

Enterococcal Endocarditis: Prospective Data from the Iranian Registry of Infective Endocarditis

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Original Article

Abstract

BACKGROUND: Enterococci are responsible for 5% to 18% of infective endocarditis (IE) cases. We aimed to determine demographic data, predisposing factors, clinical presentations, complications and echocardiographic findings concerning enterococcal endocarditis.

METHOD: Since 2006, all adult patients with a possible or definite diagnosis of IE based on the modified Duke criteria have been enrolled in the Iranian Registry of Infective Endocarditis. In this study, patients with IE of enterococcal origin were detected and their demographic characteristics, predisposing factors, complications, laboratory data and echocardiographic findings were assessed.

RESULTS: Out of 731 patients diagnosed with endocarditis. Enterococci were found in 60 patients: 32 men (53.3%) and 28 women (46.7%) at a mean age of 55.21 ± 17.9 years. Definite IE was diagnosed in 57 (95%) patients, and possible IE was suspected in 3 patients (5%). The most frequent predisposing factor was the prosthetic valve ($n=28$, 46.7%), followed by a history of previous endocarditis ($n=12$, 20%). An acute course (<6 wk) was reported in 38 patients (63.3%). Fever ($n=58$, 95%) and loss of appetite ($n=17$, 28.3%) were the most frequent symptoms. The most frequent location of involvement was the aortic valve ($n=22$, 36.7%), followed by the mitral valve ($n=20$, 33.3%). Vegetation was detected in 53 patients (88.3%), abscess formation in 8 (13%). Fifteen patients (25%) had heart failure, and 11 (18%) had central nervous system complications. The mortality rate was 20%.

CONCLUSION: Given the serious complications and the high mortality rate in the patients with IE of enterococcal origin, which may be due to these organisms' intrinsic resistance to many antibiotics, we suggest further studies to determine more effective antibiotic regimens and even individualized antibiotic therapies for enterococcal endocarditis.

Keywords: Endocarditis, Enterococcus, Staphylococcus aureus

Date of submission: 01 Oct. 2019, *Date of acceptance:* 26 June 2020

Introduction

Enterococci are the second (after staphylococci) most common cause of healthcare-associated endocarditis and the third (after staphylococci and streptococci) most frequent cause of community-acquired endocarditis.¹⁻³ Enterococci are gram-positive facultatively anaerobic bacteria that are normal commensals of the gastrointestinal tract. The 2 most common species responsible for enterococcal infections are *Enterococcus faecalis* (*E. faecalis*) and *E. faecium*.⁴

Enterococcal species can cause such different types of infections as urinary tract infections, bacteremia, endocarditis and meningitis. Infective endocarditis (IE) is one of the most life-threatening infections caused by enterococci.

How to cite this article: Moradnejad P, Maleki M, Lotfian S, Sadeghpour A, Firouzi A, Pasha H, et al. **Enterococcal Endocarditis: Prospective Data from the Iranian Registry of Infective Endocarditis.** ARYA Atheroscler 2022; 18(5): 2733.

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The most frequent sources of bacteremia are genitourinary and gastrointestinal tracts in patients with community-acquired bacteremia, and the most common sources of nosocomial bacteremia are intravascular and urinary catheters. Other sources of bacteremia include intra-abdominal, biliary tract, wound and bone infections.⁴

Enterococci cause not only bloodstream infections in community-associated and hospital-associated clinical settings but also native and prosthetic valve endocarditis and community-acquired and nosocomial endocarditis. Enterococci are responsible for between 5% and 18% of IE cases, with the incidence rate seemingly on the rise.⁵⁻⁶

Most cases of enterococcal endocarditis are due to *E. faecalis* species.⁷⁻⁹ Indeed, *E. faecalis* is responsible for more than 90% of enterococcal IE cases. Overall, *E. faecalis* is the third most common cause of IE, accounting for 9% to 17% of all cases. Patients with *E. faecalis* IE are frequently older than those with streptococcal and staphylococcal IE.^{10, 11} Dahl et al.⁸ reported a high prevalence rate for IE (26%) in patients with *E. faecalis* bacteremia.

Enterococcal endocarditis is more common in men and the elderly with comorbidities, and it usually originates from genitourinary and gastrointestinal tracts.¹²⁻¹⁵ Most cases of enterococcal endocarditis manifest a subacute course, with the most frequent presentations being nonspecific, including fever and constitutional symptoms such as weight loss, anorexia, generalized pain of muscles and joints, and malaise.^{4, 8}

The most common complication of enterococcal endocarditis is heart failure and embolization, and the brain is the most common organ involved.

Enterococci are intrinsically resistant to several antibiotics, and they have the ability to acquire antibiotic-resistance genes. A bactericidal regimen should be used for the treatment of enterococcal endocarditis and other endovascular infections.

Because of the intrinsic resistance of enterococci to many antibiotics, the mortality rate is high.⁴

In the present study, we aimed to determine demographic data, predisposing factors, clinical presentations, complications and echocardiographic findings concerning enterococcal endocarditis.

Methods

Since 2006, all adult patients with a definite (2 major, or 1 major plus 3 minors, or 5 minor criteria) or possible (1 major plus 1 minor, or 3 minor criteria)

diagnosis of IE based on the modified Duke criteria have been enrolled in the Iranian Registry of Infective Endocarditis (IRIE) by an expert team. IRIE, which started in 2006 due to the high number of endocarditis patients referred to Rajaei cardiovascular medical and research center, was updated in 2016 by joining to the European International Registry (Euro-Endo) and so far, patients are being studied and followed up in this way¹⁶⁻¹⁸. The present study was approved by the institutional ethics committee (IR.RHC.REC.1400.049) and conducted in accordance with the Helsinki Declaration of the World Medical Association (2000). Informed written consent was obtained from the entire study population.

The exclusion criteria were alternative diagnoses explaining the evidence of IE, symptom resolution with antibiotic therapy for ≤ 4 days, failure to fulfill possible IE criteria and partial treatment.

Patients with IE of enterococcal origin were detected via 3 blood culture sets processed under sterile conditions by using BACTEC blood culture media (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). All patient's demographic characteristics; history of previous IE and treatment; history of cardiac and non-cardiac disease; signs and symptoms; sites of infection; native or prosthetic cardiac valve; echocardiographic parameters; laboratory findings; surgical treatments; antibiotic therapies; cardiac and extra cardiac complications including embolic events, increasing vegetation size or new abscesses, heart failure, acute renal failure, mycotic aneurysms, septic shock, and persistent fever (> 7 d), prosthetic valve dysfunction were recorded.

Data transferred to the Registry Data Coordinating Center through a secure, electronic web-based data collection system named Registry. Centralized registry data security includes password-protected login to the Registry system and access provided only to Registry Data Coordinating Center personnel authorized as part of the Registry.

All data that entered to the Registry were rechecked by an expert infectious disease specialist and an expert cardiologist. The main documents and how to enter data were checked by the random audit during the study.

Statistical analysis

The mean \pm the standard deviation and frequencies (percent) were used for descriptive analysis.

The statistical analysis was performed with the SPSS software, version 18, for Windows (SPSS Inc, Chicago, Illinois).

Results

Patient Demographics and Characteristics

Out of 731 patients diagnosed with endocarditis according to the modified Duke criteria, 371 (50.8%) had culture-positive IE. The most frequent causative microorganisms were staphylococci and enterococci (Figure 1). Enterococci were found in 60 patients, consisting of 32 men (53.3%) and 28 women (46.7%) at a mean age of 55.21 ± 17.9 years, who were subsequently included in the current study. Definite IE was diagnosed in 57 patients (95%), and possible IE was suspected in 3 patients (5%) based on the modified Duke criteria (Table 1 & Table 2).

The most common predisposing factor was the prosthetic valve ($n=28$, 46.7%), followed by a history of previous endocarditis ($n=12$, 20%). One patient had a

history of congenital heart disease (a perimembranous ventricular septal defect), and 2 patients (3.3%) had undergone dental procedures in the preceding 6 months.

Twenty-two patients (36%) had taken antibiotics in a 2-week period leading up to admission.

The study population's demographic characteristics, clinical features and predisposing factors are presented in Table 1 and Table 2.

Clinical and Laboratory Characteristics of IE

Among the 60 patients with enterococcal endocarditis, 38 (63.3%) had an acute course (<6 wks.), and 22 (36.7%) had a subacute course (>6 wks.).

Fever ($n=58$, 95%) and loss of appetite ($n=17$, 28.3%) were the most frequent symptoms. The most common clinical features are shown in Table 1.

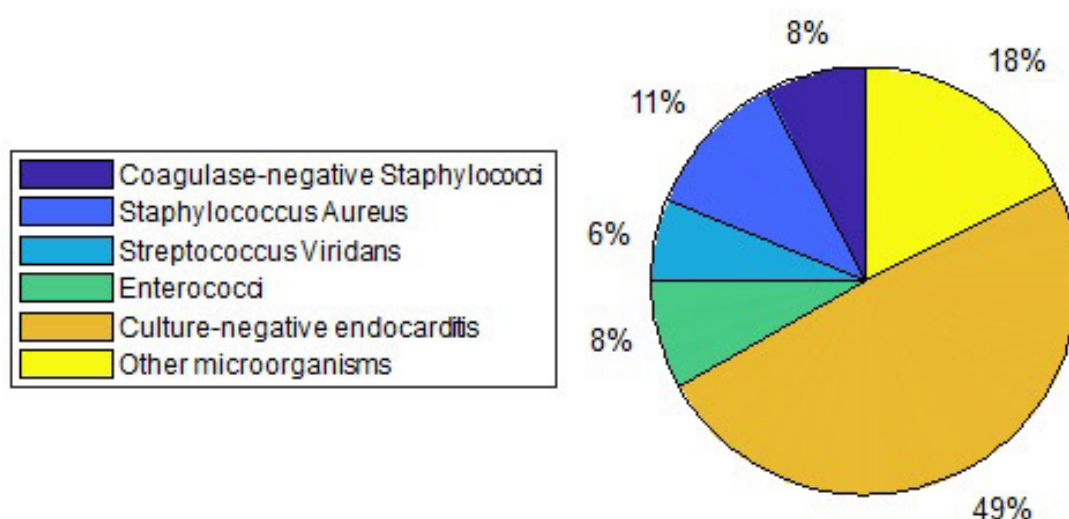


Figure 1. Types of Microorganisms in culture positive patients with Infective Endocarditis

Table 1. Demographic data and clinical features in 731 episodes of infective endocarditis in comparison with 60 episodes of enterococcal endocarditis

	Enterococci (n=60)	Total (n=731)
Sex		
Male	32(53.3%)	485(66.3%)
Female	28(46.7)	246(33.7)
Age (y)		
Mean age	55.21	47.90
Range	18-93	16-93
Clinical Features		
Fever	57(95.0%)	641(87.8%)
Loss of appetite	17(28.3%)	164(22.5)
Nausea-vomiting	5(8.30%)	46(6.30%)
Sweating	2(3.30%)	70(9.50%)
Headache	1(1.70%)	40(5.50%)
Muscle pain	1(1.70%)	39(5.30%)

The results of laboratory tests are presented in Table 4, which demonstrates that 50 patients (83.3%) suffered from anemia, 24 (40%) had leukocytosis, and 21 (35%) exhibited elevated erythrocyte sedimentation rates.

Echocardiographic Data and Complications of IE

Among the 60 patients with enterococcal endocarditis, 28 (46%) had prosthetic valve endocarditis, 31 (51%) native valve IE, and 1 cardiac device-related (implantable cardioverter-defibrillator) IE.

Echocardiography was performed in all the

patients and showed that left-sided IE was more common than right-sided IE. The most frequent location of involvement was the aortic valve (n=22, 36.7%), followed by the mitral valve (n=20, 33.3%). With respect to isolated right-sided IE, the involvement was reported in the tricuspid valve (n=4, 6.7%) and the pulmonary valve (n=3, 5%). Additionally, 1 patient (1%) had device-related IE.

Vegetation was detected in 53 patients (88.3%), abscess formation in 8 (13%), pseudoaneurysms in 3 (5%) and fistulae in 2 (3.3%). The echocardiographic findings are illustrated in Table 3 and Table 4.

Table 2. Diagnoses, clinical courses, predisposing factors, and therapeutic protocols in 60 episodes of enterococcal endocarditis

Duke Criteria	
Definite endocarditis	57
Possible endocarditis	3
Clinical Course	
Acute (<6 wk)	38
Subacute (>6 wk)	22
Predisposing Factors	
Prosthetic valve	28
Previous infective endocarditis	12
Diabetes mellitus	10
Chronic kidney disease	7
Dialysis	3
Intravenous drug use	2
Immune deficiency	2
Intracardiac devices (implantable cardioverter-defibrillator or cardiac resynchronization therapy)	2
Congenital heart disease (perimembranous ventricular septal defect)	1
Therapeutic Protocols	
Antibiotic therapy alone	37
Antibiotic therapy + surgery	23

Table 3. Echocardiographic findings in 60 episodes of enterococcal endocarditis

Echocardiographic Findings	
Native valve endocarditis	31
Prosthetic valve endocarditis	
Late	24
early	4
Cardiac device-related infective endocarditis (implantable cardioverter-defibrillator)	1
Location of vegetation	
Aortic valve	22
Mitral valve	20
Tricuspid valve	4
Pulmonary valve	3
Multivalve (aortic + mitral valve)	3
Ventricular septal defect	1
Abscess	8
pseudoaneurysm	3
Fistula	2

Table 4. Echocardiographic findings, laboratory data, and complications in 731 episodes of infective endocarditis in comparison with 60 episodes of enterococcal endocarditis

	Enterococci (n=60)	Total (n= 731)
Echocardiographic Findings		
Vegetation	53	662
Abscess	8	100
Paravalvular pseudoaneurysm	3	64
fistula	2	24
New prosthetic dehiscence	0	28
Laboratory Data		
Anemia	50(83.3%)	624(85.5%)
Leukocytosis	24(40.0%)	253(34.6%)
Elevated erythrocyte sedimentation rate	21(35.0%)	171(23.4%)
Thrombocytopenia	13(21.7%)	164(22.5%)
Complications		
Heart failure	15(25.5%)	91(12.5%)
Central nervous system complications	11(18.3%)	101(13.8%)
Death	12(20.0%)	130(17.8%)

Heart failure and central nervous system complications were reported in 15 (25%) and 11 (18%) patients, respectively. The mortality rate was 20% (n=12) (Table 4).

All the patients were treated with the standard antibiotic regimen for enterococcal endocarditis, and cardiac surgery was performed in 23 patients (38%) (Table 2).

Discussion

IE, caused by enterococci, is one of the most life-threatening infections. Enterococci are responsible for between 5% and 18% of all IE cases, and it seems that the incidence rate is on the increase.⁶ In our investigation, the third most common cause of IE was the enterococcus (n=60, 8.2%), which is consistent with previous studies reporting enterococci as the second or third most frequent cause of IE (5%–20% of all IE cases). The most recent series have reported that enterococci account for 15% to 20% of all cases of IE.¹⁹

Bacteremia is one of the most common presentations of enterococcal infection. Some factors suggest IE in patients with enterococcal bacteremia, including community acquisition, previous valvular heart disease and cryptogenic sources.⁴ The NOVA (Number of positive blood cultures ≥ 3 [5 points], Origin of infection unknown [4 points], Valvular disease [2 points], and Auscultation of heart murmurs [1 point]) score may be a valuable tool for the prediction of endocarditis and the need for

transesophageal echocardiography in patients with enterococcal bacteremia. Patients receiving a score below 4 are considered at low risk for IE. However, clinical judgment should be exercised to guide transesophageal echocardiography.^{20, 21} In our center, patients with enterococcal bacteremia at high risk for IE (according to the NOVA score) are examined via transesophageal echocardiography.

Enterococci can cause native and prosthetic valve endocarditis, as well as community-acquired and nosocomial endocarditis. Enterococcal endocarditis may occur in intact heart valves, bearing in mind that more than 40% of patients have no underlying heart disease.⁴ Nonetheless, it frequently occurs in the setting of abnormal valves, with the usual involvement of mitral and aortic valves.^{22, 23} In our study, we detected prosthetic valve endocarditis in 28 patients, native valve endocarditis in 31 patients, and device-related (implantable cardioverter-defibrillator) IE in 1 patient. Further, aortic and mitral valves were the most frequently involved valves.

Enterococcal endocarditis is more common in men and the elderly with comorbidities, and it usually originates from genitourinary and gastrointestinal tracts. Our study population was composed of 32 men (53.3%) and 28 women (46.7%), which is compatible with previous studies in terms of sex distribution. The mean age of our patients with enterococcal endocarditis was 55.21 years, which was higher than that of other cases of endocarditis in this investigation. Diabetes mellitus, chronic lung

disease, congestive heart failure, previous IE and non-congenital valvular disease were more frequent among cases with enterococcal IE in some studies.¹⁹

Many procedures are associated with the development of enterococcal endocarditis, including colonoscopies, cystoscopies, cesarean sections and liver biopsies.^{22,24} In the current investigation, the most common predisposing factor in patients with enterococcal endocarditis was the prosthetic valve (n=28, 46.7%), followed by a history of previous endocarditis (n=12, 20%), diabetes mellitus (n=10, 16.7%) and chronic kidney disease (n=7, 11.7%).

Most cases of enterococcal endocarditis manifest a subacute course. Moreover, the most common presentations are nonspecific, including fever and constitutional symptoms such as weight loss, anorexia, generalized pain of muscles and joints, and malaise with slightly elevated white blood cell counts and C-reactive protein levels. In our study, fever (n=58, 95%), loss of appetite (n=17, 28%), and shortness of breath (n=13, 21%) were the most frequent symptoms; in addition, 50 patients (83%) had anemia, 24 (40%) suffered from leukocytosis, and 21 (35%) exhibited erythrocyte sedimentation rates.

The mean duration of nonspecific symptoms such as anorexia and weight loss were 140 days in previous reviews.^{4,8} Since the beginning of the 21st century, the classic presentation of enterococcal IE as a community-acquired, subacute course with a genitourinary source has turned into an acute course and more frequently a healthcare-associated disease, predominantly among the elderly patients with comorbidities and seldom with a clearly identifiable source.¹⁹ The peripheral signs of IE such as Osler nodes and Roth spots are uncommon. Other uncommon manifestations include spondylodiscitis, metastatic abscesses in the spleen and empyema. Among our 60 patients with enterococcal endocarditis, 38 (63.3%) had an acute course (<6 wks.) and 22 (36.7%) a subacute one (>6 wks.).

The most common complication of enterococcal endocarditis is heart failure, which develops in about 50% of patients.^{4,17} The major finding of an investigation by Pericàs *et al.*¹⁹ was the high rate of prosthetic valve involvement and heart failure. Embolization appears in between 27% and 43% of cases, and the brain is the most frequently involved organ. We found heart failure in 15 patients (25%) and central nervous system complications in 11 (18.3%).

Moreover, we detected prosthetic valve involvement and cardiac device-related IE in 29 patients (48.3%).

Not only are enterococci intrinsically resistant to several antibiotics, but also they are capable of acquiring antibiotic-resistance genes. A bactericidal regimen should be administered for the treatment of enterococcal endocarditis and other endovascular infections. Beta-lactams are not often bactericidal against enterococci, but a synergistic and bactericidal effect is achieved with the addition of an aminoglycoside. Gentamicin and streptomycin are 2 aminoglycosides recommended for this synergistic effect.^{15,25,26} A 4 to 6-week period of antibiotic therapy is reasonable for native valve IE, depending on the duration of symptoms. Patients with symptoms of longer than 3 months' duration should receive 6 weeks of antibiotics, and patients with symptoms of shorter than 3 months' duration should be given 4 weeks of antibiotics. Additionally, 6 weeks of a bactericidal regimen of antibiotics should be considered for patients with prosthetic valve endocarditis.^{15,27,28} In the present study, all the patients were treated with a standard bactericidal antibiotic regimen for 4 to 6 weeks, and cardiac surgery was performed in 23 patients.

Because of the intrinsic resistance of these organisms to many antibiotics, the mortality rate is high.⁴ In this study, 12 patients (20%) died. The mortality rate is reported to range from 11% to 35% by different studies.⁴ Two large series²² of patients with enterococcal endocarditis have shown older age, systemic embolization, and heart failure as predictors of mortality.

Conclusions

considering serious complications and high mortality rates in patients suffering from enterococcal endocarditis, which may be a consequence of the intrinsic resistance of enterococci to many antibiotics, we suggest that further studies be undertaken to determine more effective antibiotic regimens and even individualized antibiotic therapies for this potentially life-threatening infection.

Financial support

None

Acknowledgement

This research was supported by Rajaei Cardiovascular

Medical and Research Center.

Conflicts of interest

There are no conflicts of interest.

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