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Long-term mortality and causes of death associated with *Staphylococcus aureus* bacteremia. A matched cohort study

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Summary Objectives: Data describing long-term mortality in patients with *Staphylococcus aureus* bacteremia (SAB) is scarce. This study investigated risk factors, causes of death and temporal trends in long-term mortality associated with SAB.

Methods: Nationwide population-based matched cohort study. Mortality rates and ratios for 25,855 cases and 258,547 controls were analyzed by Poisson regression. Hazard ratio of death was computed by Cox proportional hazards regression analysis.

Results: The majority of deaths occurred within the first year of SAB (44.6%) and a further 15% occurred within the following 2–5 years. The mortality rate was 14-fold higher in the first year after SAB and 4.5-fold higher overall for cases compared to controls. Increasing age, comorbidity and hospital contact within 90 days of SAB was associated with an increased risk of death. The overall relative risk of death decreased gradually by 38% from 1992–1995 to 2012–2014. Compared to controls, SAB patients were more likely to die from congenital malformation, musculoskeletal/skin disease, digestive system disease, genitourinary disease, infectious disease, endocrine disease, injury and cancer and less likely to die from respiratory disease,

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nervous system disease, unknown causes, psychiatric disorders, cardiovascular disease and senility. Over time, rates of death decreased or were stable for all disease categories except for musculoskeletal and skin disease where a trend towards an increase was seen.

Conclusion: Long-term mortality after SAB was high but decreased over time. SAB cases were more likely to die of eight specific causes of death and less likely to die of five other causes of death compared to controls. Causes of death decreased for most disease categories. Risk factors associated with long-term mortality were similar to those found for short-term mortality. To improve long-term survival after SAB, patients should be screened for comorbidity associated with SAB.

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Introduction

Staphylococcus aureus is a leading cause of bacteremia and severe sepsis.^{1–4} Rates of *S. aureus* bacteremia (SAB) are high worldwide^{5–7} and continue to increase.¹ SAB is associated with an overall short-term mortality of 20–30%.⁸

While numerous studies have investigated and described short-term outcomes from SAB,^{1,9,10} there is very limited information on outcomes beyond the first year.^{11,12} A recent study of bacteremia showed that 1-year mortality was 40% and during the subsequent 2–5 years another 40% had died.^{11,12} The study included 17 causes of bacteremia, of which SAB accounted for 12% of cases.

Knowledge of short- and long-term causes of deaths after SAB could add valuable information relating to disease manifestations associated with SAB. For example, whether or not SAB may be an indicator disease of future comorbidity and risk of death. Recently, we showed that the risk of cardiovascular and venous thromboembolism was significantly increased for SAB cases compared to controls during the first year of follow up.^{13,14} Few studies have analyzed long-term causes of death after sepsis^{10,11,15,16} and just one study included a control group.¹¹ Further, the increase in incidence of SAB has been associated with an ageing and comorbid population.^{1,4,17,18} Both are factors that may affect outcomes and trends in causes of death may be changing.

We used the on-going nationwide registration of all Danish cases of SAB to generate a population-based matched cohort study. We analyzed long-term outcomes, risk factors, mortality rates and causes of death and compared these to population controls without SAB.

Methods

Data sources

Every resident of Denmark is given a personal identifier at birth or immigration by the Civil Registration System (CRS).¹⁹ The personal identifier eliminates multiple registrations, and enables tracking of each individual in multiple registries. Information on demography and vital status (death, emigration and loss to follow up) is updated daily.

The nationwide Danish Staphylococcal Bacteremia Database (DSBD) contains consecutive registrations of SAB, defined as a positive blood culture submitted from the Clinical Microbiological Departments on a voluntary basis to

the National Reference Laboratory at Statens Serum Institut.²⁰

The Danish National Patient Register (NPR) is updated monthly and contains information on all admissions to Danish hospitals and discharge diagnosis codes according to the International Classification of Disease (ICD)-8 until the end of 1993 and ICD-10 from 1994.²¹

The Danish Register of Causes of Death (DRCD) has in its present form registered causes of death to all Danish citizens or individuals with residence in Denmark since 1970.²² It is the attending physician who registers the cause of death, due to primary- (immediate cause of death), secondary- or tertiary- and an underlying cause of death. Over time the coding has changed, using ICD-8 to the end of 1993 and from 1994 to today using ICD-10 codes.²³ We used the underlying cause of death for our analysis. Causes of death are classified manually resulting in a delay of 1–2 years. Thus, reliable data were not yet available for the year period 2012–2014 and these years were excluded from analyses of causes of death.

The study was approved by the Danish Data Protection Agency (record no. 2014-41-3376).

Study population

Cases

A case was defined as an individual with a first episode of SAB and a hospital admission in the NPR before or within 3 days after sample date and a discharge hereafter. Cases were included from the DSBD from January 1, 1992 to October 31, 2014.

Population control cohort

For each case we randomly selected 10 population controls from CRS matched to the corresponding case on age and gender. The control had to be alive and at risk of a first time hospitalization with SAB on the index date (date of SAB in NPR) of the corresponding case.

Variables

Age was analyzed in five strata (0–15; 16–35; 36–55; 56–75 and >75 years). Time periods were divided into four-year periods depending on the date of SAB, except for the last period from 2012 to 2014.

We used in- or out-patient hospital contact 90 days prior to the SAB sample date as a proxy for hospital-acquired or healthcare-associated SAB. Based on data from this cohort from 1995 to 2008¹⁷ in which information on community-

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