Trends in Enterococcus faecium Bacteremia: Exploring Risk Factors with Emphasis on Prior Antibiotic Exposure

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Article

Trends in *Enterococcus faecium* Bacteremia: Exploring Risk Factors with Emphasis on Prior Antibiotic Exposure

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Abstract: Enterococcal bacteraemia (EB) is on the rise both in Sweden and globally. While *Enterococcus faecalis* (*E. faecalis*) is susceptible to ampicillin and piperacillin/tazobactam (pip/taz), *Enterococcus faecium* (*E. faecium*) is not. The use of pip/taz has increased dramatically in Sweden, but it is unknown if this has affected the relative incidence of *E. faecalis*/*E. faecium* bacteraemia. Here we investigate whether the number and proportion of *E. faecium* bacteraemia (EfmB) cases have increased. Additionalle, risk factors associated with EfmB with focus on prior antibiotic exposure are analyzed. Medical journals of 360 patients with EB admitted to Sahlgrenska University Hospital were reviewed. The proportion of EfmB cases increased from 41% in 2015 to 51% in 2021. Hospital-acquired infection, previous exposure to pip/taz, and carbapenems were identified as independent risk factors for EfmB. There were considerable patient related differences between the EfmB and EfsB groups but there was no difference in mortality rates. In conclusion, the increasing proportion of EfmB cases is concerning and was seen parallell to the expanding use of pip/taz, one possible contributing factor. Our findings suggest that a cautious approach to antibiotic use is essential to prevent the spread of antibiotic-resistant bacteria.

Keywords: enterococcal bacteraemia; antibiotic resistance; *Enterococcus faecium;* piperacillin/tazobactam

1. Introduction

Enterococci are aerobic gram-positive bacteria that typically inhabit the human gastrointestinal tract (1). Among human enterococcal infections, the predominant causative agents are *Enterococcus faecalis (E. faecalis)* and *Enterococcus faecium (E. faecium*), with the latter being less prevalent, though proportions may vary among studies(2). Despite generally low virulence, these bacteria can precipitate severe infections, particularly in immunocompromised individuals (2). Notably, enterococcal species demonstrate intrinsic resistance to various antibiotic classes, encompassing cephalosporins and most carbapenems. While *E. faecalis* typically remains sensitive to ampicillin and subsequently piperacillin, over 80% of *E. faecium* isolates in Sweden exhibit penicillin resistance (3). Enterococci can acquire additional resistance rendering them insensitive to vancomycin (4), which is of critical concern globally, albeit still rare in Sweden where vancomycin resistance is reported in less than one percent of enterococcal blood culture isolates (3). Enterococcal bacteraemia (EB) has increased globally and is associated with high in-hospital mortality rate, ranging from 11-36%, with comorbidities and previous antibiotic exposure emerging as risk factors (5-7).

In Sweden, efforts to limit antibiotic resistance through stringent antibiotic policies favoring narrow-spectrum antibiotics has a longstanding tradition. During the early 2000-ies, in face of the

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emerging occurrence of extended-spectrum beta-lactamase (ESBL) in *Enterobactereales* and the first reported outbreak of multiresistant ESBL-producing K. pneumoniae in Scandinavia, a reduction of cephalosporin use was strongly favoured(8). Consequently, there was an upsurge in the utilization of alternative antibiotics effective against gram-negative or polymicrobial infections, such as piperacillin/tazobactam (pip/taz) (9). However, this shift in antibiotic protocols may inadvertently contribute to the selective pressure favoring ampicillin-resistant enterococci, including *E. faecium*.

The objective of this study was twofold: firstly, to evaluate whether the incidence of *E. faecium* bacteremia (EfmB) relative to *E. faecalis* bacteremia (EfsB) increased between 2015 and 2021; secondly, to analyze the risk factors associated with acquiring EfmB, with a particular focus on prior antibiotic exposure.

2. Materials and Methods

2.1. Study Population

This retrospective cohort study was conducted at Sahlgrenska University Hospital, a 1,500 bed university hospital in Western Sweden. All patients over 18 years, with positive blood cultures for *E. faecium* or *E. faecalis* between 2015–2021, were included in the patient population while only patients with an EB in 2015, 2018 and 2021 were included in the medical record review and in the risk factor analysis. Each patient was included only once per year. Patient data, including demographic and medical information, was collected through medical record review. An episode of EB was defined as the presence of at least one positive blood culture containing either *E. faecium* or *E. faecalis*. The day of bacteremia onset was defined as the day of collection of the positive blood culture. Bacteremia was classified as hospital-acquired if the positive blood culture was obtained 48 hours or more after hospital admission; otherwise, it was considered community-acquired. Variables of interest included hospital vs. community-acquired bacteraemia, predisposing factors, comorbidities, prior hospital antibiotic exposure within 90 days preceding the positive blood culture, and mortality rates in-hospital and at 30 days, 90 days, and 1 year.

2.2. Statistical Analysis

Patients were categorized based on whether they had EfmB or EfsB. Continuous data were presented as median and interquartile ranges, while categorical variables were expressed as numbers and percentages. The statistical analysis was performed in SPSS statistics version 29 and a p-value below 0.05 was considered significant. Pearson Chi-square was used to compare categorical variables, and the Mann-Whitney U test was employed to compare medians between continuous data. Univariate and multivariate logistic regression model were used to identify risk factors for contracting EfmB over EfsB. Variables that exhibited statistical significance in the univariate analysis were incorporated into the multivariate regression analysis to ascertain their persistent significance after adjusting for potential confounding factors.

3. Results

3.1. Epidemiology and Demographics

In the years 2015, 2018 and 2021, 171 patients with bacteraemia caused by *E. faecium* and 189 with *E. faecalis* were included in the study (Table 1). In 2015, 98 unique patients had an episode of EB compared to 113 patients in 2020 and 149 patients in 2021. Simultaneously, the total number of blood cultures processed at the Microbiological Laboratory at Sahlgrenska University Hospital increased from 46 573 in 2015 to 49 264 in 2018 and 52 790 in 2021 (data not shown).

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Table 1. Demographic and clinical characteristics of study patients 2015, 2018 and 2021.

	***E. faecalis* n=189 (%)**	***E. faecium* n=171 (%)**	***p***
2015 n=98	58/98 (59)	40/98 (41)	ns
2018 n=113	59/113 (52)	54/113 (48)	ns
2021 n=149	72/149 (49)	77/149 (51)	ns
Demographics			
Age (years)	76 (67–83)	67 (56–75)	<0.001
Women	56 (30)	66 (39)	ns
In-hospital stay (days)	36 (30–54)	68 (56–90)	<0.001
Bacteraemia duration[1]	10 (6–20)	15 (10–31)	<0.001
Hospital acquired bacteraemia	69 (37)	127 (74)	<0.001
Co-morbidities			
Diabetes	48 (25)	37 (22)	ns
Chronic kidney disease	31 (16)	20 (14)	ns
Hypertension	96 (51)	67 (39)	0.027
Heart failure	27 (14)	16 (9)	ns
Colon cancer	13 (7)	15 (9)	ns
Hematological malignancy	12 (6)	28 (16)	0.003
Other cancer	55 (29)	49 (29)	ns
copd[2]	15 (8)	13 (8)	ns
Liver failure	21 (11)	19 (11)	ns
Gastric ulcer	14 (7)	18 (11)	ns
ibd[3]	3 (2)	4 (2)	ns
Immunosuppression	27 (14)	48 (28)	0.001
Dementia	13 (7)	7 (4)	ns
No comorbidities	11 (6)	10 (6)	ns
Predisposing hospital procedures			
Urine catheter	93 (49)	94 (55)	ns
Drain port	30 (16)	58 (34)	<0.001
Central vascular catheter	55 (29)	116 (68)	<0.001
Recent surgery	73 (39)	101 (59)	<0.001
Mortality			
In-hospital	42 (22)	35 (20)	ns
30 days	51 (27)	41 (24)	ns
90 days	65 (34)	56 (33)	ns
1 year[4]	54/116 (47)	49/94 (54)	ns

Continuous data are presented as median and interquartile range. Categorical variables are listed as numbers and percentages. [1]From bacteraemia onset to hospital discharge, [2] Chronic obstructive pulmonary disease. [3] Inflammatory bowel disease. [4]Assessed in 2015 and 2018.

The occurrence and distribution of bacteraemia caused by *E. faecium* and *E. faecalis* were evaluated for the entire study period from 2015 to 2021 (n=840). Although there was a rise in the number of EB cases over the years, this did not correspond to a statistically significant increase. Initially, the proportion of cases attributed to *E. faecium* was below 40%, with an upward trend in the later years of the study (Figure 1). All *E. faecalis* isolates and 9.9% of the *E. faecium* isolates were sensitive to ampicillin.

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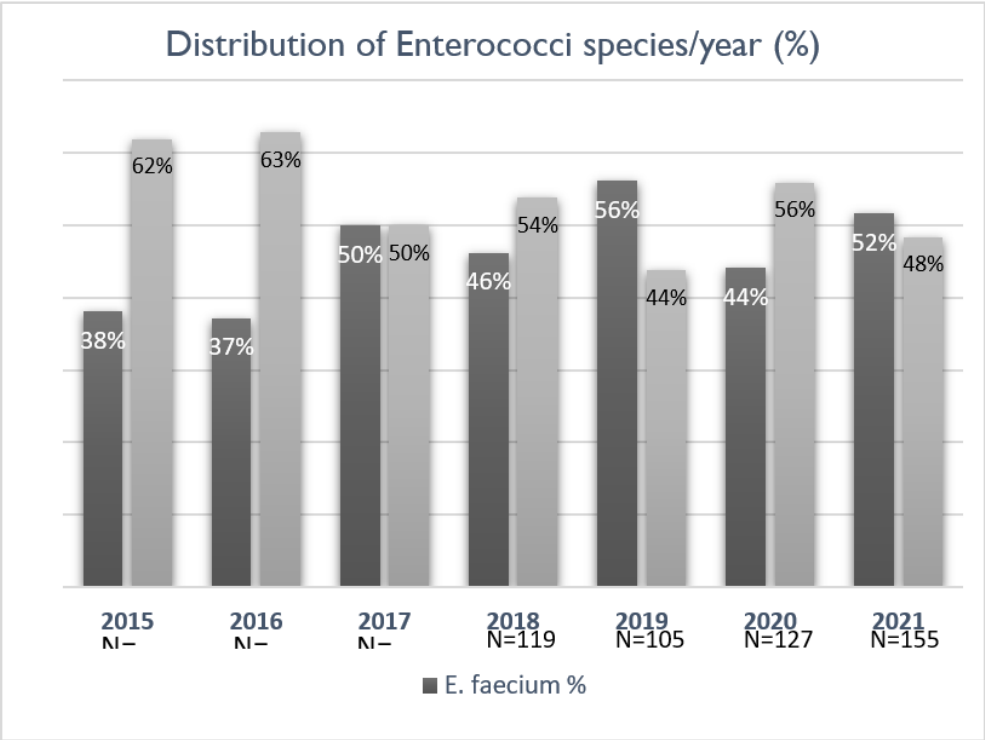

Figure 1. Occurrence and distribution of *Enterococci faecium* and *Enterococci faecalis* in blood cultures at Sahlgrenska University Hospital 2015–2021.

Patients with EfsB were older (76 vs. 67 years, p<0.001) compared to those with EfmB. The two enterococcal species were both more prevalent in males. Among comorbidities, hypertension was more prevalent in patients with EfsB (96/189, 51%) compared to those with EfmB (67/171, 39%) (p=0.027). Hematological malignancy (28/179, 16% vs. 12/196, 6%, p=0.003) and immunosuppression (48/171, 28% vs. 27/189, 14%, p=0.002) were more common in patients with EfmB. Regarding predisposing procedures, the presence of a urinary catheter at the onset of bacteremia did not differ between the two sub-populations, while the use of a drain port, central vascular catheter, or recent surgery was more prevalent in patients with EfmB. Bacteraemia was monomicrobial in a majority of the patients (137/189, 72% of EfsB vs. 138/171, 81% of EfmB, ns).

The unadjusted in-hospital mortality rates were 22% (42/189) and 20% (35/171) in the *E. faecalis* and *E. faecium* groups (ns). At 90-days post bacteraemia onset, mortality reached 34% (65/189) in the *E. faecalis* group and 33% (56/171) in the *E. faecium* group. One year mortality (assessed 2015 and 2018) was 47% and 54%, respectively.

3.2. Changing Antibiotic Prescription Practices

From 2011 to 2021, the consumption of pip/taz increased from 16,000 to 47,000 daily defined doses (DDD) per year at Sahlgrenska University Hospital as shown in Figure 2. Notably, in 2016, pip/taz emerged as the most prescribed antibiotic in the hospital, with its prescription rate steadily escalating thereafter. This increase was partially offset by a reduction in the use of cephalosporins and ciprofloxacin, although not entirely compensated. Furthermore, there was a notable rise in meropenem usage over the years, with a particularly steep incline observed from 2020 to 2021, partly attributed to revised standard dose recommendations.

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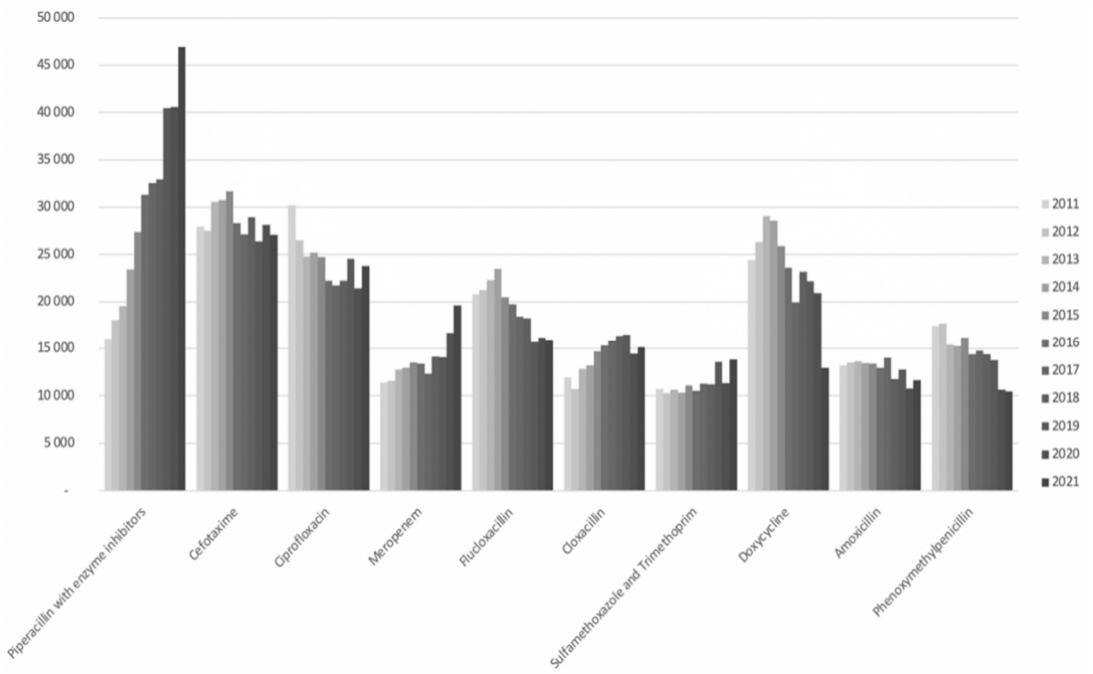

Figure 2. In-hospital antibiotic use 2011–2021 at Sahlgrenska University Hospital. Daily Defined Dose (DDD) according to World Health Organization, except for cloxacillin where a Prescribed Daily Dose (PDD) of 6 grams daily was applied.

3.3. Antibiotic Use Prior To Bacteraemia Onset

Data on antibiotic usage within 90 days before collection of the first positive blood culture with *E. faecalis* or *E. faecium* is presented in Table 2. Among patients with EfsB, 40 (21%) had received pip/taz, while the corresponding number was higher in patients with EfmB, 95 (56%) ($p<0.001$). The use of meropenem, the preferred carbapenem in the hospital, and ciprofloxacin, the predominant flouroquinolone in use, was also more prevalent in patients with EfmB. A minority of the patients in both groups had not been prescribed any antibiotics within three months before the onset of bacteraemia, and this was less common in the EfmB compared to the EfsB patients (9% vs. 38%; $p<0.001$).

Table 2. Antibiotic treatment within 90 days before positive blood culture.

	E. faecalis **n=189 (%)**	***E. faecium*** **n=171 (%)**	***p***
Pip/Taz[1]	40 (21)	95 (56)	<0.001
Cephalosporins	32 (17)	42 (22)	ns
Meropenem	14 (7)	71 (42)	<0.001
Ciprofloxacin	28 (15)	51 (30)	<0.001
No antibiotics	71 (38)	15 (9)	<0.001

Variables are listed as numbers and percentages. [1] Piperacillin-Tazobactam.

3.4. Variables Associated with E. faecium bacteraemia

In the logistic regression analysis, several variables were found to be associated with an increased odds ratio (OR) of having bacteremia with *E. faecium* compared to *E. faecalis* (Table 3). Hospital acquisition exhibited an unadjusted OR of 5.02 (95% confidence interval (CI) 3.19-7.90) and an adjusted OR (aOR) of 2.23 (95% CI 1.19–4.15) for EfmB in comparison to EfsB. Other factors related to hospital care, such as prior surgery, the presence of a central venous catheter, urinary catheter, or surgical drain, demonstrated increased ORs for *E. faecium* in univariate comparison but not after adjusting for covariates.

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Table 3. Univariate and multivariate logistic regression model for variables associated with *Enterococcus faecium* bacteraemia.

	OR[1] (95% CI[2])	*p*	aOR[3] (95% CI[2])	*p*
Age	0.96 (0.95–0.98)	<0.001		
Hospital acquired	5.02 (3.19–7.90)	<0.001	**2.23** (1.19–4.15)	**0.012**
Hypertension	0.62 (0.41–0.95)	0.027		
Hematological malignancy	2.89 (1.42–5.88)	0.003		
Immunosuppression	2.34 (1.38–3.96)	0.002		
Drain port	2.72 (1.65–4.50)	<0.001		
Central vascular catheter	5.14 (3.28–8.05)	<0.001		
Recent surgery	2.29 (1.50–3.50)	<0.001		
Pip/Taz[4] within 90 d	4.66 (2.94–7.39)	<0.001	**2.63** (1.49–4.67)	**<0.001**
Carbapenems within 90 d	8.88 (4.76–16.56)	<0.001	**4.26** (2.12–8.56)	**<0.001**
Quinolones within 90 d	2.44 (1.46–4.10)	<0.001		
No antibiotics within 90 d	0.16 (0.09–0.29)	<0.001		

If the patient had received pip/taz within 90 days before the date of the positive blood culture aOR for *E faecium* was 2.63 (95% CI 1.49–4.67). Similarly, if the patient had received meropenem, the aOR was 4.26, 95% CI 2.12–8.56. The univariate OR for *E. faecium* associated with the use of ciprofloxacin was 2.44 (95% CI 1.46–4.10), but this was not significant after adjusting for other variables (aOR 1.88, 95% CI 0.98–3.63, p=0.059).

4. Discussion

Our study, conducted over a six-year period 2015–2021 at Sahlgrenska University Hospital, aimed to investigate the potential increase in bacteraemia caused by *E. faecium* in relation to changes in antibiotic use. While our findings did not establish a significant rise, a trend towards a higher proportion of *E. faecium* compared to *E. faecalis* in the later years of the study was observed. This trend aligns with similar observations documented internationally, indicating a global increase in the prevalence of *E. faecium* bacteraemia (9-12). Moreover, the overall number of EB appeared to increase over the study period. Similar trends of rising prevalence of bacteraemia caused by *E. faecium* have been documented internationally including in studies conducted in the United Kingdom, the Netherlands, Denmark, and the United States (10-13) although opposite trends have been reported (13). It is worth noting that vancomycin-resistant enterococci (VRE) are uncommon in Sweden, unlike in the United States, where VRE accounts for a majority of EB cases. In contrast to the findings of rising EfmB incidence, a study from Switzerland reported an increase in *E. faecalis* cases (14). Notably, the reasons behind these shifts in enterococcal epidemiology remain complex and likely vary across different regions and patient cohorts.

Compared to a Danish study from 2014, our cohort exhibited a slightly higher proportion of *E. faecium* cases (6). In another cohort study conducted over 10 years in Japan, *E. faecalis* accounted for 48% of cases, *E. faecium* for 30%, and other enterococcal species for 22% (15).

Additionally, our study identified several demographic and clinical factors differing patients with bacteraemia caused by *E. faecium* compared to *E. faecalis*. Patients with EfsB were older and exhibited a higher prevalence of hypertension while hematological malignancy and immunosuppression was more common in the EfmB patients. Additionally, certain predisposing procedures, including the presence of a central vascular catheter or recent surgery, were more commonly observed in patients with EfmB. The relatively high frequency *of E. faecium* in our cohort can be attributed to the tertiary care setting at Sahlgrenska University Hospital, which includes facilities for solid organ transplantation, stem cell transplantation and specialized oncology units, among other highly advanced medical facilities. These units treat highly vulnerable and immunodeficient patients prone to nosocomial infections, and there was an independent higher OR for nosocomial aquistion of bacteraemia caused *E. faecium*

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In our population, the trend towards a higher proportion of EfmB coincided with increased use of the antibiotic piperacillin/tazobactam, which from 2016 was the most commonly used antibiotic in the hospital. Pip/taz has an excellent antimicrobial effect against *E. faecalis* while 90% of *E. faecium* strains in the study are resistant, thus likely being favored by this shift in antibiotic prescription practices. The substantial increase in the utilization of pip/taz over the study period, coupled with a concurrent rise in meropenem usage, reflects dynamic changes in antimicrobial stewardship practices and treatment preferences (15). To what extent the adoption of pip/taz as the most prescribed antibiotic in the hospital may have contributed to the observed trends in EB epidemiology remains unclear. Alternative broad-spectrum antibiotics that may be used also exert selective pressure on microbial populations. Therefore, further investigations are warranted to elucidate the complex interplay between antibiotic utilization patterns and the emergence of antimicrobial resistance.

Antibiotic exposure within 90 days prior to the onset of bloodstream infection was very common, observed in 91% of patients with EfmB and 62% of patients with EfsB. Notably, exposure to pip/taz was independently associated with a higher risk of *E. faecium*, with an adjusted odds ratio of 2.63 in the logistic regression model. The relationship between previous meropenem exposure and increased odds for E. faecium was even stronger, which was somewhat unexpected but consistent with recent studies. The findings suggest a potential effect of meropenem, particularly at high concentrations, on ampicillin-susceptible enterococci, despite this antibiotic being considered ineffective against *E. faecalis*(16). The sequential use of both antibiotics in individual patients and other unaccounted patient-related factors may also contribute to this association. Although there was a association between previous ciprofloxacin use and subsequent EfmB in the univariate comparison, it did not remain significant after adjustment. However, the selective pressure of fluoroquinolone use on enterococci, regardless of species, is likely.

Our study has several limitations that should be considered when interpreting the results. Firstly, it is a retrospective study, which inherently comes with certain limitations including reliance on existing medical records and potential for bias in data collection. Furthermore, the COVID-19 pandemic, particularly the second wave which occurred during the final years of the study may have influenced our findings. The pandemic likely led to changes in healthcare-seeking behavior, hospital admissions, and antibiotic prescribing practices, which could have impacted the incidence and characteristics of EB cases included in our study. Moreover, there are inherent differences between patients prone to bacteremia caused by *E. faecium* and those prone to *E. faecalis*, including underlying comorbidities, immune status, and healthcare exposures, among others. Additionally, our study was conducted at a single tertiary care center, which may limit the generalizability of our findings to other healthcare settings or populations. Despite these limitations, our study provides valuable insights into the epidemiology and clinical characteristics of enterococcal bacteremia, contributing to the existing body of literature on this topic. Future research, including prospective studies and multi-center collaborations, is warranted to further elucidate the factors influencing the incidence and outcomes of enterococcal bacteremia and to inform evidence-based interventions for its prevention and management.

5. Conclusions

In conclusion, our study reveals an upward trend in the proportion of bacteraemia caused by *E. faecium* over the study period of 2015 to 2021. Although the reasons for this shift remain unclear, one possible contributing factor could be changes in antibiotic usage patterns. Notably, our analysis identified three independent variables associated with a higher likelihood of acquiring EfmB compared to EfsB. These variables include nosocomial infection and prior exposure to either pip/taz or meropenem within 90 days before the diagnosis of EfmB.

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