



HAL
open science

Impact of *Enterococcus faecalis* endocarditis treatment on risk of relapse

Pierre Danneels, Jean François Hamel, Léa Picard, Schéhérazade Rezig, Pauline Martinet, Aurélien Lorleac'h, Jean Philippe Talarmin, Rodolphe Buzelé, Thomas Guimard, Gwenaël Le Moal, et al.

► To cite this version:

Pierre Danneels, Jean François Hamel, Léa Picard, Schéhérazade Rezig, Pauline Martinet, et al.. Impact of *Enterococcus faecalis* endocarditis treatment on risk of relapse. *Clinical Infectious Diseases*, 2023, 76 (2), pp.281-290. 10.1093/cid/ciac777 . inserm-03782705

HAL Id: inserm-03782705

<https://inserm.hal.science/inserm-03782705>

Submitted on 21 Sep 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **Impact of *Enterococcus faecalis* endocarditis treatment on risk of relapse.**

2 Pierre Danneels^{1,2}, Jean-François Hamel³, Léa Picard^{4,2}, Schéhérazade Rezig^{5,2}, Pauline Martinet^{5,2},
 3 Aurélien Lorleac'h^{6,2}, Jean-Philippe Talarmin^{7,2}, Rodolphe Buzelé^{8,2}, Thomas Guimard^{9,2}, Gwenaël Le
 4 Moal^{10,2}, Julia Brochard-Libois^{11,2}, Aurélie Beaudron^{12,2}, Julien Letheulle^{13,2}, Cyrielle Codde^{14,2}, Rachel
 5 Chenouard^{15,2}, David Boutoille^{16,2}, Adrien Lemaignan^{17,2}, Louis Bernard^{17,2}, Vincent Cattoir^{18,19,20},
 6 Vincent Dubée^{1,2,21} and the EFEMER study group.*

7 * EFEMER study group members listed in the Acknowledgments.

8 ¹Infectious Diseases and Tropical Medicine, Angers University Hospital. Angers, France;

9 ²Groupe d'Epidémiologie et Recherche en Infectiologie Clinique du Centre et de l'Ouest (GERICCO),
 10 France;

11 ³Biostatistics Department, Angers University Hospital. Angers, France;

12 ⁴Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital. Rennes, France;

13 ⁵Infectious Diseases and Tropical Medicine, La Cavale Blanche University Hospital. Brest, France;

14 ⁶Infectious Diseases and Tropical Medicine, Groupe Hospitalier Bretagne Sud. Lorient, France;

15 ⁷Infectious Diseases and Tropical Medicine, Cornouaille Hospital. Quimper, France;

16 ⁸Infectious Diseases and Tropical Medicine, Saint-Brieuc General Hospital. Saint-Brieuc, France;

17 ⁹Infectious Diseases and Tropical Medicine, Vendée Departmental Hospital. La Roche Sur Yon, France;

18 ¹⁰Infectious Diseases and Tropical Medicine, Poitiers University Hospital. Poitiers, France;

19 ¹¹Infectious Diseases and Tropical Medicine, Saint Nazaire General Hospital. St-Nazaire, France;

20 ¹²Department of Bacteriology, Le Mans General Hospital. Le Mans, France;

21 ¹³Service de médecine polyvalente, Centre Hospitalier de Laval. Laval, France;

22 ¹⁴Infectious Diseases and Tropical Medicine, Limoges University Hospital. Limoges, France;

23 ¹⁵Department of Bacteriology, Angers University Hospital. Angers, France;

24 ¹⁶Service des Maladies Infectieuses et Tropicales, Centre Hospitalier Universitaire, CIC-UIC 1413 INSERM,
 25 Centre Hospitalier Universitaire de Nantes, Nantes, France;

26 ¹⁷Infectious Diseases and Tropical Medicine, Tours University Hospital. Tours, France;

27 ¹⁸Department of Bacteriology, Pontchaillou University Hospital. Rennes, France;

28 ¹⁹National Reference Center for Enterococci, Pontchaillou University Hospital. Rennes, France;

1 ²⁰University of Rennes 1, INSERM unit U1230, Rennes, France;

2 ²¹Univ Angers, Nantes Université, INSERM, CNRS, Immunology and New Concepts in ImmunoTherapy,
3 INCIT, UMR 1302/EMR6001. F-44000 Nantes, France.

4

5

6 **Corresponding author:** Vincent Dubée, Infectious Diseases and Tropical Medicine, University Hospital. 4,
7 rue Larrey, 49100 Angers, France. Phone: +33 241353279. ORCID: 0000-0002-9982-4741. E-mail:

8 vincent.dubee@chu-angers.fr

9

10 **Alternate corresponding author:** Pierre Danneels, Infectious Diseases and Tropical Medicine, University
11 Hospital. 4, rue Larrey, 49100 Angers, France. E-mail: pierre.danneels@hotmail.fr

12 **Running title:**

13 Relapses in *E. faecalis* endocarditis

14

15

ACCEPTED MANUSCRIPT

1 **Abstract**

2 **Background:**

3 *Enterococcus faecalis* infective endocarditis (EFIE) are characterized by a higher frequency of relapses
4 than other infective endocarditis. The role of the treatment on their occurrence remains poorly
5 understood. The aim of this study was to investigate whether the antibiotic regimen could impact the
6 risk of relapse in EFIE.

7 **Materials:**

8 This was a multicenter retrospective study of patients diagnosed with definite EFIE between 2015 and
9 2019 in 14 French hospitals. The primary endpoint was the occurrence of relapses within the year
10 following endocarditis diagnosis. As death was a competing risk for relapse, Fine & Gray models were
11 used for studying risk factors and impact of treatment.

12 **Results:**

13 Of the 279 patients included, 83 (29.7%) received the amoxicillin-gentamicin (A-G) combination, 114
14 (40.9%) amoxicillin-ceftriaxone (A-C), 63 (22.6%) A-G and A-C (A-G/A-C) sequentially, 9 (3.2%) amoxicillin
15 (A), and 10 received other treatments. One-year-relapse rate was 9.3% (26 patients). Relapse occurred
16 after a median delay of 107 days from EFIE diagnosis; 6 occurred after 6 months, and 6 were diagnosed
17 by blood cultures in asymptomatic patients. In multivariate analysis, surgery during treatment was a
18 protective factor against one-year relapse and death.

19 The cumulative incidence of relapse one year after endocarditis was 46.2% for patients treated with
20 amoxicillin, 13.4% with A-G, 14.7% with A-C, and 4.3% with A-G/A-C ($P \geq .05$ in multivariate analysis).

21 **Conclusion:**

22 Relapses after treatment of EFIE are frequent, frequently asymptomatic, and may occur more than 6
23 months after the initial episode.

24 **Keywords:** *E. faecalis*; Endocarditis; Relapse; Amoxicillin; Drug Therapy, Combination

25

26

1 INTRODUCTION

2 Enterococcal infective endocarditis (IE) account for around 13-18% of all endocarditis cases, *E. faecalis*
3 being the enterococcal species causing most cases (around 90%) [1,2]. *Enterococcus faecalis* infective
4 endocarditis (EFIE) incidence has been increasing in the past few years [3–5], possibly due to the
5 increasing use of Transcatheter Aortic Valve Implantation (TAVI) [6–8].

6 The synergistic combination of amoxicillin and gentamicin (A-G) was the reference treatment for EFIE [9].
7 This dual therapy has the disadvantage of a high risk of acute kidney injury (25% of patients), and loses
8 its synergistic effect against isolates with high-level aminoglycoside resistance (HLAR) [10,11]. The
9 combination of ampicillin and ceftriaxone has shown synergistic activity *in vitro* against *E. faecalis*, and
10 retrospective studies have shown that this combination had a similar clinical cure rate for EFIE as the A-G
11 combination, with a better safety profile [10,12,13].

12 For these reasons, since 2015, the European Society of Cardiology (ESC) recommends using the
13 combination of ampicillin or amoxicillin with ceftriaxone (A-C) as first-line therapy for non-HLAR EFIE and
14 preferred therapy for HLAR EFIE [11].

15 However, the combination of high-dose amoxicillin with gentamicin or ceftriaxone has never been
16 compared with amoxicillin monotherapy; and some authors question the benefits of the combination,
17 suggesting that the same efficacy could be obtained with amoxicillin monotherapy [14,15].

18 Compared to endocarditis due to other pathogens, enterococcal endocarditis had a significantly higher
19 6-month relapse rate estimated to be around 7% [8,16]. The 6-month threshold in relapse definition has
20 been set empirically to differentiate relapse from reinfection [11]. However, molecular bacterial typing
21 analyses based on Pulsed Field Gel Electrophoresis (PFGE) [17] have shown that, in the case of EFIE,
22 relapse may occur up to one year after the initial episode [18,19]. Thus, the real frequency of relapses
23 could be underestimated. Due to their scarcity, the impact of treatment on the risk of relapse has not
24 been explored and there is still limited data about clinical characteristics, management, and outcome of
25 these relapses.

26 The aims of this study were to describe the rate and clinical features of relapses in a large retrospective
27 cohort of EFIE, and to investigate whether the choice of the antibiotic regimen could have an impact on
28 the occurrence of relapse.

29

1 METHODS

2 Design, Settings, and Patients

3 This observational multicenter retrospective study was conducted in 14 hospitals in western France,
4 serving a population catchment area of around 10 million people. Among these, seven have a cardiac
5 surgery department and an endocarditis team. All adult patients (≥ 18 years old) who fulfilled the
6 modified Duke criteria, according to ESC guidelines, for definite *E. faecalis* IE were enrolled [11]. Patients
7 could only be included once. The inclusion period was from January 2015 to December 2019. Patients
8 with possible endocarditis diagnosis, those with pacemaker lead-related endocarditis without valvular
9 involvement, and those without available treatment data were not included.

10 Depending on the site, patients were identified through (i) screening of *E. faecalis* bacteremia cases, (ii)
11 pre-existing IE local cohorts, or (iii) cross-reference of *E. faecalis* bacteremia cases with French hospital
12 discharge database. There was no standardized follow-up; frequency of follow-up visits, and biological
13 monitoring (including systematic drawing of blood cultures) after treatment of EFIE were performed
14 according to local practice.

15 Data collection

16 Data for clinical, microbiological, echocardiographic variables, as well as management of EFIE and follow-
17 up, were collected from the patients' clinical records. The data collected were entered into an
18 anonymous database designed for the present study.

19 Ethics

20 The study was approved by an institutional review board, the Ethical Committee of Research in Tropical
21 and Infectious Diseases (CER-MIT 2022-0105). Patients were informed of the study in accordance with
22 French legal standards: written consent was not required, but all subjects included received an
23 information letter.

24

1 **Definitions**

2 All definitions used in the study are detailed in Supplementary Table 1.

3 Relapse was defined as the occurrence of a new blood or valve culture growing *E. faecalis* after
4 antibiotics discontinuation. Recurrences occurring more than 1 year after the initial episode are generally
5 considered as reinfections (infection with a new *E. faecalis* isolate unrelated to the first one). We
6 classified these episodes as relapses only if the new isolate could be identified as isogenic using Whole
7 Genome Sequencing (WGS) carried out on a MiSeq platform (Illumina Inc., San Diego, CA, USA). WGS was
8 preferred to PFGE because it performs better to differentiate relapse from reinfection [21,22]. Strains
9 were considered isogenic if there was less than 20 allele differences using core genome Multi Locus
10 Sequence Typing (cgMLST) [23,24].

11 Patients who received amoxicillin were classified into four groups according to the treatment received:
12 A-G, A-C, A-G/A-C (sequential treatment) or amoxicillin (A) if they received neither gentamicin nor
13 ceftriaxone. Those who did not receive amoxicillin were in the "other" group.

14 Patients were considered to have received a "complete treatment" when their treatment duration
15 matched ≥ 41 days of the treatment for A, A-C, and vancomycin-gentamicin (considered as "other"); ≥ 41
16 days of amoxicillin including ≥ 14 days in combination with gentamicin for A-G; and ≥ 41 days of
17 combination for sequential treatment A-G/A-C. If the patient died during the administration of a
18 treatment, the treatment was considered complete.

19 **Study endpoints**

20 The primary endpoint was the occurrence of a relapse during the year following endocarditis diagnosis.
21 Secondary endpoints were relapse regardless of time of occurrence and one-year all-cause mortality.

22 **Statistical Analysis**

23 Quantitative variables were expressed as medians with interquartile range [IQR]. Qualitative variables
24 were expressed as crude numbers and percentages. Continuous variables were compared using the
25 Kruskal-Wallis test. Categorical variables were compared using the Chi2-test or Fischer exact test if
26 required. Fine and Gray models were used for determining risk factors for relapse (by calculating
27 adjusted Sub Hazard Ratio [aSHR]), considering death as a competing event. Cox models were used for
28 analyzing risk factors for death. For each considered endpoint (relapse or death), several models were
29 considered. The first was the simplest model (referring to the univariate analysis), considering only the

1 antibiotic therapy as an explaining covariate. The second allowed to adjust this effect on potential
2 confounding factors defined a priori on clinical-scientific criteria. Confounding factors for both outcomes
3 were gender, Charlson score (including age), surgery performed during treatment, surgery indicated but
4 not performed and initial admission in hospital with cardiac surgery department. There was also
5 prosthetic valve for relapse and acute cardiac injury for death. These two models were performed first
6 on the whole population, then as sensitivity analyses on the sub-population having received complete
7 treatment. For each endpoint, the considered follow-up was one year.

8 All tests were two-tailed, and significance was set at $P < .05$. Statistical analyses were performed using
9 STATA (v14.2 for Windows, StataCorp).

10

11 **RESULTS**

12 **Demographics and baseline characteristics**

13 Over the period, 283 patients met the inclusion criteria and 279 were included in the study (treatment
14 data were not available for 4 patients, Supplementary Table 2). Demographic, clinical, and
15 microbiological characteristics are presented in Table 1. The patients were mainly male, and the median
16 age was 74 years. Prosthetic valve endocarditis accounted for 41.9% (n=117) of cases. Among
17 endocarditis occurring less than one year following prosthesis implantation, TAVI accounted for 60.5%
18 (n=23).

19 **Valve surgery**

20 Valve surgery was performed during antibiotic therapy in 32.3% of patients (n=90) with a median delay
21 of 10 days after starting treatment (Table 2). The surgery rate for patients initially managed in hospital
22 with cardiac surgery department was 46.4% (89/192). Patients with prosthetic valve infection had fewer
23 surgical procedures than those with native valve endocarditis (19.7% vs. 46.9%, $P < .0001$).

24 Of the 99 patients operated on, the time of surgery was available for 96 patients and the microbiological
25 analysis for 71. The proportion of negative valve cultures increased over time of antibiotic duration, but
26 positive valve cultures were found throughout the treatment period and even afterwards (Figure 1). Two
27 patients operated on 141 and 192 days after the end of antibiotic treatment, because of persistent valve
28 regurgitation without infectious syndrome, had their valve growing *E. faecalis*.

29

1 **Antibiotic regimen**

2 Overall, the A-C therapy was administered to 177 patients (63.4%) and A-G therapy to 146 (52.3%). Of
3 them, 63 patients (22.6%) received a sequential A-G/A-C treatment (only two of them had at first A-C
4 and then A-G) defining the A-G/A-C group. Twenty-two patients (7.9%) received additional oral antibiotic
5 therapy (fluoroquinolone [n=11], rifampicin [n=8] or linezolid [n=4]), mainly because of associated
6 infectious embolism (73%, n=16). Nine patients received A therapy; only one of them underwent surgery
7 during treatment (Supplementary Table 3). Overall, 69.2% patients (n=193) received a complete
8 antibiotic treatment.

9 During the study period, the A-C regimen was increasingly used, becoming the predominant treatment in
10 2018-2019 (50.0%, 67/134), while use of A-G and sequential A-G/A-C trended to decrease
11 (Supplementary Figure 1).

12 Comparing patients who received an amoxicillin-based combination in univariate analysis, A-G patients
13 had less chronic heart failure ($P=.09$) and were less likely to have acute heart failure ($P=.01$) than patients
14 treated with A-C or with A-G/A-C (Table 1). A-C patients were older ($P=.002$), had a higher Charlson
15 score ($P=.004$), had more chronic renal failure ($P=.03$), were more likely to have vertebral osteomyelitis
16 ($P=.08$), and received suppressive antimicrobial therapy more frequently ($P=.005$). A-C/A-G patients were
17 more susceptible to have acute kidney injury during hospitalization ($P=.005$).

18 **Outcome**

19 One year after the diagnosis of EFIE, 74 patients (26.5%) had died, 26 patients (9.3%) had relapsed of
20 their endocarditis (median delay 103 days, seven of whom died within one year), 72 (25.8%) were lost to
21 follow-up, and 114 (40.9%) were considered to be cured (Table 3). Considering only patients alive at the
22 end of antibiotic treatment with available follow-up data, 11.2% (22/197) had relapsed at 6 months and
23 15.7% (26/166) at 1 year. Two patients relapsed thereafter; the total relapse rate was 10.0%.

24 One-year-relapse occurred in only one of the 90 patients who underwent surgery during antibiotic
25 treatment versus 25 of the 189 who did not (aSHR 0.07, CI 95% 0.01-0.56; $P=.01$). Prosthetic valve was
26 not associated with a higher relapse risk (aSHR 1.15, CI 95% 0.53-2.48, $P=.73$), as the other variables
27 included in the model.

28 In multivariate analysis, characteristics associated with one-year mortality were elevated Charlson index
29 (aHR 1.17, CI 95% 1.07-1.28, $P<.001$) and acute heart failure (aHR 2.59, CI 95% 1.58-4.25, $P<.001$), while

1 surgery during treatment was a protective factor (aHR 0.42, CI 95% 0.21-0.83, $P=0.01$). The association
2 was not significant for surgery indicated but not performed (aHR 1.63, CI 95% 0.945-2.82, $P=0.08$) and
3 initial admission in a hospital with cardiac surgery department (aHR 0.65, CI 95% 0.41-1.04, $P=0.07$).

4 **Comparison of the A-G combination with other regimens**

5 The cumulative incidence of relapse one year after endocarditis diagnosis was 46.2% (95% CI 17.8%-
6 85.8%) for patients treated with A, 13.4% (7.2%-24.2%) for patients treated with A-G, and 14.7% (8.6%-
7 24.5%) with A-C therapy (Figure 2a). The lowest incidence was 4.3% (1.1%-16.0%) for patients
8 sequentially treated with A-G/A-C.

9 When comparing the risk of relapse according to the treatment received, with A-G as a reference, no
10 significant difference was observed in univariate and multivariate analysis. In a sensitivity analysis
11 considering only patients who received complete treatment, treatment with A showed a significantly
12 higher risk of relapse than A-G in multivariate analysis (aSHR 5.41, 1.19-24.6, $P=0.03$, Supplementary
13 Figure 2).

14 Patients treated with A-C had a significantly higher risk of death compared to A-G in univariate analysis
15 but not in multivariate analysis (Figure 2b).

16 Details on outcome of patients who received other treatments are available in the Supplementary
17 Materials.

18

19 **Characteristics and management of relapses**

20 At the time of relapse diagnosis, 8/27 patients (29.6%) were asymptomatic (Table 4). Nineteen patients
21 (67.9%) had a colonic examination (15 colonoscopies and 4 virtual colonoscopies); 14/19 (74%) had
22 polyps, and none had colon cancer. Ten colonoscopies were performed before relapse.

23 Eight patients (28.6%) died of their relapsed endocarditis; one was asymptomatic at diagnosis; none of
24 them had undergone cardiac surgery. Three patients (10.7%) presented 2 consecutive relapses despite a
25 well-conducted antibiotic therapy, two of them had an indication for surgery at the time of the first
26 relapse.

27

1 DISCUSSION

2 Our study highlights a high rate of relapse in EFIE and suggests that the choice of treatment may have an
3 impact on their risk of occurrence.

4 Few cohorts of EFIE are described and to date, the most extensive are those of Pericás et al. (n=468),
5 Chirouze et al. (n=453) and Fernández-Hidalgo et al. (n=248) [6,8,10]. In our cohort, we observed a lower
6 rate of surgery during treatment compared to the others (32.3% vs 36%-42%). This may be explained by
7 the inclusion in our cohort of patients managed in hospitals without cardiac surgery, which was not the
8 case in the aforementioned studies. Our study confirms the widespread use of the A-C treatment [5,25].

9 The primary aim of this study was to assess the risk of relapse according to the treatment received. To
10 assess this issue, we classified patients according to the treatment effectively received. By contrast
11 Fernández-Hidalgo et al. considered the antibiotic regimen “scheduled” and Pericàs et al. considered the
12 first dose administered [8,10]. In some patients, we observed a significant number of therapeutic
13 modifications during the treatment, decided by the referring physicians. To circumvent this issue, we
14 performed sensitivity analyses considering only patients who received a complete course of the assigned
15 treatment regimen.

16 One of the original features of the study is the large number of relapses observed (10.0%). This may be
17 explained by several factors, including a lower rate of surgery and the abolition of the time threshold for
18 defining relapse. Fernández-Hidalgo et al. reported a rate of 3.1% but the follow-up stopped 3 months
19 after completing antimicrobial therapy. Our relapse rate of 7.9% (n=22) at 6 months is more consistent
20 with those found in other cohorts (6.2% to 7.3%) [26–28]. A recent study showed a relapse rate of 10.2%
21 (6/59) with a 1-year delay used for relapse definition [29].

22 As reported by Fernández-Hidalgo et al., we found no difference between A-C and A-G treatments in the
23 risk of relapse. We observed that patients treated with A-C had increased mortality compared to those
24 treated with A-G in univariate analysis. This may be explained by older patients, a higher Charlson score,
25 and a higher incidence of acute heart failure in the A-C group.

26 Three of five patients who received a full and complete course of amoxicillin monotherapy relapsed
27 despite receiving 12 g/day for 42 days. This is consistent with data previously described, with low patient
28 numbers [30]. In our opinion, the difference observed between monotherapy and combination therapy
29 is sufficient to put an end to the questioning of amoxicillin use in combination [14,15].

1 Surprisingly, the lower relapse rate was observed in patients who received the A-G/A-C treatment. This
2 group of patients had a higher rate of acute kidney injury, often related to gentamicin toxicity, and
3 tended to have more surgery during treatment. These two events probably prompted the clinicians to
4 switch treatment from A-G to A-C. To the best of our knowledge, use of this sequential treatment has
5 not been reported and described, although our data suggest that it is already widespread. Further
6 studies are needed to evaluate the efficacy and safety of a sequential regimen comprising 7 to 14 days of
7 A-G followed by A-C combination. A prospective study including long-term patient follow-up is still
8 necessary [31,32].

9 Studies suggested a higher frequency of relapse among non-operated prosthetic valve-related-
10 endocarditis: 11% to 17.4%, consistent with our 12.8% rate [33,34]. Our data suggest that the presence
11 of a prosthetic valve is not associated with relapse, whereas surgery seems to be the best way to prevent
12 it. Surgery during treatment was associated with a reduced risk of one-year death and relapse in
13 multivariate analysis.

14 Sterilization by antibiotics without surgery may be insufficient in some cases. This is supported by cases
15 of positive valve culture regardless of the duration of antibiotics administered before surgery, as
16 previously described [35–37]. This is probably favored by the known natural tolerance to penicillin or
17 phenotypic and genetic changes in enterococci that may confer a selective advantage [38,39].

18 Using WGS we demonstrated that true relapse may occur more than one year after the initial diagnosis
19 and patients may be asymptomatic at the time of relapse diagnosis. This encourages prolonged
20 surveillance, with systematic blood culture, of patients who have been treated for EFIE, especially if they
21 have not undergone surgery.

22 The strength of our study is its multicentric and exhaustive aspect: inclusion of most hospitals, including
23 all referral centers, in a large area; and the pragmatic approach for evaluation of treatment efficacy
24 considering the antibiotic regimen really received by the patient. The limitations of this study are mainly
25 inherent to its retrospective design, leading to missing data, significant proportion of patients lost to
26 follow-up, and impossibility to fully control confounding factors in treatment effects despite multivariate
27 analysis. The low number of relapses and of patients treated with amoxicillin alone leads to a lack of
28 power in the analysis of treatment efficacy. The definition of acute kidney failure did not allow a reliable
29 assessment of this complication. Finally, we did not evaluate the role of serum concentrations of
30 antibiotics, which could be interesting to better understand the mechanisms of relapse.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37

CONCLUSION

Relapses after treatment of EFIE are frequent, may be asymptomatic, and can occur more than one year after the initial episode. We showed that the choice of ceftriaxone or gentamicin as combined antibiotics does not seem to have an impact on the risk of relapse. Although our results should be interpreted with caution given the retrospective nature of the study and the lack of power arising from the rarity of relapses, our findings suggest that treatment with amoxicillin monotherapy should not be used in this indication. We also showed that surgery associated with antibiotic therapy is the best way to prevent relapse. Thus, non-operated patients with EFIE should particularly undergo careful clinical and biological observation, including systematic drawing of blood cultures, during extended follow-up.

Acknowledgements. We thank all the staff who take care of the patients.

EFEMER Study Group

Pierre DANNEELS, MD
pierre.danneels@hotmail.fr
Infectious Diseases and Tropical Medicine, Angers University Hospital. Angers, France

Vincent DUBEE, MD, PhD
vincent.dubee@chu-angers.fr
Infectious Diseases and Tropical Medicine, Angers University Hospital. Angers, France

Jean-François HAMEL, MD, PhD
JeanFrancois.Hamel@chu-angers.fr
Biostatistics Department, Angers University Hospital. Angers, France

Marie KEMPF, MD, PhD
MaKempf@chu-angers.fr
Department of Bacteriology, Angers University Hospital. Angers, France

Rachel CHENOUEAU, MD
Rachel.Chenouard@chu-angers.fr
Department of Bacteriology, Angers University Hospital. Angers, France

Camille RIHET
crihet@orange.fr

1 Infectious Diseases and Tropical Medicine, Angers University Hospital. Angers, France
2
3 Clémence VANNIER
4 cvann@etud.univ-angers.fr
5 Infectious Diseases and Tropical Medicine, Angers University Hospital. Angers, France
6
7 Aurélie BEAUDRON, MD
8 agarchetbeaudron@ch-lemans.fr
9 Department of bacteriology, Le Mans General Hospital. Le Mans, France
10
11 Lucia PEREZ, MD
12 lperez@ch-lemans.fr
13 Infectious Diseases and Tropical Medicine, Le Mans General Hospital. Le Mans, France
14
15 David BOUTOILLE, MD, PhD
16 david.boutoille@chu-nantes.fr
17 Infectious Diseases and Tropical Medicine, Nantes University Hospital. Nantes, France
18
19 Anne-Gaëlle LEROY, MD
20 AnneGaelle.LEROY@chu-nantes.fr
21 Department of Bacteriology, Nantes University Hospital. Nantes, France
22
23 Louis BERNARD, MD, PhD
24 prlbernard@orange.fr
25 Infectious Diseases and Tropical Medicine, Nantes University Hospital. Nantes, France
26
27 Adrien LEMAIGNEN, MD, PhD,
28 adrien.lemaignen@univ-tours.fr
29 Infectious Diseases and Tropical Medicine, Nantes University Hospital. Nantes, France
30
31 Marie Frédérique LARTIGUE, MD, PhD
32 marie-frederique.lartigue@univ-tours.fr
33 Department of Bacteriology, Tours University Hospital. Tours, France
34
35 Cécile LEBRUN, MD
36 C.LEBRUN@chu-tours.fr
37 Department of Bacteriology, Tours University Hospital. Tours, France
38
39 Vincent CATTOIR, MD, PhD
40 Vincent.CATTOIR@chu-rennes.fr
41 Department of Bacteriology, Pontchaillou University Hospital. Rennes, France
42
43 Matthieu REVEST, MD, PhD
44 Matthieu.REVEST@chu-rennes.fr
45 Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital. Rennes, France
46
47 Léa PICARD, MD
48 Lea.PICARD@chu-rennes.fr

1 Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital. Rennes, France
2
3 Léa POUSSIER, MD
4 Lea.POUSSIER@chu-rennes.fr
5 Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital. Rennes, France
6
7 Camile MOALIGOU, MSc
8 camimoali@gmail.com
9 Department of Bacteriology, Pontchaillou University Hospital. Rennes, France
10
11 Sophie NOGUES
12 Sophie.NOGUES@chu-rennes.fr
13 Department of Bacteriology, Pontchaillou University Hospital. Rennes, France
14
15 Asma Zouari SASSI
16 Asma.ZOUARI.SASSI@chu-rennes.fr
17 Department of Bacteriology, Pontchaillou University Hospital. Rennes, France
18
19 François Guérin, MD, PhD
20 Francois.GUERIN@chu-rennes.fr
21 Department of Bacteriology, Pontchaillou University Hospital. Rennes, France
22
23 Gwenaël LE MOAL, MD
24 Gwenael.LE-MOAL@chu-poitiers.fr
25 Infectious Diseases and Tropical Medicine, Poitiers University Hospital. Poitiers, France
26
27 Chloé PLOUZEAU-JAYLE, MD
28 Chloe.PLOUZEAU-JAYLE@chu-poitiers.fr
29 Department of Bacteriology, Poitiers University Hospital. Poitiers, France
30
31 Jean-Philippe TALARMIN, MD
32 jp.talarmin@ch-cornouaille.fr
33 Infectious Diseases and Tropical Medicine, Cornouaille Hospital. Quimper, France
34
35 Marie-Sarah FANGOUS, MD
36 ms.fanfous@ch-cornouaille.fr
37 Department of Bacteriology, Cornouaille Hospital. Quimper, France
38
39 Cyrielle CODDE, MD
40 cyrielle.CODDE@chu-limoges.fr
41 Infectious Diseases and Tropical Medicine, Limoges University Hospital. Limoges, France
42
43 Jean-François FAUCHER, MD, PhD
44 jean-francois.foucher@unilim.fr
45 Infectious Diseases and Tropical Medicine, Limoges University Hospital. Limoges, France
46
47 Julia BROCHARD-LIBOIS, MD
48 j.brochard@ch-saintnazaire.fr

1 Infectious Diseases and Tropical Medicine, Saint-Nazaire General Hospital. St-Nazaire, France
2
3 Thomas GUIMARD, MD
4 thomas.guimard@chd-vendee.fr
5 Infectious Diseases and Tropical Medicine, Vendée Departmental Hospital. La Roche Sur Yon, France
6
7 Hélène PELERIN, PhD
8 helene.pelerin@chd-vendee.fr
9 Infectious Diseases and Tropical Medicine, Vendée Departmental Hospital. La Roche Sur Yon, France
10
11 Hélène BERTHOME, MD
12 helene.berthome@chd-vendee.fr
13 Department of Bacteriology, Vendée Departmental Hospital. La Roche Sur Yon, France
14
15 Rodolphe BUZELE, MD
16 rodolphe.buzele@ch-stbrieuc.fr
17 Infectious Diseases and Tropical Medicine, Saint-Brieuc General Hospital. St-Brieuc, France
18
19 Aurélien LORLEAC'H, MD
20 a.lorleach@ghbs.bzh
21 Infectious Diseases and Tropical Medicine, Groupe Hospitalier Bretagne Sud. Lorient, France
22
23 Scheherazade REZIG, MD
24 scheherazade.rezig@chu-brest.fr
25 Infectious Diseases and Tropical Medicine, La Cavale Blanche University Hospital. Brest, France
26
27 Pauline MARTINET, MD
28 pauline.martinet@chu-brest.fr
29 Infectious Diseases and Tropical Medicine, La Cavale Blanche University Hospital. Brest, France
30
31 Didier JAN, MD
32 didier.jan@chlaval.fr
33 Department of Bacteriology, Laval General Hospital. Laval, France
34
35 Julien LETHEULLE, MD
36 julien.letheulle@chlaval.fr
37 Service de médecine polyvalente, Laval General Hospital. Laval, France
38
39 Paul LE TURNIER, MD
40 Paul.LETURNIER@ch-cayenne.fr
41 Infectious Diseases and Tropical Medicine, Cayenne General Hospital. Cayenne, France
42

43
44 **Funding.** VC reports support from Santé publique France. No funding was received for this study.

1 **Potential conflicts of interest.** ALO reports payment or honoraria for lectures, presentations, speakers
2 bureaus, manuscript writing or educational events for Post-university learning for general practitioner –
3 subject: sexual transmitted disease – may 2022 – payed by organism named “EDUPRAT” and support for
4 attending meetings and/or travel from Journées nationales d’infectiologie – annual congress of the
5 Infectious Disease French Society (SPILF) – Bordeaux, France, June 2022 – support by the Nestlé
6 Company Nestlé Home Care (NHC).

7 VC reports grants or contracts from Agence Nationale pour la Recherche (ANR) and Fondation pour la
8 Recherche Médicale (FRM), consulting fees from bioMérieux, Mylan / Viatris, and Eumédica, payment or
9 honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events for
10 Mylan / Viatris, and Pfizer, Support for attending meetings and/or travel from bioMérieux, Pfizer,
11 Ménarini, and Shionogi.

12 JPT reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or
13 educational events for THERMO FISHER DIAGNOSTICS, and Support for attending meetings and/or travel
14 from Pfizer.

15 The authors: No other reported conflicts of interest.

16

17

18

1 References

- 2 1. Habib G, Erba PA, Iung B, et al. Clinical presentation, aetiology and outcome of infective
3 endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a
4 prospective cohort study. *Eur Heart J* **2019**; 40:3222–3232.
- 5 2. Fernández-Hidalgo N, Escolà-Vergé L, Pericàs JM. Enterococcus faecalis endocarditis: what's next?
6 *Future Microbiol* **2020**; 15:349–364.
- 7 3. Østergaard L, Bruun NE, Voldstedlund M, et al. Prevalence of infective endocarditis in patients with
8 positive blood cultures: a Danish nationwide study. *Eur Heart J* **2019**; 40:3237–3244.
- 9 4. Olmos C, Vilacosta I, Fernández-Pérez C, et al. The Evolving Nature of Infective Endocarditis in
10 Spain: A Population-Based Study (2003 to 2014). *J Am Coll Cardiol* **2017**; 70:2795–2804.
- 11 5. Escolà-Vergé L, Fernández-Hidalgo N, Larrosa MN, Fernandez-Galera R, Almirante B. Secular trends
12 in the epidemiology and clinical characteristics of Enterococcus faecalis infective endocarditis at a
13 referral center (2007-2018). *Eur J Clin Microbiol Infect Dis* **2021**; 40:1137–1148.
- 14 6. Chirouze C, Athan E, Alla F, et al. Enterococcal endocarditis in the beginning of the 21st century:
15 analysis from the International Collaboration on Endocarditis-Pro prospective Cohort Study. *Clin*
16 *Microbiol Infect* **2013**; 19:1140–1147.
- 17 7. Khan A, Aslam A, Satti KN, Ashiq S. Infective endocarditis post-transcatheter aortic valve
18 implantation (TAVI), microbiological profile and clinical outcomes: A systematic review. *PLoS One*
19 **2020**; 15.
- 20 8. Pericàs JM, Llopis J, Muñoz P, et al. A Contemporary Picture of Enterococcal Endocarditis. *J Am Coll*
21 *Cardiol* **2020**; 75:482–494.
- 22 9. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy,
23 and management of complications: a statement for healthcare professionals from the Committee
24 on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the
25 Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia,
26 American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation*
27 **2005**; 111:e394-434.
- 28 10. Fernández-Hidalgo N, Almirante B, Gavalda J, et al. Ampicillin plus ceftriaxone is as effective as
29 ampicillin plus gentamicin for treating enterococcus faecalis infective endocarditis. *Clin Infect Dis*
30 **2013**; 56:1261–1268.
- 31 11. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective
32 endocarditis The Task Force for the Management of Infective Endocarditis of the European Society
33 of Cardiology (ESC) Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the
34 European Association of Nuclear Medicine (EANM). *Eur Heart J* **2015**; 36:3075–3128.
- 35 12. El Rafei A, DeSimone DC, Narichania AD, et al. Comparison of Dual β -Lactam therapy to penicillin-
36 aminoglycoside combination in treatment of Enterococcus faecalis infective endocarditis. *J Infect*
37 **2018**; 77:398–404.

- 1 13. Mirna M, Topf A, Schmutzler L, Hoppe UC, Lichtenauer M. Time to abandon ampicillin plus
2 gentamicin in favour of ampicillin plus ceftriaxone in *Enterococcus faecalis* infective endocarditis? A
3 meta-analysis of comparative trials. *Clin Res Cardiol* **2021**;
- 4 14. Gelfand MS, Cleveland KO. Combination therapy for enterococcal endocarditis. *Clin Infect Dis* **2013**;
5 57:767.
- 6 15. Koehler P, Jung N, Cornely OA, Rybniker J, Fätkenheuer G. Combination Antimicrobial Therapy for
7 *Enterococcus faecalis* Infective Endocarditis. *Clin Infect Dis* **2019**;
- 8 16. Dahl A, Iversen K, Tonder N, et al. Prevalence of Infective Endocarditis in *Enterococcus faecalis*
9 Bacteremia. *J Am Coll Cardiol* **2019**; 74:193–201.
- 10 17. Chu VH, Sexton DJ, Cabell CH, et al. Repeat infective endocarditis: differentiating relapse from
11 reinfection. *Clin Infect Dis* **2005**; 41:406–409.
- 12 18. Leroy A-G, Corvec S, Danneels P, et al. Reply to Lopez-Cortes, et al. *Clin Infect Dis* **2020**;
- 13 19. López-Cortés LE, Fernández-Cuenca F, Luque-Márquez R, de Alarcón A. Enterococcal Endocarditis:
14 Relapses or Reinfections? *Clin Infect Dis* **2021**; 72:360–361.
- 15 20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic
16 comorbidity in longitudinal studies: development and validation. *J Chronic Dis* **1987**; 40:373–383.
- 17 21. Tenover FC, Arbeit RD, Goering RV, et al. Interpreting chromosomal DNA restriction patterns
18 produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. *J Clin Microbiol*
19 **1995**; 33:2233–2239.
- 20 22. Salipante SJ, SenGupta DJ, Cummings LA, Land TA, Hoogstraat DR, Cookson BT. Application of
21 whole-genome sequencing for bacterial strain typing in molecular epidemiology. *J Clin Microbiol*
22 **2015**; 53:1072–1079.
- 23 23. Neumann B, Prior K, Bender JK, et al. A Core Genome Multilocus Sequence Typing Scheme for
24 *Enterococcus faecalis*. *J Clin Microbiol* **2019**; 57:e01686-18.
- 25 24. Kjær Hansen S, Andersen L, Detlefsen M, et al. Using core genome multilocus sequence typing
26 (cgMLST) for vancomycin-resistant *Enterococcus faecium* isolates to guide infection control
27 interventions and end an outbreak. *J Glob Antimicrob Resist* **2021**; 24:418–423.
- 28 25. Ramos-Martínez A, Pericàs JM, Fernández-Cruz A, et al. Four weeks versus six weeks of ampicillin
29 plus ceftriaxone in *Enterococcus faecalis* native valve endocarditis: A prospective cohort study.
30 *PLoS One* **2020**; 15:e0237011.
- 31 26. Iversen K, Ihlemann N, Gill SU, et al. Partial Oral versus Intravenous Antibiotic Treatment of
32 Endocarditis. *N Engl J Med* **2019**; 380:415–424.
- 33 27. Briggs S, Broom M, Duffy E, et al. Outpatient continuous-infusion benzylpenicillin combined with
34 either gentamicin or ceftriaxone for enterococcal endocarditis. *J Antimicrob Chemother* **2021**;

- 1 28. Fernández Guerrero ML, Goyenechea A, Verdejo C, Roblas RF, de Górgolas M. Enterococcal
2 endocarditis on native and prosthetic valves: a review of clinical and prognostic factors with
3 emphasis on hospital-acquired infections as a major determinant of outcome. *Medicine (Baltimore)*
4 **2007**; 86:363–377.
- 5 29. Herrera-Hidalgo L, Lomas-Cabezas JM, López-Cortés LE, et al. Ampicillin Plus Ceftriaxone Combined
6 Therapy for Enterococcus faecalis Infective Endocarditis in OPAT. *J Clin Med* **2021**; 11:7.
- 7 30. Geraci JE, Martin WJ. Antibiotic therapy of bacterial endocarditis. VI. Subacute enterococcal
8 endocarditis; clinical, pathologic and therapeutic consideration of 33 cases. *Circulation* **1954**;
9 10:173–194.
- 10 31. Beganovic M, Luther MK, Rice LB, Arias CA, Rybak MJ, LaPlante KL. A Review of Combination
11 Antimicrobial Therapy for Enterococcus faecalis Bloodstream Infections and Infective Endocarditis.
12 *Clin Infect Dis* **2018**; 67:303–309.
- 13 32. Peterson SC, Lau TTY, Ensom MHH. Combination of Ceftriaxone and Ampicillin for the Treatment of
14 Enterococcal Endocarditis: A Qualitative Systematic Review. *Ann Pharmacother* **2017**; 51:496–503.
- 15 33. Lecomte R, Laine J-B, Issa N, et al. Long-term outcome of patients with non-operated prosthetic
16 valve infective endocarditis: is relapse the main issue? *Clin Infect Dis* **2019**;
- 17 34. Casalta J-P, Thuny F, Fournier P-E, et al. DNA persistence and relapses questions on the treatment
18 strategies of Enterococcus infections of prosthetic valves. *PLoS ONE* **2012**; 7:e53335.
- 19 35. Gisler V, Dürr S, Irincheeva I, et al. Duration of Pre-Operative Antibiotic Treatment and Culture
20 Results in Patients With Infective Endocarditis. *J Am Coll Cardiol* **2020**; 76:31–40.
- 21 36. Voldstedlund M, Fuursted K, Bruun NE, Arpi M. Comparison of heart valve culture between two
22 Danish endocarditis centres. *Scand J Infect Dis* **2012**; 44:405–413.
- 23 37. Mekontso Dessap A, Zahar J-R, Voiriot G, et al. Influence of preoperative antibiotherapy on valve
24 culture results and outcome of endocarditis requiring surgery. *J Infect* **2009**; 59:42–48.
- 25 38. Sandoe JAT, Wysome J, West AP, Heritage J, Wilcox MH. Measurement of ampicillin, vancomycin,
26 linezolid and gentamicin activity against enterococcal biofilms. *J Antimicrob Chemother* **2006**;
27 57:767–770.
- 28 39. Royer G, Roisin L, Demontant V, et al. Microdiversity of Enterococcus faecalis isolates in cases of
29 Infective Endocarditis: selection of non-synonymous mutations and large deletions is associated
30 with phenotypic modifications. *Emerg Microbes Infect* **2021**; :1–181.

31

1 **Table 1.** Characteristics of 279 cases of endocarditis due to *E. faecalis* according to the treatment received.

Variable	Total (n=279)	A-G combination (n=83)	A-C combination (n=114)	A-G/A-C combinations (n=63)	Amoxicillin (n=9)	Other treatment (n=10)
Demographic features and underlying conditions						
Age, years	74 [66-83]	71 [61-79]	78 [67-86]	73 [67-79]	71 [67-81]	81,5 [74-85]
Gender, male	221 (79.2)	70 (84.3)	86 (75.4)	51 (81.0)	5 (55.6)	9 (90.0)
Initial admission in hospital with cardiac surgery department	182 (65.2)	51 (61.4)	77 (67.5)	43 (68.3)	4 (44.4)	7 (70.0)
Comorbidities						
Diabetes mellitus	74 (26.5)	19 (22.9)	34 (29.8)	15 (23.8)	2 (22.2)	4 (40.0)
Chronic lung disease	37 (13.3)	15 (18.1)	12 (10.5)	7 (11.1)	1 (11.1)	2 (20.0)
Congestive heart failure	97 (34.8)	21 (25.3)	46 (40.4)	21 (33.3)	2 (22.2)	7 (70.0)
Moderate/severe chronic renal failure	47 (16.8)	8 (9.6)	27 (23.7)	9 (14.3)	0 (0.0)	3 (30.0)
Immunodeficiency	26 (9.3)	10 (12.0)	10 (8.8)	4 (6.3)	1 (11.1)	1 (10.0)
Neoplasm	50 (17.9)	15 (18.1)	20 (17.5)	11 (17.5)	0 (0.0)	4 (40.0)
Charlson comorbidity index	5 [3-7]	4 [3-6]	6 [4-7]	5 [2-6]	4 [4-5]	7,5 [5-9]
Type of IE and underlying cardiac condition						
Native valve IE	162 (58.1)	52 (62.7)	67 (58.8)	31 (49.2)	6 (66.7)	6 (60.0)
Prosthetic valve IE	117 (41.9)	31 (37.3)	47 (41.2)	32 (50.8)	3 (33.3)	4 (40.0)
TAVI	35 (12.5)	5 (6.0)	22 (19.3)	5 (7.9)	1 (11.1)	2 (20.0)
Intra-Cardiac Device (ICD)	55 (19.7)	12 (14.5)	24 (21.1)	16 (25.4)	0 (0.0)	3 (30.0)
Previous endocarditis	23 (8.2)	6 (7.2)	9 (7.9)	7 (11.1)	1 (11.1)	0 (0.0)
IV drug use	9 (3.2)	6 (7.2)	1 (0.9)	2 (3.2)	0 (0.0)	0 (0.0)
Clinical features						
Acquisition						
Community	190 (68.1)	58 (69.9)	71 (62.3)	48 (76.2)	7 (77.8)	6 (60.0)
Health care-associated	89 (31.9)	25 (30.1)	43 (37.7)	15 (23.8)	2 (22.2)	4 (40.0)
< 1 year after prosthesis implantation	38 (13.6)	8 (9.6)	22 (19.3)	7 (11.1)	0 (0.0)	1 (10.0)

Duration of symptoms before diagnosis, days	10 [2-30]	9 [1-30]	14 [3-33]	12 [7-30]	3 [1-8]	14,5 [7-30]
Clinical complication	216 (77.4)	60 (72.3)	90 (78.9)	53 (84.1)	5 (55.6)	8 (80.0)
Acute heart failure	116 (41.6)	24 (28.9)	54 (47.4)	31 (49.2)	3 (33.3)	4 (40.0)
Heart conduction disturbance	21 (7.5)	8 (9.6)	7 (6.1)	6 (9.5)	0 (0.0)	0 (0.0)
Acute kidney injury	83 (29.7)	15 (18.1)	35 (30.7)	27 (42.9)	1 (11.1)	5 (50.0)
Systemic embolic event	140 (50.2)	41 (49.4)	56 (49.1)	34 (54.0)	3 (33.3)	6 (60.0)
Vertebral osteomyelitis	36 (12.9)	7 (8.4)	20 (17.5)	5 (7.9)	1 (11.1)	3 (30.0)
CNS embolism	63 (22.6)	24 (28.9)	20 (17.5)	18 (28.6)	0 (0.0)	1 (10.0)
Bleeding	30 (10.8)	7 (8.4)	8 (7.0)	11 (17.5)	0 (0.0)	4 (40.0)
Echocardiographic findings						
TEE performed	214 (76.7)	72 (86.7)	81 (71.1)	50 (79.4)	6 (66.7)	5 (50.0)
Vegetation	222 (79.6)	72 (86.7)	82 (71.9)	53 (84.1)	8 (88.9)	7 (70.0)
Aortic	141 (50.5)	51 (61.4)	44 (38.6)	34 (54.0)	7 (77.8)	5 (50.0)
Mitral	100 (35.8)	29 (34.9)	43 (37.7)	25 (39.7)	1 (11.1)	2 (20.0)
Tricuspid	14 (5.0)	2 (2.4)	9 (7.9)	2 (3.2)	1 (11.1)	0 (0.0)
Pulmonary	2 (0.7)	1 (1.2)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Multivalvular	33 (11.8)	11 (13.3)	13 (11.4)	8 (12.7)	1 (11.1)	0 (0.0)
ICD Lead associated endocarditis	15 (5.4)	5 (6.0)	5 (4.4)	5 (7.9)	0 (0.0)	0 (0.0)
Echocardiographic complication	182 (65.2)	54 (65.1)	75 (65.8)	44 (69.8)	4 (44.4)	5 (50.0)
Microbiological features						
Polymicrobial initial blood culture	11 (3.9)	6 (7.2)	2 (1.8)	2 (3.2)	1 (11.1)	0 (0.0)
Duration of bacteremia, days*	2 [0.7-5]	1 [0.3-2]	2 [0.8-13]	2 [0.7-3]	9 [2-49]	4 [2-10]
Control blood culture after the start of antibiotics	204/256 (79.7)	50/75 (66.7)	90/108 (83.3)	50/58 (86.2)	6/6 (100.0)	8/9 (88.9)
Time to first negative blood culture after the start of antibiotics, days	1 [1-3]	1 [0-3]	1 [1-3]	1 [1-3]	5 [3-9]	4 [4-7]
Persistent bacteremia						
≥ 3 days	19/256 (7.4)	3/75 (4.0)	7/108 (6.5)	4/58 (6.9)	1/6 (16.7)	4/9 (44.4)
≥ 7 days	4/256 (1.6)	0/75 (0.0)	1/108 (0.9)	0/58 (0.0)	1/6 (16.7)	2/9 (22.2)

- 1 Quantitative variables are expressed as median [IQR], qualitative variables are expressed by numbers (%). Percentages were calculated with all patients in
2 the column as the denominator, except for variables with missing data, for which the number of patients with available data is mentioned.
- 3 TAVI: transcatheter aortic valve implantation. ICD: Intra-cardiac Device; IE: Infective endocarditis; CNS: Central Nervous System; TEE: TransEsophageal
4 Echocardiography
- 5 *Data available for 264 patients, if the patient had only one positive blood culture (n=28) the duration considered was 0 days.

ACCEPTED MANUSCRIPT

1 **Table 2.** Management of 279 cases of endocarditis due to *E. faecalis* according to the treatment received.

Variable	Total (n=279)	A-G combination (n=83)	A-C combination (n=114)	A-G/A-C combinations (n=63)	Amoxicillin (n=9)	Other treatment (n=10)
Surgery						
Valve surgery						
Indicated	142 (50.9)	41 (49.4)	58 (50.9)	39 (61.9)	2 (22.2)	2 (20.0)
Indicated but not performed	42 (15.1)	9 (10.8)	21 (18.4)	9 (14.3)	1 (11.1)	2 (20.0)
Performed	99 (35.5)	31 (37.3)	37 (32.5)	30 (47.6)	1 (11.1)	0 (0.0)
Performed during antibiotic treatment	90 (32.3)	28 (33.7)	35 (30.7)	27 (42.9)	0 (0.0)	0 (0.0)
Interval between the start of antibiotics and surgery	10 [5-18]	11 [5-16]	11 [3-18]	9 [4-17]	-	-
Antibiotic treatment						
Antibiotic duration						
Total duration, days	42 [38-45]	42 [32-44]	42 [41-45]	43 [42-47]	42 [26-42]	42.5 [42-46]
Amoxicillin duration, days	42 [31-44]	42 [29-43]	42 [31-43]	42 [41-47]	41 [5-42]	-
Ceftriaxone duration, days	40 [21-42]	-	41 [26-43]	32 [17-42]	-	-
Gentamicin duration, days	14 [3-15]	14 [14-19]	-	4 [2-12]	-	12 [1-19]
Complete treatment	193 (69.2)	49 (59.0)	85 (74.6)	52 (82.5)	6 (66.7)	1 (10.0)
Antibiotic dose						
Amoxicillin, g per day	12 [10-12]	12 [12-12]	12 [10-12]	12 [10-12]	12 [8-12]	-
Amoxicillin, mg/kg/day	156 [128-187]	156 [129-180.5]	153 [126-187]	171 [130-190]	155 [106-203]	-
Ceftriaxone, g/day	4 [4-4]	-	4 [4-4]	4 [3-4]	-	-
Gentamicin, mg/kg/day	3 [2.9-3.4]	3 [2.9-3.3]	-	3 [2.9-3.6]	-	3.1 [3.1-3.3]
Other treatment						
Glycopeptide	29 (10.4)	6 (7.2)	9 (7.9)	4 (6.3)	2 (22.2)	8 (80.0)
Oral other treatment	22 (7.9)	6 (7.2)	9 (7.9)	3 (4.8)	2 (22.2)	2 (20.0)
Other treatment duration, days	23 [6-35]	22 [0-31]	15 [0-29]	19 [6-32]	18 [8-31]	42 [28-45]

Suppressive antibacterial treatment	12 (4.3)	0 (0.0)	10 (8.8)	1 (1.6)	0 (0.0)	1 (10.0)
Outpatient antibiotic therapy	89 (31.9)	28 (33.7)	36 (31.6)	18 (28.6)	3 (33.3)	4 (40.0)
Duration, days	18 [12-25]	15 [12-25]	21 [15-27]	15 [10-23]	17 [8-22]	21.5 [14-25]
Colonoscopy						
Colonoscopy performed	145 (52.0)	54 (65.1)	52 (45.6)	30 (47.6)	5 (55.6)	4 (40.0)
Lesion discovered	84 (30.1)	30 (36.1)	30 (26.3)	17 (27.0)	3 (33.3)	4 (40.0)

1

2 Quantitative variables are expressed as median [IQR], qualitative variables are expressed by numbers (%). Percentages were calculated with all patients in
 3 the column as the denominator, except for variables with missing data, for which the number of patients with available data is mentioned.

4 Other treatment: (vancomycin, teicoplanin, daptomycin, fluoroquinolone, rifampicin, linezolid, piperacillin-tazobactam or ceftaroline)

1 **Table 3.** Outcome of 279 cases of endocarditis due to *E. faecalis* according to the treatment received and those who received a complete treatment.

Outcome	Total (n=279)	A-G combination (n=83)	A-C combination (n=114)	A-G/A-C combinations (n=63)	Amoxicillin (n=9)	Other treatment (n=10)
All patients						
Mortality						
At the end of treatment	41 (14.7)	8 (9.6)	19 (16.7)	9 (14.3)	3 (33.3)	2 (20.0)
At 6 months	65 (23.3)	11 (13.3)	36 (31.6)	13 (20.6)	3 (33.3)	2 (20.0)
At 1 year	74 (26.5)	15 (18.1)	37 (32.5)	16 (25.4)	3 (33.3)	3 (30.0)
Relapse						
At 6 months	22 (7.9)	9 (10.8)	10 (8.8)	1 (1.6)	2 (22.2)	0 (0.0)
At 1 year	26 (9.3)	9 (10.8)	12 (10.5)	2 (3.2)	3 (33.3)	0 (0.0)
All relapses	28 (10.0)	9 (10.8)	13 (11.4)	2 (3.2)	3 (33.3)	1 (10.0)
Patients with complete treatment						
Mortality						
At the end of treatment	33/193 (17.1)	6/49 (12.2)	17/85 (20.0)	9/52 (17.3)	1/6 (16.7)	-
At 6 months	48/193 (24.9)	7/49 (14.3)	28/85 (32.9)	12/52 (23.1)	1/6 (16.7)	-
At 1 year	53/193 (27.5)	10/49 (20.4)	29/85 (34.1)	13/52 (25.0)	1/6 (16.7)	-
Relapse						
At 6 months	16/193 (8.3)	4/49 (8.2)	9/85 (10.6)	1/52 (1.9)	2/6 (33.3)	-
At 1 year	19/193 (9.8)	4/49 (8.2)	10/85 (11.8)	2/52 (3.8)	3/6 (50.0)	-
All relapses	19/193 (9.8)	4/49 (8.2)	10/85 (11.8)	2/52 (3.8)	3/6 (50.0)	-

2

3 Qualitative variables are expressed by numbers (%). Percentages were calculated with all patients in the column as the denominator, except for variables

4 with missing data, for which the number of patients with available data is mentioned.

1 **Table 4.** Characteristics, management, and outcome of 28 patients who experienced relapse.

Characteristics	Value n=28
Time from EFIE diagnosis to relapse	
< 3 months	10 (35.7)
3-6 months	12 (42.9)
6-12 months	4 (14.3)
12-24 months	1 (3.6)
>24 months	1 (3.6)
Presentation at relapse diagnosis	
Asymptomatic	8/27 (29.6)
Systematic blood culture control	6/27 (22.2)
Delayed surgery with positive valve culture	2/27 (7.4)
Symptomatic	19/27 (70.4)
Fever/sepsis	19/27 (70.4)
Cardiac failure	5/27 (18.5)
Systemic embolic event	7/27 (25.9)
Management of relapse	
Surgery	7 (25.0)
Antibiotic treatment	
A-C	12/26 (46.2)
A-G	5/26 (19.2)
A-G/A-C	4/26 (15.4)
Glycopeptide	4/26 (15.4)
Suppressive antibiotic therapy	7/26 (26.9)
Outcome of relapse	
Endocarditis-related death	8 (28.6)
Cure	20 (71.4)
Relapse	3 (10.7)

2
3 All results are no. of patients / no. of patients with available data (%). Percentages were calculated with
4 all patients in the column as the denominator, except for variables with missing data, for which the
5 number of patients with available data is mentioned.

1 **Figure 1.** Valve culture result according to the time between the start of antibiotics and surgery.
 2 **Figure 2.** Cumulative incidence of relapse and survival probability according to the treatment received.
 3 a: Cumulative incidence of relapse according to the treatment received in a Fine and Gray model (death
 4 considered as a competitive risk).
 5 b: Survival probability according to the treatment received in a Cox model.
 6 Comparison of different treatments with A-G combination considered as reference (a and b).
 7 aSHR: adjusted Sub-distribution Hazard Ratio
 8 aHR: adjusted Hazard Ratio

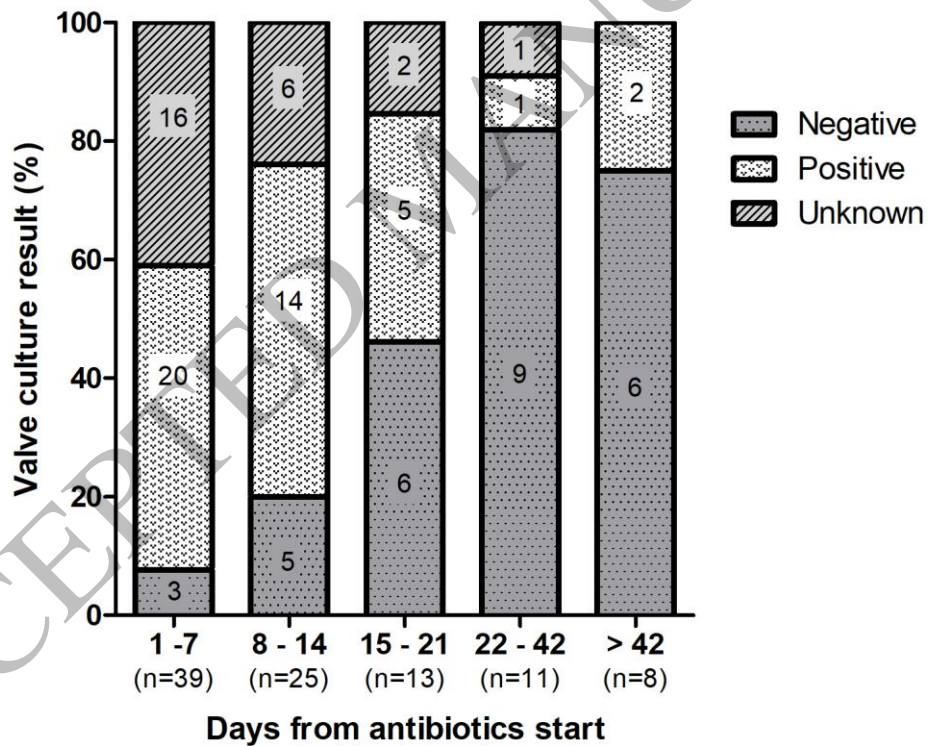


Figure 1
 128x107 mm (x DPI)

12
 13
 14
 15

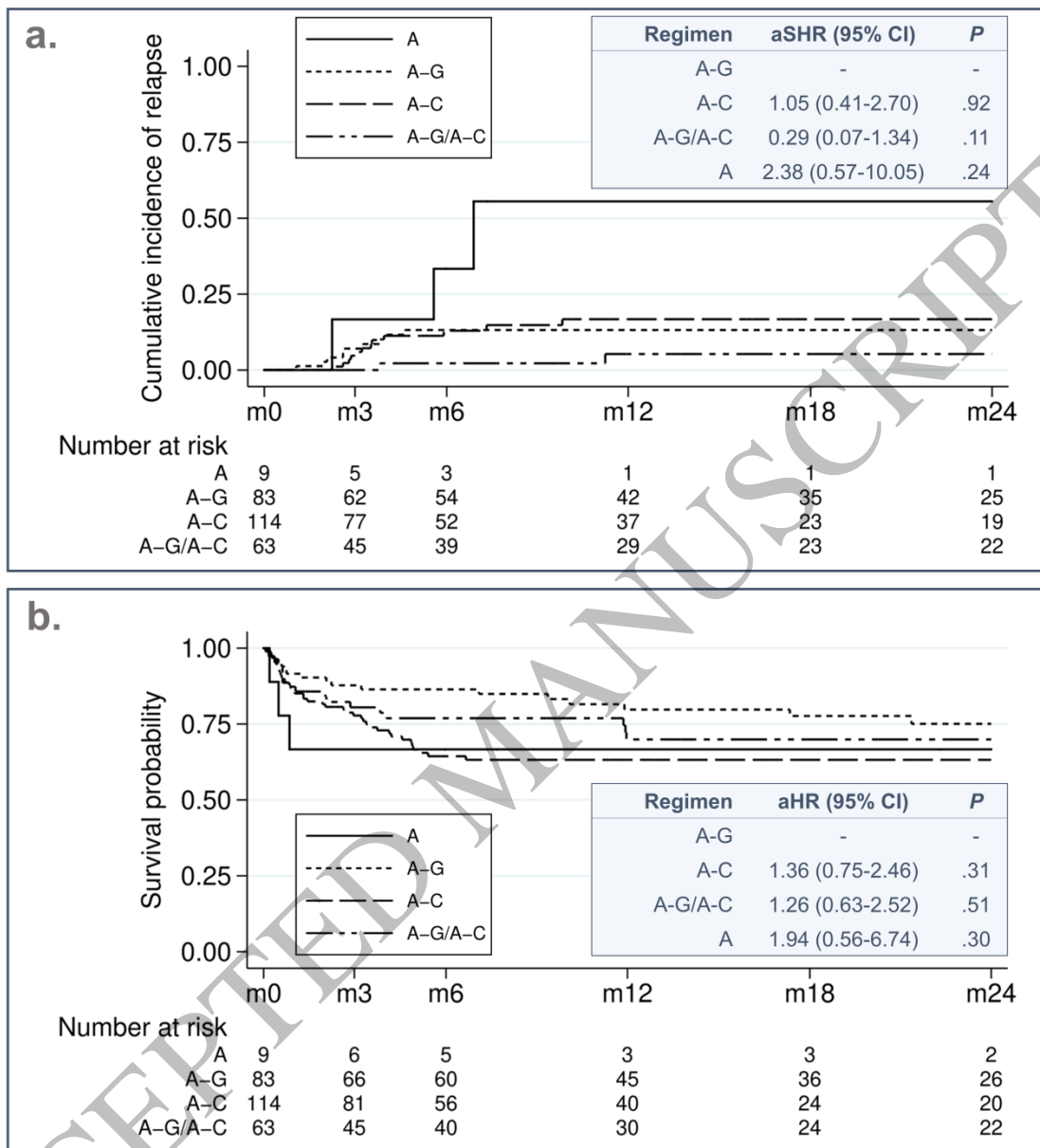


Figure 2
413x434 mm (x DPI)

1
2
3