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MAJOR ARTICLE

Impact of *Enterococcus faecalis* Endocarditis Treatment on Risk of Relapse

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

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

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

The cumulative incidence of relapse 1 year after endocarditis was 46.2% for patients treated with 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).

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

Keywords. *e. faecalis*; endocarditis; relapse; amoxicillin; drug therapy combination.

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

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

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

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

Compared to endocarditis due to other pathogens, enterococcal endocarditis had a significantly higher 6-month relapse rate estimated to be around 7% [8, 16]. The 6-month threshold in relapse definition has been set empirically to differentiate relapse from reinfection [11]. However, molecular bacterial typing analyses based on pulsed field gel electrophoresis (PFGE) [17] have shown that, in the case of EFIE, relapse may occur up to 1 year after the initial episode [18, 19]. Thus, the real frequency of relapses could be underestimated. Due to their scarcity, the impact of treatment on the risk of relapse has not been explored, and there is still limited data about clinical characteristics, management, and outcome of these relapses.

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

METHODS

Design, Settings, and Patients

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

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

Data Collection

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

Ethics

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

Definitions

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

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

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

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

Study Endpoints

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

Statistical Analysis

Quantitative variables were expressed as medians with interquartile range [IQR]. Qualitative variables were expressed as crude numbers and percentages. Continuous variables were compared using the Kruskal-Wallis test. Categorical variables were compared using the χ^2 test or Fischer exact test if required. Fine and Gray models were used for determining risk factors for relapse (by calculating adjusted sub hazard ratio [aSHR]), considering death as a competing event. Cox models were used for analyzing risk factors for death. For each considered endpoint (relapse or death), several models were considered. The first was the simplest model (referring to the univariate

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

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

RESULTS

Demographics and Baseline Characteristics

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

Valve Surgery

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

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

Antibiotic Regimen

Overall, the A-C therapy was administered to 177 patients (63.4%) and A-G therapy to 146 (52.3%). Of them, 63 patients (22.6%) received a sequential A-G/A-C treatment (only two of them had at first A-C and then A-G) defining the A-G/A-C group. Twenty-two patients (7.9%) received additional oral antibiotic therapy (fluoroquinolone [n = 11], rifampicin [n = 8] or linezolid [n = 4]), mainly because of associated infectious embolism (73%, n = 16). Nine patients received A therapy; only 1 of them underwent surgery during treatment (Supplementary Table 3). Overall, 69.2% patients (n = 193) received a complete antibiotic treatment.

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

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

Outcome

One year after the diagnosis of EFIE, 74 patients (26.5%) had died, 26 patients (9.3%) had relapsed of their endocarditis (median delay 103 days,7 of whom died within 1 year), 72 (25.8%) were lost to follow-up, and 114 (40.9%) were considered to be cured (Table 3). Considering only patients alive at the end of antibiotic treatment with available follow-up data, 11.2% (22/197) had relapsed at 6 months and 15.7% (26/166) at 1 year. Two patients relapsed thereafter; the total relapse rate was 10.0%.

One-year relapse occurred in only 1 of the 90 patients who underwent surgery during antibiotic treatment versus 25 of the 189 who did not (aSHR 0.07, 95% CI: .01–.56; $P = .01$). Prosthetic valve was not associated with a higher relapse risk (aSHR 1.15, 95% CI: .53–2.48, $P = .73$), as the other variables included in the model.

In multivariate analysis, characteristics associated with 1-year mortality were elevated Charlson index (adjusted hazard ratio [aHR] 1.17, 95% CI: 1.07–1.28, $P < .001$) and acute heart failure (aHR 2.59, 95% CI: 1.58–4.25, $P < .001$), while surgery during treatment was a protective factor (aHR 0.42, 95% CI: .21–.83, $P = .01$). The association was not significant for surgery indicated but not performed (aHR 1.63, 95% CI: .945–2.82, $P = .08$) and initial admission in a hospital with cardiac surgery department (aHR 0.65, 95% CI: .41–1.04, $P = .07$).

Comparison of the A-G Combination With Other Regimens

The cumulative incidence of relapse 1 year after endocarditis diagnosis was 46.2% (95% CI: 17.8%–85.8%) for patients treated with A, 13.4% (7.2%–24.2%) for patients treated with A-G, and 14.7% (8.6%–24.5%) with A-C therapy (Figure 2*A*). The

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, y	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)
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 y 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, d	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, d[a]	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, d	1 [1–3]	1 [0–3]	1 [1–3]	1 [1–3]	5 [3–9]	4 [4–7]
Persistent bacteremia						
≥3 d	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 d	4/256 (1.6)	0/75 (0.0)	1/108 (0.9)	0/58 (0.0)	1/6 (16.7)	2/9 (22.2)

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

Abbreviations: CNS, central nervous system; *E. faecalis*, *Enterococcus faecalis*; ICD, intra-cardiac device; IE, infective endocarditis; IV, intravenous; TAVI, transcatheter aortic valve implantation; TEE, transesophageal echocardiography.

[a]Data available for 264 patients, if the patient had only one positive blood culture ($n = 28$) the duration considered was 0 days.

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, d	42 [38–45]	42 [32–44]	42 [41–45]	43 [42–47]	42 [26–42]	42.5 [42–46]
Amoxicillin duration, d	42 [31–44]	42 [29–43]	42 [31–43]	42 [41–47]	41 [5–42]	…
Ceftriaxone duration, d	40 [21–42]	…	41 [26–43]	32 [17–42]	…	…
Gentamicin duration, d	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 d	12 [10–12]	12 [12–12]	12 [10–12]	12 [10–12]	12 [8–12]	…
Amoxicillin, mg/kg/d	156 [128–187]	156 [129–180.5]	153 [126–187]	171 [130–190]	155 [106–203]	…
Ceftriaxone, g/d	4 [4–4]	…	4 [4–4]	4 [3–4]	…	…
Gentamicin, mg/kg/d	3 [2.9–3.4]	3 [2.9–3.3]		3 [2.9–3.6]	…	3.1 [3.1–3.3]
Other treatment	50 (17.9)	10 (12.0)	17 (14.9)	9 (14.3)	4 (44.4)	10 (100.0)
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, d	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, d	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)

Quantitative variables are expressed as median [interquartile range (IQR)], qualitative variables are expressed by no. (%). Percentages were calculated with all patients in the column as the denominator, except for variables with missing data, for which the number of patients with available data is mentioned.

Other treatment: vancomycin, teicoplanin, daptomycin, fluoroquinolone, rifampicin, linezolid, piperacillin-tazobactam, or ceftaroline.

Abbreviation: *E. faecalis*, *Enterococcus faecalis*.

lowest incidence was 4.3% (1.1%–16.0%) for patients sequentially treated with A-G/A-C.

When comparing the risk of relapse according to the treatment received, with A-G as a reference, no significant difference was observed in univariate and multivariate analysis. In a sensitivity analysis considering only patients who received complete treatment, treatment with A showed a significantly higher risk of relapse than A-G in multivariate analysis (aSHR 5.41, 95% CI: 1.19–24.6, $P = .03$, Supplementary Figure 2).

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

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

Characteristics and Management of Relapses

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

Eight patients (28.6%) died of their relapsed endocarditis; 1 was asymptomatic at diagnosis; none of them had undergone cardiac surgery. Three patients (10.7%) presented 2 consecutive relapses despite a well-conducted antibiotic therapy; 2 of them had an indication for surgery at the time of the first relapse.

DISCUSSION

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

Few cohorts of EFIE are described and to date, the most extensive are those of Pericás et al (n = 468), Chirouze et al (n = 453) and Fernández-Hidalgo et al (n = 248) [6, 8, 10]. In our cohort, we observed a lower rate of surgery during treatment compared to the others (32.3% vs 36%–42%). This may be explained by the inclusion in our cohort of patients managed in

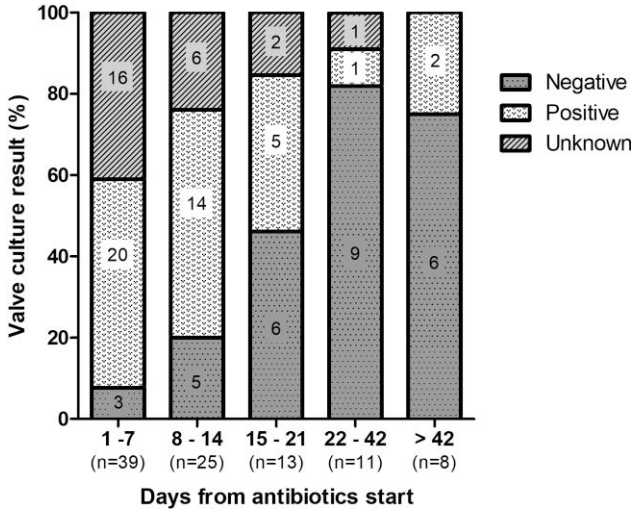

Figure 1. Valve culture result according to the time between the start of antibiotics and surgery.

hospitals without cardiac surgery, which was not the case in the aforementioned studies. Our study confirms the widespread use of the A-C treatment [5, 25].

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

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

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

Three of 5 patients who received a full and complete course of amoxicillin monotherapy relapsed despite receiving 12 g/day for 42 days. This is consistent with data previously described, with low patient numbers [30]. In our opinion, the difference observed between monotherapy and combination therapy is sufficient to put an end to the questioning of amoxicillin use in combination [14, 15].

Surprisingly, the lower relapse rate was observed in patients who received the A-G/A-C treatment. This group of patients had a higher rate of acute kidney injury, often related to

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 m	65 (23.3)	11 (13.3)	36 (31.6)	13 (20.6)	3 (33.3)	2 (20.0)
At 1 y	74 (26.5)	15 (18.1)	37 (32.5)	16 (25.4)	3 (33.3)	3 (30.0)
Relapse						
At 6 m	22 (7.9)	9 (10.8)	10 (8.8)	1 (1.6)	2 (22.2)	0 (0.0)
At 1 y	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 m	48/193 (24.9)	7/49 (14.3)	28/85 (32.9)	12/52 (23.1)	1/6 (16.7)	…
At 1 y	53/193 (27.5)	10/49 (20.4)	29/85 (34.1)	13/52 (25.0)	1/6 (16.7)	…
Relapse						…
At 6 m	16/193 (8.3)	4/49 (8.2)	9/85 (10.6)	1/52 (1.9)	2/6 (33.3)	…
At 1 y	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)	…

Qualitative variables are expressed by no. (%). Percentages were calculated with all patients in the column as the denominator, except for variables with missing data, for which the number of patients with available data is mentioned.
Abbreviation: *E. faecalis*, *Enterococcus faecalis*.

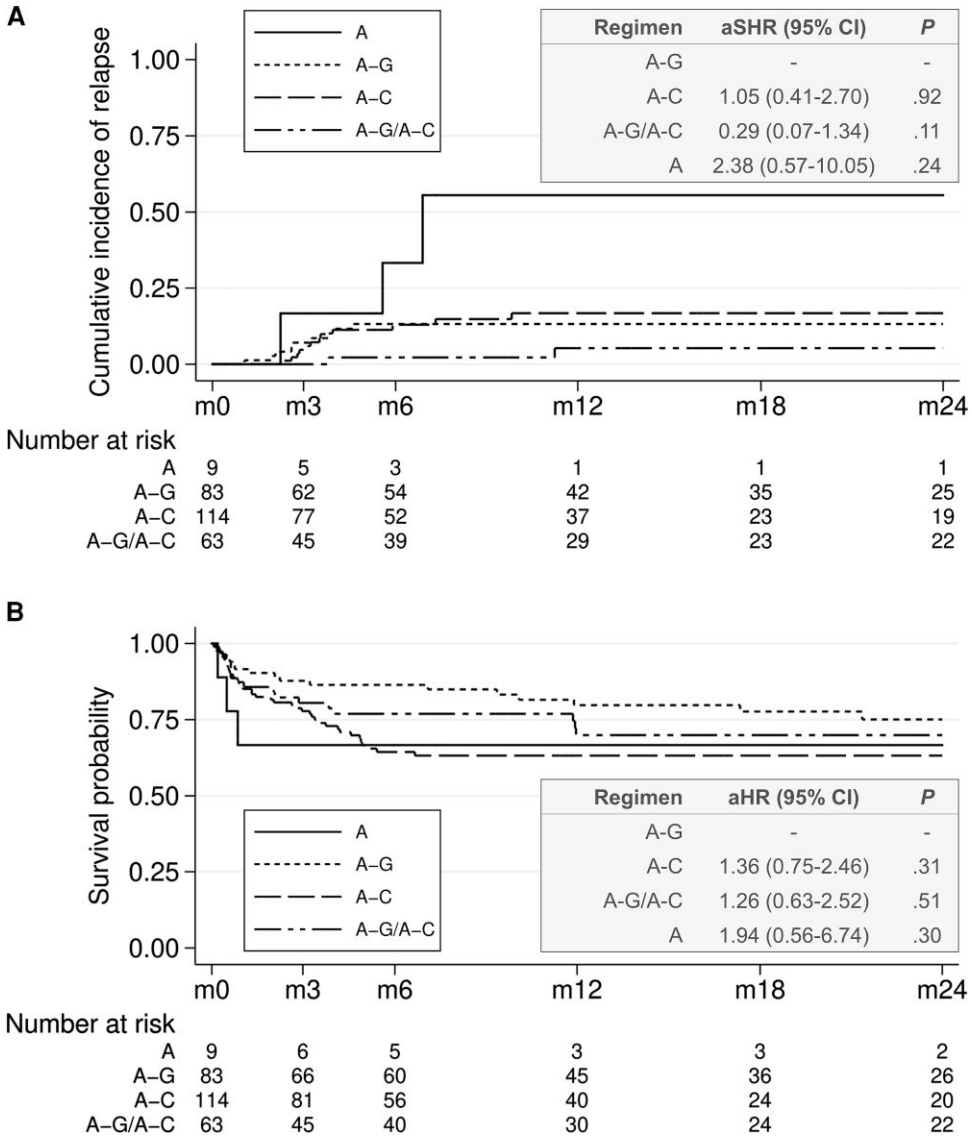

Figure 2. Cumulative incidence of relapse and survival probability according to the treatment received. *A*: Cumulative incidence of relapse according to the treatment received in a Fine and Gray model (death considered as a competitive risk). *B*: Survival probability according to the treatment received in a Cox model. Comparison of different treatments with A-G combination considered as reference (*A* and *B*). Abbreviations: aHR, adjusted hazard ratio; aSHR, adjusted sub-distribution hazard ratio; CI, confidence interval.

gentamicin toxicity, and tended to have more surgery during treatment. These 2 events probably prompted the clinicians to switch treatment from A-G to A-C. To the best of our knowledge, use of this sequential treatment has not been reported and described, although our data suggest that it is already widespread. Further studies are needed to evaluate the efficacy and safety of a sequential regimen comprising 7 to 14 days of A-G followed by A-C combination. A prospective study including long-term patient follow-up is still necessary [31, 32].

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

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

Using WGS we demonstrated that true relapse may occur more than 1 year after the initial diagnosis and patients may be asymptomatic at the time of relapse diagnosis. This

Table 4. Characteristics, Management, and Outcome of 28 Patients Who Experienced Relapse

Characteristics	Value n = 28
Time from EFIE diagnosis to relapse	
<3 m	10 (35.7)
3–6 m	12 (42.9)
6–12 m	4 (14.3)
12–24 m	1 (3.6)
>24 m	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)

All results are no. of patients/no. of patients with available data (%). Percentages were calculated with all patients in the column as the denominator, except for variables with missing data, for which the number of patients with available data is mentioned.
Abbreviation: EFIE, *Enterococcus faecalis* infective endocarditis.

encourages prolonged surveillance, with systematic blood culture, of patients who have been treated for EFIE, especially if they have not undergone surgery.

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

CONCLUSION

Relapses after treatment of EFIE are frequent, may be asymptomatic, and can occur more than 1 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.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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