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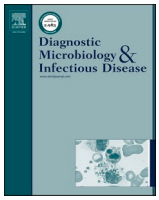

Original Article

Eubacterium bacteremia – a retrospective observational study of a seldom found anaerobic pathogen

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ABSTRACT

Background: Human infections due to *Eubacterium* are rare and knowledge of the condition is limited. This study aimed to describe clinical characteristics and outcome in patients with *Eubacterium* bacteremia.
Methods: Episodes of *Eubacterium* bacteremia were identified through the clinical microbiology laboratory in Lund, Sweden. Medical records were retrospectively reviewed. Blood isolates of *Eubacterium* were collected and antibiotic susceptibility testing was performed with agar dilution.
Results: Seventeen patients with *Eubacterium* bacteremia were identified of whom six had monomicrobial bacteremia. The incidence was 1.7 cases of *Eubacterium* bacteremia per million inhabitants and year. The median age was 67 years (interquartile range 63-79 years), and six patients had some form of malignancy. Most of the patients an abdominal focus of infection and the 30-day mortality was low ($n = 1$).
Conclusions: Invasive infections with *Eubacterium* have a low incidence. The condition has a low mortality and an abdominal focus of infection, and malignancy, is common.

1. Introduction

The genus *Eubacterium* contains Gram-positive anaerobic bacteria and was first presented as a taxon by Prévot in 1938 [1]. Since the original description, the genus has been reorganized many times with *Eubacterium limosum* defined as the type species [2]. Though recognized as part of the human gut flora for many years, and with some species found in cases of periodontitis, invasive infections such as bacteremia have only been seldom described [3].

Human infections due to *Eubacterium* have concerned intra-abdominal infections and abscesses, especially occurring in immunocompromised patients [4–6]. In addition, subacute endocarditis due to *Eubacterium* has also been described [6,7].

Other anaerobic bacteria that also involve the gastrointestinal tract encompass *Clostridium* species and *Bacteroides* species. Abdominal infections due to these two bacteria have mainly concerned intra-abdominal abscesses and cholangitis and cholecystitis [8,9]. As for these two bacteria, findings of *Eubacterium* in clinical samples from the blood have also been associated with malignancy such as adenocarcinoma of the colon [10].

The species of the genus *Eubacterium* have undergone several reclassifications in the last decades. This means that a large proportion of the few existing case reports of what was at the time classified as different species of *Eubacterium* since then has been reclassified as other genera [2,11–20]. In this study, only *Eubacterium* species recognized under the 2022 International Code of Nomenclature of Prokaryotes (ICPN) and registered in the List of Prokaryotic names with Standing in Nomenclature (LPSN) (http://lpsn.dsmz.de; accessed 1 Sept. 2023) are included [21,22].

Our study aimed to describe the clinical characteristics and outcomes in patients with invasive infections due to *Eubacterium.* In addition, we aimed to perform antibiotic susceptibility testing of blood isolates of *Eubacterium* causing human invasive infections.

1.1. Method and materials

1.1.1. Study cohort

Patients who had findings of *Eubacterium* in blood cultures from 2015

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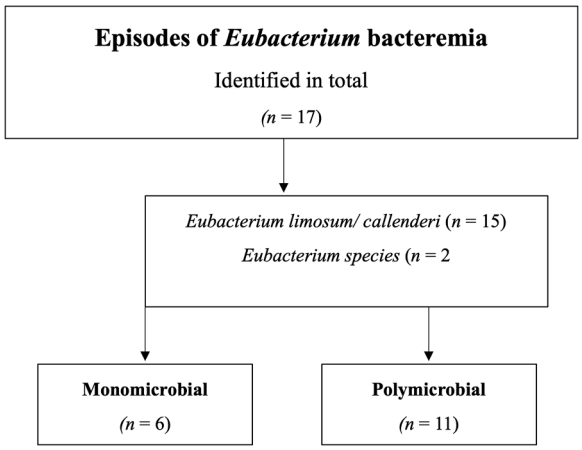

Fig. 1. Inclusion of episodes of *Eubacterium* bacteremia Flow scheme of identification of episodes of *Eubacterium* bacteremia and included episodes- Findings of other bacteria together with *Eubacterium* are listed in the column of polymicrobial episodes.

to 2021 were identified by searching the laboratory information system of Clinical Microbiology, Region Skåne, Lund, Sweden. This university hospital laboratory serves all in-patient and out-patient clinics in the region, both private and public. It is the only laboratory in the region which has a population of 1.4 million.

1.1.2. Data collection

Medical records were retrospectively reviewed, with the inclusion criteria being the growth of *Eubacterium* in blood culture (both monomicrobial and polymicrobial). Pre-determined exclusion criteria were patients who had in-hospital care during the bacteremia episode outside the region, and patients whose electronic medical records were unavailable. No exclusion was done based on age or treating clinic within the region. Clinical data were collected according to a pre-determined protocol, including age, bacterial species, the presence of other bacteria in blood culture, previous abdominal surgery, Charlson comorbidity index [23,24], chemotherapeutics or immunomodulatory drugs, fever, leukocytosis or leucopenia within 48 hours of the samples being taken. To determine sepsis and septic shock during the first 48 hours, the sepsis-3 criteria were used, and evaluated according to the Sequential Organ Failure Assessment (SOFA) score [25]. Data on antibiotic susceptibility testing using Etest on fastidious anaerobe agar, which had been entered into the laboratory information system when the isolates had originally been identified, was also extracted.

1.2. Identification of Eubacterium and antibiotic susceptibility testing

During the study period, the blood culture system used was Bactec FX (Beckton Dickinson), utilizing a standard incubation time of 5 days with two pairs of anaerobic and aerobic bottles being the recommended and most often used standard in clinical practice. The Microflex LT/SH smart matrix-assisted laser desorption/ionization–time of flight mass spectrometry (MALDI-TOF MS) using the Bruker MBT Compass software and MBT DB10833 library (Bruker Daltonics) was used to determine the bacterial species according to the International Code of Nomenclature of Prokaryotes (ICNP) [21]. The library included five species of *Eubacterium; E. brachy, E. tenue, E. yurii, E. callanderi and E. limosum*. Two of the species, *E. limosum* and *E. callenderi,* could only be securely identified as a group. Thus they could not be separated from each other and not identified at the species level by MALDI-TOF MS. A score of 2.0 or more was required for determining an isolate to the species or group level. Isolates with a score between 1.7 and 2.0 were determined to the genus level.

Frozen blood isolates of *Eubacterium* from the patients included in the study were retrieved from the culture collection of Clinical Microbiology, Region Skåne (CMRS) and cultured. The recovered bacterial isolates were sent to Clinical Microbiology at Karolinska University Hospital in Stockholm, which is a national reference laboratory for antimicrobial susceptibility testing of anaerobic bacteria. In this laboratory, agar dilution[26] was performed for clindamycin, metronidazole, benzylpenicillin, piperacillin-tazobactam, and meropenem.

Table 1
Clinical characteristics of patients with *Eubacterium* bacteremia, *n* = 17.

Clinical characteristics	
Age, median, *y*, (IQR)	67 (63–79)
Gender, male *n,* (IQR)	9 (53)
CCI, median, (IQR)	2 (0–3)
Myocardial infection, *n* (%)	3 (18)
Congestive heart failure, *n*, (%)	2 (12)
Chronic obstructive pulmonary disease, *n*, (%)	2 (12)
Liver disease, *n*, (%)	2 (12)
Solid tumour[b] *n*, (%)	5 (29)
Lymphoma *n*, (%)	1 (6)
Clinical presentation	
Fever[a], *n*, (%)	14 (82)
Shaking chills	4 (24)
Focus of infection, *n*, (%)	
Abdomen	9 (53)
Unknown	6 (35)
Lower respiratory tract	1 (6)
Urinary tract	1 (6)
Clinical course	
Length of stay, *d, n*, (IQR)	7 (5–13)
Antibiotic treatment (total), *d*, median, (IQR)	11 (10–19)
Intravenous treatment	6 (4-11)
Per oral treatment	5 (0-7)
Intensive care unit treatment, *d*, median, (IQR)	1 (6)
Outcome	
Sepsis *n*, (%)	6 (35)
30-day mortality rate, *n*, (%)	1 (6)
90-day mortality rate, *n*, (%)	2 (12)
180-day mortality rate, *n*, (%)	4 (24)
1-year mortality rate, *n*, (%)	5 (29)
Laboratory findings[c]	
CRP, mg/L, median, (IQR)	168 (128–343)
WBC count x10^9/L median, (IQR)	12.4 (7.4-18.6)

Data are presented as No. (%) unless otherwise indicated. Abbreviations used are interqartile range (IQR), Charlson comorbidity index score (CCI), C-reactive protein (CRP), white blood cell count (WBC).
[a] Within 48 hours from hospital admission.
[b] Other than lymphoma.
[c] The worst value within 48 hours from blood culture obtainment.

2. Results

2.1. Inclusion of episodes of Eubacterium

A total of 17 patients with *Eubacterium* bacteremia were identified and included in the study, giving an incidence of approximately 1.7 cases of *Eubacterium* bacteremia per million inhabitants and year. The species of *Eubacterium* detected were *E. limosum/E. callenderi* (*n* = 15). Two isolates were not possible to identify at the species or group level. Six patients had monomicrobial findings of *Eubacterium* and 11 patients were found to have polymicrobial findings from blood, Fig. 1.

2.2. Clinical features

Table 1 summarizes the clinical characteristics of patients with *Eubacterium* bacteremia. Median age was 67 years (interquartile range (IQR) 63–79 years and 53% were men. A total of six patients had any form of malignancy. Six patients developed sepsis within 48 hours of blood culture obtainment, one required treatment at the intensive care unit, and one died within 30 days of hospital admission. That patient developed sepsis and died within 24 hours of blood culture obtainment.

Table 2
Co-pathogens found in blood culture in patients with polymicrobial bacteremia.

Microorganisms found	Number of patients with finding
Eggerthella lenta	2
Eggerthella lenta, Escherichia coli	2
CoNS	2
Eggertella sp.	1
Gemella morbillorum	1
Escherichia coli, Bacteroides uniformis	1
Parabacteroides sp., Bacteroides uniformes	1
Bifidobacterium sp., Parabacteroides distasonis, Bacteroides vulgatus, Veillonella sp.	1

Patients with monomicrobial findings of *Eubacterium* had a median age of 79 years, and predominantly affected men (67%). One patient died within 30 days from hospital admission in which time to death was one day. Most of the patients presented fever and two patients had any form of malignancy, of whom one had a gastrointestinal tumor. A total of four patients had an identified focus of infection to the abdomen, encompassing perforated diverticulitis, appendicitis, perforated rectum, and pelvic abscess. Co-pathogens found in patients with polymicrobial bacteremia are listed in Table 2. Five patients with polymicrobial bacteremia had focus of infection to the abdomen, one to the respiratory lower tract and five patients had an unknown focus of infection.

2.3. Antibiotic susceptibility testing

In 14 patients the *Eubacterium* isolates were possible to retrieve from the storage freezers and re-cultured for MIC determination by agar dilution at the national reference laboratory at Karolinska University Hospital in Stockholm, Sweden. Fig. 2 shows the MIC distributions achieved by agar dilution. Altogether the MICs for meropenem, metronidazole, and piperacillin-tazobactam were low, whereas the MICs for clindamycin and benzylpenicillin tended to be higher.

3. Discussion

This is to our knowledge the largest study of invasive human infections caused by *Eubacterium*. Our study showed that it often strikes men with comorbidities in which malignancy is commonly present. The focus of infection is often to the abdomen and the 30-day mortality rate is relatively low.

The high frequency of malignancy that was seen amongst the patients with *Eubacterium* bacteremia is similar to what has been noticed in patients with infections due to other anaerobic bacteria found in the gastrointestinal tract, such as *Clostridium* species and *Bacteroides* species [8,27], and is consistent with what little has been published with regards to invasive infections with *Eubacterium* [7,10]. The fact that many of the patients had a suspected focus of infection in the abdomen is also consistent with what is known about *Eubacterium* in the normal flora.

Both 30-day and 90-day mortality rates were relatively low. The patient who died, within 30 days from hospital admission, died due to aspiration pneumonia. This is in line with other publications about *Eubacterium* but strikingly lower than data regarding clostridial infections. The co-pathogens seen in patients with patients with polymicrobial infections with *Eubacterium* were also different than the ones reported from patients with clostridial bacteremia [6,8].

The vast majority of isolates had MIC values for clindamycin above

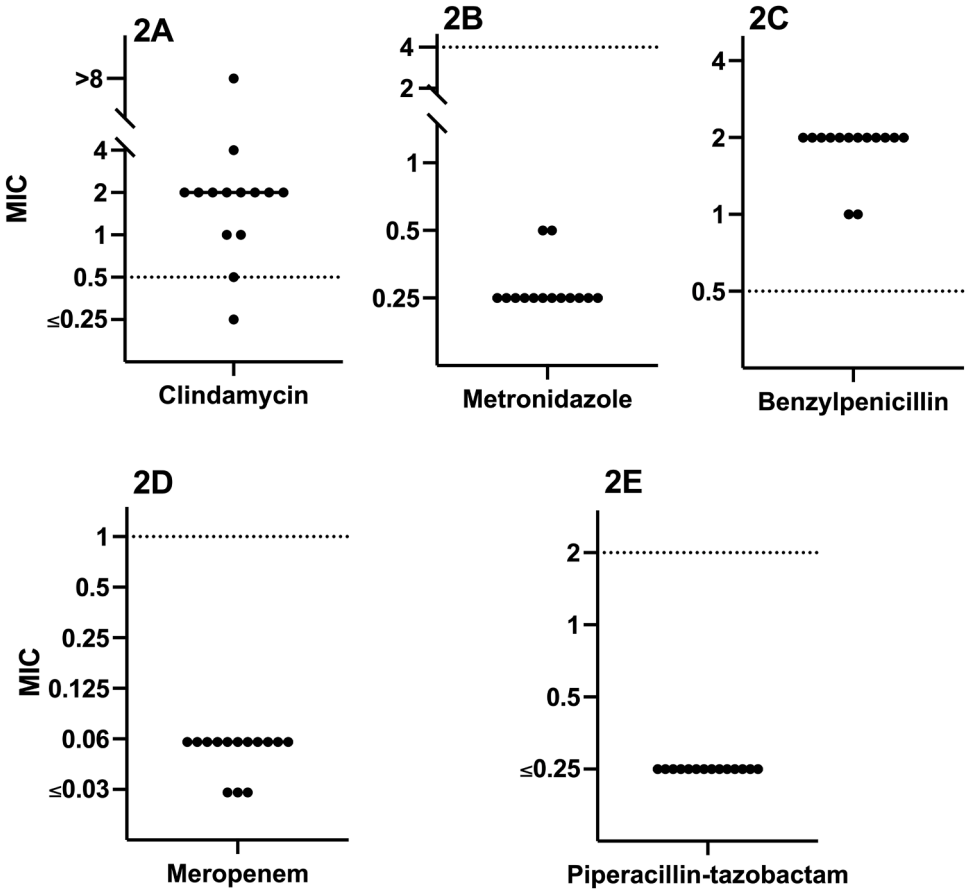

Fig. 2. Antibiotic resistance patterns of invasive isolated of *Eubacterium* bacteremia Scatter plots showing the MIC distributions obtained by agar dilution. The dotted lines show the MIC values above which EUCAST recommends against using the antibiotic in question against anaerobic bacteria without species-specific antibiotic breakpoints. A total of 14 blood isolates of *Eubacterium* were available for antibiotic susceptibility testing.

the limit where EUCAST recommends against using the antibiotics, and all isolates had MIC values above the limit for benzylpenicillin. All isolates had low MIC values, compared to the cut-off recommended by EUCAST, for metronidazole, meropenem and piperacillin-tazobactam [28]. While there are no EUCAST breakpoints for *Eubacterium*, these data indicate that metronidazole, meropenem and piperacillin-tazobactam might be useful when suspecting *Eubacterium* to be the causative pathogen in an infection. Using benzylpenicillin and clindamycin in cases of *Eubacterium* bacteremia is less likely to be successful if the results from this study are representative. All patients except two received antibiotic treatments including at least one of meropenem, piperacillin-tazobactam, or metronidazole. Sadly, the *Eubacterium* isolate from one patient who was treated with a combination of a third-generation cephalosporin and clindamycin was not possible to retrieve and test with agar dilution. Interestingly, one patient who did not receive treatment with any of the *in vitro* effective antibiotics yet survived, indicating that the pathogenic potential of the bacterium might be low.

Due to the retrospective design of the study, there is a potential for selection bias as not all patients undergo blood culture. Since previous research indicates that the proportion of patients undergoing blood culture is comparatively high in South of Sweden [29], we believe this risk of bias to be small. As is the case in retrospective studies, data were limited to what was recorded at the time of the bacteremia episode which impacts the possible analyses. Although it is to date one of the biggest cohorts of *Eubacterium* bacteremia the sample size is low, (n = 17), in which only 6 episodes had monomicrobial findings of *Eubacterium*.

4. Conclusion

Though this study is small, it represents one of the largest studies of invasive infections due to *Eubacterium*. Invasive infections with *Eubacterium* occur but are very rare in this setting. It often involves infection to the abdomen, the 30-day mortality rate is relatively low, and the isolates found are often sensitive to antibiotics commonly used in cases of abdominal infection where anaerobes are suspected.

Author contributions

TS extracted data from medical records and performed data acquisition. KL was responsible for agar dilution. AB and TS drafted the manuscript and AB performed data analysis and visualization. BO, KH and TS provided resources. TS, AB, KL, KH, and BN designed the study, critically revised the manuscript, and approved the final version of the manuscript.

Ethics

The study design was approved by the Swedish Ethical Review Authority (2022-01226). Due to the study's observational nature, the need for patient consent was waived.

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CRediT authorship contribution statement

Anna Bläckberg: Conceptualization, Formal analysis, Methodology, Writing – original draft, Funding acquisition. **Karin Holm:** Conceptualization, Methodology, Writing – review & editing. **Karin Liderot:** Investigation, Resources, Writing – review & editing. **Bo Nilson:** Investigation, Methodology, Validation, Writing – review & editing. **Torgny Sunnerhagen:** Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft.

Declaration of competing interest

No potential conflict of interest was reported by the authors.

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