

# Gram-negative infective endocarditis: a retrospective analysis of 10 years data on clinical spectrum, risk factor and outcome

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## Abstract

Infective endocarditis (IE) is a significant cause of morbidity and mortality. Underlying congenital heart disease and acquired valvular disease significantly increases the IE risk, which is still prevalent in developing countries. Gram-negative organism related IE prevalence appears to be rising with limited data on their presentation and outcomes. This study hopes to shed further light on this subject. This retrospective cross-sectional study occurred in a tertiary care center in South India.

A retrospective cross-sectional study performed in a single tertiary care center in South India. All patients with IE from 2006 to 2016 were included in this study. The details of clinical presentation, laboratory investigations, clinical course, microbiology, and outcomes were obtained. Patients fulfilling the modi-

fied Duke's criteria and a culture-proven diagnosis of gram-negative IE were eligible for inclusion. A total of 27 patients were enrolled from Jan 2006 to Dec 2016, among whom 78% were male. Prior structural heart disease was common in our cohort (41%) with renal (55%) and embolic (51%) complications being the most common systemic complications. A comparison of mortality with survivors found that congenital and acquired structural heart disease had a higher risk of mortality. Non-fermenting GNB accounted for 52% of the cohort, with *Pseudomonas* accounting for 19%. *E. coli* was the most common bacilli isolated, constituting 37% of the cohort. Assessment of risk factors for adverse outcomes found that renal dysfunction and intravascular device were significant with multivariate-logarithmic analysis showing renal dysfunction as an independent risk factor. In-hospital mortality in this series was 30%.

In conclusion, gram-negative IE was more prevalent among males. Underlying structural heart disease was the most common risk factor associated with the disease. Renal dysfunction and embolic complications were the most common complications in this cohort. *E. coli* and NFGNB accounted for 70% of the offending organisms. In-hospital mortality was similar to patients with IE secondary to common organisms. The presence of renal dysfunction was an independent risk factor for an adverse outcome.

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## Introduction

Infective endocarditis (IE) is an infection of the heart chambers and valves and is associated with significant morbidity and mortality [1,2]. It is a conventional differential for patients presenting with pyrexia of unknown origin (PUO) in the background of pre-existing valvular heart disease [3,4]. The most common bacterial agents causing IE are gram-positive cocci. Over the last 50 years, incidences of gram-negative endocarditis is increasing [5,6]. However, there is limited data on its characteristics and outcomes. In this retrospective cross-sectional study, we evaluated the patients with gram-negative IE regarding the same.

## Aims

In this study, we aimed to analyze the epidemiological, clinical, laboratory characteristics of patients with gram-negative IE. We also assessed the various risk factors and outcomes among these patients.

## Methodology

The retrospective cross-sectional study was conducted in a tertiary care health center in South India. The medical records of all patients with a diagnosis of IE were reviewed. Patients admitted from 2006 to 2016 were recruited. The total number of admissions during the same period was 75,719. Among these, 256 patients were diagnosed to have IE. Among these, 27 patients fulfilled the modified Duke's criteria for the diagnosis of IE and had culture-proven isolates of gram-negative organisms. Those who did not fulfill the diagnostic criteria were excluded from the study. Details of demography, clinical features, hematological, biochemical, and microbiological parameters were obtained. The principal investigator tried to ascertain the presence of risk factors, treatment details, and outcomes in each patient. A trained physician did data recruitment, analysis, and interpretation. Data were entered in Microsoft Excel and were analyzed using Stata 13.

## Results

Among the 75,719 patients, 256 patients were identified to have IE (0.33%) (Figure 1). Among these, the prevalence of gram-negative endocarditis was 10.7% (N=27). Analysis of the baseline characteristics (Table 1) revealed that the median age of patients was 48.5 years, with the youngest being 18 years and the oldest 75 years. Seventy-eight percent (N=21) of the patients were male; 40% (N=11) had a prior history of structural heart diseases, including rheumatic valvular heart disease, and valve replacement; 35% (N=10) of these patients had a prior history of IE. History of prolonged fever was present in all patients (100%), followed by the presence of significant weight loss in 40% (N=11) patients. On clinical examination, new-onset murmur (N=16) and a palpable spleen (N=9) were present in 60% and 33%, respectively.

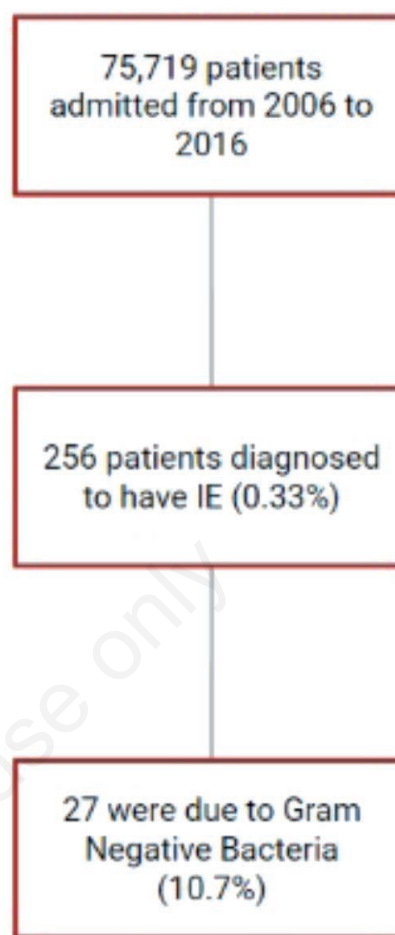


Figure 1. Strobe diagram showing number of patients in the study.

Table 1. Showing demographic information, risk factors, and clinical features and systemic complications.

Variable	Full cohort	Good outcome	Bad outcome	p-Value*	OR (95% CI)
<b>Demographic Details</b>					
Age (median years, min-max)	48.5 yrs (18-75)	47 (18-69)	50 (24-75)	0.577	—
Gender (Males value, %)	21/27 (78%)	9 (42%)	12 (57%)	1.000	0.67 (0.1 - 4.5)
<b>Clinical Features (Value, %)</b>					
Fever	27/27 (100%)	11 (100%)	16 (100%)	—	—
Weight Loss	11/27 (41%)	5 (45%)	6 (55%)	—	—
New murmur	16/27 (60%)	8 (50%)	8 (50%)	—	—
Splenomegaly	9/27 (33%)	6 (67%)	3 (33%)	—	—
<b>Risk Factors (Value,%)</b>					
Prior structural heart disease	11/23 (41%)	4 (36%)	7 (63%)	0.292	2.5 (0.5-13.1)
Past history of infective endocarditis	10/23 (35%)	4 (36%)	6 (54%)	0.667	1.9 (0.3-11.0)
Previous cardiac surgery	11/23 (41%)	4 (36%)	7 (64%)	0.414	2.5 (0.5-13.2)
Previous Intravascular device	7/23 (25%)	4 (57%)	3 (43%)	0.045	0.6 (0.1-3.5)
<b>Systemic Complications (Value, %)</b>					
Renal dysfunction	15/27 (55%)	3 (20%)	12 (80%)	0.022	8.0 (1.4-45.8)
Embolic phenomenon	14/26 (51%)	5 (36%)	9 (64%)	0.462	1.8 (0.4-8.7)
Metastatic infection	10/26 (37%)	3 (30%)	7 (70%)	0.448	2.1 (0.4-10.8)
Neurological complications	10/26 (37%)	3 (30%)	7 (70%)	0.428	2.3 (0.4-12.4)

\* p-value: statistical analysis performed against 'bad outcome'.

All the blood cultures were obtained as per the requirement of Duke’s criteria, and all the patients fulfilled the major criteria for blood culture positivity. Analysis of microbiological species showed that 37% (10) had *E. coli* with non-*pseudomonas* NFGNB constituting 33% (9). *Pseudomonas* species were grown in 19% (5), while *Salmonella*, *Citrobacter*, and *Hemophilus* were grown in one each (Table 2). The incubation period (time to reporting of cultures) was less than 48 hours in 25% (7) of the patients. Of the remaining 21 cases, 70% (16) took 2 to 7 days, while 30% (5) took more than a week to grow. The organisms’ antibiotic sensitivity profile revealed sensitivity to 3rd generation Cephalosporins in 45% (12) of the cases; 41% (11) cases were resistant to cefoperazone, while 11 % (3) were resistant to carbapenems.

On evaluating risk factors, it was found that the prevalence of underlying structural heart disease was present in 40% of our cases with rheumatic heart disease accounting for nearly all of them. 35% of our cohort also had previously been diagnosed and treated for IE. Almost 40% of the group had a prior history of cardiac surgery commonly for valve replacement due to severe stenotic lesions widely seen in rheumatic heart disease. Among these patient’s analyses of complications showed that renal dysfunction was present in 60% (16) of the cases, while 52% (14) had an embolic phenomenon. Among the embolic event, metastatic infection and neurological complications like stroke or TIA were noted in 37% (10) cases. The other complications reported were mesenteric ischemia and peripheral end artery occlusion. Analysis of risk factors of our cohort with in-hospital mortality revealed that previous intravascular device and the presence of renal dysfunction was associated with higher mortality (Table 2). The in-hospital mortality was found to be 30% (Figure 2).

Analysis of the antibiotic sensitivity profile was obtained from the records (Table 2). A large proportion of *Pseudomonas* (60%)

and NFGNB (44%) were ESBL, while 30% of *E. coli* were in the same category. Aminoglycoside and fluoroquinolone susceptibility pattern for *Pseudomonas* was above 80%. However, it was below 50% for *E. coli* and NF-GNB. Sensitivity patterns towards colistin were 100% in all the isolates. The culture with *Salmonella*, *Citrobacter* and *Hemophilus* were sensitive to all three classes of antibiotics.

A comparison between the various risk factors, complications, and microbiological parameters was done, between the survivors and the nonsurvivors (Table 3). Congenital and structural heart disease was present in 50% and 100% of the deaths, respectively, compared to none in the survivors. Analysis of etiological agents revealed that NF-GNB and *E. coli* were associated with the highest mortality (44%) while *Pseudomonas* and other organisms had done well with therapy.

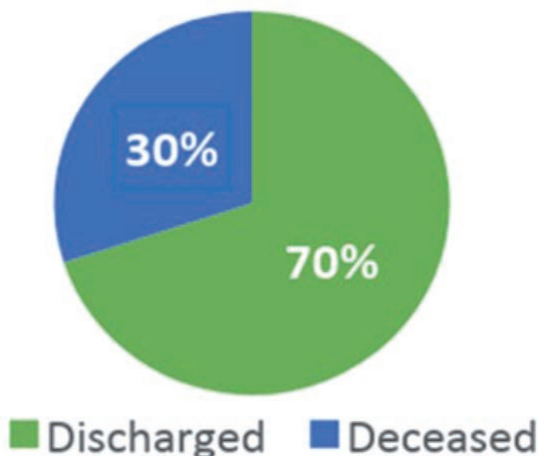
As some of the patients had been discharged in an unstable clinical condition with the risk of mortality, they were analyzed with in-hospital mortality groups as “adverse-outcome” against the remaining survivors (Table 4). Microbiological analysis of ESBL vs. non-ESBL infection was not significant.

## Discussion

Our study analyzed the risk factors commonly associated with IE. We also determined the complications and outcomes in patients admitted with gram-negative IE. Studies on IE have been scanty from the developing countries. Most data available on IE are from developed countries [7]. Subacute IE is much more prevalent in the Indian subcontinent as compared to the western population due to the higher prevalence of rheumatic heart disease [8]. Western pop-

**Table 2. Antibiotic sensitivity profile.**

	<i>E. coli</i> (10)	NF-GNB (9)	<i>Pseudomonas</i> (5)	Others (3)
Aminoglycosides	42%	34%	80%	100%
Cefpodoxime	30%	44%	60%	100%
Fluoroquinolones	30%	44%	80%	100%
Colistin	100%	90%	100%	—



**Figure 2. Showing outcome as in-hospital mortality.**

**Table 3. Comparison of risk factors between survivors and mortality.**

Variable	Survivors (%)	Mortality (%)
<b>Risk factors (%)</b>		
Congenital heart disease	0%	50%
Structural heart disease	0%	100%
Previous infective endocarditis	50%	92%
<b>Complications (%)</b>		
Embolic phenomenon	0%	25%
Metastatic infection	0%	20%
Neurological complication	0%	20%
<b>Microbiology (value, %)</b>		
<i>Escherichia coli</i>	4 (57%)	3 (43%)
<i>Pseudomonas</i>	5 (100%)	0
Non-fermenting gram-negative bacteria	7 (58%)	5 (42%)
Others	3 (100%)	0

ulation-based studies report an incidence of fewer than 10 cases for 100,000 years [9]. In our study, we found that IE accounted for 1 in 300 in hospital admission. IE in our study was commonly seen in patients being evaluated for Pyrexia of Unknown Origin (PUO).

Gram-positive organisms account for more than 70% of cases of infective endocarditis and are the primary etiological agent for community-acquired and hospital-acquired cases of IE [10]. Common gram-positive organisms implicated are staphylococcus, streptococcus, and enterococcus. Aerobic gram-negative organisms, which are a common cause for bloodstream infections, do not usually cause IE [11]. These commonly present as acute febrile illness progressing to sepsis. Gram-negative organisms account for less than 5% of the IE. The organisms commonly implicated are *E. coli*, *Klebsiella* sp, *Enterobacteriaceae* and *Pseudomonas* species [11]. In our study, gram-negative endocarditis accounted for 10.6% of the cases. There are no population-based studies from India regarding the prevalence of gram-negative organism related IE.

The median age of patients with IE was 25 years, given the higher prevalence of rheumatic heart disease [8]. Although early studies had shown that males had a higher prevalence of IE, recent studies have shown a change in trend with equal distribution between the sexes [9]. In our study, the median age was 49 years, with a male preponderance of 78%. This difference could be attributed to patterns of health-seeking behavior in our community and recruitment bias. The presence of prior structural cardiac lesions accounts for 40%-70% of cases with IE [12,13]. Health care exposure has been identified as a novel risk factor in addition to the traditional risk factors of underlying structural heart lesions (congenital or acquired). Patients having indwelling catheters, invasive lines, intracardiac devices are at a higher risk for IE. Among these patients, the risk of drug-resistant organisms, complications, and mortality tends to be higher [14]. In our study, the common predisposing factors were underlying structural heart disease (rheumatic heart disease), previous infective endocarditis, and a prior history of cardiac surgery. Intravascular lines or devices which can act as a nidus for infection can also predispose to IE secondary to gram-negative organisms [15]. One of the patients in the cohort had an infected ICD lead.

Fever has been the most common clinical feature at the presentation of IE, similar to our study [16]. The incidence of new-onset murmur was found to be 48%, and weight loss was seen in 30% of patients in one large prospective study [16]. The prevalence of new-onset murmur and weight loss in our study was 60% and 40%, respectively. While the previous study reported splenomegaly in 11% of patients, 33% of our patients had presented with splenomegaly [17].

In our study, 60% of patients had renal dysfunction, either defined as an elevated creatinine or presence of casts suggestive of an underlying systemic immune disorder. The literature on the prevalence of renal involvement in patients with IE is scanty. However, in this study, renal dysfunction is shown to be associated with poor outcomes. Embolic complications can be subdivided into those with and without involving the central nervous system. Neurological events, including stroke, were reported in 17% to 40% of patients. While non-stroke embolization accounts for 23% of the cohort [18,19]. Septic embolization involving visceral organs, pulmonary vasculature, bones, and joints have been associated with high morbidity and mortality. The extent and outcome of embolization are dependent on early diagnosis and initiation of treatment, especially in patients with native valve endocarditis [20]. In our study, the evidence of systemic embolization was found in 52%, with 37% of these presenting with neurological complications like transient ischemic attacks or stroke. Metastatic infections were observed in 37% of our patients, with the involvement of visceral organs and osteomyelitis being the more common. There was one case of mesenteric ischemia, which subsequently led to infarction.

Gram-positive organisms account for more than 70% of cases of IE and are the primary etiological agent for community-acquired and hospital-acquired cases of IE. The species commonly included are *staphylococcus*, *streptococcus*, and *enterococcus*. Gram-negative organisms account for less than 5% of the total incidence of IE [16,21]. In a previous case series of 56 patients with gram-negative endocarditis, HACEK organisms accounted for 100% of the cases [22]. In our study, nearly 50% of cultures had grown non-fermenting GNB, of which 20% were speciated to be due to *Pseudomonas*. 38% of our cultures had grown *E. coli* while there were isolated cases of *Salmonella*, *Citrobacter* and *Hemophilus*. It was noted that 78% of the cultures required a minimum incubation period of 48 hours to identify the organism, while 20% required an incubation period of more than a week. Sensitivity profile data revealed only 45% were sensitive to cephalosporins, while carbapenems or colistin were required in the remaining cases. As compared to IE secondary to the gram-positive organism, gram-negative IE is associated with similar morbidity and mortality [16,22-24]. Our study found an in-hospital mortality rate of 30% similar to published literature [25].

Statistical analysis of risk factors and complications of IE with mortality revealed that renal dysfunction and the presence of intravascular devices were associated with a higher risk of mortality [26,27]. These factors were put-through multivariate logarithmic regression analysis, which showed that renal dysfunction pos-

**Table 4. Risk factors associated with a bad outcome.**

Variable	Value (%)	p-Value	Odds Ratio (95% CI)	Log-regression analysis	Adjusted OR (95% CI)
ESBL Microorganism Infection	15/27 (55)	0.130	3.8 (0.7-19.5)	N/A	N/A
<b>Risk factors</b>					
Renal Dysfunction	12/16 (75)	0.022	8.0 (1.4-45.8)	0.038	0.068 (0.005-0.860)
Use of an intravascular device	11/15 (72)	0.020	7.3 (1.3-42.3)	0.481	0.432 (0.042-4.473)
ICU Admission	6/16 (22)	0.054	N/A	N/A	N/A
<b>Investigations:</b>					
Coagulopathy	5/13 (40)	0.041	N/A	0.999	N/A
Albumin less than 3.0 mg/dl	9/15 (60)	1.00	1.2 (0.2-6.4)	N/A	N/A
Creatinine more than 1.4 mg/dl	11/14 (78)	0.54	N/A	N/A	N/A

itively correlated with adverse-outcome. Our study had several limitations; we did not have details of cardiac imaging, transesophageal echocardiogram, details of surgical management, details of recurrence, and long term outcomes on these patients [28-30]. The strength of our study was the sample size, longer duration of the study, availability of microbiological diagnosis, and antibiotics susceptibility pattern for all patients [31-33].

In view of high mortality (30%), IE continues to be a feared disease across the developed world. More than half of the patients have a normal heart at diagnosis, and the proportion of healthcare-related IE is on the rise [33]. With the increasing longevity of the population, coupled with the utilization of invasive procedures, indwelling devices, catheters in the management of patients, the prevalence of IE is on the rise [33,34]. Healthcare-related IE contributes to one-third of patients with IE in high-income countries [35]. A large proportion of gram-negative endocarditis in our cohort is also primarily as a result of healthcare-related events. Furthermore, the microbiological sensitivity patterns reveal that drug resistance is becoming a problem contributing to patient morbidity and the cost of treatment [36,37]. Epidemiology, microbiological profile, drug susceptibility, adverse drug effects, and management guidelines on IE are continually changing [35,38-40]. The present study should serve as a marker to increase our vigilance towards IE secondary to gram-negative organisms, and promote further studies in this area.

## Conclusions

Gram-negative IE was prevalent more among the male population, with underlying structural heart disease. Renal dysfunction and embolic complications are the most common complications in this subgroup of patients. *E. coli* and NFGNB account for 70% of the offending organisms. Reported in-hospital mortality is 30%. Presence of renal dysfunction is an independent risk factor for adverse outcome

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