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ORIGINAL ARTICLE

**Non-HACEK gram-negative bacilli endocarditis: A multicentre retrospective case-control study**

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**Running head:** Non-HACEK gram-negative bacilli endocarditis

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## ABSTRACT

**Background:** Infective endocarditis (IE) caused by non-HACEK gram negative bacilli (GNB) are poorly characterized and may be emerging as a consequence of medical progress.

**Methods:** We performed an observational retrospective case-control study. Cases were non-HACEK GNB IE, definite or possible (modified Duke criteria), diagnosed in adults between 2007 and 2020 in 6 French referral hospitals. Two controls were included for each case (IE due to other bacteria, matched by sites and diagnosis date).

**Results:** Non-HACEK GNB were identified in 2.4% (77/3230) of all IE during the study period, with a mean age of  $69.2 \pm 14.6$  years, and a large male predominance (53/77, 69%). Primary pathogens were *Escherichia coli* (n=33), *Klebsiella* sp. (n=12), and *Serratia marcescens* (n=9), including 8 (10%) multidrug-resistant GNB. Compared to controls (n=154: 43% *Streptococcus* sp., 41% *Staphylococcus* sp., 12% *Enterococcus* sp.), non-HACEK GNB IE were independently associated with intravenous drug use (IVDU, 8% vs 2%,  $P=0.003$ ), active neoplasia (15% vs 6%,  $P=0.009$ ), haemodialysis (9% vs 3%,  $P=0.007$ ) and healthcare-associated IE (36% vs 18%,  $P=0.002$ ). Urinary tract was the main source of infection (n=25, 33%) and recent invasive procedures were reported in 29% of cases. Non-HACEK GNB IE were at lower risk of embolism (31% vs 47%,  $P=0.002$ ). One-year mortality was high (n=28, 36%). Comorbidities, particularly malignant hemopathy and cirrhosis, were associated with increased risk of death.

**Conclusions:** Non-HACEK GNB are rarely responsible for IE, mostly as healthcare-associated IE in patients with complex comorbidities (end-stage renal disease, neoplasia), or in IVDUs.

**Keywords.** Endocarditis; Gram-negative bacilli; intravenous drug use; healthcare-associated;

*Escherichia coli*

## **Introduction**

Infective endocarditis (IE) is a life-threatening disease, mostly related to gram-positive cocci: staphylococci, streptococci, and enterococci being responsible for 80%–90% of IE in contemporary studies (1,2). Indeed, although gram-negative bacilli (GNB) are commonly encountered in bacteremia, they have a low propensity to affect cardiac valves, with the notable exception of the HACEK group: *Haemophilus* sp., *Aggregatibacter* sp., *Cardiobacterium* sp., *Eikenella* sp., and *Kingella* sp (3).

Non-HACEK GNB IE is rare (1.8-5.3 % of all IE), and still poorly characterized (2,4–7). Initial reports documented that intravenous drug use (IVDU) is a major risk factor (8–10). More recent studies suggested that non-HACEK GNB IE may be an emerging disease, especially in elderly or immunocompromised patients, often as healthcare-associated infections (4,5,11–13). Of note, non-HACEK GNB responsible for IE are often not susceptible to empirical antimicrobial regimens recommended by international guidelines (14,15), as they primarily target gram-positive cocci. Moreover, the emergence of multidrug-resistance (MDR) disproportionately affects GNB, especially for healthcare-associated infections, which is of particular concern for difficult-to-treat infections such as IE (16–18).

First, we aimed to better characterize the epidemiology, characteristics, and outcome of non-HACEK GNB IE, and identify the most salient features compared to other IE, through a case-control contemporary multicentre cohort. Secondary objectives were to compare patients' outcome in cases and controls, and to assess factors related to mortality in non-HACEK GNB IE.

## **Methods**

### ***Design and patients***

This observational retrospective case-control study was conducted in 6 western France hospitals: four teaching hospitals with an endocarditis team (Angers, Nantes, Rennes and Tours) and two referral hospitals with expertise in IE, but no cardiac surgery in-site (Quimper and Vannes), with an overall population catchment area of 4 million inhabitants.

Patients with IE were identified using the national hospital discharge database (PMSI), except for Rennes and Nantes hospitals, where a prospective electronic database of all IE cases has been maintained since, respectively, 1990 and 2013. Medical files were screened retrospectively to select all cases of definite or possible IE according to modified Duke criteria (19). The date of diagnosis as well as pathogen(s) involved were collected through this first step. We included all adult patients ( $\geq$  18 years old) with non-HACEK GNB IE diagnosed between January 2007 and April 2020. In 2 sites, period enrolment was shorter: 2007-2018 (Tours), and 2007-2010 then 2018-2020 (Angers), due to lapses in database. For each site, all cases were collected during the study periods. We excluded polymicrobial IE due to both GNB and gram-positive.

Two controls were included for each case, with the following criteria: bacterial IE not due to non-HACEK GNB, diagnosed in the same site immediately before and after each case. A control could only be included once.

### ***Data collection***

Data on comorbidities, intravenous drug use, recent healthcare contact, clinical and microbiological variables, management, and outcome until one-year follow-up, were collected on a standardized questionnaire from medical charts, after being anonymized. When one-year follow-up was not available in medical files, one investigator contacted the general practitioner. The data collected were entered into a secure database approved by the National Committee on Data Processing and Freedoms (CNIL #920018).

### ***Definitions***

Definitions, outcomes, and variables were determined *a priori*. Healthcare-associated infection was defined as previously reported (20): either nosocomial, ie first symptoms developed >48 h after hospital admission, and up to 30 days after discharge (up to 1 year after implantation of any foreign device), or non-nosocomial healthcare-associated infection, ie symptoms onset within 30 days after any healthcare procedures, but not fulfilling criteria for nosocomial infection. In addition, IE in patients who underwent invasive procedures, ie any surgical or exploratory activity in which the body is pierced by a device or instrument within 60 days before first symptoms, was also classified as healthcare-associated. Intracardiac devices included permanent pacemakers or cardioverter-defibrillators. The Charlson comorbidity index (21) was calculated retrospectively using comorbidities reported on admission, and was not age-adjusted. We collected data on antibacterial treatments received after IE was suspected, and categorized empirical treatment according to drug-susceptibility testing results, as ‘appropriate’ when it was active in vitro on the non-HACEK BGN responsible for IE, or inappropriate otherwise. Relapse was defined as a new diagnosis of IE caused by the same microorganism, with similar drug-susceptibility profile, within 12 months after the index IE. Only one episode per patient could be enrolled, to avoid duplicates.

### ***Ethics***

The study was approved by the French Ethical Committee of Research in Tropical and Infectious Diseases (CER-MIT, no. 2019-0905), and the Expert Committee for Research, Studies and Evaluations in the Field of Health (CEREES, no. TPS 311-648). Patients were informed by letter about the study, and could refuse to participate, but written informed consent was waived.

### ***Statistical analysis***

Quantitative variables were expressed as mean  $\pm$  standard deviation, or as median with interquartile range [IQR]. Qualitative variables were expressed by numbers (%). Continuous variables were compared using the Mann-Whitney or the Student test as appropriate. Categorical variables were compared using the  $\chi^2$  test with Yates correction or the Fisher exact test, as appropriate. Multivariate

analyses were performed using exact logistic regression. Variables with  $P$  value  $<0.2$  in univariate analysis, and variables associated with non-HACEK GNB IE or with outcome in the literature were included in the multivariate model. A step-by-step descendant procedure selected variables until only variables with a significant effect remain in the final model. The survival curves were performed by the Cox model and compared by a log-rank test. Significance was set at  $P<0.05$ . Statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, North Carolina).

## Results

Of the 3,230 patients with possible or definite IE managed in participating sites during the study period, 77 (2%) had endocarditis due to non-HACEK GNB, with a mean age of  $69.2 \pm 14.6$  years, and male predominance (53/77, 69%). Six patients (8% of non-HACEK GNB IE) reported recent IVDU.

## Microbiology

Table 1 details the microbiology of non-HACEK GNB IE. Main pathogens were *Escherichia coli* (n=33, 43%), *Klebsiella sp.* (n=12, 16%) and *Serratia marcescens* (n=9, 12%). One patient (1%) had IE due to two concomitant bacteria (*Proteus sp.* and *Escherichia coli* IE). Eight cases (10%) were MDR: extended-spectrum beta-lactamase (ESBL) producing *Enterobacterales* (n=6), carbapenem-resistant *S. marcescens* (n=1) and MDR *Pseudomonas aeruginosa* (n=1). Microbiological documentation was mostly obtained by blood cultures (n=75, 97%). For the 12 patients who underwent valve surgery, non-HACEK GNB was documented on cardiac valves in 9, by valve cultures (n=5), or 16S-rRNA PCR (n=4, including 2 with blood cultures-negative IE). The median number of positive blood cultures was 3 sets [1-4]. Two patients who received antibiotics before blood cultures sampling had blood culture-negative IE and the diagnosis was obtained through PCR on heart valves, and 3 patients had only one set of positive blood cultures (all with *E. coli* IE).

Controls (n=154) were streptococcal IE (n=66, 43%), including 22 *Streptococcus gallolyticus*, staphylococcal IE (n=63, 41%), including 48 *Staphylococcus aureus*, enterococcal IE (n=18, 12%), and miscellaneous (n=7, 5%): HACEK (n=2), *Cutibacterium acnes* (n=2), *Corynebacterium striatum* (n=2), and *Lactobacillus* sp. (n=1).

### **Comparison of non-HACEK GNB IE and controls (tables 2 and 3)**

Most patients with non-HACEK GNB IE had acute endocarditis, with time from symptoms onset to diagnosis <2 weeks and <1 week in, respectively, 73% (n=56) and 56% (n=43). Main findings at diagnosis were fever (n=68, 88%), and heart failure (n=26, 34%). IE primarily affected the mitral (n=35, 46%), and the aortic valve (n=34, 44%). Six patients had right-sided IE, and 8 had pluri-valvular IE.

As compared with controls (Table 2), non-HACEK GNB IE was more common in patients with malignancies (especially abdominal), high Charlson comorbidity index, presumed genitourinary source of IE, central venous catheter, invasive procedure within 60 days and healthcare-associated IE. On multivariate analysis, malignancies, IVDU and haemodialysis remained independently associated with non-HACEK GNB IE (Table 3). Non-HACEK GNB IE were associated with higher risk of heart failure at diagnosis (2.78 [1.11; 6.95], P=0.29), but lower risk of embolic event (0.21 [0.08; 0.56], P=0.002).

### **Treatment of non-HACEK GNB IE**

Fifty-six patients (73%) with non-HACEK GNB IE received appropriate empirical treatment, as compared to 139 (90.3%) controls (P=0.067), and 58 (76%) received an active antibacterial regimen within 14 days after symptoms onset. They all received at least one  $\beta$ -lactam, 52 (68%) received an aminoglycoside and 33 (43%) a fluoroquinolone. Nineteen patients (25%) received a carbapenem, as empirical treatment (n=8), or based on drug-susceptibility testing (n=11). Fifty-eight patients (75%) were treated with dual therapy, and 6 (8%) with a three-drug regimen; 25 patients (33%) remained



on combination therapy throughout IE treatment. The median duration of IE treatment was 42 days [31-46].

Only 12 patients (16%) underwent cardiac surgery during the acute phase of IE, because of severe heart failure (n=8), and/or severe valvular regurgitation (n=6). Valve replacement was performed in 9 (8 bioprosthesis, 1 mechanic valve), and valve repair in 3. Among the 11 patients with intracardiac device-related IE, devices were extracted in 9, of whom 6 required implantation of a new device.

### ***Outcome and prognostic factors***

Three patients with non-HACEK GNB IE relapsed, respectively within 1 month, 3-6 months (patient who underwent surgery), and after 6 months of antibacterial treatment discontinuation. One-year mortality was 36% (n=28), including 14 deaths during antibacterial treatment. There was a trend towards better survival in patients with IE due to other bacteria, as compared to IE due to non-HACEK GNB (Figure 1A). Among patients with non-HACEK GNB IE, Charlson comorbidity index (1.2 per one point-increment [1.03-1.39], P=0.018), cirrhosis (aOR 5.03 [2.04-12.4], P=0.004) and malignant hemopathy (aOR 3.63 [1.18-11.14], P=0.024) were independent predictors of death. There was a trend towards better survival in patients with non-HACEK GNB IE who underwent cardiac surgery, as compared to those who didn't (Figure 1B).

### **Discussion**

The primary findings of this contemporary multicentre case-control study on non-HACEK GNB IE are the followings. First, non-HACEK GNB were responsible for a small proportion of IE (77/3,230, 2%), despite concerns that non-HACEK GNB IE may emerge as a consequence of medical progress. Second, in a country with free access to needle-exchange programs, IVDU was responsible for a small subset of non-HACEK GNB IE (8%). Third, *E. coli*, *K. pneumoniae* and *S. marcescens* were the main non-

HACEK GNB responsible for IE. Fourth, as compared to IE related to other bacteria, non-HACEK GNB IE were more likely to be healthcare-associated, in patients with neoplasia or haemodialysis, with acute heart failure on admission. Fifth, despite early diagnosis and appropriate antibacterial treatment in most cases, the prognosis remains dismal, with one-year mortality at 36%. This may be related to high prevalence of underlying comorbidities, including malignancies, sub-optimal empirical treatment, and to the low proportion of patients who underwent cardiac surgery (16%).

This cohort of 77 non-HACEK GNB IE is the largest to date, followed by the Prospective Multicenter Italian Endocarditis Study (PMIES) cohort (n=58) (13), and the International Collaboration on Endocarditis (ICE) cohort (n=49) (4). Our findings are in line with previous cohorts regarding increased risk in patents with comorbidities (especially haemodialysis and malignancies), with recent invasive procedure and, to a lesser extent, IVDUs. We confirmed the high prevalence of acute heart failure at diagnosis, and the dismal prognosis. Our cohort differs from previous cohorts regarding the low proportion of non-fermenting GNB IE: 9%, vs 19-30% in most cohorts of non-HACEK GNB IE (4,5,13,22,23), up to 78% in USA cohorts (24–26). This may be in part related to large differences in the proportion of IVDUs among non-HACEK GNB IE worldwide, in line with striking heterogeneities in harm reduction policies and access to needle-exchange programs: Indeed, more than one third of non-HACEK GNB IE in USA cohorts occur in IVDUs (8,26), as compared to <10% in other cohorts (4,5,22), as in our. Of note, *S. marcescens* was the main non-HACEK GNB responsible for IE among IVDUs in our cohort.

Contrarily to previous studies (4,13,23), we found no association between non-HACEK GNB IE and diabetes, immunosuppressive therapy, or intracardiac devices, despite high baseline prevalence (respectively 26%, 16% and 14%), as these conditions were also common in controls. The low proportion of non-fermenting GNB in our cohort, which represent most non-staphylococcal infections of intracardiac devices (27), may also play a role. To our knowledge, our study would be the first to report haemodialysis as an independent risk factor for non-HACEK GNB IE, more common

than IVDUs in our cohort, while haemodialysis patients represented <2% of non-HACEK GNB IE in previous cohorts (13,22).

On multivariate analysis, only Charlson comorbidity index, cirrhosis and malignant hemopathy were independently associated with mortality. Unfortunately, none of them is modifiable by the time the patient is admitted. However, the low proportion of patients who underwent cardiac surgery in our cohort (16%), despite large indications according to international guidelines (14,15), suggests that prognosis may be improved by expanded access to cardiac surgery. However, this was not significantly different in controls (operated patients among controls: 26%,  $P=0.07$ ). In addition, among the 65 patients with non-HACEK GNB IE who were not operated, 10 (15%) presented with shock, and 33 (51%) were older than 75 years. Although these are not absolute contraindications for cardiac surgery, it may have contributed to low proportion of cardiac surgery in this group.

The reasons why non-HACEK GNB are so rarely associated with IE, despite they represent a substantial proportion of community-acquired and hospital-acquired bacteremia worldwide, have been investigated through several landmark studies. Two main factors may explain this paradox: i) non-HACEK GNB, especially *Enterobacterales*, are much more susceptible to serum bactericidal activity, as compared to Gram-positive cocci commonly associated with IE; ii) in addition, most non-HACEK GNB have a low propensity to adhere to damaged endothelium, with the exception of *Salmonella* spp. (28,29). This has been dramatically illustrated by experimental models of IE, showing that an inoculum of at least  $10^7$  CFU/mL of *E. coli* are required to colonize sterile vegetations, whereas  $10^4$  CFU/mL is usually enough for *S. aureus* (30).

Our study has limitations. Firstly, as data were collected retrospectively, it has potential biases and confounding factors. Secondly, this study was underpowered to detect risk or prognostic factors in certain subgroups, due to limited sample size. Thirdly, as this study was conducted in six sites over a large period (2007-2020), there may be heterogeneity in practices. However, this study was performed in referral centres, where patients were managed by a multidisciplinary team,

according to international guidelines. Lastly, our findings may not be generalizable to other geographical areas. Our study also has strengths: This is the largest cohort of non-HACEK GNB IE to date, and we appaired controls by centre and diagnosis date to prevent biases related to changes in practices. Collection was exhaustive over the period to limit declaration biases, and we collected data on one-year outcome for all patients. This study adds a brick in the wall for better knowledge about this rare cause of IE, which may contribute to earlier diagnosis and better management.

In conclusion, non-HACEK GNB are responsible for <5% of all IE, mostly as healthcare-associated IE due to *Enterobacterales*, in patients with complex comorbidities (end-stage renal disease, neoplasia), or in IVDUs. Although not recommended for all patients with non-HACEK GNB bacteremia, echocardiography should be performed with a lower threshold in patients with these risk factors.

## TABLES AND FIGURES

**Table 1:** Microbiology of non-HACEK gram-negative bacilli endocarditis

	No. of patients (% of total)	One-year mortality n (%)
<b>Enterobacterales</b>	<b>69 (90%)</b>	
<i>Escherichia coli</i>	33 (43%)	9 (27%)
<i>Klebsiella</i> sp.	12 (16%)	4 (33%)
<i>Serratia marcescens</i>	9 (12%)	3 (33%)
<i>Enterobacter</i> sp.	6 (8%)	3 (50%)
<i>Citrobacter</i> sp.	2 (3%)	0
<i>Hafnia alvei</i>	2 (3%)	2 (100%)
<i>Morganella morganii</i>	1 (1%)	1 (100%)
<i>Proteus vulgaris</i>	1 (1%)	1 (100%)
<i>Providencia stuartii</i>	1 (1%)	0
<i>Raoultella ornitholytica</i>	1 (1%)	1 (100%)
<b>Non-fermenting</b>	<b>7 (9%)</b>	
<i>Pseudomonas aeruginosa</i>	5 (7%)	4 (80%)
<i>Acinetobacter ursinguii</i>	1 (1%)	0
<i>Schewanella algae</i>	1 (1%)	0
<b>Others non-HACEK <sup>§</sup></b>	<b>3 (4%)</b>	
<i>Campylobacter fetus</i>	2 (3%)	0
<i>Legionella pneumophila</i>	1 (1%)	0
<b>Co-infections</b>	1 (1%)	
<b>Multidrug-resistance *</b>	8 (10%)	

<sup>§</sup> HACEK group: *Haemophilus* sp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* sp.

\* Acquired resistance in at least two classes of antibacterial agents

**Table 2:** Comparison between patients with non-HACEK gram-negative bacilli endocarditis, and patients with endocarditis due to other bacteria

	Non-HACEK gram-negative bacilli (n=77)	Other bacteria (n=154)	P value
<b>Demographic features</b>			
Age, years	69.2 ± 14.6	70.0 ± 13.1	.68
Sex, male	53 (69)	112 (72.7)	.54
<b>Comorbidities</b>			
Intravenous drug user	6 (8)	3 (2)	.063
Charlson comorbidity index	2.4 ± 2.3	1.8 ± 2	.039
Immunocompromised *	48 (62)	79 (51)	.11
Diabetes	20 (26)	39 (25)	.99
Haemodialysis	7 (9)	5 (3)	.06
Malignancies	11 (15)	9 (6)	<b>.039</b>
Cirrhosis	8 (10)	15 (10)	.90
<b>Risk factors for endocarditis</b>			
High risk **	9 (12)	28 (19)	.32
Previous episode of endocarditis	6 (8)	10 (7)	.71
Prosthetic valve	22 (29)	45 (29)	1.0
<b>Type of endocarditis</b>			
Healthcare-associated	28 (36)	27 (18)	<b>.0017</b>
Prosthetic valve	18 (23)	38 (25)	.98
Intracardiac device-related	11 (14)	14 (9)	.23
<b>Presumed source of infection</b>			<b>&lt; .0001</b>
Genitourinary tract	25 (33)	1 (1)	
Gastrointestinal tract	13 (17)	19 (12)	
Oral / ear, nose and throat	3 (4)	18 (12)	
Skin	10 (13)	34 (22)	
Other or Unknown	26 (34)	82 (53)	
Central venous catheter	14 (18)	10 (7)	<b>.006</b>
Invasive procedure within 60 days before symptoms onset:	22 (29)	26 (16)	<b>.012</b>
Urinary procedure	3	1	
Digestive procedure	5	2	
Cardiac procedure	8	9	
<b>Complications</b>			
Abscess	4 (5)	20 (13)	.067
Valve mutilation	19 (26)	38 (25)	.95
Conduction abnormality	3 (4)	10 (7)	.55
Congestive heart failure	12 (16)	33 (21)	.29
Spondylodiscitis	5 (7)	28 (18)	<b>.017</b>
Embolitic events	24 (31)	72 (47)	<b>.023</b>
Stroke	19 (25)	38 (25)	.71
Septic shock	15 (20)	20 (13)	.19
<b>Outcome</b>			
One-year mortality	28 (36)	38 (25)	.064
Relapse	3 (5)	9 (6)	.76

\* Included: Immunosuppressive therapy, HIV infection, solid organ transplant, malignant hemopathy

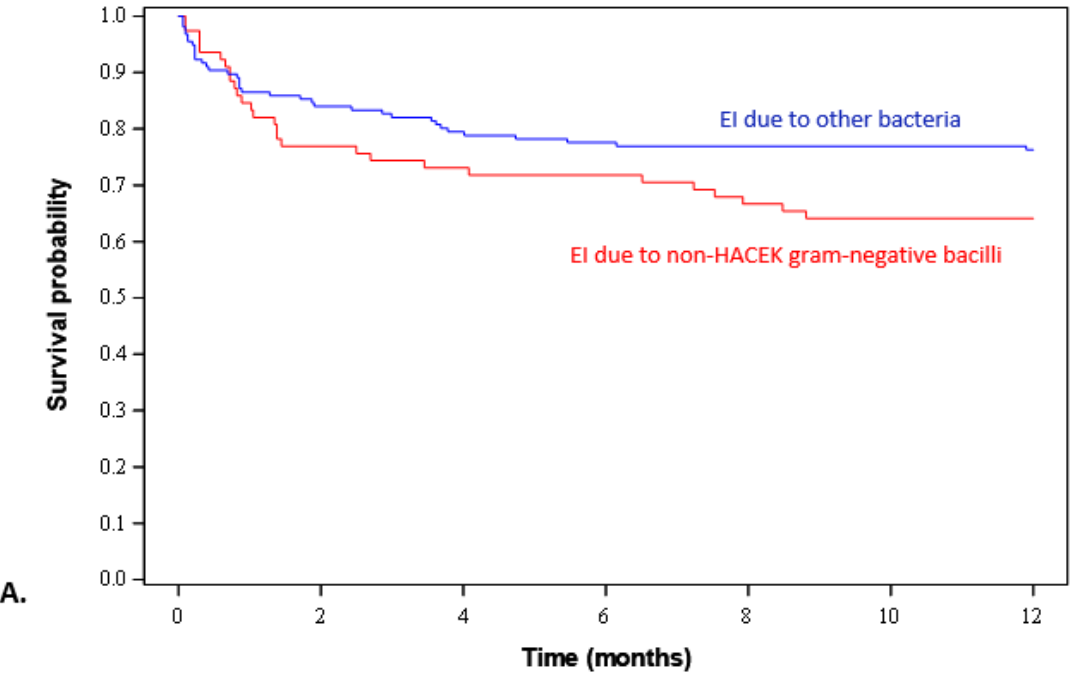
\*\* according to European guidelines (14)

**Table 3:** Factors associated with non-HACEK gram-negative bacilli endocarditis in multivariate model

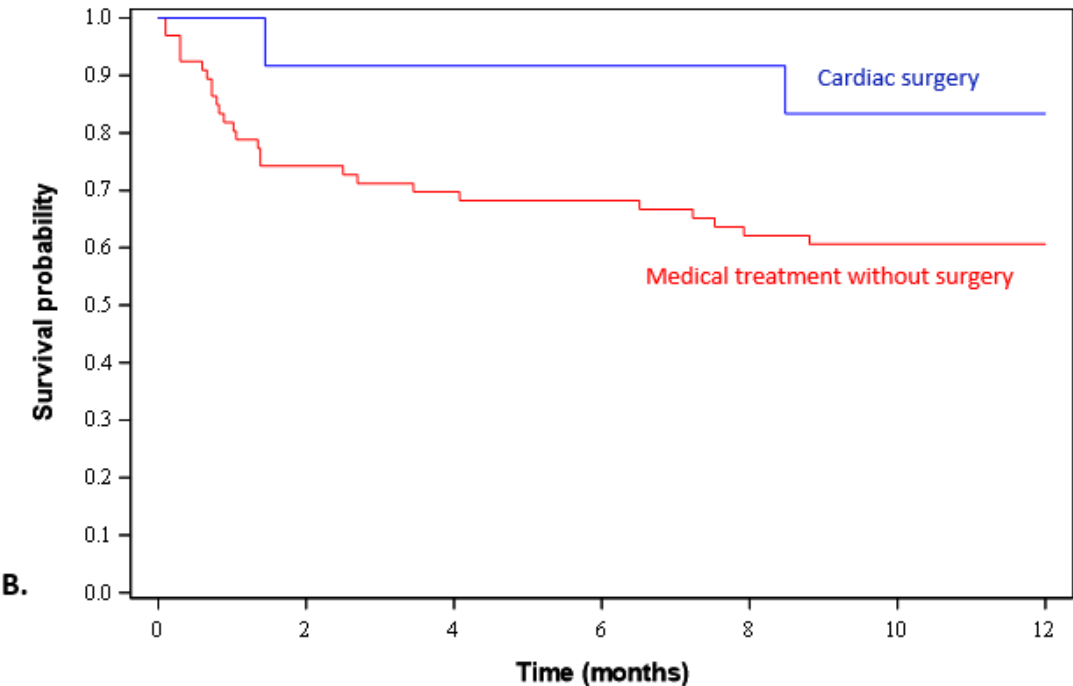
<b>Variables</b>	<b>aOR * [IC95%]</b>	<b>P value</b>
Malignancies	5.63 [1.54; 20.51]	.009
Invasive procedure within 60 days	3.66 [1.29; 10.38]	.015
Haemodialysis before endocarditis	9.36 [1.85; 47.34]	.007
Intravenous drug use	31.75 [4.62 ; 218.35]	.0004
Non genitourinary source of infection	0.01 [0.00; 0.14]	< .0001

\* aOR, adjusted odds ratio

**Figure 1:** Survival curves: **A.** non-HACEK gram-negative bacilli (GNB) infective endocarditis (IE) vs IE due to other bacteria ( $P=0.1946$ , HR 1.41 [0.84-2.39]); **B.** Among patients with non-HACEK GNB IE, medical treatment vs cardiac surgery ( $P=0.29$ )



IE due to non-HACEK GNB	77	60	57	56	52	50	50
IE due to other bacteria	154	129	122	119	118	118	117



Medical treatment	65	54	49	47	46	45	45	44	41	40	40	40	40
Cardiac surgery	12	12	11	11	11	11	11	11	11	10	10	10	10



**Author contributions**

MG, MS and PT designed the study. MS, DB, CD, JPT, AL and MR took care of the patients, identified cases and controls, and collected clinical data. CP collected and analysed microbiological data. MG, MS and PT analysed data and drafted the manuscript. All authors critically reviewed the manuscript and approved the version submitted

**Transparency declaration**

All authors declared that they have no potential conflict of interest related to the manuscript.

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