ORIGINAL PAPER

Clinical characteristics and antimicrobial susceptibility of *Eggerthella lenta* infection over a 5-year trend at a university hospital in Japan

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ABSTRACT

Eggerthella lenta (*E. lenta*) is known to cause intra-abdominal and anaerobic bloodstream infections. However, clinical insights and information on antimicrobial susceptibility in *E. lenta* infections are limited. This study aimed to elucidate the clinical characteristics and antimicrobial susceptibility of *E. lenta* infections. Patients with *E. lenta* isolated from various specimens who presented at Aichi Medical University Hospital between January 2018 and December 2022 were included. Patient information was retrospectively collected from electronic medical records. Logistic regression analysis was conducted to identify risk factors for bloodstream infections. The antimicrobial susceptibility of various antimicrobial agents against isolated strains was investigated. During the study period, seventy cases were classified as infection cases. The median age of patients was 69 years (range: 15–100 years), and 48 (68.6%) were males. The most common site of infection was the lower digestive tract (54.3%). In 70.4% of cases, polymicrobial infections occurred. Community-acquired infection was a significant risk factor for bloodstream infection, with an odds ratio of 4.94 (95% confidence interval: 1.02–23.9). The 30-day mortality rate was 10.0%. Univariate analysis showed lower mortality in patients who underwent surgical intervention than in those who did not (42.9% vs 57.1%, $p = 0.02$). The proportion of minimal inhibitory concentrations (MICs) of ≥ 32 μg/mL for piperacillin-tazobactam was 6.3%. Additionally, the proportions of MICs of ≥ 8 μg/mL for imipenem and meropenem were 1.4% and 0%, respectively. *E. lenta* should be considered when blood cultures yield gram-positive rods in community-acquired intra-abdominal infections. Effective treatment involves both antimicrobial agents and surgical interventions.

Keywords: *Eggerthella lenta*, antibiotic susceptibility, anaerobe, minimum inhibitory concentration, surgical intervention

Abbreviations:
E. lenta: *Eggerthella lenta*
BSI: bloodstream infection
MIC: minimal inhibitory concentration
PIPC/TAZ: piperacillin-tazobactam

INTRODUCTION

Eggerthella lenta (*E. lenta*), a non-spore-forming, anaerobic, gram-positive bacillus, is part of the normal human intestinal microbiota and was formerly classified under the *Eubacterium* genus.[1] Although the correct identification of *Eggerthella, Paraeggerthella*, and *Eubacterium* at the species level is difficult to achieve using conventional phenotypic methods,[2] the recent availability of simple identification methods such as matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry is making it easier to identify *E. lenta*.[3] The recent emergence of *E. lenta* as a potent etiologic agent of anaerobic bloodstream infections (BSIs) and intra-abdominal infection has prompted the investigation of its clinical significance.[4,5]

A population-based cohort study of *E. lenta* BSIs highlights the pathogen's association with severe intra-abdominal infections.[6] The study underscored the challenges posed by its elevated minimal inhibitory concentrations (MICs) to widely used antibiotics, particularly piperacillin-tazobactam (PIPC/TAZ). Despite the increasing recognition of its importance, mainly due to the high mortality associated with *E. lenta* BSI, clinical characteristics, risk factors, and appropriate antimicrobial choices remain poorly understood.

Given the limited reports on *E. lenta* infections, to clarify the clinical characteristics and antimicrobial susceptibility of *E. lenta* infections, we conducted a detailed review of clinical records and microbiological data to comprehensively determine the 5-year *E. lenta* infection rates in the Aichi Medical University Hospital.

MATERIALS AND METHODS

Study design and setting

This retrospective study included all patients with *E. lenta* infections admitted to Aichi Medical University Hospital, a 900-bed tertiary care and teaching hospital in Aichi, Japan, between January 2018 and December 2022.

E. lenta infection is defined as the isolation of *E. lenta* from any patient showing signs of infection, as determined by attending physicians. The following clinical data were collected from the patients' electronic medical records: age, sex, underlying disease, infection onset (community-acquired: infections contracted outside of a hospital or diagnosed within 48 h of admission; hospital-acquired: infections acquired after hospitalization and manifesting 48 h after admission to the hospital), site of infection, presence or absence of multiple microorganisms isolated along with *E. lenta*, Charlson comorbidity index, admission in the intensive care unit (ICU) on diagnosis, surgical intervention such as drainage or operation as treatment, duration of antibiotics usage, 30-day mortality, and recurrence rate within two months.

Identification of E. lenta and antimicrobial susceptibility testing

Clinical specimens were routinely inoculated onto Brucella HK agar (Kyokuto Pharmaceutical Co, Tokyo, Japan) and incubated for 48 h at 35 °C using an anaerobic chamber (Hirasawa, Tokyo, Japan). We used MALDI-TOF mass spectrometry (Bruker Biotyper MBT Smart, Bruker Daltonics, MA, USA) to identify the *E. lenta* based on the most dominant species in the samples.

All isolates were anaerobically subcultured on Brucella HK using AnaeroPack (Mitsubishi Gas Chemical, Tokyo, Japan) at 35 °C for 48 h. Using a 2.0 McFarland's dilution standard, bacterial

solutions were prepared from the developed pure culture colonies using ABCM anaerobic broth (Eiken Chemical, Tokyo, Japan). From this solution, 25 µL was added to 12 mL of susceptible Brucella broth 'Eiken' (Eiken Chemical, Tokyo, Japan); the solution was mixed slowly via inversion, and a volume of 100 µL each was inoculated onto 'Eiken' dry plates (Eiken Chemical). The inoculated plates were incubated for 48 h under the same conditions as those used for pure culture. The MICs of eight antimicrobial agents were determined, including ampicillin (ABPC), ampicillin/clavulanate (AMPC/CVA), PIPC/TAZ, cefmetazole (CMZ), clindamycin (CLDM), imipenem (IPM), meropenem (MEPM), and moxifloxacin (MFLX). The MICs of these antimicrobial agents were compared with those reported from susceptibility tests for *E. lenta* using the dry plate methods.[7]

Statistical analyses

Continuous variables such as age were expressed as medians and interquartile ranges (IQRs). The Mann–Whitney U test was used to compare continuous variables, whereas Fisher's exact test was used for categorical variables. Multivariable logistic regression was performed to predict the risk factors for *E. lenta* bloodstream infection. Candidate variables selected were those with *p* <0.05 on univariate analysis and our clinical practice. *P*-values <0.05 were considered statistically significant. Stata version 14.2 (STATA Inc, TX, USA) was used for the statistical analyses.

RESULTS

Patient characteristics

A total of 90 *E. lenta* isolates were obtained from inpatients and outpatients during the study period. Isolates from the same patient at the same site were considered as one specimen, resulting in 72 *E. lenta* isolates from 71 patients. Two specimens from one patient were isolated from blood and intra-abdominal abscess. Among 72 isolates, two were determined to be carriers by the attending physician. Finally, 70 cases of *E. lenta* infections were identified: 23 (32.9%) were BSI, and 47 (67.1%) occurred at other sites (non-BSI) (Table 1). The median age was 69 years (range: 15–100 years), with males constituting 68.6% of the total patients. Common comorbidities included solid organ malignancy 34.3% (24/70), diabetes mellitus 20.0% (14/70), and cerebrovascular diseases 10.0% (7/70).

Table 1 Baseline characteristics of patients with *Eggerthella lenta* infection

Variables	All (n=70)	Bloodstream infection (n=23)	Non-bloodstream infection (n=47)	*p* value
Age (years), median (IQR)	69 (58–79)	71 (58–81)	69 (57–77)	0.35
Male sex, no. (%)	48 (68.6)	17 (73.9)	31 (66.0)	0.59
Community-acquired no. (%)	53 (75.7)	21 (91.3)	32 (60.4)	0.04
Comorbidities, no. (%)				
Diabetes mellitus	14 (20.0)	5 (21.7)	9 (19.2)	1.00
Chronic kidney disease	9 (12.9)	3 (13.0)	6 (12.8)	1.00
Heart failure	3 (4.3)	3 (13.0)	0 (0.0)	0.03
Ischemic heart disease	4 (5.7)	1 (4.4)	3 (6.4)	1.00
Peripheral artery disease	3 (4.3)	0 (0.0)	3 (6.4)	0.55
Chronic liver disease	6 (8.6)	1 (4.4)	5 (10.6)	0.66
Chronic obstructive pulmonary disease	4 (5.7)	1 (4.4)	3 (6.4)	1.00
Cerebrovascular disease	7 (10.0)	1 (4.4)	6 (12.8)	0.41
Solid organ malignancy	24 (34.3)	7 (30.4)	17 (36.2)	0.79
Hematologic malignancy	0 (0)	0 (0.0)	0 (0.0)	–
Dementia	6 (8.6)	4 (17.4)	2 (4.3)	0.09
Rheumatologic disease	0 (0)	0 (0.0)	0 (0.0)	–
Source of infection				
Perforation of the lower digestive tract	22 (31.4)	6 (26.1)	16 (34.0)	0.59
Appendicitis	16 (22.9)	6 (26.1)	10 (21.3)	0.76
Skin and soft tissue infection	9 (12.9)	1 (4.4)	8 (17.0)	0.25
Surgical site infection	8 (11.4)	1 (4.4)	7 (14.9)	0.26
Bacterial translocation	5 (7.1)	5 (21.7)	0 (0.0)	<0.01
Urinary tract infection	4 (5.7)	1 (4.4)	3 (6.4)	1.00
Bile tract infection	3 (4.3)	2 (8.7)	1 (2.1)	0.25
Necrotizing fasciitis	2 (2.9)	1 (4.4)	1 (2.1)	1.00
Polymicrobial infection, no. (%)	49 (70.0)	6 (26.1)	43 (91.5)	<0.01
Charlson comorbidity index, median (IQR)	1 (0–3)	1 (0–4)	1 (0–3)	0.30
ICU admission at diagnosis, no. (%)	31 (44.3)	15 (65.2)	16 (34.0)	0.02
Surgical interventions, no. (%)	57 (81.4)	12 (52.2)	45 (95.7)	<0.01
Duration of administering antibiotics, median (IQR)	10 (7–14)	11 (8–14)	10 (7–14)	0.76
30-day all-cause mortality, no. (%)	7 (10.0)	4 (17.4)	3 (6.4)	0.21
Recurrence within two months, no. (%)	0 (0)	0 (0.0)	0 (0.0)	1

IQR: interquartile range
ICU: intensive care unit

Clinical presentation of E. lenta infection

E. lenta infections were mainly of community-acquired (75.7%). The most common site of infection was lower digestive tract (54.3%), including cases of appendicitis (Table 1). Other sources of infections were skin and soft tissue, including cases of necrotizing fasciitis (15.8%), surgical site infection (11.4%), bacterial translocation (7.1%), urinary tract infection (5.7%), and bile tract infection (4.3%). Bacterial translocations had no other obvious source of infection, causing intestinal symptoms, such as enteritis or ileus. Bacterial translocations accounted for 21.7% (5/23) of BSI. Most *E. lenta* infections were polymicrobial infections (70.0%, 49/70). The median Charlson comorbidity index was 1 point (IQR: 0–3). The rate of ICU admission at diagnosis was 44.3% (31/70). In the univariate analysis, the patients with *E. lenta* BSI were more likely to be of community-acquired ($p = 0.04$), to have heart failure ($p = 0.03$), and to be admitted to ICU at diagnosis ($p = 0.02$), and less likely to be polymicrobial infection ($p < 0.01$). In the multivariate analysis, two variables were included in the final model based on the total number of BSI cases. Multivariate logistic regression analysis indicated that community-acquired was statistically significantly associated with *E. lenta* BSIs (odds ratio: 4.94, 95% confidence interval [CI]:1.02-23.9; Table 2).

Table 2 Logistic regression analysis for risk factors associated with *Eggerthella lenta* bloodstream infection

Characteristics	Odds ratio*	*p* value	95% confidence interval
Community-acquired	4.94	0.047	1.02–23.9
Charlson comorbidity index	0.97	0.83	0.76–1.24

*Multivariable logistic regression

Treatment and outcomes

Sixty-seven patients (95.7%) received antimicrobial agents for *E. lenta* infections. Fifty-seven patients (81.4%) underwent surgical interventions (Table 1). The 30-day all-cause mortality was 10.0% (7/70). Although not statistically significant, the 30-day all-cause mortality was higher for BSI (17.4%) than for non-BSI (6.4%; $p = 0.21$). There were no patients with recurrence within two months. In the univariate analysis, risk factors associated with 30-day all-cause mortality included older age ($p < 0.01$), female sex ($p = 0.03$), chronic kidney diseases ($p = 0.04$), peripheral artery diseases ($p = 0.03$), solid organ malignancy ($p = 0.04$), and high Charlson comorbidity index ($p < 0.01$; Table 3). Furthermore, surgical intervention showed a statistical advantage in survivors compared to those who died within 30 days ($p = 0.02$). When comparing survivors with those who died, empiric PIPC/TAZ monotherapy tended to be more common among those who died (42.9% vs 14.3%, $p = 0.09$), while empiric carbapenem monotherapy (28.6% vs 57.1%, $p = 0.70$) was less common. However, these monotherapies were not statistically significantly associated with 30-day all-cause mortality. Among the 12 patients treated with empirical PIPC/TAZ alone, one survivor had an *E. lenta* isolate with a high MIC (>64 μg/mL) for PIPC/TAZ.

Table 3 Univariate 30-day mortality analysis with *Eggerthella lenta* bloodstream infections

Variables	Dead within 30-day (n=7)	Alive (n=63)	*p* value
Age (years), median (IQR)	83 (79–84)	68 (55–77)	< 0.01
Female sex, no. (%)	5 (71.4)	17 (27.0)	0.03
Community-acquired no. (%)	7 (100)	46 (73.0)	0.18
Comorbidities, no. (%)			
Diabetes mellitus	1 (14.3)	13 (20.6)	1.00
Chronic kidney disease	3 (42.9)	6 (9.5)	0.04
Heart failure	0 (0.0)	3 (4.8)	1.00
Ischemic heart disease	1 (14.3)	3 (4.8)	0.35
Peripheral artery disease	2 (28.6)	1 (1.6)	0.03
Chronic liver disease	0 (0.0)	6 (9.5)	1.00
Chronic obstructive pulmonary disease	0 (0.0)	4 (6.4)	1.00
Cerebrovascular disease	2 (28.6)	5 (7.9)	0.14
Solid organ malignancy	5 (71.4)	19 (30.2)	0.04
Hematologic malignancy	0 (0.0)	0 (0.0)	–
Dementia	2 (28.6)	4 (6.4)	0.11
Rheumatologic disease	0 (0.0)	0 (0.0)	–
Gastrointestinal perforation, no. (%)	2 (28.6)	20 (31.8)	1.00
Charlson comorbidity index, median (IQR)	4 (3–6)	1 (0–3)	< 0.01
ICU admission at diagnosis, no. (%)	3 (42.9)	28 (44.4)	1.00
Surgical interventions, no. (%)	3 (42.9)	54 (87.1)	0.02
Empiric PIPC/TAZ monotherapy	3 (42.9)	9 (14.3)	0.09
Empiric carbapenem monotherapy	2 (28.6)	36 (57.1)	0.70

IQR: interquartile range
ICU: intensive care unit
PIPC/TAZ: piperacillin-tazobactam

Antimicrobial susceptibilities

Table 4 shows the MICs of ABPC, AMPC/CVA, PIPC/TAZ, CMZ, CLDM, IPM, MEPM, and MFLX for *E. lenta* isolates.

Table 4 Antimicrobial susceptibility distribution

	Number of isolates stratified by MICs (µg/mL)										
	0.12	0.25	0.5	1	2	4	8	16	32	64	128
Ampicillin	5	6	13	31	12	3					
Ampicillin/clavulanate			53	7					2		
Piperacillin/tazobactam				3	3	5	21	26	4		1*
Cefmetazole					16	13	24	12	4		1*
Clindamycin		48	11	4	2	1	2	2			
Imipenem		6	51	10	2			1			
Meropenem		4	61	2	2	1					
Moxifloxacin			29	2	8	9	11	10			

MIC: minimal inhibitory concentration

* MIC >64 µg/mL

DISCUSSION

Over five years, we investigated the clinical characteristics of *E. lenta* infection and its antimicrobial susceptibilities at a university hospital in Japan. The majority of *E. lenta* infections were observed in the gastrointestinal infections. BSI occurrences were approximately 30%, and community-acquired infections were a risk factor for BSI. Surgical intervention was more common among survivors of *E lenta* infection.

E. lenta BSIs are often associated with high mortality rates and are commonly linked to intra-abdominal sources. The mortality rate of *E. lenta* BSI, reported to a range from of 20 to 36% in previous studies,[5-8] is similar to that observed in our study (17.4%). A university hospital in Taiwan also reported an overall 60-day mortality rate of 19%.[4] Jian et al[9] reported that *E. lenta* BSI should be considered in patients with tumors, diabetes mellitus, and appendicitis, based on literature review findings from 2000 to 2020. However, this literature review only examined *E. lenta* BSI without comparing them to non-BSI cases. In a cohort study in Canada,[6] similar to our study, diabetes mellitus and malignancy were the most common underlying diseases for BSI and non-BSI. Therefore, these underlying diseases may be the risk factors not only for *E. lenta* BSI but also for *E. lenta* infection itself. We showed that community-acquired infection is a risk for *E. lenta* BSI. Primary infections were mainly of the gastrointestinal tract, and BSIs due to postoperative gastrointestinal tract infection were rare. Therefore, *E. lenta* should be considered as a differential diagnosis when gram-positive rods are isolated from blood cultures in community-acquired gastrointestinal tract infections, including gastrointestinal perforation.

The CLSI recommends the agar dilution method for antimicrobial susceptibility testing of *E. lenta*, with breakpoints determined based on its MICs. However, as this method is labor-intensive and requires specialized laboratory facilities, alternative methods such as E-tests, disc diffusion tests, and dry plates, which are simpler and quicker to perform and are commonly used in routine work, have been utilized to determine the antimicrobial susceptibilities of *E. lenta*.[5,7,10-12] This study compared the antimicrobial susceptibility of *E. lenta* with that reported in a previous report,[7] which assessed the antimicrobial susceptibility of *E. lenta* using the dry plate method. In this study, the proportion of MICs of 1 µg/mL or more for ABPC was 65.7% (46/70), compared to 84.6% in the previous report. The proportion of MICs of 32 µg/mL or more for PIPC/TAZ was

6.3% (4/63) in our study and 7.7% in the previous report. The proportion of MICs of 32 µg/mL or more for CMZ was 7.1% (5/70) in our study and 0% in the previous report. Moreover, in our study, the proportion of MICs of 4 µg/mL or more for CLDM was 7.1% (5/70), compared to 7.7% in the previous report. The proportion of MICs of 8 µg/mL or more for IPM was 1.4% (1/70) in the current study and 0% in the previous study. The proportion of MICs of 8 µg/mL or more for MEPM was 0% both in our study and in the previous report. In our study, the proportion of MICs of 4 µg/mL or more for MFLX was 43.5% (30/69), compared to 38.5% in the previous report. A retrospective study showed no remarkable differences between the agar dilution and the E-test methods for determining the antimicrobial susceptibility of *E. lenta*, except for PIPC/TAZ, where a slightly higher percentage of resistant isolates was observed with the E-test.[11] However, there is a lack of studies directly comparing the results of antimicrobial susceptibility testing obtained using dry plate methods to those obtained via agar dilution methods. Future research is needed to elucidate the extent of correlation between the results from these two methods and to determine if the established breakpoints are applicable to the dry plate methods.

Previous studies showed that the mortality due to *E. lenta* BSI is associated with empiric PIPC/TAZ monotherapy and ICU stay.[6,8] In recent years, increased MIC of PIPC/TAZ has been reported.[4,6,10,11] These data suggest that PIPC/TAZ may be ineffective as an empiric therapy. There has been a debate on the PIPC/TAZ breakpoints for *E. lenta*,[6] and future options for treating *E. lenta* infections need to be considered. Although the all-cause 30-day mortality tended to be higher in our study when empirical PIPC/TAZ was used alone, the difference between groups was not statistically significant. Furthermore, our data demonstrated a statistically significantly greater incidence of surgical interventions among survivors compared to non-survivors of *E. lenta* infections, which predominantly manifested as intra-abdominal infections. Established guidelines for managing intra-abdominal infections emphasize the critical importance of timely and adequate source control.[13] Although the reduced susceptibility of *E. lenta* to PIPC/TZP should be noted, the present findings indicate that appropriate surgical management is an important factor in determining patient outcomes in *E. lenta* infections.

Several limitations in our study should be considered. First, the retrospective nature of our analysis introduced inherent biases and limitations related to data availability and accuracy. Second, the single-center design may limit the generalizability of our findings to broader populations. Third, the limited sample size, although reflecting the rarity of *E. lenta* infections, may affect the statistical power of certain analyses. Nevertheless, the strength of our study lies in its comprehensive analysis over five years. The careful collection of clinical and microbiological data increases the reliability of our findings and contributes to the evolving understanding of this pathogen.

In conclusion, our retrospective analysis of *E. lenta* infections at a university hospital in Japan indicates that *E. lenta* should be considered in cases where blood cultures yield gram-positive rods in community-acquired intra-abdominal infections. Moreover, aggressive surgical interventions remain essential for *E. lenta* infection.

ETHICS APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. The Institutional Review Board (IRB) of Aichi University Hospital (Aichi, Japan) approved this study (approval number: 2023-222) and waived the need for informed consent from the patients. All procedures were performed in accordance with the IRB guidelines and regulations.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conceptualization and Methodology. Material preparation, data collection, and analysis were performed by Nobuaki Mori and Akiko Nakamura. The first draft of the manuscript was written by Nobuaki Mori and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

FUNDING

ACKNOWLEDGMENTS

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