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Causative Microorganisms in Infective Endocarditis: Prospective Data from the Iranian Registry of Infective Endocarditis (IRIE)

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A R T I C L E   I N F O

A B S T R A C T

Background: Infective Endocarditis (IE) is a life-threatening disease. Regardless of improved healthcare, the incidence of IE has increased over time. A variety of microorganisms have been found to be associated with IE.

Objectives: This study aimed to determine the incidence of various microorganisms in patients admitted with IE and to assess their relationships with in-hospital complications.

Methods: This prospective cross-sectional study was conducted on patients with definite or possible IE based on the Duke criteria at a tertiary referral center between 2016 and 2021. Blood cultures were performed for all the patients to document the positive or negative blood cultures as well as the types of microorganism. Statistical analyses were performed using the SPSS 18 software.

Results: The study population consisted of 286 patients (181 males (63.3%) and 105 females (36.7%)) with the mean age of 49.67 ± 17.11 years. The most common cardiac predisposing factor was the prosthetic valve (n = 110, 38.5%) followed by a history of congenital heart disease (n = 68, 23.8%), while the most frequent non-cardiac predisposing factors were a history of chronic kidney disease (n = 75, 26.2%) and diabetes mellitus (n = 53, 18.5%). The most frequent causative microorganisms were coagulase-negative *Staphylococcus* (n = 37, 12.9%), *Staphylococcus aureus* (n = 31, 10.4%), *Enterococcus* (n = 29, 10.1%), and *Streptococcus viridans* (n = 14, 4.9%). The most common complications were acute renal failure (26.6%), heart failure (17.5%), and pulmonary involvement (8.4%).

Conclusions: The frequencies of microorganisms related to IE, especially culture-negative IE, vary in different countries, precluding the practical use of a specific guideline around the world. Further research is, therefore, required to determine the epidemiology and microbiology of IE in different countries with a view to eventually devising an individualized guideline appropriate to the epidemiology and microbiology of IE in every country.

1. Background

Infective Endocarditis (IE) is a life-threatening disease and advances in healthcare have failed to stem the rise in its incidence over time (1, 2). This disease is associated with various microorganisms. The most common etiologic agents in patients with IE are *Staphylococci* (*Staphylococcus aureus* [*S aureus*] and coagulase-negative *Staphylococcus* [*CoNS*]), *Streptococci* (viridans-group *Streptococcus* and *Streptococcus bovis* [*S bovis*]), and *Enterococci* (3-6). Nonetheless, fungi, *Brucella species* (*spp*), *Coxiella burnetii*, *Tropheryma whipplei*, *Legionella spp*, *Chlamydia psittaci*, *Bartonella spp*, and, sometimes, polymicrobial microorganisms comprise the less frequent

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microorganisms (5, 7, 8). The clinical presentation of IE is highly variable, with the disease being likely to follow an acute or subacute course. The former usually presents with high fever, systemic toxicity, and leukocytosis. The latter form, however, presents with low-grade fever, night sweats, and weight loss.

The development of IE is predisposed by several factors including rheumatic heart disease, mitral valve prolapse, aortic valve disease, congenital heart disease, prosthetic valves, intracardiac devices, injection drug use, chronic hemodialysis, poor dentition or dental infection, and a history of IE. The incidence of these factors is variable over time and between different countries. For instance, chronic rheumatic heart disease, which was the underlying lesion in 37% to 76% of IE cases in the past, has been replaced by prosthetic valves, intracardiac devices, or intravascular prostheses (5). On the other hand, coexisting circumstances such as diabetes mellitus, hemodialysis, and intravenous drug use increase the risk of IE. Consequently, viridans-group *Streptococcus*, the most common cause of IE in the past, has been superseded by *S aureus* and *CoNS*, as the current leading causes of IE (5).

IE is associated with a variety of complications, the probability of which is based on such factors as the causative microorganism, the underlying disease, and the duration of the disease prior to treatment. The complications of IE comprise metastatic infections and cardiac, renal, neurological, and pulmonary involvements.

2. Objectives

The present study aims to determine the incidence of various microorganisms in patients admitted with IE and to assess their relationships with in-hospital complications.

3. Methods

This prospective cross-sectional study was conducted on the patients with IE enrolled in the Iranian Registry of Infective Endocarditis (IRIE) from 2016 to 2021. Ever since its establishment in 2006, the IRIE has registered the reported cases of IE (9). All the patients who met the definition of possible or definite IE according to the modified Duke criteria were included in this study. The exclusion criteria were alternative diagnoses explaining the evidence of IE, symptom resolution with antibiotic therapy for ≤ 4 days, failure to fulfill the possible IE criteria, and partial treatment. In total, 286 patients were assessed in the current investigation.

The study population's demographic characteristics, risk factors, history of IE, signs and symptoms, echocardiographic findings, outcomes, and complications were recorded. Blood cultures were performed for all the patients to document positive or negative blood cultures as well as the types of microorganism. In doing so, three blood culture sets were drawn from each patient under sterile conditions and the samples were processed using the BD BACTEC blood culture medium. Blood and tissue samples including valve samples were tested via serology and Polymerase Chain Reaction (PCR) for *Coxiella burnetii* infection only in 52 patients with culture-negative endocarditis because of budget constraints. These patients were evaluated by the Raoult criteria for Q fever endocarditis.

The study protocol was approved by the Ethics Committee of the center (IR.RHC.REC.1400.049) following the Helsinki Declaration of the World Medical Association (2000). In addition, written informed consent forms were obtained from all the patients.

3.1. Statistical Analysis

All statistical analyses were performed using the SPSS software, version 18 for Windows (SPSS Inc, Chicago, Illinois). Descriptive analysis included mean ± Standard Deviation (SD) and frequency.

4. Results

The study population consisted of 286 patients (181 males (63.3%) and 105 females (36.7%)) with the mean age of 49.67 ± 17.11 years (range: 16 – 86 years) who were diagnosed with possible or definite IE based on the Duke criteria. The most common symptoms were fever (n = 228, 79.9%), general malaise (n = 124, 43.45%), shortness of breath (n = 117, 40.9%), loss of appetite (n = 23, 8%), and chest pain (n = 23, 8%) (Table 1). The most frequent cardiac predisposing factor was the prosthetic valve (n = 110, 38.5%) followed by a history of congenital heart disease (n = 68, 23.8%), while a history of chronic kidney disease (n = 75, 26.2%) and diabetes mellitus (n = 53, 18.5%) were the most common non-cardiac predisposing factors (Table 2).

Table 1. Demographic Data, Clinical Features, and Echocardiographic Findings

Characteristics	N (%)
Sex	
Male	182 (63.4)
Female	105 (36.6)
Clinical features	
Fever	228 (79.7)
Malaise	124 (43.4)
Shortness of breath	118 (41.2)
Loss of appetite	23 (8)
Chest pain	23 (8)
Sweating	15 (5.2)
Headache	11 (3.8)
Muscle pain	7 (2.4)
Neurological events	
Stroke	21 (7.3)
Transient ischemic attacks	3 (1)
Echocardiographic findings	**N (%)**
Vegetation	244 (85.3)
Leaflet perforation	43 (15.03)
Abscesses	33 (11.53)
Paravalvular pseudoaneurysms	27 (9.44)
Dehiscence of prosthetic valves	8 (2.79)
Fistulae	8 (2.79)

Both transthoracic and transesophageal echocardiographic examinations were performed in all the patients. The most common echocardiographic finding was vegetation followed by leaflet perforation, abscesses, paravalvular pseudoaneurysms, fistulae, and prosthetic valve dehiscence (Table 1). Additionally, prosthetic valve IE and native valve IE were reported in 110 (38.5%) and 176 (61.5%) patients, respectively.

Table 2. Predisposing Factors

Predisposing Factors	N (%)
Cardiac predisposing factors	
Prosthetic valves	110 (38.5)
Previous infective endocarditis	68 (23.8)
Congenital heart disease	38 (13.3)
Intracardiac devices (implantable cardioverter-defibrillators and pacemakers)	33 (11.5)
Rheumatic heart disease	24 (8.4)
Degenerative cardiac lesions	17 (5.94)
Non-cardiac predisposing factors	
Chronic renal failure	75 (26.2)
Diabetic mellitus	53 (18.5)
Dialysis	39 (13.6)
History of immunosuppressive agent use	20 (7)
Recent dental procedure	19 (6.6)
History of corticotherapy	15 (5.2)
Intravenous drug use	13 (4.5)

Table 3. Microorganism Types and Complications

Microorganisms	N (%)
Coagulase-negative *Staphylococci* (*CoNS*)	37 (13)
Methicillin-sensitive *CoNS*	20 (7)
Methicillin-resistant *CoNS*	17 (5.9)
Staphylococcus aureus	30 (10)
Methicillin-resistant *Staphylococcus aureus*	17 (5.9)
Methicillin-sensitive *Staphylococcus aureus*	13 (4.5)
Enterococcus	29 (10.1)
Gram-negative *Bacillus*	17 (5.9)
Streptococcus viridans	14 (4.9)
Alpha hemolytic *Streptococcus*	10 (3.5)
Candida albicans	4 (1.4)
Coxiella burnetii (n = 126)	16 (12.6)
Brucella	3 (1)
Aggregatibacter	2 (0.7)
Non-hemolytic *Streptococcus*	1 (0.3)
Complications	**N (%)**
Acute renal failure	76 (26.6)
Heart failure	50 (17.5)
Death	48 (16.8)
Pulmonary involvement	24 (8.4)
Transient ischemic attacks	21 (7.3)
Persistent fever after seven days	18 (6.3)
Cardiogenic shocks	13 (4.5)
Splenic (abscesses or infarctions)	11 (3.8)
Septic shocks	7 (2.4)
Stroke	5 (1.7)
Glomerulonephritis	4 (1.3)
Spondylitis	1 (0.3)

The blood cultures were incubated in the BD BACTEC system. The cultures were positive in 147 patients (51.3%), with the most frequent causative microorganisms being *CoNS* (n = 37, 12.9%), *S aureus* (n = 31, 10.4%), *Enterococcus* (n = 29, 10.1%), and *S viridans* (n = 14, 4.9%). The less common microorganisms were Gram-negative *bacillus* (n = 8, 2.8%), *S bovis* (n = 4, 1.4%), *Candida spp* (n = 4, 1.4%), and *Brucella spp* (n = 3, 1%) (Table 3). The frequencies of the microorganisms in the study population have been depicted in Figure 1.

Out of the initially recruited 286 patients, 126 were investigated for *Coxiella burnetii* infection. Among these patients, 52 (41%) were culture-negative. Blood and tissue samples including valve samples (if available) were tested for *Coxiella burnetii* infection via serology and Polymerase Chain Reaction (PCR) in the 52 patients with culture-negative endocarditis. According to the Raoult criteria, 16 patients (12.7%) were diagnosed with Q fever endocarditis; 11 patients with definite Q fever endocarditis and 5 patients with possible Q fever endocarditis.

The most common complications were acute renal failure (26.6%), heart failure (17.5%), and pulmonary involvement (8.4%) (Table 3). The frequencies of the complications according to the types of microorganism have been presented in Table 4. Furthermore, death was reported in 48 patients (16.8%).

5. Discussion

In the present study, the most common cause of IE was *CoNS* (n = 37, 12.9%), which showed a rise compared with a previous study registered in the IRIE (9). A prior investigation reported that the most common cause of
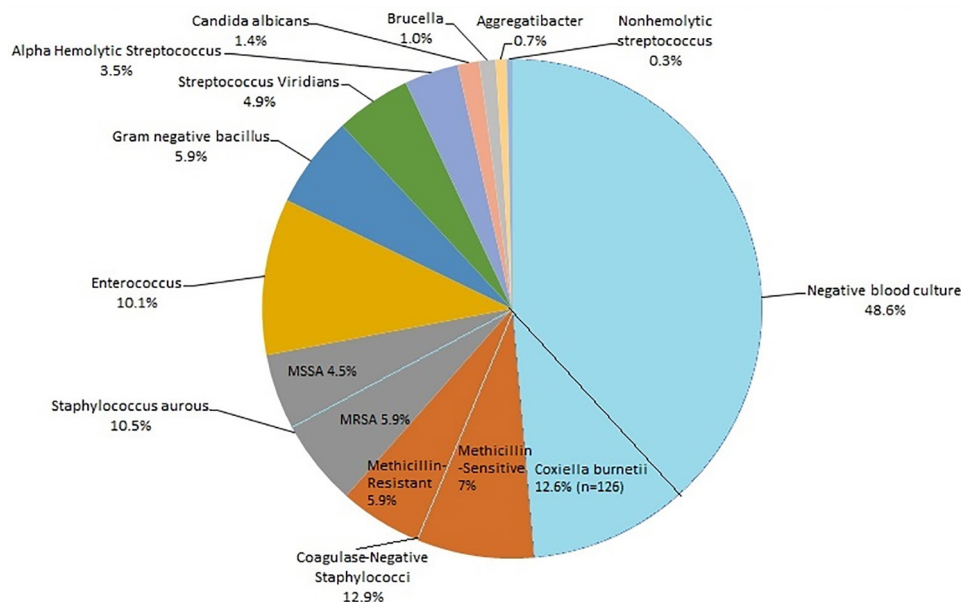

Figure 1. The Frequencies of Causative Microorganisms in Infective Endocardites

Table 4. Frequencies of Complications According to the Types of Microorganism

Characteristics	N (%)
Coagulase-negative Staphylococci	
Acute renal failure	14 (37.8)
Heart failure	7 (18.9)
Pulmonary complications	6 (16.2)
Persistent fever after seven days	5 (13.5)
Cardiogenic shocks	3 (8.1)
Septic shocks	3 (8.1)
Transient ischemic attacks	3 (8.1)
Staphylococcus aureus	
Acute renal failure	7 (23.3)
Heart failure	7 (23.3)
Cardiogenic shocks	4 (13.3)
Transient ischemic attacks	3 (10)
Stroke	2 (6.6)
Enterococcus	
Heart failure	11 (37.9)
Acute renal failure	6 (20.6)
Cardiogenic shocks	2 (6.8)
Transient ischemic attacks	1 (3.4)
Persistent fever after seven days	1 (3.4)
Gram-negative Bacillus	
Acute renal failure	7 (41.1)
Splenic complications	4 (23.5)
Heart failure	3 (17.6)
Alpha Hemolytic Streptococcus	
Transient ischemic attacks	2 (20)
Pulmonary involvement	2 (20)
Persistent fever after seven days	1 (10)
Cardiogenic shocks	1 (10)
Acute renal failure	1 (10)
Candida	
Acute renal failure	2 (50)
Heart failure	1 (25)
Persistent fever after seven days	1 (25)
Septic shocks	1 (25)
Transient ischemic attacks	1 (25)

IE was *S aureus* (10%) followed by *Enterococci* (9%), *CoNS* (8%), and *S viridans* (6%) (5). This shift in the microbiology of IE could be related to several factors such as increased healthcare contacts and invasive procedures. In fact, the incidence of *CoNS* IE seems to be on the rise, which may be a consequence of an increase in healthcare-associated procedures such as intravenous catheterization and hemodialysis. Indeed, *CoNS* is one of the significant causes of native and prosthetic valve IE. The incidence rate of prosthetic valve IE due to *CoNS* has been found to range from 15% to 40%. Such cases are usually healthcare-associated (owing to inoculation at the time of surgery) and manifest themselves within one year of valve replacement. Heart failure also develops in about 50% of patients suffering from *CoNS* prosthetic valve IE, with more than 80% of these cases developing complications such as intracardiac abscesses. Further, native valve IE caused by *CoNS* occurs in 5-12% of cases subsequent to the hematogenous seeding of damaged heart valves and endocardium. The clinical course of *CoNS*-induced native valve IE is subacute, and prolonged duration of clinical presentation is common and can be identified by low-grade fever, weight loss, and night sweats. Additionally, patients generally exhibit a variety of complications such as embolic events, congestive heart failure, and rhythm conduction abnormalities (5). Among the patients with *CoNS* IE in the current study, a variety of complications was reported as follows: 14 cases (37.8%) of acute renal failure, seven cases (18.9%) of heart failure, six cases (16.2%) of pulmonary involvement, five cases (13.5%) of persistent fever after seven days, three cases (8.1%) of cardiogenic shocks, three cases (8.1%) of septic shocks, and three cases (8.1%) of transient ischemic attacks.

In the present research, the second most frequent cause of IE was *S aureus*. At present, *S aureus* is the most common cause of IE in developed countries, probably because of increased healthcare contacts. IE caused by *S aureus* is usually more severe than IE induced by other microorganisms and follows an acute course with multiple peripheral septic emboli, valve destruction, and mixed cardiogenic and septic shocks (10). According to the present study results, the most frequent complications of *S aureus* IE were acute renal failure (n = 7, 23.3%), heart failure (n = 7, 23.3%), cardiogenic shocks (n = 4, 13.3%), transient ischemic attacks (n = 3, 10%), and stroke (n = 2, 6.6%).

The third most frequent cause of IE was *Enterococci* in the current investigation (n = 29, 10.1%), which was consistent with the previous studies reporting *Enterococci* as the second or third most common cause of IE (after *Staphylococci* and *Streptococci*), accounting for 5 - 20% of all IE cases. In a worldwide observation cohort study on 2781 patients with endocarditis, *Enterococci* was the third most common etiologic agent after *S aureus* and *Streptococci* (5). Enterococcal IE follows a subacute course, and the past two decades have witnessed a rise in the incidence of enterococcal bacteremia. In patients with enterococcal bacteremia, several factors denote IE including community acquisition, previous valvular heart disease, and unknown sources (5). The most common complication of enterococcal endocarditis is heart failure, which occurs in nearly 50% of patients. Among the patients with enterococcal endocarditis in the present study, heart failure occurred in 11 patients (37.9%, P = 0.007), acute renal failure in six (26.6%), cardiogenic shocks in two (6.8%), and transient ischemic attacks in only one (3.4%). Embolization also develops in 27 - 43% of all enterococcal endocarditis cases, with the brain being the most common end organ (11).

In the pre-antibiotic era, *S viridans* was the most common cause of IE (75%). Nevertheless, the current incidence rate of streptococcal endocarditis has been estimated to be as low as 20% (5). In the current study, *S viridans* endocarditis had an incidence rate of 4.9% and was the fifth common cause of IE. As discussed previously, such changes in epidemiology reflect an increase in the number of patients acquiring IE in association with intravenous catheters or prosthetic valves. In Iran, patients tend to take antibiotics before visiting a doctor, which may explain the high rate of negative blood cultures in patients with *S viridans* endocarditis.

A normal inhabitant of the gastrointestinal tract; i.e., *S bovis*, accounts for approximately 7% of all endocarditis cases and approximately 20% of streptococcal endocarditis ones. In the current research, four patients (1.4%) were

diagnosed with *S bovis* endocarditis. Bacteremia and endocarditis due to *S bovis* have been strongly associated with the carcinoma of the colon and other lesions of the gastrointestinal tract. Therefore, a colonoscopy should be performed if this organism is isolated from blood cultures (5).

The HACEK group bacteria (*Haemophilus*, *Aggregatibacter* [formerly *Actinobacillus* spp.], *Cardiobacterium*, *Eikinella*, and *Kingella*) have been found to be responsible for almost 2% of all IE cases (7). In the present study, only two patients (0.7%) were diagnosed with *Aggregatibacter* endocarditis.

Gram-negative *Bacilli* have been reported to account for just about 2% of all IE cases. *Salmonella spp*, *Escherichia coli*, *Pseudomonas*, and *Klebsiella* are the common causes of Gram-negative *Bacilli* IE. In the present study, 17 patients (5.9%) were diagnosed with IE induced by Gram-negative *Bacilli* including *Escherichia coli*, *Pseudomonas*, and *Klebsiella*. Congestive heart failure is also common in Gram-negative bacilli IE, and the prognosis is poor (5). According to the current study findings, three (17.6%), seven (41.1%), and four (23.5%) patients developed heart failure, acute renal failure, and splenic complications, respectively.

Endocarditis is the most common cardiovascular complication of brucellosis and has been reported in 1% of all brucellosis cases (12). Medical therapy and valve replacement are usually essential for *Brucella* endocarditis (5). The incidence of *Brucella* endocarditis has been estimated as approximately 10% in some countries (5). According to a previous investigation in Iran, 5.9% of culture-positive IE cases were *Brucella* endocarditis (13). In the present study, *Brucella* was responsible only for 1% of IE cases. Such a low incidence rate could be associated with the fact that the study hospital was a tertiary referral center, to which only patients in need of surgery were referred.

IE resulting from *Coxiella burnetii* (the etiologic agent of Q fever) has been reported in different countries (14-17). The epidemiology of Q fever, which is a zoonosis, also varies around the world (18). The most common reservoirs of *Coxiella burnetii* are ticks, cattle, sheep, and goats, while a variety of animals such as cats and dogs may be infected. Q fever is acquired through occupational exposure, raw milk consumption, exposure to infected parturient cats, and sometimes aerosol transmission (5). Endocarditis is the most common manifestation of chronic Q fever and one of the causes of culture-negative IE (19). The diagnosis is mostly confirmed via serological tests and, sometimes, PCR on blood, cardiac valves, or emboli. The significant point is that serological tests should be interpreted based on clinical judgment and other available information (18, 20). In the current research, the presence of Q fever was explored by the Raoult criteria in 126 patients with IE, 52 of whom (41%) were culture-negative. Among these cases, 16 patients (12.6%) were diagnosed with Q fever endocarditis. The high prevalence of *Coxiella burnetii* IE in Iran necessitates the evaluation for Q fever endocarditis in culture-negative IE cases, given the association between untreated Q fever endocarditis and high mortality rates (18).

Fungal IE is rare, and *Candida* is the most common cause of fungal endocarditis. *Aspergillus spp* are the second cause of fungal endocarditis (21, 22). Other fungi that cause IE include *Cryptococcus*, *Mucor*, and *Histoplasma* (5). In the current investigation, the incidence rate of *Candida* endocarditis was 1.4%, which was consistent with the data obtained from ICE-PCS that reported the diagnosis of *Candida* endocarditis in only 1% of 2700 patients with definite IE (23). Other types of fungus were not detected in this study. The complications of *Candida* endocarditis include congestive heart failure, embolic events, and myocarditis. In the present study, acute renal failure, heart failure, septic shock, and transient ischemic attacks were reported among the patients with *Candida* endocarditis.

Culture-negative IE occurs in 2.5 - 50% of all IE cases (5, 18, 24). The incidence of culture-negative IE varies from country to country, because of several factors such as the prior use of antibiotics, initiation of antibiotics before blood culture sampling, and diagnostic protocols (25). The present study results revealed culture-negative IE in 48.6% of all the IE cases, which was in agreement with the results of a previous study on IE in Iran (9). The high prevalence of culture-negative IE in Iran might be due to several factors including the common use of antibiotics by patients before visiting a doctor, non-IE, fungal IE, and IE due to obligate intracellular parasites such as *Coxiella burnetii*, *Tropheryma whipplei*, and *Chlamydia*, which are not investigated in the routine diagnostic process amongst patients with IE (5, 18, 24).

5.1. Conclusions

In conclusion, the frequencies of microorganisms associated with IE, especially culture-negative IE, vary in different countries, precluding the practical use of a specific guideline around the globe. Hence, further research is needed to elucidate the epidemiology and microbiology of IE in different countries with the aim of eventually formulating an individualized guideline applicable to the epidemiology and microbiology of IE in every country.

5.2. Ethical Approval Code:

IR.RHC.REC.1400.049.

5.3. Informed Consent

Written informed consent approved by the local Ethics Committee of the institute was obtained from all the participants.

material in the manuscript (registration No. 400028).

Financial Disclosure

The authors have no financial interests related to the material in the manuscript.

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