

Diagnosis and treatment of infective endocarditis - experience from the Clinic for infectious diseases at Clinical Hospital Centre Rijeka in a 10-year period

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UNIVERSITY OF RIJEKA
MEDICAL FACULTY
INTEGRATED UNDERGRADUATE AND GRADUATE STUDY
STUDY OF MEDICINE

Marin Gobac

DIAGNOSIS AND TREATMENT OF INFECTIVE ENDOCARDITIS - EXPERIENCE FROM
THE CLINIC FOR INFECTIOUS DISEASES AT CLINICAL HOSPITAL CENTRE RIJEKA IN
A 10-YEAR PERIOD

GRADUATION THESIS

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3. _____

Thesis contains 36 pages, 2 pictures, 8 tables, 4 graphs and 31 literature quotations.

I want to dedicate this thesis to my parents, Mirela and Josip, who devoted their entire lives to provide every possible mean for me to pursue the career I am most passionate about, and who taught me that being a human being is the most essential priority before anything else, even being a doctor.

Also, I would like to dedicate this thesis to my Ana, who is the light of my life and without her I would be lost.

Lastly, I would like to thank my mentor for numerous consultations, availability and constructive criticism so that this thesis would achieve its maximum.

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List of abbreviations:

[18F] FDG-PET/CT	18F-Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography
CHF	Congestive Heart Failure
CNS	Central Nervous System
CoNS	Coagulase-Negative <i>Staphylococci</i>
CT	Computed Tomography
CT-A	Computed Tomography Angiography
ESC	European Society of Cardiology
GIT	Gastrointestinal Tract
GUT	Genitourinary Tract
HIV	Human Immunodeficiency Virus
IBD	Inflammatory Bowel Disease
IDU-IE	Injection Drug Use-Related Infective Endocarditis
IE	Infective Endocarditis
IVDU	Intravenous Drug Use
MDC	Modified Duke Criteria
MRSA	Methicillin-Resistant <i>Staphylococcus aureus</i>
MSSA	Methicillin-Sensitive <i>Staphylococcus aureus</i>

NBTE	Nonbacterial Thrombotic Endocarditis
NVE	Native Valve Endocarditis
PET	Positron Emission Tomography
PVE	Prosthetic Valve Endocarditis
SAG	<i>Streptococcus anginosus</i> Group
SAH	Subarachnoid Haemorrhage
SIE	Streptococcal Infective Endocarditis
TTE	Transthoracic Echocardiography
US	Ultrasound
WBC SPECT/CT	White Blood Cell Single-Photon Emission Computed Tomography/Computed Tomography

1. Introduction

Infective endocarditis (IE) is the inflammation of the endocardium and the valves that separate the heart's four chambers. It is predominantly caused by bacteria and presents with a wide range of symptoms. If not promptly identified and treated, numerous cardiac and systemic complications can arise. In 2019, the estimated incidence of IE was 13.8 cases per 100 000 subjects per annum and IE accounted for 66 300 deaths worldwide. This disease has shown a male predominance, with a male to female ratio of approximately 2 to 1. The average age of patients with IE is over 65 years. This increased incidence among the elderly is likely related to the higher prevalence of predisposing factors in this age group; patients with prosthetic valves (and with any material used for cardiac valve repair), non-rheumatic degenerative valve disease, congenital valve abnormalities (including bicuspid aortic valve disease), previous history of IE, cardiovascular implanted electronic devices (CIEDs) and hypertrophic cardiomyopathy. Although rheumatic heart disease was once a significant risk factor, it now accounts for less than 5% of cases in the current antibiotic era. Recreational intravenous drug use has emerged as a significant risk factor, responsible for about 10% of all infective endocarditis cases (1,2).

1.1. Etiology

The etiology of IE, in an enviable 90% of cases, are Gram-positive bacteria; primarily *Streptococcus* spp., *Staphylococcus* spp. and *Enterococcus* spp.. Less common causative agents include Gram-negative and atypical bacteria and fungi (1).

Of all Gram-positive bacteria, Staphylococci are responsible for approximately 30% of IE in the developed world (2). As singular agents, *Staphylococcus aureus*, *Streptococcus viridans*, *Streptococcus bovis*, Enterococci and the HACEK organisms (*Haemophilus aphrophilus*,

Aggregatibacter actinomycetemcomitans, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*) form the group of the most common pathogenic microorganisms responsible for IE. In only 1% of cases, *Candida* and *Aspergillus* cause severe and frequently fatal IE. *Streptococcus anginosus* group (SAG), *Staphylococcus lugdunensis* (a coagulase-negative *Staphylococcus*), the aforementioned HACEK group, and *Streptococcus pneumoniae* (which leads to an Austrian syndrome; the triad of endocarditis, meningitis and pneumonia) can also cause IE, usually with a more demanding clinical presentation (2).

Table 1. Causative agents of IE with their respected clinical characteristics

<i>Staphylococcus aureus</i>	<ul style="list-style-type: none"> - Most common cause of IE - More than 50% cases present on healthy and fully functional valves - Bacteraemia caused by an infected intravenous line - Near 50% of mortality rate
Coagulase-negative <i>Staphylococci</i> (CoNS)	<ul style="list-style-type: none"> - Presents with subacute form IE - 30% of PVE and 5% of NVE - <i>S. lugdunensis</i> form is extremely aggressive
<i>Streptococcus viridans</i>	<ul style="list-style-type: none"> - 50–60% of subacute cases - Immunologic events cause symptoms and clinical signs
Streptococcal Group B	<ul style="list-style-type: none"> - Acute; most frequently in pregnant women and immunocompromised patients

	<ul style="list-style-type: none"> - Mortality approaches 40% - Forming of arterial thrombi and heart failure are frequent complications - Valve replacement often needed
Streptococcal Group D	<ul style="list-style-type: none"> - Subacute form; primary infection in GI and GU tract - Third most common cause of IE - Rising antimicrobial resistance
<i>Streptococcus anginosus</i> group (SAG)	<ul style="list-style-type: none"> - Presents acutely or subacutely - Up to 15% of all Streptococcal IE - Can form abscesses (most frequently found in CNS)
Nonenterococcal group D	<ul style="list-style-type: none"> - Presents with subacute form IE - Correlated to colon cancer and IBD - Susceptible to penicillin
<i>Bartonella</i>	<ul style="list-style-type: none"> - In patients with poor socio-economic status - False negative blood cultures may occur
<i>Pseudomonas</i>	<ul style="list-style-type: none"> - Subacute or chronic right-sided IE - Therapy also requires surgical treatment
HACEK group	<ul style="list-style-type: none"> - Presents with subacute form IE - 5% of IE - Surgical therapy needed in addition to antimicrobial therapy

Fungal	- Most common causative agent of NVE and PVE is <i>Candida albicans</i>
Polymicrobial etiology	- <i>Pseudomonas</i> and Enterococci most frequent coinfection - Persistent in IVDU patients

GI = gastrointestinal (tract)
 GU = genitourinary (tract)
 IBD = inflammatory bowel disease
 IE = infective endocarditis
 IVDU = intravenous drug use
 NVE = natural valve endocarditis
 PVE = prosthetic valve endocarditis

1.2. Epidemiology

The incidence of IE has experienced an exceptional increase during the last five decades, which unfortunately we are unable to stop, but not because of the changes in the virulence of the causative agent, but due to the changes in the characteristics of risk populations for IE. Those arise as a result of the increase in the frequency of nosocomial infections and the increase in life expectancy. Today, the annual incidence is 6 to 13 cases per 100,000 people; in contrast to the period from 1970 to 2000, when it was only 5 to 7 cases (3). Likewise, the number of hospitalizations correlating to IDU-IE is increasing due to the exceptional increase in intravenous drug use. To put this into perspective, from the year 2000 to the year 2013 in the United States. alone, the number of hospitalizations increased by approximately 40%, but hospitalized cases due to IDU-IE increased by 238% in patients between the ages of 15 and 34. Furthermore, in Germany, the prevalence of IE was 11.6 per 100,000 people in the period from 2005 to 2015 (4).

The average age of patients with IE is >65 years and presents rarely in children and adolescents. Degenerative valvular diseases, an increase in the number of artificial valve procedures and a higher rate of nosocomial infections have led to the increase in the average age of patients with IE.

Due to the aforementioned changes, an increase in the incidence of IE caused by *Staphylococcus* spp. (MSSA, MRSA) was recorded (5). Predisposing factors for the occurrence of IE are neglected oral hygiene (*viridans Streptococci*), previously treated IE patients, colon cancer (*Streptococcus bovis*), haemodialysis and HIV infection. In 30% of cases IE involves artificial valves, while 30% of nosocomial correlated cases of IE are recorded on native valves.

Table 2. Risk factors for IE

Older age (with certain comorbidities) <ul style="list-style-type: none"> • Diabetes • Ischemic heart disease • Chronic renal disease • Infectious diseases
Intravenous drug use
Rheumatic heart disease (and recovered patients)
Artificial heart valves
Built-in pacemakers (and intravenous catheters)
Dental procedures
Congenital heart defects
Heart valve diseases
Haemodialysis
Colon cancer
Poor oral hygiene

Overall, the most important risk factors are advanced age (with certain comorbidities; listed above), surgically placed artificial valves, intravenous drug use (right-sided IE most often), congenital heart

defects, diabetes and structural heart diseases such as mitral valve prolapse or rheumatic heart disease (6).

1.3. Pathogenesis

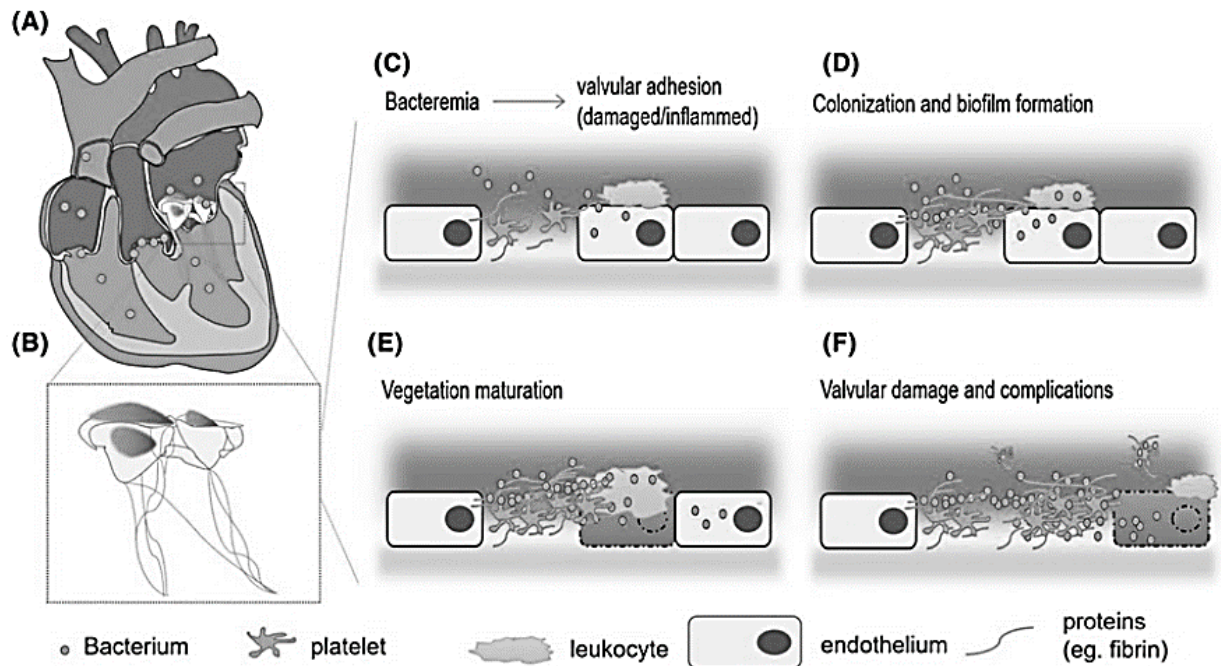
The pathogenesis of IE, and its resulting complications, is the result of complex events between the causative microorganism, endothelium of heart valves, and the host immune response. The healthy endothelium of the cardiac endocardium is resistant to colonization and infection. For an infection to occur, two basic prerequisites must be met (5). The presence of bacteria in the blood and the existence of mechanical damage to the surface of the valves. The damage is most often caused by chronic turbulent blood flow, which exposes the subendothelial extracellular matrix, consequently activating platelets and causing the formation of fibrin and platelet deposits. This is the process of sterile thrombus formation called NBTE, and the pathogenesis of NBTE itself involves a combination of a hypercoagulable state and an injured and/or inflamed endothelium. Conditions that increase the risk of NBTE are precisely those that lead to incomplete valve closure; these conditions include aortic stenosis, mitral regurgitation, aortic regurgitation, and ventricular septal defect. They provide a suitable place for thrombus formation. Migrating thrombophlebitis or Trousseau's syndrome is often encountered as a final diagnosis precisely because it initially presents as NBTE (3).

Furthermore, the adherence of the causative agent is the most important event in the pathogenesis of IE itself after the two basic prerequisites, mentioned previously, are met. The process of pathogen adherence to a previously sterile thrombus is followed by the stimulation of local procoagulant activity and the formation, characteristic for IE, called vegetation; made of platelets, fibrin, erythrocytes, inflammatory cells and the causative agent itself. The pathogen attracts leukocytes and at the same time stimulates angiogenesis inside the valves, which leads to additional

growth of the vegetation. The granulation tissue of the vegetation, created in the process of healing the mechanical damage itself, fixes to the substrate, reducing its chance of detachment. The process of swelling of the granulation tissue leads to the permeation of the vegetation itself and its transformation into a connective scar, which leads to a permanently deformed and damaged valve (7,8).

Infective endocarditis can have various localizations. If it affects the valves of any cardiac orifice, it is called valvular, but if the inflammation is localized to the endocardium of the atria or the ventricles, it is classified as mural endocarditis. Considering the appearance of the changes, it can be classified as fibrotic, verrucous and ulcerative (9). Verrucous endocarditis is manifested by warty formations on the valves, ulcerative endocarditis indicates the presence of ulcerations on the valves and, if the valves are fibrously deformed and thickened, fibrotic endocarditis. The primary origin of the infection is not necessarily known, and if it is, it is usually found in (micro)traumas of the skin, pharynx or GIT and erosions of the mucous membrane of the oral cavity (3,5,6).

The consequence of valve dysfunction is congestive heart failure mostly due to leaflet perforation and rupture, as well as mitral chordal rupture, which leads to severe valvular regurgitation. Paravalvular abscesses or fistulae are caused by the local spread of the infection, as well as the involvement of the surrounding myocardium, the conduction system of the heart between the aortic root, septal leaflet of the tricuspid valve and the mitral annulus. If part of the vegetation is torn off, systemic embolization (spleen, liver, kidneys, brain) is common (3,5,6,7).



Picture 1. Possible pathogenesis of IE (8)

1.4. Clinical presentation

We distinguish three main clinical forms of endocarditis according to the clinical presentation and its characteristics; acute, subacute and chronic, which will be discussed later in this chapter. The most common symptom, which may be absent in subacute endocarditis, is fever, present in more than 90% of patients. IE is suspected if the fever is accompanied by an auscultatory heart murmur and a positive blood culture for the typical causative agents of IE. Some of the accompanying symptoms can be splenomegaly, conjunctival bleeding, lumbar pain and petechial rash on the skin. Neurological manifestations often occur in the form of meningitis, cerebritis, SAH or stroke, which can be haemorrhagic or ischemic (4,5). Physical signs of interest, since they are almost pathognomonic for IE, are Janeway's lesions, Osler's nodes, splinter haemorrhages, and Roth's spots. Roth's spots indicate haemorrhages with pale centres located on the retina, while Osler's nodules and Janeway lesions appear on the skin due to immunological and vascular phenomena.

In the formation of Janeway's lesions, the main etiology is septic embolization with the formation of microabscesses, exclusively in the dermis of the feet or palms, which appear as painless macular or papular, painless, slightly erythematous lesions. The deposition of immune complexes comprising of circulating antibodies causes an inflammatory reaction that leads to the formation of Osler's nodules, which are described as painful, swollen lesions on erythematous and warm skin.

Acute IE occurs very suddenly, which can be explained by the high virulence of its causative agents, which lead to the creation of abundant exudative pathological changes. It manifests itself in the form of a vegetation which, relatively often, decomposes and forms septic thromboemboli. Deep erosion of the endocardium is observed at the base of the vegetation, the detachment of which often leads to a deep ulcer. The most common causative agent of acute IE is *Staphylococcus aureus*. Subacute endocarditis occurs gradually with milder symptoms since the pathogen's virulence is lower. Overcome rheumatic fever, previously damaged valve or calcified aortic stenosis are some of the predisposing factors for the development of SIE. The most common causative agent is the saprophyte of the oral cavity, *Streptococcus viridans*. Fibrosis, valve deformation and mononuclear inflammatory infiltrate are the main characteristics of chronic endocarditis, which, arising from subacute or indolently during chronic diseases, can last for months (4,5).

Infective endocarditis is associated with certain risks and complications that usually require surgical intervention. Three main clinical complications are HF, uncontrolled infection and septic embolization (in particular, to the CNS circulation). Congestive heart failure, caused by valvular regurgitation, is the most common complication, closely correlated with ICU admission. In up to 80% of patients, cerebrovascular complications occur in the form of ischemia or microhaemorrhages, which are often clinically "invisible". Blindness, acute or chronic limb ischemia, paraplegia, myocardial infarction or kidney abscesses are some of the embolic

complications. Infrequent complications are aortic valve dissection, pericarditis, arthritis or vertebral osteomyelitis. Distal systemic complications include the possible dissemination of infection and the occurrence of septic shock, deposition of immune complexes in the kidneys with consequent glomerulonephritis, and septic infarctions of the brain, lungs or kidneys (3,5).

1.5. Diagnosis

Infective endocarditis remains a diagnostic challenge due to its variable clinical presentation; it should be considered in all patients with sepsis or FUO in the presence of predisposing factors. The fulminant course of the disease requires a rapid diagnosis based on a detailed history and physical examination as well as laboratory findings and blood culture with the use of imaging methods (10,11). In year 1994 and later modified in y 2000; the Modified Duke Criteria (MDC) were published; an algorithm that lists major microbiological and radiological signs along with the presence of minor ones and results in a diagnosis of definitive endocarditis, probable endocarditis or rejected endocarditis (3,11). The sensitivity of MDC is 70%-79%, and a definitive diagnosis requires the inclusion of clinical factors and multimodality imaging approach (echocardiography, cardiac/whole-body CT, cerebral MRI, [18F] FDG-PET/CT, and WBC SPECT/CT).

The most important microbiological test, according to the MDC, in the diagnosis of IE is the blood culture, which must be taken before starting antimicrobial therapy. Three sets of blood cultures from peripheral blood should be taken, in more than 6 hours apart, before the start of antimicrobial therapy when subacute or chronic endocarditis is suspected (12). In acute IE with sepsis or septic shock, antimicrobial therapy is administered immediately after taking 2 sets of blood cultures. If the blood cultures are negative, in patients with high clinical suspicion of existing IE, serological testing should be performed for less common causative pathogens of IE, including *Coxiella burnetti*, *Bartonella* spp., *M. pneumoniae*, *Legionella* spp., *C. pneumoniae*, and *Brucella* spp.

Transthoracic echocardiography of the heart (TTE) is often, due to its minimal invasiveness, the first choice in imaging diagnostics, but its comprehensive sensitivity is 70% for NVE and only 50% for PVE. The preferred imaging method, whose only drawback is its semi-invasiveness, is transoesophageal echocardiography due to its high sensitivity (90%-92%). The final diagnosis is based on the MDC, which includes microbiological, imaging and clinical features of the disease (13). An increase in the sensitivity of MDC can be achieved if neuroimaging with CT-A or MR of the heart is included in routine management of suspected IE patients; though the ESC have updated the MDC in 2023 which has shown greater sensitivity than the aforementioned MDC in this thesis (14).

MODIFIED DUKE CRITERIA FOR INFECTIVE ENDOCARDITIS	
Major Criteria	
1. Blood cultures positive	
(a) Typical pathogens derived from 2 separate blood cultures (<i>S. viridans</i> , <i>S. bovis</i> , <i>S. aureus</i> , HACEK) in the absence of a primary focus	
(b) Persistently positive blood cultures	
(c) Single positive blood culture for <i>Coxiella burnetii</i> or antiphase I IgG titer > 1:800	
2. Evidence of endocardial involvement	
3. Positive echocardiogram for IE	
(a) Oscillating intracardiac mass on valve or supporting structures	
(b) Abscess	
(c) Dehiscence of prosthetic valve	
(d) New valvular regurgitation	
Minor Criteria	
1. Predisposing heart condition or IVDA	
2. Temperature > 38°C	
3. Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions	
4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor	
5. Microbiologic evidence: positive blood culture but does not meet a major criterion as noted above or serologic evidence of active infection with organism consistent with IE	
Definitive IE	Possible IE
1. Histopathologic confirmation OR	1. 1 major and 1 minor OR
2. 2 major criteria OR	2. 3 minor
3. 1 major, 3 minor OR	
4. 5 minor	
Rejected IE	
1. Firm alternate diagnoses explaining clinical evidence for endocarditis	
2. Resolution of IE syndrome with ≤ 4 days of antibiotics	
3. No histopathologic evidence of IE on surgical pathology or autopsy after ≤ 4 days of antibiotics	
4. Does not meet criteria as above.	

Picture 2. Modified Duke Criteria for the diagnosis of IE (11)

1.6. Treatment and prophylaxis

The basis of IE treatment is the timely and early administration of intravenous bactericidal antimicrobials, in high doses over an appropriate period of time (3). With the aim of eradicating the infection, the toxic effects of antibiotics on the patient's organism and the increase in resistance of the pathogen itself are often ignored and should be taken into consideration. Initial therapy is often empirical and consists of starting the patient on vancomycin, broad-spectrum penicillin antibiotic or a 3rd or 4th generation cephalosporin (4). Directed antimicrobial regimen to specific pathogen causing IE is listed in Table 3 (4,5).

Table 3. Antimicrobial regimen for IE based on its etiology

Pathology	Preffered antimicrobial regimen
NVE (<i>Staphylococcus aureus</i> , <i>Streptococcus bovis</i> , viridans <i>Streptococci</i> , <i>Enterococcus</i> spp., HACEK group)	IV vancomycin – first dose 20mg/kg; then every 12h 15mg/kg IV cefepime – 2g every 8h
PVE (<i>Staphylococcus aureus</i> , CoNS, <i>Enterococcus</i> spp.)	IV vancomycin – first dose 20mg/kg; then every 12h 15mg/kg IV cefepime – 2g every 8h
Blood culture-negative endocarditis (<i>Coxiella burnetii</i> , <i>Bartonella</i> spp., <i>Brucella</i> spp.)	IV vancomycin IV ceftriaxone IV gentamicin - 3 mg/kg per 24h in 3 doses (1 dose – 1mg/kg)

CoNS = Coagulase-negative *Staphylococci*

HACEK = *Haemophilus aphrophilus*, *Aggregatibacter actinomycetemcomitans*, *Cardiobacteriumhominis*, *Eikenella corrodens*, *Kingella kingae*

IV = intravenous

NVE = natural valve endocarditis

PVE = prosthetic valve endocarditis

The treatment of Streptococcal IE, caused by the viridans group of Streptococci or *Streptococcus bovis*, is based on the susceptibility of these causative organisms to penicillin. In strains of Streptococci that are sensitive to penicillin, monotherapeutic parenteral administration of penicillin or ceftriaxone is effective, while vancomycin is an option if there is an allergy or intolerance to penicillin. Likewise, the addition of gentamicin to the initial therapy is justified in more resistant strains of viridans Streptococci and in patients with prosthetic valves (15).

Staphylococcal IE treatment depends on whether the causative agent is coagulase positive (*Staphylococcus aureus*) or coagulase negative (i.e. *Staphylococcus lugdunensis*), Staphylococcal sensitivity towards methicillin, and on the presence or absence of prosthetic valves and prosthetic material. β -lactams, such as cefazolin, are the drugs of first choice in the treatment of IE caused by MSSA. Aminoglycosides and rifampicin are not recommended for NVE caused by MSSA or MRSA. NVE caused by MRSA is treated with vancomycin, but daptomycin can also serve as an acceptable alternative. PVE is recommended to be treated with a combination of β -lactams for MSSA (vancomycin for MRSA) and rifampicin with gentamicin in the initial 2 weeks of treatment (16).

Due to the increase in resistance to penicillin and aminoglycosides, Enterococcal IE requires exhaustive treatment. Synergistic bactericidal action can be achieved by the combination of penicillin and aminoglycosides, in which the penicillin causes the intracellular entry of aminoglycosides. If there is a high risk of developing nephrotoxicity or ototoxicity, then a combination of ampicillin and ceftriaxone is resorted to, especially with resistant strains of Enterococci (16).

Surgical treatment is used in up to 50% of patients and is becoming the backbone in reducing mortality in the treatment of IE accompanied by complications. Indications are numerous, while

the most common is CHF mostly because of leaflet perforation and rupture, as well as mitral chordal rupture, lead to new severe valvular regurgitation (or worsening of pre-existent valvular regurgitation) and subsequent acute HF. Others include persistent fever and persistent positive blood cultures (>7 days), large vegetations on the valves (>1cm), perivalvular infection in the form of an abscess or fistula, and severe aortic or mitral regurgitation with consequent hemodynamic insufficiency (5).

Antimicrobial prophylaxis for IE is recommended for high-risk patients, including those with artificial heart valves, a history of IE, congenital heart defects (with residual damage), and cyanotic uncorrected congenital heart defects. Likewise, prophylaxis is recommended during high-risk surgical procedures, which include all dental procedures, respiratory tract operations with incision or biopsy of the respiratory mucosa, procedures on infected skin/skin structures, and placement of a prosthetic heart valve. In prophylaxis, first generation cephalosporins (cefazolin, cephalexime or ceftriaxone) and clindamycin or vancomycin, in case of allergy to β -lactams, are most often used (3,5).

As it has been demonstrated in several observational studies, there is an importance of an endocarditis team in the diagnosis, management and clinical outcomes of patients with IE. The members of the endocarditis team should include specialists with direct involvement in the diagnostic and therapeutic processes.

2. Aim of the study

The aim of this study is to analyse the incidence of infective endocarditis in a 10-year period at the Clinic for Infectious Disease, Clinical Hospital Centre Rijeka, with emphasis on demographic

factors, infectious agents, clinical presentation, empiric and targeted therapy, and treatment outcome.

3. Participants and procedures

This study included 56 patients treated at the Clinic for Infectious Diseases of the Rijeka Clinical Hospital Centre in the period from January 1st, 2014, to December 31st, 2023. Patient data were extrapolated from IBIS system with the consent of the Rijeka Clinical Hospital Centre Ethics Committee from February 28, 2024 (Class: 003-05/24-1/27; Reg. Number: 2170-29-02/1-24- 2).

Median values were calculated using the formulas below.

When the number of observations is odd the formula is:

$$p = \frac{n + 1}{2}$$
$$\tilde{x} = x_p$$

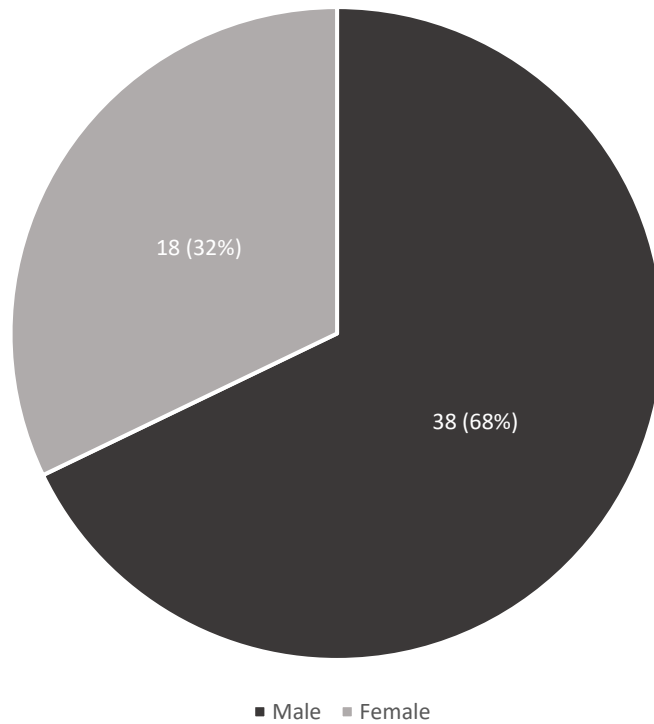
When the number of observations is even the formula is:

$$p = \frac{n}{2}$$
$$\tilde{x} = \frac{x_p + x_{p+1}}{2}$$

where n is the number of observations.

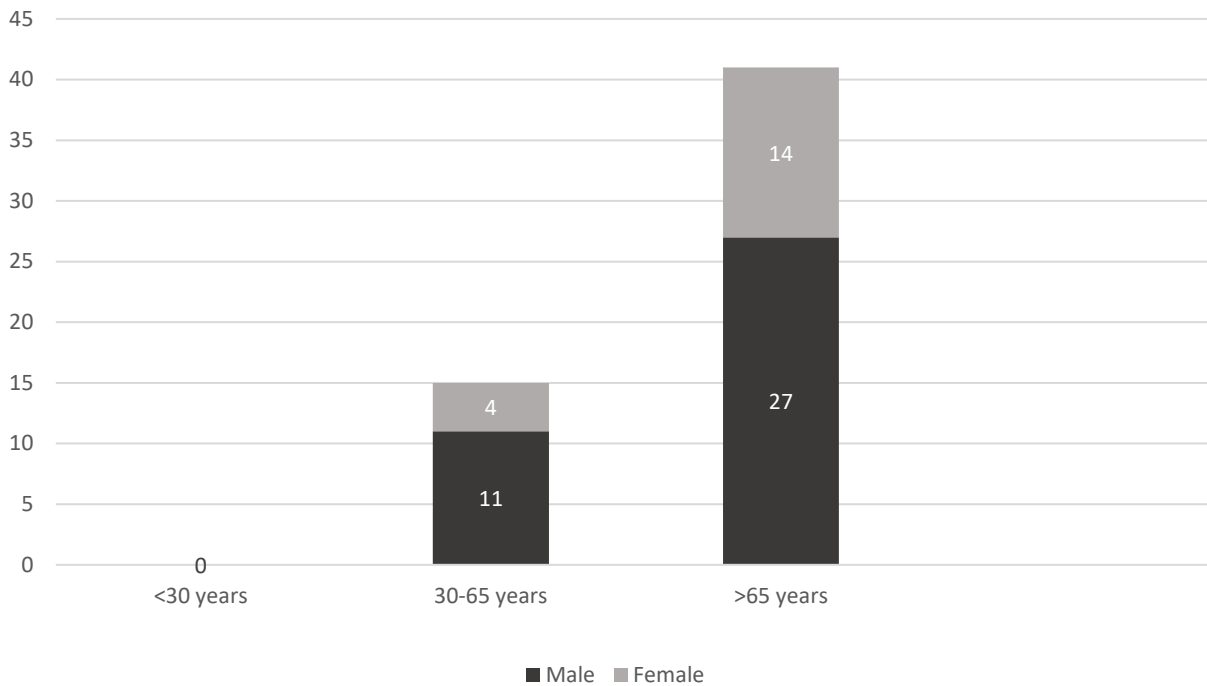
4. Results

Of the 56 patients included in this study, 38 were male (68%) and 18 were female (32%).



Graph 1. Patient gender distribution

According to the extrapolated age data, the patients were classified into 3 groups; patients under 30 years of age (n=0; 0%), patients between 30 and 65 years of age (n=15; 26.8%) and patients over 65 years of age (n=41; 73.2%). The overall median age value is 69 years of age. The youngest patient was a 31-year-old male, and the oldest patient was also a 92-year-old male.

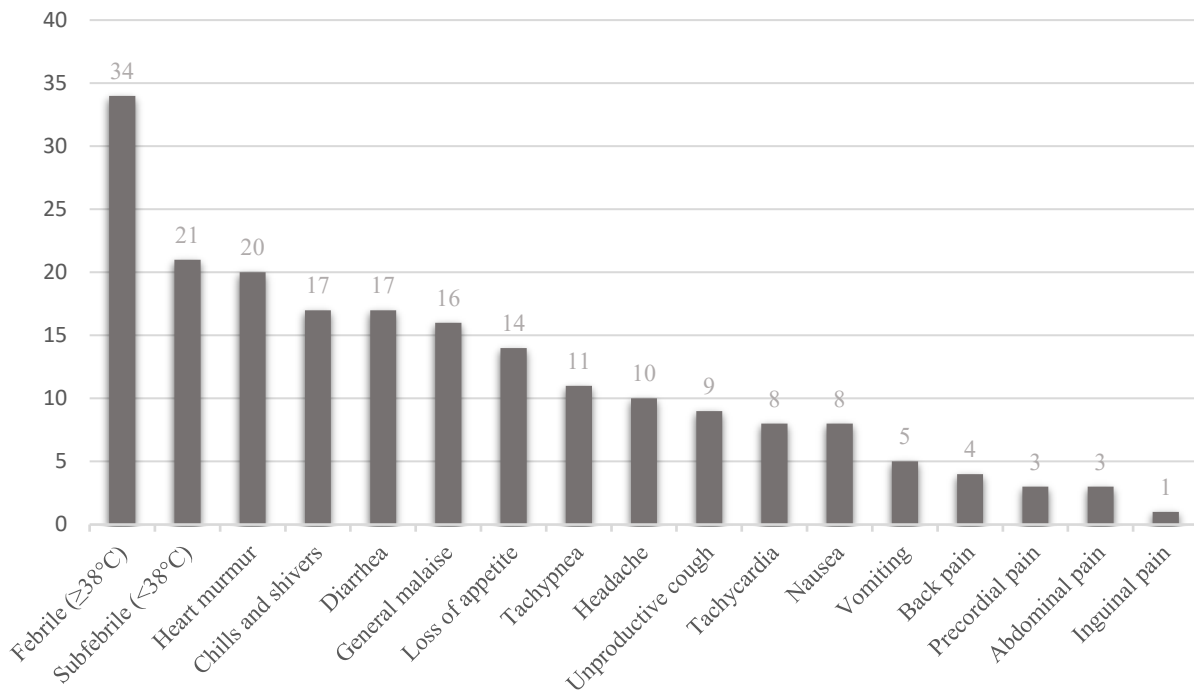


Graph 2. Age groups of patients

The leading symptom among all patients was fever (98.2%). In 60.7% of patients body temperature was $\geq 38^{\circ}\text{C}$, while 37.5% of patients were subfebrile (body temperature of $37-38^{\circ}\text{C}$). Heart murmur was present in 35.7% of patients, chills and shivers in 30.4%, diarrhoea in 30.4%, general malaise in 28.6% and loss of appetite in 25% of patients. Other less frequently reported symptoms included tachypnoea (19.6%), headache (17.9%), unproductive cough (16.1%), tachycardia (14.3%), nausea (14.3%), vomiting (8.9%), back pain (7.1%), precordial pain (5.4%), abdominal pain (5.4%) and inguinal pain (1.8%).

In terms of the duration of symptoms before admittance to the hospital, 19 patients (33.9%) reported having a fever ($\geq 38^{\circ}\text{C}$) persistent for longer than one week while even 28 patients (50%) reported having a remittent temperature curve lasting for more than two weeks, characterized with

alterations of low-grade fever (37-38°C) and febrile periods. 23 patients (41.1%) reported being lethargic and feeling general malaise for a month before admittance, while 16 of them had the aforementioned symptoms on the day of the admittance. Chills and shivers were present for a median period of 4 days in 17 of patients.



Graph 3. Prevalence of symptoms in patients with IE

Most of the patients had an underlying disease(s) or condition(s) that, in some part, predisposed them in the development of IE during bacteriemia. A significant number of patients had an anamnesis of previous heart disease, either structural or functional (prosthetic heart valves, atrial fibrillation, aortic regurgitation, aortic stenosis, coronary heart disease).

52 patients (92.9%) had 2 or more underlying diseases. The most frequent pair of comorbidities was arterial hypertension combined with diabetes mellitus type II; this combination was present in

15 patients (28.8%). Of those 15 patients, 8 (53.3%) of them had already been diagnosed with atrial fibrillation, 4 (26.7%) with chronic kidney disease and the other 3 (20%) with aortic regurgitation.

Second most frequent pair of underlying diseases was the combination of hypertension and coronary heart disease which was recorded in 13 patients (25%). 8 (61.5%) out of those 13 patients had artificial heart valves (7 biological, 1 mechanical) while 4 (30.8%) had an implanted pacemaker. The one remaining patient (7.7%) had a diagnosis of aortic stenosis in addition to having hypertension and coronary heart disease.

Out of all 56 patients, only 4 patients (7.1%) had only one underlying condition; 3 of those patients were intravenous drug users without other comorbidities while the 4th patient had a chronic hepatitis C infection.

Table 4. Distribution of patients by comorbidities and predisposing factors

Comorbidities with certain predisposing factors	Number of patients
Older age (>65 years)	41
Hypertension	33
Coronary heart disease	23
Diabetes mellitus (type 1 and type 2)	18
Atrial fibrillation	15
Artificial heart valves (mechanical and biological)	14
Implanted pacemaker	10
Chronic kidney disease	9
Hyperlipoproteinemia	7
Aortic regurgitation	7
IVDU	6

Tooth extraction	5
Active infectious diseases	4
Aortal stenosis	3
Colorectal cancer	2

IVDU = intravenous drug use

Blood laboratory analysis revealed increased values of pro-inflammatory parameters in sera of patients with IE and most probable bacterial etiology of the disease. Additionally, the subacute course of the disease was characterized with mild anaemia and low haematocrit.

The overall median values of laboratory blood parameters are shown in table 5. It is important to mention that all the values except Troponin T and NT-proBNP were analyzed from 56 patients. Troponin T was drawn from 15 patients, and NT-proBNP on admittance was drawn from 3 patients oppose to the maximum values during hospitalization which were drawn from 9 patients.

There were no significant deviations in elevated laboratory values depending on the gender of the patients.

Table 5. Median laboratory blood parameters

Laboratory Blood Parameter	Blood parameter value on admittance	Maximum value of blood parameter during hospitalization	Blood parameter value on hospital discharge	Reference values
Leukocytes (x 10 ⁹ /L)	11.5	11.3	8.4	3.4-9.7
Neutrophiles (x 10 ⁹ /L)	9.7	8.9	6.9	2.06-6.49
Erythrocytes (x 10 ¹² /L)	3.87	3.54	3.63	♂ 4.34-5.72 ♀ 3.86-5.08
Thrombocytes (x 10 ⁹ /L)	196	233	214	140-450
Haemoglobin (g/L)	116	102	104	♂ 138-175 ♀ 119-158
ESR (mm/h)	25	22	13	♂ 2-13 ♀ 4-24
CRP (mg/L)	176	117	51	<5
Haematocrit (L/L)	0.333	0.242	0.298	♂ 0.415-0.530 ♀ 0.356-0.470
Creatinine (x µmol/L)	146	187	56	♂ 64-104 ♀ 49-90
AST (U/L)	43	63	23	8-38
ALT (U/L)	34	46	20	10-48
GGT (U/L)	47	69	49	♂ 11-55 ♀ 9-35
Troponin T (ng/L)*	46	101	-	<14
NT-proBNP (ng/L)	3317**	1769***	-	♂ <879 ♀ <623

ALT = Alanine aminotransferase

AST = Aspartate aminotransferase

CRP = C-reactive protein

ESR = Erythrocyte sedimentation rate

GGT = Gamma-glutamyl transferase

NT-proBNP = N-terminal pro-brain natriuretic peptide

* analysed from 15 patients

** analysed from 3 patients

*** analysed from 9 patients

The annual case counts of different causative agents is shown in table 6. Of all causative agents, *Staphylococcus aureus* is leading in a total of 20 patients (35.7%), followed by *Enterococcus faecalis* with 14 (25%), *Streptococcus viridans* with 7 (12,5%) and *Streptococcus agalactiae* as causative agent in 5 (8.9%) cases of IE. One case was recorded for each of the following causative agents: β -haemolytic *Streptococcus* group F (BHS-F), *Serratia marcescens*, *Escherichia coli*, *Streptococcus oralis*, *Streptococcus salivarius*, *Staphylococcus lugdunensis*, *Corynebacterium* spp., and *Streptococcus sanguinis*. Sterile cultures / undefined agents were found in 2 investigated patients.

Most of the isolates presented with good antimicrobial sensitivity to standard antibiotics. There were no significant deviations in the antimicrobial sensitivity of isolates during the analysed period, and the majority of patients (83.9%) had no record of hospitalization in their recent medical history, which was, overall, favourable for treatment; as well as the fact that the causative agents weren't multi-drug resistant bacteria.

Table 6. Annual distribution of IE causative agents

Godina	<i>Staphylococcus aureus</i>	<i>Enterococcus faecalis</i>	<i>Streptococcus viridans</i>	<i>Streptococcus agalactiae</i>	β HS-F	<i>Serratia marcescens</i>	<i>Escherichia coli</i>	<i>Streptococcus oralis</i>	<i>Streptococcus salivarius</i>	<i>Staphylococcus lugdunensis</i>	<i>Corynebacterium</i> spp.	<i>Streptococcus sanguinis</i>	Sterile culture/agent unidentified
2014.	3	1	1	x	x	x	x	x	x	x	x	x	x
2015.	2	1	1	x	x	1	x	x	x	x	x	x	x
2016.	5	1	x	x	1	x	1	x	x	x	1	1	1
2017.	3	1	1	1	x	x	x	1	x	x	x	x	1
2018.	4	1	x	x	x	x	x	x	x	x	x	x	x
2019.	1	2	x	1	x	x	x	x	x	x	x	x	x
2020.	x	2	x	x	x	x	x	x	x	x	x	x	x
2021.	x	1	3	x	x	x	x	x	x	x	x	x	x
2022.	1	2	1	1	x	x	x	x	1	1	x	x	x
2023.	1	2	x	2	x	x	x	x	x	x	x	x	x
Total	20	14	7	5	1	1	1	1	1	1	1	1	2

Antibiotic sensitivity of causative agents is shown in table 7. The distribution of empiric and directed therapy among patients is shown in table 8.

Table 7. Antibiotic sensitivity of isolated bacteria from patients with IE

	<i>Staphylococcus aureus</i>			<i>Enterococcus faecalis</i>			<i>Streptococcus viridans</i>			<i>Streptococcus agalactiae</i>			<i>BHS-F</i>			<i>Serratia marcescens</i>			<i>Escherichia coli</i>			<i>Streptococcus oralis</i>			<i>Streptococcus salivarius</i>			<i>Staphylococcus lugdunensis</i>			<i>Corynebacterium spp.</i>			<i>Streptococcus sanguinis</i>								
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R			
Sensitivity	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Ampicillin	3	0	0	10	0	1	5	0	0	4	0	0	x	x	x	0	0	1	1	0	0	1	0	0	1	0	0	1	0	0	x	x	x	x	x	x	x	x	x	1	0	0
Teicoplanin	1	0	0	9	0	0	2	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1	0	0			
Linezolid	1	0	0	3	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1	0	0	x	x	x						
Gentamicin	8	0	0	9	0	2	2	0	0	1	0	0	x	x	x	1	0	0	1	0	0	x	x	x	x	x	x	1	0	0	1	0	0	1	0	0	x	x	x			
Norfloxacin	x	x	x	2	0	0	x	x	x	1	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Vancomycin	2	0	0	9	0	0	2	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1	0	0	x	x	x						
Nitrofurantion	x	x	x	2	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1	0	0						
Imipenem/cilastatin	x	x	x	6	3	1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Azithromycin	x	x	x	x	x	x	1	0	1	3	0	2	1	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Clarithromycin	1	0	0	x	x	x	0	0	1	3	0	2	1	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Clindamycin	8	0	0	x	x	x	4	0	0	5	0	0	1	0	0	x	x	x	x	x	x	1	0	0	1	0	0	1	0	0	0	0	1	x	x	x						
Penicillin	2	0	5	x	x	x	3	0	0	2	0	0	1	0	0	x	x	x	x	x	x	x	x	x	0	0	1	x	x	x	0	0	1	1	0	0						
Moxifloxacin	2	0	0	x	x	x	3	0	0	1	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1	0	0	x	x	x	1	0	0						
Cloxacillin	12	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1	0	0	x	x	x	x	x	x						
Erythromycin	8	0	0	2	0	0	2	0	0	x	x	x	x	x	x	1	0	0	x	x	x	x	x	x	x	x	x	1	0	0	x	x	x	x	x	x						
Rifampicin	2	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
TMP-SMX	7	0	3	x	x	x	1	0	0	x	x	x	x	x	x	x	x	x	1	0	0	x	x	x	x	x	x	1	0	0	x	x	x	x	x	x						
Ceftriaxone	3	0	0	x	x	x	2	0	0	3	0	0	x	x	x	x	x	x	1	0	0	1	0	0	1	0	0	x	x	x	x	x	x	x	x	x						
Cefuroxime	3	0	0	x	x	x	2	0	0	x	x	x	x	x	x	x	x	x	1	0	0	1	0	0	1	0	0	x	x	x	x	x	x	1	0	0						
Amoxicillin	x	x	x	3	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1	0	0						
Piperacillin/tazobactam	x	x	x	1	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Levofloxacin	x	x	x	x	x	x	x	x	x	1	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Methicillin	1	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x									
Ciprofloxacin	6	0	3	0	0	1	1	0	0	x	x	x	x	x	x	1	0	0	1	0	0	x	x	x	x	x	x	x	x	x	0	0	1	x	x	x						
Cefazolin	2	0	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x									
Cefepime	x	x	x	x	x	x	1	0	0	x	x	x	x	x	x	x	x	x	1	0	0	x	x	x	x	x	x	x	x	x	x	x	x									

Empirically, in most cases co-amoxiclav therapy was prescribed (n=17, 30.4%), followed by gentamicin (n=8; 14.3%), ceftriaxone and ciprofloxacin (n=7; 12.5%). As a directed antimicrobial therapy, ampicillin was prescribed to 16, ceftriaxone to 15, and cloxacillin to 14 of patients, while gentamicin was prescribed to 19 patients, but always in a combination with β -lactam antibiotic; predominantly with ampicillin, ceftriaxone or flucloxacillin. If we compare the applied empiric and targeted therapy - the first line of selected antibiotics consists of β -lactams (ampicillin, (flu)cloxacillin, ceftriaxone) with gentamicin, vancomycin and/or their combinations.

Table 8. Distribution of empiric and directed therapy among patients

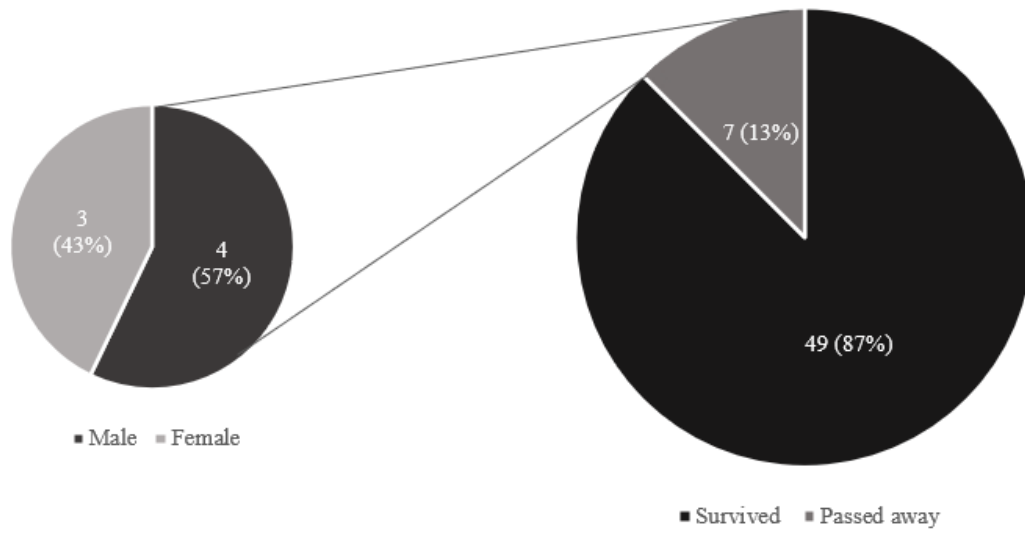
	Antibiotic	Number of patients
Empiric therapy	Co-amoxiclav	17
	Gentamicin	8
	Ceftriaxone	7
	Ciprofloxacin	7
	Vancomycin	6
	Metronidazole	3
	Ampicillin	2
	(Flu)cloxacillin	2
	Cephazolin	1
	Clindamycin	1
Directed therapy	(Flu)cloxacillin	20
	Gentamicin	19
	Ampicillin	16
	Ceftriaxone	15
	Vancomycin	7
	Co-amoxiclav	3
	Penicillin	3
	Ciprofloxacin	3
	Azithromycin	1
	Clarithromycin	1
	Clindamycin	1

The average duration of antimicrobial therapy (and hospitalization) lasted for 5 weeks; 10 patients (17.9%) were discharged after 4 weeks, 34 patients (60.7%) after 5 weeks, 8 patients (21.4%) after 6 weeks, 3 patients (5.4%) after 7 weeks and 1 patient (1.8%) after 8 weeks.

33 patients (58.9%) were transferred from the Clinic for Infectious Disease to the Clinic for Cardiovascular Diseases to continue their treatment; from this we can conclude that 23 patients were fully treated and rehabilitated solely at the Clinic for Infectious Disease. From 33 transferred patients, 14 patients (42.4%) required surgery, all of which were done at the Cardiac surgery Department with Intensive Care Unit.

Out of 56 patients, 42 (75%) received only antibiotic therapy while 14 (25%) underwent surgery in addition to already receiving antibiotic therapy. Of 14 surgeries that were performed, the most frequent one was mitral valve repairment; it had been done on 9 (64.3%) patients. Of those 9 patients; only 2 (22.2%) had a complication in terms of a perivalvular abscess. Second most conducted surgery was aortic valve repairment which had been done on 4 (28.6%) patients. Out of 14 patients that underwent surgery, 2 (14.3%) of them passed away in the following one-year period, while 12 (85.7%) recovered fully.

Patient survival outcomes are shown in graph 4. According to the mentioned distribution, one in seven patients (14.3%) passed away; from which we can extrapolate the mortality rate of 12.5%.



Graph 4. Patient survival outcomes

5. Discussion

The expected age at which patients become ill with infective endocarditis is older than 65 years (16,17). According to literature, most patients fall ill with IE between 60 and 79 years of age, with an average of 62.2 years (18–21). Erichsen et al. observed that the mean age of IE diagnosis in both sexes has increased steadily, but no study reports variations towards one sex (18). In the gender distribution, the male gender dominates in over 68% of cases (22). Despite sex differences influencing the response to infectious diseases, in this case, they are largely overlooked. Indeed, IE reportedly occurs more frequently in men, with a male-female ratio ranging between 2:1 and 9:1. Beyond this, however, sex differences are not adequately defined for causative agents, pre-existing conditions, management, and outcomes among IE patients (23–26). The most common symptom with which patients were admitted to the hospital was fever $\geq 38^{\circ}\text{C}$, which was present in 60.7% of patients. The following symptoms include low grade fever (37-38°C (37.5%)), heart murmur (35.7%), chills and shivers (30.4%), diarrhoea (30.4%), general malaise (28.6%) and loss of appetite (25%). Other symptoms included tachypnoea (19.6%), headache (17.9%), unproductive cough (16.1%), tachycardia (14.3%), nausea (14.3%), vomiting (8.9%), back pain (7.1%), precordial pain (5.4%), abdominal pain (5.4%) and inguinal pain (1.8%) (27). The leading comorbidity in over 58.9% of cases was hypertension. They are followed by coronary heart disease in 41.2% and diabetes mellitus in 32.1% of cases. Factors of cardiac etiology (atrial fibrillation, presence of artificial heart valves, implanted pacemaker and aortic regurgitation) are mentioned in slightly more than 26.7% of cases. In addition to the above, we also include hyperlipoproteinemia and IVDU with an insignificant percentage of frequency (<10%). However, although the last in a series of predisposing factors - tooth extraction and colorectal cancer - with a percentage of less than 1%, they are sometimes few, if not the only ones, that influence the differential diagnosis (28).

The laboratory examines the complete blood count, the presence of leucocytosis, which in this case is between 11.3 and 11.5 ($\times 10^9/L$), and thrombocytopenia which was not exposed in this study, i.e. thrombocytes remained within the reference values.

CRP is significantly increased and is associated with more severe complications and mortality (28). Low levels of cardiac enzymes correlate with maintained myocardial function in observed patients. A positive blood culture is usually the only specific laboratory finding (29). This time, in 96% of cases the causative agent was verified, while sterile cultures were found in only 2 cases. For the diagnosis of infective endocarditis, the revised Duke clinical diagnostic criteria and the criteria of the European Society of Cardiology are used, which have been modified and expanded with imaging results, and are based on microbiological, clinical and echocardiographic findings (11). The etiology of infective endocarditis, in an enviable 90% of cases, is caused by Gram-positive bacteria; primarily *Streptococcus* spp., *Staphylococcus* spp. and *Enterococcus* spp. According to the guidelines of the European Society of Cardiology, the recommended antibiotic therapy for the initial empiric treatment of infectious endocarditis consists of ampicillin, amoxicillin and gentamicin (and/or their combinations), but in this study the most used empiric therapy included was co-amoxiclav, gentamicin and ceftriaxone (and/or their combinations). In infective endocarditis caused by *Staphylococcus* spp., targeted therapy includes cloxacillin and/or gentamicin, which is also confirmed by this finding. In IE caused by *Enterococcus* spp., the second most common causative agent, the treatment of choice is β -lactam antibiotic in combination with gentamicin. Although in this research it was found that death occurred in every 7 patients, the percentage of 12.5% is, fortunately, lower than the average, which according to the literature is 18-27% (30,31).

6. Conclusion

Infective endocarditis is a disease that predominantly affects men (68%). The median age at which it occurs is 69 years.

The leading symptom of IE is fever $\geq 38^{\circ}\text{C}$ lasting for a minimum of 7 days, while the secondary symptoms include heart murmur, chills and shivers, diarrhoea, general malaise and loss of appetite. The majority of IE patients express predisposing factors, and most often in combinations - of which arterial hypertension with diabetes mellitus type II is the leading one. Next in line is arterial hypertension in combination with coronary heart disease. Habits also presented an important predisposing factor for IE, especially IV drug abuse.

All patients demonstrated leucocytosis and a significantly increased CRP, which is associated with more severe complications and mortality. In 96% of cases, we found positive blood cultures; the remaining percentage were sterile.

Leading causative agent of IE in our patients was *Staphylococcus aureus*, isolated in 35.7% of cases, followed by *Enterococcus faecalis* in 25%, *Streptococcus viridans* in 12.5% and *Streptococcus agalactiae* in 8.9% of cases. Fortunately, most of the isolates presented antimicrobial sensitivity to wide-spectrum antibiotics. Co-amoxiclav was prescribed empirically in most cases, but directed antimicrobial therapy comprised mainly ampicillin, ceftriaxone, and (flu)cloxacillin. Gentamicin was routinely administered in combination with β -lactam antibiotics. In 75% of patients, antibiotic therapy was successful in eliminating the IE, while in 25%, in addition to antibiotic therapy, surgery was also required. The mortality rate in our patients was 12.5%, fortunately, lower than the average (30,31).

7. Summary

Infective endocarditis is a disease whose incidence is rising in patients of all ages; with male gender predominance of 2:1 ratio. Degenerative valvular diseases, an increase in the number of artificial valve procedures and a higher rate of nosocomial infections have led to the increase in the average age of patients with IE. IE is associated with high morbidity and mortality and, if left untreated, IE is considered to be always fatal. In recognizing this disease, the most important is to diagnose it on the basis of history and clinical examination. Modified Duke Criteria are generally accepted and applied in diagnostics today, even though they show low sensitivity without using imaging methods. Treatment of patients requires the joint involvement of infectious disease specialists, microbiologists and cardiologists, cardiac imaging experts and cardiac surgeons. Antimicrobial therapy is used in all cases due to the nature of infective agents; surgery is becoming the backbone in reducing mortality being used in up to 50% of patients. Adherence to therapeutic guidelines and indications for surgery can significantly improve the survival and quality of life of these patients.

Keywords: infective endocarditis, antimicrobial therapy, surgery, predisposing factors

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9. Curriculum vitae

Marin Gobac was born in Pakrac on December 24th, 1999. In July 2018, he enrolled at the Faculty of Medicine of the University of Rijeka. During his study, he worked as a peer teacher at the Department of Anatomy and the Department of Histology and Embryology.