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MAJOR ARTICLE

Prevalence and Mortality of Infective Endocarditis in Community-Acquired and Healthcare-Associated *Staphylococcus aureus* Bacteremia: A Danish Nationwide Registry-Based Cohort Study

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Background. *Staphylococcus aureus* bacteremia (SAB) can be community-acquired or healthcare-associated, and prior small studies have suggested that this mode of acquisition impacts the subsequent prevalence of infective endocarditis (IE) and patient outcomes.

Methods. First-time SAB was identified from 2010 to 2018 using Danish nationwide registries and categorized into community-acquired (no healthcare contact within 30 days) or healthcare-associated (SAB >48 hours of hospital admission, hospitalization within 30 days, or outpatient hemodialysis). Prevalence of IE (defined from hospital codes) was compared between groups using multivariable adjusted logistic regression analysis. One-year mortality of *S aureus* IE (SAIE) was compared between groups using multivariable adjusted Cox proportional hazard analysis.

Results. We identified 5549 patients with community-acquired SAB and 7491 with healthcare-associated SAB. The prevalence of IE was 12.1% for community-acquired and 6.6% for healthcare-associated SAB. Community-acquired SAB was associated with a higher odds of IE as compared with healthcare-associated SAB (odds ratio, 2.12 [95% confidence interval {CI}, 1.86–2.41]). No difference in mortality was observed with 0–40 days of follow-up for community-acquired SAIE as compared with healthcare-associated SAIE (HR, 1.07 [95% CI, .83–1.37]), while with 41–365 days of follow-up, community-acquired SAIE was associated with a lower mortality (HR, 0.71 [95% CI, .53–.95]).

Conclusions. Community-acquired SAB was associated with twice the odds for IE, as compared with healthcare-associated SAB. We identified no significant difference in short-term mortality between community-acquired and healthcare-associated SAIE. Beyond 40 days of survival, community-acquired SAIE was associated with a lower mortality.

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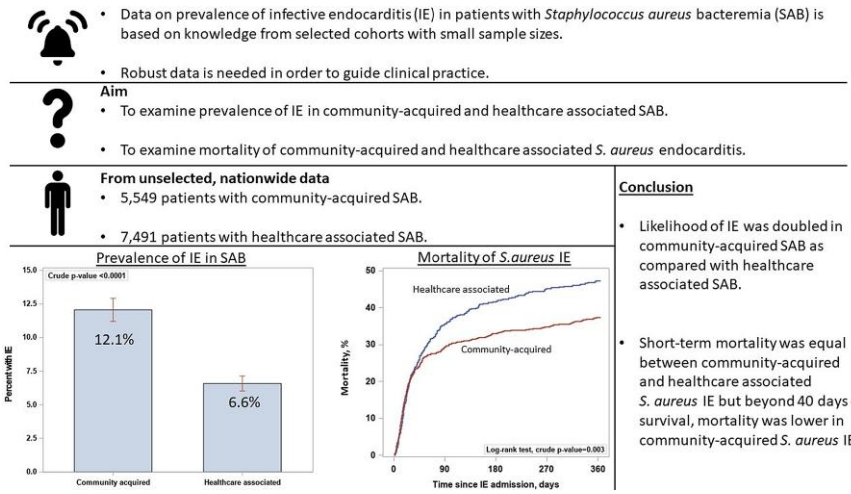
Graphical Abstract



Keywords. community-acquired; endocarditis; healthcare-associated; infective endocarditis; *Staphylococcus aureus* bacteremia.

Infective endocarditis (IE) may be a serious complication among patients with *Staphylococcus aureus* bacteremia (SAB) as it is associated with a high in-hospital mortality of around 20%–30% [1, 2]. *Staphylococcus aureus* is the most frequent microbiological etiology of IE in Western high-income countries [3, 4]. Therefore, several studies have examined the prevalence of IE among patients with SAB in order to optimize the diagnostic workup in this patient group [5–13]. From these studies the prevalence of IE among patients with SAB has been estimated to be between 10% and 29% [5–12]. Several studies have shown that the prevalence of IE is higher among patients with community-acquired SAB than patients with healthcare-associated SAB [5, 7, 9, 13, 14]. However, these studies have been limited by low numbers (in the range of 91 to 2008 patients, with the majority of studies from single centers) [5–12]. Furthermore, these studies have been underpowered to identify differences in outcomes between different subgroups of patients with *S aureus* IE (SAIE). Knowledge on this matter may guide clinical awareness and threshold for initiation of IE diagnostic workup among patients with SAB. From a Danish, nationwide cohort, we set out to examine the prevalence of IE among patients with community-acquired versus healthcare-associated SAB. Furthermore, we aimed to examine differences in mortality among patients with SAIE according to mode of bacteremia acquisition.

METHODS

Data Sources

In Denmark, every citizen has a unique identification number, which makes it possible to link national registries. For this study, we included the following nationwide registries: The Danish Civil Registration Registry, The National Patient Registry, The National Prescription Registry, and The Danish Microbiology Database. The Danish Civil Registration Registry holds information on date of birth, sex, date of death, and migration status [15]. The National Patient Registry records every hospitalization since 1977 and every outpatient visit since 1994 [16]. Every hospital visit has 1 primary diagnosis code and up to several secondary diagnosis codes as completed by the treating physician. Since 1994, diagnosis codes have been based upon the *International Classification of Diseases, Tenth Revision*. The National Patient Registry was used to identify episodes of IE and comorbidity. The Prescription Registry holds information on every redeemed drug from a Danish pharmacy since 1994 [17]. This registry was used to identify concomitant pharmacotherapy. The Danish Microbiology Database was established in 2010 and collects microbiological data from all Danish Departments of Clinical Microbiology. The registries are considered of high quality and have been described in detail previously [15–18].

Study Population and Exposure Definition (Community-Acquired and Healthcare-Associated)

The study population consisted of all patients registered in the Danish Microbiology Database with first-time SAB in the period from January 2010 to May 2018. Nonresidents (n = 102) and patients with invalid data (n = 12) were excluded from the analysis. The study population was categorized as having community-acquired SAB or healthcare-associated SAB. Healthcare-associated SAB was defined as (*i*) patients with

blood cultures (with SAB) taken >48 hours of hospital admission; (*ii*) patients with SAB discharged from hospital or with an emergency room (ER) visit within 30 days of SAB without fulfilling (*i*); and (*iii*) patients with outpatient hemodialysis within 30 days of SAB not fulfilling (*i*) and (*ii*). Community-acquired SAB was categorized according to absence of the abovementioned contacts.

Outcomes

The primary outcome was the prevalence of IE in relation to SAB. SAB was considered related to an episode of IE if the patient was admitted for IE within 30 days of SAB or during an admission for IE. IE was defined as a first-time primary or secondary diagnosis code of IE (*ICD-10* codes: I33, I38, I398) with a length of hospital stay >14 days except if the patient died and had a length of IE hospital stay ≤14 days. Using these criteria, the positive predictive value of IE in the National Patient Registry has been found to be 90% [19, 20].

Secondary outcomes were the 90-day and 1-year mortalities for patients with SAIE according to mode of bacteremia acquisition. Date of death was provided from the Danish Civil Registration Registry.

Covariates

Comorbidities were based on diagnosis codes from an in-hospital or outpatient visit as specified in Supplementary Table 1 using *ICD-10* codes (from 1994). Concomitant pharmacotherapy was defined as a redeemed prescription within 6 months prior to SAB. Diabetes mellitus was defined as a redeemed prescription of an antidiabetic drug within 6 months of SAB, or a diagnosis code of diabetes mellitus. Redemption of a prescription on systemic use antibiotics 90 days prior to SAB was examined across study groups.

Statistical Analysis

Baseline characteristics between study groups were compared with categorical variables presented in counts and percentages and continuous variables presented with a median and 25th and 75th percentiles. The prevalence of IE was calculated as the number of IE cases divided by the total number of patients with SAB for each study group. Analyses were stratified by sex and age groups (<40, 40–49, 50–59, 60–69, 70–79, ≥80 years). In a multivariable adjusted logistic regression analysis, the associated likelihood of IE was compared between study groups. The following covariates were included in the multivariable adjusted model: sex, age, prosthetic heart valve, cardiac implantable electronic device (CIED), calendar year, diabetes mellitus, malignancy, and chronic renal failure.

Mortality was calculated as a percentage of patients who died within 90 days of follow-up and 1 year of follow-up, divided by the number of patients at risk when follow-up was initiated for patients with SAIE according to mode of bacteremia acquisition. Furthermore, mortality was depicted in graphical terms using 1-Kaplan Meier estimates for patients with SAIE according to mode of bacteremia acquisition. In multivariable adjusted Cox proportional hazard analysis, the associated rate of 1-year mortality was compared for patients with SAIE according to mode of bacteremia acquisition including the following covariates: mode of bacteremia acquisition, heart failure, chronic obstructive pulmonary disease (COPD), chronic renal failure, liver disease, sex, CIED, prosthetic heart valve, diabetes mellitus, malignancy, age, and calendar year. The assumption of proportional hazards was violated for mode of bacteremia acquisition and the analysis was conducted with follow-up of (*i*) 0–40 days and (*ii*) a landmark analysis of 41–365 days. Estimates from the logistic regression analysis were presented with odds ratio (OR) and 95% confidence intervals (CIs) and estimates from the Cox regression analyses were presented with hazard ratio (HR) and 95% CI. A P value < .05 was considered statistically significant. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, North Carolina).

Sensitivity and Supplementary Analyses

We performed 2 sensitivity analyses. First, the prevalence of IE among patients with healthcare-associated SAB was stratified by mode of healthcare association: (*i*) hospital admission within 30 days; (*ii*) ER visit within 30 days; (*iii*) SAB >48 hours of hospital admission; and (*iv*) outpatient hemodialysis within 30 days of SAB. For community-acquired SAB, patients were stratified by patients with a healthcare contact without intervention (eg, telephone contact, medical examination, initial clinical examination in relation to outpatient visit, outpatient chest radiograph) and patients with SAB without any of the abovementioned medical contacts. Second, hospital admission or ER visit within 60 days of SAB was defined as healthcare associated (instead of 30 days).

Ethical Considerations

In Denmark, registry-based studies that are not conducted for the sole purpose of statistics and scientific research do not require ethical approval or informed consent by law [21]. However, the study is approved by the data responsible institute (Capital Region of Denmark, approval number P-2019-348) in accordance with the General Data Protection Regulation. All personal identifiers were anonymized and subclassifications with ≤3 patients were not reported in order to assure anonymization as by rules of Statistics Denmark. Categorizations with <4 observations were pooled with other groups to assure anonymization.

RESULTS

We identified 13 167 patients with first-time SAB in the period from January 2010 to May 2018. After applying exclusion criteria, 13 040 patients were identified including 5549 patients

Table 1. Baseline Characteristics for Community-Acquired and Healthcare-Associated *Staphylococcus aureus* Bacteremia

	Community-Acquired SAB (n = 5549)		Healthcare-Associated SAB (n = 7491)	
Characteristic	No.	(%)	No.	(%)
Male sex	3462	(62.4)	4722	(63.0)
Age, y, median (IQR)	70.9	(57.4–81.8)	69.0	(56.3–79.0)
Calendar period				
2010–2012	1665	(30.0)	2410	(32.2)
2013–2015	2127	(38.3)	2882	(38.5)
2016–2018[a]	1757	(31.7)	2199	(29.4)
Medical history				
AMI	451	(8.1)	919	(12.3)
PCI	335	(6.0)	638	(8.5)
CABG	206	(3.7)	454	(6.1)
Prosthetic heart valve	212	(3.8)	278	(3.7)
CIED	325	(5.9)	511	(6.8)
Chronic heart failure	821	(14.8)	1564	(20.9)
Atrial fibrillation/flutter	1021	(18.4)	1720	(23.0)
Stroke	656	(11.8)	1050	(14.0)
Diabetes mellitus	1409	(25.4)	2002	(26.7)
Alcohol abuse	620	(11.2)	1039	(13.9)
COPD	771	(13.9)	1158	(15.5)
Malignancy	231	(4.2)	307	(4.1)
Chronic renal failure	427	(7.7)	1719	(22.9)
Liver disease	517	(9.3)	819	(10.9)
Medication				
Statin	1552	(28.0)	2267	(30.3)
β-blocker	1492	(26.9)	2558	(34.1)
RASi	1804	(32.5)	2579	(34.4)
OAC	827	(14.9)	1221	(16.3)
Loop diuretics	1573	(28.3)	2747	(36.7)

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; OAC, oral anticoagulant therapy; PCI, percutaneous coronary intervention; RASi, renin-angiotensin system inhibitor; SAB, *Staphylococcus aureus* bacteremia.

[a]Data from 2018 only available until 14 May.

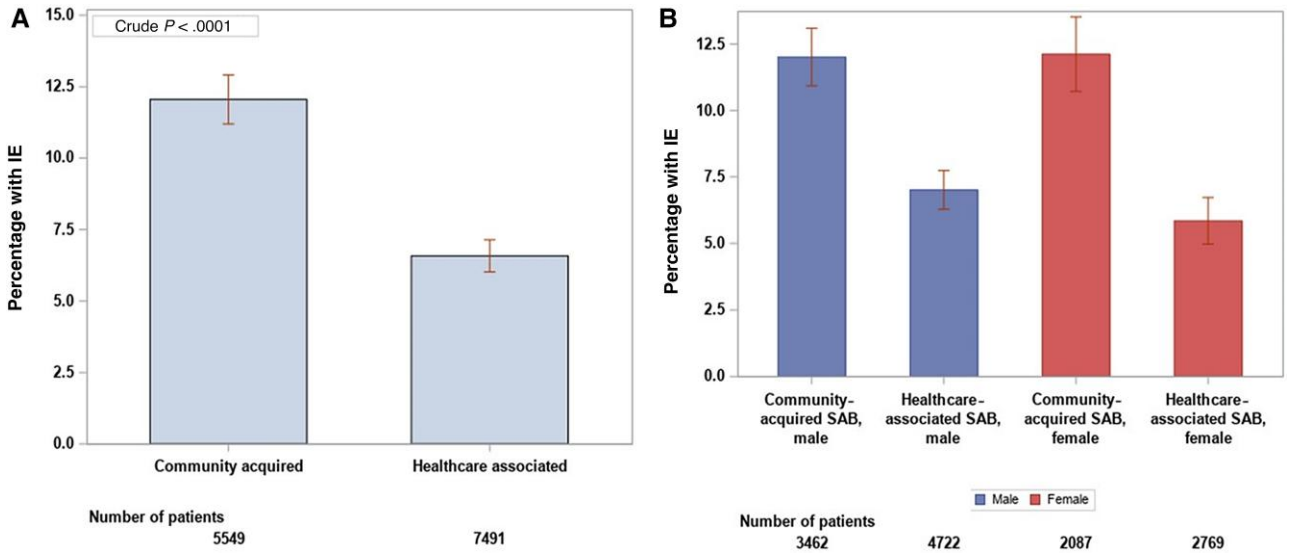


Figure 1. *A,* Prevalence of infective endocarditis (IE) among patients with community-acquired and healthcare-associated *Staphylococcus aureus* bacteremia (SAB). *B,* Prevalence of IE stratified by sex.

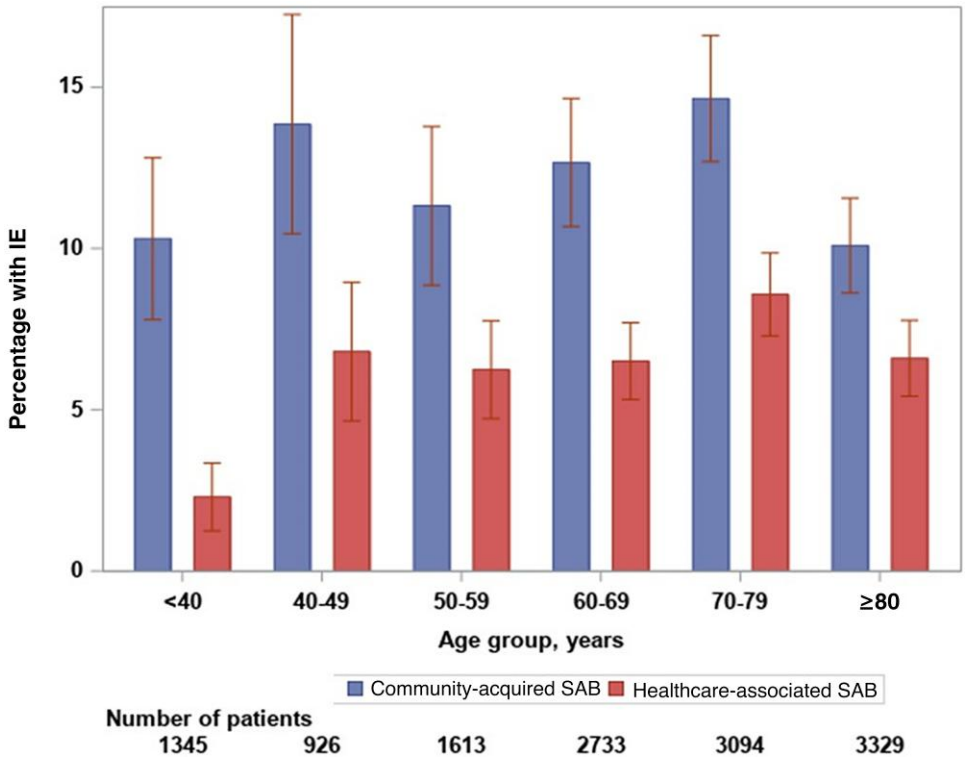


Figure 2. Prevalence of infective endocarditis (IE) among patients with community-acquired and healthcare-associated *Staphylococcus aureus* bacteremia (SAB), stratified by age group. Box-whiskers show 95% confidence intervals.

(42.6%) categorized as having community-acquired SAB and 7491 (57.4%) as healthcare-associated SAB. Among patients with healthcare-associated SAB, 3434 (45.8%) were diagnosed during hospital admission or ER contact within 30 days of SAB, 3537 (36.8%) were diagnosed after >48 hours of hospital admission, and 520 (6.9%) received outpatient hemodialysis within 30 days of SAB (Supplementary Table 2). Baseline characteristics for the 2 study groups are presented in Table 1, showing no major differences in sex, age, or calendar distribution, whereas the burden of comorbidities was higher among patients with healthcare-associated SAB—especially with regard to heart failure, malignancy, and chronic renal failure. Furthermore, no major differences were seen for prosthetic heart valve or CIED (Table 1). We found that 36.6% of patients with community-acquired SAB redeemed a prescription of antibiotics within 90 days of SAB, while the corresponding number was 33.8% for healthcare-associated SAB. Differences between subgroups of community-acquired and healthcare-associated SAB are shown in Supplementary Table 3.

Prevalence of IE

The prevalence of IE among patients with community-acquired SAB and healthcare-associated SAB was 12.1% and 6.6%, respectively (Figure 1). In the adjusted analysis, community-acquired SAB was associated with higher odds of IE, as compared with healthcare-associated SAB (OR, 2.12 [95% CI, 1.87–2.41]). No differences were seen in the prevalence of IE between sex (Figure 1). Age was identified as an effect modifier on the prevalence of IE for the 2 study groups ($P = .002$ for interaction). Across all age groups, community-acquired SAB was associated with a statistically significant higher associated odds of IE (Figure 2 and Supplementary Table 4). The highest prevalence of IE was observed among community-acquired SAB in the age group 70–79 years (Figure 2). Patients <40 years of age with community-acquired SAB were associated with the highest odds of IE as compared to healthcare-associated SAB (OR, 5.58 [95% CI, 3.06–10.17]) (Supplementary Table 4).

Characteristics of SAIE

Overall, 1162 patients with SAIE were identified; 669 (57.6%) were community acquired and 493 (42.4%) were healthcare associated. A higher burden of comorbidities was observed among healthcare-associated SAIE—especially with regard to heart failure, myocardial infarction, stroke, and COPD (Table 2). However, a higher proportion of patients with community-acquired SAIE underwent heart valve surgery during IE admission (18.4%) as compared with healthcare-associated SAIE (10.8%) (Table 2). Among patients with a previous implanted prosthetic heart valve, we identified that 22.7% underwent surgery for IE among patients with community-acquired SAIE, while the corresponding number was 23.4% for patients with healthcare-associated SAIE.

Table 2. Baseline Characteristics for Community-Acquired and Healthcare-Associated *Staphylococcus aureus* Infective Endocarditis

	Community-Acquired SAIE (n = 669)		Healthcare-Associated SAIE (n = 493)	
Characteristic	No.	(%)	No.	(%)
Male sex	416	(62.2)	331	(67.1)
Age, y, median (IQR)	71.1	(58.2–79.7)	71.7	(61.0–79.2)
Calendar period				
2010–2012	191	(28.6)	150	(30.4)
2013–2015	278	(41.6)	201	(40.8)
2016–2018	200	(29.9)	142	(28.8)
IE surgery	123	(18.4)	53	(10.8)
Length of IE hospital stay, median (IQR)	39.0	(24.0–50.0)	41.0	(26.0–54.0)
Medical history				
PCI	70	(10.5)	72	(14.6)
CABG	42	(6.3)	47	(9.5)
Prior prosthetic heart valve	88	(13.2)	64	(13.0)
CIED	104	(15.5)	86	(17.4)
Heart failure	128	(19.1)	154	(31.2)
AMI	75	(11.2)	88	(17.8)
Afib	136	(20.3)	158	(32.0)
Stroke	73	(10.9)	99	(20.1)
Diabetes mellitus	165	(24.7)	161	(32.7)
Alcohol abuse	60	(9.0)	49	(9.9)
COPD	68	(10.2)	86	(17.4)
Malignancy	23	(3.4)	22	(4.5)
Chronic renal failure	51	(7.6)	174	(35.3)
Liver disease	57	(8.5)	41	(8.3)
Medication				
Statin	231	(34.5)	203	(41.2)
β-blocker	209	(31.2)	258	(52.3)
RASi	264	(39.5)	227	(46.0)
OAC	142	(21.2)	136	(27.8)
Loop diuretics	181	(27.1)	226	(45.8)

Abbreviations: Afib, atrial fibrillation; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; IE, infective endocarditis; IQR, interquartile range; OAC, oral anticoagulant therapy; PCI, percutaneous coronary intervention; RASi, renin-angiotensin system inhibitor; SAIE, *Staphylococcus aureus* infective endocarditis.

Mortality

With up to 90 days of follow-up, mortality was 29.5% for community-acquired SAIE and 35.5% for healthcare-associated SAIE (Figure 3*A*) and with a maximum of 1 year of follow-up, the mortality was 37.3% for community-acquired versus 47.3% for healthcare-associated SAIE (Figure 3*B*). In adjusted analysis, no statistically significant difference was identified between groups with 0–40 days of follow-up (adjusted HR, 1.07 [95% CI, .83–1.37]), with healthcare-associated SAIE as reference group. With 41–365 days of follow-up, community-acquired SAIE was associated with a lower mortality as compared with healthcare-associated SAIE (adjusted HR, 0.71 [95% CI, .53–.95]). Crude mortality with 40 days of follow-up was 23.4% and 24.9% for patients with community-acquired SAIE and healthcare-associated SAIE, respectively (Supplementary Figure 1*A*). Examining 41–365 days of follow-up, 512 and 371 patients with community-acquired and healthcare-associated SAIE were available with a mortality of 18.2% and 29.9%, respectively (Supplementary Figure 1*B*).

Sensitivity Analysis

We stratified patients with community-acquired SAB into patients with a healthcare contact without an intervention (n = 2645 [47.7%]) (most frequent mode of contact was initial clinical examination in an outpatient setting) and found that the prevalence of IE was 10.1% (Supplementary Table 2). For community-acquired SAB without any healthcare contact within 30 days of SAB, the prevalence of IE was 13.8% (Supplementary Table 2). For healthcare-associated SAB, the prevalence of IE was stable and without major differences among patients with hospital admission of ER visit within 30 days of SAB (6.8%), and patients with SAB >48 hours after hospital admission (5.4%) (Supplementary Table 2). As for patients with outpatient hemodialysis within 30 days of SAB, the prevalence of IE was significantly higher (13.3%) (Supplementary Table 2). When healthcare-associated SAB was related to a hospital admission or ER visit within 60 days, no major differences were seen from the main results (Supplementary Table 5).

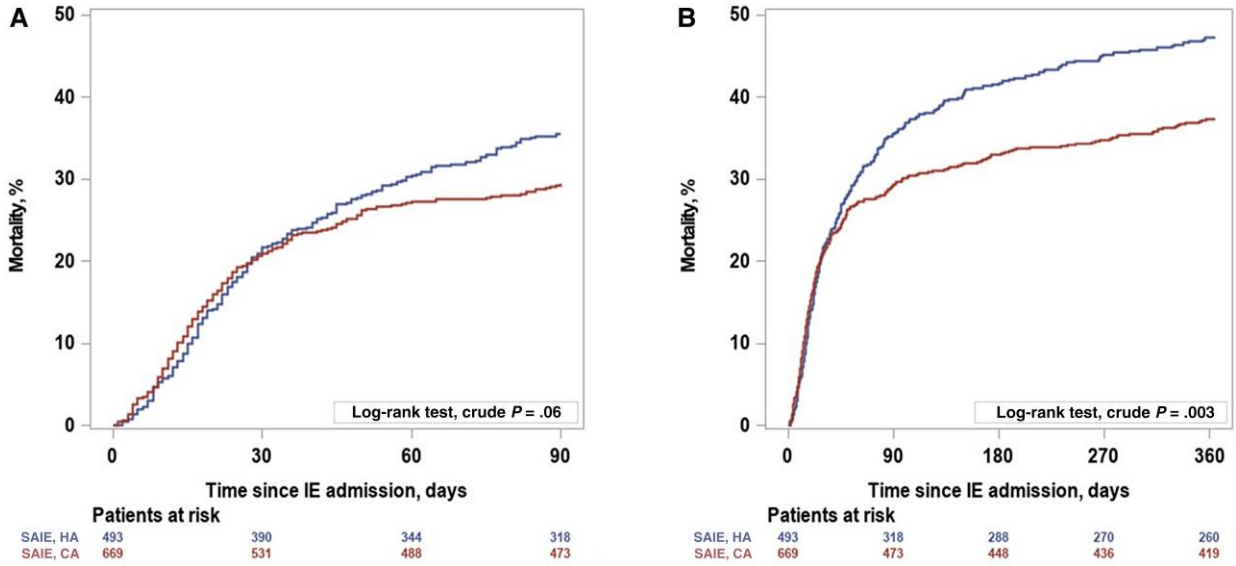


Figure 3. Ninety-day (*A*) and 1-year (*B*) mortality for patients with *Staphylococcus aureus* infective endocarditis, stratified by mode of acquisition. Abbreviations: CA, community acquired; HA, healthcare associated; SAIE, *Staphylococcus aureus* infective endocarditis.

DISCUSSION

This nationwide study of patients with first-time SAB had 2 major findings. First, the prevalence of IE was 1 in 8 patients among patients with community-acquired SAB, which was twice the prevalence of IE among patients with healthcare-associated SAB. Second, we found no statistically significant difference in 40-day mortality for patients with community-acquired SAIE as compared with healthcare-associated SAIE. Beyond 40 days, and with a maximum of 1 year of follow-up, community-acquired SAIE was associated with a lower mortality compared with healthcare-associated SAIE.

Prevalence of IE

We identified more than twice the odds of IE among patients with community-acquired SAB, as compared with healthcare-associated SAB. The risk of IE among patients with SAB has been well-studied previously, and the general prevalence of IE has ranged between 10% and 29% and as low as around 4% in the subgroup of patients with healthcare-associated SAB [5–7, 9, 12, 13, 22]. Differences between studies is likely related to the populations studied and whether systematic echocardiographic screening was conducted [5, 7]. A Danish prospective, multicenter, cohort study examined the prevalence of IE among patients with SAB where all patients, systematically, underwent transesophageal echocardiography (TEE) [5]. The authors found a prevalence of IE of 22%, which was 31% for community-acquired SAB, 14% for hospital-acquired SAB, and 17% for healthcare-associated SAB [5]. Our data provide lower estimates of the prevalence of IE than the estimates presented by Rasmussen et al [5]. The difference in prevalence of IE from our study may be explained by systematically performed TEE, and a selected population in which TEE was applicable and where patients had consented for the procedure. Community-acquired SAB has been identified to be an independent risk factor associated with IE [5–7] where diagnostic delay may have been longer in patients with community-acquired SAB as compared with healthcare-associated SAB, which may have increased the risk of IE. Furthermore, it is reasonable to think that antibiotics more often had been administered among patients with healthcare-associated SAB as compared with community-acquired SAB before SAB diagnosis, which may have reduced the burden of IE among healthcare-associated SAB as compared with community-acquired SAB. Prior studies have been of small size (the largest previous study had a sample size of around 2000 patients with SAB [9]) from selected cohorts where absolute estimates of the prevalence of IE may not be applicable for all patients with SAB [5, 6, 12]. It has previously been suggested that mode of bacteremia acquisition is a factor in the clinical risk stratification of which patients should undergo TEE [6]. Our study brings robust data to the current notion that community-acquired SAB is associated with a higher likelihood of SAIE as compared with healthcare-associated SAB, indicating that community-acquired SAB serves as a parameter that should increase the clinician's awareness of IE. Of note, patients undergoing outpatient hemodialysis close to SAB had a similar high prevalence of IE as community-acquired SAB. It is known that patients undergoing outpatient hemodialysis are at high risk of IE [23, 24], which likely is explained by frequent use of intravenous access during hemodialysis. We bring novel data showing that when bacteremia occurs among this patient group, IE is

more likely to complicate the infection as compared with other healthcare-associated SAB. Patients undergoing hemodialysis frequently have calcified heart valves leading to a vulnerable endocardium with a higher likelihood of bacterial adhesion [25].

Mortality

We found no statistically significant difference in short-term mortality among patients with community-acquired SAIE as compared with healthcare-associated SAIE. Mortality following SAIE has been studied previously and data from the International Collaboration of Endocarditis showed an in-hospital mortality of native valve SAIE of 28% and 1-year mortality of 43% [26]. Other IE-prevalence studies among patients with SAB have identified a 12-week case fatality rate of 39.4% (n = 87) [7], and a 6-month mortality of 26% (n = 14) [5]. Furthermore, a French study showed that SAIE was associated with higher in-hospital mortality as compared with other microbiological etiologies, regardless of mode of acquisition (community acquired vs healthcare associated) [27]. These findings are in line with our data with a 90-day mortality of 29.4% and 35.5% for community-acquired and healthcare-associated SAIE, respectively. We bring novel knowledge showing no difference in mortality by mode of acquisition for SAIE, which previous studies have had difficulties investigating due to low power. Furthermore, from 1-year mortality curves it was seen that mortality was similar between groups up until 40 days of follow-up, from this timepoint mortality curves diverged. These results underline, as previously described [27], that mortality was not affected by mode of bacteremia acquisition, but divergence of mortality curves with long-term follow-up may be related to the higher burden of comorbidities among patients with healthcare-associated SAIE.

Limitations

Our study suffers some limitations. First, the rate of TEE among patients with SAB was not reported. The TEE procedure code has been validated in the Danish National Patient Registry with a positive predictive value of 96% [28]; however, no study has validated the negative predictive value of TEE, and our concern from clinical practice is that nonelective TEE is poorly registered. Second, we had no data on antibiotic resistance, so we were not able to distinguish methicillin-resistant *S aureus* (MRSA) from methicillin-susceptible *S aureus*. However, in Denmark, MRSA constitutes a very small proportion of SAB (<2%) [29]. Third, several of the definitions of "healthcare associated" must be acknowledged as arbitrary; however, in sensitivity analyses, estimates remained stable. In relation to this limitation, data on procedures from private practitioners (eg, gastroscopy, colonoscopy) were not available. Fourth, the outcome of IE was based upon diagnosis codes where clinical and echocardiographic evaluations were not accessible. In a previously published validation study, we have identified the positive predictive value of the IE codes at 90%; however, the validation studies were limited by that no objective criteria were prespecified before medical records were reviewed. Fifth, the negative predictive value of these codes in the National Patient Registry has never been examined. This is of importance especially when studying a cohort of patients with SAB. Sixth, the design of this study was of observational character and unmeasured confounding factors may have influenced the estimates presented. No causal relations, only associations, can be made from the data presented, although confounding factors were minimized using multivariable adjusted models.

CONCLUSIONS

In a nationwide study of patients with SAB, we found that the prevalence of IE was twice as high in patients who acquired SAB in the community as compared to healthcare-associated SAB. We found no statistically significant difference in associated mortality with up to 40 days of follow-up for SAIE by mode of acquisition (community acquired vs healthcare associated). Beyond 40 days the associated mortality was lower among patients with community-acquired SAIE as compared with healthcare-associated SAIE.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Patient consent. In Denmark, registry-based studies that are not conducted for the sole purpose of statistics and scientific research do not require ethical approval or informed consent by law [21]. However, the study is approved by the data responsible institute (Capital Region of Denmark—approval number P-2019–348) in accordance with the General Data Protection Regulation.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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