Occurrence and determinants of enterococcal bloodstream infections: a population-based study

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ABSTRACT

Background: Although enterococci are common causes of bloodstream infections (BSIs), few studies have examined their epidemiology in non-selected populations.

Objective: To examine the incidence and risk factors for development of enterococcal BSI.

Methods: Surveillance for incident enterococcal BSI was conducted among all residents of the western interior of British Columbia, Canada during 2011–2018.

Results: The overall annual incidence was 10.0 per 100,000 and was 6.6 and 2.7 per 100,000 for \textit{E. faecalis} and \textit{E. faecium}, respectively. Among the overall cohort of 145 incident cases of enterococcal BSI, 22 (15.2\%) were community-associated, 63 (43.5\%) were healthcare associated and 60 (41.4\%) were hospital-onset. Enterococcal BSI was predominantly a disease of older adults with rare cases occurring among those aged less than 40 years. Males showed significantly increased risk compared to females (14.3 vs. 5.6 per 100,000; incidence rate ratio; IRR; 2.6; 95\% confidence interval; CI; 1.8–3.8; \(p < .0001\)) and this was most pronounced with advanced age. Several co-morbid illnesses were associated with increased risk (IRR; 95\% CI) for development of enterococcal BSI most importantly cancer (8.8; 6.0–12.9; \(p < .0001\), congestive heart failure (5.7; 3.1–9.7; \(p < .0001\)), diabetes mellitus (4.4; 3.0–6.3; \(p < .0001\)) and stroke (3.7; 1.9–6.5; .0001). As compared to patients with \textit{E. faecalis}, patients with \textit{E. faecium} BSI were more likely to be of hospital-onset, more likely to have an intra-abdominal/pelvic focus, and trended towards higher 30-day case-fatality rate.

Conclusions: Enterococci are relatively common causes of BSI. Although \textit{E faecalis} and \textit{E faecium} share commonalities they are epidemiologically distinguishable on several criteria.

KEYWORDS
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Introduction

Enterococcus species, most commonly E. faecalis and E. faecium are among the most common causes of both community- and hospital-onset bloodstream infections (BSIs) [1–3]. Enterococcal BSI usually develops from genitourinary and gastrointestinal sources and while most are uncomplicated, severe disease may occur as with endocarditis [4]. Enterococci are intrinsically resistant or tolerant to many anti-microbials with increasing resistance to vancomycin and linezolid challenging ability to treat these infections [5,6]. These infections have a propensity disproportionately affecting the very young and very old with an overall case-fatality rate of approximately 25% [1–3].

Population based studies are regarded as an ideal method to define the epidemiology of a pathogen. These studies examine all residents within a defined geographic region to reduce selection biases and the incidence rates can be determined if the population size is known [7,8]. Although there have been many hospital based studies conducted previously, to our knowledge, there have only been two population based studies that have reported on the epidemiology of enterococcal BSI [1,2]. These include a study from Canada (2000–2008) [1] and Denmark (2006–2009) with none within the past decade [2]. This study aimed to determine the incidence and risk factors for development of enterococcal BSI in a contemporary population in the western interior of British Columbia, Canada.

Methods

A population-based surveillance cohort design was utilized as previously described [9]. Case patients with enterococcal BSI were identified by surveillance and individually reviewed. All other patients in the general population were considered as controls with demographic information obtained using census data and underlying illnesses estimated from surveys. Between 1 January 2011 and 31 December 2018, only residents of the western interior of British Columbia, Canada with an incident enterococcal BSI were included. Non-residents to the area were excluded. A waiver of individual informed consent was obtained from the Interior Health Research Ethics Board (201314052-I).

The regional microbiology laboratory identified all residents with an enterococcal BSI from community and hospital setting as previously described [10]. Enterococcal isolates were isolated, further speciated using standard Clinical and Laboratory Standards Institute (CLSI) techniques into E. faecium, E. faecalis or alternate species [11].

Hospital-onset BSIs were defined as those that were obtained after first 48h of hospital admission. Community-onset BSI included those taken in the outpatient setting as well those obtained within the first 48h of hospital admission. Community-onset BSIs were sub-classified into community-associated or healthcare-associated using the criteria of Friedman et al. [12]. A BSI episode was defined from the first isolates identified and any within a 30-day period. Those found after 30 days were defined as a new BSI episode. A senior infectious disease consultant reviewed each case via chart review which included all consultations, admission and discharge summaries that were available within the electronic health record. Patient comorbidities were classified using the method of Charlson et al. [13].

StatA (version 15.1; StataCorp LP, College Station, TX) was used to analyse all data. Incidence rates were calculated using the annual population (2011–2018 average population ≈182,000 per year) of the region from the provincial registry [14]. Population-based risk factors for developing enterococcal BSI were calculated using prevalence estimates to determine the population at risk as previously described [15–24]. Risk factors were expressed as incidence rate ratios (IRRs) with 95% confidence intervals (CIs).

Fisher’s exact test was used to compare categorical data and the Mann-Whitney test was used to compare non-normally distributed continuous data. p Values less than .05 were regarded as statistically significant.

Results

During the eight years of surveillance, a total of 145 incident enterococcal BSI occurred among 140 regional residents; five patients had second episodes. Most of the incident infections were due to Enterococcus faecalis (96 cases), with E. faecium occurring in 40, E. casseliflavus in five, E. gallinarum in two, and in two cases speciation was not available.

The overall annual incidence was 10.0 per 100,000. The annual incidence was 6.6 per 100,000 for E. faecalis of which none were vancomycin resistant. Enterococcus faecium occurred at an annual incidence of 2.7 per 100,000; 1.3 per 100,000 of these were due to vancomycin resistant strains. Among the overall cohort of enterococcal BSI, 22 (15.2%) were community-associated, 63 (43.5%) were healthcare associated and 60 (41.4%) were of hospital-onset. None of the 19 vancomycin resistant E. faecium were community-associated, with 13 (68%) being hospital-onset and six (32%) healthcare-associated.
The mean (standard deviation) patient age was 69.6 (±12.7) years and 105 (72.4%) were in males. Enterococcal BSI was predominantly a disease of older adults with rare cases occurring among those aged less than 40 years of age as shown in Figure 1. Males were at significant increased risk for enterococcal BSI as compared to females (14.3 vs. 5.6 per 100,000; IRR 2.6; 95% CI, 1.8–3.8; \( p < .0001 \)) and this was most pronounced with advanced age (Figure 1).

A number of co-morbid medical illnesses, most notably cancer, congestive heart failure and diabetes mellitus were associated with increased risk for developing enterococcal BSI as shown in Table 1.

Patient characteristics differed between individuals with incident \( E. \text{faecalis} \) as compared to \( E. \text{faecium} \) BSI on several variables as shown in Table 2. The majority of \( E. \text{faecalis} \) infections were community-onset whereas the converse was true for \( E. \text{faecium} \). When each of the individual Charlson co-morbidities were assessed only liver disease (5/96; 5% vs. 9/40; 23%; \( p = .005 \)) and peptic ulcer disease (3/96; 3% vs. 6/40; 15%; \( p = .02 \)) were significantly different among \( E. \text{faecalis} \) and \( E. \text{faecium} \) cases. Patients with \( E. \text{faecium} \) were almost twice as likely to die as compared to those with \( E. \text{faecalis} \) BSI (16/40; 40% vs. 23/96; 24%; relative risk 1.7; 95% CI, 1.0–2.8; \( p = .07 \)) although this was not statistically significant.

**Discussion**

This study has shown that the enterococcal genus is a common cause for BSI occurring at an annual incidence of 10.0 per 100,000 population. We further observed

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**Figure 1.** Incidence of enterococcal bloodstream infection by age and gender, western interior, 2011–2018.
that advanced age and a number of comorbidities are associated with an increased risk of developing an enterococcal BSI. More than one in four patients with enterococcal BSI did not survive to 30-days. Enterococcal BSIs are associated with a major burden of illness.

There are only two previously published population-based studies to compare our observations [1,2]. Billington et al. examined enterococcal BSI in the Calgary area of Canada during 2000–2008 and found an incidence rate of 6.9/100,000, of which 4.5 and 1.6 per 100,000 population were due to E. faecalis and E. faecium, respectively [1]. In comparison, Pinholt et al. found a much higher incidence of 19.6 per 100,000 population in two Danish regions between 2006 and 2009, of which 13.0 and 6.6 per 100,000 population were due to E. faecalis and E. faecium, respectively [2]. Case-fatality rates for E. faecalis and E. faecium BSI were comparable between the Canadian (17% and 30%) and Danish (21% and 35%) studies [1,2]. Our study found an incidence rate that is midway (10 per 100,000 per year) between these two prior studies with case-fatality rates for E. faecalis (24%) and E. faecium (40%) that is higher than observed in these reports. While there may be many factors that may potentially explain the differences observed among these studies including different distribution of co-morbid illnesses, age and anti-microbial resistance, it is evident that enterococcal BSIs are associated with a major burden of illness.

In addition to increasing age, a number of comorbidities increase the risk of developing an enterococcal BSI. In keeping with the Danish and Canadian studies, diabetes, cancer, renal disease, dementia, cerebrovascular accidents and congestive heart failure were all associated with an increased risk of developing enterococcal BSI [1,25]. Notably, peripheral vascular disease (PVD) is a significant risk factor for developing any community BSI, but has not been previously identified as significant risk factor for developing an enterococcal BSI [9]. The link with PVD may be associated with other comorbidities that are typically associated with these patients, such as diabetes [26]. Interestingly, other comorbidities that can affect immunity, such as HIV and rheumatic disease, were not associated with developing enterococcal BSI. In the Canadian study, rheumatoid arthritis was associated with an increased risk of enterococcal BSI, while HIV was only associated to increased risk of developing E. faecium [1]. Other studies have identified that HIV predisposes individuals to opportunistic infections with an increased risk specifically for enterococcal aetiologies as compared to HIV-negative controls [27]. Our present study may have been underpowered to detect a significant increased risk with HIV. The incidence of enterococcal BSI is likely to increase as the population ages and medicine continues to manage more complex and co-morbid patients.

There were a number of enterococcal species identified, the two most ubiquitous were E. faecalis and E. faecium. While E. faecalis was more common overall, E. faecium was more commonly found in the hospital setting (68% vs. 33%), rarely in the community (8% vs. 17%) and was associated with a higher 30-day case-fatality (40% vs. 24%). These findings are congruent with the Danish and Canadian studies [1,2]. It is unclear whether the higher mortality associated with E faecium is due to inherent virulence mechanisms, differences in antibiotic resistance, or independent host immunity and comorbidities, or, more likely a combination of these factors. Current meta-analysis further demonstrate increased vancomycin resistance in E faecium, which is frequently associated with higher rates of recurrence, higher crude case-fatality rates and higher case-fatality rates [6,28]. In keeping with previous studies, E. faecium was most commonly found from intra-abdominal/pelvic sources (58%), while E. faecalis was most commonly from a genitourinary source (30%) [1,2,29]. Although E. faecalis and E. faecium belong to the same genus, they differ in their capacity to acquire resistance, infect body sites and result in death.

Although this study benefits from its population-based design, there are some limitations that merit discussion. First, chart reviews for clinical aspects including risk factors were conducted retrospectively and the possibility exists that co-morbidities could be missed or

| Variable                      | E. faecalis (n = 96) | E. faecium (n = 40) | p Value |
|------------------------------|----------------------|---------------------|---------|
| Onset                        |                      |                     | .001    |
| Community-associated         | 16 (17%)             | 3 (8%)              |         |
| Healthcare-associated        | 48 (50%)             | 10 (25%)            |         |
| Hospital-onset               | 32 (33%)             | 27 (68%)            |         |
| Mean (SD) age                | 70.6 (12.5)          | 66.9 (12.2)         | .1      |
| Male                         | 72 (75%)             | 27 (68%)            | .4      |
| Focus of infection           |                      |                     | <.001   |
| No focus/primary             | 20 (21%)             | 8 (20%)             |         |
| Bone/joint                   | 2 (2%)               | 4 (10%)             |         |
| Soft tissue                  | 5 (%)                | 0                   |         |
| Lower respiratory            | 1 (1%)               | 0                   |         |
| Cardiovascular               | 18 (19%)             | 1 (3%)              |         |
| Intra-abdominal/pelvic       | 21 (22%)             | 23 (58%)            |         |
| Genitourinary                | 29 (30%)             | 4 (10%)             |         |
| Median Charlson (IQR)        | 2 (1–4)              | 2 (1–4)             | .8      |
| Vancomycin resistance        | 0                    | 19 (48%)            | <.001   |
| Polymicrobial                | 22 (23%)             | 7 (18%)             | .6      |
| 30-Day case-fatality         | 23(24%)              | 16 (40%)            | .07     |

Table 2. Characteristics of enterococcal bloodstream infection by species.
miss-classified. However, attempts were made to classify according to standard definitions and charts were reviewed by an experienced infectious diseases consultant. Second, because the definition of BSI required a positive blood culture, the incidence rate observed was dependent on a specimen being sent for culture [30]. No protocols were used to direct this practice and the decision to culture was based on the attending physician. This is a limitation of all studies of this design. Third, we did not have individual linked data on co-morbidities in control patients within the population and therefore had to use prevalence estimates. As a result, the IRRs we observed should be viewed with caution especially when close to unity. In addition, this precluded calculation of an overall Charlson score for the controls and the conduct of multivariable analysis to assess independent effects of each co-morbidity examined. Finally, the number of cases included represented a relatively small cohort such that the study had limited power to detect differences between enterococcal species and other clinical variables.

In summary, this study represents the third investigation of enterococcal BSI conducted at the population level. We observed that enterococcal BSI are common, are associated with advancing age and a number of co-morbid illnesses, and have a high associated case-fatality rate. Enterococcal BSI is associated with a major burden of illness that may be expected to increase in the coming years related to aging populations.

Disclosure statement

None of the authors has conflicts of interest to disclose.

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