**Title:** A contemporary picture of enterococcal endocarditis: prospective study of 516 cases from the GAMES Cohort

**Short Title:** Prognostic factors of enterococcal endocarditis

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## Abstract

**Background:** Enterococcal endocarditis (EE) is a growing entity in Western countries. However, quality data from large studies is lacking.
**Objectives**: To describe the characteristics and analyze the prognostic factors of EE in the GAMES cohort.
**Methods:** Post-hoc analysis of a prospectively collected cohort of patients from 35 Spanish centers from 2008 to 2016. Characteristics and outcomes of 516 cases of EE were compared to those of 3,308 cases of non-enterococcal endocarditis (NEE). Logistic regression and Cox proportional hazards regression analysis were performed to investigate risk factors for in-hospital and one-year mortality, and relapses.
**Results:** Patients with EE were significantly older, presented more frequently chronic lung disease, chronic heart failure, prior endocarditis, degenerative valve disease and had higher median age-adjusted Charlson score. EE more frequently involved the aortic valve and prosthesis (64.3% vs. 46.7%; P<0.001; and 35.9% vs. 28.9%; P=0.002, respectively) but less frequently pacemakers/defibrillators (1.5% vs. 10.5%; P<0.001), and showed higher rates of acute heart failure (45% vs. 38.3%;P=0.005). Cardiac surgery was less frequently performed in EE (40.7% vs.45.9%;P=0.024). No differences in in-hospital mortality and one-year mortality were found, whereas relapses were significantly higher in EE (3.5% vs. 1.7%; P=0.035). Increasing Charlson score, LogEuroSCORE, acute heart failure, septic shock and paravalvular complications were risk factors for mortality, whereas prior endocarditis was protective and persistent bacteremia constituted the sole risk factor for relapse.
**Conclusions:** Besides other baseline and clinical differences, EE more frequently affects prosthetic valves and less frequently pacemakers/defibrillators. EE presents higher rates of relapse than NEE.

**Condensed abstract:** Enterococcal endocarditis (EE) is a growing issue in Western countries. By comparing 516 cases of EE with 3,308 cases of NEE, we found older median age and higher comorbidity rates among EE than in NEE, as well as higher rates of aortic valve and prosthetic valve involvement, and heart failure. Mortality did not significantly differ between EE and NEE, whereas relapses were higher in EE. Risk factors for mortality in EE were Charlson score, LogEuroSCORE, acute heart failure, septic shock and paravalvular complications, whereas persistent bacteremia was associated with a higher likelihood of relapses.

**Keywords:** Infective endocarditis, enterococci, heart failure, relapses, prosthetic valves, epidemiology.

**Abbreviations:** CNS, central nervous system; EE, enterococcal endocarditis; HCA, healthcare-associated; IE, infective endocarditis; MRSA, methicillin-resistant *S. aureus*; NEE, non-enterococcal endocarditis; PCM/DF, pacemakers/defibrillators; TAVI, transaortic valve implantation; TEE, transesophageal echocardiography

## Introduction

Enterococci have been identified as a growing pathogen, primarily in health-care associated infections in the U.S., where vancomycin-resistant strains pose a serious challenge to the health system [1]. However, enterococci are also playing an increasingly important role in infective endocarditis (IE) [2], with most recent series placing it as the third leading causative agent in high-income countries, reaching up to 15-20% of total cases [3-6]. Moreover, enterococci are the leading causative agent of transaortic valve implants (TAVI)-associated IE [7].

Most cases (around 90%) of enterococcal IE are caused by *E. faecalis* [8]. Since the turn of the 21$^{st}$ century, the classically described clinical presentation of enterococcal IE as a community-acquired, subacute pauci-symptomatic disease of genitourinary source [10] is progressively turning in a more aggressive, acute, more frequently healthcare-associated (HCA) disease of occurring predominantly amongst elderly patients with a large burden of comorbidities and seldom a clear identifiable source. [9,10].

The focus of recent relevant studies addressing enterococcal IE is largely placed on the genetic and molecular aspects [11,12], impact of antimicrobial resistance (e.g. vancomycin, high-level aminoglycoside resistance and daptomycin resistance) [1,8,11,12], therapeutic options [13-15] or the use of TEE to detect IE [16-18], whereas there is a relative paucity of studies explaining the main clinical and epidemiological changes of enterococcal IE in the last two decades and their underlying mechanisms, such as its potential association with colorectal neoplasms [19,20].

We aimed to investigate the main characteristics of enterococcal IE in a cohort of 516 patients prospectively collected from 2008 to 2016 and to compare them with those of non-enterococcal IE.

## Methods

*Design*: multicenter prospective observational study including 35 Spanish centers between 2008 and 2016. The characteristics of the GAMES cohort, collection of data variables through a specific central registration depository, and definitions are described elsewhere [5]. The work-up for searching potential sources of the infection, including gastrointestinal tract screening, was not systematic but was decided by the treating physician. Persistent bacteremia was defined as positive blood cultures beyond seven days of effective antibiotic therapy; relapse refers to a new episode of IE due to the same microorganism within the next 6 months after the initial episode; acute renal failure was defined in the data collection sheet as a worsening equal or higher than 25% of serum creatinine or glomerular clearance occurring within a lapse of 72h; community-acquired IE was defined as IE diagnosed within the first 48 hours of admission in a patient who did not fulfill the criteria for HCA infection. HCA infection encompasses nosocomial and non-nosocomial HCA IE [21]. Nosocomial IE was defined as IE in a patient who had been hospitalized for >48 hours before the onset of signs or symptoms consistent with IE. Non-nosocomial HCA IE was an IE diagnosed within 48 hours of admission of an outpatient.

*Patients*: adult individuals with definite or possible IE diagnosed according to the modified Duke criteria [22].

*Outcomes*: in-hospital and one-year mortality (death due to any causes within 30 days and 365 days from the admission, respectively), and relapses.

*Statistical analysis*: Categorical variables were summarized as percentages and continuous variables as means and standard deviations. Categorical variables were compared using the chi-square test (or Fisher's exact test where necessary). Continuous variables were compared using the Kruskal-Wallis test. Cox proportional hazards regression analysis was utilized to investigate risk factors for one-year mortality and relapses. Variables with $P<0.20$ in the

univariate analysis were included in the models. Kaplan-Meier survival curves free of mortality at one year and relapses were generated with log-rank test analysis and considering censored episodes according to the time measured for each endpoint. A two-sided $P<0.05$ was considered to be statistically significant. Statistical analyses were performed using SPSS for Windows, Version 16.0 (SPSS Inc, Chicago, Illinois, USA).

## Results

Patients with enterococcal IE were significantly older and had higher rates of comorbidities, leading to a significantly higher median age-adjusted Charlson score (**Table 1**). Diabetes mellitus, chronic lung disease, congestive heart failure, previous IE, and non-congenital valve disease were all significantly more frequent among enterococcal IE, whereas ischemic cardiomyopathy and chronic renal failure, although more frequent too among enterococcal IE, did not reach statistical significance. On the other hand, iv drug use, HIV infection and congenital heart abnormalities were significantly more common among patients with non-enterococcal IE. The proportion of prosthetic valve IE was significantly higher in the enterococcal IE group, whereas PCM/DF-associated IE was significantly more frequent in the non-enterococcal IE group. The aortic valve was significantly more frequently involved in enterococcal IE cases, while the tricuspid and pulmonary valve were more commonly affected in non-enterococcal IE. Around half of the cases in both groups had an unknown source of the infection. The median time elapsed between the appearance of symptoms and hospital admission was not different between the two groups. Genitourinary and gastrointestinal foci were significantly more common among enterococcal IE episodes; meanwhile, oral, vascular and cutaneous sources were significantly more frequent in the non-enterococcal IE group. *E. faecalis* caused 90.7% of cases in the enterococcal IE group, being *S. aureus*, coagulase-negative staphylococci, and viridans group streptococci the more frequent causative agents in the non-enterococcal IE group. As for the proportion of cases from the global cohort, *S. aureus* represented 22.8%, coagulase-negative staphylococci 17.4%, viridans group streptococci 16.1%, enterococci 13.5%, Bovis group streptococci 6.4% and other streptococci 5%. Enterococci accounted for 9.5% of cases in patients aged less than 65 years and 16.4% among patients ≥65 years old (P<0.001). There were no cases of enterococcal IE caused by vancomycin-resistant enterococci. The site of acquisition did not

significantly differ between the two groups. Clinically, non-enterococcal IE presented with significantly higher rates of extensive CNS emboli, pulmonary emboli, and septic shock, as well as perivalvular abscesses, intracardiac fistula and pseudoaneurysm in the echocardiography, whereas enterococcal IE presented significantly higher rates of new onset heart failure and splenic abscesses. Enterococcal IE received a significantly longer median time of antibiotic therapy (42 vs. 36 days; P<0.001), being rates of cardiac surgery higher among non-enterococcal IE patients. Remarkably, 8 patients in the enterococcal IE group did not undergo cardiac surgery when indicated due to advanced liver disease, whereas this happened in 21 patients in the non-enterococcal group (1.5% vs. 0.6%; P=0.025, not shown). In-hospital and one-year mortality did not differ between both groups, yet relapses were significantly higher among patients with enterococcal IE.

The characteristics and outcomes of enterococcal and non-enterococcal IE are compared in the Supplementary material among native valve IE cases (**Supplementary Table 1**), prosthetic valve IE cases (**Supplementary Table 2**) and patients undergoing cardiac surgery (**Supplementary Table 3**). Notably, both in-hospital and one-year mortality were significantly higher among patients with non-enterococcal prosthetic valve IE, whereas relapses were significantly higher among patients with enterococcal prosthetic valve IE.

A comparison of HCA vs. community-acquired enterococcal IE cases is shown in **Table 2**. Notably, HCA enterococcal cases more frequently involved prosthetic valves and had higher rates of chronic liver and renal disease, including dialysis, and transplantation, and immunosuppres therapy, whereas community-acquired enterococcal IE involved native valves significantly more frequently and presented higher rates of iv drug use and HIV infection. Outcomes did not significantly differ between the two groups.

The characteristics and outcomes of enterococcal IE caused by *E. faecalis* are compared to those enterococcal IE cases caused by other species in **Table 3**. Of note, patients with *E.*

198 *faecalis* IE showed a trend to elder ages and presented significantly higher rates of chronic
199 congestive heart failure, chronic dialysis, prosthetic valve IE, and paravalvular abscess.
200 Patients with *E. faecalis* IE significantly received as initial antibiotic treatment double beta-
201 lactam combinations, whereas there were no differences between groups associated with
202 beta-lactam plus aminoglycoside initial combinations. Non-*E. faecalis* IE was more
203 frequently treated with other type of antibiotic treatment, being vancomycin combined with
204 an aminoglycoside the third most common combination among *E. faecalis* IE patients. Ten
205 (62.5%) of the 16 relapses occurring in patients with *E. faecalis* IE had received double beta-
206 lactam therapy, 5 (31.2%) received beta-lactam plus aminoglycosides and 1 (6.3%)
207 vancomycin plus gentamicin. The two relapses occurring in non-*E.faecalis* IE patients had
208 received other type of combinations. Outcomes did not significantly differ between the two
209 groups.
210 In the multivariate analysis, increasing age-adjusted Charlson score, paravalvular
211 complications, new onset of heart failure, septic shock and logistic EuroSCORE were
212 identified as risk factors for one-year mortality and prior episode of IE was protective.
213 Persistent bacteremia was identified as a risk factor for relapse (**Table 4**). Curves for mortality
214 and relapse over time are shown in the **Central Illustration**.
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## Discussion

### Epidemiology and main clinical characteristics

Ours is the largest national series of enterococcal IE described to date. In terms of epidemiological findings, this study confirms some of the common traits of the enterococcal IE profile described in studies conducted during the last fifteen years, but we also found some differences in this regard. Remarkably, as foreseen in the previous literature, median age, female sex, comorbidities, unknown source of infection and healthcare acquisition among enterococcal IE cases are on the rise. For example, Chirouze et al provided data on 500 cases of enterococcal IE from the International Collaboration on Endocarditis (ICE) collected from 2000 to 2006 and compared them with 823 cases of IE caused by oral streptococci and 293 cases of D group streptococcal IE [4]. North America was the region where more cases of enterococcal IE came from (50%), 90.6% of cases were caused by *E. faecalis*, median age was 65 years, 72.6% of cases occurred in men, 22.4% had diabetes, 8.4% were on chronic hemodialysis, 11.2% had cancer, 12.5% of cases had a prior episode of IE, 23.4% of cases overall were healthcare-associated and enterococcal IE involved prosthetic valves (in 29.1% of cases) significantly more frequently than streptococcal IE [4]. As in the case of another study from the ICE [23], we found that enterococcal IE is significantly more frequent among patients aged 65 years or more. By comparing to all other etiologies of IE, we have also identified that enterococcal IE is significantly less frequent among iv drug users, people living with HIV, patients with congenital heart disease, whereas it significantly more often the aortic valve and affected people with chronic diseases such as respiratory diseases, ischemic myocardiopathy, chronic heart failure, chronic renal disease or degenerative valve disease.

From a clinical standpoint, the two major findings of our study are the high rate of prosthetic valve involvement and heart failure. In addition, we found that in spite of presenting very

similar profiles in all other aspects, *E. faecalis* produced significantly more prosthetic valve IE cases than other enterococcal species while the latter produced significantly more native valve IE, which has not been noted before.

**Complications and outcome**

Heart failure was a prognostic factor for mortality among patients with EE. However, when analyzing native and prosthetic valve IE separately, we did not find higher heart failure rates in prosthetic enterococcal IE. Heart failure as a common trait of enterococcal IE has previously been defined in some reports [24,25] but remarkably not in the Chirouze et al study [4]. In our cohort of enterococcal IE, we also find higher rates of moderate-severe aortic and mitral regurgitation than in other types of IE. We hypothesize this might be due to the higher frequency of heart abnormalities of elderly patients rather than to a special ability for valve tissue destruction inherent to enterococci, which is consistent with the lower rates of paravalvular complications we observed among patients with enterococcal IE and the fact than the median time elapsed from the onset of symptoms to admission was not different between enterococcal and non-enterococcal IE.

Whereas we did not find significant differences in in-hospital and one-year mortality between enterococcal and non-enterococcal IE overall, both were significantly lower in enterococcal prosthetic valve IE than in non-enterococcal prosthetic valve IE in spite of the aforementioned lower rates of cardiac surgery.

Although enterococcal IE classically presents with higher rates of relapse than other types of IE [8], the risk factors associated with this phenomenon have been scarcely investigated to date. Moreover, no other large study on enterococcal IE had previously confirmed a significantly higher rate, including the ICE study led by Chirouze, which did not provide data on relapses [4]. In our study, persistent bacteremia was found to be a risk factor for relapsing enterococcal IE. To the best of our knowledge, this is a novel finding. Persistent bacteremia

might be related to high initial bloodstream enterococcal inoculum, which may strongly depend on the source of the infection or the presence of intravascular devices, non-drained infectious foci and the type of initial antibiotic treatment, as well as to the characteristics of the bacterium. Persistent bacteremia, together with other recently identified potential risk factors for enterococcal IE relapses such as advanced liver disease [15] and genome modifications and phenotypic adaptation of changes of enterococcal strains [26] in *E. faecalis* IE, merit further investigation.

**Treatment features**

The length of antibiotic treatment was six weeks in median in both native and prosthetic valve enterococcal endocarditis. Among other determinants, this might reflect the high proportion of cases treated with double beta-lactam combination according to current guidelines [27,28], as well as the increasing complexity of enterococcal IE leading to six-week courses also for ampicillin plus gentamicin provided the average complication rates that likely precludes the use of shorter courses. Furthermore, lesser patients with enterococcal IE had indication and did indeed undergo cardiac surgery, and again this general observation only kept true for patients with prosthetic valve IE (less than a third of whom were operated) and not for native valve IE. Almost two thirds among the latter had indication for cardiac surgery while it was barely 50% among patients with prosthetic valve IE. The leading indication for cardiac surgery among native valve enterococcal IE was congestive heart failure and valve regurgitation; both of them were significantly more common in native than in prosthetic enterococcal IE.

**Limitations**

This study is constrained by several limitations. Firstly, we could not assess the epidemiological evolution of enterococcal IE along the study period because the database was still being updated with case report forms from cases of 2015 and 2016 sent by participating

centers. Secondly, EE cases were compared to the rest of the GAMES cohort IE cases instead of being compared only to oral and D-group streptococcal IE. However, our findings strongly suggest that the profile of EE is no longer similar to that of to the classical community-acquired streptococcal IE. Thirdly, due to a low proportion of cases including information of the antibiotic resistance profile of enterococci, we were not able to describe this aspect properly neither could we perform any analysis on the impact of high-level aminoglycoside resistance and vancomycin resistance on the prognosis of enterococcal IE. Fourthly, since most participating centers of the GAMES cohort are reference hospitals for cardiac surgery, the implications of a potential referral bias should be acknowledged. Fifth, the low number of non-*E. faecalis* enterococcal IE hampers the direct extrapolation of the results of the comparison between *E. faecalis* and non-*E. faecalis* IE. Finally, the long duration of the study period might represent a historical bias.

**Conclusions**

In conclusion, this study shows that enterococcal IE is an entity in constant evolution that constitutes the fourth common cause of IE in Spain. It affects mainly male and elderly patients with lots of comorbidities and prior episodes of IE; it is healthcare-associated in almost 50% of cases, involves prosthetic valves and entails heart failure and relapses more commonly than non-enterococcal IE. Although native enterococcal IE and non-enterococcal IE did not present significant differences on mortality rates, prosthetic valve enterococcal IE showed lower rates of in-hospital mortality and one-year mortality than non-enterococcal prosthetic IE. Relapses in enterococcal IE are associated to persistent bacteremia. Further studies investigating the relationship between relapses of enterococcal IE and potential contributing factors are warranted.

## Perspectives

**Competency in Medical Knowledge 1:** Enterococcal endocarditis is changing epidemiologically while becoming increasingly frequent worldwide.

**Competency in Medical Knowledge 2:** Its clinical presentation is overall less severe than non-enterococcal endocarditis, yet it present higher rates of relapses and more frequently affects prosthetic valves.

**Competency in Medical Knowledge 3:** The outcomes of *Enterococcus faecalis* endocarditis (almost 90% of enterococcal endocarditis cases) are not significantly different from those of non-*E. faecalis* enterococcal endocarditis.

**Competency in Patient Care:** Enterococcal endocarditis should be suspected in elderly patients, especially in the healthcare setting. Follow-up after the initial admission is especially important due to an increased risk of relapses.

**Translational Outlook:** Future research might encompass a multidimensional inquiry on the characteristics of the bacterium, the host and medical and surgical management underlying the higher rates of relapses found among patients with enterococcal endocarditis.

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## Figure Legends

**Central Illustration.**

Mortality and relapses in enterococcal endocarditis vs. non-enterococcal endocarditis.

(a) Kaplan-Meier curve for mortality at one year

(b) Kaplan-Meier curve for relapses over time.

436 **Table 1. Comparison of characteristics and outcome of enterococcal endocarditis and**
437 **endocarditis caused by other microorganisms from the GAMES Cohort (2008-2016).**

| | **Enterococcal IE (N=516)** | **Non-enterococcal IE (N=3,308)** | ***P*** |
|---|---|---|---|
| **Median age, years (IQR)** | 72 (64-78) | 68 (55-77) | <0.001 |
| **Male sex (%)** | 357 (69.2%) | 2206 (66.7%) | 0.254 |
| **Comorbidities** | | | |
| Diabetes mellitus | 168 (32.6%) | 913 (27.6%) | 0.025 |
| Chronic lung disease | 139 (26.9%) | 560 (16.9%) | <0.001 |
| Ischemic cardiomyopathy | 152 (29.5%) | 841 (25.4%) | 0.060 |
| Congestive heart failure | 197 (38.2%) | 1077 (32.6%) | 0.014 |
| Moderate/severe liver disease | 24 (4.7%) | 144 (4.4%) | 0.764 |
| - Child Pugh score, mean (SD) | 11 (2.83) | 8.4 (2.46) | 0.160 |
| - MELD score, mean (SD) | 20.6 (8.1) | 19.7 (8.8) | 0.733 |
| Moderate/severe chronic renal failure | 94 (18.2%) | 489 (14.8%) | 0.058 |
| Hemodialysis | 24 (4.7%) | 157 (4.7%) | 0.924 |
| Neoplasm | 94 (18.2%) | 508 (15.4%) | 0.114 |
| Transplantation | 9 (1.7%) | 64 (1.9%) | 0.760 |
| Immunosuppressant therapy | 38 (7.4%) | 192 (5.8%) | 0.201 |
| IV drug use | 5 (1%) | 78 (2.4%) | 0.006 |
| HIV | 4 (0.8%) | 61 (1.8%) | 0.018 |
| Previous IE | 63 (12.2%) | 215 (6.5%) | <0.001 |
| Congenital cardiac abnormality | 5 (1%) | 218 (6.6%) | <0.001 |

| | | | |
|---|---|---|---|
| Non-congenital valve disease | 252 (48.8%) | 1431 (43.3%) | 0.018 |
| Median age-adjusted Charlson score (IQR) | 5 (4-7) | 4 (3-6) | <0.001 |
| **Type of endocarditis** | | | |
| Native | 324 (62.7%) | 2007 (60.7%) | 0.355 |
| Prosthetic* | 185 (35.8%) | 955 (28.9%) | 0.002 |
| PCM/DF[+] | 8 (1.5%) | 346 (10.5%) | <0.001 |
| **Valve involvement[+]** | | | |
| Aortic | 332 (64.3%) | 1545 (46.7%) | <0.001 |
| Mitral | 226 (43.8%) | 1416 (42.8%) | 0.672 |
| Tricuspid | 15 (2.9%) | 186 (5.6%) | 0.001 |
| Pulmonary | 0 | 51 (1.5%) | <0.001 |
| **Diagnosis of endocarditis according to modified Duke criteria** | | | 0.029 |
| Definite | 431 (83.5%) | 2626 (79.4%) | |
| Possible | 85 (16.5%) | 682 (20.6%) | |
| **Median time of symptoms duration until admission in non-nosocomial cases, days (IQR)** | 6.5 (1.3-22.8) | 6.5 (2-18) | 0.549 |
| **Source** | | | |
| Oral | 8 (1.6%) | 220 (6.7%) | <0.001 |
| Respiratory | 2 (0.4%) | 40 (1.2%) | 0.096 |
| Genitourinary | 92 (17.8%) | 106 (3.2%) | <0.001 |
| Gastrointestinal | 82 (15.9%) | 172 (5.2%) | <0.001 |
| Vascular | 62 (12%) | 637 (19.3%) | <0.001 |
| Cutaneous | 10 (1.9%) | 260 (7.9%) | <0.001 |

| | | | |
|---|---|---|---|
| Other | 19 (3.8%) | 202 (6.3%) | 0.031 |
| Unknown | 262 (50.8%) | 1708 (51.6%) | 0.734 |
| **Etiology** | | | NA |
| Enterococci<br>*E. faecalis*<br>*E. faecium*<br>Other enterococci[±] | <br>468 (90.7%)<br>36 (7%)<br>12 (2.3%) | <br>-<br>-<br>- | |
| S. *aureus*<br>MSSA<br>MRSA | -<br>-<br>- | 870 (26.3%)<br>849 97.6%)<br>21 (2.4%) | |
| Viridans group streptococci | - | 616 (18.6%) | |
| Coagulase-negative staphylococci | - | 664 (20.1%) | |
| Bovis group streptococci | - | 244 (7.4%) | |
| Other streptococci | - | 193 (5.8%) | |
| Other | - | 711 (21.5%)[×] | |
| **Acquisition** | | | |
| Community | 282 (54.7%) | 1953 (59%) | 0.062 |
| Health-care associated<br>Nosocomial<br>Non-nosocomial health-care associated | 219 (42.4%)<br>168 (32.6%)<br>51 (9.9%) | 1229 (37.1%)<br>954 (28.8%)<br>275 (8.3%) | 0.093<br>0.092<br>0.262 |
| Unknown | 15 (2.9%) | 116 (3.5%) | 0.486 |
| **Clinical complications** | | | |
| New onset or worsening heart failure<br>NYHA I | 232 (45%)<br>12 (5.2%) | 1270 (38.4%)<br>114 (9%) | 0.005<br>0.054 |

| | | | |
|---|---|---|---|
| NYHA II | 35 (15.1%) | 214 (16.9%) | 0.506 |
| NYHA III | 95 (40.9%) | 413 (32.5%) | 0.013 |
| NYHA IV | 90 (38.8%) | 529 (41.6%) | 0.416 |
| Persistent bacteremia | 69 (13.4%) | 378 (11.4%) | 0.223 |
| CNS emboli | 86 (16.7%) | 663 (20%) | 0.058 |
| Hemorrhagic | 11 (12.8%) | 110 (16.6%) | 0.367 |
| Extensive (>2cm) | 0 | 109 (16.4%) | 0.001 |
| Multiple (>3) | 6 (7%) | 68 (10.3%) | 0.337 |
| Other major emboli | 95 (18.4%) | 687 (20.8%) | 0.202 |
| Pulmonary emboli | 6 (1.2%) | 183 (5.5%) | <0.001 |
| Vertebral osteomyelitis | 18 (3.5%) | 97 (2.9%) | 0.479 |
| Non-vertebral osteomyelitis | 6 (1.2%) | 52 (1.6%) | 0.536 |
| Renal abscess | 14 (2.7%) | 87 (2.6%) | 0.914 |
| Splenic abscess | 66 (12.8%) | 310 (9.4%) | 0.028 |
| Heart conduction abnormality | 39 (7.6%) | 297 (9%) | 0.262 |
| Acute renal failure | 191 (37%) | 1177 (35.6%) | 0.530 |
| Septic shock | 37 (7.2%) | 432 (13.1%) | <0.001 |
| **Echocardiographic findings** | | | |
| TEE performed | 391 (75.8%) | 2583 (78.1%) | 0.253 |
| Median ejection fraction (IQR) | 60% (55-65) | 60% (55-65) | 0.536 |
| Median vegetation size in mm (IQR) | 8 (3-14) | 8 (3-14) | 0.088 |
| Moderate-severe aortic regurgitation | 193 (37.4%) | 882 (26.7%) | <0.001 |
| Moderate-severe mitral regurgitation | 197 (38.2%) | 1111 (33.6%) | 0.048 |
| Perivalvular abscess | 62 (12%) | 514 (15.5%) | 0.024 |

| | | | |
|---|---|---|---|
| Intracardiac fistula | 4 (0.8%) | 86 (2.6%) | <0.001 |
| Pseudoaneurysm | 18 (3.5%) | 183 (5.5%) | 0.023 |
| Leaflet perforation/rupture | 70 (13.6%) | 436 (13.2%) | 0.082 |
| **Treatment characteristics** | | | |
| Antibiotics properly indicated | 493 (95.5%) | 3168 (95.8%) | 0.817 |
| Median length of antibiotic treatment, days (IQR) | 42 (30-46) | 36 (24-44) | <0.001 |
| Cardiac surgery | | | |
| Indicated | 316 (61.2%) | 2182 (66%) | 0.040 |
| Operated during admission | 210 (40.7%) | 1520 (45.9%) | 0.024 |
| New surgery during the first year after admission | 23 (4.5%) | 144 (4.4%) | 0.915 |
| **Outcomes** | | | |
| In-hospital mortality | 123 (23.8%) | 892 (27%) | 0.123 |
| Mortality at 1-year | 159 (30.8%) | 1100 (33.3%) | 0.266 |
| Relapses | 18 (3.5%) | 57 (1.7%) | 0.035 |

HIV: Human immunodeficiency syndrome; IQR: Interquartile range; MSSA: methicillin-susceptible *S. aureus;* MRSA: methicillin-resistant *S. aureus*; NA: not analyzed; PCM/DF: pacemakers/defibrillators

[*] There were 17 cases of endocarditis over TAVI, 3 of them occurring in the EE group and 14 in the NEE group (0.5% vs. 0.4%, P=0.802).

[+]Only episodes in which only PCM/DF are affected are included in this group. Episodes have been classified as native or prosthetic valve where a concomitant valve involvement exists.

The sum does not equal 100% because episodes with multivalve involvement are also counted.

[±] In 9 cases there was not identification at the species level (*Enterococcus spp*.), whereas the 3 remaining cases corresponded to one case of *E. durans, E. avium* and *E. gallinarum* each.

[×]Negative culture: 342 (48.1%); Gram negative bacilli: 163 (22.9%); Polymicrobial: 69 (9.7%); *Candida spp*: 64 (9.0%); Anaerobic bacteria: 39 (5.5%); Other fungi: 11 (1.5%); Miscellany: 23 (3.2%).

**Table 2. Comparison of Health-Care acquired vs. Community-acquired Enterococcal Endocarditis.**

| | **Community-acquired (N=282)** | **Nosocomial-HCA (N=168)** | **Non-nosocomial HCA (N=51)** | ***P*** |
|---|---|---|---|---|
| **Enterococcal species** | | | | 0.342 |
| *E. faecalis* | 256 (90.8%) | 153 (91.1%) | 47 (92.2%) | |
| *E. faecium* | 17 (6%) | 15 (8.9%) | 4 (7.8%) | |
| Other | 9 (3.2%)* | 0 | 0 | |
| **Median age, years (IQR)** | 73 (64-80) | 73 (64-78) | 71 (62-79) | 0.332 |
| **Male sex (%)** | 195 (69.1%) | 120 (71.4%) | 31 (60.7%) | 0.222 |
| **Comorbidities** | | | | |
| Diabetes mellitus | 97 (34.4%) | 46 (27.3%) | 17 (33.3%) | 0.296 |
| Chronic lung disease | 73 (25.9%) | 49 (29.1%) | 12 (23,5) | 0.700 |
| Ischemic cardiomyopathy | 78 (27.7%) | 56 (33.3%) | 12 (23.5%) | 0.285 |
| Congestive heart failure | 101 (35.8%) | 74 (44%) | 19 (37.2%) | 0.221 |
| Moderate/severe liver disease | 8 (2.8%) | 7 (4.2%) | 8 (15.7%) | 0.022 |
| Moderate/severe chronic renal failure | 43 (15.2%) | 37 (22%) | 12 (23.5%) | 0.120 |
| Hemodialysis | 4 (1.4%) | 11 (6.5%) | 8 (15.6%) | <0.001 |
| Neoplasm | 49 (17.4%) | 28 (16.6%) | 13 (25.4%) | 0.329 |
| Transplantation | 2 (0.7%) | 6 (3.6%) | 1 (2%) | 0.806 |
| Immunosuppressant therapy | 15 (5.3%) | 18 (10.7%) | 4 (7.8%) | 0.105 |
| IV drug use | 5 (1.8%) | 0 | 0 | 0.024 |
| HIV | 4 (1.4%) | 0 | 0 | 0.045 |

| | | | | |
|---|---|---|---|---|
| Previous IE | 28 (9.9%) | 24 (14.2%) | 10 (19.6%) | 0.101 |
| Congenital cardiac abnormality | 4 (1.4%) | 2 (1.2%) | 1 (2%) | 0.918 |
| Non-congenital valve disease | 134 (47.5%) | 89 (52.9%) | 23 (45%) | 0.445 |
| Median age-adjusted Charlson score (IQR) | 5 (4-7) | 5 (4-7) | 6 (4-8) | 0.425 |
| **Type of endocarditis** | | | | |
| Native | 192 (68.1%) | 87 (51.7%) | 37 (72.5%) | <0.001 |
| Prosthetic | 86 (30.5%) | 79 (47%) | 13 (25.4%) | <0.001 |
| PCM/DF* | 4 (1.4%) | 3 (1.7%) | 0 | 0.103 |
| **Valve involvement**[+] | | | | |
| Aortic | 179 (63.5%) | 105 (62.5%) | 37 (72.5%) | 0.403 |
| Mitral | 122 (43.3%) | 75 (44.6%) | 24 (47%) | 0.868 |
| Tricuspid | 10 (3.5%) | 4 (2.4%) | 1 (2%) | 0.398 |
| Pulmonary | 0 | 0 | 0 | 1.000 |
| **Clinical complications** | | | | |
| New onset or worsening heart failure | 126 (44.7%) | 78 (46.7%) | 23 (45.1%) | 0.849 |
| Persistent bacteremia | 36 (12.8%) | 23 (13.7%) | 8 (15.6%) | 0.652 |
| CNS emboli | 43 (15.2%) | 30 (17.8%) | 10 (19.6%) | 0.372 |
| Other major emboli | 57 (20.2%) | 28 (16.7%) | 6 (11.8%) | 0.220 |
| Pulmonary emboli | 2 (0.7%) | 4 (2.3%) | 0 | 0.280 |
| Vertebral osteomyelitis | 9 (3.2%) | 7 (4.1%) | 2 (3.9%) | 0.779 |
| Non-vertebral osteomyelitis | 5 (1.8%) | 0 | 1 (1.9%) | 0.152 |
| Renal abscess | 8 (2.8%) | 0 | 0 | 0.695 |
| Splenic abscess | 40 (14.2%) | 6 (3.5%) | 3 (5.8%) | <0.001 |
| Heart conduction abnormality | 22 (7.8%) | 12 (7.1%) | 3 (5.8%) | 0.880 |

| | | | | |
|---|---|---|---|---|
| Acute renal failure | 112 (39.7%) | 51 (30.3%) | 19 (37.2%) | 0.134 |
| Septic shock | 19 (6.7%) | 14 (8.3%) | 3 (5.8%) | 0.761 |
| **Echocardiographic findings** | | | | |
| TEE performed | 206 (73%) | 134 (79.8%) | 40 (78.4%) | 0.093 |
| Median ejection fraction (%, IQR) | 60 (55-65) | 60 (50-65) | 60 (50-68) | 0.465 |
| Median vegetation size (mm, IQR) | 8 (3-15) | 10 (7-19) | 10.5 (8-13) | 0.729 |
| Moderate-severe aortic regurgitation | 107 (37.9%) | 54 (32.1%) | 24 (47%) | 0.133 |
| Moderate-severe mitral regurgitation | 119 (42.2%) | 49 (29.1%) | 25 (49%) | 0.006 |
| Perivalvular abscess | 23 (8.2%) | 28 (16.6%) | 9 (17.6%) | 0.011 |
| Intracardiac fistula | 2 (0.7%) | 2 (1.2%) | 0 | 0.235 |
| Pseudoaneurysm | 5 (1.8%) | 6 (3.6%) | 5 (9.8%) | 0.010 |
| Leaflet perforation/rupture | 44 (15.6%) | 19 (11.3%) | 6 (11.7%) | 0.163 |
| **Treatment characteristics** | | | | |
| Median length of antibiotic treatment, days (IQR) | 42 (29-46) | 42 (33-47) | 42 (28-46) | 0.317 |
| Cardiac surgery | 121 (42.9%) | 57 (33.9%) | 23 (45.1%) | 0.127 |
| **Outcomes** | | | | |
| In-hospital mortality | 60 (21.3%) | 45 (25.5%) | 16 (31.3%) | 0.186 |
| One-year mortality | 79 (28%) | 53 (31.5%) | 22 (43.1%) | 0.094 |
| Relapses[±] | 10 (3.5%) | 3 (1.7%) | 4 (7.8%) | 0.109 |

455 [*] 8 cases due to *Enterococcus spp*. and 1 case of *E. durans* IE

456 [±] One case of relapse among EE was not included because it had an unknown source of
457 acquisition.

458

459 **Table 3. Comparison of *E. faecalis* vs. non-*E. faecalis* Enterococcal Endocarditis**

| | ***E. faecalis* IE (N=468)** | ***Non-E. faecalis* IE (N=48)** | ***P*** |
|---|---|---|---|
| **Median age, years (IQR)** | 73 (64.5-79) | 68.5 (59.5-76) | 0.080 |
| **Male sex (%)** | 325 (69.4%) | 32 (66.7%) | 0.697 |
| **Comorbidities** | | | |
| Diabetes mellitus | 151 (32.3%) | 17 (35.4%) | 0.663 |
| Chronic lung disease | 130 (27.8%) | 9 (18.8%) | 0.133 |
| Ischemic cardiomyopathy | 140 (29.9%) | 12 (25%) | 0.457 |
| Congestive heart failure | 187 (40%) | 10 (20.8%) | 0.002 |
| Moderate/severe liver disease | 20 (4.3%) | 4 (8.3%) | 0.322 |
| Moderate/severe chronic renal failure | 88 (18.8%) | 6 (12.5%) | 0.217 |
| Hemodialysis | 24 (5.1%) | 0 | <0.001 |
| Neoplasm | 81 (17.3%) | 13 (27.1%) | 0.142 |
| Transplantation | 8 (1.7%) | 1 (2.1%) | 0.862 |
| Immunosuppressant therapy | 33 (7.1%) | 5 (10.4%) | 0.461 |
| IV drug use | 4 (0.9%) | 1 (2.1%) | 0.560 |
| HIV | 3 (0.6%) | 1 (2.1%) | 0.491 |
| Previous IE | 57 (12.2%) | 6 (12.5%) | 0.949 |
| Congenital cardiac abnormality | 6 (1.3%) | 1 (2.1%) | 0.706 |
| Non-congenital valve disease | 229 (48.9%) | 23 (47.9%) | 0.893 |
| Median age-adjusted Charlson score (IQR) | 5 (4-7) | 5 (3-7) | 0.227 |
| **Type of endocarditis** | | | |
| Native | 287 (61.3%) | 37 (77.1%) | 0.015 |
| Prosthetic | 174 (37.2%) | 11 (22.9%) | 0.028 |
| PCM/DF* | 7 (1.5%) | 0 | 0.109 |

| | | | |
|---|---|---|---|
| **Valve involvement**[+] | | | |
| Aortic | 302 (64.5%) | 30 (62.5%) | 0.782 |
| Mitral | 203 (43.4%) | 23 (47.9%) | 0.549 |
| Tricuspid | 14 (3%) | 1 (2.1%) | 0.681 |
| Pulmonary | 0 | 0 | 1.000 |
| **Acquisition** | | | |
| Community | 256 (54.7%) | 26 (54.2%) | 0.944 |
| Health-care associated | 197 (42.1%) | 22 (45.8%) | 0.617 |
| Nosocomial | 153 (32.7%) | 15 (31.3%) | 0.838 |
| Non-nosocomial health-care associated | 44 (9.4%) | 7 (14.6%) | 0.326 |
| Unknown | 15 (3.2%) | 0 | 0.124 |
| **Clinical complications** | | | |
| New onset or worsening heart failure | 214 (45.7%) | 18 (37.5%) | 0.264 |
| Persistent bacteremia | 61 (13%) | 8 (16.7) | 0.517 |
| CNS emboli | 75 (16%) | 11 (22.9%) | 0.274 |
| Other major emboli | 85 (18.2%) | 10 (20.8%) | 0.663 |
| Pulmonary emboli | 4 (0.9%) | 2 (4.2%) | 0.256 |
| Vertebral osteomyelitis | 17 (3.6%) | 1 (2.1%) | 0.577 |
| Non-vertebral osteomyelitis | 6 (1.3%) | 0 | 0.358 |
| Renal abscess | 12 (2.6%) | 2 (4.2%) | 0.590 |
| Splenic abscess | 60 (12.8%) | 6 (12.5%) | 0.949 |
| Heart conduction abnormality | 36 (7.7%) | 3 (6.3%) | 0.697 |
| Acute renal failure | 172 (36.8%) | 19 (39.6%) | 0.702 |
| Septic shock | 31 (6.6%) | 6 (12.5%) | 0.232 |
| **Echocardiographic findings** | | | |
| TEE performed | 358 (76.5%) | 33 (68.8%) | 0.267 |
| Median ejection fraction (IQR) | 60 (55-66) | 60 (55-65) | 0.805 |

| | | | |
|---|---|---|---|
| Median vegetation size, mm (IQR) | 8 (3-14) | 6 (3-8) | 0.110 |
| Moderate-severe aortic regurgitation | 179 (38.2%) | 14 (29.2%) | 0.191 |
| Moderate-severe mitral regurgitation | 183 (39.1%) | 14 (209.2%) | 0.153 |
| Paravalvular abscess | 60 (12.8%) | 2 (4.2%) | 0.008 |
| Intracardiac fistula | 3 (0.6%) | 1 (2.1%) | 0.491 |
| Pseudoaneurysm | 16 (3.4%) | 2 (4.2%) | 0.803 |
| Leaflet perforation/rupture | 63 (13.5%) | 7 (14.6%) | 0.585 |
| **Treatment characteristics** | | | |
| Median length of antibiotic treatment, days (IQR) | 42 (30-46) | 42 (28-44) | 0.389 |
| Cardiac surgery | 192 (41%) | 18 (37.5%) | 0.632 |
| Initial antibiotic treatment | | | |
| Double beta-lactam combination | 318 (67.9%) | 11 (22.9%) | <0.001 |
| Beta-lactam plus aminoglycoside | 96 (20.3%) | 5 (10.4%) | 0.092 |
| Other | 54 (11.4%)[±] | 32 (66.7%) | <0.001 |
| **Outcomes** | | | |
| In-hospital mortality | 109 (23.3%) | 14 (29.2%) | 0.391 |
| Mortality at 1-year | 144 (30.8%) | 15 (31.3%) | 0.945 |
| Relapses | 16 (3.4%) | 2 (4.2%) | 0.803 |

± Vancomycin plus aminoglycoside: 11 (20.4%); Vancomycin plus other: 8 (14.8%); Daptomycin: 7 (13%); Daptomycin plus beta-lactam: 5 (9.3%); Daptomycin plus fosfomycin: 1 (1.8%); Beta-lactam alone: 7 (13%); Beta-lactam plus quinolone: 4 (7.4%); Linezolid: 2 (3.7%); Other: 9 (16.7%).

**Table 4. Analysis of Risk Factors for In-Hospital Mortality, One-year Mortality and Relapses for 516 cases of Enterococcal Endocarditis.**

| | One-Year Mortality | | | | Relapses | | | |
|---|---|---|---|---|---|---|---|---|
| | ***Univariate*** | | ***Multivariate*** | | ***Univariate*** | | ***Multivariate*** | |
| | **HR (95%CI)** | ***P*** | **HR (95%CI)** | ***P*** | **HR (95%CI)** | ***P*** | **HR (95%CI)** | ***P*** |
| *E. faecalis* | 0.99 (0.58, 1.68) | 0.970 | | | 0.71 (0.16, 3.14) | 0.663 | | |
| Initial antibiotic treatment included gentamicin | N.A. | | | | N.A. | | | |
| Male sex | 0.94 (0.67, 1.31) | 0.722 | | | 0.44 (0.16, 1.17) | 0.103 | 0.50 (0.19, 1.36) | 0.174 |
| Age (years) | 1.00 (0.99, 1.01) | 0.534 | | | 1.02 (0.98, 1.07) | 0.322 | | |
| Diabetes mellitus | 1.56 (1.14, 2.14) | 0.006 | 1.00 (0.63, 1.62) | 0.972 | 0.69 (0.22, 2.14) | 0.524 | | |
| Congestive heart failure | 1.10 (0.80, 1.51) | 0.561 | | | 0.98 (0.36, 2.70) | 0.976 | | |
| Moderate-severe chronic renal failure | 1.97 (1.40, 2.79) | <0.001 | | | 1.05 (0.30, 3.67) | 0.943 | | |
| Moderate-severe liver disease | 2.58 (2.52, 4.40) | <0.001 | 2.62 (1.31, 5.24) | 0.007 | 2.95 (0.67, 12.96) | 0.152 | 2.03 (0.45, 9.16) | 0.351 |

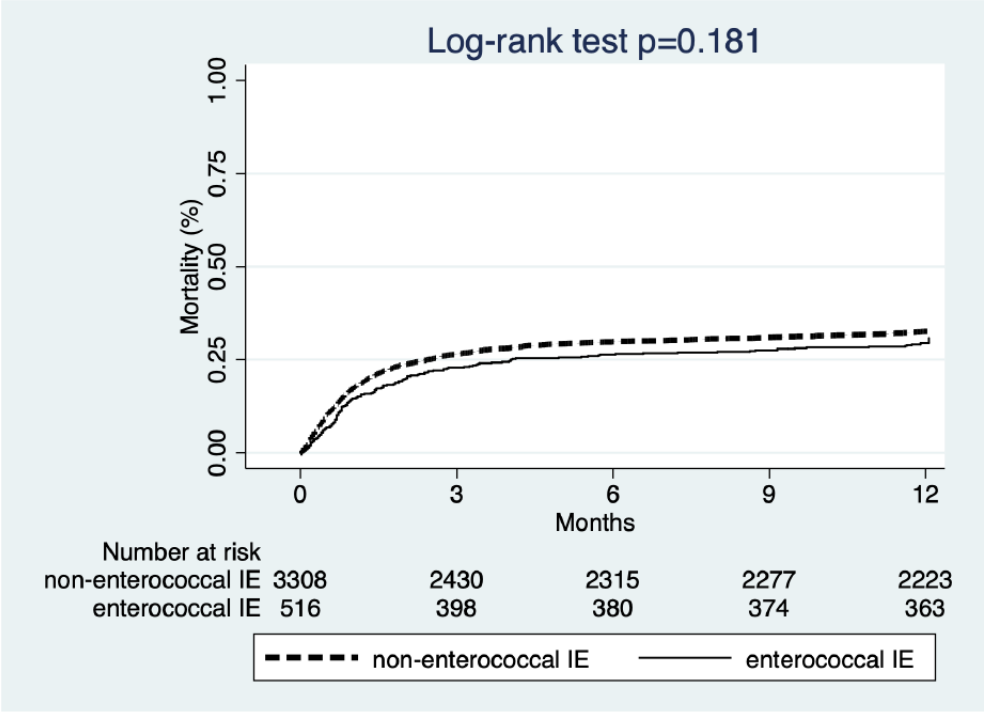
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Previous IE | 0.53 (0.30, 0.96) | 0.041 | 0.42 (0.21, 0.84) | 0.012 | 2.45 (0.79, 7.59) | 0.124 | | |
| Age-adjusted Charlson score | 1.16 (1.10, 1.23) | <0.001 | 1.12 (1.01, 1.24) | 0.010 | 0.93 (0.76, 1.14) | 0.497 | | |
| Community acquisition | 0.79 (0.58, 1.08) | 0.154 | | | 1.17 (0.42, 3.29) | 0.765 | | |
| Prosthetic IE | 0.78 (0.56, 1.09) | 0.158 | | | 1.82 (0.68, 4.85) | 0.232 | | |
| Urinary source | 1.31 (0.89, 1.91) | 0.172 | | | 0.65 (0.15, 2.85) | 0.576 | | |
| Aortic valve IE | 1.08 (0.78, 1.50) | 0.623 | | | 0.42 (0.16, 1.14) | 0.094 | 0.42 (0.16, 1.15) | 0.095 |
| Mitral valve IE | 1.07 (0.79, 1.48) | 0.602 | | | 2.15 (0.78, 5.92) | 0.133 | 1.67 (0.49, 5.78) | 0.412 |
| Paravalvular complications* | 1.52 (1.09, 2.12) | 0.014 | 1.87 (1.22, 2.87) | 0.040 | 0.19 (0.03, 1.43) | 0.115 | 0.22 (0.03, 1.73) | 0.153 |
| Vegetation size ≥ 10mm | 0.79 (0.46, 1.37) | 0.414 | | | 0.96 (0.16, 5.72) | 0.961 | | |
| New onset heart failure | 2.37 (1.72, 3.27) | <0.001 | 2.42 (1.53, 3.83) | <0.001 | 0.94 (0.35, 2.52) | 0.904 | | |

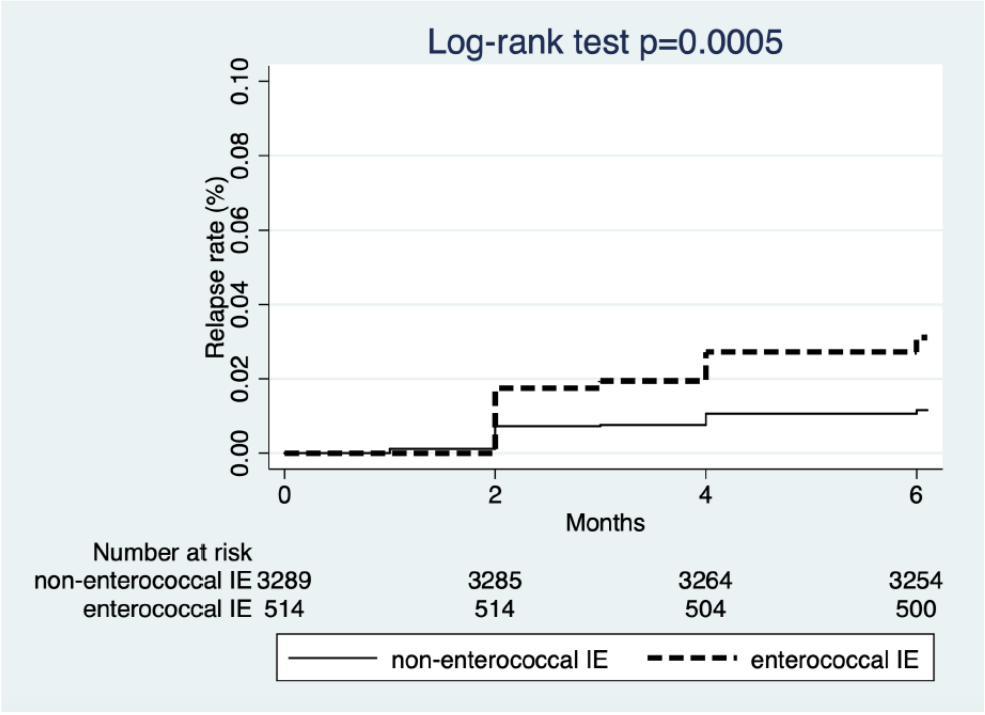
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Persistent bacteremia | 1.37 (0.90, 2.07) | 0.143 | | | 3.99 (1.45, 10.98) | 0.007 | 4.03 (1.43, 11.33) | 0.008 |
| CNS emboli | 1.23 (0.83, 1.83) | 0.313 | | | 1.12 (0.32, 3.94) | 0.852 | | |
| Other emboli | 1.05 (0.71, 1.57) | 0.787 | | | 0.99 (0.28, 3.48) | 0.993 | | |
| New heart conduction abnormality | 1.58 (0.94, 2.66) | 0.082 | | | N.A. | | | |
| Acute renal failure | 1.86 (1.36, 2.54) | <0.001 | 1.30 (0.84, 2.00) | 0.241 | 1.31 (0.49, 3.52) | 0.589 | | |
| Septic shock | 3.09 (1.99, 4.77 | <0.001 | 1.76 (1.04, 2.99) | 0.033 | N.A. | | | |
| Inappropriate initial antibiotics | 1.71 (0.90, 3.25) | 0.102 | | | N.A. | | | |
| Cardiac surgery | 0.62 (0.45, 0.87) | 0.006 | 0.88 (0.54, 1.43) | 0.613 | 0.33 (0.09, 1.15) | 0.083 | 0.48 (0.13, 1.71) | 0.253 |
| Logistic EuroSCORE | 1.02 (1.01, 1.03 | <0.001 | 1.02 (1.01, 1.03) | 0.002 | 1.00 (0.98, 1.03) | 0.923 | | |

467 * Paravalvular complications include at least one of the following: periannular abscess, pseudoaneurysm, fistula, or leaflet perforation/rupture.

468 N.A.= Non-assessed due to low number of events

**Central Illustration.** Mortality and relapses in enterococcal endocarditis vs. non-enterococcal endocarditis. (a) Kaplan-Meier curve for mortality at one year; (b) Kaplan-Meier curve for relapses over time.



**Clinical areas and patient features in which enterococcal endocarditis is of special relevance:**

- Elderly patients
- TAVI*
- Prosthetic valve endocarditis
- Degenerative left-sided valve disease
- Aortic involvement
- Chronic lung disease
- Chronic heart failure
- Hemodialysis*****

* Shown in other large series

**Title:** A contemporary picture of enterococcal endocarditis: prospective study of 516 cases from the GAMES Cohort

**Short Title:** Prognostic factors of enterococcal endocarditis

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## Abstract

**Background:** Enterococcal endocarditis (EE) is a growing entity in Western countries. However, quality data from large studies is lacking.
**Objectives**: To describe the characteristics and analyze the prognostic factors of EE in the GAMES cohort.
**Methods:** Post-hoc analysis of a prospectively collected cohort of patients from 35 Spanish centers from 2008 to 2016. Characteristics and outcomes of 516 cases of EE were compared to those of 3,308 cases of non-enterococcal endocarditis (NEE). Logistic regression and Cox proportional hazards regression analysis were performed to investigate risk factors for in-hospital and one-year mortality, and relapses.
**Results:** Patients with EE were significantly older, presented more frequently chronic lung disease, chronic heart failure, prior endocarditis, degenerative valve disease and had higher median age-adjusted Charlson score. EE more frequently involved the aortic valve and prosthesis (64.3% vs. 46.7%; P<0.001; and 35.9% vs. 28.9%; P=0.002, respectively) but less frequently pacemakers/defibrillators (1.5% vs. 10.5%; P<0.001), and showed higher rates of acute heart failure (45% vs. 38.3%;P=0.005). Cardiac surgery was less frequently performed in EE (40.7% vs.45.9%;P=0.024). No differences in in-hospital mortality and one-year mortality were found, whereas relapses were significantly higher in EE (3.5% vs. 1.7%; P=0.035). Increasing Charlson score, LogEuroSCORE, acute heart failure, septic shock and paravalvular complications were risk factors for mortality, whereas prior endocarditis was protective and persistent bacteremia constituted the sole risk factor for relapse.
**Conclusions:** Besides other baseline and clinical differences, EE more frequently affects prosthetic valves and less frequently pacemakers/defibrillators. EE presents higher rates of relapse than NEE.

**Condensed abstract:** Enterococcal endocarditis (EE) is a growing issue in Western countries. By comparing 516 cases of EE with 3,308 cases of NEE, we found older median age and higher comorbidity rates among EE than in NEE, as well as higher rates of aortic valve and prosthetic valve involvement, and heart failure. Mortality did not significantly differ between EE and NEE, whereas relapses were higher in EE. Risk factors for mortality in EE were Charlson score, LogEuroSCORE, acute heart failure, septic shock and paravalvular complications, whereas persistent bacteremia was associated with a higher likelihood of relapses.

**Keywords:** Infective endocarditis, enterococci, heart failure, relapses, prosthetic valves, epidemiology.

**Abbreviations:** CNS, central nervous system; EE, enterococcal endocarditis; HCA, healthcare-associated; IE, infective endocarditis; MRSA, methicillin-resistant *S. aureus*; NEE, non-enterococcal endocarditis; PCM/DF, pacemakers/defibrillators; TAVI, transaortic valve implantation; TEE, transesophageal echocardiography

## Introduction

Enterococci have been identified as a growing pathogen, primarily in health-care associated infections in the U.S., where vancomycin-resistant strains pose a serious challenge to the health system [1]. However, enterococci are also playing an increasingly important role in infective endocarditis (IE) [2], with most recent series placing it as the third leading causative agent in high-income countries, reaching up to 15-20% of total cases [3-6]. Moreover, enterococci are the leading causative agent of transaortic valve implants (TAVI)-associated IE [7].

Most cases (around 90%) of enterococcal IE are caused by *E. faecalis* [8]. Since the turn of the 21$^{st}$ century, the classically described clinical presentation of enterococcal IE as a community-acquired, subacute pauci-symptomatic disease of genitourinary source [10] is progressively turning in a more aggressive, acute, more frequently healthcare-associated (HCA) disease of occurring predominantly amongst elderly patients with a large burden of comorbidities and seldom a clear identifiable source. [9,10].

The focus of recent relevant studies addressing enterococcal IE is largely placed on the genetic and molecular aspects [11,12], impact of antimicrobial resistance (e.g. vancomycin, high-level aminoglycoside resistance and daptomycin resistance) [1,8,11,12], therapeutic options [13-15] or the use of TEE to detect IE [16-18], whereas there is a relative paucity of studies explaining the main clinical and epidemiological changes of enterococcal IE in the last two decades and their underlying mechanisms, such as its potential association with colorectal neoplasms [19,20].

We aimed to investigate the main characteristics of enterococcal IE in a cohort of 516 patients prospectively collected from 2008 to 2016 and to compare them with those of non-enterococcal IE.

## Methods

*Design*: multicenter prospective observational study including 35 Spanish centers between 2008 and 2016. The characteristics of the GAMES cohort, collection of data variables through a specific central registration depository, and definitions are described elsewhere [5]. The work-up for searching potential sources of the infection, including gastrointestinal tract screening, was not systematic but was decided by the treating physician. Persistent bacteremia was defined as positive blood cultures beyond seven days of effective antibiotic therapy; relapse refers to a new episode of IE due to the same microorganism within the next 6 months after the initial episode; acute renal failure was defined in the data collection sheet as a worsening equal or higher than 25% of serum creatinine or glomerular clearance occurring within a lapse of 72h; community-acquired IE was defined as IE diagnosed within the first 48 hours of admission in a patient who did not fulfill the criteria for HCA infection. HCA infection encompasses nosocomial and non-nosocomial HCA IE [21]. Nosocomial IE was defined as IE in a patient who had been hospitalized for >48 hours before the onset of signs or symptoms consistent with IE. Non-nosocomial HCA IE was an IE diagnosed within 48 hours of admission of an outpatient.

*Patients*: adult individuals with definite or possible IE diagnosed according to the modified Duke criteria [22].

*Outcomes*: in-hospital and one-year mortality (death due to any causes within 30 days and 365 days from the admission, respectively), and relapses.

*Statistical analysis*: Categorical variables were summarized as percentages and continuous variables as means and standard deviations. Categorical variables were compared using the chi-square test (or Fisher's exact test where necessary). Continuous variables were compared using the Kruskal-Wallis test. Cox proportional hazards regression analysis was utilized to investigate risk factors for one-year mortality and relapses. Variables with $P<0.20$ in the

univariate analysis were included in the models. Kaplan-Meier survival curves free of mortality at one year and relapses were generated with log-rank test analysis and considering censored episodes according to the time measured for each endpoint. A two-sided $P<0.05$ was considered to be statistically significant. Statistical analyses were performed using SPSS for Windows, Version 16.0 (SPSS Inc, Chicago, Illinois, USA).

## Results

Patients with enterococcal IE were significantly older and had higher rates of comorbidities, leading to a significantly higher median age-adjusted Charlson score (**Table 1**). Diabetes mellitus, chronic lung disease, congestive heart failure, previous IE, and non-congenital valve disease were all significantly more frequent among enterococcal IE, whereas ischemic cardiomyopathy and chronic renal failure, although more frequent too among enterococcal IE, did not reach statistical significance. On the other hand, iv drug use, HIV infection and congenital heart abnormalities were significantly more common among patients with non-enterococcal IE. The proportion of prosthetic valve IE was significantly higher in the enterococcal IE group, whereas PCM/DF-associated IE was significantly more frequent in the non-enterococcal IE group. The aortic valve was significantly more frequently involved in enterococcal IE cases, while the tricuspid and pulmonary valve were more commonly affected in non-enterococcal IE. Around half of the cases in both groups had an unknown source of the infection. The median time elapsed between the appearance of symptoms and hospital admission was not different between the two groups. Genitourinary and gastrointestinal foci were significantly more common among enterococcal IE episodes; meanwhile, oral, vascular and cutaneous sources were significantly more frequent in the non-enterococcal IE group. *E. faecalis* caused 90.7% of cases in the enterococcal IE group, being *S. aureus*, coagulase-negative staphylococci, and viridans group streptococci the more frequent causative agents in the non-enterococcal IE group. As for the proportion of cases from the global cohort, *S. aureus* represented 22.8%, coagulase-negative staphylococci 17.4%, viridans group streptococci 16.1%, enterococci 13.5%, Bovis group streptococci 6.4% and other streptococci 5%. Enterococci accounted for 9.5% of cases in patients aged less than 65 years and 16.4% among patients ≥65 years old (P<0.001). There were no cases of enterococcal IE caused by vancomycin-resistant enterococci. The site of acquisition did not

significantly differ between the two groups. Clinically, non-enterococcal IE presented with significantly higher rates of extensive CNS emboli, pulmonary emboli, and septic shock, as well as perivalvular abscesses, intracardiac fistula and pseudoaneurysm in the echocardiography, whereas enterococcal IE presented significantly higher rates of new onset heart failure and splenic abscesses. Enterococcal IE received a significantly longer median time of antibiotic therapy (42 vs. 36 days; P<0.001), being rates of cardiac surgery higher among non-enterococcal IE patients. Remarkably, 8 patients in the enterococcal IE group did not undergo cardiac surgery when indicated due to advanced liver disease, whereas this happened in 21 patients in the non-enterococcal group (1.5% vs. 0.6%; P=0.025, not shown). In-hospital and one-year mortality did not differ between both groups, yet relapses were significantly higher among patients with enterococcal IE.

The characteristics and outcomes of enterococcal and non-enterococcal IE are compared in the Supplementary material among native valve IE cases (**Supplementary Table 1**), prosthetic valve IE cases (**Supplementary Table 2**) and patients undergoing cardiac surgery (**Supplementary Table 3**). Notably, both in-hospital and one-year mortality were significantly higher among patients with non-enterococcal prosthetic valve IE, whereas relapses were significantly higher among patients with enterococcal prosthetic valve IE.

A comparison of HCA vs. community-acquired enterococcal IE cases is shown in **Table 2**. Notably, HCA enterococcal cases more frequently involved prosthetic valves and had higher rates of chronic liver and renal disease, including dialysis, and transplantation, and immunosuppres therapy, whereas community-acquired enterococcal IE involved native valves significantly more frequently and presented higher rates of iv drug use and HIV infection. Outcomes did not significantly differ between the two groups.

The characteristics and outcomes of enterococcal IE caused by *E. faecalis* are compared to those enterococcal IE cases caused by other species in **Table 3**. Of note, patients with *E.*

198 *faecalis* IE showed a trend to elder ages and presented significantly higher rates of chronic
199 congestive heart failure, chronic dialysis, prosthetic valve IE, and paravalvular abscess.
200 Patients with *E. faecalis* IE significantly received as initial antibiotic treatment double beta-
201 lactam combinations, whereas there were no differences between groups associated with
202 beta-lactam plus aminoglycoside initial combinations. Non-*E. faecalis* IE was more
203 frequently treated with other type of antibiotic treatment, being vancomycin combined with
204 an aminoglycoside the third most common combination among *E. faecalis* IE patients. Ten
205 (62.5%) of the 16 relapses occurring in patients with *E. faecalis* IE had received double beta-
206 lactam therapy, 5 (31.2%) received beta-lactam plus aminoglycosides and 1 (6.3%)
207 vancomycin plus gentamicin. The two relapses occurring in non-*E.faecalis* IE patients had
208 received other type of combinations. Outcomes did not significantly differ between the two
209 groups.
210 In the multivariate analysis, increasing age-adjusted Charlson score, paravalvular
211 complications, new onset of heart failure, septic shock and logistic EuroSCORE were
212 identified as risk factors for one-year mortality and prior episode of IE was protective.
213 Persistent bacteremia was identified as a risk factor for relapse (**Table 4**). Curves for mortality
214 and relapse over time are shown in the **Central Illustration**.
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## Discussion

### Epidemiology and main clinical characteristics

Ours is the largest national series of enterococcal IE described to date. In terms of epidemiological findings, this study confirms some of the common traits of the enterococcal IE profile described in studies conducted during the last fifteen years, but we also found some differences in this regard. Remarkably, as foreseen in the previous literature, median age, female sex, comorbidities, unknown source of infection and healthcare acquisition among enterococcal IE cases are on the rise. For example, Chirouze et al provided data on 500 cases of enterococcal IE from the International Collaboration on Endocarditis (ICE) collected from 2000 to 2006 and compared them with 823 cases of IE caused by oral streptococci and 293 cases of D group streptococcal IE [4]. North America was the region where more cases of enterococcal IE came from (50%), 90.6% of cases were caused by *E. faecalis*, median age was 65 years, 72.6% of cases occurred in men, 22.4% had diabetes, 8.4% were on chronic hemodialysis, 11.2% had cancer, 12.5% of cases had a prior episode of IE, 23.4% of cases overall were healthcare-associated and enterococcal IE involved prosthetic valves (in 29.1% of cases) significantly more frequently than streptococcal IE [4]. As in the case of another study from the ICE [23], we found that enterococcal IE is significantly more frequent among patients aged 65 years or more. By comparing to all other etiologies of IE, we have also identified that enterococcal IE is significantly less frequent among iv drug users, people living with HIV, patients with congenital heart disease, whereas it significantly more often the aortic valve and affected people with chronic diseases such as respiratory diseases, ischemic myocardiopathy, chronic heart failure, chronic renal disease or degenerative valve disease.

From a clinical standpoint, the two major findings of our study are the high rate of prosthetic valve involvement and heart failure. In addition, we found that in spite of presenting very

similar profiles in all other aspects, *E. faecalis* produced significantly more prosthetic valve IE cases than other enterococcal species while the latter produced significantly more native valve IE, which has not been noted before.

**Complications and outcome**

Heart failure was a prognostic factor for mortality among patients with EE. However, when analyzing native and prosthetic valve IE separately, we did not find higher heart failure rates in prosthetic enterococcal IE. Heart failure as a common trait of enterococcal IE has previously been defined in some reports [24,25] but remarkably not in the Chirouze et al study [4]. In our cohort of enterococcal IE, we also find higher rates of moderate-severe aortic and mitral regurgitation than in other types of IE. We hypothesize this might be due to the higher frequency of heart abnormalities of elderly patients rather than to a special ability for valve tissue destruction inherent to enterococci, which is consistent with the lower rates of paravalvular complications we observed among patients with enterococcal IE and the fact than the median time elapsed from the onset of symptoms to admission was not different between enterococcal and non-enterococcal IE.

Whereas we did not find significant differences in in-hospital and one-year mortality between enterococcal and non-enterococcal IE overall, both were significantly lower in enterococcal prosthetic valve IE than in non-enterococcal prosthetic valve IE in spite of the aforementioned lower rates of cardiac surgery.

Although enterococcal IE classically presents with higher rates of relapse than other types of IE [8], the risk factors associated with this phenomenon have been scarcely investigated to date. Moreover, no other large study on enterococcal IE had previously confirmed a significantly higher rate, including the ICE study led by Chirouze, which did not provide data on relapses [4]. In our study, persistent bacteremia was found to be a risk factor for relapsing enterococcal IE. To the best of our knowledge, this is a novel finding. Persistent bacteremia

might be related to high initial bloodstream enterococcal inoculum, which may strongly depend on the source of the infection or the presence of intravascular devices, non-drained infectious foci and the type of initial antibiotic treatment, as well as to the characteristics of the bacterium. Persistent bacteremia, together with other recently identified potential risk factors for enterococcal IE relapses such as advanced liver disease [15] and genome modifications and phenotypic adaptation of changes of enterococcal strains [26] in *E. faecalis* IE, merit further investigation.

**Treatment features**

The length of antibiotic treatment was six weeks in median in both native and prosthetic valve enterococcal endocarditis. Among other determinants, this might reflect the high proportion of cases treated with double beta-lactam combination according to current guidelines [27,28], as well as the increasing complexity of enterococcal IE leading to six-week courses also for ampicillin plus gentamicin provided the average complication rates that likely precludes the use of shorter courses. Furthermore, lesser patients with enterococcal IE had indication and did indeed undergo cardiac surgery, and again this general observation only kept true for patients with prosthetic valve IE (less than a third of whom were operated) and not for native valve IE. Almost two thirds among the latter had indication for cardiac surgery while it was barely 50% among patients with prosthetic valve IE. The leading indication for cardiac surgery among native valve enterococcal IE was congestive heart failure and valve regurgitation; both of them were significantly more common in native than in prosthetic enterococcal IE.

**Limitations**

This study is constrained by several limitations. Firstly, we could not assess the epidemiological evolution of enterococcal IE along the study period because the database was still being updated with case report forms from cases of 2015 and 2016 sent by participating

centers. Secondly, EE cases were compared to the rest of the GAMES cohort IE cases instead of being compared only to oral and D-group streptococcal IE. However, our findings strongly suggest that the profile of EE is no longer similar to that of to the classical community-acquired streptococcal IE. Thirdly, due to a low proportion of cases including information of the antibiotic resistance profile of enterococci, we were not able to describe this aspect properly neither could we perform any analysis on the impact of high-level aminoglycoside resistance and vancomycin resistance on the prognosis of enterococcal IE. Fourthly, since most participating centers of the GAMES cohort are reference hospitals for cardiac surgery, the implications of a potential referral bias should be acknowledged. Fifth, the low number of non-*E. faecalis* enterococcal IE hampers the direct extrapolation of the results of the comparison between *E. faecalis* and non-*E. faecalis* IE. Finally, the long duration of the study period might represent a historical bias.

**Conclusions**

In conclusion, this study shows that enterococcal IE is an entity in constant evolution that constitutes the fourth common cause of IE in Spain. It affects mainly male and elderly patients with lots of comorbidities and prior episodes of IE; it is healthcare-associated in almost 50% of cases, involves prosthetic valves and entails heart failure and relapses more commonly than non-enterococcal IE. Although native enterococcal IE and non-enterococcal IE did not present significant differences on mortality rates, prosthetic valve enterococcal IE showed lower rates of in-hospital mortality and one-year mortality than non-enterococcal prosthetic IE. Relapses in enterococcal IE are associated to persistent bacteremia. Further studies investigating the relationship between relapses of enterococcal IE and potential contributing factors are warranted.

## Perspectives

**Competency in Medical Knowledge 1:** Enterococcal endocarditis is changing epidemiologically while becoming increasingly frequent worldwide.

**Competency in Medical Knowledge 2:** Its clinical presentation is overall less severe than non-enterococcal endocarditis, yet it present higher rates of relapses and more frequently affects prosthetic valves.

**Competency in Medical Knowledge 3:** The outcomes of *Enterococcus faecalis* endocarditis (almost 90% of enterococcal endocarditis cases) are not significantly different from those of non-*E. faecalis* enterococcal endocarditis.

**Competency in Patient Care:** Enterococcal endocarditis should be suspected in elderly patients, especially in the healthcare setting. Follow-up after the initial admission is especially important due to an increased risk of relapses.

**Translational Outlook:** Future research might encompass a multidimensional inquiry on the characteristics of the bacterium, the host and medical and surgical management underlying the higher rates of relapses found among patients with enterococcal endocarditis.

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**Figure Legends**

**Central Illustration.**

Mortality and relapses in enterococcal endocarditis vs. non-enterococcal endocarditis.

(a) Kaplan-Meier curve for mortality at one year

(b) Kaplan-Meier curve for relapses over time.

436 **Table 1. Comparison of characteristics and outcome of enterococcal endocarditis and**
437 **endocarditis caused by other microorganisms from the GAMES Cohort (2008-2016).**

| | **Enterococcal IE (N=516)** | **Non-enterococcal IE (N=3,308)** | ***P*** |
|---|---|---|---|
| **Median age, years (IQR)** | 72 (64-78) | 68 (55-77) | <0.001 |
| **Male sex (%)** | 357 (69.2%) | 2206 (66.7%) | 0.254 |
| **Comorbidities** | | | |
| Diabetes mellitus | 168 (32.6%) | 913 (27.6%) | 0.025 |
| Chronic lung disease | 139 (26.9%) | 560 (16.9%) | <0.001 |
| Ischemic cardiomyopathy | 152 (29.5%) | 841 (25.4%) | 0.060 |
| Congestive heart failure | 197 (38.2%) | 1077 (32.6%) | 0.014 |
| Moderate/severe liver disease | 24 (4.7%) | 144 (4.4%) | 0.764 |
| - Child Pugh score, mean (SD) | 11 (2.83) | 8.4 (2.46) | 0.160 |
| - MELD score, mean (SD) | 20.6 (8.1) | 19.7 (8.8) | 0.733 |
| Moderate/severe chronic renal failure | 94 (18.2%) | 489 (14.8%) | 0.058 |
| Hemodialysis | 24 (4.7%) | 157 (4.7%) | 0.924 |
| Neoplasm | 94 (18.2%) | 508 (15.4%) | 0.114 |
| Transplantation | 9 (1.7%) | 64 (1.9%) | 0.760 |
| Immunosuppressant therapy | 38 (7.4%) | 192 (5.8%) | 0.201 |
| IV drug use | 5 (1%) | 78 (2.4%) | 0.006 |
| HIV | 4 (0.8%) | 61 (1.8%) | 0.018 |
| Previous IE | 63 (12.2%) | 215 (6.5%) | <0.001 |
| Congenital cardiac abnormality | 5 (1%) | 218 (6.6%) | <0.001 |

| | | | |
|---|---|---|---|
| Non-congenital valve disease | 252 (48.8%) | 1431 (43.3%) | 0.018 |
| Median age-adjusted Charlson score (IQR) | 5 (4-7) | 4 (3-6) | <0.001 |
| **Type of endocarditis** | | | |
| Native | 324 (62.7%) | 2007 (60.7%) | 0.355 |
| Prosthetic* | 185 (35.8%) | 955 (28.9%) | 0.002 |
| PCM/DF[+] | 8 (1.5%) | 346 (10.5%) | <0.001 |
| **Valve involvement[+]** | | | |
| Aortic | 332 (64.3%) | 1545 (46.7%) | <0.001 |
| Mitral | 226 (43.8%) | 1416 (42.8%) | 0.672 |
| Tricuspid | 15 (2.9%) | 186 (5.6%) | 0.001 |
| Pulmonary | 0 | 51 (1.5%) | <0.001 |
| **Diagnosis of endocarditis according to modified Duke criteria** | | | 0.029 |
| Definite | 431 (83.5%) | 2626 (79.4%) | |
| Possible | 85 (16.5%) | 682 (20.6%) | |
| **Median time of symptoms duration until admission in non-nosocomial cases, days (IQR)** | 6.5 (1.3-22.8) | 6.5 (2-18) | 0.549 |
| **Source** | | | |
| Oral | 8 (1.6%) | 220 (6.7%) | <0.001 |
| Respiratory | 2 (0.4%) | 40 (1.2%) | 0.096 |
| Genitourinary | 92 (17.8%) | 106 (3.2%) | <0.001 |
| Gastrointestinal | 82 (15.9%) | 172 (5.2%) | <0.001 |
| Vascular | 62 (12%) | 637 (19.3%) | <0.001 |
| Cutaneous | 10 (1.9%) | 260 (7.9%) | <0.001 |

| | | | |
|---|---|---|---|
| Other | 19 (3.8%) | 202 (6.3%) | 0.031 |
| Unknown | 262 (50.8%) | 1708 (51.6%) | 0.734 |
| **Etiology** | | | NA |
| Enterococci | | | |
| *E. faecalis* | 468 (90.7%) | - | |
| *E. faecium* | 36 (7%) | - | |
| Other enterococci[±] | 12 (2.3%) | - | |
| S. *aureus* | - | 870 (26.3%) | |
| MSSA | - | 849 97.6%) | |
| MRSA | - | 21 (2.4%) | |
| Viridans group streptococci | - | 616 (18.6%) | |
| Coagulase-negative staphylococci | - | 664 (20.1%) | |
| Bovis group streptococci | - | 244 (7.4%) | |
| Other streptococci | - | 193 (5.8%) | |
| Other | - | 711 (21.5%)[×] | |
| **Acquisition** | | | |
| Community | 282 (54.7%) | 1953 (59%) | 0.062 |
| Health-care associated | 219 (42.4%) | 1229 (37.1%) | 0.093 |
| Nosocomial | 168 (32.6%) | 954 (28.8%) | 0.092 |
| Non-nosocomial health-care associated | 51 (9.9%) | 275 (8.3%) | 0.262 |
| Unknown | 15 (2.9%) | 116 (3.5%) | 0.486 |
| **Clinical complications** | | | |
| New onset or worsening heart failure | 232 (45%) | 1270 (38.4%) | 0.005 |
| NYHA I | 12 (5.2%) | 114 (9%) | 0.054 |

| | | | |
|---|---|---|---|
| NYHA II | 35 (15.1%) | 214 (16.9%) | 0.506 |
| NYHA III | 95 (40.9%) | 413 (32.5%) | 0.013 |
| NYHA IV | 90 (38.8%) | 529 (41.6%) | 0.416 |
| Persistent bacteremia | 69 (13.4%) | 378 (11.4%) | 0.223 |
| CNS emboli | 86 (16.7%) | 663 (20%) | 0.058 |
| Hemorrhagic | 11 (12.8%) | 110 (16.6%) | 0.367 |
| Extensive (>2cm) | 0 | 109 (16.4%) | 0.001 |
| Multiple (>3) | 6 (7%) | 68 (10.3%) | 0.337 |
| Other major emboli | 95 (18.4%) | 687 (20.8%) | 0.202 |
| Pulmonary emboli | 6 (1.2%) | 183 (5.5%) | <0.001 |
| Vertebral osteomyelitis | 18 (3.5%) | 97 (2.9%) | 0.479 |
| Non-vertebral osteomyelitis | 6 (1.2%) | 52 (1.6%) | 0.536 |
| Renal abscess | 14 (2.7%) | 87 (2.6%) | 0.914 |
| Splenic abscess | 66 (12.8%) | 310 (9.4%) | 0.028 |
| Heart conduction abnormality | 39 (7.6%) | 297 (9%) | 0.262 |
| Acute renal failure | 191 (37%) | 1177 (35.6%) | 0.530 |
| Septic shock | 37 (7.2%) | 432 (13.1%) | <0.001 |
| **Echocardiographic findings** | | | |
| TEE performed | 391 (75.8%) | 2583 (78.1%) | 0.253 |
| Median ejection fraction (IQR) | 60% (55-65) | 60% (55-65) | 0.536 |
| Median vegetation size in mm (IQR) | 8 (3-14) | 8 (3-14) | 0.088 |
| Moderate-severe aortic regurgitation | 193 (37.4%) | 882 (26.7%) | <0.001 |
| Moderate-severe mitral regurgitation | 197 (38.2%) | 1111 (33.6%) | 0.048 |
| Perivalvular abscess | 62 (12%) | 514 (15.5%) | 0.024 |

| | | | |
|---|---|---|---|
| Intracardiac fistula | 4 (0.8%) | 86 (2.6%) | <0.001 |
| Pseudoaneurysm | 18 (3.5%) | 183 (5.5%) | 0.023 |
| Leaflet perforation/rupture | 70 (13.6%) | 436 (13.2%) | 0.082 |
| **Treatment characteristics** | | | |
| Antibiotics properly indicated | 493 (95.5%) | 3168 (95.8%) | 0.817 |
| Median length of antibiotic treatment, days (IQR) | 42 (30-46) | 36 (24-44) | <0.001 |
| Cardiac surgery | | | |
| Indicated | 316 (61.2%) | 2182 (66%) | 0.040 |
| Operated during admission | 210 (40.7%) | 1520 (45.9%) | 0.024 |
| New surgery during the first year after admission | 23 (4.5%) | 144 (4.4%) | 0.915 |
| **Outcomes** | | | |
| In-hospital mortality | 123 (23.8%) | 892 (27%) | 0.123 |
| Mortality at 1-year | 159 (30.8%) | 1100 (33.3%) | 0.266 |
| Relapses | 18 (3.5%) | 57 (1.7%) | 0.035 |

HIV: Human immunodeficiency syndrome; IQR: Interquartile range; MSSA: methicillin-susceptible *S. aureus;* MRSA: methicillin-resistant *S. aureus*; NA: not analyzed; PCM/DF: pacemakers/defibrillators

[*] There were 17 cases of endocarditis over TAVI, 3 of them occurring in the EE group and 14 in the NEE group (0.5% vs. 0.4%, P=0.802).

[+]Only episodes in which only PCM/DF are affected are included in this group. Episodes have been classified as native or prosthetic valve where a concomitant valve involvement exists.

The sum does not equal 100% because episodes with multivalve involvement are also counted.

[±] In 9 cases there was not identification at the species level (*Enterococcus spp*.), whereas the 3 remaining cases corresponded to one case of *E. durans, E. avium* and *E. gallinarum* each.

[×]Negative culture: 342 (48.1%); Gram negative bacilli: 163 (22.9%); Polymicrobial: 69 (9.7%); *Candida spp*: 64 (9.0%); Anaerobic bacteria: 39 (5.5%); Other fungi: 11 (1.5%); Miscellany: 23 (3.2%).

453 **Table 2. Comparison of Health-Care acquired vs. Community-acquired Enterococcal**
454 **Endocarditis.**

| | **Community-acquired (N=282)** | **Nosocomial-HCA (N=168)** | **Non-nosocomial HCA (N=51)** | ***P*** |
|---|---|---|---|---|
| **Enterococcal species** | | | | 0.342 |
| *E. faecalis* | 256 (90.8%) | 153 (91.1%) | 47 (92.2%) | |
| *E. faecium* | 17 (6%) | 15 (8.9%) | 4 (7.8%) | |
| Other | 9 (3.2%)* | 0 | 0 | |
| **Median age, years (IQR)** | 73 (64-80) | 73 (64-78) | 71 (62-79) | 0.332 |
| **Male sex (%)** | 195 (69.1%) | 120 (71.4%) | 31 (60.7%) | 0.222 |
| **Comorbidities** | | | | |
| Diabetes mellitus | 97 (34.4%) | 46 (27.3%) | 17 (33.3%) | 0.296 |
| Chronic lung disease | 73 (25.9%) | 49 (29.1%) | 12 (23,5) | 0.700 |
| Ischemic cardiomyopathy | 78 (27.7%) | 56 (33.3%) | 12 (23.5%) | 0.285 |
| Congestive heart failure | 101 (35.8%) | 74 (44%) | 19 (37.2%) | 0.221 |
| Moderate/severe liver disease | 8 (2.8%) | 7 (4.2%) | 8 (15.7%) | 0.022 |
| Moderate/severe chronic renal failure | 43 (15.2%) | 37 (22%) | 12 (23.5%) | 0.120 |
| Hemodialysis | 4 (1.4%) | 11 (6.5%) | 8 (15.6%) | <0.001 |
| Neoplasm | 49 (17.4%) | 28 (16.6%) | 13 (25.4%) | 0.329 |
| Transplantation | 2 (0.7%) | 6 (3.6%) | 1 (2%) | 0.806 |
| Immunosuppressant therapy | 15 (5.3%) | 18 (10.7%) | 4 (7.8%) | 0.105 |
| IV drug use | 5 (1.8%) | 0 | 0 | 0.024 |
| HIV | 4 (1.4%) | 0 | 0 | 0.045 |

| | | | | |
|---|---|---|---|---|
| Previous IE | 28 (9.9%) | 24 (14.2%) | 10 (19.6%) | 0.101 |
| Congenital cardiac abnormality | 4 (1.4%) | 2 (1.2%) | 1 (2%) | 0.918 |
| Non-congenital valve disease | 134 (47.5%) | 89 (52.9%) | 23 (45%) | 0.445 |
| Median age-adjusted Charlson score (IQR) | 5 (4-7) | 5 (4-7) | 6 (4-8) | 0.425 |
| **Type of endocarditis** | | | | |
| Native | 192 (68.1%) | 87 (51.7%) | 37 (72.5%) | <0.001 |
| Prosthetic | 86 (30.5%) | 79 (47%) | 13 (25.4%) | <0.001 |
| PCM/DF* | 4 (1.4%) | 3 (1.7%) | 0 | 0.103 |
| **Valve involvement**[+] | | | | |
| Aortic | 179 (63.5%) | 105 (62.5%) | 37 (72.5%) | 0.403 |
| Mitral | 122 (43.3%) | 75 (44.6%) | 24 (47%) | 0.868 |
| Tricuspid | 10 (3.5%) | 4 (2.4%) | 1 (2%) | 0.398 |
| Pulmonary | 0 | 0 | 0 | 1.000 |
| **Clinical complications** | | | | |
| New onset or worsening heart failure | 126 (44.7%) | 78 (46.7%) | 23 (45.1%) | 0.849 |
| Persistent bacteremia | 36 (12.8%) | 23 (13.7%) | 8 (15.6%) | 0.652 |
| CNS emboli | 43 (15.2%) | 30 (17.8%) | 10 (19.6%) | 0.372 |
| Other major emboli | 57 (20.2%) | 28 (16.7%) | 6 (11.8%) | 0.220 |
| Pulmonary emboli | 2 (0.7%) | 4 (2.3%) | 0 | 0.280 |
| Vertebral osteomyelitis | 9 (3.2%) | 7 (4.1%) | 2 (3.9%) | 0.779 |
| Non-vertebral osteomyelitis | 5 (1.8%) | 0 | 1 (1.9%) | 0.152 |
| Renal abscess | 8 (2.8%) | 0 | 0 | 0.695 |
| Splenic abscess | 40 (14.2%) | 6 (3.5%) | 3 (5.8%) | <0.001 |
| Heart conduction abnormality | 22 (7.8%) | 12 (7.1%) | 3 (5.8%) | 0.880 |

| | | | | |
|---|---|---|---|---|
| Acute renal failure | 112 (39.7%) | 51 (30.3%) | 19 (37.2%) | 0.134 |
| Septic shock | 19 (6.7%) | 14 (8.3%) | 3 (5.8%) | 0.761 |
| **Echocardiographic findings** | | | | |
| TEE performed | 206 (73%) | 134 (79.8%) | 40 (78.4%) | 0.093 |
| Median ejection fraction (%, IQR) | 60 (55-65) | 60 (50-65) | 60 (50-68) | 0.465 |
| Median vegetation size (mm, IQR) | 8 (3-15) | 10 (7-19) | 10.5 (8-13) | 0.729 |
| Moderate-severe aortic regurgitation | 107 (37.9%) | 54 (32.1%) | 24 (47%) | 0.133 |
| Moderate-severe mitral regurgitation | 119 (42.2%) | 49 (29.1%) | 25 (49%) | 0.006 |
| Perivalvular abscess | 23 (8.2%) | 28 (16.6%) | 9 (17.6%) | 0.011 |
| Intracardiac fistula | 2 (0.7%) | 2 (1.2%) | 0 | 0.235 |
| Pseudoaneurysm | 5 (1.8%) | 6 (3.6%) | 5 (9.8%) | 0.010 |
| Leaflet perforation/rupture | 44 (15.6%) | 19 (11.3%) | 6 (11.7%) | 0.163 |
| **Treatment characteristics** | | | | |
| Median length of antibiotic treatment, days (IQR) | 42 (29-46) | 42 (33-47) | 42 (28-46) | 0.317 |
| Cardiac surgery | 121 (42.9%) | 57 (33.9%) | 23 (45.1%) | 0.127 |
| **Outcomes** | | | | |
| In-hospital mortality | 60 (21.3%) | 45 (25.5%) | 16 (31.3%) | 0.186 |
| One-year mortality | 79 (28%) | 53 (31.5%) | 22 (43.1%) | 0.094 |
| Relapses[±] | 10 (3.5%) | 3 (1.7%) | 4 (7.8%) | 0.109 |

455 [*] 8 cases due to *Enterococcus spp*. and 1 case of *E. durans* IE

456 [±] One case of relapse among EE was not included because it had an unknown source of
457 acquisition.

458

459 **Table 3. Comparison of *E. faecalis* vs. non-*E. faecalis* Enterococcal Endocarditis**

| | ***E. faecalis* IE (N=468)** | ***Non-E. faecalis* IE (N=48)** | ***P*** |
|---|---|---|---|
| **Median age, years (IQR)** | 73 (64.5-79) | 68.5 (59.5-76) | 0.080 |
| **Male sex (%)** | 325 (69.4%) | 32 (66.7%) | 0.697 |
| **Comorbidities** | | | |
| Diabetes mellitus | 151 (32.3%) | 17 (35.4%) | 0.663 |
| Chronic lung disease | 130 (27.8%) | 9 (18.8%) | 0.133 |
| Ischemic cardiomyopathy | 140 (29.9%) | 12 (25%) | 0.457 |
| Congestive heart failure | 187 (40%) | 10 (20.8%) | 0.002 |
| Moderate/severe liver disease | 20 (4.3%) | 4 (8.3%) | 0.322 |
| Moderate/severe chronic renal failure | 88 (18.8%) | 6 (12.5%) | 0.217 |
| Hemodialysis | 24 (5.1%) | 0 | <0.001 |
| Neoplasm | 81 (17.3%) | 13 (27.1%) | 0.142 |
| Transplantation | 8 (1.7%) | 1 (2.1%) | 0.862 |
| Immunosuppressant therapy | 33 (7.1%) | 5 (10.4%) | 0.461 |
| IV drug use | 4 (0.9%) | 1 (2.1%) | 0.560 |
| HIV | 3 (0.6%) | 1 (2.1%) | 0.491 |
| Previous IE | 57 (12.2%) | 6 (12.5%) | 0.949 |
| Congenital cardiac abnormality | 6 (1.3%) | 1 (2.1%) | 0.706 |
| Non-congenital valve disease | 229 (48.9%) | 23 (47.9%) | 0.893 |
| Median age-adjusted Charlson score (IQR) | 5 (4-7) | 5 (3-7) | 0.227 |
| **Type of endocarditis** | | | |
| Native | 287 (61.3%) | 37 (77.1%) | 0.015 |
| Prosthetic | 174 (37.2%) | 11 (22.9%) | 0.028 |
| PCM/DF* | 7 (1.5%) | 0 | 0.109 |

| | | | |
|---|---|---|---|
| **Valve involvement**[+] | | | |
| Aortic | 302 (64.5%) | 30 (62.5%) | 0.782 |
| Mitral | 203 (43.4%) | 23 (47.9%) | 0.549 |
| Tricuspid | 14 (3%) | 1 (2.1%) | 0.681 |
| Pulmonary | 0 | 0 | 1.000 |
| **Acquisition** | | | |
| Community | 256 (54.7%) | 26 (54.2%) | 0.944 |
| Health-care associated | 197 (42.1%) | 22 (45.8%) | 0.617 |
| Nosocomial | 153 (32.7%) | 15 (31.3%) | 0.838 |
| Non-nosocomial health-care associated | 44 (9.4%) | 7 (14.6%) | 0.326 |
| Unknown | 15 (3.2%) | 0 | 0.124 |
| **Clinical complications** | | | |
| New onset or worsening heart failure | 214 (45.7%) | 18 (37.5%) | 0.264 |
| Persistent bacteremia | 61 (13%) | 8 (16.7) | 0.517 |
| CNS emboli | 75 (16%) | 11 (22.9%) | 0.274 |
| Other major emboli | 85 (18.2%) | 10 (20.8%) | 0.663 |
| Pulmonary emboli | 4 (0.9%) | 2 (4.2%) | 0.256 |
| Vertebral osteomyelitis | 17 (3.6%) | 1 (2.1%) | 0.577 |
| Non-vertebral osteomyelitis | 6 (1.3%) | 0 | 0.358 |
| Renal abscess | 12 (2.6%) | 2 (4.2%) | 0.590 |
| Splenic abscess | 60 (12.8%) | 6 (12.5%) | 0.949 |
| Heart conduction abnormality | 36 (7.7%) | 3 (6.3%) | 0.697 |
| Acute renal failure | 172 (36.8%) | 19 (39.6%) | 0.702 |
| Septic shock | 31 (6.6%) | 6 (12.5%) | 0.232 |
| **Echocardiographic findings** | | | |
| TEE performed | 358 (76.5%) | 33 (68.8%) | 0.267 |
| Median ejection fraction (IQR) | 60 (55-66) | 60 (55-65) | 0.805 |

| | | | |
|---|---|---|---|
| Median vegetation size, mm (IQR) | 8 (3-14) | 6 (3-8) | 0.110 |
| Moderate-severe aortic regurgitation | 179 (38.2%) | 14 (29.2%) | 0.191 |
| Moderate-severe mitral regurgitation | 183 (39.1%) | 14 (209.2%) | 0.153 |
| Paravalvular abscess | 60 (12.8%) | 2 (4.2%) | 0.008 |
| Intracardiac fistula | 3 (0.6%) | 1 (2.1%) | 0.491 |
| Pseudoaneurysm | 16 (3.4%) | 2 (4.2%) | 0.803 |
| Leaflet perforation/rupture | 63 (13.5%) | 7 (14.6%) | 0.585 |
| **Treatment characteristics** | | | |
| Median length of antibiotic treatment, days (IQR) | 42 (30-46) | 42 (28-44) | 0.389 |
| Cardiac surgery | 192 (41%) | 18 (37.5%) | 0.632 |
| Initial antibiotic treatment | | | |
| Double beta-lactam combination | 318 (67.9%) | 11 (22.9%) | <0.001 |
| Beta-lactam plus aminoglycoside | 96 (20.3%) | 5 (10.4%) | 0.092 |
| Other | 54 (11.4%)[±] | 32 (66.7%) | <0.001 |
| **Outcomes** | | | |
| In-hospital mortality | 109 (23.3%) | 14 (29.2%) | 0.391 |
| Mortality at 1-year | 144 (30.8%) | 15 (31.3%) | 0.945 |
| Relapses | 16 (3.4%) | 2 (4.2%) | 0.803 |

± Vancomycin plus aminoglycoside: 11 (20.4%); Vancomycin plus other: 8 (14.8%); Daptomycin: 7 (13%); Daptomycin plus beta-lactam: 5 (9.3%); Daptomycin plus fosfomycin: 1 (1.8%); Beta-lactam alone: 7 (13%); Beta-lactam plus quinolone: 4 (7.4%); Linezolid: 2 (3.7%); Other: 9 (16.7%).

**Table 4. Analysis of Risk Factors for In-Hospital Mortality, One-year Mortality and Relapses for 516 cases of Enterococcal Endocarditis.**

| | One-Year Mortality | | | | Relapses | | | |
|---|---|---|---|---|---|---|---|---|
| | ***Univariate*** | | ***Multivariate*** | | ***Univariate*** | | ***Multivariate*** | |
| | **HR (95%CI)** | ***P*** | **HR (95%CI)** | ***P*** | **HR (95%CI)** | ***P*** | **HR (95%CI)** | ***P*** |
| *E. faecalis* | 0.99 (0.58, 1.68) | 0.970 | | | 0.71 (0.16, 3.14) | 0.663 | | |
| Initial antibiotic treatment included gentamicin | N.A. | | | | N.A. | | | |
| Male sex | 0.94 (0.67, 1.31) | 0.722 | | | 0.44 (0.16, 1.17) | 0.103 | 0.50 (0.19, 1.36) | 0.174 |
| Age (years) | 1.00 (0.99, 1.01) | 0.534 | | | 1.02 (0.98, 1.07) | 0.322 | | |
| Diabetes mellitus | 1.56 (1.14, 2.14) | 0.006 | 1.00 (0.63, 1.62) | 0.972 | 0.69 (0.22, 2.14) | 0.524 | | |
| Congestive heart failure | 1.10 (0.80, 1.51) | 0.561 | | | 0.98 (0.36, 2.70) | 0.976 | | |
| Moderate-severe chronic renal failure | 1.97 (1.40, 2.79) | <0.001 | | | 1.05 (0.30, 3.67) | 0.943 | | |
| Moderate-severe liver disease | 2.58 (2.52, 4.40) | <0.001 | 2.62 (1.31, 5.24) | 0.007 | 2.95 (0.67, 12.96) | 0.152 | 2.03 (0.45, 9.16) | 0.351 |

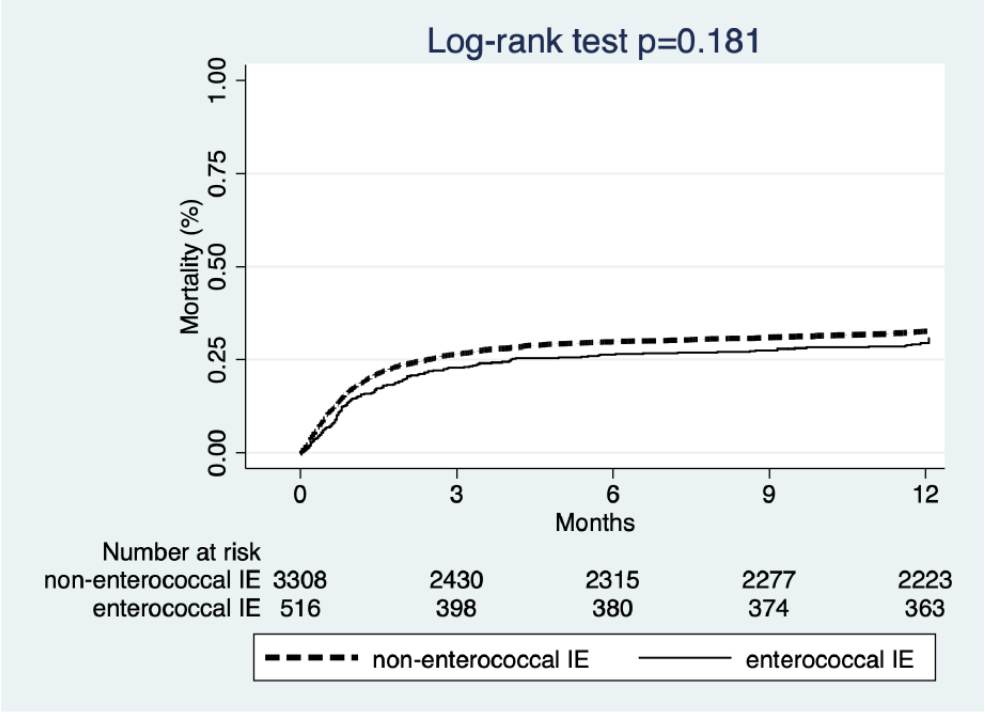
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Previous IE | 0.53 (0.30, 0.96) | 0.041 | 0.42 (0.21, 0.84) | 0.012 | 2.45 (0.79, 7.59) | 0.124 | | |
| Age-adjusted Charlson score | 1.16 (1.10, 1.23) | <0.001 | 1.12 (1.01, 1.24) | 0.010 | 0.93 (0.76, 1.14) | 0.497 | | |
| Community acquisition | 0.79 (0.58, 1.08) | 0.154 | | | 1.17 (0.42, 3.29) | 0.765 | | |
| Prosthetic IE | 0.78 (0.56, 1.09) | 0.158 | | | 1.82 (0.68, 4.85) | 0.232 | | |
| Urinary source | 1.31 (0.89, 1.91) | 0.172 | | | 0.65 (0.15, 2.85) | 0.576 | | |
| Aortic valve IE | 1.08 (0.78, 1.50) | 0.623 | | | 0.42 (0.16, 1.14) | 0.094 | 0.42 (0.16, 1.15) | 0.095 |
| Mitral valve IE | 1.07 (0.79, 1.48) | 0.602 | | | 2.15 (0.78, 5.92) | 0.133 | 1.67 (0.49, 5.78) | 0.412 |
| Paravalvular complications* | 1.52 (1.09, 2.12) | 0.014 | 1.87 (1.22, 2.87) | 0.040 | 0.19 (0.03, 1.43) | 0.115 | 0.22 (0.03, 1.73) | 0.153 |
| Vegetation size ≥ 10mm | 0.79 (0.46, 1.37) | 0.414 | | | 0.96 (0.16, 5.72) | 0.961 | | |
| New onset heart failure | 2.37 (1.72, 3.27) | <0.001 | 2.42 (1.53, 3.83) | <0.001 | 0.94 (0.35, 2.52) | 0.904 | | |

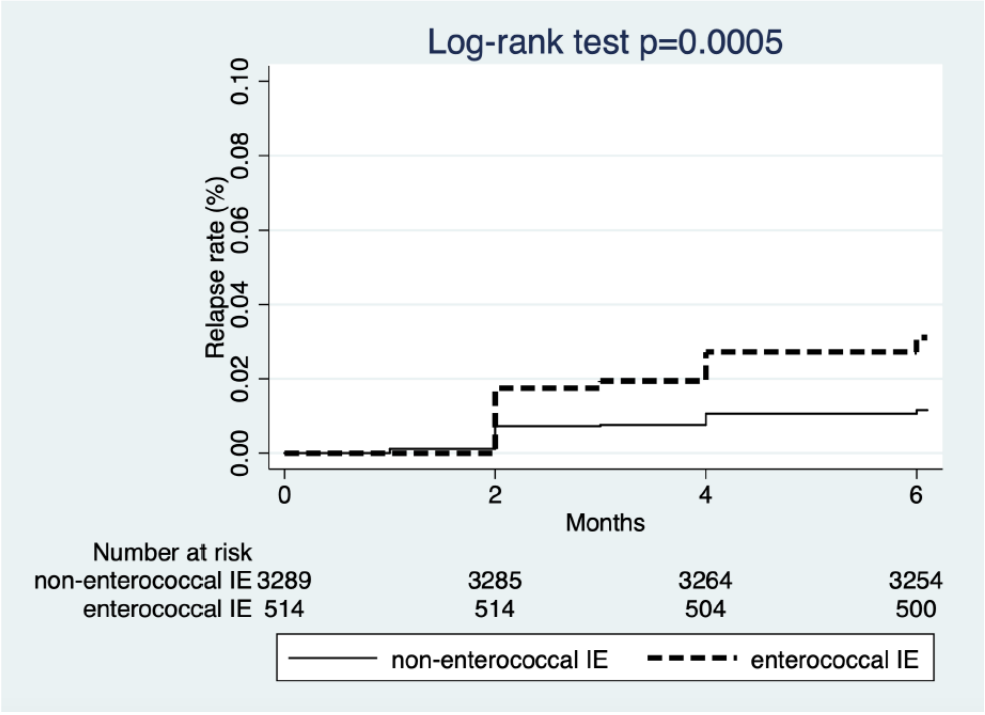
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Persistent bacteremia | 1.37 (0.90, 2.07) | 0.143 | | | 3.99 (1.45, 10.98) | 0.007 | 4.03 (1.43, 11.33) | 0.008 |
| CNS emboli | 1.23 (0.83, 1.83) | 0.313 | | | 1.12 (0.32, 3.94) | 0.852 | | |
| Other emboli | 1.05 (0.71, 1.57) | 0.787 | | | 0.99 (0.28, 3.48) | 0.993 | | |
| New heart conduction abnormality | 1.58 (0.94, 2.66) | 0.082 | | | N.A. | | | |
| Acute renal failure | 1.86 (1.36, 2.54) | <0.001 | 1.30 (0.84, 2.00) | 0.241 | 1.31 (0.49, 3.52) | 0.589 | | |
| Septic shock | 3.09 (1.99, 4.77 | <0.001 | 1.76 (1.04, 2.99) | 0.033 | N.A. | | | |
| Inappropriate initial antibiotics | 1.71 (0.90, 3.25) | 0.102 | | | N.A. | | | |
| Cardiac surgery | 0.62 (0.45, 0.87) | 0.006 | 0.88 (0.54, 1.43) | 0.613 | 0.33 (0.09, 1.15) | 0.083 | 0.48 (0.13, 1.71) | 0.253 |
| Logistic EuroSCORE | 1.02 (1.01, 1.03 | <0.001 | 1.02 (1.01, 1.03) | 0.002 | 1.00 (0.98, 1.03) | 0.923 | | |

467 * Paravalvular complications include at least one of the following: periannular abscess, pseudoaneurysm, fistula, or leaflet perforation/rupture.

468 N.A.= Non-assessed due to low number of events

**Central Illustration.** Mortality and relapses in enterococcal endocarditis vs. non-enterococcal endocarditis. (a) Kaplan-Meier curve for mortality at one year; (b) Kaplan-Meier curve for relapses over time.



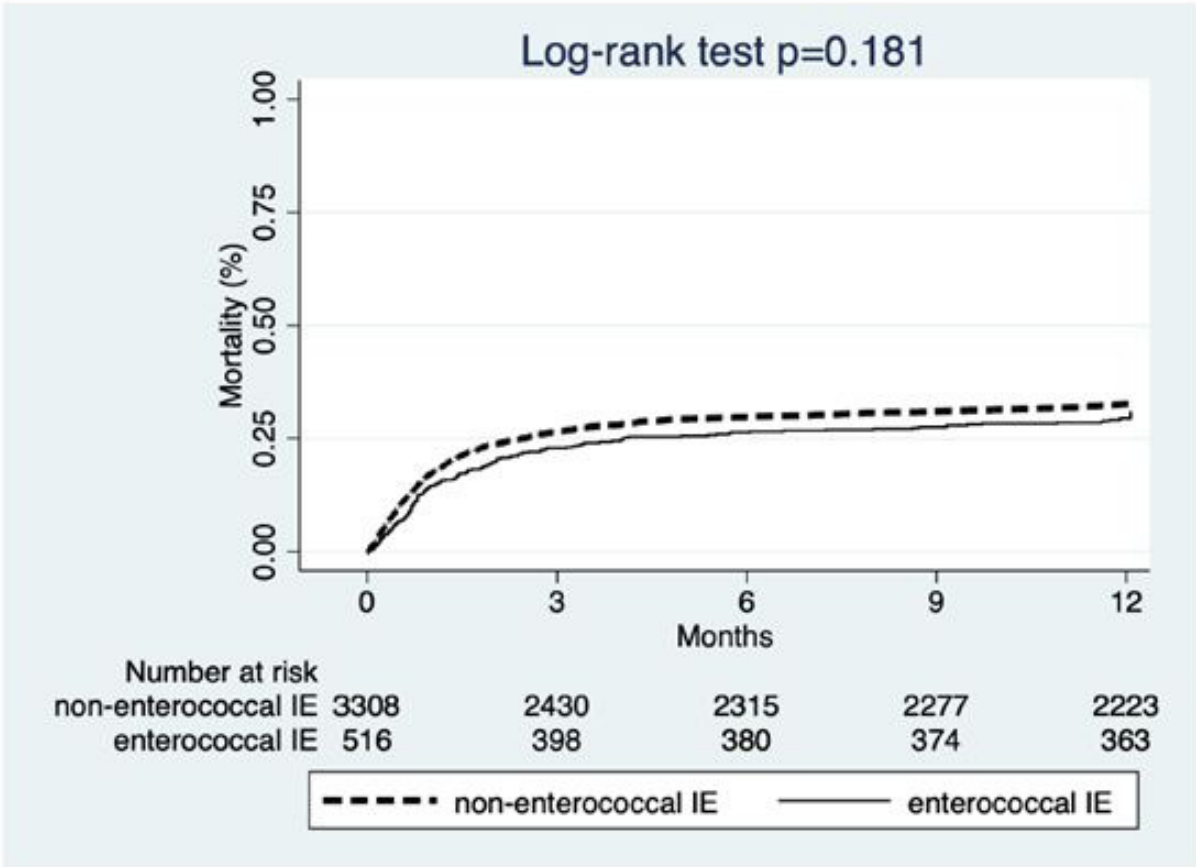



**Clinical areas and patient features in which enterococcal endocarditis is of special relevance:**

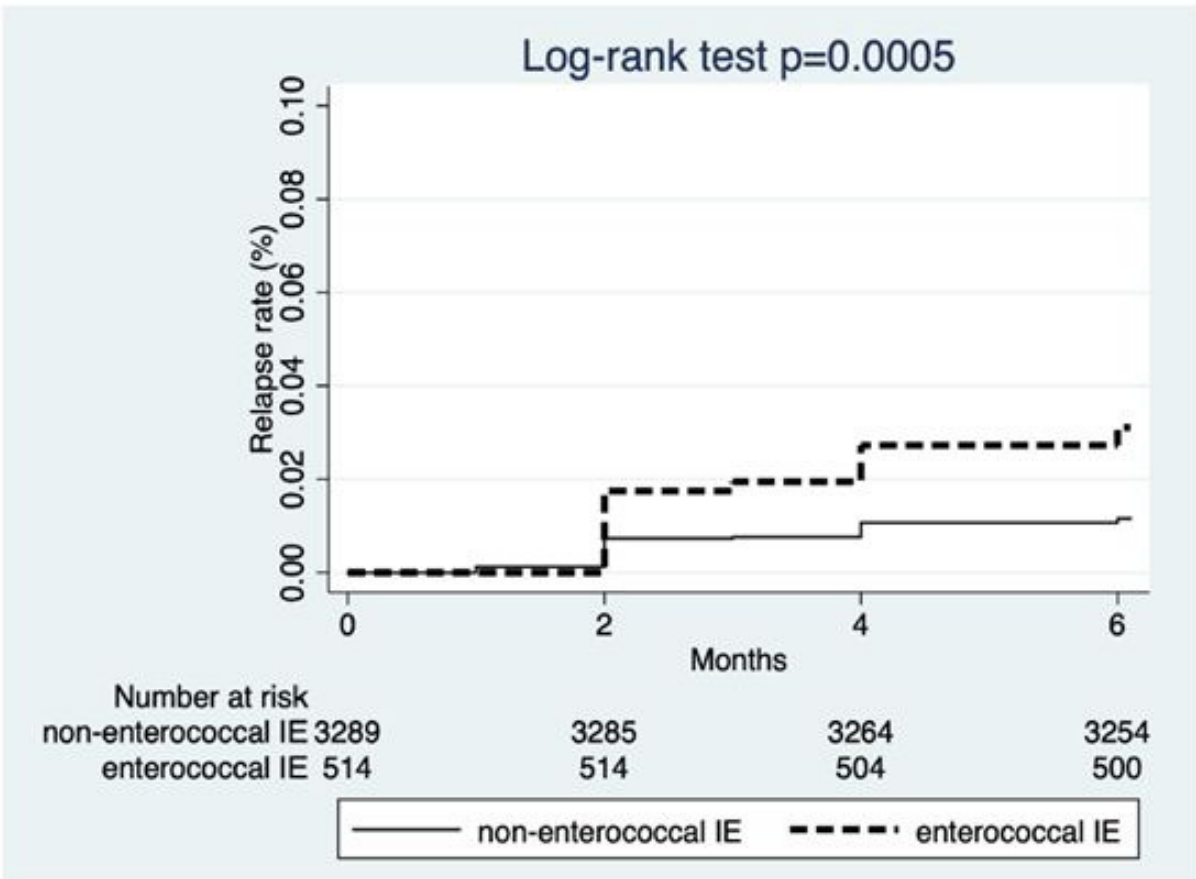
- Elderly patients
- TAVI*
- Prosthetic valve endocarditis
- Degenerative left-sided valve disease
- Aortic involvement
- Chronic lung disease
- Chronic heart failure
- Hemodialysis*****

* Shown in other large series

**a.**


Log-rank test p=0.181
Mortality (%)
0.00
0.25
0.50
0.75
1.00
0
3
6
9
12
Months
Number at risk
non-enterococcal IE 3308 2430 2315 2277 2223
enterococcal IE 516 398 380 374 363
non-enterococcal IE
enterococcal IE

**b.**


Log-rank test p=0.0005
Relapse rate (%)
0.00
0.02
0.04
0.06
0.08
0.10
0
2
4
6
Months
Number at risk
non-enterococcal IE 3289 3285 3264 3254
enterococcal IE 514 514 504 500
non-enterococcal IE
enterococcal IE