Incidence, clinical characteristics and 30-day mortality of enterococcal bacteraemia in Denmark 2006–2009: a population-based cohort study

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Abstract

Enterococci currently account for approximately 10% of all bacteraemias, reflecting remarkable changes in their epidemiology. However, population-based data of enterococcal bacteraemia are scarce. A population-based cohort study comprised all patients with a first episode of *Enterococcus faecalis* or *Enterococcus faecium* bacteraemia in two Danish regions during 2006–2009. We used data collected prospectively during clinical microbiological counselling and hospital registry data. We determined the incidence of mono- and polymicrobial bacteraemia and assessed clinical and microbiological characteristics as predictors of 30-day mortality in monomicrobial bacteraemia by logistic regression analysis. We identified 1145 bacteraemic patients, 700 (61%) of whom had monomicrobial bacteraemia. The incidence was 19.6/100 000 person-years (13.0/100 000 person-years for *E. faecalis* and 6.6/100 000 person-years for *E. faecium*). The majority of bacteraemias were hospital-acquired (*E. faecalis*, 45.7%; *E. faecium*, 85.2%). Urinary tract and intra-abdominal infections were the predominant foci for the two species, respectively. Infective endocarditis (IE) accounted for 25% of patients with community-acquired *E. faecalis* bacteraemia. Thirty-day mortality was 21.4% in patients with *E. faecalis* and 34.6% in patients with *E. faecium*. Predictors of 30-day mortality included age, co-morbidity and hospital-acquired bacteraemia. In addition, intra-abdominal infection, unknown focus and high-level gentamicin resistance were predictors of mortality in *E. faecalis* patients. *E. faecium* was associated with increased risk of mortality compared with *E. faecalis*. The study emphasizes the importance of enterococci both in terms of incidence and prognosis. The frequency of IE in patients with *E. faecalis* bacteraemia emphasizes the importance of echocardiography, especially in community-acquired cases.

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Introduction

Over the past two decades *Enterococcus faecalis* and *Enterococcus faecium* have become increasingly important pathogens worldwide, especially due to hospital-acquired infections. *Enterococcus* spp. are rated as the third leading cause of hospital-acquired bacteraemia in the United States and account for 9.4% of the bacteraemias [1]. Consistent with this, an Italian multicentre study reported enterococci in 11.4% of all bacteraemias during a 1-year survey [2]. Similarly, Danish surveillance data demonstrated rising incidences of *E. faecalis* and *E. faecium* bacteraemia, with increases from 2002 to 2009 of 51% and 201%, respectively [3,4]. Enterococci are generically resistant to all cephalosporins and clinical use of carbapenems and fluoroquinolones is not recommended as first-line treatment. In addition, acquired resistance to penicillins, aminoglycosides and glycopeptides has increased

(www.ecdc.europa.eu/en/activities/surveillance/EARS-Net). The 30-day mortality of enterococcal bacteraemia is above 25% for vancomycin-susceptible strains [5–7] and above 45% for resistant strains [5,8].

Prior studies of enterococcal bacteraemia have predominantly focused on the association between antimicrobial resistance and outcome [8–12]. Few studies have distinguished between hospital-acquired, community-acquired and healthcare-associated bacteraemia despite the fact that risk factors for bacteraemia (intravascular devices and invasive medical procedures) and risk of acquiring an infection with resistant enterococci are different for patients with these modes of acquisition [4].

The current changes in the epidemiology of enterococcal infections have created a need for studies of enterococcal bacteraemia that include information of clinical relevance. The aim of this Danish population-based cohort study was to determine the incidence of enterococcal bacteraemia during the period 2006–2009. Further, we gave special attention to monomicrobial bacteraemia to avoid the impact of other pathogens on mortality and determined (i) clinical characteristics of patients with hospital-acquired, community-acquired and healthcare-associated bacteraemia and (ii) predictors of 30-day mortality according to species.

Methods

Setting

We conducted this population-based cohort study in the North Denmark Region and the Capital Region of Denmark between 2006 and 2009 (approximately 1 750 000 inhabitants; 1 450 000 were adults ($\geq$ 16 years); this equals ~35% of the Danish population). Patients admitted to a tertiary national referral centre within the Capital Region were not included in the study. The centre only had a limited local patient uptake. The Danish National Health service provides tax-supported healthcare for all residents, including free access to primary care and public hospitals. Therefore, all acutely ill patients were admitted to a public hospital in their region of residence. All Danish residents have a unique personal identification number that permits individual-level linkage between health administrative registries [13].

Identification of patients

Clinical microbiological service. In the Capital Region the service to hospitals was provided by the Departments of Clinical Microbiology at Herlev and Hvidovre Hospitals and in the North Denmark Region by the Department of Clinical Microbiology at Aalborg Hospital. The blood culture systems were either BACTEC (BD, Franklin Lakes, NJ, USA) (Herlev) or BacT/Alert (bioMèrieux, Marcy l'Etoil, France) (Hvidovre and Aalborg). Clinicians were notified about positive blood cultures by a physician from the Department of Clinical Microbiology. At this contact antimicrobial therapy was discussed taking consideration of the Gram strain report. The second notification occurred as soon as the identity of the pathogen and the susceptibility pattern became available. The physicians making the calls recorded pertinent information (see below) in an electronic form integrated with the laboratory information system (ADBakt, Ramsta, Sweden).

Bacteraemia research database. We identified all adult patients ($\geq$ 16 years) with a first episode of bacteraemia with *E. faecalis* or *E. faecium* in a bacteraemia research database holding all episodes of bacteraemia in the catchment population since 2006. Besides demographic and microbiological data, including antibiogram, the database includes information on the focus of the bacteraemia, medical speciality, origin of bacteraemia (community-acquired, hospital-acquired or healthcare-associated) and empirical antimicrobial therapy.

Microbiology. Enterococcus faecalis and *Enterococcus faecium* were identified using conventional methods [14] or VITEK II (bioMérieux). Minimum inhibitory concentrations (MICs) were determined for penicillin, ampicillin, vancomycin and gentamicin by use of either E-test or VITEK II. MIC $\geq$ 256 mg/L was recorded as high-level gentamicin resistant (HLGR). MIC breakpoints refer to the standards according to EUCAST (www.eucast.org).

Origin

The bacteraemic episode was considered hospital-acquired when diagnosed $\geq$ 48 h after hospital admission [15]. A bacteraemia diagnosed within 48 h of hospital admission was considered to be community-acquired [15]. Patients with community-acquired bacteraemia and regular hospital visits (e.g. for haemodialysis or chemotherapy) or a hospital stay during the 30 days prior to admission were considered as having healthcare-associated bacteraemia [16,17].

Focus of infection

The probable focus of infection was confirmed as follows: (i) microbiologically confirmed if an isolate indistinguishable from the blood isolate was cultured from a clinically plausible site; (ii) clinically confirmed if there were signs and symptoms of a compatible localized infection (infective endocarditis (IE), definite or possible, was defined in accordance with the modified Duke criteria [18]); or (iii) unknown in cases not

fulfilling the two categories above. Cases with two or more probable foci were classified as having an unknown focus.

Empirical antimicrobial therapy

We defined empirical antimicrobial therapy as the therapy given not later than 24 h after the first positive blood culture was drawn. Treatment with benzyl-penicillin, ampicillin, piperacillin/tazobactam, vancomycin or linezolid was considered appropriate if the enterococcal isolate was susceptible *in vitro*, the dosage was adequate according to national recommendations and the patient received intravenous treatment.

Co-morbidity

Information on co-morbidity was obtained from the Danish National Patient Registry (DNPR). The DNPR contains data on all somatic inpatient contacts since 1977 and all somatic outpatient and emergency room contacts since 1995, including discharge diagnoses coded according to the International Classification of Diseases system. For each patient we used all records in the DNPR prior to the current admission to calculate the Charlson co-morbidity index (CCI) [19]. In this prognostic index, 19 major disease categories (e.g. malignancy, cardiovascular diseases and diabetes mellitus) are assigned a score, with higher scores given to more severe diseases. We defined three co-morbidity levels: low (CCI = 0), medium (CCI = 1–2) and high (CCI $\geq$ 3).

Mortality

We obtained data on mortality from the Danish Civil Registration System, in which vital status, including all deaths and emigrations, are registered and updated daily [13]. Follow-up started on the day the first positive blood culture was drawn and lasted for 30 days (or until death).

Statistical analysis

The incidence of bacteraemia was calculated by dividing the number of incident cases with the catchment population on 1 July of that year in the Capital Region (the population who belonged to the local uptake area of the National referral centre were excluded) and in the North Denmark Region of Denmark (Statistics Denmark, www.statbank.dk).

We used Student's *t*-test and Fisher's exact test to compare means and categorical variables, respectively, and a logistic regression model to examine predictors of 30-day mortality and compute odds ratios (ORs) with 95% confidence intervals (95% CIs). We adjusted for *a priori* known predictors of mortality in patients with enterococcal bacteraemia (age, origin of bacteraemia, co-morbidity level, focus of infection and antimicrobial therapy) in the exploratory multivariable model.

All statistical analyses were performed with Stata®, vs. 11.2 (StataCorp, College Station, TX, USA).

Results

Incidence

During the 4-year study period, 1145 patients were identified with first-time enterococcal bacteraemia; 700 (61%) had monomicrobial bacteraemia. The overall incidence of enterococcal bacteraemia was 19.6/100 000 person-years (*E. faecalis* 13.0/100 000 person-years and *E. faecium* 6.6/100 000 person-years) (Fig. 1). The annual incidence of *E. faecalis* and *E. faecium* showed a rising trend, with increases of 33% and 61%, respectively.

Descriptive epidemiology of monomicrobial bacteraemia

During the study period, 457 monomicrobial bacteraemias (65%) were caused by *E. faecalis* and 243 (35%) by *E. faecium* (Table 1). Most patients with *E. faecalis* bacteraemia were admitted to a medical ward (66%) and 30.9% of the patients with *E. faecium* were admitted to the intensive care unit. The majority of enterococcal bacteraemias were hospital-acquired (*E. faecalis* 45.7% and *E. faecium* 85.2%) and 85% of the patients had coexisting chronic diseases (CCI $\geq$ 1). Few patients received appropriate antimicrobial therapy within the first day (*E. faecalis*, 17.7%; *E. faecium*, 7.4%).

Urinary tract infection was the most common focus of *E. faecalis* bacteraemia in all three modes of acquisition (34.6–41.7%) (Table 2). IE was the focus of infection in 13.3% of patients with *E. faecalis* bacteraemia and the prevalence was particularly high in the group with community-acquired bacteraemia (25%). The most frequent focus of *E. faecium* was intra-abdominal infection, with a high prevalence in all three modes of acquisition (36.2–49.9%). The focus of infection was unknown in 30% and 40% of the patients with *E. faecalis* and *E. faecium*, respectively.

Ampicillin resistance in *E. faecium* was frequent (87.7%) (Table 1). Also, HLGR strains were frequently present, being more frequent in *E. faecium* (64.4%) than in *E. faecalis* (38.2%). Conversely, resistance to vancomycin (<2%) was rare. The frequency of resistant strains (HLGR enterococci and ampicillin-resistant *E. faecium*) was much higher in hospital-acquired and healthcare-associated bacteraemia compared with community-acquired bacteraemia (Table 2).

Infective endocarditis

Sixty-one patients with monomicrobial *E. faecalis* bacteraemia were diagnosed with IE. The number of cases with IE doubled from 11 in 2006 (0.8/100 000 person-years) to 22 in 2009

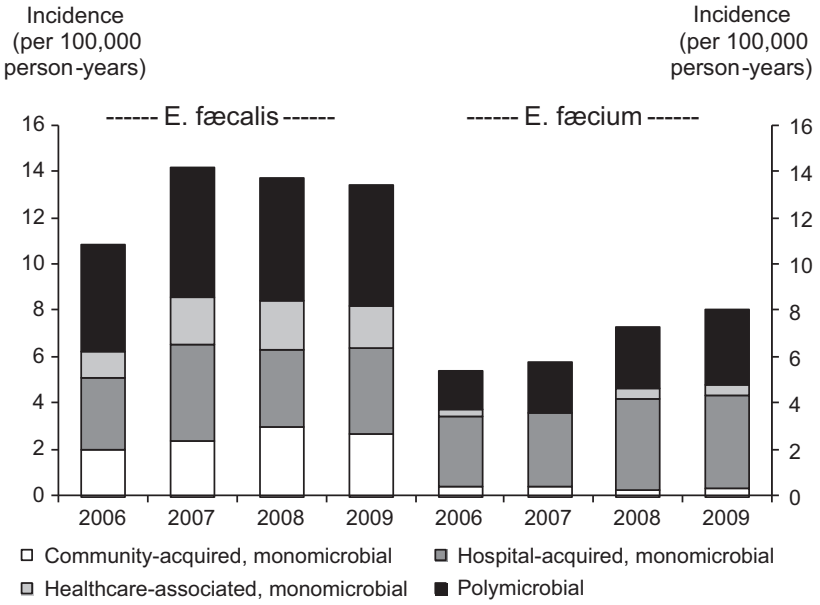

FIG. 1. Incidence of mono- and polymicrobial *E. faecalis* and *E. faecium* bacteraemia 2006–2009.

TABLE 1. Demographic, clinical and microbiological characteristics of monomicrobial *E. faecalis* and *E. faecium* bacteraemia patients

Variable	*E. faecalis n* (%)	*E. faecium n* (%)	p-value
Total	457 (100)	243 (100)	–
Age median [IQR]/mean [SD][a]	75 [64–82]/71.8 [14]	69 [59–76]/67.2 [14]	<0.001
Male	324 (70.9)	140 (57.6)	<0.001
Speciality			
Medicine	304 (66.5)	104 (42.8)	<0.001
Surgery	117 (25.6)	64 (26.3)	0.860
Intensive care unit	36 (7.9)	75 (30.9)	<0.001
Origin of bacteraemia			
Community acquired	144 (31.5)	18 (7.4)	<0.001
Hospital acquired	209 (45.7)	207 (85.2)	<0.001
Healthcare associated	104 (22.8)	18 (7.4)	<0.001
Charlson co-morbidity index			
Index low (0)	67 (14.7)	39 (16.0)	0.660
Index medium (1–2)	161 (35.2)	83 (34.2)	0.803
Index high (≥3)	229 (50.1)	121 (49.8)	1.000
Empirical antimicrobial therapy			
Appropriate therapy	81 (17.7)	18 (7.4)	<0.001
Focus of infection			
Urinary tract	171 (37.4)	16 (6.6)	<0.001
Intra-abdominal	56 (12.3)	93 (38.3)	<0.001
IV-catheter	15 (3.3)	17 (7.0)	0.035
Infective endocarditis	61 (13.3)	2 (0.8)	<0.001
Respiratory tract	4 (0.9)	14 (5.8)	<0.001
Miscellaneous	13 (2.8)	4 (1.6)	0.440
Unknown	137 (30.0)	97 (39.9)	0.009
Antimicrobial resistance			
Ampicillin resistant	6 (1.3)[b]	213 (87.7)	<0.001
Vancomycin resistant	7 (1.5)[c]	3 (1.3)[d]	1.000
HLGR[e]	174 (38.2)[b]	154 (64.4)[f]	<0.001

[a]data are *n* (%), except for age, which is years: median [interquartile range, IQR] and mean [standard deviation, SD].
[b]*n* = 455.
[c]*n* = 453.
[d]*n* = 240.
[e]High level gentamicin resistance.
[f]*n* = 239.

(1.4/100 000 person-years). Men were over-represented (78.7%) and most infections were community acquired (59%). Age (median age 75 years, IQR 69–80 years) and distribution of co-morbidity were similar to non-IE *E. faecalis* patients. Nonetheless, we noticed that 29.5% had no coexisting chronic disease (CCI = 0) prior to the acquisition of IE. All *E. faecalis* strains that caused IE were susceptible to ampicillin and vancomycin. Eighteen per cent were HLGR, similar to the frequency in community-acquired bacteraemia (data not shown).

Mortality

The 30-day mortality was 21.4% among patients with monomicrobial *E. faecalis* bacteraemia (Table 3). Increasing age, co-morbidity, hospital acquisition, intra-abdominal infection, unknown focus and HLGR strains were associated with increased risk of mortality. Patients with IE had low 30-day mortality (8.2%) but this was not significantly different from patients with urinary tract infections. Three-month and 1-year mortality for *E. faecalis* IE were 16.4% and 27.9%, respectively (data not shown).

The 30-day mortality among patients with monomicrobial *E. faecium* bacteraemia was 34.6%. A burden of co-morbidity, increasing age and hospital acquisition appeared to predict mortality in patients with *E. faecium* bacteraemia (Table 4).

Further, we found increased risk of mortality in patients with monomicrobial *E. faecium* bacteraemia compared with patients with monomicrobial *E. faecalis* bacteraemia (OR 1.54 (1.02–2.32)) (Table S1).

Discussion

To our knowledge, this is the first population-based study of enterococcal bacteraemia. We found a rising trend in incidence and an overall incidence of approximately 20/100 000 person-years. In accordance with other studies the

TABLE 2. Demographic, clinical and microbiological characteristics distributed according to species and origin of monomicrobial enterococcal bacteraemia

Variable	*E. faecalis*			*E. faecium*		
	Community acquired *n* (%)	Hospital acquired *n* (%)	Healthcare associated *n* (%)	Community acquired *n* (%)	Hospital acquired *n* (%)	Healthcare associated *n* (%)
Total	144 (100)	209 (100)	104 (100)	18 (100)	207 (100)	18 (100)
Age, median [IQR][a]	78 [70–84]	73 [64–80]	71 [60–80]	76 [67–81]	68 [59–75]	77 [65–84]
Male	100 (69.4)	145 (69.4)	79 (76.0)	10 (55.6)	116 (56.0)	14 (77.8)
Speciality						
Medicine	122 (84.7)[1]	105 (50.2)[2]	77 (74.0)	13 (72.2)[1]	78 (37.7)[2]	13 (72.2)
Surgery	17 (11.8)[1]	74 (35.4)	26 (25.0)[3]	4 (22.2)	57 (27.5)	3 (16.7)
Intensive care unit	5 (3.5)[1]	30 (14.4)[2]	1 (1.0)	1 (5.6)[1]	72 (34.8)	2 (11.1)
Charlson co-morbidity index						
Index low (0)	29 (20.1)	28 (13.4)	10 (9.6)[3]	7 (38.9)[1]	30 (14.5)	2 (11.1)
Index medium (1–2)	51 (35.4)	73 (34.9)	37 (35.6)	4 (22.2)	71 (34.3)	8 (44.4)
Index high ($\geq$ 3)	64 (44.4)	108 (51.7)	57 (54.8)	7 (38.9)	106 (51.2)	8 (44.4)
Empirical antimicrobial therapy						
Appropriate therapy	27 (18.8)	34 (16.3)	20 (19.2)	4 (22.2)	14 (6.8)	0 (0.0)
Focus of infection						
Urinary tract	60 (41.7)	75 (35.9)	36 (34.6)	2 (11.1)	13 (6.3)	1 (5.6)
Intra-abdominal	9 (6.2)[1]	30 (14.3)	17 (16.3)[3]	9 (49.9)	75 (36.2)	9 (49.9)
IV-catheter	0 (0.0)[1]	11 (5.3)	4 (3.9)[3]	0 (0.0)	17 (8.2)	0 (0.0)
Infective endocarditis	36 (25.0)[1]	14 (6.7)	11 (10.6)[3]	0 (0.0)	1 (0.5)	1 (5.6)
Respiratory tract	1 (0.7)	3 (1.4)	0 (0.0)	1 (5.6)	13 (6.3)	0 (0.0)
Miscellaneous	0 (0.0)	9 (4.3)	4 (3.8)	1 (5.6)	2 (1.0)	1 (5.6)
Unknown	38 (26.4)	67 (32.1)	32 (30.8)	5 (27.8)	86 (41.5)	6 (33.3)
Antimicrobial resistance						
Ampicillin resistant	0 (0.0)	5 (2.4)	1 (1.0)[b]	7 (38.9)[1]	191 (92.3)	15 (83.3)[3]
Vancomycin resistant	1 (0.7)[c]	4 (1.9)[d]	2 (1.9)[b]	0 (0.0)	3 (1.5)[e]	0 (0.0)
HLGR[f]	28 (19.6)[g,1]	94 (45.0)	52 (50.5)[b, 3]	2 (11.8)[h,1]	145 (71.1)[i,2]	7 (38.9)

[a]Data are *n* (%), except for age, which is years: median [interquartile range, IQR].
[b]*n* = 103.
[c]*n* = 142.
[d]*n* = 143.
[e]*n* = 206.
[f]High level gentamicin resistance.
[g]*n* = 208.
[h]*n* = 17.
[i]*n* = 204.
[1]p <0.05 community-acquired vs. hospital-acquired bacteraemia.
[2]p <0.05 hospital-acquired vs. healthcare-associated bacteraemia.
[3]p <0.05 healthcare-associated vs. community-acquired bacteraemia.

majority of enterococcal bacteraemias were hospital-acquired, associated with a considerable burden of co-morbidity and high mortality [6,7,9,12]. We demonstrated a high frequency of resistant enterococcal strains in hospitalized patients, which indicates that resistant strains could be hospital-associated clones. Spread of ampicillin-resistant *E. faecium* strains has previously been confirmed in Danish hospitals [4].

Mortality was higher in patients with advanced age, co-morbidity and hospital-acquired bacteraemia. In addition, an unknown focus of infection was a predictor of mortality in patients with *E. faecalis* bacteraemia. Though it should be noted that this category also included patients with two or more likely foci, it underlines the importance of identifying the underlying focus (e.g. by imaging techniques). Further, we found that *E. faecium* bacteraemia was associated with high mortality compared with *E. faecalis* bacteraemia, which is in accordance with two previous studies [6,20]. Virulence differences between species may be an explanation. A better efficacy of β-lactam antibiotics administered to most patients with *E. faecalis* bacteraemia compared with vancomycin administered to most patients with *E. faecium* bacteraemia may be another explanation.

The frequency of IE was higher than anticipated in *E. faecalis* bacteraemia patients (13.3%) and even higher among patients with a community-acquired infection (25%). As echocardiography is not routinely used in all cases of enterococcal bacteraemia, the frequency of IE may be even higher. This finding is of clinical importance: in this high-risk group echocardiography should be considered in all patients to optimize antimicrobial therapy, prevent complications and undertake timely valve replacement. Fernandez Guerrero *et al.* [21] reviewed studies examining *E. faecalis* bacteraemia and assessed the association between the origin and focus of the bacteraemia. IE was found in 60 of 1036 patients (5.7%, range 2.4–14%) included in nine studies (55–178 patients). Subgroup analysis indicated a higher frequency among patients with community-acquired bacteraemia (12.5%, range 2.7–34%), in accordance with the present study. In contrast to this study, polymicrobial bacteraemia was included in most studies. Polymicrobial bacteraemia is rare in IE [22] and the restriction to monomicrobial bacteraemia may partly explain a higher frequency of IE in this study.

Notably few patients received appropriate antimicrobial therapy within the first day after blood was drawn for culture,

TABLE 3. Thirty-day mortality in monomicrobial *E. faecalis* bacteraemia patients

Predictors	30-day mortality *n* (%)	Unadjusted OR (95% CI[a])	Adjusted OR[b] (95% CI)
Total	98 (21.4)	–	–
Age group (years)			
15–64	14 (12.1)	1.0	1.0
65–79	42 (21.7)	2.01 (1.05–3.87)	2.34 (1.17–4.65)
≥ 80	42 (28.6)	2.91 (0.99–3.16)	3.97 (1.94–8.13)
Charlson co-morbidity index			
Index low (0)	7 (10.5)	1.0	1.0
Index medium (1–2)	33 (20.5)	2.21 (0.92–5.28)	1.79 (0.72–4.46)
Index high (≥ 3)	58 (25.3)	2.90 (1.26–6.72)	2.44 (1.01–5.85)
Origin of bacteraemia			
Community acquired	23 (16.0)	1.0	1.0
Hospital acquired	55 (26.3)	1.88 (1.09–3.23)	1.85 (1.02–3.35)
Healthcare associated	20 (19.2)	1.25 (0.65–2.43)	1.33 (0.64–2.71)
Focus of infection			
Urinary tract	28 (16.4)	1.0	1.0
Intra-abdominal	14 (25.0)	1.70 (0.82–3.53)	2.04 (0.94–4.46)
Infective endocarditis	5 (8.2)	0.45 (0.17–1.24)	0.62 (0.22–1.75)
Miscellaneous[c]	5 (15.6)	0.95 (0.34–2.67)	1.01 (0.34–2.98)
Unknown	46 (33.6)	2.58 (1.51–4.42)	3.01 (1.71–5.31)
Empirical antimicrobial therapy			
Appropriate therapy	20 (24.7)	1.0	1.0
Inappropriate therapy	78 (20.7)	0.80 (0.45–1.40)	0.80 (0.44–1.46)
Antimicrobial resistance			
Non-HLGR	50 (17.8)	1.0	1.0
HLGR[d]	47 (27.0)	1.71 (1.08–2.69)	1.65 (0.99–2.74)

[a]Confidence interval.
[b]Adjusted for age, Charlson co-morbidity index level, origin, focus of infection and empirical antimicrobial therapy.
[c]Bone, joint, skin, soft tissue, IV-catheter and respiratory tract.
[d]High level gentamicin resistance.

TABLE 4. Thirty-day mortality in monomicrobial *E. faecium* bacteraemia patients

Predictors	30-day mortality, *n* (%)	Unadjusted OR (95% CI[a])	Adjusted OR[b] (95% CI)
Total	84 (34.6)	–	–
Age group (years)			
15–64	24 (26.7)	1.0	1.0
65–79	45 (40.5)	1.88 (1.03–3.42)	1.78 (0.95–3.30)
≥ 80	15 (35.7)	1.53 (0.70–3.35)	1.84 (0.80–4.28)
Charlson co-morbidity index			
Index low (0)	6 (15.4)	1.0	1.0
Index medium (1–2)	31 (37.4)	3.28 (1.23–8.71)	2.84 (1.04–7.72)
Index high (≥ 3)	47 (38.8)	3.49 (1.36–8.97)	2.92 (1.10–7.73)
Origin of bacteraemia			
Community acquired	2 (11.1)	1.0	1.0
Hospital acquired	76 (36.7)	4.64 (1.04–20.74)	4.29 (0.91–20.31)
Healthcare associated	6 (33.3)	4.00 (0.68–23.41)	3.34 (0.55–20.43)
Focus of infection			
Intra-abdominal	30 (32.3)	1.0	1.0
Miscellaneous[c]	19 (35.2)	1.20 (0.66–2.20)	1.15 (0.55–2.40)
Unknown	35 (36.5)	1.14 (0.56–2.31)	1.16 (0.62–2.16)
Empirical antimicrobial therapy			
Appropriate therapy	5 (27.8)	1.0	1.0
Inappropriate therapy	79 (35.1)	1.41 (0.48–4.09)	0.95 (0.30–2.95)
Antimicrobial resistance			
Non-HLGR	27 (31.8)	1.0	1.0
HLGR[d]	56 (36.4)	1.23 (0.70–2.15)	1.07 (0.58–1.97)
Ampicillin susceptible	5 (16.7)	1.0	1.0
Ampicillin resistant	79 (37.1)	2.95 (1.08–8.01)	2.13 (0.67–6.75)

[a]Confidence interval.
[b]Adjusted for age, Charlson co-morbidity index level, origin, focus of infection and empirical antimicrobial therapy.
[c]Urinary tract, IV-catheter, infective endocarditis, respiratory tract, bone, joint, skin and soft tissue.
[d]High level gentamicin resistance.

but this did not have a discernible impact on mortality. The low frequency of appropriate therapy was expected because cefuroxime has been the preferred drug of choice in patients presenting with sepsis, and vancomycin is rarely included in empirical antimicrobial therapy because of a very low prevalence of methicillin-resistant *Staphylococcus aureus* in Denmark. Previous studies have shown that appropriate antimicrobial therapy is associated with improved prognosis [6,7,23,24]. However, this study indicates that the first-day treatment is not essential for outcome, as found in some studies on Gram-negative bacteraemia [25,26]. On the other hand, an association between outcome and early appropriate antimicrobial therapy within the first 24 h after diagnosis may be difficult to demonstrate, especially in a group of patients who rarely present with severe sepsis [7]. This should not diminish the clinical significance of enterococcal bacteraemia and additional factors can influence the efficacy of antibiotics *in vivo*. In principle, betalactam antibiotics and glycopeptides are bactericidal, but the cidal action may be delayed and dependent at least partly on the immune system, which might be affected in our patients with a high burden of co-morbidity.

A limitation of the study was the lack of clinical information on the severity of bacteraemia. We expect clinical attention to be more meticulous in patients with severe infection and expect that broad-spectrum coverage is secured more diligently in patients who are severely ill (confounding by indication). Additionally, information about the time of initiation of antimicrobial treatment was often imprecise and in most cases we had to rely on the date of initiation (and not hour). Similarly, the time of the draw of blood for cultures was also only recorded by date.

The main strengths of our study were the population-based design and the large sample size. Data were collected concurrently with the clinical episodes and independently of the aims of the current study. The Danish Civil Registration System enabled complete follow-up.

Conclusion

In conclusion, enterococcal bacteraemia was mainly hospital acquired and associated with high mortality. The 30-day mortality was particularly high in patients with *E. faecalis* bacteraemia with unknown focus, and identifying the focus of infection should be given high priority in order to improve outcome. The high frequency of IE, especially in community-acquired *E. faecalis* bacteraemia, raises the question of wether echocardiography should be recommended for all patients with community-acquired *E. faecalis* bacteraemia.

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Transparency Declaration

The authors declare no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Thirty-day mortality in monomicrobial enterococcal bacteraemia patients.

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