

Original article

# Prevalence of colorectal disease in *Enterococcus faecalis* infective endocarditis: results of an observational multicenter study



Laura Escolà-Vergé,<sup>a,\*</sup> Maddalena Peghin,<sup>b</sup> Filippo Givone,<sup>b</sup>  
María Teresa Pérez-Rodríguez,<sup>c</sup> Milagros Suárez-Varela,<sup>c</sup> Yolanda Meije,<sup>d</sup>  
Gabriela Abelenda,<sup>d</sup> Benito Almirante,<sup>a</sup> and Nuria Fernández-Hidalgo<sup>a</sup>

<sup>a</sup>Servicio de Enfermedades Infecciosas, Hospital Universitari Vall d'Hebron, Departamento de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain

<sup>b</sup>Clinica di Malattie Infettive, Dipartimento di Medicina, Università di Udine e Ospedale Santa Maria della Misericordia, Udine, Italy

<sup>c</sup>Unidad de Enfermedades Infecciosas, Servicio de Medicina Interna, Complejo Hospitalario Universitario de Vigo, Instituto de Investigación Biomédica Galicia-Sur, Vigo, Pontevedra, Spain

<sup>d</sup>Unidad de Enfermedades Infecciosas, Servicio de Medicina Interna, Hospital de Barcelona, Societat Cooperativa d'Instal·lacions Assistencials Sanitàries (SCIAS), Barcelona, Spain

## Article history:

Received 28 May 2019

Accepted 22 July 2019

Available online 20 August 2019

## Keywords:

*Enterococcus faecalis*

Infective endocarditis

Colonoscopy

Portal of entry

Colorectal neoplasm

## ABSTRACT

**Introduction and objectives:** The aim of this study was to determine the prevalence of colorectal disease in *Enterococcus faecalis* infective endocarditis (EFIE) patients.

**Methods:** An observational, retrospective, multicenter study was performed at 4 referral centers. From the moment that a colonoscopy was systematically performed in EFIE in each participating hospital until October 2018, we included all consecutive episodes of definite EFIE in adult patients. The outcome was an endoscopic finding of colorectal disease potentially causing bacteremia.

**Results:** A total of 103 patients with EFIE were included; 83 (81%) were male, the median age was 76 [interquartile range 67-82] years, and the median age-adjusted Charlson comorbidity index was 5 [interquartile range 4-7]. The presumed sources of infection were unknown in 63 (61%), urinary in 20 (19%), gastrointestinal in 13 (13%), catheter-related bacteremia in 5 (5%), and others in 2 (2%). Seventy-eight patients (76%) underwent a colonoscopy, and 47 (60%) had endoscopic findings indicating a potential source of bacteremia. Thirty-nine patients (83%) had a colorectal neoplastic disease, and 8 (17%) a nonneoplastic disease. Of the 45 with an unknown portal of entry who underwent a colonoscopy, gastrointestinal origin was identified in 64%. In the subgroup of 25 patients with a known source of infection and a colonoscopy, excluding those with previously diagnosed colorectal disease, 44% had colorectal disease.

**Conclusions:** Performing a colonoscopy in all EFIE patients, irrespective of the presumed source of infection, could be helpful to diagnose colorectal disease in these patients and to avoid a new bacteremia episode (and eventually infective endocarditis) by the same or a different microorganism.

© 2019 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

## Prevalencia de enfermedad colorrectal en la endocarditis infecciosa por *Enterococcus faecalis*: resultados de un estudio multicéntrico observacional

## RESUMEN

**Introducción y objetivos:** El objetivo del estudio fue determinar la prevalencia de patología colorrectal en los pacientes con endocarditis infecciosa por *Enterococcus faecalis* (EIEF).

**Métodos:** Se realizó un estudio observacional, retrospectivo y multicéntrico en 4 hospitales de referencia. Se incluyeron todos los episodios consecutivos de EIEF definitivos en adultos desde el momento en que se empezó a realizar una colonoscopia por protocolo en cada centro participante hasta octubre de 2018. Se recogieron los hallazgos endoscópicos de patología colorrectal potencialmente causante de una bacteriemia.

**Resultados:** Se incluyeron 103 pacientes con EIEF; 83 (81%) eran varones, la edad mediana era 76 [intervalo intercuartílico 67-82] años, y la mediana del índice de Charlson ajustado por edad fue 5 [intervalo intercuartílico 4-7]. El presunto origen de la infección fue desconocido en 63 (61%), urinario en 20 (19%), digestivo en 13 (13%), bacteriemia de catéter en 5 (5%), y otros en 2 (2%). En 78 (76%) pacientes se realizó una colonoscopia, y en 47 (60%) había hallazgos endoscópicos que indicaban un potencial foco de bacteriemia. Treinta y nueve (83%) tenían una enfermedad colorrectal neoplásica, y 8 (17%) no neoplásica. De los 45 pacientes con puerta de entrada desconocida y colonoscopia, un posible origen gastrointestinal se identificó en 64%. En el subgrupo de 25 con foco de entrada conocido y colonoscopia, excluyendo aquellos con enfermedad colorrectal ya previamente diagnosticada, 44% tenían patología colorrectal.

## Palabras clave:

*Enterococcus faecalis*

Endocarditis infecciosa

Colonoscopia

Puerta de entrada

Neoplasia colorrectal

## SEE RELATED CONTENT:

<https://doi.org/10.1016/j.rec.2020.03.006>

\* Corresponding author: Servicio de Enfermedades Infecciosas, Hospital Universitari Vall d'Hebron, Departamento de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain.

E-mail address: [lauraescola@gmail.com](mailto:lauraescola@gmail.com) (L. Escolà-Vergé).

<https://doi.org/10.1016/j.rec.2019.07.007>

1885-5857/© 2019 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

**Conclusiones:** Realizar una colonoscopia en la EIEF, sin tener en cuenta la puerta de entrada, puede ayudar a diagnosticar la enfermedad colorrectal en estos pacientes y evitar una nueva bacteriemia (y eventualmente endocarditis infecciosa) por el mismo u otro microorganismo.

© 2019 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

## Abbreviations

EFIE: *Enterococcus faecalis* infective endocarditis

IE: infectious endocarditis

## INTRODUCTION

Enterococci are normal commensals of the gastrointestinal tract and are able to cause infection by translocation through the epithelial cells of the intestine, gaining access to the lymphatic system and bloodstream through mechanisms that have not yet been elucidated.<sup>1,2</sup> Therefore, lesions in the colonic mucosa could be a portal of entry of bacteremia, such as in *Streptococcus gallolyticus* infective endocarditis (IE).<sup>3,4</sup>

In developed countries, *Enterococcus faecalis* is the third cause of IE.<sup>5</sup> *E. faecalis* infective endocarditis (EFIE) affects older patients with comorbidities,<sup>6–8</sup> a population with a higher incidence of colorectal disease.<sup>9</sup> Moreover, 5% of patients with IE regardless of the etiology will have an additional episode of IE with a higher mortality risk.<sup>10</sup> Therefore, identifying the portal of entry and treating it are particularly important to lower the risk for a new IE episode.<sup>11,12</sup>

A recent retrospective study performed in a selected cohort of patients showed that patients with EFIE of unknown origin had a higher prevalence of colorectal lesions (31 of 61, 50.8%) than those with EFIE with a known origin (1 of 6, 16.7%); however, in that study a colonoscopy was not systematically performed in all patients, particularly not in EFIE patients with a presumed known source of infection.<sup>13</sup> Considering the importance of controlling potential portals of entry in EFIE to avoid new bacteremia by the same or a different microorganism,<sup>11</sup> the question arises of whether to systematically perform a colonoscopy in patients with EFIE.

The objective of this study was to assess the prevalence of colorectal disease in patients with EFIE, regardless of whether the infection source was known.

## METHODS

### Design, setting, and patients

This observational, retrospective, multicenter study was performed at 4 referral centers for IE: *Hospital Universitari Vall d'Hebron* (HUVH), a 1000-bed teaching hospital in Barcelona (Spain), *Complejo Hospitalario Universitario de Vigo* (CHUV), a 1200-bed teaching hospital in Vigo, Pontevedra (Spain), *Presidio Ospedaliero Universitario Santa Maria della Misericordia* (POUSMdM), a 1000-bed teaching hospital in Udine (Italy), and *Hospital de Barcelona* (HdB), a 250-bed private hospital in Barcelona (Spain). All 4 centers are referral centers for cardiac surgery.

Considering the importance of controlling the portal of entry to avoid recurrences, since January 2014 a colonoscopy has been systematically performed in EFIE patients at POUUSMdM, since July 2014 at HUVH, and since January 2015 at CHUV, and HdB. From the moment that a colonoscopy was systematically performed in each participating hospital until October 2018, all consecutive episodes of definite EFIE in adult patients (aged  $\geq 18$  years) were included in

the study. Only the first episode of EFIE in each patient was recorded. Patients were retrospectively identified from the Infectious Diseases Registry of each participating hospital, in which all consecutive episodes of IE are prospectively recorded.

### Endpoints

The endpoint was an endoscopic finding of colorectal disease that could potentially cause bacteremia.

### Variables related to infective endocarditis

The definition of variables related to IE can be found in detail in the methods of the supplementary data.<sup>14–20</sup>

### Variables related to colonoscopy

We included all colonoscopies performed after the onset of IE symptoms or 6 months before EFIE diagnosis, as well as those performed during treatment and 6-month follow-up. Assessment of bowel preparation was performed according to gastroenterologist reports and was classified as good (no fecal remains or very few that allowed an adequate surface examination), average (some semisolid stool that could be suctioned or washed away and allowed adequate surface examination) or poor (abundant fecal remains that could not be suctioned or washed away and that prevented adequate surface examination),<sup>21</sup> and the possibility of cecal intubation was recorded.

Endoscopic findings of the colonoscopy and adverse events were also recorded. Adverse events related to the procedure included colonic perforation, lower gastrointestinal bleeding, and allergic reactions to sedative medication.

We recorded all endoscopic findings. We did not include uncomplicated diverticula and uncomplicated hemorrhoids to be a potential cause of bacteremia. Among any endoscopic findings that could potentially cause bacteremia, we classified colonic lesions into neoplastic and nonneoplastic diseases according to the histopathological report. We conducted the classification based on the most advanced lesion identified. If no histopathological report was available, we classified the lesion as nonneoplastic.

Colorectal neoplasms included colorectal adenomas and colorectal carcinomas. Adenomas were divided into nonadvanced colorectal adenomas (tubular adenomas with a diameter  $< 10$  mm) or advanced colorectal adenomas (adenomas measuring  $\geq 10$  mm, with villous architecture, high-grade dysplasia, or intramucosal carcinoma). The criterion for colorectal carcinoma was the presence of malignant cells beyond the muscularis mucosae.<sup>22</sup> Nonneoplastic diseases included colonic mucosal inflammation, angiodysplasias, ulcers, and nonneoplastic polyps. All patients with endoscopic findings were referred to the gastroenterologist for follow-up.

### Data collection

Demographic, clinical, diagnostic, treatment, outcome and follow-up data were obtained from the prospective IE registry of each center. Data on colonoscopy (date of performance, pathologi-

cal findings, and adverse events) were retrospectively collected from the patients' medical charts and entered in a database created specifically for this study.

### Statistical analysis

Quantitative variables are reported as the median and interquartile range [IQR], and qualitative variables as number and percentage. Differences between patients according to the source of infection or the presence or absence of endoscopic findings in colonoscopy were assessed by the chi-square test or Fisher exact test for categorical variables, as appropriate, and the 2-sample Wilcoxon rank-sum (Mann-Whitney) test for continuous variables. Statistical analyses were performed using STATA software, version 15. A 2-tailed *P* value < .05 was considered statistically significant.

### Ethics

The study was approved by the hospital ethics committee of Hospital Universitari Vall d'Hebron, Barcelona (Spain), (approval PR(AG)332/2018) and the remaining participating centers. Informed consent from patients was not required.

## RESULTS

### Patients included in the study

A total of 103 episodes of definite EFIE were included in the study. Of these cases, 78 (76%) patients underwent a colonoscopy (figure 1). Of those with a colonoscopy, 47 (60%) had endoscopic findings indicating a potential source of bacteremia. The epidemiological, clinical, and outcome characteristics are shown in table 1 of the supplementary data.

### Colonoscopy findings

Table 1 shows the endoscopic findings in all patients undergoing a colonoscopy and divided by groups depending on whether

the source of infection was known (excluding patients with previously diagnosed colorectal disease) or unknown. For more detailed information see table 2 of the supplementary data.

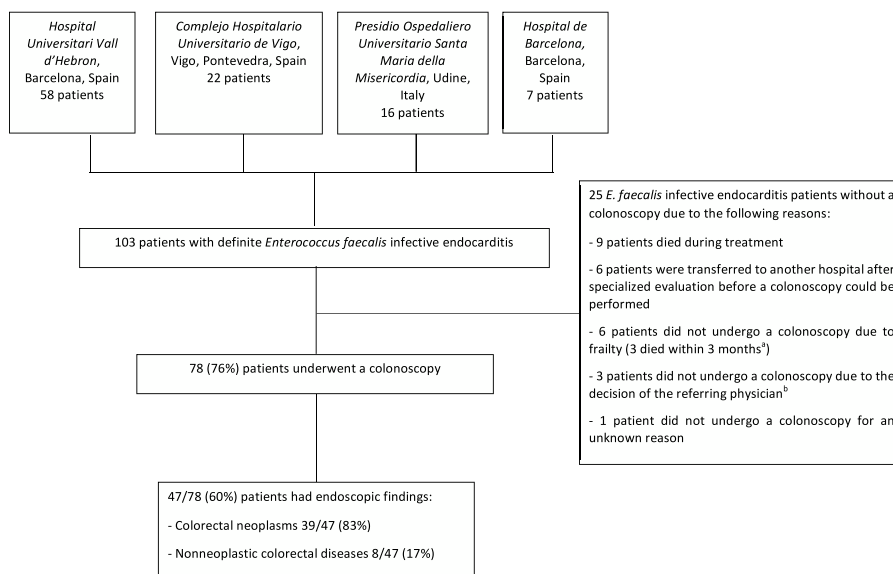
Of the 78 patients who underwent a colonoscopy, 47 (60%) had endoscopic findings indicating a potential source of bacteremia. Thirty-nine patients (83%) had a colorectal neoplastic disease, and 8 (17%) had a nonneoplastic disease. Of the 39 patients with a colorectal neoplasm, 19 had a nonadvanced colorectal adenoma, 18 had an advanced colorectal adenoma, and 2 had a colorectal carcinoma. Of the 8 patients with a nonneoplastic disease, 3 patients had nonmalignant ulcers, 2 patients had colorectal mucosa inflammation (1 due to ischemic colitis and the other to radiation proctitis), 2 patients had angiodysplasias, and 1 patient had a polyp without a histopathological report.

A colonoscopy was available in 45 (71%) of the 63 patients with an unknown source of infection, 25 (78%) of the 32 patients with a known source of infection (including urinary tract, hepatobiliary source, catheter-related bacteremia source and other sources), and all 8 patients with a previously diagnosed colorectal disease as the presumed source of infection. Of 45 patients with an unknown portal of entry who underwent a colonoscopy, a potential gastrointestinal origin was identified in 29 (64%). Of 25 patients with a known source of infection and a colonoscopy, excluding those with previously diagnosed colorectal disease, 11 (44%) patients had colorectal disease (table 1 and table 2 of the supplementary data).

### Bowel preparation and adverse events related to colonoscopy

Bowel preparation was considered good in 27 colonoscopies, average in 42 colonoscopies, poor in 6 colonoscopies and was not available in 2 colonoscopies. Cecal intubation was feasible in 74 patients (95%), and unknown in 1 patient. A polypectomy was performed in all 38 patients with polyps, and a biopsy was performed in 3 patients (1 of the 3 ulcers and in 2 suspected colorectal carcinomas).

Regarding complications, 4 (5%) patients had lower gastrointestinal bleeding. All bleedings occurred after polypectomy for advanced adenomas at a median of 10 days, including 2 cases in patients receiving acenocoumarin (both patients required red cell transfusion) and the other 2 in patients receiving enoxaparin (1 patient also required red cell transfusion). A second colonoscopy



**Figure 1.** Flowchart. <sup>a</sup> The reasons were acute pulmonary edema, bronchoaspiration, and hematologic malignancy, respectively. <sup>b</sup> One patient had a previous urinary tract infection due to *E. faecalis*, 1 patient was a 32-year-old woman with recurrent urinary tract infections, and 1 patient had undergone a hemicolectomy for a colon adenocarcinoma 8 months previously.

**Table 1**  
Colonoscopy findings among all patients with EFIE and according to known or unknown source of infection

	All EFIE N=103	Unknown source n=63	Known source excluding colorectal disease <sup>a</sup> n=32
Colonoscopy performed	78/103 (76)	45/63 (71)	25/32 (78)
Endoscopic findings being potential portal of entry <sup>b</sup>	47/78 (60)	29/45 (64)	11/25 (44)
Colorectal neoplasms	39/47 (83)	26/29 (90)	9/11 (82)
Nonadvanced colorectal adenoma	19	12	6
Advanced colorectal adenoma	18	13	3
Colorectal carcinoma <sup>c</sup>	2	1	0
Nonneoplastic colorectal disease	8/47 (17)	3/29 (10)	2/11 (18)
Colorectal ulcer <sup>d</sup>	3	1	1
Mucosal inflammation	2	1	0
Bleeding vascular lesion	2	0	1
Polyp without histopathological report <sup>e</sup>	1	1	0

EFIE, Enterococcus faecalis infective endocarditis.

Data are expressed as No. or proportion (%).

<sup>a</sup> Regarding digestive source, we included 5 cases with a presumed hepatobiliary source of infection: 2 cholangitis, 2 endoscopic retrograde cholangiopancreatographies, and 1 radiofrequency ablation of hepatocellular carcinoma. We excluded 8 cases of colorectal disease diagnosed during the 3-months prior to endocarditis diagnosis: 3 colitis (1 infectious with a polyp found in the colonoscopy, 1 ischemic with mucosal inflammation and the other also presumed to be ischemic without pathological findings in the colonoscopy), 3 lower gastrointestinal bleedings (1 due to vascular lesions, 1 due to an advanced colorectal carcinoma, and 1 due to a colorectal ulcer), 1 rectal carcinoma, and 1 recent polypectomy.

<sup>b</sup> We excluded uncomplicated diverticula and uncomplicated hemorrhoids as a potential portal of entry of bacteremia.

<sup>c</sup> Both were nonadvanced colorectal carcinomas (T1N0M0).

<sup>d</sup> A biopsy was performed in only 1 ulcer and showed signs of ischemic disease.

<sup>e</sup> Polyp resected but not recovered for histopathological study.

was performed in the 4 patients with bleeding, and endoscopic hemoclips were placed in 3 patients. There were no reported colonic perforations or allergic reactions to sedative medication.

### Comparison of patient characteristics according to the presence or absence of endoscopic findings

Table 2 shows the baseline characteristics of the EFIE patients according to the presence or absence of relevant endoscopic findings. Age and comorbidities were similar. There were no significant differences between the presumed sources of infection, although an unknown origin and gastrointestinal source had more endoscopic findings than the urinary tract. Complications, surgical treatment, and outcomes were similar in the 2 groups, with the exception of the only 2 relapses that both occurred in patients with relevant endoscopic findings and neither had previous surgical indication. One patient received 26 days of intravenous antibiotic therapy and relapsed at day 23 after treatment completion. Colonoscopy was performed during treatment of the first episode of EFIE, and small ulcers were identified in the sigmoid colon. The other patient received 44 days of treatment and relapsed at day 48 after completing antibiotic treatment with negative blood cultures in between. Colonoscopy was performed 14 days after relapse, not during the treatment of the first episode of EFIE, and 3 nonadvanced adenomas and 1 advanced adenoma were identified.

## DISCUSSION

Our results demonstrate that a potential source of bacteremia arising in the bowel is frequent in EFIE, irrespective of whether another source of infection is already suspected; thus, colonoscopy should be considered in these patients.

In IE, it is fundamental to identify and to control the presumed source of the bacteremia to eradicate it and decrease the risk of a new IE episode by the same or a different microorganism.<sup>12</sup> Previous studies have suggested performing a colonoscopy if the microorganism causing the IE may have originated in the gastrointestinal tract,

particularly in patients aged  $\geq 50$  years, as well as in those with a familial history of colonic polyposis.<sup>11,23,24</sup> As the presumed source of infection in EFIE is often unknown,<sup>8,13</sup> colonoscopy could be useful to identify a source. Moreover, as enterococci are found in the gastrointestinal tract and the population at risk of EFIE are older<sup>6,7</sup> and have a higher incidence of colorectal disease,<sup>9</sup> even though there is a clear portal of entry, performing a colonoscopy might be useful to treat potential portals of entry of a new bacteremia episode, as patients with 1 IE episode are at higher risk of a new episode with higher associated mortality.<sup>10</sup>

In our study, colonoscopy was able to identify a presumed origin in 64% of patients without a clear origin, with most of the colonic findings being treatable. In addition, not only patients with an unknown presumed source of infection had relevant endoscopic findings. Forty-four percent of patients with a known origin had endoscopic findings, including patients for whom the presumed source of infection was the urinary tract. Unfortunately, we did not identify characteristics that differentiate these patients with endoscopic findings. Although patients without endoscopic findings could be expected to be younger, we identified no differences in age between the 2 groups. Likewise, the positivity of urinary cultures was not associated with the absence of endoscopic findings. Finally, as patients with colorectal disease, particularly neoplastic disease, might have microscopic gastrointestinal bleeding with subsequent anemia, we analyzed whether patients with colorectal findings had lower levels of hemoglobin, ferritin or transferrin saturation; however, we found no differences.

In our series, there were 80% of men with a median age of 76 years, and it is known that men are at higher age-specific risk for advanced colorectal neoplasm than women<sup>25</sup>; thus, we might suggest that we potentially found the expected number and type of findings in this population. However, a previous screening study of colonic disease performed in Austria in 3098 men aged between 70 and 79 years reported that the prevalence of adenomas was 31.7% and that of advanced adenomas was 10.7%.<sup>9</sup> In our series, 23.1% of patients had advanced adenomas ( $P < .001$ ). Although our study cannot prove causality, the prevalence of colorectal disease in EIEF is high. These findings are in consonance with those of Pericàs et al.<sup>13</sup> However, although we found that the

**Table 2**Demographic features, comorbidities, presumed source of infection, complications, surgical treatment, and outcomes of episodes of *Enterococcus faecalis* IE depending on the presence or absence of relevant endoscopic findings in the colonoscopy

	No endoscopic findings n = 31	Endoscopic findings n = 47	P
<i>Demographics</i>			
Age, y	76 [67-82]	75 [67-82]	.842
Male sex	24 (77)	38 (81)	.713
<i>Comorbidities</i>			
Aged-adjusted Charlson comorbidity index	5 [3-6]	5 [3-6]	.800
Previously diagnosed known colonic disease	7 (23)	15 (32)	.370
Diabetes mellitus	8 (26)	13 (28)	.857
Chronic renal failure	7 (23)	11 (23)	.933
Neoplasm	4 (13)	4 (9)	.706
Transplantation	2 (6)	4 (9)	1
Immunosuppressive therapy	2 (6)	5 (11)	.697
Liver cirrhosis	1 (3)	2 (4)	1
<i>Healthcare-associated infection</i>	14 (45)	22 (47)	.886
<i>Presumed source of infection</i>			
Unknown	16 (52)	29 (62)	.377
Urinary	9 (29)	7 (15)	.130
Gastrointestinal	3 (10)	9 (19)	.344
Catheter-related bacteremia	2 (6)	2 (4)	1
Others <sup>a</sup>	1 (3)	0	.397
<i>Positive urine culture for E. faecalis at the same time as positive blood cultures</i>	5/28 (18)	7/41 (17)	1
<i>Symptom duration, d</i>	32 [9-38]	17 [6-48]	.759
<i>Hemoglobin, g/dL</i>	10.7 [9.7-12]	10.3 [9.4-11.5]	.567
<i>Ferritin, ng/mL<sup>b</sup></i>	274 [134-488]	284 [205-476]	.615
<i>Transferrin saturation, %<sup>c</sup></i>	12 [9-19]	15 [9-25]	.297
<i>Type of IE</i>			
Native valve IE	19 (61)	26 (55)	.601
Prosthetic valve IE	10 (32)	20 (43)	.360
Cardiac implantable electronic device	2 (6)	1 (2)	.560
<i>Heart valve affected</i>			
Aortic	16 (52)	23 (49)	.871
Mitral	8 (26)	16 (34)	.441
Aortic and mitral	5 (16)	8 (17)	.918
Tricuspid	1 (3)	0	.397
Unknown	1 (3)	0	.397
<i>Complications (some patients had &gt; 1 complication)</i>			
Heart failure	8 (26)	19 (40)	.184
Symptomatic embolism	7 (23)	5 (11)	.203
New renal failure	5 (16)	7 (15)	1
Paravalvular complication	5 (16)	7 (15)	1
Stroke	3 (10)	6 (13)	1
<i>Surgery indicated (some patients had &gt; 1 indication)</i>			
Heart failure	9/15 (60)	12/19 (63)	.733
Uncontrolled infection	5/15 (33)	8/19 (42)	.918
Embolic prevention	5/15 (33)	3/19 (16)	.254
Cardiac implantable electronic device infection	2/15 (13)	1/19 (5)	.560
<i>Surgery performed during the active phase of infection (if indicated)</i>	12/15 (80)	14/19 (74)	1
<i>Duration of antimicrobial treatment (d) in all patients</i>	43 [41-46]	42 [41-48]	.829
<i>Duration of antimicrobial treatment (d) in survivors</i>	43 [42-47]	43 [42-49]	.926
<i>Mortality during treatment</i>			
Overall	2/31 (6)	3 (6)	1
Surgery indicated not performed	2/31 (6)	1 (2)	.464
Surgery indicated and performed	0	1 (2)	1
No surgery indicated	0	1 (2)	1



**Table 2** (Continued)Demographic features, comorbidities, presumed source of infection, complications, surgical treatment, and outcomes of episodes of *Enterococcus faecalis* IE depending on the presence or absence of relevant endoscopic findings in the colonoscopy

	No endoscopic findings n = 31	Endoscopic findings n = 47	P
Follow-up in survivors after finishing antibiotic treatment (mo)	6.4 [3.9-9.9]	9.3 [4.6-19.3]	.081
3-months mortality	2/29 (7)	2/44 (5)	1
Surgery during follow-up	0	3/44 (7)	.272
Relapse	0	2/44 (5)	.515

IE, infective endocarditis; IQR, interquartile range.

Data are expressed as No. (%) or median [interquartile range].

<sup>a</sup> The source of infection in this case was an infected abdominal aortic endoprosthesis.<sup>b</sup> Values of ferritin available in 12 and 24 patients, respectively.<sup>c</sup> Values of transferrin saturation available in 12 and 23 patients, respectively.

prevalence of colorectal neoplasms is higher than 50% in patients with EFIE with an unclear focus of infection, we also found that patients with nongastrointestinal sources of infection benefited from a colonoscopy as 44% had relevant endoscopic findings.

### Limitations

This study has several limitations. The main limitations are its retrospective nature and the sample size, inherent in EFIE as it is a serious but rare disease. The source of infection is typically presumed; however, it is very difficult to determine the exact moment in which bacteremia occurs. Although patients with EFIE were included from the moment that a colonoscopy was systematically performed in each participating center, colonoscopy was not performed in all EFIE cases, mainly due to the patient's rapid transfer to another center after surgery was refused or due to comorbidities or poor patient clinical course. Moreover, some colorectal lesions could have gone unnoticed due to inadequate bowel preparation. On the other hand, we compared the percentage of adenomas found in our cohort characterized mainly by men in their late seventies with a noncontemporaneous cohort of patients from a different country undergoing colonoscopy as colorectal screening,<sup>9</sup> which can lead to a bias given that some patients in our cohort had previous colorectal disease, and some had symptoms attributable to the gastrointestinal tract. In this regard, due to the retrospective design of the study, we have no information regarding specific risk factors for colon cancer in our cohort.

### CONCLUSIONS

In conclusion, although to date the recent American and European guidelines recommend colonoscopy only in patients with *S. gallolyticus* bacteremia or IE to determine whether malignancy or other mucosal lesions are present,<sup>16,26</sup> colonic disease is also very common in *E. faecalis* endocarditis, even in patients with a presumed known portal of entry. Consequently, performing a colonoscopy in all EFIE patients, irrespective of the presumed source of infection, could be helpful to avoid a new bacteremia episode (and eventually IE) due to the same or a different microorganism.

### ACKNOWLEDGEMENTS

L. Escolà-Vergé has a Río Hortega contract in the call 2018 Strategic Action Health from *Instituto de Salud Carlos III* of Spanish Health Ministry for 2019 to 2020.

### FUNDING

This research did not receive a specific grant from any funding agency in the public, commercial, or nonprofit sectors.

### CONFLICTS OF INTEREST

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

#### WHAT IS KNOWN ABOUT THE TOPIC?

- *Enterococcus faecalis* is the third cause of IE, which mainly affects old patients with comorbidities, a population with a higher incidence of colorectal disease.
- Five percent of patients with IE will have an additional episode of IE with a higher mortality risk, and therefore identifying the portal of entry and treating it are important to lower the risk of a new IE episode.
- A recent retrospective study showed that patients with EFIE of unknown origin had a higher prevalence of colorectal lesions (31 of 61, 50.8%) than those with EFIE with a known origin (1 of 6, 16.7%); however, colonoscopy was not systematically performed in all patients, particularly not in those with a known origin.

#### WHAT DOES THIS STUDY ADD?

- Colonic disease is very common in *E. faecalis* endocarditis, even in patients with a presumed known portal of entry.
- Sixty percent of *E. faecalis* endocarditis patients undergoing a colonoscopy had endoscopic findings indicating a potential source of bacteremia. Of these patients, 83% had neoplastic colorectal disease.
- In the subgroup of patients with a presumed known source of infection, colonoscopy indicated colorectal disease in 44%.
- Performing a colonoscopy in all EFIE patients, irrespective of the presumed source of infection, could help to avoid a new bacteremia episode by the same or a different microorganism.

## APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at <https://doi.org/10.1016/j.rec.2019.07.007>.

## REFERENCES

- Bennett JE, Dolin R, Blaser MJ. *Mandell Douglas and Bennett's Principles and Practice of Infectious Diseases 8th Edition*. 2015;2327–2337.
- Fisher K, Phillips C. The ecology, epidemiology and virulence of *Enterococcus*. *Microbiology*. 2009;155:1749–1757.
- Klein RS, Recco RA, Catalano MT, Edberg SC, Casey JI, Steigbigel NH. Association of *Streptococcus bovis* with carcinoma of the colon. *N Engl J Med*. 1977;297:800–802.
- Boleij A, van Gelder MMHJ, Swinkels DW, Tjalsma H. Clinical importance of *Streptococcus gallolyticus* infection among colorectal cancer patients: systematic review and meta-analysis. *Clin Infect Dis*. 2011;53:870–878.
- Murdoch DR. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: The International Collaboration on Endocarditis—Prospective Cohort Study. *Arch Intern Med*. 2009;169:463.
- Anderson DJ, Murdoch DR, Sexton DJ, et al. Risk factors for infective endocarditis in patients with enterococcal bacteremia: a case-control study. *Infection*. 2004;32:72–77.
- McDonald JR, Olaison L, Anderson DJ, et al. Enterococcal endocarditis: 107 cases from the international collaboration on endocarditis merged database. *Am J Med*. 2005;118:759–766.
- Fernández-Hidalgo N, Almirante B, Gavalda J, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating *Enterococcus faecalis* infective endocarditis. *Clin Infect Dis*. 2013;56:1261–1268.
- Ferlitsch M, Reinhart K, Pramhas S, et al. Sex-specific prevalence of adenomas, advanced adenomas, and colorectal cancer in individuals undergoing screening colonoscopy. *JAMA*. 2011;306:1352.
- Alagna L, Park LP, Nicholson BP, et al. Repeat endocarditis: analysis of risk factors based on the International Collaboration on Endocarditis – Prospective Cohort Study. *Clin Microbiol Infect*. 2014;20:566–575.
- Delahaye F, M'Hammedi A, Guerpillon B, et al. Systematic search for present and potential portals of entry for infective endocarditis. *J Am Coll Cardiol*. 2016;67:151–158.
- Botelho-Nevers E, Thuny F, Casalta JP, et al. Dramatic reduction in infective endocarditis-related mortality with a management-based approach. *Arch Intern Med*. 2009;169:1290.
- Pericàs JM, Corredoira J, Moreno A, et al. Relationship between *Enterococcus faecalis* infective endocarditis and colorectal neoplasm: preliminary results from a cohort of 154 patients. *Rev Esp Cardiol*. 2017;70:451–458.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
- Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30:633–638.
- Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) Endorsed by: European Association of Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36:3075–3128.
- Fernández-Hidalgo N, Almirante B, Tornos P, et al. Contemporary epidemiology and prognosis of health care-associated infective endocarditis. *Clin Infect Dis*. 2008;47:1287–1297.
- Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and by the International Society of Chemotherapy (ISC) for Infection and Cancer *Eur Heart J*. 2009;30:2369–2413.
- Kellum JA, Levin N, Bouman C, Lameire N. Developing a consensus classification system for acute renal failure. *Curr Opin Crit Care*. 2002;8:509–514.
- Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1–45.
- Rembacken B, Hassan C, Riemann JF, et al. Quality in screening colonoscopy: position statement of the European Society of Gastrointestinal Endoscopy (ESGE). *Endoscopy*. 2012;44:957–968.
- Strum WB. Colorectal Adenomas. *N Engl J Med*. 2016;374:1065–1075.
- Silva EC, de F, Montalvão CR, Bonafé S. Infectious Endocarditis from *Enterococcus faecalis* associated with tubular adenoma of the sigmoid colon. *Case Rep Infect Dis*. 2017;2017:1–4.
- Khan Z, Siddiqui N, Saif MW. *Enterococcus faecalis* infective endocarditis and colorectal carcinoma: case of new association gaining ground. *Gastroenterol Res*. 2018;11:238–240.
- Brenner H, Hoffmeister M, Arndt V, Haug U. Gender differences in colorectal cancer: implications for age at initiation of screening. *Br J Cancer*. 2007;96:828–831.
- Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2015;132:1435–1486.