



Incidence, Risk Factors, and Outcomes for *Enterococcus* spp. Blood Stream Infections: A Population-Based Study



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ABSTRACT

Background: Enterococci are a clinically significant cause of bloodstream infections (BSI), particularly in the nosocomial setting. The purpose of this study was to characterize the incidence, risk factors for acquisition, microbiological characteristics and mortality of enterococcal BSI within the well-defined population of a large Canadian health region.

Methods: Surveillance for all episodes of enterococcal BSI occurring among residents of the Calgary Health Zone (population 1.2 million) between 2000 and 2008 was conducted using an electronic surveillance system. Clinical features, microbiology, and outcomes were obtained.

Results: A total of 710 incident episodes of enterococcal BSI were identified for an annual incidence of 6.9 episodes per 100,000; the incidences of *E. faecalis* and *E. faecium* BSI were 4.5, and 1.6 per 100,000, respectively. *Enterococcus faecalis* infections were associated with a urinary focus, genitourinary malignancy, and abnormal genitourinary anatomy. *E. faecium* infections were associated with a gastrointestinal focus. Resistance to ampicillin, vancomycin and ciprofloxacin was higher in *E. faecium* infection. The overall case fatality rate was 22.8%, and was higher for *E. faecium* infection.

Conclusions: This is the second population-based study to assess the risk factors for enterococcal BSI and compare the characteristics of infection with *E. faecalis* and *E. faecium*. Results suggest that BSI with *E. faecalis* and *E. faecium* should be regarded as two clinically different entities with unique sets of risk factors and microbiologic characteristics.

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1. Introduction

Enterococcus species are a frequent cause of blood stream infections (BSI) in North America^{1–6}. In-hospital mortality associated with enterococcal BSI has been estimated between 25–50%^{7–12}, leading to the recognition of the *Enterococcus* species as formidable pathogens. The treatment of enterococcal BSI is

complicated by high rates of antimicrobial resistance, with all enterococci being inherently resistant to cephalosporins and an increasing prevalence of vancomycin and ampicillin resistance being encountered in many health regions. Resistance to aminoglycosides as synergistic agents has also become more prevalent^{9,13}.

The two most ubiquitous *Enterococcus* species, *E. faecalis* and *E. faecium*, are often considered to be similar entities and treated as such. However, *E. faecium* has been associated with BSI in a more severely ill subset of patients, has higher rates of antibiotic resistance, and has been associated with higher mortality than *E. faecalis* BSI^{7,8,14,15}.

Enterococcal BSI are often associated with a urinary tract, intra-abdominal, or endovascular source^{3,7,14,16–21}. Older age, male gender, liver disease, renal impairment, diabetes, hematologic

Abbreviations: BSI, bloodstream infection(s); CSI, Charlson Severity Index; CHZ, Calgary Health Zone; GI, gastrointestinal; PUD, peptic ulcer disease.

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transplant, malignancy, and prior treatment with antibiotics have all been associated with the acquisition of BSI in other non-selected observational cohort studies^{7,8,14,20,21}. However, the data from these studies is mainly derived from selected tertiary care hospitals, subjecting these reports to referral biases^{1,2,5,7,14,17–21}. This type of bias can be overcome by conducting population-based studies which allows investigators to minimize selection biases by studying a well-defined geographic region²². The purpose of this study was to characterize the incidence, risk factors for acquisition, microbiological characteristics and clinical outcomes of enterococcal BSI within the well-defined population of a large Canadian health region, while also comparing *E. faecalis* to *E. faecium* BSI.

2. Methods

2.1. Study Population

Our study population involved the Calgary Health Zone (CHZ). This healthcare region provides medical and surgical care to the residents of Calgary, Airdrie, and a large surrounding catchment area (total population 1.2 million) in the province of Alberta, Canada. Only patients requiring acute liver, heart, or lung transplantation surgery are routinely referred elsewhere. All persons who resided in the CHZ and developed enterococcal BSI between 2000 and 2008 were included in the study. Approval was obtained from Conjoint Health Research Ethics Board at the University of Calgary and CHZ prior to commencement of this study.

2.2. Study Protocol

We employed a retrospective, population-based surveillance cohort design. Surveillance for enterococcal infections was performed using the Electronic Surveillance System²³. This system utilizes data from regional laboratory, hospital, and vital statistics information systems with application of clinically validated algorithms to identify and classify patients with incident BSI. All patients with blood samples submitted for culture from hospitals, nursing homes, and clinics in the CHZ are identified. Further clinical and outcome data including demographics, pre-existing co-morbidities, hospital admission, and mortality are obtained on patients admitted to any of the 4 major acute care hospitals (representing >95% of hospital admissions in the CHZ). Information regarding co-morbidities was established from ICD-9 and ICD-10 codes²⁴.

2.3. Definitions

Enterococcal BSI was defined by its isolation from 1 or more sets of aseptically obtained blood culture bottles and cultured using the BacT/Alert automated instrument (Organon Teknika, Durham, NC, USA). Clinical isolates were cultured, confirmed as *Enterococcus*, further speciated into *E. faecium*, *E. faecalis* or alternate species and then tested for antimicrobial susceptibility by standard Clinical and Laboratory Standards Institute (CLSI) techniques²⁵. Enterococcal cultures obtained from non-blood sites within 48 hours of the index incident blood culture draw, as well as clinical assessment of the patient, was evaluated to determine the primary source of infection. An incident case in a CHZ resident was defined as the first new isolation of *Enterococcus* from the blood; repeated isolation of the same species of *Enterococcus* within 365 days of the first isolation was deemed to represent the same incident infection. A single incident event was also considered if more than one species of *Enterococcus* was isolated from the same blood culture sample or if two samples were collected within 48 h of one another that showed the same species. Polymicrobial bacteraemia

was defined as an episode with more than one clinically important bacterial isolate detected within 48 hours of incident draw. Residency status and population statistics were established using the 2003 boundaries of the CHZ²⁶.

Nosocomial acquired BSI were those in which the first positive culture was obtained 48 hours or more after hospital admission or within 48 hours of discharge from the hospital. Community-onset BSI were those in which the first positive culture was obtained less than 48 hours after hospital admission or more than 48 hours after discharge from hospital. Community-onset BSI were further classified as either health-care associated or community-acquired as previously described²³.

2.4. Statistical Analysis

Analysis was performed using Stata version 11.0 (Stata Corp, College Station, Tex). Non-normally distributed variables were reported as medians with interquartile ranges (IQRs) and compared using the rank-sum test for pairs or median test for groups. Differences in proportions among categorical data were assessed using the Fisher's exact test for pairwise comparisons and the chi² test for multiple groups. Incidence of enterococcal BSI was calculated by dividing the number of incident cases by the total population of the region. Population-based risk factors for developing enterococcal BSI were quantified by dividing the incidence of these infections among those with a given factor by those without the factor. Regional demographic data were used to determine the population at risk for assessment of age and gender²⁷. To determine risk factors, the population at risk was ascertained using local patient registry data, regional or Canadian survey data, or published North American epidemiology studies^{28–39}. Risks were expressed as incident rate ratios and reported with 95% confidence intervals. A logistic regression model was developed to assess independent factors associated with in-hospital death. Factors found to be significant at the P<0.1 level in univariate analysis were included in the initial model, and backwards stepwise variable elimination was then performed to develop the final model. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test, and discrimination was assessed using the area under the receiver operating characteristic curve. For all statistical comparisons a P value of less than 0.05 was deemed statistically significant.

3. Results

A total of 710 enterococcal BSI occurred in 695 CHZ residents in our 9-year study period. Of the 695 patients who developed enterococcal BSI during the study period, 7 had two episodes >365 days apart, 1 had three separate infections >365 days apart, and 6 had two infections >48 h but <365 days apart with two different species of *Enterococcus*. Eleven patients had an infection in which two different species of *Enterococcus* were isolated within 48 h of each other.

Basic patient demographic data (age, gender and residency), acquisition data (nosocomial, health-care associated, community acquired), and 30-day mortality were available for all 710 incident episodes of enterococcal BSI. Of these cases, 654 (92%) were admitted to one of the 4 major acute care hospitals in the CHZ. Additional detailed clinical data regarding co-morbidities were available for 653 of these patients.

For the 710 episodes of enterococcal BSI, speciation was available in 667 (94%). The most commonly isolated enterococcal species in incident BSI was *E. faecalis*, which comprised 467 (70%) of isolates. *Enterococcus faecium* was the second most common species, comprising 169 (25%) of isolates. Of the remaining 31 (4%) isolates, 8 were *E. gallinarium*, 8 were *E. cassiflavus*, 2 were

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