

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.

Keywords: bacteraemia, bloodstream infection, Enterococcus, epidemiology, mortality, population-based

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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 (≥ 16 years); this equals $\sim 35\%$ 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 (bioMérieux, Marcy l'Etoile, 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 stain 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 (≥ 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 ≥ 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 ≥ 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

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