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ORIGINAL RESEARCH

Temporal Changes, Patient Characteristics, and Mortality, According to Microbiological Cause of Infective Endocarditis: A Nationwide Study

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BACKGROUND: Monitoring of microbiological cause of infective endocarditis (IE) remains key in the understanding of IE; however, data from large, unselected cohorts are sparse. We aimed to examine temporal changes, patient characteristics, and in-hospital and long-term mortality, according to microbiological cause in patients with IE from 2010 to 2017.

METHODS AND RESULTS: Linking Danish nationwide registries, we identified all patients with first-time IE. In-hospital and long-term mortality rates were assessed according to microbiological cause and compared using multivariable adjusted logistic regression analysis and Cox proportional hazard analysis, respectively. A total of 4123 patients were included. *Staphylococcus aureus* was the most frequent cause (28.1%), followed by *Streptococcus* species (26.0%), *Enterococcus* species (15.5%), coagulase-negative staphylococci (6.2%), and "other microbiological causes" (5.3%). Blood culture–negative IE was registered in 18.9%. The proportion of blood culture–negative IE declined during the study period, whereas no significant changes were seen for any microbiological cause. Patients with *Enterococcus* species were older and more often had a prosthetic heart valve compared with other causes. For *Streptococcus* species IE, in-hospital and long-term mortality (median follow-up, 2.3 years) were 11.1% and 58.5%, respectively. Compared with *Streptococcus* species IE, the following causes were associated with a higher in-hospital mortality: *S aureus* IE (odds ratio [OR], 3.48 [95% CI, 2.74–4.42]), *Enterococcus* species IE (OR, 1.48 [95% CI, 1.11–1.97]), coagulase-negative staphylococci IE (OR, 1.79 [95% CI, 1.21–2.65]), "other microbiological cause" (OR, 1.47 [95% CI, 0.95–2.27]), and blood culture–negative IE (OR, 1.99 [95% CI, 1.52–2.61]); and the following causes were associated with higher mortality following discharge (median follow-up, 2.9 years): *S aureus* IE (hazard ratio [HR], 1.39 [95% CI, 1.19–1.62]), *Enterococcus* species IE (HR, 1.31 [95% CI, 1.11–1.54]), coagulase-negative staphylococci IE (HR, 1.07 [95% CI, 0.85–1.36]), "other microbiological cause" (HR, 1.45 [95% CI, 1.13–1.85]), and blood culture–negative IE (HR, 1.05 [95% CI, 0.89–1.25]).

CONCLUSIONS: This nationwide study showed that *S aureus* was the most frequent microbiological cause of IE, followed by *Streptococcus* species and *Enterococcus* species. Patients with *S aureus* IE had the highest in-hospital mortality.

Key Words: bloodstream infection ■ infective endocarditis ■ microbiological cause ■ nationwide study ■ population study

See Editorial by Primus and Woldman

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CLINICAL PERSPECTIVE

What Is New?

- Data from a nationwide, Danish cohort of patients with infective endocarditis found that *Staphylococcus aureus*, *Streptococcus* species, and *Enterococcus faecalis* were the most frequent microbiological causes, with no significant temporal changes.
- Patients with *S aureus* infective endocarditis were associated with the highest in-hospital mortality.

What Are the Clinical Implications?

- Continuous epidemiologic monitoring is needed.
- We need further details on specific subgroups, such as patients with prosthetic valve endocarditis, pacemaker infective endocarditis, and infective endocarditis and chronic hemodialysis.

Nonstandard Abbreviations and Acronyms

BC	blood culture
BSI	bloodstream infection
CoNS	coagulase-negative staphylococci
HACEK	*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*
ICE-PCS	International Collaboration on Endocarditis–Prospective Cohort Study
IE	infective endocarditis

Infective endocarditis (IE) remains a disease with a high mortality. Knowledge on the microbiological cause is crucial to secure optimal treatment and to perform a risk assessment.[1] Several reports have shown an increasing incidence of IE in the general population in the Western world over the past 2 decades, with estimates around 3.0 to 10.5/100 000 person years.[2–5] Knowledge on microbiological cause and the association with risk factors and patient characteristics is crucial to secure optimal treatment and risk assessment. It is therefore important to investigate temporal changes that may occur in parallel with the increasing incidence of IE.

Prosthetic heart valves, cardiac implantable devices, renal dialysis, and a variety of invasive procedures are established risk factors for the development of IE.[6–11] Such risk factors may lead to a change in the microbiological cause, which could potentially call for altered initial empiric treatment in patients with IE. Current knowledge on microbiological cause of IE is extracted from studies based on selected cohorts, poorly validated IE codes, and incomplete microbiological data.[3–5,12] Robust data from large-scale and unselected (eg, nationwide) cohorts are needed. Epidemiologic reports from different geographical regions are of value in the investigations of the global burden of IE, where differences in microbiology and antibiotic resistance exist. Data are sparse from unselected cohorts describing temporal changes and differences in patient characteristics by type of microbial causes of IE. We conducted such a study with a nationwide cohort coming from Denmark.

METHODS

Data Sources

Every Danish citizen is provided with a unique identifier, making it possible to cross-link different national administrative registries. We used the Danish National Patient Registry, The Prescription Registry, The Danish Population Registry, and the Danish Microbiology Database. The Danish National Patient Registry holds information on every hospital admission in Denmark since 1977. The registry is based on the discharge papers from hospitals in Denmark coded by physicians. The *International Classification of Diseases, Eighth Revision* (*ICD-8*), was used up until 1994; and since then, the *International Classification of Diseases, Tenth Revision* (*ICD-10*), has been used. We used the National Patient Registry to identify the study population and comorbidity that was assessed as a primary or secondary diagnosis code before index date (for codes used, please see Table S1). The National Patient Registry also holds information on surgical procedures, and heart valve surgery during IE admission was assessed (Table S1). The Prescription Registry holds information on every filled prescription from a Danish pharmacy since 1994, with data of drug type and date of collection. The Anatomical Therapeutic Chemical Classification System is used to classify drug types. Concomitant pharmacotherapy was used to assess conditions requiring medication, defined as a filled prescription 6 months before index date. The Population Registry holds information on migration status, sex, date of birth, and date of death. The Danish registries are validated, complete, and described in detail previously.[13–15]

Study Population, Aim, and Follow-Up

We identified all patients with a first-time diagnosis of IE (*ICD-10* codes I33, I38, and I398; Table S1) in the period from 2010 to 2017. We included patients with an in-hospital, primary, or secondary diagnosis code of IE with a length of hospital stay >14 days and patients hospitalized with IE who died in hospital with a length of hospital stay ≤14 days. The positive predictive value

of the IE *ICD-10* codes, using a 14-day admission criterion, has been identified at 90% in the Danish National Patient Registry.[16,17] Patients who had no blood culture (BC) drawn in a period of 30 days before IE admission and up until the date of IE discharge were excluded.

The main aim of this study was to examine temporal changes in microbiological causes of IE. Secondary aims were to examine temporal changes in patient characteristics and to identify differences in patient characteristics according to microbiological cause. Furthermore, we assessed in-hospital and long-term mortality according to microbiological cause. For analyses of mortality, patients were followed up from date of IE admission until death or December 31, 2018, whichever came first. Hence, maximum follow-up time was 9 years.

Danish Microbiology Database and Definition of Microbiological Cause

Eleven publicly funded departments of clinical microbiology provide microbiological service for all hospitals in Denmark. All microbiological data from these departments have, since 2010, been collected in a national microbiological database, Danish Microbiology Database, as described in detail previously.[18] We used BC data from Danish Microbiology Database to identify a potential microbiological cause for included patients with IE. To account for diagnostic delay, a BC of up to 30 days before IE admission was considered related to the IE episode. Figure 1 shows a flowchart of the patient selection process, where it is shown that 102 patients (2.4%) were excluded as no BC was drawn in relation to the IE diagnosis. The microbiological cause was divided into the following groups: *Staphylococcus aureus*, *Streptococcus* species, *Enterococcus* species, coagulase-negative staphylococci (CoNS), "other microbiological cause," and BC negative. A hierarchy was made so that IE-relevant bloodstream infections (BSIs) (*Enterococcus* species, HACEK [*Haemophilus* {not including *Haemophilus influenzae*}, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*], *S aureus*, and *Streptococcus* species) were identified as the microbiological cause before any other BSIs. *Abiotrophia defectiva* and *Granulicatella adiacens* were grouped under *Streptococcus* species. HACEK organisms were grouped under "other microbiological cause" because of a low number of HACEK IE cases. If CoNS was cultured, this was only considered the cause if there was no positive culture of *Enterococcus* species, HACEK, *S aureus*, or *Streptococcus* species. If the patient had no positive BC as specified above (*S aureus*, *Streptococcus* species, *Enterococcus* species, or CoNS), the cause was defined as "other microbiological cause." Table S1 shows the specific bacteria assessed. Polymicrobial BSIs during IE admission were defined as another positive BC (including yeast infection), additional to the primary pathogen cultured, within a period of 14 days before IE admission and up until IE discharge.

Statistical Analysis

For comparison of baseline characteristics, the study population was divided according to time of diagnosis: (1) 2010 to 2011, (2) 2012 to 2013, (3) 2014 to 2015, and (4) 2016 to 2017. Categorical variables were presented in counts and percentages, whereas age was presented as medians with interquartile ranges.

The microbiological cause of IE was plotted for each year in the study period (2010–2017) as a proportion of the total number of first-time IE episodes

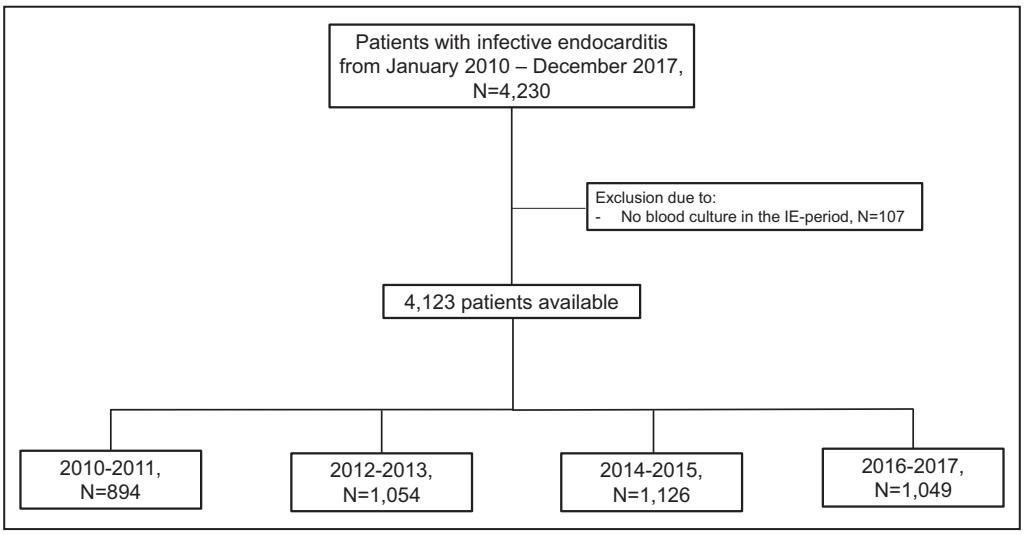

Figure 1. Patient selection.
Flowchart of the patient selection. IE indicates infective endocarditis.

per calendar year and was stratified by sex and age groups. A Cochrane-Armitage trend test was used to examine temporal changes in the microbiological causes of IE. We calculated in-hospital mortality per microbiological cause, dividing the number of deaths during IE admission by the total number of IE episodes for the specific microbiological cause. Furthermore, difference in in-hospital mortality was assessed per microbiological cause in a multivariable adjusted logistic regression analysis including the following covariates: microbiological cause (*Streptococcus* species IE as reference), sex, age, calendar year, prior prosthetic heart valve insertion, diabetes (using prescriptions on antidiabetics as a surrogate), dialysis, cardiac implantable electronic device, native aortic valve disease, and native mitral valve disease. Age and calendar years were included in the regression analysis as continuous variables. Furthermore, we examined long-term all-cause mortality following IE admission, according to microbiological cause, using Kaplan-Meier estimates (in the following, expressed as "long-term mortality"). Long-term mortality was compared by microbiological cause using multivariable Cox proportional hazard. The covariates included were the same as for the logistic regression analysis. The assumption of proportional hazards was violated when follow-up was initiated from IE admission; hence, follow-up was changed to the date of IE discharge for this analysis. $P<0.05$ was considered statistically significant. All statistical analyses were performed using the SAS statistical software, version 9.4 (SAS Institute, Inc, Cary, NC).

Sensitivity Analyses

For CoNS IE, we conducted a sensitivity analysis for the assessment of contamination. In this analysis, it was required that positive CoNS BCs were identified at 2 different time points with a minimum of 1 hour between BCs within a 5-day period. Furthermore, this was also conducted for *Bacillus* species, *Cutibacterium* species, *and Corynebacterium* species; however, because of small sample size, the analysis was not reported.

In a second sensitivity analysis, we assessed diagnostic delay up to 180 days before IE admission to identify difference in the proportion of BC-negative IE. Hence, we included BCs drawn within a period of 6 months before IE admission and up until IE discharge.

Ethical Approval

In Denmark, registry-based studies do not need approval from the ethics committee. All personal identifiers were anonymized, and subclassifications with ≤3 patients were not reported to ensure anonymization as by rules of Statistics Denmark. Categorizations with <4 observations were pooled with other groups to ensure anonymization. The study was approved by the Danish Data Protection Agency (P-2019-348). The data underlying this article were provided by Statistics Denmark by permission. The authors (L.Ø. and E.L.F.) had full access to all the data in the study and take responsibility for their integrity and the data analysis.

RESULTS

A total of 4123 patients with IE were identified in the period from 2010 to 2017 (67.6% men; median age, 71.8 years; interquartile range, 61.6–79.6 years). Table 1 shows the baseline characteristics for the patients with IE per calendar period. Overall, most patients were men, and patients in the most recent time period (2016–2017) were older and more had a prosthetic heart valve, a history of cancer, or diabetes compared with patients diagnosed in the earlier time periods. We found a reduction in the proportion of patients undergoing surgery during IE admission: 219 (24.8%) in 2010 to 2011, 226 (21.4%) in 2012 to 2013, 202 (18.0%) in 2014 to 2015, and 187 (17.6%) in 2016 to 2017.

Throughout the study period, *S aureus* was the most common cause (28.1%), followed by *Streptococcus* species (26.0%), *Enterococcus* species (15.5%), and CoNS (6.2%) (Table S2 shows the type of CoNS species). "Other microbiological causes" constituted 5.3% (Table S3 shows the specific causes constituted in this group), whereas BC-negative IE constituted 18.9% of the IEs over the study period. Table 2 shows baseline patient characteristics by type of microbiological cause. Patients with *Enterococcus* species were older, and a higher proportion of patients had a prosthetic heart valve compared with other causes. Patients with *S aureus* and CoNS IE more often had renal disease and more often underwent renal dialysis compared with patients with other causes.

We identified that 158 patients (13.6%) with *S aureus* IE underwent surgery during IE admission; this number was 276 (25.7%) for *Streptococcus* species, 128 (20.1%) for *Enterococcus* species, 63 (24.3%) for CoNS, 45 (20.8%) for "other microbiological causes," and 164 (21.1%) for BC-negative IE. We found that 9.3% (N=382) of the patients had at least 2 sets of positive BCs with different species, of which 1 was the IE-causing agent. Among these patients, 21.7% (N=106) had ≥3 BSIs (including the primary IE-causing agent) (Table S4 shows the other BSIs other than the primary cause).

Temporal Changes in Microbiological Causes

Figure 2 shows the proportion of the microbiological causes of IE by calendar year. Although there were no temporal changes for *S aureus*, *Enterococcus* species,

Table 1. Baseline Characteristics of Patients With IE by Calendar Period

Characteristic	2010–2011		2012–2013		2014–2015		2016–2017	
Total, N	894		1054		1126		1049	
Men, N (%)	605	(68.4)	739	(70.0)	728	(65.0)	713	(67.0)
Age, median (IQR), y	68.4	(57.0–77.7)	71.5	(62.0–80.1)	72.3	(63.1–79.5)	72.9	(63.4–80.1)
Medical history, N (%)								
Heart failure	210	(23.8)	247	(23.4)	259	(23.1)	263	(24.7)
Myocardial infarction	117	(13.2)	134	(12.7)	137	(12.2)	125	(11.7)
Aortic valve disease	231	(26.1)	320	(30.3)	335	(29.9)	351	(33.0)
Mitral valve disease	74	(8.4)	75	(7.1)	84	(7.5)	100	(9.4)
Prosthetic heart valve	136	(15.4)	211	(20.0)	209	(18.7)	247	(23.2)
CIED	131	(14.8)	161	(15.3)	201	(17.9)	185	(17.4)
Cerebrovascular disease	137	(15.5)	181	(17.2)	184	(16.4)	186	(17.5)
Chronic renal failure	109	(12.3)	169	(16.0)	173	(15.4)	157	(14.8)
Dialysis	56	(6.3)	66	(6.3)	85	(7.6)	62	(5.8)
COPD	108	(12.2)	151	(14.3)	121	(10.8)	152	(14.3)
Liver disease	47	(5.3)	58	(5.5)	65	(5.8)	60	(5.6)
Cancer	150	(17.0)	197	(18.7)	244	(21.8)	250	(23.5)
Prescribed medication 6 mo before IE, N (%)								
Aspirin	310	(35.1)	386	(36.6)	332	(29.6)	261	(24.5)
Anticoagulant treatment	191	(21.6)	269	(25.5)	332	(29.6)	343	(32.2)
Antidiabetics	156	(17.6)	164	(15.5)	201	(17.9)	224	(21.1)
Corticosteroids	95	(10.7)	128	(12.1)	136	(12.1)	135	(12.7)
Lipid-lowering treatment	312	(35.3)	428	(40.6)	454	(40.5)	435	(40.9)
Diuretics	428	(48.4)	493	(46.7)	503	(44.9)	486	(45.7)
β-Blockade treatment	312	(35.3)	407	(38.6)	438	(39.1)	431	(40.5)
Antibiotics	472	(53.4)	584	(55.4)	587	(52.4)	562	(52.8)
Antirheumatic drugs	192	(21.7)	197	(18.7)	188	(16.8)	184	(17.3)
Immunosuppressants other than corticosteroids	13	(1.5)	22	(2.1)	17	(1.5)	14	(1.3)

CIED indicates cardiac implantable electronic device; COPD, chronic obstructive pulmonary disorder; IE, infective endocarditis; and IQR, interquartile range.

Streptococcus species, CoNS, and for "other microbiological cause," we found a notable decline in the proportion of BC-negative IE (from 24.1% in 2010 to 18.4% in 2017; *P*=0.005 for trend).

Sex Differences in Microbiological Cause

The overall proportion of *Enterococcus* species IE was lower among women than men (10.9% for women versus 17.7% for men; *P*<0.0001), whereas the proportion of *S aureus* IE was higher among women than men (31.1% for women versus 26.6% for men; *P*=0.003), as was BC-negative IE (21.2% versus 17.8%; *P*=0.01) (Figure 3). For *Streptococcus* species (*P*=0.95), CoNS (*P*=0.68), and other (*P*=0.29), no difference according to sex was observed.

Although with small numbers, the decline in the proportion of patients with BC-negative IE during the study period was mainly driven by male patients (*P*=0.02 for men and *P*=0.16 for women for trend in temporal changes). No sex differences were seen for temporal changes for *S aureus* IE, *Streptococcus* species IE, *Enterococcus* species IE, CoNS IE, or other IE.

Age Differences in Microbiological Cause

Figure 4 shows the proportion of the various microbiological causes by age groups. In patients aged >79 years compared with patients aged <40 years, we identified a significantly lower proportion of *S aureus* IE (27.5% versus 37.7%, respectively; *P*<0.0001). A stepwise increase in the proportion of *Enterococcus* species IE was found with increasing age (21.6% in those aged >79 years versus 3.8% in those aged <40 years; *P*<0.0001). We observed no significant difference between age groups for *Streptococcus* species IE (*P*=0.90) and CoNS IE (*P*=0.08), and "other microbiological cause" (6.6% versus 3.5%, respectively; *P*=0.06). For BC-negative IE, the highest proportion was seen for those aged 60 to 69 years.

Table 2. Baseline Characteristics of Patients With IE by Microbiological Cause

Characteristic	*Staphylococcus aureus*		*Streptococcus* species		*Enterococcus* species		CoNS		Other microbiological cause		BC negative	
Total, N	1158		1073		638		259		216		779	
Men, N (%)	742	(64.1)	724	(67.5)	492	(77.1)	178	(68.7)	153	(70.8)	496	(63.7)
Age, median (IQR), y	70.9	(58.6–79.4)	71.7	(61.2–79.9)	76.1	(69.1–81.7)	70.5	(59.6–77.6)	69.7	(60.8–77.5)	70.3	(60.0–77.8)
Medical history, N (%)												
Heart failure	282	(24.4)	190	(17.7)	187	(29.3)	71	(27.4)	50	(23.1)	199	(25.5)
Myocardial infarction	178	(15.4)	90	(8.4)	91	(14.3)	35	(13.5)	27	(12.5)	92	(11.8)
Aortic valve disease	240	(20.7)	317	(29.5)	272	(42.6)	94	(36.3)	89	(41.2)	225	(28.9)
Mitral valve disease	67	(5.8)	97	(9.0)	58	(9.1)	30	(11.6)	18	(8.3)	63	(8.1)
Prosthetic heart valve	133	(11.5)	207	(19.3)	203	(31.8)	57	(22.0)	51	(23.6)	152	(19.5)
CIED	190	(16.4)	109	(10.2)	113	(17.7)	69	(26.6)	40	(18.5)	157	(20.2)
Cerebrovascular disease	197	(17.0)	143	(13.3)	137	(21.5)	47	(18.1)	39	(18.1)	125	(16.0)
Chronic renal failure	269	(23.2)	83	(7.7)	96	(15.0)	51	(19.7)	26	(12.0)	83	(10.7)
Dialysis	139	(12.0)	28	(2.6)	31	(4.9)	37	(14.3)	10	(4.6)	24	(3.1)
COPD	142	(12.3)	100	(9.3)	130	(20.4)	30	(11.6)	27	(12.5)	103	(13.2)
Liver disease	67	(5.8)	63	(5.9)	48	(7.5)	15	(5.8)	11	(5.1)	26	(3.3)
Cancer	230	(19.9)	226	(21.1)	138	(21.6)	57	(22.0)	53	(24.5)	137	(17.6)
Prescribed medication 6 mo before IE, N (%)												
Aspirin	376	(32.5)	271	(25.3)	233	(36.5)	83	(32.0)	73	(33.8)	253	(32.5)
Anticoagulant treatment	264	(22.8)	264	(24.6)	250	(39.2)	83	(32.0)	65	(30.1)	209	(26.8)
Antidiabetics	253	(21.8)	160	(14.9)	121	(19.0)	51	(19.7)	31	(14.4)	129	(16.6)
Corticosteroids	142	(12.3)	101	(9.4)	104	(16.3)	26	(10.0)	21	(9.7)	100	(12.8)
Lipid-lowering treatment	446	(38.5)	378	(35.2)	310	(48.6)	107	(41.3)	86	(39.8)	302	(38.8)
Diuretics	541	(46.7)	418	(39.0)	364	(57.1)	138	(53.3)	88	(40.7)	361	(46.3)
β-Blockade treatment	476	(41.1)	335	(31.2)	294	(46.1)	116	(44.8)	80	(37.0)	287	(36.8)
Antibiotics	549	(47.4)	493	(45.9)	447	(70.1)	137	(52.9)	127	(58.8)	452	(58.0)
Antirheumatic drugs	193	(16.7)	209	(19.5)	122	(19.1)	43	(16.6)	40	(18.5)	154	(19.8)
Immunosuppressants other than corticosteroids	21	(1.8)	7	(0.7)	11	(1.7)	5	(1.9)	<4		19	(2.4)

BC indicates blood culture; CIED, cardiac implantable electronic device; CoNS, coagulase-negative staphylococci; COPD, chronic obstructive pulmonary disorder; IE, infective endocarditis; and IQR, interquartile range.

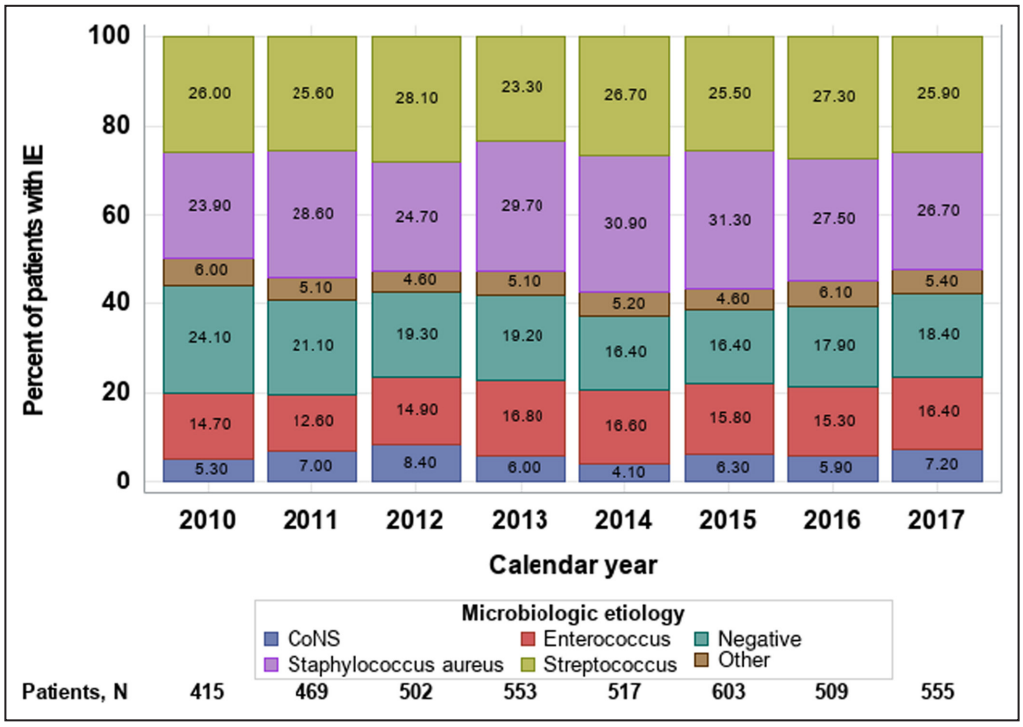

Figure 2. Temporal changes in microbiological cause in patients with infective endocarditis (IE).
CoNS indicates coagulase-negative staphylococci.

Mortality by Type of Microbiological Cause

The overall in-hospital mortality was 18.7%. The in-hospital mortality was highest for *S aureus* IE (28.2%), followed by BC-negative IE (18.6%), *Enterococcus* species IE (16.8%), CoNS IE (16.6%), "other microbiological cause" (13.9%), and streptococcal IE (11.1%). In adjusted analysis, we identified an increased associated likelihood of in-hospital mortality for *S aureus* IE (odds ratio [OR], 3.48 [95% CI, 2.74–4.42]), *Enterococcus* species IE (OR, 1.48 [95% CI, 1.11–1.97]), CoNS IE (OR, 1.79 [95% CI, 1.21–2.65]), "other microbiological cause" (OR, 1.47 [95% CI, 0.95–2.27]), and BC-negative IE (OR, 1.99 [95% CI, 1.52–2.61]) compared with *Streptococcus* species IE.

Figure 5 depicts rate of mortality with 1 year of follow-up with the following rates: *S aureus* IE, 42.2%;

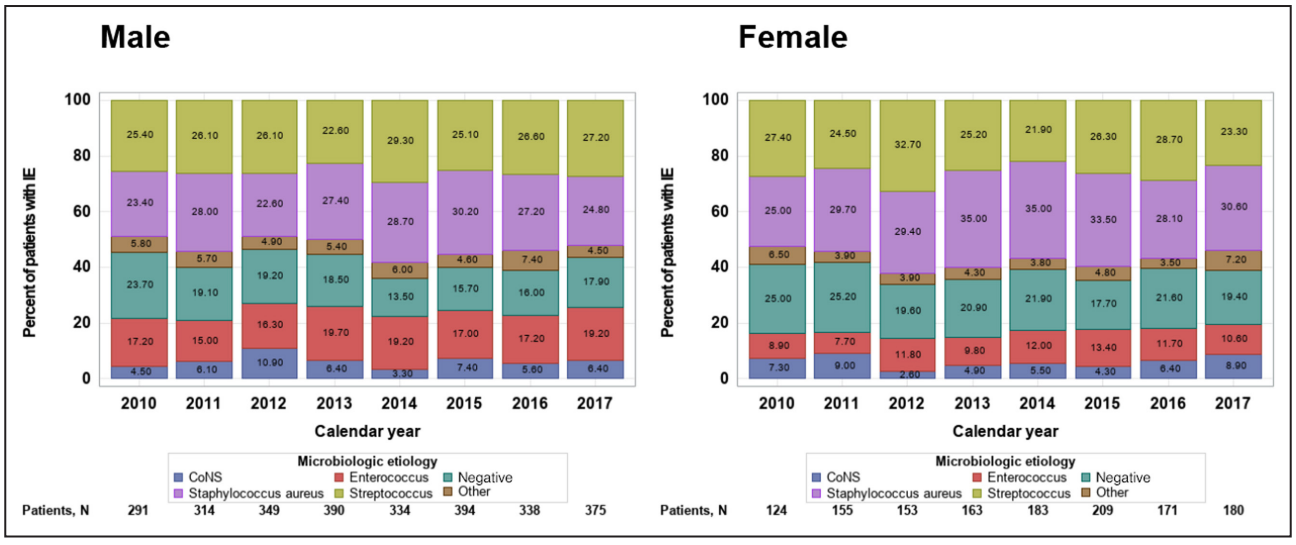

Figure 3. Temporal changes in microbiological causes in patients with infective endocarditis (IE) by sex.
Temporal changes in microbiological causes in patients with IE for men and women. CoNS indicates coagulase-negative staphylococci.

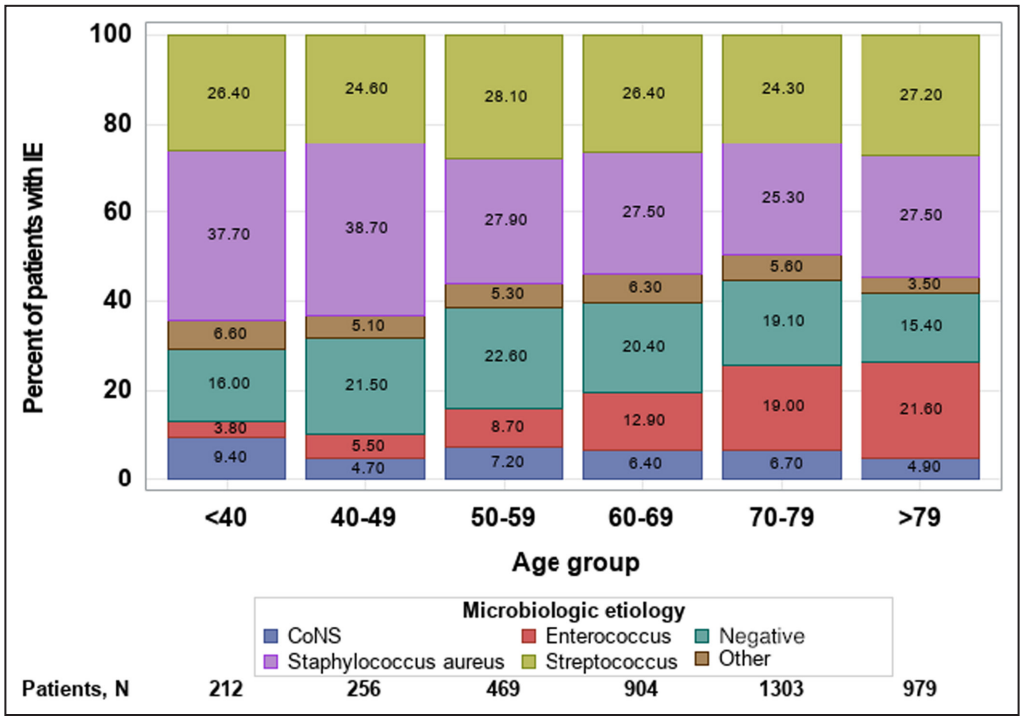

Figure 4. Microbiological causes in patients with infective endocarditis (IE) by age groups.
CoNS indicates coagulase-negative staphylococci.

Enterococcus species IE, 35.4%; *Streptococcus* species IE, 23.0%; CoNS IE, 29.0%; "other microbiological cause," 33.3%; and BC-negative IE, 31.1%. The right panel shows long-term mortality (median follow-up, 2.3 years; interquartile range, 0.36–4.6 years) with the following rates: *S aureus* IE, 70.1%; *Enterococcus* species IE, 74.4%; *Streptococcus* species IE, 58.5%; CoNS IE, 62.4%; "other microbiological cause," 60.6%; and BC-negative IE, 62.4%. We found differences in the magnitude of the mortality according to follow-up time; and for patients discharged alive (N=3353; median follow-up, 2.9 years; interquartile range, 1.3–5.1 years; Figure S1), adjusted analysis showed an increased associated mortality for patients with *S aureus* IE (hazard ratio [HR], 1.39 [95% CI, 1.19–1.62]), *Enterococcus* species IE (HR, 1.31 [95% CI, 1.11–1.54]), CoNS IE (HR, 1.07 [95% CI, 0.85–1.36]), "other microbiological cause" (HR, 1.45 [95% CI, 1.13–1.85]), and BC-negative IE (HR, 1.05 [95% CI, 0.89–1.25]) when compared with *Streptococcus* species IE.

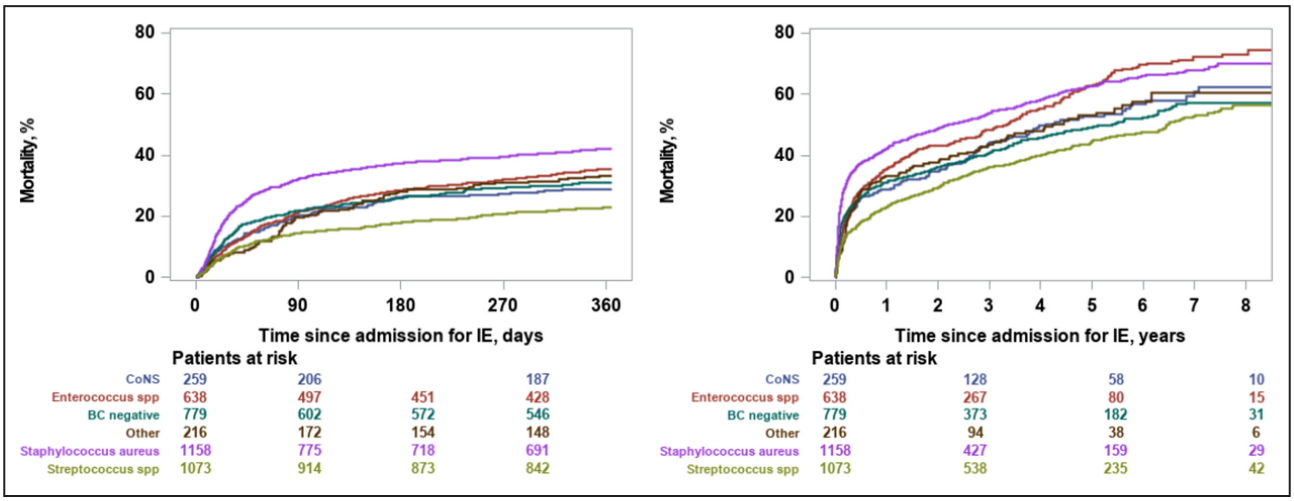

Figure 5. Mortality rate by type of microbiological cause.
The left panel shows mortality with up to 1 year of follow-up. The right panel shows mortality with long-term follow-up (median follow-up, 2.3 years). BC indicates blood culture; CoNS, coagulase-negative staphylococci; and IE, infective endocarditis.

Sensitivity Analyses

For the first sensitivity analysis, we required that positive CoNS BCs were identified at 2 different time points within a 5-day period. Using this criterion, the number of CoNS IE episodes was reduced from 259 to 130 throughout the study period. In-hospital mortality was 14.0% (N=18) for patients without multiple positive CoNS BCs within 5 days, whereas this was 19.2% (N=25) for patients with multiple BCs.

In the second sensitivity analysis, we allowed a 180-day diagnostic delay, and BCs within 180 days before IE admission were assessed to identify the microbiological cause. No major differences were seen from the main analysis with *S aureus* as the most common cause (28.5%), followed by *Streptococcus* species (26.6%), *Enterococcus* species (15.6%), and CoNS (6.5%) over the study period. Additional causes constituted 5.2%, whereas BC-negative IE constituted 17.6% of the IE episodes.

DISCUSSION

This study investigated the microbiological cause of IE in a nationwide cohort from 2010 to 2017. The study had 2 major findings. First, *S aureus* was the most frequent microbiological cause, followed by *Streptococcus* species and *Enterococcus* species, with no temporal changes in the period from 2010 to 2017. Second, *S aureus* IE was associated with the highest in-hospital mortality. Following discharge, patients with *S aureus* IE and *Enterococcus* species IE were associated with the highest mortality.

Temporal Changes in Microbiological Cause

Previous population-based studies have investigated the microbiological cause of IE in an epidemiologic perspective. A study from Spain, including patients (16 867 episodes of IE) admitted to hospitals included in the Spanish National Health Service, identified *Staphylococcus* species (28.7%) as the most frequent microbiological cause, followed by *Streptococcus* species (20.4%) and *Enterococcus* species (13.1%).[3] However, in 30% of IE cases, the microbiological cause was missing.[3] Furthermore, an Italian study including 680 patients from 17 referral centers identified *S aureus* as the most frequent microbiological cause (27.0%), followed by CoNS (21.6%), viridans group streptococci (14.8%), and *Enterococcus faecalis* (14.2%).[19] Of notice, this study included 19 patients who had no BC taken, and 25.0% of the patients had BC-negative IE.[19] In addition, a population-based study from the United States found an increase in the incidence of IE in the period from 2000 to 2011. The authors identified *S aureus* as the most frequent microbiological cause, accounting for 33% of the IE cases in 2000 and 40% in 2011, whereas *Streptococcus* species accounted for 24.8% in 2000 to 27.0% in 2011. Although the sample size was large (IE episodes=457 052), the database, which the study was based on, could not distinguish if multiple hospitalizations were from the same patient, and data on microbiological cause were not complete.[5] Furthermore, the hospital codes and microbiological cause were not validated. These findings have been confirmed from other studies from the United States.[20,21] These studies were all limited by the incomplete registration of the microbiological causes with approximately two thirds to three fourths of the IE cases having a microbiological cause registered. An older community-based study from the Olmsted County investigated the incidence of IE over 3 decades (1970–2000) and identified *Streptococcus* species as the most frequent microbiological cause (54%), followed by *Staphylococcus* species (33% with *S aureus* constituting 80%) and *Enterococcus* species (6%).[22] This study's main strength was the long-term follow-up; however, contemporary data are needed as risk factors are evolving, including more pacemaker implantations, more prosthetic heart valves, older general population, and more patients in dialysis,[23–29] which may lead to a change in the microbiological cause of IE. A study from the ICE-PCS (International Collaboration on Endocarditis–Prospective Cohort Study) also identified *S aureus* as the leading microbiological cause (31.4%) of IE in selected cohort of 1776 patients with IE.[30] However, referral bias is a limitation of the studies from the ICE-PCS cohort (including primarily voluntary tertiary centers with special interest in IE), which has to be taken into account.[31,32] In our study, it was possible to follow up a nationwide unselected patient cohort, cross-linking data from a central database of BCs, which reduced many of the drawbacks seen in previous studies.

Patient Characteristics

We identified that patients with *S aureus* IE and CoNS IE more often had renal disease and more often underwent dialysis before IE admission compared with patients with other microbiological causes. Furthermore, patients with *Enterococcus* species IE were older, were more often men, and more often had a prosthetic heart valve (one third of patients) compared with patients with IE with another microbiological cause. Furthermore, we identified that *Enterococcus* species rarely were the microbiological cause in patients with IE who were aged <50 years, but the proportion of *Enterococcus* species IE was increasing with increasing age, and more than one fifth of patients aged >79 years had *Enterococcus* species as the microbiological cause. An explanation to this difference may be

that an older population has more gastrointestinal and urogenital disease, which often is the port of entry for *Enterococcus* species.[33]

Mortality

A study from the ICE-PCS investigated patients with *Enterococcus* species IE (N=500) and found a 1-year mortality of 28.9%.[34] Our study is in line with these findings as we found a mortality at 35.4% at 1 year in patients with *Enterococcus* species IE. *S aureus* IE has been associated with a poor prognosis in several studies, and our study supports this.[3,35] We found that *S aureus* IE resulted in an in-hospital mortality of 28.2%, which was the highest among all microbiological causes. Differences within patient characteristics may explain differences in the related mortality; however, the virulence of *S aureus* IE seems closely related to an increased risk of systemic emboli, increasing morbidity and mortality.[35,36]

LIMITATIONS

Our study has some limitations. First, except from microbiological diagnostics, all of our data were derived from hospital coding, and clinical characteristics, such as symptoms, echocardiography findings, and laboratory findings other than microbiological cause, were not available. Misclassification is always a concern in registry-based studies; however, the IE codes in the Danish National Patient Registry have recently been validated with a positive predictive value of 90%.[17] Contamination of cultures may also have affected our results, especially on CoNS. Furthermore, we did not have direct patient-level information on antibiotic susceptibility or how this changed on a national level over time. The data for our study did not include valve cultures or 16S/18S polymerase chain reaction test results, and this may have affected the proportion of culture-negative cases; however, we do not expect this to influence our results by much since about 25% of patients in Denmark underwent surgery in the study period and 21.1% of patients with negative BCs underwent surgery.

In conclusion, using data from a nationwide, unselected cohort of patients with IE, we identified that *S aureus* was the most frequent cause of IE, followed by *Streptococcus* species, accounting for about 25% of IE cases each. A decline in the proportion of BC-negative IE was seen throughout the study period, and no temporal changes were seen for other causes. We identified differences in patient characteristics by type of microbiological cause, which may help increase clinical awareness in certain subgroups. *S aureus* IE was associated with the highest in-hospital mortality. Following discharge after IE, patients with *S aureus* IE and *Enterococcus* species IE were associated with the highest mortality.

ARTICLE INFORMATION

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Supplemental Material

Tables S1-S4
Figure S1

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Supplemental Material

Table S1. Codes and bacteria.

Category	Codes and bacteria
Microorganism	
Coagulase-negative staphylococci	*S. capitis, S. caprae, S. epidermidis, S. haemolyticus, S. hominis, S. lugdunensis, S. pettenkoferi, S. warneri.* Coagulase-negative staphylococci not specified further.
Enterococcus spp.	*E. avium, E. casseliflavus, E. cecorum, E. durans, E. faecalis, E. faecium, E. gallinarum, E. raffinosus.*
Staphylococcus aureus	
Streptococcus spp.	*S. alactolyticus, S. anginosus, S. canis, S. constellatus, S. cristatus, S. dysgalactiae, S. equinis, S. gallolyticus, S. gordonii, S. infantarius, S. intermedius, S. lutetiensis, S. massiliensis, S. mitis, S. mutans, S. oralis, S. parasanguinis, S. pneumoniae, S. salivarius, S. sanguinis, S. suis, S. thermophilus, S. vestibularis.* Haemolytic and non-haemolytic not specified further. *Abiotrophia defectiva* and *Granulicatella adiacens* was also classified as *Streptococcus spp.*
Outcome	
Infective endocarditis	ICD-10: DI33, DI38, DI398; ICD8: 421
Comorbidity	
Cancer	ICD10: DC00-DC97; ICD8: 140-209
Renal disease	ICD10: DN03-04, DN17-19, DR34, DI12-13; ICD8: 582-586, 588.
Renal dialysis	ICD-10: Z992. BJFD2
Chronic obstructive lung disease	ICD10: DJ42, DJ44; ICD8: 490-492
Heart failure	ICD10: DI42, DI50, DI110, DJ819; ICD8: 4270, 4271.
Cerebrovascular disease	ICD10: DI60-DI69; ICD8: 430-438.
Ischemic heart disease	ICD10: DI20-25; ICD8: 410-414.
Gastritis	ICD-10: DK25-DK27, DK29, DK22.1, ICD-8: 531-534.
Dementia	ICD-10: DG30, DG31.1-31.2, ICD-8: 290
Prosthetic heart valve	KFKD, KFMD, KFGE, KFJF
Pacemaker	BFCA0 and BFCB0
Atrial flutter/fibrillation	ICD-10: DI48; ICD8: 4274.
Aortic valve disease	ICD-10: DI35; ICD8: 395, 396
Mitral valve disease	ICD-10: DI34 ICD8: 394, 396
Rheumatic disease	ICD-10: M05-06, M32-34, M353; ICD8: 7100, 7101, 7104, 7140, 7141, 7142, 7148, 725.
Pharmacotherapy	
Aspirin	ATC code: B01AC06, N02BA01
Anticoagulant therapy	ATC code: B01AA, B01AE07, B01AF01, B01AF02
Antidiabetics	ATC code: A10
Corticosteroid medication	ATC code: H02
Lipid lowering medication	ATC code: C10
Antirheumatic drugs	ATC code: M01
Immunosuppressants	ATC code: L04
Antibiotics	ATC code: J01

ICD: international classification of diseases, ATC: Anatomical Therapeutical Classification System, RAS: renin angiotensin system.

Table S2. Species for CoNS-IE.

Etiology	**N (%)**
Staphylococcus epidermidis	145 (56.0)
Staphylococcus species not specified in further detail	47 (18.1)
Staphylococcus lugdunensis	26 (10.0)
Staphylococcus hominis	18 (6.9)
Staphylococcus capitis	16 (6.2)
Staphylococcus haemolyticus	7 (2.7)
Total	259 (100.0)

CoNS: coagulase-negative staphylococci, IE: infective endocarditis

Table S3. Type of etiology for the category termed 'other microbiological etiology'.

Etiology	**N, (%)**
Etiologies with low number (<4)*	62 (28.7)
HACEK	36 (16.7)
Escherichia coli	31 (14.4)
Candida spp	18 (8.3)
Cutibacterium acnes	15 (6.9)
Aerococcus urinae	14 (6.5)
Klebsiella pneumoniae	11 (5.1)
Serratia marcescens	7 (3.2)
Enterobacter cloacae	6 (2.8)
Pseudomonas aeruginosa	6 (2.8)
Unknown	5 (2.3)
Klebsiella oxytoca	5 (2.3)
Total	216 (100.0)

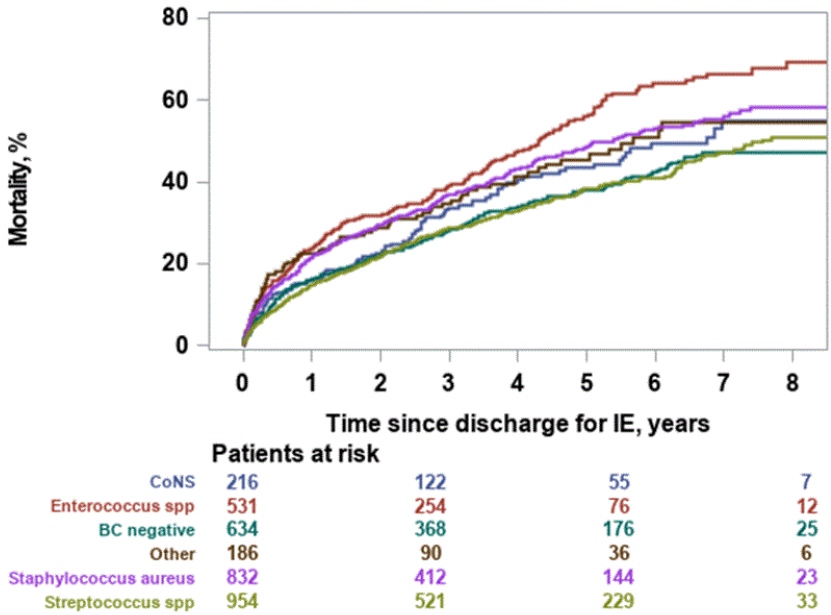
*By rules of anonymity it is not allowed to specify in more detail.
HACEK: *Haemophilus spp, Aggregatibacter spp, Cardiobacterium spp, Eikenella spp, Kingella spp.*

Table S4. Type of additional BSI for polymicrobial infection.

Microorganism	**N, (%)**
CoNS	137 (28.1)
Etiologies with low number (<4)*	83 (17.0)
Candida spp.	47 (9.6)
Enterococcus faecium	45 (9.2)
Escherichia coli	31 (6.4)
Enterobacter cloacae	22 (4.5)
Klebsiella pneumoniae	17 (3.5)
Streptococcus spp	16 (3.3)
Serratia marcescens	14 (2.9)
Enterococcus faecalis	13 (2.7)
Pseudomonas aeruginosa	13 (2.7)
Staphylococcus aureus	9 (1.8)
Klebsiella oxytoca	8 (1.6)
Bacillus spp	6 (1.2)
Citrobacter freundii	6 (1.2)
Corynebacterium spp	6 (1.2)
Acinetobacter spp	5 (1.0)
Not classified	5 (1.0)
Cutibacterium acnes	5 (1.0)
Total	488 (100.0)

CoNS: coagulase-negative staphylococci, BSI: blood stream infection.
*By rules of anonymity it is not allowed to specify in more detail.
One patient could have had more than one additional BSI.

Figure S1. Mortality rate by type of microbiological etiology from IE discharge.



Mortality by type of microbiological etiology from IE discharge. IE: infective endocarditis, CoNS: coagulase-negative staphylococci.