalence of this chronic disease is rapidly increasing on a global scale [6–7]. Patients with DM may experience higher mortality from *S. aureus* bacteraemia (SAB) than patients without DM because of generally decreased immunity [8], potential diabetes complications including renal disease, and a high prevalence of shared negative prognostic factors of SAB including advanced age and comorbidity [3].

Data regarding the prognostic impact of DM in patients with SAB remain sparse and conflicting, however, and to our knowledge, no study has examined this impact of DM as a primary objective. Previous investigations have been limited by small numbers of patients with DM, use of non-validated algorithms to identify DM patients, and failure to incorporate concurrent chronic conditions [9–14]. We find no studies that have assessed whether the prognostic influence of DM on SAB differs across gender, age categories, or comorbidity levels, and DM has been treated as one entity disregarding duration of disease, quality of glycaemic control, and complications. Moreover, only one of these studies [11] has differentiated SAB with recent preadmission healthcare exposure (healthcare-associated (HCA)-SAB) from patients without it, although the two patient groups have been suggested to differ considerably with regard to prognosis [15–17].

Detailed data including complete follow-up are needed to clarify whether DM is associated with increased mortality in patients with SAB. This knowledge may extend our understanding of the clinical course of patients with SAB, help define high-risk groups to assist in risk stratification and patient triage, and contribute to overall optimized care for patients with DM. Therefore, we conducted a large historical population-based cohort study to elucidate 30-day all-cause mortality in patients with community-acquired SAB (CA-SAB), comparing patients with and without DM. We ascertained the prognostic impact of DM on mortality among patients with and without recent preadmission healthcare contact, and stratified by age, sex, marital status, and comorbidity level. Finally, we explored 30-day mortality in SAB patients according to characteristics of patients with DM (e.g., duration of DM, quality of glycaemic control, renal function, and presence of DM complications).

Patients and Methods

Setting

This historical cohort study was conducted using routinely recorded data from population-based medical registries and databases in Northern Denmark between January 1, 2000, and December 31, 2011 (catchment population ~ 1.8 million). Tax-supported, unrestricted healthcare is provided for the entire Danish population through a national insurance program. All Danish citizens are assigned a unique identification number (the civil registration number) upon birth or immigration, which allows unambiguous cross-linkage of records between the data sources [18–19].

Patients with *S.aureus* bacteraemia

We identified all patients hospitalized with CA-SAB in the databases of the regions' four departments of clinical microbiology from 1995 onwards. Identification and susceptibility testing of *S. aureus* isolates are described in S1 Appendix. Eligible cases were defined by the presence of ≥1 monomicrobial positive blood culture with *S. aureus* in patients aged ≥15 years. Because recurrence of SAB may influence prognosis [20], we limited inclusion to patients with an incident episode of bacteraemia with *S. aureus*, defined as no prior SAB diagnosis within at least 5 years of the current hospitalization.

We defined CA-SAB as SAB in patients in whom one or more positive blood cultures was obtained ≤2 days of admission. Patients whose first blood culture was obtained >2 days after admission were excluded because we considered these infections to have been hospital-acquired. Patients with CA-SAB and healthcare contact within 30 days of the current admission were further sub-classified as HCA-SAB if one or more of the following criteria were fulfilled: one or more hospital admissions, one or more contacts with hospital outpatient surgical clinics, or one or more contacts with hospital outpatient clinics of oncology, haematology, or nephrology [21].

Data on recent healthcare contacts were obtained from the Danish National Patient Registry (DNPR) [22–23], which holds data on all citizens admitted to Danish hospitals since 1977 and on outpatient clinic visits since 1995. For each contact, data include dates of hospital admission and discharge, up to 20 discharge diagnoses, and information on surgical procedures.

Patients with diabetes

Patients with DM were diagnosed prior to admission and identified using a validated three-step algorithm [24]. First, patients with a discharge or outpatient diagnosis of DM registered at any time prior to admission were identified in the DNPR. Second, patients with a glycosylated haemoglobin A1c (HbA1c) level diagnostic of DM (≥48 mmol/mol or ≥6.5%) measured at any time predating the admission were identified via the clinical laboratory information system (LABKA) research database [25]. The LABKA database contains information on specimens submitted for analysis by hospitals and practitioners in Northern Denmark for the entire study period, including the exact time of blood sample collection. Third, the Aarhus University Prescription Database [26] (AUPD) contains data on all filled prescriptions in the study area according to the anatomical therapeutic chemical (ATC) classification system. Using this register, we identified patients with at least one recorded prescription for any glucose-lowering medication at any time prior to the current hospitalization (for diagnostic, laboratory, and ATC codes, see S2 Appendix). Patients with DM were classified as either type 1 diabetes (persons diagnosed before age 30 years, using insulin monotherapy, and with no history of oral glucose-lowering medications) or type 2 diabetes (the remaining patients with DM).

Characteristics of patients with diabetes

Duration of DM was computed as the time elapsed between the first record of diabetes in any of the three registers and the date that the first positive blood culture was sampled. Data on diabetes micro- and macrovascular complications were obtained from the DNPR [22–23] (for diagnostic codes, see S2 Appendix). The level of glycaemic control was ascertained using the most recent HbA1c measurement within one year of the current hospitalization (available for 70% of the patients), and we obtained data on blood glucose level on the date of admission (available for 55% of the patients). To assess baseline renal function prior to admission, we retrieved the most recent creatinine measurement requested by an outpatient hospital clinic or general practitioner in the period from one year to seven days before the current admission

(available for 78% of the patients). Estimated glomerular filtration rates (eGFR) were calculated using the four-variable version of the Modification of Diet in Renal Disease equation [27] (equation provided in S2 Appendix).

Demographics, comorbidity, and medication

We obtained data on age, sex, and marital status from the Danish Civil Registration System, which is electronically updated daily and holds records of demographic data and all changes in vital status and migration for the entire Danish population since 1968 [18–19].

We used all diagnoses recorded in the DNPR up to 10 years prior to the current admission date to identify previous comorbidity included in the Charlson Comorbidity Index (CCI). The CCI is a validated comorbidity scoring system [28–29] covering the number and severity of 19 major disease categories. Because DM constituted the exposure variable of interest, we removed this condition from the CCI and designated the index as a modified CCI (m-CCI). Three levels of comorbidity were defined: "low" (0), corresponding to patients with no pre-existing registered comorbidity; "intermediate" (1–2); and "high" (>2). Furthermore, we obtained data on several factors not registered in the m-CCI, including alcohol- and drug-related diagnoses, hypertension, and dialysis (within 30 days of the current admission) (for diagnostic codes, see S2 Appendix). Because certain medications might influence SAB prognosis via immunomodulatory effects [30], we also retrieved information on the following filled prescriptions via the AUPD[24]: any previous use of antihypertensive treatment, statins, anticoagulants, and use of immunosuppressant drugs and antibiotic treatment within 30 days of the admission (for ATC codes, see S2 Appendix). We assessed all-cause 30-day mortality for patients with and without DM using the Danish Civil Registration System [18–19].

Statistical analyses

Follow-up was initiated on the date the first positive blood culture was drawn, and vital status was followed until death, migration, or for 30 days, whichever came first. Patient characteristics were tabulated according to diabetes status. Using the Kaplan–Meier method, we computed mortality function curves (1 –survival function) and cumulative mortality at 30 days for patients with and without DM. We compared 30-day mortality rates for patients with and without DM using a Cox proportional hazards model to estimate hazard ratios as a measure of mortality rate ratios (MMRs) with corresponding 95% confidence intervals (CIs). Because the influence of DM on mortality may differ among patients with and without preadmission healthcare contacts [15–17], we repeated all analyses with restriction of the study cohort alternately to patients with CA-SAB and HCA-SAB, respectively. To ascertain the potential differential impact of DM in subgroups of patients, we stratified the analyses by gender, age category (15–39, 40–59, 60–79, 80+ years), marital status (married, divorced or widowed, never married), and m-CCI level ("low", "intermediate", and "high"). We adjusted for age, gender, m-CCI score, hypertension, alcohol-related conditions, marital status, and preadmission use of statins and antibiotics. In a subgroup analysis limited to patients with DM, we ascertained 30-day mortality according to duration of DM, level of glycaemic control, presence of DM complications, level of glucose on admission, and baseline preadmission renal function.

All Cox regression analyses were preceded by a graphical verification of the proportional hazards assumption. The statistical analyses were performed using Stata 11.2 for Windows (Stata Corp, College Station, TX). According to Danish law, individual informed consent is not required for observational registry-based studies. The project was approved by the Danish Data Protection Agency (ref. no. 2012-41-0942). Data were not anonymized prior to analysis.

Results

Descriptive data

From 2000 to 2011, we identified 2638 patients with incident CA-SAB (Table 1), of whom 713 (27.0%) had DM.

There were slightly more men among patients with DM compared to patients without DM (63.4% vs. 60.5%). Median age was 71 and 68 years for patients with and without DM, respectively. Of the 2638 patients with SAB, 69% had one or more conditions registered in the m-CCI and patients with DM were more likely than those without DM to have a high m-CCI score. The proportion of patients classified as HCA-SAB did not differ notably between patients with and without DM (44% and 42%, respectively). Compared to patients without healthcare association (CA-SAB), patients with HCA-SAB had considerably more comorbidity registered in the m-CCI whereas patients with CA-SAB were older (median age 66 years vs. 72 years) and more frequently male (60% versus 63%).

Thirty-day mortality

Thirty-day cumulative mortality was 25.8% in patients with DM and 24.3% in patients without DM (Table 2 and Fig 1).

Overall, patients with DM experienced no increased risk of dying within 30 days of blood culture compared to patients without DM (adjusted MRR (aMRR) = 1.01 (95% CI, 0.84–1.20). In corresponding analyses restricted to patients with CA-SAB and HCA-SAB, the aMRRs were 1.13 (95% CI, 0.91–1.41) and 0.84 (95% CI, 0.62–1.14), respectively. Table 3 displays the prognostic impact of DM across gender, age groups, marital status, and level of comorbidity.

Compared to patients without DM, the aMRRs were 0.94 (95% CI, 0.74–1.20) for male patients with DM and 1.13 (95% CI, 0.87–1.47) for female patients with DM. Age did not affect 30-day mortality; compared to patients without DM in the same age group, the aMRR values were as follows: 4.69 (95% CI, 0.47–46.41) for patients aged 15–39 years; 1.18 (95% CI, 0.66–2.10) for patients aged 40–59 years; 0.89 (95% CI, 0.68–1.16) for patients aged 60–79 years; and 1.12 (95% CI, 0.86–1.48) for patients $\geq$80 years. Analyses restricted to patients with CA-SAB (see S1 Table) and to patients with HCA-SAB (data not shown) revealed comparable results.

Thirty-day mortality according to characteristics of patients with diabetes

Table 4 shows cumulative and relative 30-day mortality for patients with DM (n = 713) according to characteristics of patients with diabetes.

Duration of DM did not seem to influence 30-day mortality. Compared with 0–3 years of DM duration, the aMRRs were 0.72 (0.47–1.12) for 3–5 years of DM duration, 0.77 (95% CI, 0.49–1.21) for 6–10 years, and 0.87 (95% CI, 0.59–1.27) for >10 years. The presence of micro- or macrovascular complications did not affect 30-day mortality: Compared with DM patients without complications, the aMRRs were 0.99 (95% CI, 0.56–1.72) for patients with microvascular complications and 1.04 (0.59–1.84) for those with macrovascular complications, respectively. Likewise, no consistent pattern or major differences in mortality were observed according to the level of glycaemic control, glucose level on admission, and renal function prior to admission. Restricting the analyses to CA-SAB or HCA-SAB did not substantially change these results (data not shown).

Discussion

In this cohort study of 2638 patients, we observed substantial mortality associated with incident CA-SAB, but patients with DM did not experience higher 30-day mortality than patients

Table 1. Characteristics of 2638 patients hospitalized with incident community-acquired *S. aureus* bacteraemia in Northern Denmark, 2000–2011.

	Patients with diabetes	Patients without diabetes
Numbers (%)	713 (27.0)	1925 (73.0)
Age (years), median (IQR)	71.1 (60.6–79.9)	68.1 (53.9–79.1)
15–39 years	27 (3.8)	206 (10.7)
40–59 years	143 (20.1)	462 (24.0)
60–79 years	367 (51.5)	815 (42.3)
≥80 years	176 (24.7)	442 (23.0)
Sex		
Men	452 (63.4)	1164 (60.5)
Women	261 (36.6)	761 (39.5)
S. aureus bacteraemia		
Community acquired	398 (55.8)	1125 (58.4)
Healthcare associated	315 (44.2)	800 (41.6)
MRSA	3 (0.4)	10 (0.5)
Marital status		
Married	343 (48.1)	927 (48.2)
Divorced or widowed	264 (37.0)	622 (32.3)
Never married	106 (14.9)	376 (19.5)
Selected comorbidities in the modified Charlson Comorbidity Index		
Former myocardial infarction	98 (13.7)	122 (6.3)
Congestive heart failure	164 (23.0)	184 (9.6)
Peripheral vascular disease	163 (22.9)	165 (8.6)
Cerebrovascular disease	116 (16.3)	199 (10.3)
Chronic pulmonary disease	118 (16.6)	245 (12.7)
Moderate to severe renal disease	184 (25.8)	252 (13.1)
Any solid cancer	101 (14.2)	414 (21.5)
Modified Charlson Comorbidity Index score		
Low (0)	156 (21.9)	654 (34.0)
Intermediate (1–2)	286 (40.1)	726 (37.7)
High (>2)	271 (38.0)	545 (28.3)
Comorbidities, other types		
Hypertension	296 (41.5)	355 (18.4)
Dialysis within 30 days of admission	111 (15.6)	153 (8.0)
Conditions related to alcohol abuse	67 (9.4)	168 (8.7)
Conditions related to drug abuse	10 (1.4)	63 (3.3)
Preadmission medication use		
Immunosuppressive therapy	6 (0.8)	22 (1.1)
Systemic antibiotic therapy	162 (22.7)	374 (19.4)
ACE inhibitors	493 (69.1)	593 (30.8)
Beta blockers	376 (52.7)	659 (34.2)
Acetylsalicylic acid	427 (60.0)	694 (36.1)
Statins	321 (45.0)	304 (15.8)
Renal function prior to admission		
eGFR >90 mL/min per 1.73 m^2	90 (12.6)	279 (14.5)
eGFR 60–90 mL/min per 1.73 m^2	155 (21.7)	450 (23.4)
eGFR <60 mL/min per 1.73 m^2	311 (43.6)	491 (25.5)
eGFR missing	157 (22.0)	705 (36.6)

(*Continued*)

Table 1. (*Continued*)

	Patients with diabetes	Patients without diabetes
CRP on day of blood culture (mg/L), median (IQR)	171 (76–274)	177 (76–287)
<10 mg/L	11 (1.5)	36 (1.9)
10–100 mg/L	177 (24.8)	452 (23.5)
>100 mg/L	406 (56.9)	1088 (56.5)
CRP missing	119 (16.7)	349 (18.1)

Patients with type 1 diabetes = 5.9%.

IQR: interquartile range. MRSA: methicillin resistant *S. aureus*. ACE inhibitor: angiotensin-converting enzyme inhibitor. eGFR: estimated glomerular filtration rate. CRP: C-reactive protein.

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without DM. Patients with and without recent healthcare exposure did not differ substantially in terms of prognosis, and we observed no considerable differences in 30-day mortality related to gender, age group, marital status, or comorbidity level in patients with and without DM. Other factors with no effect on mortality were duration of DM, presence of micro- and macrovascular complications, renal function, and other characteristics of patients with diabetes.

A few studies on SAB outcome have included DM among several covariates in the prognostic models [9–14]. Our study supports results from a large pooled analysis of five observational cohort studies including 3395 adult patients with SAB [14]. In that analysis, the investigators identified an adjusted 30-day hazard ratio of 1.12 (95% CI, 0.95–1.33) and a corresponding 90-day estimate of 1.03 (95% CI, 0.88–1.19) comparing patients with and without DM. Our findings are also in accordance with a Swiss cohort study [13] reporting no association between DM and in-hospital mortality in 308 SAB patients from a single tertiary-care centre.

In contrast to our findings, however, three studies [9–10,31] have reported that DM is associated with increased mortality in patients with SAB. A US cohort study [9] including 293 patients with SAB reported an adjusted odds ratio of 2.4 (95% CI, 1.2–4.7) for 30-day mortality among patients with DM compared to those without DM. A cohort study including 424

Table 2. Crude and adjusted 30-day mortality in patients with incident *S. aureus* bacteraemia (SAB).

	n	30-day mortality (95% CI)	MRR[1] (95% CI)	aMRR[2] (95% CI)
All SAB				
No diabetes	1925	24.3 (22.5–26.3)	1.00 (ref.)	1.00 (ref.)
Diabetes	713	25.8 (22.8–29.2)	1.07 (0.90–1.27)	1.01 (0.84–1.20)
Type 1 diabetes	40	5.0 (1.3–18.6)	0.19 (0.47–0.75)	0.59 (0.14–2.39)
Type 2 diabetes	673	27.0 (23.9–30.6)	1.13 (0.95–1.34)	1.01 (0.85–1.21)
CA-SAB				
No diabetes	1125	24.9 (22.5–27.5)	1.00 (ref.)	1.00 (ref.)
Diabetes	398	30.4 (26.1–35.2)	1.26 (1.02–1.56)	1.13 (0.91–1.41)
HCA-SAB				
No diabetes	800	23.5 (20.7–26.6)	1.00 (ref.)	1.00 (ref.)
Diabetes	315	20.0 (15.9–24.9)	0.84 (0.63–1.11)	0.84 (0.62–1.14)

CI: confidence interval. CA-SAB: community-acquired SAB. HCA-SAB: healthcare-associated SAB.

[1]MRR: unadjusted mortality rate ratio.

[2]aMRR: MRR adjusted for age, gender, marital status, conditions included in the modified Charlson Comorbidity Index, hypertension, alcohol-related conditions, any previous statin use prior to admission, and antibiotic therapy 30 days prior to admission.

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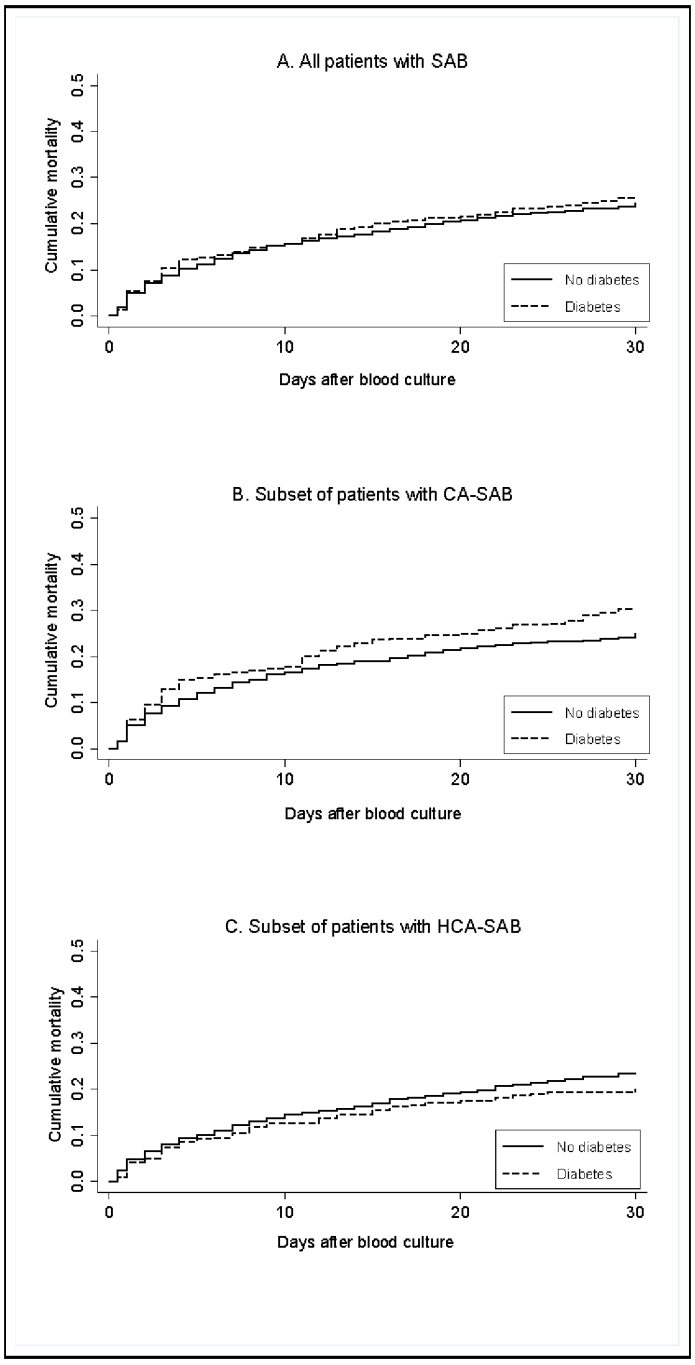

Fig 1. Cumulative 30-day mortality among incident *S. aureus* bacteraemia (SAB) patients with and without diabetes. (A) Cumulative 30-day mortality including the entire cohort of SAB patients (community-acquired SAB (CA-SAB) and healthcare-associated SAB (HCA-SAB)). (B) Cumulative 30-day mortality in the subset of patients with CA-SAB. (C) Cumulative mortality in the subset of patients with HCA-SAB.

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patients with SAB from New Zealand [10] reported an age- and sex-adjusted relative risk of 1.5 (95% CI, 1.0–2.4) for patients with DM compared to patients without. However, both studies were limited by relatively small patient numbers (n<500), selected study populations, and a lack of detailed data on DM. In a clinical trial designed to evaluate treatment of infective

Table 3. Adjusted mortality within 30 days comparing incident community-acquired *S. aureus* bacteraemia in patients with and without diabetes, stratified by sex, age, marital status, and modified Charlson Comorbidity Index score.

	Patients without diabetes	Patients with diabetes	
	30-day mortality (95% CI)	30-day mortality (95% CI)	aMRR[1] (95% CI)
Overall	24.3 (22.5–26.3)	25.8 (22.8–29.2)	1.00 (0.84–1.20)
Sex			
Male	22.0 (19.7–24.5)	21.9 (18.4–26.0)	0.94 (0.74–1.20)
Female	27.9 (24.8–31.2)	32.6 (27.3–38.6)	1.13 (0.87–1.47)
Age			
15–39	2.9 (1.3–6.4)	3.7 (0.5–23.5)	4.69 (0.47–46.41)
40–59	13.9 (11.0–17.4)	12.6 (8.1–19.2)	1.18 (0.66–2.10)
60–79	26.0 (23.1–29.2)	23.7 (19.7–28.4)	0.89 (0.68–1.16)
80+	42.1 (37.6–46.8)	44.3 (37.3–52.0)	1.12 (0.86–1.48)
Marital status			
Married	20.9 (18.5–23.7)	21.9 (17.9–26.6)	1.02 (0.77–1.35)
Divorced or widowed	34.7 (31.1–38.6)	31.8 (26.6–37.8)	0.93 (0.71–1.20)
Never married	15.4 (12.2–19.5)	23.6 (16.6–32.9)	1.42 (0.84–2.40)
Modified Charlson Comorbidity Index score			
Low (0)	19.3 (16.4–22.5)	19.2 (13.9–26.3)	0.93 (0.61–1.40)
Intermediate (1–2)	24.7 (21.7–28.0)	26.2 (21.5–31.7)	1.04 (0.79–1.38)
High (>2)	29.9 (26.3–33.9)	29.2 (24.1–35.0)	1.02 (0.76–1.36)

Reference group: patients without diabetes. CI: confidence interval.

[1]aMRR: Mortality rate ratio adjusted for age, gender, marital status, conditions included in the modified Charlson Comorbidity Index, hypertension, alcohol-related conditions, any previous statin use prior to admission, and antibiotic therapy 30 days prior to admission.

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endocarditis due to *S. aureus*, Kanafani et al. [31] observed an overall mortality at 6 weeks of 22.1% in patients with DM compared to 11.4% in patients without DM. These estimates, however, were based on a subgroup analysis including a limited number of DM patients with concurrent infective endocarditis (n = 86), which may in part explain the observed difference in outcome. In addition, Kanafani et al. did not distinguish between CA-SAB and hospital-acquired SAB; indeed, investigators did not discern between patients with CA-SAB and HCA-SAB in any of these three previous studies [9–10,31].

Several explanations are possible for the observed lack of increased mortality in patients with DM. In these patients, the inflammatory response to an acute infectious challenge is impeded [8,31], which might influence SAB prognosis in a positive direction. Nevertheless, in our study, we observed almost similar levels of C-reactive protein (CRP) on admission among patients with and without DM. Furthermore, persons with DM may interact with the health-care system more frequently than do those in the general population, and physicians may be more likely to admit a patient with DM on suspicion of infection compared to patients without DM. Consequently, time to blood culture sampling and initiation of antibiotic therapy could have been shorter in patients with DM. Such surveillance bias would lead to underestimation of DM-related mortality; however, the proportions of patients classified as HCA-SAB did not differ notably among the two groups, the CRP levels on admission were comparable, and patients with DM were not more likely to have received preadmission antibiotic treatment than patients without DM. These factors could counter but do not preclude bias associated with the clinical management of patients with DM in our setting. The majority of patients in our cohort were characterized by advanced age and several concurrent comorbid conditions.

Table 4. Thirty-day mortality in 713 patients with diabetes and incident community-acquired *S. aureus* bacteraemia according to characteristics of patients with diabetes.

	n	30-day mortality (95% CI)	MRR[1] (95% CI)	aMRR[2] (95% CI)
Duration of diabetes				
0–2 years	176	29.0 (22.9–36.3)	1.00 (ref.)	1.00 (ref.)
3–5 years	144	24.3 (18.1–32.2)	0.79 (0.51–1.20)	0.72 (0.47–1.12)
6–10 years	123	26.0 (19.2–34.7)	0.84 (0.54–1.31)	0.77 (0.49–1.21)
>10 years	270	24.4 (19.8–30.0)	0.81 (0.56–1.16)	0.87 (0.59–1.27)
Hba1c				
<7%	243	26.3 (21.2–32.3)	1.00 (ref.)	1.00 (ref.)
≥7–<8%	94	34.0 (25.4–44.6)	1.35 (0.88–2.06)	1.71 (1.10–2.65)
≥8–<9%	72	18.1 (10.9–29.1)	0.66 (0.37–1.20)	0.93 (0.51–1.69)
≥9%	93	20.4 (13.6–30.1)	0.74 (0.44–1.23)	1.01 (0.60–1.71)
Unknown	211	26.5 (21.1–33.1)	1.01 (0.70–1.44)	1.14 (0.78–1.65)
Diabetes complications				
Absent	257	27.6 (22.6–33.5)	1.00 (ref.)	1.00 (ref.)
Microvascular	96	17.7 (11.4–26.9)	0.62 (0.36–1.05)	0.99 (0.56–1.72)
Macrovascular	215	30.2 (24.6–36.9)	1.11 (0.80–1.57)	1.04 (0.59–1.84)
Micro/macrovascular	145	21.4 (15.6–29.0)	0.74 (0.48–1.12)	0.98 (0.56–1.71)
Glucose on admission				
5–10 mmol/L	133	28.6 (21.7–37.1)	1.00 (ref.)	1.00 (ref.)
10–15 mmol/L	122	31.1 (23.7–40.2)	1.16 (0.74–1.81)	1.39 (0.88–2.19)
15–20 mmol/L	67	20.9 (13.0–32.7)	0.70 (0.38–1.29)	0.89 (0.48–1.66)
>20 mmol/L	58	29.3 (19.4–42.8)	1.08 (0.61–1.92)	1.37 (0.77–2.43)
Unknown	321	22.4 (18.3–27.4)	0.77 (0.52–1.14)	0.86 (0.56–1.27)
Renal function prior to admission (eGFR)				
>90 mL/min per 1.73 m^2	90	22.2 (15.0–32.3)	1.00 (ref.)	1.00 (ref.)
60–90 mL/min per 1.73 m^2	155	27.1 (20.8–34.8)	1.24 (0.73–2.11)	1.03 (0.58–1.81)
<60 mL/min per 1.73 m^2	311	25.1 (20.6–30.3)	1.11 (0.68–1.82)	0.95 (0.56–1.61)
eGFR missing	157	28.0 (21.7–35.8)	1.28 (0.76–2.17)	1.13 (0.64–1.98)

CI: confidence interval. HbA1c: Haemoglobin A1c, using the most recent measurement within one year of the current hospitalization. eGFR: estimated glomerular filtration rate (mL/min per 1.73m^2).

[1]MRR: unadjusted mortality rate ratio.

[2]aMRR: MRR adjusted for age, gender, marital status, conditions included in the modified Charlson Comorbidity Index (excluding the morbidity in question), hypertension, any previous statin use prior to admission, and antibiotic therapy 30 days prior to admission.

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These characteristics may reflect that the high mortality associated with SAB is more dependent on the combined burden of age and comorbidities and less so on individual comorbid conditions such as DM and characteristics (e.g., glycaemic control) and complications associated with DM.

Our study's strengths include its considerable size, the use of routinely recorded clinical data, and the population-based design with information at the individual level and virtually complete follow-up for death. In contrast to previous studies, in the current work, patients with DM were identified via a previously validated algorithm [24], and detailed data on characteristics of DM patients were available. Our study also has a number of limitations. Misclassification of patients with DM would bias our results towards the null, and although our ascertainment of DM was based on three separate comprehensive registries, we cannot entirely preclude that some patients with DM may have been missed (e.g., patients treated with diet

and lifestyle changes alone). Furthermore, we cannot rule out that some cases of SAB were missed if the patient had received preadmission antibiotic treatment, if the patient had been hospitalized outside of the catchment area, or had died before blood culture sampling [32]. If either of these outcomes pertained to patients with DM in particular, mortality in this group might have been underestimated. Moreover, the DNPR does not include information on comorbidity (including diabetes and diabetes complications) diagnosed in the primary care sector. Due to the historical design or our study, we lacked data on infective foci, including central venous catheters and other vascular access devices, which have been associated with SAB outcome in previous studies [3]. A difference in distribution of foci among patients with and without DM could have biased our estimates. Socioeconomic factors influence prognosis in patients with SAB [3,33], but we did not have access to data on educational level and personal income. Nevertheless, based on the equal and cost-free access to healthcare in Denmark, we do not expect these potential confounders to be unevenly distributed among patients with and without DM.

In conclusion, CA-SAB patients with DM did not experience higher 30-day all-cause mortality compared to patients without DM, and we observed no substantial differences in mortality across subsets of patients. However, the considerable 30-day mortality identified in our study emphasizes the need for continued research on prognostic factors of SAB to facilitate improved management and patient outcomes.

Supporting Information

S1 Appendix. Identification and susceptibility testing of *S.aureus* isolates.
(PDF)

S2 Appendix. Codes for diagnoses, procedures, medication and blood tests.
(PDF)

S1 Table. Crude and adjusted mortality within 30 days comparing incident *S.aureus* bacteraemia patients with and without diabetes, stratified by sex, age, marital status and modified Charlson Comorbidity Index score. Analyses restricted to patients with community-acquired *S. aureus* bacteraemia (n = 1523).
(PDF)

Author Contributions

Conceived and designed the experiments: JS RWT HCS HN MS. Performed the experiments: JS TF. Analyzed the data: JS. Contributed reagents/materials/analysis tools: TF. Wrote the paper: JS RWT HCS HN MS.

References

1. Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, Kirby A, Tilley R, Estée Török M, et al. Clinical management of Staphylococcus aureus bacteraemia. Lancet Infect Dis 2011; 11:208–22. doi: 10.1016/S1473-3099(10)70285-1 PMID: 21371655
2. Kern WV. Management of *Staphylococcus aureus* bacteremia and endocarditis: progress and challenges. Curr Opin Infect Dis 2010; 23:346–358. doi: 10.1097/QCO.0b013e32833bcc8a PMID: 20592532
3. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors or mortality in Staphylococcus aureus bacteremia. Clin Microbiol Rev 2012; 25:362–86. doi: 10.1128/CMR.05022-11 PMID: 22491776
4. Lesens O, Methlin C, Hansmann Y, Remy V, Martinot M, Bergin C et al. Role of comorbidity in mortality related to Staphylococcus aureus bacteremia: A prospective study using the Charlson Weighted Index of comorbidity. Infect Control Hosp Epidemiol 2003; 24:890–6. PMID: 14700403

5. Mejer N, Westh H, Schønheyder HC, Jensen AG, Larsen AR, Skov R, et al. Stable incidence and continued improvement in short term mortality of Staphylococcus aureus bacteraemia between 1995 and 2008. BMC Infect Dis 2012; 12:260. doi: 10.1186/1471-2334-12-260 PMID: 23075215
6. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 2014; 103:161–75
7. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011; 94:311–21. doi: 10.1016/j.diabres.2011.10.029 PMID: 22079683
8. Thomsen RW, Mor A. Diabetes and risk of community-acquired respiratory tract infections, urinary tract infections, and bacteremia. The Open Infectious Diseases Journal 2012; 6:27–39.
9. Mylotte JM, Tayara A. *Staphylococcus aureus* bacteremia: predictors of 30-day mortality in a large cohort. Clin Infect Dis 2000; 31:1170–4. PMID: 11073748
10. Hill PC, Birch M, Chambers S, Drinkovic D, Ellis-Pegler RB, Everts R, et al. Prospective study of 424 cases of *Staphylococcus aureus* bacteraemia: determination of factors affecting incidence and mortality. Intern Med J 2001; 31:97–103. PMID: 11480485
11. Leibovici L, Samra Z, Konisberger H, Kalter-Leibovici, Pitlik SD, Drucker M. Bacteremia in adult diabetic patients. Diabetes Care 1991; 14:89–94. PMID: 2060428
12. Laupland KB, Church DL, Mucenski M, Sutherland LR, Davies HD. Population-based study of the epidemiology of and the risk factors for invasive Staphylococcus aureus infections. J Infect Dis 2003; 187:1452–9. PMID: 12717627
13. Kaech C, Elzi L, Sendi P, Frei R, Laifer G, Bassetti S, et al. Course and outcome of Staphylococcus aureus bacteremia: a retrospective analysis of 308 episodes in a Swiss tertiary-care centre. Clin Microbiol Infect 2006; 12:345–352. PMID: 16524411
14. Kaasch AJ, Barlow G, Edgeworth JD, Fowler VG, Hellmich M, Hopkins S, et al. Staphylococcus aureus bloodstream infection: A pooled analysis of five prospective, observational studies. J infect 2014; 68:242–251. doi: 10.1016/j.jinf.2013.10.015 PMID: 24247070
15. Vallés J, Calbo E, Anoro E, Fontanals D, Xercavins M, Espejo E, et al. Bloodstream infections in adults: Importance of healthcare-associated infections. J Infect 2008; 56:27–34. PMID: 18022242
16. Lenz R, Leal JR, Church DL, Gregson DB, Ross T, Laupland KB. The distinct category of healthcare associated bloodstream infections. BMC Infect Dis 2012; 12:85. doi: 10.1186/1471-2334-12-85 PMID: 22487002
17. Shorr A, Tabak YP, Killian AD, Gupta V, Liu LZ, Kollef MH. Healthcare-associated bloodstream infections: A distinct entity? Insights from a large U.S. database. Crit Care Med 2006; 10:2588–95.
18. Pedersen CB. The Danish Civil Registration System. Scan J Public Health 2011; 39:22–25.
19. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014; 29:541–549. doi: 10.1007/s10654-014-9930-3 PMID: 24965263
20. Wiese L, Mejer N, Schønheyder HC, Westh H, Jensen AG, Larsen AG, et al. A nationwide study of comorbidity and risk of reinfection after Staphylococcus aureus bacteraemia. J Infect 2013; 67:199–205. doi: 10.1016/j.jinf.2013.04.018 PMID: 23664855
21. Smit J, Søgaard M, Schønheyder H, Nielsen H, Frøslev T, Thomsen RW. Classification of healthcare-associated Staphylococcus aureus bacteremia: Influence of different definitions on prevalence, patient characteristics, and outcome. Infect Control Hosp Epidemiol 2016; 37(2):208–211 doi: 10.1017/ice.2015.259 PMID: 26503397
22. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011; 39:30–33. doi: 10.1177/1403494811401482 PMID: 21775347
23. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015; 7:449–490. doi: 10.2147/CLEP.S91125 PMID: 26604824
24. Thomsen RW, Hundborg HH, Lervang HH, Johnsen SP, Sørensen HT, Schønheyder HC. Diabetes and outcome of community- acquired pneumococcal bacteremia. Diabetes Care 2004; 27:70–6. PMID: 14693969
25. Grann AF, Erichsen R, Nielsen AG, Frøslev T, Thomsen RW. Existing data sources for clinical epidemiology: The clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. Clin Epidemiol 2011; 1:133
26. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol 2010; 2:273–279. doi: 10.2147/CLEP.S13458 PMID: 21152254

27. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145:247–254. PMID: 16908915

28. Charlson M, Pompei P, Ales KL. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chron Dis 1987; 40:373–83. PMID: 3558716

29. Thygesen SK, Christiansen CF, Christensen S, Lash T, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 2011; 11:83. doi: 10.1186/1471-2288-11-83 PMID: 21619668

30. López-Cortes LE, Gálvez-Acebal J, del Toro MD, Velasco C, de Cueto M, Caballero FJ, et al. Effect of statin therapy in the outcome of blood stream infections due to Staphylococcus aureus. A prospective cohort study. PLoS One 2013; 8:e82958. doi: 10.1371/journal.pone.0082958 PMID: 24376617

31. Kanafani Z a, Kourany WM, Fowler VG, Levine DP, Vigliani GA, Campion M, et al. Clinical characteristics and outcomes of diabetic patients with Staphylococcus aureus bacteremia and endocarditis. Eur J Clin Microbiol Infect Dis 2009; 28:1477–82. doi: 10.1007/s10096-009-0808-3 PMID: 19730900

32. Søgaard M, Engebjerg MC, Lundbye-Christensen S, Schønheyder HC. Changes in blood culture methodology have an impact on time trends of bacteraemia: a 26-year regional study. Epidemiol Infect 2011; 139:772–776. doi: 10.1017/S095026881000169X PMID: 20619078

33. Koch K, Nørgaard M, Schønheyder HC, Thomsen RW, Søgaard M, for the Danish Collaborative Bacteremia Network (DACOBAN). Effect of socioeconomic status in mortality after bacteremia in working-age patients. A Danish population-based cohort study. PLoS One 2013; 8:e70082. doi: 10.1371/journal.pone.0070082 PMID: 23936145

S1 Appendix 1

Identification and susceptibility testing of *S.aureus* isolates

Setting

During the study period a reform of local government merged four counties into two heath regions: Central Denmark Region and North Denmark Region, collectively referred to as Northern Denmark. Three departments of clinical microbiology served Central Denmark Region and were situated in Aarhus (Aarhus University Hospital), Viborg (Regional Hospital of Viborg) and Herning (Regional Hospital West Jutland). North Denmark Region was served by one department of clinical microbiology at Aalborg University Hospital, Aalborg.

The total number of beds in non-psychiatric wards was 5.528 in 2000 and 4.058 in 2011.

Number of hospitals in the two health regions and their predecessors

	2000	2011
Central Denmark Region	17	5
North Denmark Region	7	4

Blood cultures

Blood cultures were ordered by the attending physician and blood samples were drawn by trained biotechnicians. The BacT/Alert system (bioMérieux, Marcy l'Etoil, France) was used throughout the study period at all hospital sites. Recommendations differed between the two health regions: In Central Denmark Region a standard blood culture for adults comprised two sets with two bottles each (one aerobic and one anaerobic bottle), whereas the standard in North Denmark Region was one set with three bottles (two aerobic and one anaerobic bottle).

Identification and susceptibility testing of *Staphylococcus aureus*

S. aureus was identified by horse plasma tube coagulase test or an equivalent commercial latex agglutination test. All blood culture isolates were referred to the Staphylococcal Reference Laboratory at Statens Serum Institut (Copenhagen) for national surveillance which included phage typing up to 2006 and *spa*-typing thereafter.[1-2]

Susceptibility testing was undertaken locally by disk diffusion and confirmatory testing was performed at Statens Serum Institut.[3-5] Screening for methicillin resistance varied between departments 2000-2002, but in 2003 the cefoxitin disk diffusion test was implemented both locally and at Statens Serum Institut.[4-5] Detection of the *mecA* gene cassette was done by either in-house polymerase chain reaction (PCR) or the EVIGENE™ hybridization test.[2,7]

Methicillin-resistant *S. aureus* (MRSA) became notifiable in Denmark in 2006. Due to the low prevalence of methicillin-resistance extra precautions were taken in this study by cross-referencing local data with the Danish national *S. aureus* bacteremia database at Statens Serum Institut.

References

1. DANMAP 2006 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. ISSN 1600-2032. http://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/Danmap_2003.ashx (Accessed June 1 2015).
2. Larsen AR, Stegger M, Sørum M. spa typing directly from a mecA, spa and pvl multiplex PCR assay-a cost-effective improvement for methicillin-resistant Staphylococcus aureus surveillance. Clin Microbiol Infect. 2008 Jun;14(6):611-4.
3. DANMAP 2000 – Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. ISSN 1600-2032. http://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/Danmap_2000.ashx (Accessed June 1 2015).
4. DANMAP 2003 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. ISSN 1600-2032. http://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/Danmap_2003.ashx (accessed June 1 2015)
5. Skov R, Smyth R, Clausen M, Larsen AR, Frimodt-Møller N, Olsson-Liljequist B, Kahlmeter G. Evaluation of a cefoxitin 30 microg disc on Iso-Sensitest agar for detection of methicillin-resistant Staphylococcus aureus. J Antimicrob Chemother. 2003 Aug;52(2):204-7. Epub 2003 Jul 1. PubMed PMID: 12837728.

6. Skov RL, Pallesen LV, Poulsen RL, Espersen F. Evaluation of a new 3-h hybridization method for detecting the mecA gene in Staphylococcus aureus and comparison with existing genotypic and phenotypic susceptibility testing methods. J Antimicrob Chemother. 1999 Apr;43(4):467-75.

S2 Appendix 2

Codes for diagnoses, procedures, medication and blood tests

Formula for estimation of glomerular filtration rates (eGFR)

Preadmission comorbid conditions. Diagnoses codes are according to the 8th and 10th revision of the International Classification of Diseases, ICD-8 and ICD-10

Condition	ICD-8	ICD-10
Diabetes	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10-E14. O24 (except O24.4), G63.2, H36.0, N08.3
Myocardial infarction	410	I21-I23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50, I11.0, I13.0, I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445	I70, I71, I72, I73, I74, I77
Cerebrovascular disease	430-438	I60-I69, G45, G46
Dementia	290.09-290.19, 293.09	F00-F03, F05.1, G30
Chronic pulmonary disease	490-493, 515-518	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease	530.91, 530.98, 531-534	K22.1, K25-K28

Mild liver disease	571, 573.01, 573.04	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0
Hemiplegia	344	G81, G82
Moderate to severe renal disease	403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Any tumor	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203, 275.59	C81-C85, C88, C90, C96
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Metastatic solid tumor	195-198, 199	C76-C80
AIDS	079.83	B21-B24
Hypertension	400-404	I10-I13
Osteoporosis	723.09	M80-M82
Conditions related to alcohol abuse	291.09-291.99, 303.09-303.29, 303.91-303.99	F10, K86.0, Z72.1. T51, K29.2, G62.1, G31.2, I42.6, K70
Conditions related to drug abuse	304.09-304.99	F11-F16, F18-F19, T40
Microvacular complications:		
• Diabetic retinopathy	250.01, 249.01	H36.0, E10.3, E11.3, E12.3, E13.3, E14.3, H28.0, H33.4, H45.0

• Diabetic nephropathy	250.02, 249.02	N08.3, E10.2, E11.2, E12.2, E13.2, E14.2
• Diabetic neuropathy	250.03, 249.03	E10.4, E11.4, E14.4, G59.0, G63.2
Macrovascular complications:		
• Ischemic heart disease including atherosclerosis	410.09-414.99	I20-I25
• Stroke, transient cerebral ischemia and cerebrovascular disease	432.00-437.99	G45, I61, I63-I66, I67.2, I67.8-I67.9, I69.1, I69.3-I69.8
• Peripheral arterial disease	440.09-440.29	I70.2, I74.2-I74.5 I73.9A, I73.9B, I73.9C E10.5, E11.5

Procedures. Codes regarding dialysis are according to Danish Treatment codes and according to the 10th revision of the International Classification of Diseases, ICD-10.

	Danish treatment codes	**ICD-10**
Dialysis	98300, 94340, 94350 BJFD0, BJFD2	Z99.2, Z49, Z49.2, BJFD
Surgery	All surgical codes (K-codes) in the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures.	

Medication codes are according to the Anatomical Therapeutic Classification (ATC)

Type of medication	ATC codes
Antidiabetic medication:	
All antidiabetic medication	A10A, A10B
• Insulin	A10A
• Metformin	A10BA02
• Sulfonylureas	A10BB, A10BC
• Any other antidiabetic drugs	A10 without A10A, A10BA02, A10BB, A10BC
Immunosuppressive therapy	L01, L04
Systemic antibiotic therapy	J01
ACE inhibitors	C09
Beta-blockers	C07
Acetylsalicylic acid	B01AC06
Other thrombocyte function inhibitors	B01AC04, B01AC07, B01AC30
Statins or lipid lowering agents	C10AA, C10B, B04AB, C10AB, C10AC, C10AD, C10AX

Blood tests according to local analysis codes and Nomenclature for Properties and Units (NPU)-codes

Blood test	Local analysis and NPU-codes
C-reactive protein	DNK05027, ASS00653, ASS00010, AAA94016, ASS00080, 1314609, ASS00080, 5027, 1314610, 1414610, 16, 113039, 1810752, 1311097, 1314610, 1314612, 1314611, 1414609, 1314614,1414614, 19748, 1423, 1314612 NPU19748, NPU01423
Creatinine	ASS00356, ASS00354, ASS00355, 11026, 1511235,1511236, 1610154, 1710301,1711807, 1811807, 1817156, 18016,1155,1311235, 1411235, 38927, 4998, 1611807 NPU18016, NPU01807, NPU18105, NPU04998

HbA1c	AAB00091, AAA00740, AAB00061, AAB00092, 12155 NPU03835, NPU02307, NPU27300
Glucose	ASS00203, ASS00204, DNK35842, 352, 1460, 161, 1462, 1311500, 1311551, 1311597, 132600, 1321000, 1411500, 1411551, 1411597, 8792, 2195, 35842, 112069, 112195, 113016, 114325, 1511500, 1511631, 1511700, 161034, 1610823, 1616560, 161635, 1710343, 1712188, 1812188, 1812195, 1817225, 1817426,140600, AAA00317, AAA00320, AAA00321, AAA00230, AAA00308, AAA00311, AAA00314 NPU02193, NPU02195, NPU08509, NPU08972, NPU22068, NPU22069, NPU02187, NPU02192, NPU04093, NPU22095, NPU08869-NPU08916, NPU22069-NPU22089, NPU22099-NPU22126, NPU08519-NPU08567, NPU21531, NPU21533

Formula for estimation of glomerular filtration rates (eGFR)

GFR (mL/min/1.73 m2) = 175 x (Scr/88.4)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if African American) (SI units).

Scr = serum creatinine.

S1 Table. Crude and adjusted mortality within 30 days comparing incident *S.aureus* bacteremia patients with and without diabetes, stratified by sex, age, marital status and modified Charlson Comorbidity Index score. Analyses restricted to patients with community-acquired *S. aureus* bacteremia (n=1523).

	Patients without diabetes	**Patients with diabetes**	
	30-day mortality (95% CI)	**30-day mortality (95% CI)**	**Adj. MRR[1] (95% CI)**
Overall	24.8 (22.4-27.5)	30.6 (26.3-35.4)	1.13 (0.90-1.41)
Sex			
Male	22.2 (19.3-25.5)	24.9 (20.1-30.6)	0.98 (0.72-1.32)
Female	29.0 (25.0-33.5)	41.5 (33.7-50.3)	1.40 (1.00-1.96)
Age			
15-39	3.3 (1.3-8.6)	10.0 (14.7-52.7)	35.07 (1.06-1156.99)
40-59	12.9 (9.3-17.8)	21.0 (12.8-33.4)	2.03 (1.01-4.06)
60-79	25.3 (21.5-29.6)	24.0 (18.7-30.5)	0.83 (0.57-1.19)
80+	41.8 (35.6-47.4)	48.3 (39.8-57.6)	1.31 (0.95-1.81)
Marital status			
Married	19.4 (16.1-23.3)	22.9 (17.2-30.1)	1.04 (0.70-1.56)
Divorced or widowed	35.8 (31.4-40.6)	36.7 (30.1-44.3)	1.08 (0.80-1.46)
Never married	16.3 (12.2-21.7)	34.0 (22.9-48.4)	2.13 (1.16-3.92)

Modified Charlson Comorbidity Index			
Low (0)	19.4 (16.3-23.1)	21.2 (14.9-29.7)	1.05 (0.67-1.66)
Intermediate (1-2)	29.0 (24.9-33.6)	29.7 (23.5-37.1)	1.02 (0.73-1.42)
High (3+)	31.4 (25.0-38.9)	42.7 (33.8-52.8)	1.39 (0.90-2.13)

Reference group: patients without diabetes. CI, confidence interval.

[1]Adj. MRR: Mortality rate ratio adjusted for age, gender, marital status, conditions included in the modified Charlson Comorbidity Index, hypertension, alcohol related conditions, any previous statin use prior to admission, and antibiotic therapy 30 days prior to admission.

Study 4

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Chronic heart failure and mortality in patients with community-acquired *Staphylococcus aureus* bacteremia: a population-based cohort study

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Abstract

Background: Patients with chronic heart failure (CHF) may experience higher mortality of *Staphylococcus aureus* bacteremia (SAB) than patients without CHF due to insufficient cardiovascular responses during systemic infection. We investigated 90-day mortality in SAB patients with and without CHF.

Methods: Using population-based medical databases, we conducted a cohort study of all adult patients with community-acquired SAB (CA-SAB) in Northern Denmark, 2000-2011. Ninety-day mortality after SAB for patients with and without CHF was estimated by the Kaplan-Meier method. Based on Cox regression analysis, we computed hazard ratios as estimates of mortality rate ratios (MRRs) overall and stratified by CHF-related conditions (e.g., cardiomyopathy and valvular heart disease), CHF severity (defined by daily dosage of loop-diuretics), and CHF duration while adjusting for potential confounders.

Results: Among 2638 SAB patients, 390 (14.8 %) had a history of CHF. Ninety-day mortality was 45 % in patients with CHF and 30 % in patients without CHF, which yielded an adjusted MRR (aMRR) of 1.24 (95 % CI, 1.04-1.48). Compared to patients without CHF, the excess risk of death was most pronounced among patients with valvular heart disease (aMRR = 1.73 (95 % CI, 1.26–2.38)), patients with daily loop-diuretic dosages of 81–159 mg/day (aMRR = 1.55 (95 % CI, 1.11–2.14)) and ≥160 mg/day (aMRR = 1.62 (95 % CI, 1.21–2.18)), and among patients with <3 years of CHF duration (aMRR = 1.43 (95 % CI, 1.14–1.78)).

Conclusion: CA-SAB patients with CHF experienced increased 90-day mortality compared to patients without CHF.

Keywords: Congestive heart failure, *Staphylococcus aureus*, Bacteremia, Mortality, Prognosis

Background

Staphylococcus aureus bacteremia (SAB) continues to be associated with considerable morbidity and a 30-day mortality of 20–40 % in developed countries [1, 2]. Chronic heart failure (CHF) currently affects more than 23 million persons worldwide, and hospitalizations and readmissions for CHF remain a major public health problem [3, 4]. Patients with CHF may experience higher mortality from SAB than patients without CHF due to insufficient cardiovascular responses to severe systemic infection [5]. Further, CHF and SAB share several negative prognostic factors including male sex, high age, and comorbidity [2].

Still, data on the prognostic impact of CHF in patients with SAB are limited and inconsistent, and to our knowledge no prior prognostic study has addressed CHF as the main exposure in this clinical setting. Previous studies have been restricted by a limited number of SAB patients (N < 400) [6–9], often from referral centers [9], and CHF has not been defined according to strictly specified criteria [6–9]. Other limitations include incomplete information on comorbid conditions [8, 9], and lack of follow-up after discharge [8, 9]. Detailed information on the prognostic influence of CHF in patients with

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SAB may extend our understanding of the clinical course of SAB patients and contribute to improved treatment for patients with CHF. Therefore, we conducted a population-based cohort study to examine the prognostic impact of CHF in patients with community-acquired SAB (CA-SAB).

Methods

Setting

This cohort study was conducted using routinely recorded data from population-based medical registries in Northern Denmark between 1 January 2000 and 31 December 2011 (catchment population ~ 1.8 million inhabitants). Tax-supported, unfettered healthcare is provided for the entire Danish population through a national health insurance program [10, 11]. Northern Denmark is served by two University hospitals and a dwindling number of regional hospitals (22 regional hospitals in 2000 and 7 regional hospitals in 2011). All Danish residents are assigned a unique identification number which allows unambiguous linkage of registry data at the individual level [10, 11].

Patients with *S.aureus* bacteremia

Using the databases of the departments of clinical microbiology within the area, we identified all patients hospitalized with CA-SAB from 1995 onwards. We included patients ≥15 years with ≥1 positive blood cultures with *S.aureus* as the sole isolate (information on blood culture practice and susceptibility testing is provided in Additional file 1: Identification and susceptibility testing of *S. aureus* isolates). Because recurrence of SAB may affect prognosis [12], we limited the study to patients with incident SAB, defined as no prior SAB diagnosis within at least 5 years of the current hospitalization.

CA-SAB was defined as SAB in patients, in whom one or more positive blood cultures had been obtained within the first two days of admission. Patients with a first blood cultured obtained >2 days after admission were excluded, because we consider these infections to be hospital-acquired. Patients with CA-SAB and healthcare contacts recently preceding the current admission were sub-classified as healthcare-associated SAB (HCA-SAB) if one or more of the following criteria were met: ≥1 hospital admission, ≥1 contacts to hospital outpatient surgical clinics (including minor surgery), or ≥1 contacts to clinics of hematology, oncology or nephrology, all within a 30-day window of the current admission.

Data on recent health care contacts were retrieved using the Danish National Patient Registry (DNPR) [13]. This register holds data on all citizens and permanent residents admitted 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.

Patients with chronic heart failure

Patients diagnosed with CHF at any time before the current admission were identified from the DNPR [13]. We defined CHF as a previous hospital discharge diagnosis or outpatient diagnosis of congestive heart failure, pulmonary edema with mention of heart failure, left ventricular failure, unspecified heart failure, cardiomyopathy, or hypertensive heart disease with congestive heart failure (with or without hypertensive renal disease or renal failure). CHF patients were further classified according to presence of CHF-related conditions: 1) cardiomyopathy (with or without any of the following diagnoses), 2) valvular heart disease (with or without any of the other diagnoses except cardiomyopathy), 3) previous myocardial infarction (with or without atrial fibrillation), 4) atrial fibrillation only, and 5) none of the above concomitant conditions. All diagnostic codes are provided in Additional file 2: Codes for diagnoses, procedures, medication, and blood tests.

Severity of CHF is not included in the diagnostic codes in the DNPR. Thus, as a proxy for CHF severity, patients were categorized according to daily dosage of redeemed prescriptions of loop-diuretics: non-users (no loop-diuretics), low dose (≤40 mg/day), medium dose (41–80 mg/day), high dose (81–159 mg/day), and very high dose (≥160 mg/day). We computed mean loop-diuretic dosages by dividing the number of dispensed tablets by a dispensing time interval of 180 days, as described previously [14, 15]. Loop-diuretic dosages have been shown to correlate positively with worsened New York Heart Association functional class and mortality risk, but not with glomerular filtration rate in CHF patients [15]. Data on filled prescriptions were retrieved from the Aarhus University Prescription Database (AUPD) [16], which holds data on redeemed prescriptions in the study area according to the Anatomical Therapeutic Chemical (ATC) classification system (ATC codes are provided in Additional file 2: Codes for diagnoses, procedures, medication, and blood tests). We calculated duration of CHF as the time elapsed between the first diagnosis of CHF and the sampling date of the first positive blood culture.

Comorbidity, laboratory test results, and mortality

Data on sex, age, and marital status was retrieved from the Danish Civil Registration System, which is updated electronically on a daily basis and keeps track of demographic data and changes in vital status and migration for all Danish residents since 1968 [10, 11]. We computed a modified Charlson Comorbidity Index (m-CCI) using all available diagnoses registered in the DNPR up to 10 years before the current hospitalization excluding CHF from the index (the exposure variable of interest).

The CCI is a validated comorbidity scoring system covering both the number and severity of 19 major disease categories [17, 18]. Patients were classified as having a low (score = 0), intermediate (score = 1–2), or a high comorbidity level (score >2). We further collated data on a number of conditions not included in the m-CCI, counting hypertension, drug- and alcohol-related conditions and dialysis (within 30 days of the current admission). Using the AUPD [16], we obtained data on the following filled prescriptions: Any previous use of antihypertensive treatment, statins (and other lipid lowering agents), anticoagulants, and use of immunosuppressant drugs, and antibiotics within 30 days of the SAB-related hospitalization (ATC codes are provided in Additional file 2: Codes for diagnoses, procedures, medication, and blood tests). The LABKA Database (CSC Scandihealth, Denmark) keeps laboratory test results from patients in Northern Denmark for the entire study period including the exact time of blood sample collection [19]. Using this database, we obtained information on white blood count levels on the date the first positive blood culture was drawn (laboratory codes are available in Additional file 2: Codes for diagnoses, procedures, medication, and blood tests). Data on all-cause mortality was retrieved from the Danish Civil Registration System [10, 11].

Statistical analyses

All patients were followed from the date the first positive blood culture was drawn until death, emigration or 90 days, whichever came first. Patient characteristics (including demographics, comorbidity, and preadmission medication use) were tabulated according to CHF status. We computed the 90-day mortality risk using the Kaplan-Meier method (1 – survival function) and graphically displayed 90-day mortality for patients with and without CHF. Ninety-day mortality rates for patients with vs. without CHF were compared using a Cox proportional hazards model estimating hazard ratios as a measure of mortality rate ratios (MMRs) with corresponding 95 % confidence intervals (CIs). CHF exposure was further subcategorized according to CHF-related conditions, CHF severity and CHF duration. To examine whether mortality differed among subsets of CHF patients, we stratified the analyses by sex, age category (15–39, 40–59, 60–79, 80+ years), and m-CCI level ("low", "intermediate", and "high"). All MRRs were adjusted for age, sex, conditions included in the m-CCI, hypertension, alcohol related conditions, marital status (as a marker of socioeconomic status) and preadmission use of antibiotic therapy (within 30 days). The assumption of proportional hazards in the Cox models was assessed graphically and found appropriate. We conducted all statistical analyses using Stata 11.2 for Windows (Stata Corp, College Station, TX).

Results

Descriptive data

During the study period 2638 patients aged ≥15 years were hospitalized with incident CA-SAB, of which 390 (14.8 %) had CHF (Table 1). Median age was 77 (interquartile range (IQR), 70–82) and 67 (IQR, 54–78) years for patients with and without CHF, respectively. There were slightly more men among patients with CHF compared to patients without CHF (64.9 % vs. 60.6 %). Forty-eight percent of patients with CHF were classified as HCA vs. 41.4 % among patients without CHF. Methicillin-resistant *S.aureus* (MRSA) was rarely observed (0.5 % of all patients). Patients with CHF had considerably more hospital-diagnosed comorbidity than patients without CHF, including diabetes (31.0 % vs. 12.8 %), chronic pulmonary disease (30.8 % vs. 10.8 %), renal disease (33.3 % vs. 13.6 %), and hypertension (49.5 % vs. 20.4 %). Compared to patients without CHF, patients with CHF were more likely to have filled prescriptions for angiotensin-converting-enzyme inhibitors, beta blockers, acetylsalicylic acid, and statins.

Ninety-day mortality

Ninety-day cumulative mortality was 44.6 % in patients with CHF and 30.4 % in patients without CHF, respectively (Table 2 and Fig. 1). This yielded an unadjusted MRR of 1.60 (95 % CI, 1.36–1.89), and an adjusted MRR of 1.24 (1.04–1.48). Compared to 30.4 % among patients without CHF, 90-day mortality was 30.8 % among patients with concomitant cardiomyopathy (aMRR = 1.04 (95 % CI, 0.63–1.72)), 60 % among patients with a history of valve disease (aMRR = 1.73 (95 % CI, 1.26–2.38)), 41.2 % among patients with previous myocardial infarction (aMRR = 1.17 (95 % CI, 0.83–1.65)), and 41.0 % among CHF patients with none of the above concomitant conditions (aMRR = 1.12 (0.83–1.50)).

Compared to patients without CHF, an increased risk of death within 90 days was observed among patients with dosages of 81–159 mg/day (aMRR = 1.55 (95%CI, 1.11–2.14)) and ≥160 mg/day (1.62 (95 % CI, 1.21–2.18)), whereas no association was noted among patients with daily intakes of loop-diuretics ≤80 mg/day (Table 2). Ninety-day mortality was 50 % among patients with CHF of <3 years as compared to 30.4 % among patients with no CHF, corresponding to an aMRR of 1.43 (95 % CI, 1.14–1.78). Longer duration of CHF did not appear to be associated with a poor outcome: Thus, compared with patients with no history of CHF, the aMRR was 1.01 (95 % CI, 0.71–1.46) for ≥3- < 6 years of CHF, 1.22 (95 % CI, 0.84-1.78) for ≥6- < 10 years of CHF and 0.97 (95 % CI, 0.61–1.54) for ≥10 years of CHF history. We observed no

Table 1 Characteristics of 2638 patients hospitalized with incident *Staphylococcus aureus* bacteremia in Northern Denmark, 2000-2011

	Patients with chronic heart failure	Patients without chronic heart failure
Numbers (%)	390 (14.8)	2248 (85.2)
Age, median (IQR)	76.6 (66.9–82.2)	67.4 (54.4–78.3)
15–39 years	12 (3.1)	221 (9.8)
40–59 years	48 (12.3)	557 (24.8)
60–79 years	194 (49.7)	988 (44.0)
≥ 80 years	136 (34.9)	482 (21.4)
Sex		
Men	253 (64.9)	1363 (60.6)
Women	137 (35.1)	885 (39.4)
S.aureus bacteremia		
Community-acquired	203 (52.1)	1320 (58.7)
Healthcare-associated	187 (48.0)	928 (41.3)
MRSA	3 (0.8)	10 (0.4)
Marital status		
Married	203 (52.1)	1067 (47.5)
Divorced or widowed	152 (39.0)	734 (32.7)
Never married	35 (9.0)	447 (19.9)
Selected comorbid conditions		
Diabetes mellitus	121 (31.0)	287 (12.8)
Peripheral vascular disease	99 (25.4)	229 (10.2)
Cerebrovascular disease	76 (19.5)	239 (10.6)
Chronic pulmonary disease	120 (30.8)	243 (10.8)
Moderate to severe renal disease	130 (33.3)	306 (13.6)
Hypertension	193 (49.5)	458 (20.4)
Conditions related to alcohol abuse	26 (6.7)	209 (9.3)
Conditions related to drug abuse	4 (1.0)	69 (3.1)
Dialysis within 30 days of admission	61 (15.6)	203 (9.0)
Modified Charlson Comorbidity Index		
Low (0)	42 (10.8)	720 (32.0)
Intermediate (1–2)	129 (33.1)	826 (36.7)
High (>2)	219 (56.2)	702 (31.2)
Preadmission medication use		
Immunosuppressive therapy[a]	3 (0.8)	25 (1.1)
Systemic antibiotic therapy[a]	82 (21.0)	454 (20.2)
ACE inhibitors[b]	298 (76.4)	788 (35.1)
Beta blockers[b]	271 (69.5)	764 (34.0)
Acetylsalicylic acid[b]	301 (71.2)	820 (36.5)
Statins[b]	174 (44.6)	451 (20.1)
Clinical biochemistry		
White blood count (10^9/L)[c]		
< 3.5	11 (2.8)	100 (4.5)
3.5–10	52 (13.3)	440 (19.6)
> 10	262 (67.2)	1292 (57.5)
Unknown	65 (16.7)	416 (18.5)

IQR interquartile range, *MRSA* methicillin resistant *Staphylococcus aureus*, *ACE inhibitors* angiotensin-converting-enzyme inhibitors
[a]Any use within 30 days of the current admission. [b]Any previous use prior to the current admission
[c]Measured on the date the first positive blood culture was drawn

consistent pattern or major differences in 90-day mortality according to sex, age, or m-CCI level (Table 3).

Discussion

In this large cohort study of 2638 patients with incident SAB, we observed a 24 % increase in 90-day all-cause mortality associated with CHF. Compared to patients without CHF, the excess risk of death within 90 days was most pronounced among CHF patients with concomitant valvular disease, patients with CHF of less than 3 years duration, and patients with a daily loop-diuretic dosage above 80 mg/day.

Our results are in line with the limited existing knowledge on the impact of CHF on mortality in SAB patients [6–9]. In a Norwegian cohort study of 374 patients with SAB, Paulsen et al. [6] observed an age- and sex-adjusted odds ratio (OR) of 2.4 (95 % CI, 1.21–4.80) for 30-day mortality comparing patients with and without CHF. In a Swiss cohort study [9] including 308 SAB patients from a single referral center, the authors observed an unadjusted OR of 2.4 (95 % CI, 1.0–5.6) of death within 90 days associated with CHF. A Columbian cohort study [7] examining risk factors of 90-day mortality in 267 cancer patients with SAB reported a hazard ratio of 10.6 (95 % CI, 1.8–63.7) comparing patients with and without CHF. Finally, a Taiwanese cohort study of 227 patients with persistent MRSA-SAB [8], found an 30-day mortality OR of 2.85 (95 % CI, 1.44–5.65) for patients with CHF compared to patients without. However, several issues should be taken into account when interpreting the results of these previous studies: Small and selected study populations [7, 8], limited numbers of patients with CHF (n < 70) [6–9], and insufficient adjustment for concomitant comorbid conditions [8, 9], could partly explain the findings. Moreover, in contrast to our study, none of the previous studies investigated the impact of CHF on mortality according to CHF-related conditions, CHF severity or duration of CHF [6–9].

Table 2 Ninety-day mortality in incident *Staphylococcus aureus* bacteremia patients with versus without chronic heart failure (CHF)

	Number	Mortality % (95 % CI)	Crude MRR (95 % CI)	Adjusted[a] MRR (95 % CI)
CHF				
Absent	2248	30.4 (28.6–32.4)	1.00 (ref.)	1.00 (ref.)
Present	390	44.6 (39.8–49.7)	1.60 (1.36–1.89)	1.24 (1.04–1.48)
CHF-related conditions				
CHF absent	2248	30.4 (28.6–32.4)	1.0 (ref.)	1.0 (ref.)
Cardiomyopathy	52	30.8 (20.1–45.2)	0.99 (0.60–1.62)	1.04 (0.63–1.72)
Valvular heart disease	70	60.0 (48.8–71.4)	2.44 (1.79–3.34)	1.73 (1.26–2.38)
Myocardial infarction	85	41.2 (31.6–52.4)	1.45 (1.04–2.05)	1.17 (0.83–1.65)
Atrial fibrillation	66	50.0 (38.7–62.5)	1.81 (1.27–2.57)	1.21 (0.85–1.73)
None of the above	117	41.0 (32.7–50.5)	1.46 (1.09–1.95)	1.12 (0.83–1.50)
CHF severity[b]				
CHF absent	2248	30.4 (28.6–32.4)	1.00 (ref.)	1.00 (ref.)
Non-users	99	32.2 (24.1–42.5)	1.08 (0.76–1.54)	0.99 (0.69–1.42)
Low dose (≤40 mg/day)	39	38.5 (25.3–55.5)	1.30 (0.78–2.16)	0.83 (0.50–1.40)
Medium dose (41–80 mg/day)	82	42.7 (32.8–54.1)	1.52 (1.08–2.14)	1.13 (0.80–1.59)
High dose (81–159 mg/day)	75	53.3 (42.6–64.9)	2.05 (1.49–2.83)	1.55 (1.11–2.14)
Very high dose (≥160 mg/day)	95	54.7 (45.1–64.9)	2.10 (1.59–2.79)	1.62 (1.21–2.18)
Duration of CHF				
CHF absent	2248	30.4 (28.6–32.4)	1.00 (ref.)	1.00 (ref.)
< 3 years	188	50.0 (43.1–57.3)	1.83 (1.48–2.27)	1.43 (1.14–1.78)
≥ 3- < 6 years	81	39.5 (29.8–51.0)	1.39 (0.98–1.99)	1.01 (0.71–1.46)
≥ 6- < 10 years	69	42.0 (31.4–54.5)	1.52 (1.05–2.21)	1.22 (0.84–1.78)
≥ 10 years	52	36.5 (25.1–51.1)	1.25 (0.79–1.97)	0.97 (0.61–1.54)

CI confidence interval, *MRR* mortality rate ratio
[a]Adjusted for age, sex, conditions included in the modified Charlson Comorbidity Index (excluding the condition in question), hypertension, alcohol related conditions, marital status, and antibiotic treatment within 30 days of admission
[b]Defined by daily loop-diuretic dosage

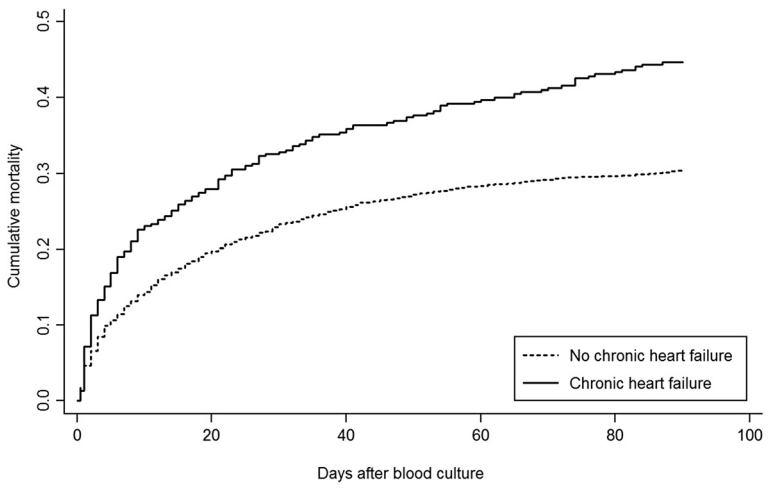

Fig. 1 Cumulative mortality risk among incident *Staphylococcus aureus* bacteremia patients with and without chronic heart failure

Table 3 Ninety-day mortality comparing incident community-acquired *Staphylococcus aureus* bacteremia in patients with and with chronic heart failure (CHF), stratified by sex, age, and modified Charlson Comorbidity Index level

	Patients without CHF	Patients with CHF	
	Mortality % (95 % CI)	Mortality % (95 % CI)	Adjusted[a] MRR
Overall	30.4 (28.6–32.4)	44.6 (39.8–49.7)	1.2 (1.0–1.5)
Sex			
Male	27.8 (25.5–30.3)	38.7 (33.1–45.0)	1.2 (1.0–1.5)
Female	34.5 (31.4–37.7)	55.5 (47.4–63.9)	1.3 (1.0–1.7)
Age			
15–39 years	5.4 (3.1–9.4)	n/a[b]	n/a[b]
40–59 years	18.5 (15.5–22.0)	27.1 (16.7–42.0)	1.5 (0.8–2.7)
60–79 years	31.6 (28.8–34.6)	44.9 (38.2–52.1)	1.6 (1.2–2.0)
80+ years	53.3 (48.9–57.8)	54.4 (46.3–62.9)	1.1 (0.8–1.4)
Modified Charlson Comorbidity Index level			
Low (0)	23.9 (20.9–27.2)	42.9 (30.0–59.1)	1.2 (0.7–1.9)
Intermediate (1–2)	30.4 (27.4–33.7)	43.4 (35.4–52.4)	1.2 (0.9–1.6)
High (3+)	37.2 (33.7–40.9)	45.7 (39.3–52.5)	1.3 (1.0–1.7)

Reference group: patients without CHF
CI confidence interval, *MRR* mortality rate ratio
[a]Adjusted for age, sex, conditions included in the modified Charlson Comorbidity Index (excluding CHF), hypertension, alcohol related conditions, marital status, and antibiotic treatment within 30 days of admission
[b]Not applicable due to absence of events

Several mechanisms may underlie our observations. Myocardial dysfunction is a well-known complication of sepsis [20, 21]. Cardiac dysfunction in patients with sepsis is characterized by ventricular dilatation, decreased ejection fraction, and blunted ability to increase cardiac output despite elevated catecholamine levels [20]. Patients with CHF may be especially susceptible to these mechanisms, which could partly explain our observed difference in mortality among patients with versus without this underlying condition. Still, patients with CHF were older, more frequently men, and had more comorbidity registered than those without CHF, all of which are important prognostic factors in patients with SAB [2]. Adjusting for these factors in our model attenuated the association between CHF and mortality suggesting that a considerable part of the high mortality associated with SAB is conveyed by the combined burden of age, sex and comorbidity. In our study, the increased 90-day mortality associated with CHF was most pronounced among CHF patients with valvular heart disease and among patients with short duration of CHF. CHF patients with concomitant valvular heart disease may in particular be at high risk of pulmonary edema and circulatory collapse secondary to sepsis. However, valvular heart disease represents a major risk factor for infective endocarditis [22], which may add to the poor prognosis of these patients. The mechanisms underlying the increased risk of death among patients with short duration of CHF remain unclear and may most likely be multifactorial. It is possible, however, that patients with shorter duration of CHF differ from patients with long CHF duration with regards to CHF management and clinical stability which may influence the outcome from CA-SAB.

Our study has several strengths including its size, population-based design and adjustment for relevant confounders facilitated by our access to medical databases ensuring a complete prescription and hospitalization history. All data was collected prospectively and independently of the study hypothesis, thus reducing the risk of selection and information biases, and follow-up was virtually complete. However, some important limitations should be addressed in the interpretation of our results. Identification of patients with CHF from medical databases may be hampered by inaccurate coding, which would bias our results towards unity. Yet, two recent Danish validation studies reported positive predictive values for chronic heart failure in the DNPR of 81 % [23] and 100 % [19], respectively. Physicians may be more likely to admit patients with CHF on suspicion of infection compared to patients without CHF. Such surveillance bias would induce an underestimation of the relative risk associated with SAB. However, white blood counts of patients with and without CHF were comparable, and the proportions of patients who had received antibiotics prior to the current admission were almost similar. In addition, we observed no substantial differences in the proportions of patients classified as HCA-SAB among the two groups. This argues against, but does not preclude notable bias associated with the triage and treatment of patients with CHF in our study. On the other hand, the clinical management of patients with CA-SAB was not standardized across hospitals, which might have influenced our

results. Furthermore, we lacked data on infective foci including venous catheters and other vascular access devices, which have been associated with SAB prognosis in several prior studies [1, 2].

We used loop-diuretic dosage as a proxy for CHF severity, since we did not have access to data on ejection fraction or New York Heart Association Functional Class among patients with CHF. If some patients used loop-diuretics for other reasons than CHF (e.g., concomitant renal failure) this may have led us to underestimate any differences between less severe and severe CHF, although we do not expect this to alter our overall conclusions. Finally, the medical databases did not contain data on smoking and obesity, still these potential confounders may be partly accounted for by adjustment for lifestyle-associated comorbidities included in our statistical models.

Due to the low prevalence of MRSA in our study area [24], these data and results may not be directly applicable to settings with higher MRSA prevalence. Still, our results may most likely be applicable to other healthcare systems with equal unfettered access to medical care and prescription medication including CHF drugs.

Conclusion

In summary, patients with CA-SAB and CHF experienced higher 90-day mortality than patients without CHF, which was most apparent among CHF patients with valvular heart disease, patients with a short history of CHF, and patients with high daily dosages of loop-diuretics. SAB patients with CHF may benefit from the collaborated care of infectious diseases specialists and cardiologists ensuring increased adherence to evidence-based guidelines, optimized post-discharge follow-up and possibly improved clinical outcomes.

Abbreviations

ATC codes, anatomical therapeutic chemical classification system codes; AUPD, Aarhus University prescription database; CA-SAB, community-acquired *Staphylococcus aureus* bacteremia; CHF, chronic heart failure; CI, confidence interval; DNPR, danish national patient registry; HCA-SAB, healthcare-associated *Staphylococcus aureus* bacteremia; IQR, interquartile range; m-CCI, modified Charlson comorbidity index; MRR, mortality rate ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio; SAB, *Staphylococcus aureus* bacteremia.

Additional files

Additional file 1: Identification and susceptibility testing of *S.aureus* isolates (PDF 122 kb)

Additional file 2: Codes for diagnoses, procedures, medication and blood tests (PDF 27 kb)

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Availability of data and materials

According to Danish legislation, some access restrictions apply to the data underlying the findings. Data from the registers used in our study are available for researchers who fulfill the criteria for access to confidential data. Detailed information on the application procedure for data access for researchers outside Denmark can be found at the Danish Data Protection Agency homepage (http://www.datatilsynet.dk/erhverv/tredjelande/overfoersel-til-tredjelande/).
Data from the Danish National Patient Registry and the Civil Registration System may be obtained by applying to the Danish Health Data Authority (http://sundhedsdatastyrelsen.dk/da/forskerservice) and the Central Office of Civil Registration, Copenhagen (https://cpr.dk/cpr/site.aspx?p=194&ArticleID=4327), respectively.
In order to access data from the Aarhus University Prescription Database and the LABKA database, researchers may apply to the Department of Clinical Epidemiology, at Aarhus University Hospital (www.kea.au.dk).
Microbiological data can be requested from the departments of clinical microbiology at Aalborg University Hospital (http://www.aalborguh.rn.dk/Afsnit-og-ambulatorier/Klinisk-Mikrobiologisk-Afdeling) and Aarhus University Hospital (http://www.auh.dk/om-auh/afdelinger/klinisk-mikrobiologisk-afdeling/).

Authors' contributions

JS: study concept and design, data management, analysis and interpretation, and manuscript preparation. KA, RWT, MS: study concept and preparation, data interpretation, and manuscript review. HCS: study concept and design, critical analysis of the data, manuscript review, and study supervision. All the authors have read and approved the final draft submitted.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The project was approved by the Danish Data Protection Agency (ref. no. 2012-41-0942). Due to guaranteed and complete confidentiality, Danish legislation does not require individual informed consent, consent to publish, or ethics committee approval for registry-based studies [11].

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References

1. Kern WV. Management of Staphylococcus aureus bacteremia and endocarditis: progress and challenges. Curr Opin Infect Dis. 2010;23:346–58.
2. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in Staphylococcus aureus bacteremia. Clin Microbiol Rev. 2012;25:362–86.
3. Roger VL. Epidemiology of heart failure. Circ Res. 2013;113:646–59.
4. Dunlay SM, Roger VL. Understanding the epidemic of heart failure: past, present and future. Curr Heart Fail Rep. 2014;11:404–15.
5. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369:840–51.
6. Paulsen J, Mehl A, Askim Å, Solligård E, Åsvold BO, Damås JK. Epidemiology and outcome of Staphylococcus aureus bloodstream infection and sepsis in a Norwegian county 1996-2011: an observational study. BMC Infect Dis. 2015;15:116.

7. Cuervo SI, Cortés JA, Sánchez R, Rodríguez JY, Silva E, Tibavizco D, et al. Risk factors for mortality caused by Staphylococcus aureus bacteremia in cancer patients. Enferm Infecc Microbiol Clin. 2010;28:349–54.
8. Lin SH, Liao WH, Lai CC, Tan CK, Wang CY, Huang YT, et al. Risk factors for mortality in patients with persistent methicillin-resistant Staphylococcus aureus bacteremia in a tertiary care hospital in Taiwan. J Antimicrob Chemother. 2010;65:1792–8.
9. Kaech C, Elzi L, Frei R, Laifer G, Bassetti S, Fluckiger U. Course and outcome of Staphylococcus aureus bacteremia: a retrospective analysis of 308 episodes in a Swiss tertiary-care centre. Clin Microbiol Infect. 2006;12:345–52.
10. Pedersen CB. The Danish Civil Registration System. Scan J Public Health. 2011;39:22–5.
11. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29:541–9.
12. Wiese L, Mejer N, Schønheyder HC, Westh H, Jensen AG, Larsen AR, et al. A nationwide study of comorbidity and risk of reinfection after Staphylococcus aureus bacteraemia. J Infect. 2013;67:199–205.
13. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health. 2011;39:30–3.
14. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. Am J Cardiol. 2006;97:1759–64.
15. Demant MN, Gislason GH, Køber L, Vaag A, Torp-Pedersen C, Andersson C. Association of heart failure severity with risk of diabetes: a Danish nationwide cohort study. Diabetologia. 2014;57:1595–600.
16. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol. 2010;2:273–9.
17. Charlson M, Pompei P, Ales KL. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chron Dis. 1987;40:373–83.
18. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol. 2011;11:83.
19. Grann AF, Erichsen R, Nielsen AG, Frøslev T, Thomsen RW. Existing data sources for clinical epidemiology: The clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. Clin Epidemiol. 2011;1:133–8.
20. Flynn A, Mani BC, Mather PJ. Sepsis-induced cardiomyopathy: a review of pathophysiologic mechanisms. Heart Fail Rev. 2010;15:605–11.
21. Maeder M, Fehr T, Rickli H, Ammann P. Sepsis-associated myocardial dysfunction. Chest. 2006;129:1349–66.
22. Hoen B, Duval X. Infective endocarditis. N Engl J Med. 2013;368:1425–33.
23. Kümler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, et al. Accuracy of a heart failure diagnosis in administrative registers. Eur J Heart Fail. 2008;10:658–60.
24. Laupland KB, Lyytikäinen O, Kennedy KJ, Knudsen JD, Ostergaard C, Galbraith JC, et al. The changing epidemiology of Staphylococcus aureus bloodstream infection: a multinational population-based surveillance study. Clin Microbiol Infect. 2013;19:465–71.

Additional file 1

Identification and susceptibility testing of *S.aureus* isolates

Setting

During the study period a reform of local government merged four counties into two health regions: Central Denmark Region and North Denmark Region, collectively referred to as Northern Denmark. Three departments of clinical microbiology served Central Denmark Region and were situated in Aarhus (Aarhus University Hospital), Viborg (Regional Hospital of Viborg) and Herning (Regional Hospital West Jutland). North Denmark Region was served by one department of clinical microbiology at Aalborg University Hospital, Aalborg.

The total number of beds in non-psychiatric wards was 5.528 in 2000 and 4.058 in 2011.

Number of hospitals in the two health regions and their predecessors

	2000	2011
Central Denmark Region	17	5
North Denmark Region	7	4

Blood cultures

Blood cultures were ordered by the attending physician and blood samples were drawn by trained biotechnicians. The BacT/Alert system (bioMérieux, Marcy l'Etoil, France) was used throughout the study period at all hospital sites. Recommendations differed between the two health regions: In Central Denmark Region a standard blood culture for adults comprised two sets with two bottles each (one aerobic and one anaerobic bottle), whereas the standard in North Denmark Region was one set with three bottles (two aerobic and one anaerobic bottle).

Identification and susceptibility testing of *Staphylococcus aureus*

S. aureus was identified by horse plasma tube coagulase test or an equivalent commercial latex agglutination test. All blood culture isolates were referred to the Staphylococcal Reference Laboratory at Statens Serum Institut (Copenhagen) for national surveillance which included phage typing up to 2006 and *spa*-typing thereafter (1,2).

Susceptibility testing was undertaken locally by disk diffusion and confirmatory testing was performed at Statens Serum Institut (3-5). Screening for methicillin resistance varied between departments 2000-2002, but in 2003 the cefoxitin disk diffusion test was implemented both locally and at Statens Serum Institut (4,5). Detection of the *mecA* gene cassette was done by either in-house polymerase chain reaction (PCR) or the EVIGENE™ hybridization test (2,7).

Methicillin-resistant *S. aureus* (MRSA) became notifiable in Denmark in 2006. Due to the low prevalence of methicillin-resistance extra precautions were taken in this study by cross-referencing local data with the Danish national *S. aureus* bacteremia database at Statens Serum Institut.

References

1. DANMAP 2006 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. ISSN 1600-2032. http://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/Danmap_2003.ashx (Accessed June 1 2015).
2. Larsen AR, Stegger M, Sørum M. spa typing directly from a mecA, spa and pvl multiplex PCR assay-a cost-effective improvement for methicillin-resistant Staphylococcus aureus surveillance. Clin Microbiol Infect. 2008 Jun;14(6):611-4.
3. DANMAP 2000 – Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. ISSN 1600-2032. http://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/Danmap_2000.ashx (Accessed June 1 2015).
4. DANMAP 2003 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. ISSN 1600-2032. http://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/Danmap_2003.ashx (accessed June 1 2015)

5. Skov R, Smyth R, Clausen M, Larsen AR, Frimodt-Møller N, Olsson-Liljequist B, Kahlmeter G. Evaluation of a cefoxitin 30 microg disc on Iso-Sensitest agar for detection of methicillin-resistant Staphylococcus aureus. J Antimicrob Chemother. 2003 Aug;52(2):204-7. Epub 2003 Jul 1. PubMed PMID: 12837728.
6. Skov RL, Pallesen LV, Poulsen RL, Espersen F. Evaluation of a new 3-h hybridization method for detecting the mecA gene in Staphylococcus aureus and comparison with existing genotypic and phenotypic susceptibility testing methods. J Antimicrob Chemother. 1999 Apr;43(4):467-75.

Additional file 2

Codes for diagnoses, procedures, medication and blood tests

Preadmission comorbid conditions. Diagnoses codes are according to the 8th and 10th revision of the International Classification of Diseases, ICD-8 and ICD-10

Condition	ICD-8	ICD-10
Chronic heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 784.29	I50, I11.0, I13.0, I13.2, I42.0, I42.6, I42,7, I42.8, I42.9, I25.5
Cardiomyopathy	425.99	I42
Heart valve disease	394.00-394.02, 394.08, 394.90, 394.91, 394.92, 394.98, 394.99, 395.90, 395.01, 395.02, 395.08, 395.90-395.92, 395.98-395.99, 396.00-396.04, 396.08-39.609, 396.90-396.93, 396.04, 396.08, 396.09, 396.90, 396.91-396.94, 396.98-397.01, 397.09, 398.99	I34, I35, I05-I08, I09.1, I09.8, I09.9, I36-I39
Myocardial infarction	410.09, 410.99	I21-I23
Atrial fibrillation	427.93, 427.94	I48
Diabetes	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10-E14. O24 (except O24.4), G63.2, H36.0, N08.3
Peripheral vascular disease	440, 441, 442, 443, 444, 445	I70, I71, I72, I73, I74, I77
Cerebrovascular disease	430-438	I60-I69, G45, G46
Dementia	290.09-290.19, 293.09	F00-F03, F05.1, G30

Chronic pulmonary disease	490-493, 515-518	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease	530.91, 530.98, 531-534	K22.1, K25-K28
Mild liver disease	571, 573.01, 573.04	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0
Hemiplegia	344	G81, G82
Moderate to severe renal disease	403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Any tumor	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203, 275.59	C81-C85, C88, C90, C96
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Metastatic solid tumor	195-198, 199	C76-C80
AIDS	079.83	B21-B24
Hypertension	400-404	I10-I13
Osteoporosis	723.09	M80-M82

Conditions related to alcohol abuse	291.09-291.99, 303.09-303.29, 303.91-303.99	F10, K86.0, Z72.1. T51, K29.2, G62.1, G31.2, I42.6, K70
Conditions related to drug abuse	304.09-304.99	F11-F16, F18-F19, T40

Procedures. Codes regarding dialysis are according to Danish Treatment codes and according to the 10th revision of the International Classification of Diseases, ICD-10.

	Danish treatment codes	**ICD-10**
Dialysis	98300, 94340, 94350 BJFD0, BJFD2	Z99.2, Z49, Z49.2, BJFD
Surgery	All surgical codes (K-codes) in the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures.	

Medication codes are according to the Anatomical Therapeutic Classification (ATC)

Type of medication	**ATC codes**
Loop-diuretics	C03CA01
Immunosuppressive therapy	L01, L04
Systemic antibiotic therapy	J01
ACE inhibitors	C09
Beta-blockers	C07
Acetylsalicylic acid	B01AC06
Statins	C10AA, C10B, B04AB,

Blood tests according to local analysis codes and Nomenclature for Properties and Units (NPU)-codes

Blood test	Local analysis and NPU-codes
White blood count	NPU02593, 2593, 122577, 37, 1312240, 141240

Reports/PhD theses from the Department of Clinical Epidemiology

1. Ane Marie Thulstrup: Mortality, infections and operative risk in patients with liver cirrhosis in Denmark. Clinical epidemiological studies. PhD thesis. *2000*.

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16. Lungebetændelse i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

17. Kort- og langtidsoverlevelse efter indlæggelse for nyre-, bugspytkirtel- og leverkræft i Nordjyllands, Viborg, Ringkøbing og Århus amter 1985-2004. *2005*.

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42. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1996-2007. *2008*.

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44. Akutte indlæggelsesforløb og skadestuebesøg på hospiter i Region Midtjylland og Region Nordjylland 2003-2007. Et pilotprojekt. *Not published*.

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80. Risiko for kræft blandt patienter med kronisk obstruktiv lungesygdom (KOL) i Danmark. (Online publication only). *2013*.

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