Infective Endocarditis Due to Non-HACEK Gram-Negative Bacilli: Clinical Characteristics and Risk Factors from A Prospective Multicenter Brazilian Cohort

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Abstract

Background

The aim of this study is to describe the clinical characteristics of patients with infective endocarditis (IE) due to non-HACEK Gram-negative bacilli (NGNB) and the risk factors associated with mortality in a large multicentre cohort.

Methods

This prospective observational study included consecutive patients with definitive IE diagnosed according to the modified Duke criteria in Brazil between 2006 and 2019. Patients with blood or heart valve cultures positive with NGNB were identified and studied.

Results

Of 1154 adult patients with definite IE enrolled, 38 (3.29%) had IE due to NGNB. Median age was 57 (IQR, 43-69) years. Most common etiologies were *Pseudomonas aeruginosa* and *Klebsiella* spp. (8 episodes, 21% each). IE was associated with a higher prevalence of embolic events 21/38(72.4%). Chronic renal failure 18/38(44.7%), prosthetic valves 19/38(50%) and device-related IE 6/8(15.8%) were common. Recent healthcare exposure was found in 52.6% and a central venous catheter (CVC) in 13/38(34.2%). Overall mortality was 19/38(50%). Indwelling CVC (OR 5.93; 95% CI, 1.29 to 27.3; $p = 0.017$), haemodialysis (OR 16.2; 95% CI, 1.78 to 147; $p = 0.008$) and chronic kidney disease (OR 4.8; 95% IC, 1.2 to 19.1, $p = 0.049$) were identified as risk factors associated with mortality, but not multidrug-resistant microorganisms.

Conclusions

The rate of IE due to NGNB was similar to that in previous studies. *Enterobacterales* and *P. aeruginosa* were the most common etiologies. NGNB IE was associated with the presence of central venous catheters, prosthetic valves, intracardiac devices and haemodialysis and had a high mortality rate.

Background

Infective endocarditis (IE) is a serious infection with increasing incidence in recent decades and high rates of morbidity and mortality. In recent years, infections caused by Gram-negative bacteria are on the rise, with a greater dispersion of these bacteria in health care-related settings, with high mortality rates and high costs to health-care institutions [1–3].

The reported incidence of Gram-negative IE ranges from 1.3 to 10%. Non-HACEK Gram-negative bacilli (NGNB) (species other than *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* species) are uncommon causes of IE [1, 3–5].

Due to its infrequent occurrence, estimates of NGNB IE prevalence are variable and depend on the study period and geographic location. In the 90's, NGNB IE was described in association with intravenous drug use [5–7].

More recently, studies have shed new light on the contemporary epidemiology of NGNB endocarditis and they have shown it represents approximately 2 to 6% of all cases of IE. The incidence of Gram-negative infections in general is growing. Main risk factors for IE due to NGNB include liver cirrhosis, heart valve prosthesis and urinary-source bacteraemia. Hospitalization and medical procedures, such as implantation of endovascular devices and urinary tract procedures have been strongly associated with NGNB IE [1, 8–13].

Data on NGNB IE is limited to case reports and case series; so far, no study on the issue has been reported in Brazil. The objective of this study was to describe the clinical features of NGNB IE in a multicentre cohort and risk factors associated with IE mortality.

Methods

Patients and study design

This prospective observational study included consecutive adult patients with definite IE according to the modified Duke criteria identified in 4 centers in Brazil. Cases of NGNB from these cohorts between January 2006 and December 2019 were retrospectively reviewed. Centers participating in this study were Instituto Nacional de Cardiologia, Hospital Universitário Clementino Fraga Filho, Hospital Universitário Pedro Ernesto, all located in Rio de Janeiro city, and Instituto do Coração located in São Paulo city. The study was approved by each local Ethics Committee.

Data collection

Data on patient demographics, risk factors, comorbidities, clinical manifestations, echocardiography and microbiological data, treatment and complications were collected retrospectively from each institutional database.

The diagnosis of IE was established according to the modified Duke Criteria [2]. All patients 18 years or older with IE due to NGNB from sites that met the criteria were included.

Information was recorded about the presence of a central intravascular access device in the 30 days preceding the diagnosis of IE, of cardiac implantable electronic devices (CIEDs) in the 60 days prior to diagnosis and heart surgery in the year before diagnosis.

IE was classified as native valve endocarditis (NVE), prosthetic valve endocarditis (PVE), or CIED-related.

Clinical cases were categorized as community acquired (CoA), nosocomially-acquired (NoA) and non-nosocomial health care-associated (HCA). NoA endocarditis was defined as IE developing in a patient hospitalized for more than 48 h before onset of signs and symptoms consistent with IE. HCA was defined as IE diagnosed based on signs and symptoms appearing within 48 h before hospital admission in a patient with prior health care contact. Acute and subacute IE was defined as an infection with onset of signs and symptoms for less or more than 4 weeks respectively and persistent bacteraemia was defined as the persistence of positive blood cultures after 3 days of appropriate antibiotic therapy [14]. Worsening heart failure was defined as clinical and echocardiographic deterioration of heart function.

The microbiological data with identification and resistance pattern were performed using automated methods such as BacT/Alert (bioMérieux; Marcy-L'Étiole, France) and Vitek 2 (bioMérieux). ESBL-producing (extended-spectrum beta-lactamase) bacteria were defined as microorganisms non-susceptible to third and fourth cephalosporin and MDR (multidrug resistant) bacteria as microorganisms non-susceptible to at least one agent in three or more different antimicrobial categories [15, 16].

Statistical Analysis

Continuous variables are presented as medians with 25th and 75th percentiles. Categorical variables are presented as frequencies and percentages of the specified group. Univariate comparisons were made with the χ^2-test. Proportion test (Fisher's exact test) was applied to analyze risk factors associated with mortality among patients with NGNB endocarditis.

Statistical analyses were performed using commercially available software (R, version 3.5.3 and Jamovi, version 1.1.6.0, Sydney, Australia).

Results

Of the 1,154 patients included, 38 (3.29%) had definitive NGNB endocarditis according to the modified Duke criteria during the study period. There was a male predominance (65.8%, 25/38) and median age was 57 (IQR 43-69) years. The baseline characteristics with comorbidities and predisposing factors are summarized in the table 1. Heart failure (HF) was the most common comorbidity (50%, 19/38), followed by chronic kidney disease (CKD). Prevalence of pre-existing valvular disease (63.2%, 24/38) and an indwelling central venous catheter (34.2%, 13/38) was high.

Native valve IE was present in 16/38 (42,1%) patients. Nineteen patients (50%, 19/38) had prosthetic valve and 6/38 (15,8%) CEID-related IE due to NGNB. The patients were more likely to be affected by NoA IE (52.6%, 20/38) and HCA IE (26.3%, 10/38).

As shown in table 2, the most common IE lesions were vegetations. Most patients had endocarditis localized on the aortic valve (44.7%, 17/38), followed by the mitral valve (42.1%, 16/38) and CEID-related IE (21.1%, 8/38). Native valves only were affected in 12(31.6%), prosthesis only in 18(47.3%), intracardiac devices only in 4(10.5%), native and prosthesis in 2(5.3%) and native valve and intracardiac devices in 2(5.3%).

Patients with IE due to NGNB had a high prevalence of previous cardiac surgery (57.9%, 22/38) and an indwelling central intravascular access device (34.2%, 13/38) at the time or within 30 days of IE onset.

The most common symptom was fever (57.9%, 22/38). Embolic events were observed in twenty-one patients (55.3%, 21/38). The main sites for embolic events were the brain (*n* = 6) and spleen (*n* = 5). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated in 8/38 (21.1%) and 29/38 patients (76.3%), respectively.

Microbiological spectrum and drug resistance of IE due to NGNB in the study population are detailed in table 3. In our study the most common etiologies were *Klebsiella* spp. (21%, 8/38), *Pseudomonas aeruginosa* (21%, 8/38), and *Serratia marcescens* (16%, 6/38).

Table 4 describes the antibiotic regimens received by 38 patients with NGNB endocarditis. Most patients (55%, 15/27) received an antibiotic regimen containing a non-carbapenem beta-lactam (cefepime 7/27 [25.9%], piperacillin-tazobactam 4/27 [14.8%], ceftazidime 2/27 [7.4%], ceftriaxone 2/27 [7.4%]), variably combined with an aminoglycoside or a fluoroquinolone. A substantial number of cases (41%, 11/27) were treated with a carbapenem with or without other antibiotics (including polymyxin). Combined antimicrobial regimens with amikacin and gentamicin were used in 3/27, 11.1% and 6/27, 22.2%, respectively.

Among 38 patients with NGNB IE complications, 18 cases (47.4%) presented worsening heart failure. Embolic events were the most common complication. IE complications are described in Table 5.

Cardiac surgical procedure was performed in 8 (38.4%) patients. Of the 38 patients with IE due to NGNB, there were 19 deaths (50%). As shown in Table 6, indwelling CVC (OR 5.93; 95% CI, 1.29 to 27.3; $p = 0.017$), patients undergoing haemodialysis (OR 16.2; 95% CI, 1.78 to 147; $p = 0.008$) and chronic kidney disease (OR 4.8; 95% IC, 1.2 to 19.1, $p = 0.049$) were identified as risk factors associated with mortality.

Discussion

This is the first Brazilian series describing the characteristics and risk factors associated with mortality of patients affected by IE due to NGNB. Due to its infrequent occurrence, estimates of NGNB IE prevalence are variable and depend on the study period. Such population selection bias also restricted earlier studies to large metropolitan cities. The earliest systematic review of NGNB IE conducted from 1945 to 1977, concentrated on intravenous drug users (17).

The incidence of IE cases due to NGNB varies in the literature, ranging from 2–6%, with recent series showing higher incidences. These growing numbers are probably related to the presence of cardiac and vascular devices, invasive medical procedures, recurrent hospitalisation and immunosuppression [1, 8–13]. Previous studies showed that IE due to NGNB was predominantly on the right side of the heart, especially in cases associated with the use of injectable drugs [6]. Over the decades with the increase of IE caused by NGNB, the pattern of the infection also has changed, with the left side of the heart being the most affected nowadays. IE data with involvement of the left side of the heart show that the course of the disease has a median onset of symptoms of 15 days and high rates of complications, including congestive heart failure, perivalvular abscesses, and peripheral, splenic and nervous system central embolization [6, 11, 26]. Although investigators from the ICE group showed that most cases of IE due to NGNB had a subacute diagnosis [1], our data show that in 84.2% of the cases the diagnosis was made within 30 days of the onset of symptoms. In our study the left side of the heart was the most affected.

There are few case series reporting IE due to NGNB and table 7 summarizes the main findings from them.

The incidence of NGNB endocarditis in our study was 3.29% and was similar to the incidence in a large international series previously published. The main clinical findings were HF in 19 (50%), CKD in 17 (44.7%), ACD in 10 (26.3%) and haemodialysis in 10 (26.3%) patients. Male sex was the most affected (65.8%) with a median age of 57 years (IIQ 43-69). Age and gender have been reported as important risk factors in IE due to NGNB. Historically, men and elderly are the most affected population [1, 10–12].

Non-fermenting bacteria is the main group of NGNB reported in the literature as causing IE. This group includes species as *Pseudomonas aeruginosa*, *Acinetobacter* sp., *Burkholderia cepacia* and *Stenotrophomonas malthophilia* [6, 7, 18]. In a recent epidemiological study in the United States, this bacterial group corresponded to 70% of IE due to NGNB and *Pseudomonas aeruginosa* (68%) was the main etiological agent [11]. Among the group of fermenting GNBN that causes IE, the *Enterobacteriaceae* family is the most relevant, and *Klebsiella* spp. and *Enterobacter cloacae* were the most common agents. The International Collaboration on Endocarditis (ICE) study [1], and more recently an Argentine case series [9] and an Italian cohort [10] showed that *Escherichia coli* was the main microbiological agent of IE due to NGNB; in their studies, this probably related to high rates of urinary bacteraemia and high rates of use of urinary catheters. In our series, Enterobacteria were most frequent etiologies as a group. This relates to their frequency as etiologies of nosocomial infection. *Klebsiella* sp. accounted for 21% and *Serratia marcescens* (6%). *P.aeruginosa*, a non-fermenter, accounted for 21%.These etiological agents are the main NGNB identified in central venous-catheter related bacteraemia in Brazil, which is consistent with the main risk factors to IE due to NGNB acquisition found in this study, the presence of a central venous catheter (34.2%) and patients undergoing haemodialysis (26.3%). This probably indicates a problem with infection control. The NGNB, except for *Salmonella* spp. and *Pseudomonas aeruginosa*, have limited capacity for biofilm formation and low capacity for adhesion to the endocardium [19]. However, the presence of prosthesis and of intracardiac devices facilitate adherence and the formation of vegetations. The structures most affected in the 38 cases of IE due to NGNB were prosthetic valves (50%). The incidence of NGNB endocarditis in CDEI and prosthetic valves has increased over the years due to previous health care contact and permanence of these patients in hospital institutions [1, 20].

Fever (81.6%) was the most common clinical finding and is described as one of the first signs/symptoms in IE due to NGNB [27]. Of the other minor Duke criteria [2] we found pre-existing valve disease in 63.2% of cases. Among the findings that can increase the sensitivity of the diagnosis of IE [28], our study showed elevated CRP in 76.3%, elevated ESR in 21.1%, hematuria in 13.2% and indwelling CVC in 34.2% of cases of NGNB endocarditis.

Historically, beta-lactams with or without aminoglycosides regimes, whether or not associated with fluoroquinolone are the drugs of choice for the treatment of endocarditis caused by NGNB. Current guidelines recommend the use for 6 weeks [20–22]. Mechanisms of antimicrobial resistance in NGNB have increased dramatically across the planet [23, 24], making this a public health issue [25]. Due to the varied profile of possible etiologic agents and drug resistance, indications for the treatment of IE due to MDR NGNB are still debated, because of the high risk of clinical failure. In these cases, antibiotic therapy should be individualized, combination therapy should be provided if possible, and a consultation for the evolution of a prompt surgical removal if infected valves should be performed. Despite all, MDR in NGNB was not related to mortality and was not carbapenem including regimes.

Surgical intervention in previous cohorts varies from 23 to 58% [1, 9, 10]. Although previous studies have shown benefits in combined clinical and surgical treatment, some authors reported no significant difference in outcome between clinical treatment alone versus combined medical and

surgical intervention [6, 29]. This could perhaps be explained by introduction of new antimicrobial medications against NGNB. in the last decades

Previous data on IE mortality due to NGNB show rates between 8 and 47% [1, 9–11]. In our study mortality due to NGNB endocarditis was significantly high (50%, 19/38). Of interest, MDR etiology was not a risk factor associated to mortality. On the other hand, chronic kidney disease, indwelling CVC and patients undergoing haemodialysis were associated to mortality among patients affected by NGNB endocarditis.

Our study has some limitations. First, because of the rarity of infection, we were able to investigate only a small number of patients overall. Moreover, the study was conducted at a quaternary care centers, where the complicated cases of IE might be overrepresented. The major strength of our study is that it represents the first Brazilian contemporary study describing IE due to NGNB. This is a multicenter prospective study, what increases the value of the results obtained.

Conclusion

In conclusion, healthcare contact is an emerging risk factor for NGNB endocarditis. All patients with NGNB IE should be managed in consultation with specialists. Prosthesis, endovascular devices as well as intravenous catheters and chronic renal disease were highly prevalent in NGNB endocarditis in our contemporary multicenter cohort. Mortality was associated with the presence of central catheters, chronic renal disease and haemodialysis. The frequency of NGNB IE and the role of antibiotic resistance on outcome remain to be evaluated in future studies.

Abbreviations

IE – infective endocarditis

NGNB – non-HACEK Gram-negative bacilli

CVC - central venous catheter

NVE - native valve endocarditis

CIEDs - cardiac implantable electronic devices

PVE - prosthetic valve endocarditis

CoA - community acquired endocarditis

NoA - nosocomially-acquired endocarditis

HCA - non-nosocomial health care-associated endocarditis

HF - heart failure

CKD - chronic kidney disease

ESR - erythrocyte sedimentation rate

CRP - C-reactive protein

ACD - arterial coronary disease

RHD - rheumatic heart disease

CHD - congenital heart disease

COPD - chronic obstructive pulmonary disease

IVDU - intravenous drug user

ESBL - extended-spectrum beta-lactamase

MDR - multidrug resistant

Declarations

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Competing interests: The authors declare that they have no conflict interests.

Availability of data and materials: All data generated or analyzed during this study are included in this manuscript. The datasets generated and/or analysed during the current study are publicly available.

Code availability: R, version 3.5.3 and Jamovi, version 1.1.6.0, Sydney, Australia

Author contributions: LPS,CQF, PVD, GIFB,WFOG, CW, RQG, RFS andCL contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Ethics approval: The authors confirm that all experiments were performed in accordance with relevant guidelines and regulations. The study was approved by the local Ethics Committee from Instituto Nacional de Cardiologia (No. 080/2005).

Consent to participate: Informed consent was obtained from all subjects and/or their legal guardian(s)

Consent for publication: Not applicable

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Tables

Table 1

Baseline characteristics and predisposing factors of patients with NGNB endocarditis

Variable	*n* = 38
Age, median years (IQR)	57 (43-69)
Male sex	25 (65.8%)
HF	19 (50%)
ACD	10 (26.3%)
RHD	6 (15.8%)
CHD	0 (0%)
CKD	17 (44.7%)
Haemodialysis	10 (26.3%)
Smoking	6 (15.8%)
COPD	2 (5.3%)
Diabetes	7 (18.4%)
Autoimmune disease	1 (2.6%)
HIV-1 infection	0 (0%)
Malignancies	1 (2.6%)
Pre-existing valvular disease	24 (63.2%)
CVC	13 (34.2%)
CIED	8 (21.1%)
Immunosuppression	2 (5.3%)
Previous IE	3 (7.9%)
IVDU	0 (0%)

IQR interquartile range, *HF* heart failure, *ACD* arterial coronary disease, RHD=rheumatic heart disease, *CHD* congenital heart disease, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *CVC* central venous catheter, *CIED* cardiac implantable electronic device, *IE* infective endocarditis, *IVDU* intravenous drug user

Table 2

Echocardiographic findings of patients with NGNB IE

Characteristics	No. of patients (%)
Aortic valve vegetation	17 (44,7)
Mitral valve vegetation	16 (42,1)
Tricuspid valve vegetation	4 (10,5)
CEID-related IE	8 (21,1)
New valvular regurgitation	5 (13,2)
Perivalvar abscess	1 (2,6)
Dehiscence of prosthetic valve	1 (2,6)
Leaflet perforation	1 (2,6)
Perivalvular pseudoaneurysm	2 (5,2)
Perforation	3 (7.9)
Median (range) size of vegetation (mm)	11 (5-21)

CEID cardiac implantable electronic device, *IE* infective endocarditis

Table 3 Etiologies of patients with NGNB IE

Etiologies	No. of patients (%)
Enterobacteria	
Klebsiella spp.	8 (21)
Serratia marcescens	6 (16)
Enterobacter spp.	4 (10)
Escherichia coli	2 (5)
Salmonella spp.	2 (5)
Citrobacter spp.	1 (3)
Non fermenters	
Pseudomonas aeruginosa	8 (21)
Burkholderia cepacia	3 (8)
Acinetobacter spp.	3 (8)
Stenotrophomonas maltophilia	1 (3)
Total	38 (100)
Pan-susceptible *Enterobacteriaceae*	17 (45)
Pan-susceptible *Pseudomonas aeruginosa*	8 (21)
Pan-susceptible non-fermenters	5 (13)
All MDR bacteria*	8 (21)
Total	38 (100)

*Comprising ESBL-producing *Enterobacteriaceae* and MDR strains (*Escherichia coli*, *Klebsiella* spp., *Serratia marcescens*, *Citrobacter* spp., *Enterobacter* spp., *Salmonella* spp., *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Acinetobacter* spp. strains)

Table 4 Treatment strategies for NGNB IE

Antibiotic therapy	*n* = 27
Non-carbapenem beta-lactam ± aminoglycoside ± fluoroquinolone± co-trimoxazole	15 (55%)
Carbapenem ± aminoglycoside ± fluoroquinolone± co-trimoxazole	11 (41%)
Polymyxin-containing regime (associated with amikacin and meropenem)	1 (4%)

Table 5 Complications among patients with NGNB IE

Complications	*n* = 38
Worsening HF	18 (47.4%)
Worsening kidney function	14 (26.8%)
Persistent bacteraemia	6 (15.8%)
Valvular dysfunction	3 (7.9%)
Embolic events	21 (72.4%)

Table 6 Variables associated to mortality in NGNB IE

Variables	OR	95% CI	*P*
Prosthetic valve IE	0.34	0.0911 – 1.27	0.105
Acute IE	1.0	0.175 – 5.72	1.000
Diabetes	8.31	0.890 – 77.6	0.090
HF	1.23	0.345 – 4.41	0.746
CKD	**4.80**	**1.20 – 19.1**	**0.049**
Haemodialysis	**16.2**	**1.78 – 147**	**0.008**
ACD	0.16	0.028 – 0.908	0.062
NoA IE	0.81	0.227 – 2.89	0.746
Valvular abscess	1.0	0.126 – 7.94	1.0
CNS embolization	3.04	0.509 – 18.1	0.405
Splenic embolization	1.59	0.235 – 10.8	1.0
Bacteraemia persistente	2.27	0.362 – 14.2	0.660
Worsening renal function	1.0	0.262 – 3.82	1.0
Worsening heart function	2.36	0.640 – 8.68	0.194
CVC	**5.93**	**1.29 – 27.3**	**0.017**
Previous Cardiac Surgery	0.41	0.111 – 1.56	0.189
CEID	0.525	0.106 – 2.60	0.426
Immunosuppression	5.57	0.250 – 124	0.146
Previous IE	0.472	0.039 – 5.70	0.547
Pre-existing valvular disease	0.635	0.168 – 2.40	0.501
Increased CRP	1.87	0.152 – 22.9	1.0
Pan-susceptible *Pseudomonas aeruginosa*	3.92	0.678 – 22.7	0.232
Pan-susceptible *Enterobacteriaceae*	0.525	0.144 – 1.92	0.515
MDR strains*	0.255	0.0440 – 1.48	0.232

* Comprising ESBL-producing *Enterobacteriaceae* and MDR strains (*Escherichia coli*, *Klebsiella* sp., *Serratia marcescens*, *Citrobacter* sp., *Enterobacter* sp., *Salmonella* sp., *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Acinetobacter* sp. strains), *IE* infective endocarditis, *HF* heart failure, *CKD* chronic kidney disease, *ACD* arterial coronary disease, *NoA IE* nosocomially acquired infective endocarditis, *CVC* central venous catheter, *CEID* cardiac implantable electronic device, *CRP* C-reactive protein, *ESBL* extended-spectrum beta-lactamase, *MDR* multidrug resistant

Table 7 Main findings from the IE due to NGNB

Author, Year	Study period	Study site	*N* (patients with IE due to NGNB)	NoA IE/HCA IE	Age median, years (IQR)	Male	Most common etiological agent	Type of IE	Surgical treatment	Mortality
Morpeth *et al*., 2007	2000 a 2005	International multicentre	49/2761 (1.8%)	18/46 (39%)/8/46 (17%)	63 (50-71)	29/49 (59%)	*E. coli* 14/49 (28%) e *P. aeruginosa* 11/49 (22%)	NVE 20/49 (41%), PVE 29/49 (59%), CIED N/A	25/49 (51%)	12/49 (24%)
Ertugrul *et al*., 2019	2007 a 2016	Multicentre, Turkey	26	16/26 (61%)	53 (28-84)	11/26 (42%)	*P. aeruginosa* 7/26 (27%) e *E. coli* 7/26 (27%)	NVE 21/26 (81%), PVE 5/26 (19%), CIED 1/26 (4%)	10/26 (38%)	6/26 (23%)
Burgos *et al*., 2018	1998 a 2016	Single centre, Argentina	24/355 (6.7%)	N/A	72 (N/A)	17/24 (71%)	*E. coli* 6/24 (25%) e *P. aeruginosa* 5/24 (21%)	NVE 6/24 (25%), PVE 11/24 (45.8%), CIED 7/24 (29%)	9/24 (37%)	5/24 (21%)
Falcone *et al*., 2018	2004 a 2011	Multicentre, Italy	58/1722 (3.3%)	24/58 (41%)/2/58 (3%)	69.5 (57.75-77)	39/58 (67%)	*E. coli* 18/58 (31%) e *Pseudomonas* sp. 11/58 (19%)	NVE 34/58 (59%), PVE 16/58 (28%), CIED 8/58 (13%)	25/58 (43%)	8/58 (14%)
Veve *et al*., 2020	2011 a 2019	Single centre, USA	43	N/A	40 (31-50)	22/43 (51%)	*P. aeruginosa* 30/43 (68%) e *S. marcescens* 9/43 (20%)	NVE 30/43 (70%), PVE 13/43 (30%), CIED 2/43 (1%)	10/43 (23%)	20/43 (47%)
Trifunovic *et al*., 2018	2008 a 2015	Single centre, Serbia	9/246 (3.7%)	N/A	N/A	N/A	*P. aeruginosa* 4/9 (44%) e *K. pneumoniae*, *Acinetobacter* sp., *E. coli*, *Achromobacter denitrificans*, *Citrobacter* sp., ambas com 1/9 (11%)	N/A	N/A	N/A
Loubet *et al*., 2015	2009 a 2014	Single centre, France	12/300 (4%)	2/12 (17%)/2/12 (17%)	51 (44-74)	8/12 (66%)	*E. coli* 4/12 (33%) e *P. aeruginosa* 3/12 (25%)	PVE 8/12 (67%), NVE e CIED 0/12 (0%)	7/12 (58%)	1/12 (8%)

IE infective endocarditis, *NGNB* non-HACEK Gram-negative bacilli, *NoA IE* nosocomially infective endocarditis, *HCA IE* nonnosocomial health care-associated, *IQR* interquartile range, *NVE* native valve endocarditis, *PVE* prosthetic valve endocarditis, *CIED* cardiac implantable electronic device, *N/A* not available