

Epidemiology, Microbiological and Clinical Features, Treatment, and Outcomes of Infective Endocarditis in Crete, Greece

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Background: This study aimed to evaluate the epidemiology, clinical and microbiological features, treatment, and outcomes of infective endocarditis (IE) on the island of Crete, a region with high levels of antimicrobial resistance.

Materials and Methods: Medical records of all hospitalized patients diagnosed with IE at the University Hospital of Heraklion, Crete, Greece, from 1995 to 2015, were retrospectively reviewed. Patients who met the modified Duke's criteria for definite or possible IE were included.

Results: A total of 82 IE patients (median age 67 [range 21–86] years) were included. Most patients suffered from left-sided IE (94%), while most cases of infection occurred in native valves (53.6%). Systemic inflammatory response syndrome criteria were lacking in almost half of the patient population. The leading causative microorganism was *Staphylococcus aureus*, isolated in 24 cases (29%), followed by *Streptococcus* spp. in 15 (18%) and *Enterococcus* spp. in 12 (14.5%). A number of rare and difficult to treat microorganisms had been identified, such as *Gemella morbillorum* in four cases (4.5%), *Streptococcus lugdunensis* in two (2.5%) and *Streptococcus pneumoniae* in one (1%). One patient was serologically positive for *Coxiella burnetii* (1%). All patients received empirical antimicrobial treatment, proven appropriate in 39 blood culture-positive patients (56.5%). Thirteen (16%) patients were classified as culture negative. Seven patients (8.5%) were surgically treated. In-hospital death occurred in 9 patients (11%).

Conclusion: Changes in IE profile requires continuous epidemiological updates. *Staphylococcus* and *Streptococcus* spp. remain the most common etiologic agents. However, the presence of uncommon and/or difficult to treat pathogens raise concerns on the appropriate prophylaxis as well as empirical treatment.

Key Words: Endocarditis; Epidemiology; *Staphylococcus*; Treatment outcome; Prosthetic valve endocarditis

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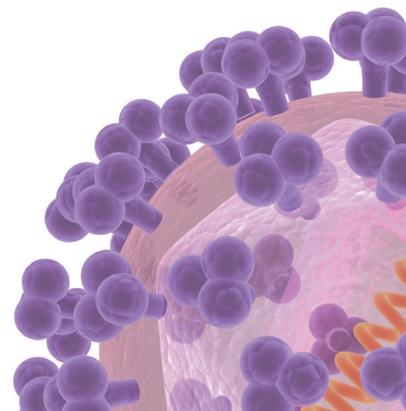
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Introduction

Infective endocarditis (IE) is a relatively uncommon infection of the endothelial surface of the heart and is associated with severe complications and high mortality, despite improvements in its management and prophylaxis [1]. IE is an evolving disease [2], and its epidemiology, microbiological causes, clinical presentation, treatment, and outcome have significantly changed over the past years, especially in developed countries [3-5]. Changes in the disease's microbiology have occurred worldwide due to changes in the predisposing conditions and age of the affected patients and may differ considerably from country to country and even within national borders [1, 4].

IE's mortality rate has been estimated at approximately 25% [4], and despite improvements in healthcare facilities in high-income countries, its incidence has not significantly decreased [4, 5]. Clinical factors such as the increasing percentage of elderly people, reduction of rheumatic heart disease in developed countries, increasing the number of invasive procedures, implantation of prosthetic valves and intracardiac devices, intravenous drug use, and the preventing human immunodeficiency virus, have significantly changed the epidemiology [3, 6-8]. Furthermore, a microbiological shift from streptococci to staphylococci and an increased rate of IE cases due to multidrug-resistant pathogens, mainly in patients with implantable devices, have been described [5, 9].

The current epidemiological status of IE is sparse in the literature, because well-conducted prospective studies were limited [10], while the criteria for definite diagnosis have not been always clear [11, 12]. Regarding the epidemiology of IE in Greece, the primary recent data come from two registries conducted only in Athens [13, 14], while data from other Greek regions are limited and based on retrospective case series and/or case reports [15, 16].

Moreover, in an era of increasing antimicrobial resistance, appropriate empirical antimicrobial treatment for IE with high mortality is of paramount importance.

This study aimed to present IE's epidemiology, causative organisms, clinical features, effective treatment, and positive outcome in a region with high levels of antimicrobial resistance.

Materials and Methods

The medical records of 82 adult patients (aged ≥ 18 years) who were definitely or possibly diagnosed with IE according to the modified Duke's criteria [1] and who visited the University

Hospital of Heraklion, Crete, Greece, from January 1995 to January 2015, were retrospectively examined.

The study was conducted in the Department of Internal Medicine and Infectious Diseases of the hospital, a 650-bed tertiary care hospital, which is a referral center of patients with IE from southern Greece, as it is the only hospital in the region with cardiothoracic surgery department. The hospital covers approximately one million inhabitants. Demographic data, clinical and imaging characteristics, microbiological data, and treatment and outcome data of each patient were recorded. IE cases have been divided into three groups: patients with prosthetic valve endocarditis (PVE), native valve endocarditis (NVE), and intracardiac device-related disease. Early PVE was defined as IE occurring < 12 months post-surgery, whereas late PVE was defined as the case occurring ≥ 12 months post-surgery [1]. Two patients had prosthetic valve along with permanent pacemaker and were included as PVE in the analysis.

Causative microorganisms were identified using conventional culture and serology [1]. The initial empirical antimicrobial therapy was considered appropriate if the causative pathogen was susceptible to the agent used [17].

Chronic kidney disease was classified according to pre-established criteria [18]. Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula [19].

The study has been conducted according to the Declaration of Helsinki for human medical studies and has been approved by the institutional medical ethics committee.

Statistical Methods

The statistical analysis was mainly descriptive. Data are presented as mean \pm standard deviation or median values or numbers (percentages). Categorical variables were compared between the two groups using the chi-square with Yates correction test. A two-tailed *P*-value of < 0.05 was considered statistically significant. Data were analyzed using the SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

A total of 82 patients (50 males) with possible (15; 18%) or definite (67; 82%) IE were included in the study (Fig. 1). The patients' median age was 67 (range, 21–86) years. Table 1 lists the clinical and demographic characteristics of the study population. Twelve patients (15%) suffered from type 2 diabetes. The

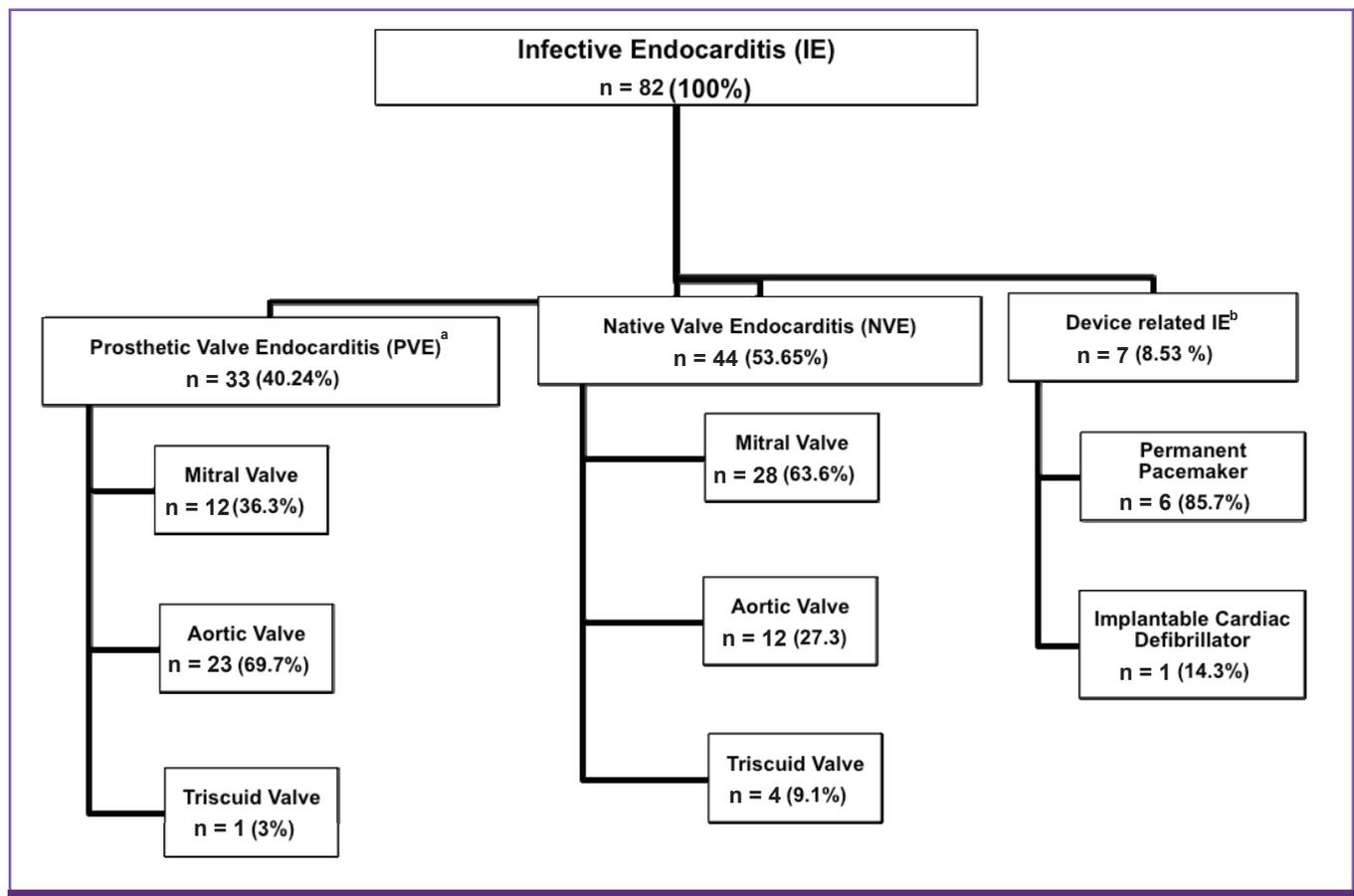


Figure 1. Summary of 82 cases with infective endocarditis.

IE, infective endocarditis; PVE, prosthetic valve endocarditis; NVE, native valve endocarditis.

^aThree patients had two prosthetic valves affected.

^bTwo patients had prosthetic valve along with permanent pacemaker.

most common symptoms upon admission were fever and weakness, present in 84% and 61% of patients, respectively. The mean duration of fever before initiation of antimicrobial therapy was 25 ± 33 days. Other symptoms were chills (45%), sweating (23%), weight loss (17%), headache (16%), arthralgia (16%), myalgia (11%), back pain (11%), and vomiting (6%). A total of 46 patients (56%) presented with systemic inflammatory response syndrome (SIRS) on admission. Two patients presented with coma and one with delirium. Clinical signs such as Janeway lesions and Roth's spots were observed in only five (6%) and two (2.5%) patients, respectively. Splenomegaly was recorded in nine (11%). In 20 patients (24.5%), a newly detected heart murmur was observed. A predisposing risk factor was present in most patients (70; 85%), while a history of rheumatic fever was present only in five (6%) (Table 1). Six patients had a history of previous IE. Five (6%) suffered major arterial emboli, while septic pulmonary infarcts were observed in four (5%). Rheumatoid factor was elevated in seven (8.5%) patients. Thirty (36.5%) pa-

tients had microscopic hematuria, while glomerulonephritis as direct complication was recorded in 11 patients (13.5%) upon admission.

The vast majority of patients suffered left-sided IE (77; 94%). Right-sided IE was recorded in five (6%) patients: due to intravenous drug use (3) and permanent pacemaker (2). Most IEs (86.5%) met at least one major criterion of the modified IE Duke's criteria [20], (Check please) while echocardiography was characteristic for IE in 69 patients (84%) (Table 2). Most cases (44) occurred in native valves. However, a significant increase in the PVE percentage from the first (1995–2004) to the second decades of the study period (2005–2015) was observed (27% vs. 50%; $P = 0.042$). Seven cases (8.5%) were associated with implanted intracardiac devices. The most commonly affected valve in PVE IE was the aortic (69.7% vs. 27.3%; $P < 0.01$), while in those with NVE was the mitral (36.3% vs. 63.6%; $P = 0.02$) (Fig. 1). Twelve patients (14.6%) presented with early PVE.

The most common microorganism isolated from the blood

Table 1. Demographic and clinical characteristics of the study population

Patients' characteristics	N = 82 (100%)
Age	62.06 ± 16.79
Male	50 (61%)
Underlying diseases	
Diabetes mellitus	12 (14.63%)
Degenerative heart disease	10 (12.2%)
COPD	7 (8.53%)
Moderate or severe chronic kidney disease	4 (4.87%)
Hepatic disorders	6 (7.32%)
Cancer	1 (1.22%)
HIV	1 (1.22%)
Alcohol abuse	1 (1.2.2%)
Risk factors for IE	
Prosthetic valve/intracardiac device	40 (48.8)
Congenital heart disease	6 (7.31%)
Previous Episode of IE	6 (7.31%)
IVDU	3 (3.65%)
Rheumatic heart disease	5 (6.1%)
Bicuspid aortic valve	1 (1.22%)
Mitral valve prolapse	7 (8.53%)
Calcific aortic stenosis	2 (2.44%)

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IE, infective endocarditis; IVDU, intravenous drug user.

was *Staphylococcus aureus* being the causative organism in almost one-third of all cases (24; 29%). Seven of these 24 isolates were methicillin-resistant (MRSA) (Table 3). Twelve cases of *Enterococcus* spp. have been isolated; no vancomycin-resistant enterococci strains have been identified among them. Four cases of gram-negative bacterial IE (5%) and another four of the anaerobic pathogen *Gemella morbillorum* (with two resistant to β -lactams and aminoglycosides) (5%) were also observed. Thirteen cases (15%) were classified as culture-negative IE, and one of had *Coxiella burnetii* as the causative organism them based on serological results (Table 3). Culture-negative IE was significantly higher in PVE patients (29% vs. 4.5%; $P < 0.01$).

Microorganisms (*Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp.) causing IE in the present population have been divided in two groups, with each group representing the organisms isolated in one decade. Comparison between the two decades of the study has not shown any significant difference regarding the type of organisms.

The initial antimicrobial therapy has been found to be appropriate in 39 out of 69 (56.5%) blood culture-positive cases. Three patients presented with reversible acute kidney failure and one

Table 2. Modified Duke's criteria of 82 cases with infective endocarditis

Modified Duke's criteria	
Major criteria	71 (86.6%)
Blood cultures positive for IE	69 (84.1%)
Typical microorganisms consistent with IE from 2 separate blood cultures	59 (71.9%)
Microorganisms consistent with IE from persistently positive blood cultures:	10 (12.2%)
Echocardiogram positive for IE	69 (84.1%)
Vegetation, valvular perforation or an aneurysm	61 (74.4%)
Abscess, pseudoaneurysm, intracardiac fistula	5 (6.09%)
New partial dehiscence of prosthetic valve	3 (3.65%)
Number of affected valves	
Single valvular IE	68 (82.9%)
Multi valvular IE	9 (11%)
Minor criteria	
Predisposition for IE	61 (74.39%)
Fever (>38°C)	69 (84.14%)
Vascular phenomena	13 (15.85%)
Immunological phenomena	13 (15.85%)
Microbiological evidence (do not meet major criteria)	7 (8.53%)

IE, infective endocarditis.

with leukopenia as direct complications of the antimicrobial therapy. Thirty patients (36%) had received antimicrobial treatment prior to hospital admission.

In-hospital death occurred in nine patients (11%). Seven (8.5%) had a IE relapse during the follow-up period. Ischemic stroke occurred in seven (8.5%), while one (1.22%) suffered from hemorrhagic stroke as an IE complication. Nineteen patients (23%) met the criteria for surgical valve repair; however, only nine of them underwent valve surgery. The remaining 10 patients refused surgical treatment.

Discussion

The changing IE profile requires continuous epidemiological updates. This is the first retrospective study on IE in Crete and southern Aegean islands. The study showed that the frequency of rheumatic heart disease-related IE was low, as compared to other developed countries [4], along with a significant increase in PVE cases in the recent years. The study also demonstrated prosthetic valves as the main predisposing factors and *S. aureus* as main causative pathogen, with a high percentage

Table 3. Microorganisms isolated from 82 patients with infective endocarditis

	All N = 82 (100%)	Prosthetic valves or device related IE N = 38 (100%)	Native valve IE N = 44 (100%)	P-value
Blood culture-positive IE	69 (84.14%)	27 (71%)	42 (95.5%)	<0.01
<i>Staphylococcus</i> spp.	30 (36.5%)	10 (26.3%)	20 (45.4%)	0.1
<i>Staphylococcus aureus</i>	24 (29.2%)	7 (18.4%)	17 (38.6%)	0.054
MRSA	7 (29.16%)	3 (42.8%)	4 (23.5%)	0.37
<i>Staphylococcus lugdunensis</i>	2 (2.44%)	0 (0%)	2 (4.5%)	0.49
Other CNS	4 (4.9%)	3 (7.9%)	1 (2.3%)	0.33
<i>Streptococcus</i> spp.	15 (18.3%)	5 (13.1%)	10 (22.7%)	0.39
Viridans streptococci	6 (7.3%)	1 (2.6%)	5 (11.36%)	0.2
<i>Streptococcus pneumoniae</i>	1 (1.22%)	0 (0%)	1 (2.3%)	0.99
<i>Streptococcus sanguis</i>	1 (1.22%)	1 (2.6%)	0 (0%)	0.46
<i>Streptococcus mitis</i>	1 (1.22%)	0 (0%)	1 (2.3%)	0.99
<i>Streptococcus bovis</i>	4 (4.9%)	2 (5.2%)	2 (4.5%)	0.99
<i>Streptococcus mutans</i>	1 (1.22%)	0 (0%)	1 (2.3%)	0.99
<i>Streptococcus milleri</i> group	1 (1.22%)	1 (2.6%)	0 (0%)	0.46
<i>Enterococcus</i> spp.	12 (14.6%)	8 (21%)	4 (9.1%)	0.21
<i>Enterococcus faecium</i>	6 (7.3%)	3 (7.9%)	3 (6.8%)	0.99
<i>Enterococcus faecalis</i>	6 (7.3%)	5 (13.1%)	1 (2.3%)	0.09
Gram-negative bacterium IE	4 (4.9%)	1 (2.6%)	3 (6.8%)	0.62
<i>Escherichia coli</i>	2 (2.44%)	0 (0%)	2 (4.5%)	0.49
<i>Pseudomonas aeruginosa</i>	1 (1.22%)	0 (0%)	1 (2.3%)	0.99
<i>Stenotrophomonas maltophilia</i>	1 (1.22%)	1 (2.6%)	0 (0%)	0.46
Facultative anaerobic				
<i>Gemella morbillorum</i>	4 (4.9%)	1 (2.6%)	3 (6.8%)	0.62
Polymicrobial IE	4 (4.9%)	2 (5.2%)	2 (4.5%)	0.99

IE, infective endocarditis; MRSA, methicillin-resistant *S. aureus*; CNS, coagulase negative staphylococci.

of MRSA (29%). Moreover, almost half of the patients were admitted to the hospital without fulfilling the SIRS criteria for sepsis.

The median age of patients with definite or possible IE was 67 years (21–86), which is consistent with the most recent published information regarding IE in Greece [14] as well as in high-income countries [4, 9, 21]. In contrast, the median age of patients in developing countries is significantly lower [3, 4, 22].

IE is an uncommon, potentially deadly, disease, and depending on the causative microorganism as well as the presence or absence of underlying heart disease, the initial clinical presentation may vary widely, although most physicians may expect a severely ill septic patient. It should be noted that in almost half of the present patients, SIRS criteria for sepsis were not observed upon admission.

Pathogens causing IE and the main risk factors vary accord-

ing to the continent, region, country, even in areas within a country, and access to cardiovascular surgery [4]. Different microbiological and risk factors have been observed between early and late PVEs. Furthermore, risk factors and causative microorganisms are different between high- and low-income countries [4]. In particular, in developed countries, degenerative heart disease, implantable intracardiac devices, and prosthetic valves have replaced rheumatic heart disease as the main risk factors [4]. In developing and low-income countries, such as regions in Asia, Latin America, and Africa, rheumatic disease and streptococci remain the main risk factor and the most common causative agents, respectively [1, 4]. In contrast, in developed and high-income countries, staphylococci are the most common pathogens [1, 4, 23]. Indeed, in the present study, only five patients (6%) had a history of rheumatic heart disease, while the most common pathogen isolated was *S. aureus*, fol-

lowed by *Streptococcus* spp. and *Enterococcus* spp. In a recent multicenter prospective cohort study in Greece from the metropolitan area of Athens [14], *Enterococcus* spp. were the leading cause of nosocomial IE. In the present study, four cases of Gram-negative bacterial IE and another four rare cases of *G. morbillorum*, a facultative anaerobic pathogen (two strains resistant to β -lactams and aminoglycosides) [15], were recorded. Additionally, a rare case of *C. burnetii* IE, an endemic pathogen on the island of Crete, has also been identified [16], showing the importance of knowledge on local epidemiology.

The microbiological shift from streptococci to staphylococci is not only important for epidemiological reasons but also for the initiation of appropriate empirical antimicrobial treatment, especially in regions with high rate of antimicrobial resistance. In the present study, the leading pathogen was *S. aureus* in both NVE and PVE. Greece is one of the leading European countries in the prevalence of MRSA, with its percentage being 39.4% according to the antimicrobial resistance surveillance report of the European Centre for Disease Prevention and Control in 2015 [24]. MRSA was detected in 29% of the *S. aureus* IE cases. Current European Society of Cardiology Guidelines [1] proposed the combination of ampicillin and flucloxacillin or oxacillin and gentamicin as initial empiric antimicrobial therapy in severely ill patients with community-acquired native valve IE or late PVE. In penicillin-allergic patients and those with early PVE or nosocomial and healthcare-associated IE, the combination of vancomycin and gentamicin is the treatment of choice. This evidence reveals a gap between the current European guidelines for initial empirical treatment of IE in NVE or late PVE, and the need for the administration of vancomycin, instead of ampicillin and flucloxacillin/oxacillin as initial antimicrobial treatment before the pathogen's isolation in countries with high percentages of MRSA, such as Greece, might be associated with a better clinical outcome. In 43.5% of the present blood culture-positive cases, the initial antimicrobial therapy was inappropriate. This can be explained, partly, due to the high levels of MRSA (29%), along with the special regional epidemiology of intracellular and anaerobic pathogens.

Blood culture-negative IE can occur in up to 31% of all IE cases [1], and its management is challenging. This type of infection commonly occurs as a consequence of previous antimicrobial administration. In the present study, 13 (16%) cases have been classified as culture-negative, which is consistent with the recently published data from developed countries in Europe and Greece [4, 9, 13, 14, 23, 25]. Interestingly in our study, culture-negative IE was significantly higher in PVE ($P < 0.01$), with previous antimicrobial use being considered the main cause,

encountered in 12 out of 13 patients.

The present study has some limitations since it was a single-center and retrospective with a relatively small number of patients. However, it highlights the local IE epidemiology and was conducted in a referral center.

In conclusion, in the present population, *S. aureus* was the leading pathogen that causes IE, whereas intracellular pathogens such as *C. burnetii* and facultative anaerobic bacteria like *G. morbillorum*, with unusual antimicrobial resistance, raise concerns on the appropriate prophylaxis and empirical treatment of IE. Consequently, IE treatment may be a more complicated issue than previously believed, especially in an era and area with dramatically increasing microbial resistance.

Conflicts of Interest

No conflicts of interest.

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