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Background: The incidence of *Enterococcus faecalis* infective endocarditis is increasing over time. Data on the impact of minimum inhibitory concentration (MIC) of amoxicillin on treatment outcomes are scarce. The objective of this study was to describe the epidemiology of *E. faecalis* infective endocarditis and to evaluate whether the MIC of amoxicillin might influence mortality.

Materials: We retrospectively included all consecutive patients diagnosed with definite *E. faecalis* infective endocarditis between 2013 and 2020 in 11 French hospitals. We extracted data from the local diagnosis-related group (DRG) database and matched these data with microbiological results. Amoxicillin MIC was determined by Etest strip. The primary endpoints were endocarditis-related mortality and risk factors for endocarditis-related mortality including amoxicillin MIC.

Results: A total of 403 patients with definite *E. faecalis* infective endocarditis were included. Patients were predominantly male (76.4%) with a median age of 74 years (67–82). Embolic complications occurred in 170 (42.1%) patients. Cardiac surgery was performed in 158 (61.5%) patients. The endocarditis-related mortality rate was 28.3% and the median delay between mortality and onset of hospitalization was 24 (9; 41) days. *E. faecalis* MIC of amoxicillin was available for 246 (61%) patients. The median MIC was 0.5 mg/L (0.4–0.7). Amoxicillin MIC was not found to be associated with in-hospital mortality. None of the variables included in the multivariate model were identified as a risk factor for mortality and there was no correlation between mortality and the duration of treatment for 4 weeks versus 6 weeks.

Conclusions: Higher amoxicillin MIC was not a risk factor leading to endocarditis-related mortality in definite *E. faecalis* infective endocarditis. However, further studies are needed to assess the effect of amoxicillin MIC on relapse.

Introduction

Infective endocarditis (IE) is a complex infection associated with a high rate of morbidity and mortality, with an overall in-hospital mortality of ∼20%.[1,2] Enterococci are responsible for 16% of all infective endocarditis, while *Enterococcus faecalis* is by far the most common species, accounting for >90% of enterococcal IE cases.[1,3] Enterococci primarily affect older individuals with underlying medical conditions as colorectal cancer[4] and are often found on prosthetic valves, especially after transcatheter aortic valve implantation.[5]

Treatment of *E. faecalis* IE is based on a combination of an aminopenicillin and gentamicin or ceftriaxone, both associations showing similar clinical effectiveness.[6]

Several factors, including adhesion to endothelial surfaces, biofilm formation, and host immune modulation,[7–9] may explain why patients with enterococcal IE are at higher risk of relapses than other causes of endocarditis.[3,10,11] Although separated since 1984, streptococci share taxonomic and biologic similarities with enterococci.[12,13]

In the context of streptococcal IE, the negative impact of an increased amoxicillin minimum inhibitory concentration (MIC) of amoxicillin on mortality has been demonstrated,[14] but, to date, no study has evaluated the impact of MIC of amoxicillin on outcomes in patients treated for *E. faecalis* IE. This retrospective multicentre study sought to describe the epidemiology *of E. faecalis* endocarditis and the impact of MIC of amoxicillin on the treatment outcomes.

Materials and methods

Study design

We conducted an observational retrospective study including all consecutive cases of definite *E. faecalis* IE from 11 French hospitals [details in Table S1 (available as Supplementary data at *JAC-AMR* Online)] between 1 January 2013 and 31 December 2020.

All patients aged 18 years or older with IE according to the modified Duke criteria (i.e. the Duke–Li classification[15,16]) with either positive blood and/or valve cultures yielding *E. faecalis*, were included in the study. We extracted data from the local diagnosis-related group (DRG) database and these data were matched with microbiological results. Prosthetic valve endocarditis was considered early onset if it occurred within the first year after valve implantation and late onset if occurred thereafter.

Exclusion criteria were: patients with suspected *E. faecalis* IE who did not meet the modified Duke criteria for definite endocarditis; patients deprived of liberty (i.e. patients under guardianship, curatorship or court protection) and/or patients who objected to the use of their data for this research.

Microbiological diagnosis

Blood cultures bottles were incubated up to 14 days in case of suspicion of endocarditis. Automated devices for blood culture incubation were BacT/ALERT (bioMérieux, Marcy-l'étoile, France) or Bactec FX (Becton Dickinson, Franklin Lakes, NJ, USA). Positive blood culture broths were plated on Columbia agar with 5% horse blood or a chocolate agar incubated in anaerobic conditions and a 5% CO_2-enriched atmosphere. Microorganisms were identified by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MALDI Biotype, Bruker) or (Vitek MS, bioMérieux) as recommended by manufacturers where available. Antimicrobial susceptibility testing was performed according to CA-SFM/EUCAST guidelines[17] in each centre using the disc diffusion method. Results of MIC of amoxicillin and penicillin G were collected when available. They were determined by Etest strips (bioMérieux®) on agar plates according to the manufacturer's recommendations. The resistant MIC Breakpoint was ≥8 mg/L according to CA-SFM/EUCAST guidelines.[17]

Data collection

Data on clinical, paraclinical and microbiological variables, as well as treatment and follow-up of *E. faecalis* IE, were collected from the patients' medical records. The data collected were integrated into an anonymous database designed for this study.

Study endpoints

The primary endpoint was endocarditis-related mortality and identification of risk factors for mortality including MIC of amoxicillin in patients with *E. faecalis* IE. Secondary endpoints were the description of clinical and demographic characteristics of patients with *E. faecalis* endocarditis.

Table 1. Demographic and clinical characteristics of 403 patients with *E. faecalis* IE, France, 2013–2020

Characteristic	Total (403)	MIC data missing (157)	MIC available (246)	*P*
Male	308 (76.4%)	119 (75.8%)	189 (76.8%)	0.81
Age, years[a]	74 [67;82]	73.8 [67;82]	74 [67;82]	0.61
Weight, kg[a]	73 [63;85]	73 [63;85]	73 [63;85]	0.65
Diabetes mellitus	105 (26.1%)	43 (27.4%)	62 (25.2%)	0.63
Chronic renal insufficiency[a]	114 (28.4%)	51 (32.7%)	63 (25.6%)	0.12
Prosthetic valve	181 (45%)	70 (17%)	111 (28%)	0.27
Biologic	130 (71.8%)	47 (67.1%)	83 (74.8%)	
Mechanic	51 (28.2%)	23 (32.9%)	28 (25.2%)	
CIED	27 (6.8%)	8 (5.2%)	19 (7.8%)	0.28
Delay between previous surgery/implantation and diagnosis of IE, month	72 [14.6;141.8]	89.7 [8.2;144.9]	63.5 [18.5;258.9]	0.42
Intensive care[a]	164 (40.8%)	68 (43.6%)	96 (39%)	0.36
Length of stay in hospital, days[a]	27 [19;41]	27 [18;44]	27 [20;39.5]	0.89

Quantitative variables are described by their median and IQR range. Categorical variables are presented as absolute numbers (percentages, %).
[a]Missing data (see details in Table S2).

Table 2. Infection characteristics and management in 403 patients with *E. faecalis* IE, France, 2013–2020

Characteristic	Total (403)	MIC data missing (157)	MIC available (246)	*P*
Community acquired infection	207 (51.2%)	82 (52.2%)	125 (50%)	0.73
Valve type[a]				**0.038**
Native	202 (51%)	84 (53.5%)	118 (48%)	
Prosthetic	152 (38.8%)	47 (29.9%)	105 (42.7%)	
CIED	27 (7%)	14 (8.92%)	12 (4.88%)	
Prosthetic and CIED	6 (1.52%)	1 (0.6%)	5 (2.03%)	
Location of valve infection[a]				
Aortic	239 (61.4%)	80 (55.2%)	159 (65.2%)	0.05
Mitral	140 (35.9%)	49 (33.6%)	91 (37.3%)	0.46
Tricuspid	16 (4.1%)	8 (5.9%)	8 (3.3%)	0.29
Pulmonary	4 (1%)	2 (1.4%)	2 (0.8%)	0.63
Number of valves involved[a]				**0.049**
1	298 (76.6%)	115 (78.8%)	183 (75.3%)	
2	48 (12.3%)	11 (7.5%)	37 (15.2%)	
3 or more	43 (11.1%)	20 (13.7%)	23 (9.5%)	
Embolic complications[a]	170 (42.1%)	63 (40.7%)	106 (43.1%)	0.63
Source of infection found[a]	172 (42.9%)	69 (44.5%)	103 (41.9%)	0.6
Antibiotic therapy[a]				
Amoxicillin/Ceftriaxone	289 (72.1%)	114 (73.6%)	175 (71.1%)	0.60
Amoxicillin/Gentamicin	77 (19.2%)	21 (13.6%)	56 (22.8%)	**0.023**
Glycopeptide/other agents	20 (5%)	8 (5.2%)	12 (4.9%)	0.90
Other combination therapy	6 (1.5%)	4 (2.6%)	2 (0.8%)	0.21
Monotherapy	9 (2.2%)	8 (5.2%)	1 (0.4%)	**0.003**
Transition to oral relay[a]	39 (13%)	22 (17.5%)	17 (9.7%)	**0.048**
Surgery performed[a]	158 (61.5%)	51 (53.7%)	107 (66%)	0.05
Delay between EI diagnosis and surgery, days[a]	9.0 [4.5;24.0]	15.0 [7.0;26.0]	8.0 [4.0;18.8]	**0.017**
Positive valve culture[a]	80 (52.3%)	20 (39.2%)	60 (58.8%)	**0.022**
Duration of bacteraemia, days[a]	3 [1;4]	3 [1;5]	3 [1;4]	0.91
Duration of combination therapy, days[a]	42 [23;44]	42 [23;44]	42 [23;44]	0.95
Duration of antimicrobial therapy, days[a]	42 [42;47]	42 [42;48]	42 [42;46]	0.45

Quantitative variables are described by their median and interquartile (IQR) range. Categorical variables are presented as absolute numbers (percentages, %).
The number in bold corresponds to "*P*" < 0.05 for the corresponding variable.
[a]Missing data (see details in Table S2).

Table 3. Endocarditis-related mortality of 403 patients with *E. faecalis* IE, France, 2013–2020

Characteristic	Total (403)	MIC data missing (157)	MIC available (246)	*P*
In-hospital mortality[a]	114 (28.3%)	46 (29.9%)	68 (28%)	0.69
Delay between mortality and onset of hospitalization, days[a]	24 [9;41]	21 [8;37]	28 [12;42]	0.46

Quantitative variables are described by their median and interquartile (IQR) range. Categorical variables are presented as absolute numbers (percentages, %).
[a]Missing data (see details in Table S2).

Ethics

In accordance with our institution policy, patients were informed that personal data were collected and stored on a secure database regularly declared to the national competent authorities (Commission Nationale Informatique et Libertés, CNIL) (IRB number 00012157). All statistical analyses were performed on anonymized data and procedures were in accordance with the ethical standards of the national research committee and the Declaration of Helsinki. For this type of observational retrospective study, formal consent was not required.

Statistical analysis

Quantitative variables were described by their median and interquartile (IQR) ranges (Q1; Q3). Student's *t*-test was used when the validity conditions were met; otherwise, a Wilcoxon test was used.

Qualitative variables were reported as numbers (proportions). A Chi-squared test was performed when the conditions for use were met, and Fisher's test was performed when the conditions were not met. Odds ratios (OR) and their confidence intervals (CI) were also reported.

To identify risk factors associated to mortality, we fitted unconditional logistic regression models. We included explanatory variables in the initial models if associated with the dependent variable at $P<0.10$ in univariate analysis. We then performed backward analysis: we kept explanatory variables associated with the dependent variable that had $P<0.10$.

The receiver operating characteristic (ROC) curve for MIC as a function of death was also plotted, along with the area under the curve (AUC) (CI 95%).

Analyses were performed using R software (R Core Team, 2021). All tests were two-tailed and a *P* value of <0.05 was considered statistically significant.

No multiple imputation method was used for addressing the presence of missing data.[18]

Results

A total of 403 patients were included in the study. Missing data are shown in the Supplementary Appendix (Table S2).

Patient characteristics

Patients were predominantly male (76.4%) with a median age of 74 years (IQR, 67–82) (Table 1). One hundred and five (26.05%) patients had diabetes mellitus, and 114 (28.3%) had chronic renal insufficiency. One hundred and eighty-one (44.9%) had a prosthetic valve (mechanical or biological), and 27 (6.7%) had a cardiac implantable electronic device (CIED). The median delay between foreign body implantation and diagnosis of IE was 72 months (IQR, 14.6–141.8). The median length of hospital stay was 27 days (IQR, 19–41) and 164 (40%) patients were admitted to intensive care units (Table 1).

IE characteristics

Among the 403 patients included in our study, 207 (51.2%) infections were community acquired. Two hundred and two patients (52.4%) had a native heart valve infection. A single valve was involved in 298 (76.6%) cases while embolic complications occurred in 170 (42.1%) individuals. The aortic valve was the most common type of valve affected (61.4%). Source of infection was conclusively identified in 172 (42.9%) cases (details available in the Supplementary Appendix, Table S3). The median duration of bacteraemia while undergoing treatment was 3 days, with an interquartile range of 1 to 4 days, as shown in Table 2.

Regarding antimicrobial therapy, the most used regimen consisted of a combination of amoxicillin and ceftriaxone, administered in 289 (72.1%) patients, followed by a combination of amoxicillin and gentamicin in 77 (19.3%) patients (Table S4). Additionally, 39 (13%) patients transitioned to oral antimicrobial treatment. The median duration of antimicrobial therapy was 42 days (IQR, 42–47 days), whereas the median duration of combination therapy was 42 days, with an interquartile range of 23 to 44 days, as shown in Table 2.

Cardiac surgery was performed in 158 (61.5%) patients. The median time lapse between the diagnosis of IE and the surgical intervention was nine days (IQR, 4.5–24). A positive culture of the infected valve was observed in 80/153 (52.3%) patients.

Additionally, there were no significant differences between patients treated for 4 weeks and those treated for 6 weeks, except for the rate of surgery, which was significantly more frequent in patients treated for 4 weeks (Table S5).

Univariate analysis showed that valve type ($P=0.038$), the number of valves involved ($P=0.049$), the choice of antimicrobial therapy, either monotherapy (0.003) or amoxicillin and gentamicin ($P=0.023$), oral antibiotic transition ($P=0.048$), the median delay between IE diagnosis and surgical intervention ($P=0.017$) and the proportion of positive valve cultures ($P=0.022$) were significantly different between patients for whom MIC of amoxicillin was available and the others (Table 2).

Outcomes

The endocarditis-related mortality rate was of 28.3% (114/403 patients), and the median delay between death and hospital admission was 24 days (IQR, 9–41) (Table 3).

In univariate analysis, risk factors for the endocarditis-related mortality rate were: chronic renal insufficiency ($P=0.045$), failure to undergo cardiac surgery ($P<0.001$), duration of bacteraemia ($P=0.041$), duration of combination therapy ($P=0.004$) and duration of antimicrobial treatment ($P=0.002$) (Table 4).

Table 4. Univariate analysis of risk factors for endocarditis-related mortality in 403 patients suffering from *E. faecalis* IE, France, 2013–2020

Characteristic	Alive (283)	Dead (114)	OR [IC95%]	*P*
Male	211 (74.6%)	94 (82.5%)	1.6 [0.9;2.8]	0.09
Age, years[a]	74 [67;82]	74 [67; 82]		0.22
Weight, kgs[a]	73 [63;85]	73 [63;85]		0.21
Diabetes mellitus	67 (23.7%)	37 (32.5%)	1.5 [1;2.5]	0.07
Chronic renal insufficiency[a]	73 (25.9%)	41 (36%)	1.6 [1;2.6]	**0.045**
Prosthetic valve				
Biologic	90 (69.2%)	38 (79.2%)	1	0.19
Mechanic	40 (30.8%)	10 (20.8%)	0.6 [0.3;1.3]	
ICED	25 (9%)	12 (10.8%)	1.2 [0.6;2.6]	0.57
Delay between previous surgery/implantation and diagnosis of IE, month	155 (54.8%)	70 (61.4%)	1.3 [0.84;2]	0.23
Intensive care[a]	106 (37.6%)	53 (46.5%)	1.4 [0.9;2.2]	0.10
Length of stay in hospital, days[a]	28 [20;41.3]	23.50 [17.8;36.3]		0.14
Location of valve infection[a]				
Aortic	165 (59.8%)	71 (66.4%)	1.3 [0.8;2.1]	0.24
Mitral	102 (36.8%)	36 (33.6%)	0.9 [0.5;1.4]	0.56
Tricuspid	8 (2.9%)	6 (5.6%)	2 [0.7;5.9]	0.23
Pulmonary	4 (1.4%)	0 (0%)		0.58
Community acquired infection	142 (50%)	64 (56%)	0.8 [0.5;1.2]	0.28
Valve type[a]				
Native	148 (52.3%)	54 (47.3%)		0.37
Prosthetic	110 (38.8%)	42 (36.9%)		0.73
ICED	16 (5.6%)	9 (7.9%)		0.49
Prosthetic and ICED	5 (1.8%)	1 (0.9%)		0.67
Number of valves involved[a]				0.11
1	221 (79.8%)	74 (69.8%)	1	
2	30 (10.8%)	18 (17%)	1.8 [0.9;3.4]	
3 or more	26 (9.4%)	14 (13.2%)	1.6 [0.8;3.2]	
Embolic complications[a]	120 (42.7%)	48 (42.1%)	1 [0.6;1.5]	0.91
Source of infection found[a]	125 (44.5%)	47 (39.7%)	0.81 [0.5;1.3]	0.36
Antibiotic therapy[a]				
Amoxicillin/Ceftriaxone	201 (71.5%)	84 (73.7%)	1.1 [0.7;1.8]	0.67
Amoxicillin/Gentamicin	60 (21.4%)	15 (13.1%)	0.6 [0.3;1]	0.06
Glycopeptide/other	12 (4.3%)	8 (7.0%)	1.7 [0.7;4.3]	0.26
Other combination therapy	2 (0.7%)	4 (3.5%)	5.1 [0.9;28.1]	0.06
Monotherapy	6 (2.1%)	3 (2.6%)	1.2 [0.3;5.]	0.72
Oral antibiotic relay[a]	28 (13.5%)	11 (12.1%)	0.9 [0.4;1.9]	0.73
Surgery performed[a]	127 (68.8%)	29 (43.8%)	0.35 [0.2–0.6]	**<0.001**
Delay diagnosis between IE and surgery, days[a]	9 [4.7;22.3]	18 [5;26]		0.22
Valve culture positive[a]	65 (53.3%)	13 (44.8%)	0.71 [0.3;1.6]	0.41
Duration of bacteraemia, days[a]	2 [1;4]	3 [2;5]		**0.041**
Duration of combination therapy, days[a]	38.4 (16.6)	31.61 (18.2)		**0.004**
Duration of antimicrobial treatment, days[a]	42 [42;47]	42 [24.3;46]		**0.002**
MIC, mg/L[a]	0.5 [0.4;0.7]	0.62 [0.5;1]		0.32

Quantitative variables are described by their median and interquartile (IQR) range. Categorical variables are presented as absolute numbers (percentages, %).
The number in bold corresponds to "*P*" < 0.05 for the corresponding variable.
ICED, intra-cardiac electronic device.
[a]Missing data (see details in Table S2).

In the context of multivariate analysis (which excluded embolic complications, surgery performed, duration of bacteraemia, duration of antimicrobial therapy and combination therapy due to missing data), none of the variables were associated with the endocarditis-related mortality rate (Table 5).

MIC of amoxicillin

MIC of amoxicillin was available for 246 patients (61%) and all strains were susceptible; the median MIC was 0.5 mg/L (IQR, 0.38–0.75) (Table 2). The distribution of MIC is shown in the Figure 1.

We found that MIC ≥ 2 mg/L (seven patients) or MIC ≥ 1 mg/L (54 patients) were not associated with mortality compared to MIC ≤ 0.125 mg/L (18 patients) (Table 6).

The ROC curve for mortality according to MIC of amoxicillin is shown in Figure 2 with an AUC of 0.54 (IQR, 0.46; 0.62).

Discussion

In our study, we did not detect a significant impact of MIC of amoxicillin on endocarditis-related mortality in patients with definite *E. faecalis* endocarditis in France during 2013–2020.

Table 5. Multivariate analysis of risk factor for endocarditis-related mortality in 403 patients with *E. faecalis* IE, France, 2013–2020

	aOR [CI 95%]	*P*
Male	1.73 [0.99;3.16]	0.06
Chronic renal insufficiency	1.44 [0.82;2.52]	0.20
Diabetes mellitus	1.42 [0.86;2.33]	0.17
Amoxicillin/Gentamicin	0.59 [0.31;1.08]	0.10

aOR, adjusted odds ratio.

In the literature, *E. faecalis*-related endocarditis has been consistently associated with elderly patients. In our study, patients were included at a median age of 74 years. Aortic valve was the main site of infections and the proportion of prosthetic-related IE was ∼46% (including those with CIED infections). Source of infections (found in 43%) were mainly digestive followed by urinary tract in 64% and 24%, respectively (Supplementary Appendix, Table S3). These results were different from other studies such as the GAMES cohort that found a prevalence of genitourinary source, gastrointestinal source or unknown source in 17.8%, 15.9%, and 50.8% cases, respectively.[3] However, an initial unknown source may be revealed when systematic colonoscopy is performed.[19] Cardiac surgery for valve replacement was performed in ∼61.5%, and this result is superior to that of other cohorts, which may be explained by many centre having a cardiac surgery team.

In our cohort, we found that the endocarditis-related mortality was similar to the 1-year mortality in the ICE cohort[20] but higher than in the study by Danneels *et al.* (14.7% at the end of treatment)[11] with a high rate of embolic complications compared to the EURO-ENDO registry (42.1% versus 20.6%),[1] which was not associated with mortality. We found no other risk factors mortality, but several potential variables (embolic complications, surgery

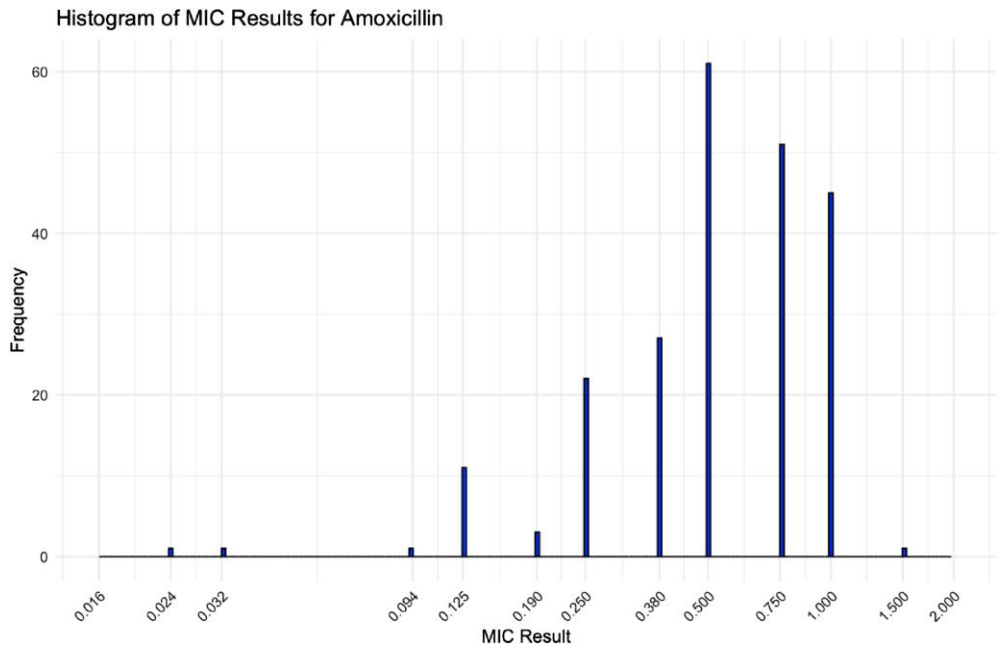

Figure 1. Distribution of *E. faecalis* MICs of amoxicillin in 246 patients affected by *E. faecalis* IE, France, 2013–2020.

Table 6. Endocarditis-related mortality according to MIC of amoxicillin values ≤0.125, ≥1 and ≥2 mg/L in 79 patients affected by *E. faecalis* IE, France, 2013–2020

	MIC ≤ 0.125 mg/L (*N* = 18)	MIC ≥ 1 mg/L (*N* = 54)	OR [CI 95%]	MIC ≥ 2 mg/L (*N* = 7)	OR [CI 95%]
Alive	13 (72.22%)	36 (66.67%)	1	5 (71.43%)	1
Dead	5 (27.78%)	18 (33.33%)	1.04 [0.15;7.22]	2 (28.57%)	1.04 [0.15;7.22]

Categorical variables are presented as absolute numbers (percentages, %).

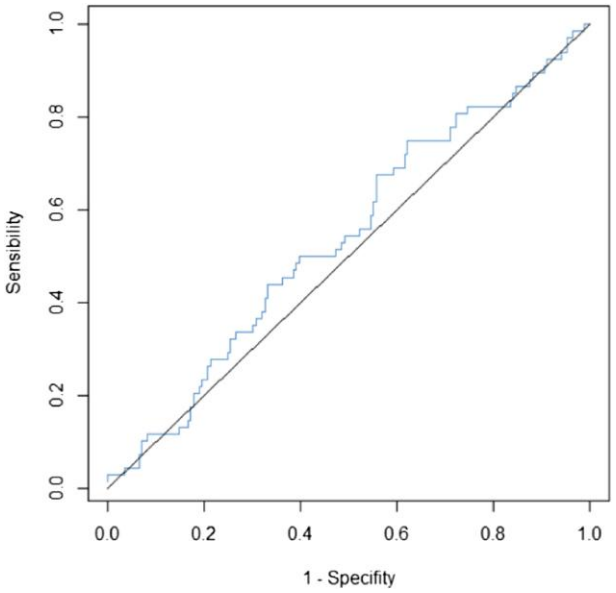

Figure 2. ROC curve for endocarditis-related mortality according to MIC.

performed, duration of bacteraemia, duration of antimicrobial therapy, and combination therapy) were excluded from multivariate analysis due to missing data. Furthermore, unlike Danneels *et al.*,[11] we did not collect data on relapses in our study.

Amoxicillin is the pivotal antibiotic for the treatment of *E. faecalis* infections.[21–25] No patients were treated with ampicillin and although the clinical breakpoints are similar with amoxicillin according to CA-SFM, we cannot draw any conclusions in this regard. In our study, the main antibiotic treatment was the association of amoxicillin and ceftriaxone in almost 72% of cases. Other protocols included gentamicin, glycopeptides or other antimicrobial drugs (Supplementary Appendix, Table S4). We do not have information on the existence of high-level resistance to aminoglycosides or adverse events such as acute kidney injury to explain the predominance of the association of amoxicillin and ceftriaxone in antimicrobial treatment; nonetheless, like other retrospective studies, this association has similar in-hospital mortality rate compared to the combination of amoxicillin and gentamicin[11,26–28] but a randomized controlled trial is still needed.[29] Fewer days on combination therapy and a shorter duration of treatment were associated with mortality, suggesting that monotherapy with amoxicillin is not sufficient to treat enterococcal endocarditis, as previously described in the study by Danneels *et al.* showing a higher rate of relapse.[11] However, 4 weeks of treatment did not appear to increase mortality compared to 6 weeks of treatment, but all patients had surgery in the short arm; this result needs to be confirmed by other studies. Transition to oral antibiotic was performed in 12% patients but the modalities were not described.

Amoxicillin MICs were not associated with endocarditis-related mortality in *E. faecalis* endocarditis when we compared MIC values <0.125 mg/L and MIC ≥ 1 or 2 mg/L. However, a low statistical power is possible because of the small number of patients in each category. We observed in our population, a modal MIC of amoxicillin of 0.5 mg/L, which is lower than that described in other data sets (Figure 1). A study in Swedish intensive care found a modal MIC of ampicillin ∼1 mg/L[30] and the European Society of Clinical Microbiology and Infectious Diseases (EUCAST) also found a modal MIC of ampicillin of 1 mg/L.[31] The primary method for determining the MIC was the Etest strip, which is not currently recommended. However, one study has demonstrated that there is a high degree of agreement between the Etest strip and microdilution.[32]

Our study had notable strengths, including its multicentre design with a large cohort of patients recruited from 11 different hospitals, including both referral and general healthcare facilities. In addition, it was a pioneering investigation to explore the impact of amoxicillin MIC in the context of *E. faecalis* endocarditis.

However, our study has also some limitations. These included an extended inclusion period, which could introduce potential period bias, the presence of substantial missing data, including patients lost to follow-up. In addition, our study selectively included cases classified as 'definite' IE according to the modified Duke criteria, thereby excluding cases classified as 'possible' IE. Notably, we did not collect data on adverse events, nor did we perform assessments to determine the occurrence of disease relapses as part of our outcome measures.

Conclusion

Enterococcal endocarditis represents a major clinical challenge, due to its increasing incidence, its severity and the complexity of its treatment. Levels of MIC of amoxicillin were not associated with endocarditis-related mortality in *E. faecalis* endocarditis. Further studies with a prospective design are required to confirm these first results and report the relapse rate.

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Transparency declarations

The authors declare that they have no conflicts of interest related to this study.

Supplementary data

Tables S1 to S5 are available as Supplementary data at *JAC-AMR* Online.

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