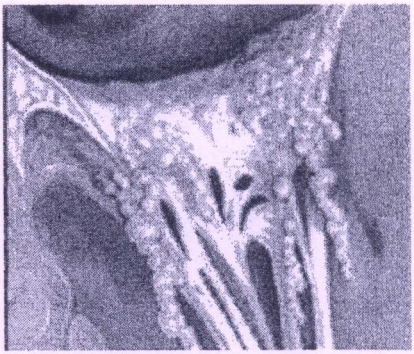
HEALTH MINISTRY, REPUBLIC OF MOLDOVA
STATE UNIVERSITY OF MEDICINE AND PHARMACY
NICOLAE TESTEMITANU

Alexandra GREJDIERU Lucia MAZUR-NICORICI
Liviu GRIB Valeriu REVENCO Minodora MAZUR
Elena SAMOHVALOV Viorica OCHIȘOR

INFECTIVE ENDOCARDITIS



CHISINAU
2014

HEALTH MINISTRY, REPUBLIC OF MOLDOVA
STATE UNIVERSITY OF MEDICINE AND PHARMACY
NICOLAE TESTEMITANU

DEPARTMENT OF INTERNAL MEDICINE
DISCIPLINE: CARDIOLOGY, MEDICAL CLINIC N3

Alexandra GREJDIERU Lucia MAZUR-NICORICI
Liviu GRIB Valeriu REVENCO Minodora MAZUR
Elena SAMOHVALOV Viorica OCHIȘOR

INFECTIVE ENDOCARDITIS

CHISINAU
CEP *Medicina*
2014

CZU 616.126-002(076.5)
I-52

Guide has been approved and recommended for editing by Methodical Council of the Internal Medicine Department, University of Medicine and Pharmacy *Nicolae Testemitanu* nr. 1 of 12.XI.2013

Autors:

Alexandra Grejdieru – MD, PhD, associate professor
Lucia Mazur-Nicorici – MD, PhD, assistent of professor
Liviu Grib – MD, PhD, professor
Valeriu Revenco – MD, PhD, professor
Minodora Mazur – MD, PhD, professor
Elena Samohvalov – MD, PhD, assistent of professor
Viorica Ochişor – MD, PhD, associate professor

Official reviewers:

Alexandru Izvoreanu – MD, PhD, professor
Alexandru Carauş – MD, PhD, professor

Editor: *Nadejda Şamşurina, Iuliana Oprea*
Computer macketing: *Iulia Don*

DESCRIEREA CIP A CAMEREI NAŢIONALE A CĂRŢII

Infective endocarditis: Guide for students / Alexandra Grejdieru, Lucia Mazur-Nicorici, Liviu Grib [et al.]; State Univ. of Medicine and Pharmacy *Nicolae Testemitanu*, Dep. of Internal Medicine, Discipline Cardiology [et al.]. – Chişinău: CEP *Medicina*, 2014. – 71 p.
Bibliogr.: p. 62-64 (31 tit.). – 50 ex.
ISBN 978-9975-118-62-0.
616.126-002(076.5)
I-52

ISBN 978-9975-118-62-0

ABBREVIATIONS

ABT	–	antibiotic therapy
AHA	–	American Heart Association
AIDS	–	acquired immunodeficiency syndrome
AO	–	aortic valve
ARF	–	acute renal failure
CNGS	–	coagulase-negative staphylococcus
CRF	–	chronic renal failure
CRP	–	C-reactive protein
DNA	–	deoxyribonucleic acid
DV	–	degenerative valvulopathies
ECG	–	electrocardiography
EchoCG	–	echocardiography
ESR	–	erythrocyte sedimentation rate
GMN	–	glomerulonephritis
HACEK	–	Haemophilus, Actinobacillus, Cardiobacterium, Eikinella, Kingella
HC	–	hemocultures
HF	–	heart failure
HIV	–	human immunodeficiency virus infection
HR	–	heart rate
ICD	–	intracardiac devices
IE	–	infectious endocarditis
IE IV	–	infectious endocarditis of the intact valves
IE LH	–	infectious endocarditis of the left heart
IE NV	–	infectious endocarditis of the native valves
IE PV	–	infectious endocarditis of the prosthetic valves
IE RH	–	infectious endocarditis of the right heart
IVDU	–	intravenous drug users
LV/RV	–	left ventricle/right ventricle
MC	–	multiple-choice test
MIC	–	minimal inhibitor concentration
MRSA	–	methicillin-resistant *Staphylococcus aureus*
MV	–	mitral valve
NMRI	–	nuclear magnetic resonance imaging
NYHA	–	New York Heart Association
PCR	–	polymerase chain reaction
SC	–	simple-choice test
TEE	–	transesophageal echocardiography
TTE	–	transthoracic echocardiography
TV	–	tricuspid valve
USG	–	ultrasonography
WBC	–	white blood cells

INTRODUCTION

Infective endocarditis (IE) is a serious disease, studied throughout two centuries by researchers from different countries. For the first time, as a term, IE was described by Wiliam Osler in 1885 [19]. Although it was proposed the classification, diagnostic criteria (Duke) and evolution variants of IE, many aspects of this disease even now represent one of the major problems in internal diseases clinic [15]. IE remains the disease in which the diagnosis is late, due to changes in clinical symptoms, numerous risk factors and new forms of this disease [8, 12]. The onset of the disease is variable depending on its etiology and clinical form: in IE caused by staphylococci and Gram-negative bacilli the onset is acute, the disease develops with fever up to 39-40°C, shivering, nocturnal sweating, fatigue, arthropathy, myalgia etc., and patients with IE caused by *Streptococcus viridans* have insidious onset with subfebrility, fatigue and general symptoms [2, 6, 27]. IE cand begin with a severe visceral complication, as infectious, embolic or hemorrhagic. Repeated auscultation of the heart reveals important changes of cardiac murmurs detected before the appearance of new murmurs. In EI the aortic or mitral valves are the most affected, and in IVDU – the tricuspid valve [5, 20]. Early injuries characteristic of IE are different-size vegetations consisting of microorganisms, thrombocytes, erythrocytes, fibrin, macrophages located more frequently on the valvular and parietal endocardium, less frequently on the aortic and arteries intima (image 1, 2).

Image 1. Vegetations on the aortic valve with valvular destruction and septic emboli.

Image 2. Big vegetations on the anterior cusp of mitral valve.

Echocardiographic examinations, especially the transesophageal one, have allowed early detection of vegetation and specific IE changes (cardiac abscess, prosthesis dehiscence, etc.) but haemoculture express-methods have facilitated the identification of the pathogen agent and its sensitivity to antibiotics within a shorter period, allowing the use of etiopathogenic therapy, positively influencing its prognosis [2, 10].

Infectious endocarditis, always fatal before the advent of antibiotics, gave hopes for a favorable prognosis in the middle of the last century, when penicillin was synthesized. Nowadays the treatment of patients with IE is costly, and needs long time treatment combining several antibiotics to be administered in high doses, which requires creating of an elaborate system for disease prevention in the groups of patients with high and moderate risk [3, 9].

The complexity and importance were the main reasons that led to the elaboration of these guidelines.

Pretests

1. SC The first clinical description of infective endocarditis belongs to:
   A. E. Libman
   B. W. Osler
   C. H. Schottmuller
   D. W. Thayer
   E. S. Jaccoud
2. SC Specify the rarely affected valve endocarditis:
   A. Mitral valve
   B. Aortic valve
   C. Tricuspid valve
   D. Pulmonary artery valve
   E. Eustachian valve
3. SC Which of the given below is a predominant infectious agent in case of IE in IVDU and in patients with prosthetic valves:
   A. *Streptococcus viridans*
   B. *β-haemolytic streptococcus*
   C. *Staphylococcus aureus*
   D. *Staphylococcus epidermidis*
   E. *Enterococcus fecalis*
4. SC Treatment of infectious endocarditis includes the following drugs, excepting:
   A. Antibiotics
   B. Antifungal drugs
   C. Cardiac glucosides
   D. Anticoagulants
   E. β-blockers
5. SC Select prophylactic dose of Amoxaciline in patients with high risk of infectious endocarditis developing:
   A. 500 mg / day within 2 hours before the dental procedure
   B. 500 mg / day after dental procedure
   C. 2-3 gr within 1 hour before dental procedure
   D. 1 g / day within 2 hours before the dental procedure
   E. 500 mg / day in 4 parts
6. SC To prevent the recurrence of a new episode in patients with history of infectious endocarditis, it is allowed to remove:
   A. 2 teeth a day
   B. 3 teeth a day
   C. 1 tooth a day
   D. 1 tooth in 3 days
   E. 1 tooth in 10 days
7. SC Name the most common and severe complication of infectious endocarditis:
   A. Embolic events
   B. "Osler" Heart failure
   C. Glomerulonephritis
   D. Encephalitis
   E. Toxic hepatitis

PRETEST CLINICAL CASES

Case 1. Patient C., a man aged 35 years, presents the following complaints: fever up to 39-40°C, chills, night sweats, weight loss – 5 kg during the last week, physical effort inspiratory dyspnea, palpitations, dry cough, and bilateral ankle edema.

The disease started 2 weeks after a skin infection – furunculosis, with fever, chills, sweating and pain in law hemithorax. The patient used intravenous drugs, he administered himself *Aspirin 500 mg /day* for the symptoms described above. His health condition worsened and he was hospitalized in the cardiology department.

Clinical and laboratory examinations revealed: moist, pale teguments, macular petechia in the region of the right foot. Reduction of respiratory amplitude in the right hemithorax, dullness of percussion sound in the right lower lobe; bilateral inferior wet rales. RR – 22 r/min. Rhythmic heart sounds, I attenuated sound in IV p. of auscultation, systolic murmur in the tricuspid valve projection. BP – 120/70 mmHg.

Cell blood count: haemoglobin – 110 g/l, RBC – 3.0 x 10^{12}/l, WBC 10,6 x 10^{9}/l, eosinophyles – 4%, nonsegmented neutrophils – 12%, segmented neutrophils – 48%, lymphocytes – 27%, monocytes – 5%, increased ESR – 70 mm/hour.

Thoracic radiography and echocardiogram are presented in the images.

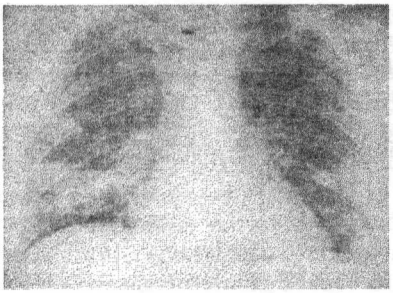


Image 3. Radiography.

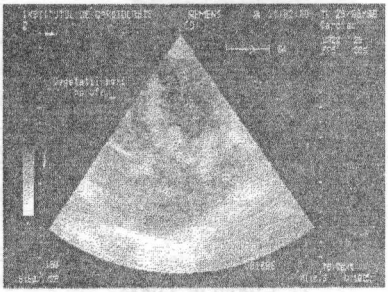


Image 4. Echocardiogram.

1. Make an initial diagnosis and justify it.
2. What further investigations are needed to make the final diagnosis?
3. Principles of treatment.

Case 2. Patient G., 70 years old, presented himself at the doctor's with fever 38°C, chills, sweating, moderate inspiratory dyspnea at moderate effort, palpitations, fatigue, loss of weight – 10 kg/month.

The disease began insidiously with subfebrile temperature, moderate physical effort inspiratory dyspnea, palpitations over 1 month after prosthesis of mitral valve. After 3-week treatment with the antibiotics: Cefazolin 4 gr /day i/m, without marked improvement in the general state, with fever persistence.

Clinical and laboratory examinations: pale, clean teguments; symmetrical lung percussion with normal pulmonary murmur. Pulmonary auscultation area reveals vesicular murmur, absence of rales, RF – 18 r/min. Heart sounds are rhythmic, prosthesis sound at the apex, HR – 85 beats/min, BP – 110/70 mmHg. The tongue is pink and wet. The liver is enlarged (+ 2 cm).

Hemogramma: hemoglobin – 100 g/l, RBC – 2.6 x 10^{12} /l, WBC – 9.2 x 10^{9}/l, eosinophyles – 1%, nonsegmented neutrophils – 9%, segmented neutrophils – 48%, lymphocytes – 34%, monocytes – 7%, increased ESR 65 mm/h, anisocytosis.

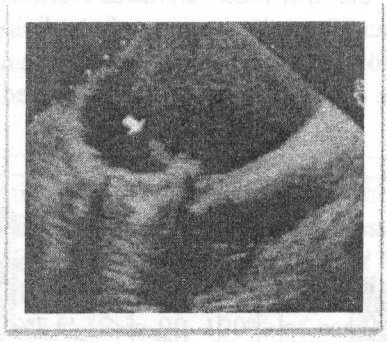


Image 5. Echocardiogram.

1. Make an initial diagnosis and justify it.
2. Describe presented EchoCG (as indicated by the arrow).
3. What further investigations are necessary for making the final diagnosis?

GENERALITIES IN INFECTIOUS ENDOCARDITIS

1. Definition of IE

Infectious endocarditis is an endovascular microbial infection of cardiovascular structures (native valves, ventricular or atrial endocardium), including endarteritis of the major intrathoracic valves (in patent arterial duct, in arteriovenous shunts, in aortic coarctation), or that of foreign intracardiac bodies (prosthetic valves, pacemaker or intracardiac defibrillator), infection being revealed in the blood flow [Prevention, Diagnostic and Treatment Guide of IE, 2009].

2. Epidemiology

Incidence of IE is between 1.9-6.2 cases per 100000 persons/year with an increasing tendency in some clinical variants/types (nosocomial IE, IE in elderly, IE in IVDU) [9, 17]. IE develops more frequently in men, the ratio between sexes varying from 1.5–2.5 to 1 [18]. IE affects at any age, with prevalence in able-bodied population. During the last years the phenomenon of „diseases ageing" was noted [19, 24]. Ana Ştirbul, Alexandra Grejdieru, Minodora Mazur from SUMPh of Moldova and a goup of researchers from the Institute of Cardiology studied a group of 408 patients of IE for 16 years. The obtained data are similar to those of ather scientists. The data of this study are presented in figures 1 and 2 [19, 20, 26, 30].

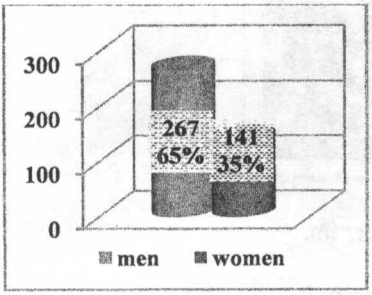


Fig. 1. IE incidence by sex, n=408.

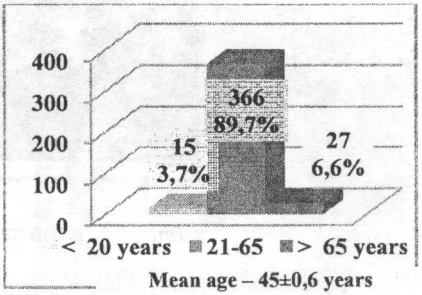


Fig. 2. IE incidence by age, n=408.

According to bibliography 55–75% of patients with IE on native valves have some predisposed conditions: rheumatic or congenital heart diseases, mitral valve prolapse, degenerative and hypertrophic heart

diseases or i/v drug abuse, in 7–25% of cases IE involves valvular prosthesis, and in 25–40% the predisposing conditions cannot be identified [10, 26]. The predisposing conditions in patients with IE from the study done in the Republic of Moldova are given below (*fig. 3*).

Rheumatic heart disease	197pt	48,3%
Congenital heart disease	31pt	7,6%
Degenerative heart disease	17pt	4,2%
Valvular prosthesis	49pt	12%
Mitral valve prolapse	8pt	2%
Permanent pacemaker	2pt	0,5%
Intact valves	105pt	25,7%

Fig. 3. Cardiac predisposing conditions in patients with IE, n=408.

Scientists describe that in 85–90% of cases of IE, the left heart is affected, and only in 5–10% – the right heart (predominantly in IVDU) [13, 23, 28]. Untreated IE is a deadly disease. In case of late diagnostics, or late treatment, the level of mortality is high: 16–20% for common IE and 24–50% for nosocomial IE [1, 21].

3. Etiology

IE is a polyetiologic disease. At present, there are 128 microorganisms known to cause IE, among them the most frequent are: *streptococci, staphylococci, Gram-negative bacilli and fungi* [2, 6, 28]. In pre-antibiotic period, the most common ethiologic agent was *Streptococcus viridans*, which caused IE in 90–100% of cases [19]. Most recent studies of the last decades empasize a change of the causative microbial spectrum, determined by new entry „gates" for the infection, the age of patients, and immunodeficiency caused by many associated diseases and unnecessary antibiotics usage [11]. This fact is explained by the increased number of germs involved, increasing the role of conditioning pathogenic flora and increasing bacterial association in IE. *Coagulase-negative staphylococcus*, previously a minor cause of IE on native valve, today are the main cause of IE of a prosthetic valve and nosocomial IE [12]. *Staphylococcus aureus* etiology prevails in IE in IVDU, especially

implying the tricuspid valve [20]. *Pseudomonas aeruginosa, Gram-negative bacilli and Candida species* cause rarely IE on native valve but are important causes of IE in drug users, prosthetic valves and nosocomial IE [8,23]. IE caused by *Enterococcus faecalis*, is associated with urogenital interventions, and *Streptococcus bovis* is the main germ in patients with gastrointestinal cancer and colon polyps, which appear more frequently in elderly [22, 29]. A main problem is IE with negative blood culture (10–50%) caused, mainly, by antimicrobial treatment, before the establishment of a certain clinic diagnosis, in other cases by specific microorganisms (*Bartonella, Coxiella, Brucella, Mycoplasma, Chlamydia*, etc.), which need specific serologic tests and PCR for identification [4, 19]. Cases of IE with negative blood cultures, have a negative influence on the evolution of the disease, delayed administration of correct treatment and determines an unfavorable prognosis. In figures 4 and 5 the etiologic spectrum in the study group of patients from the Republic of Moldova is shown.

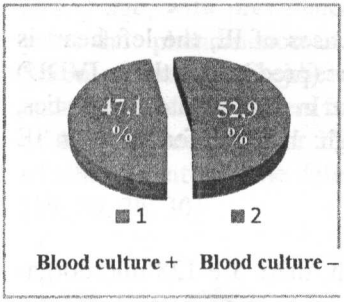


Fig. 4. Etiology profile, in patients with IE, n=408.

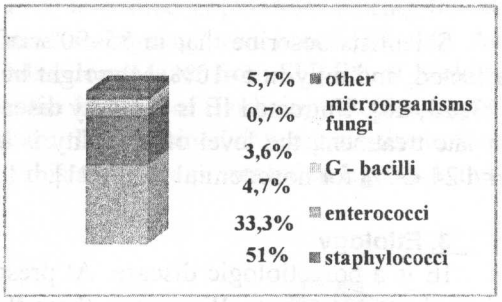


Fig. 5. Microbial spectrum in patients with IE, n=216.

4. Pathogeny

Sterile microthrombi, attached to injured endocardium, in IE of native valves, serve as a primary focus for bacterial attachement. Hemodynamic factors (mechanic stress) and immune factors play an important role in the endothelial lesions appearance. In IE the usual location is the valvular border, where the preexisting lesions might cause changes in blood flow. A source of infection or a trauma are predisposing to a bacterial dissemination, changing thrombotic, non-bacterial endocarditis into infective endocarditis. The attachement of the bacteria to thrombotic

vegetations is favored by fibronectin, a glycoprotein on the cellular surface. Afterwards, microorganisms multiply inducing thrombi formation, and neutrophils chemotaxis. The IE causative agents are mainly Gram-positive, because they have a more adhesion capacity and resistence to bactericidal action of serum. In IE of prosthetic valves the site of infection is the perivalvular tissue and the most frequent complications are prosthesis dehiscence, abscesses and perivalvular fistulas, conduction system affection, purulent pericarditis, acute obstructions with vegetations and dehiscent prostheses.

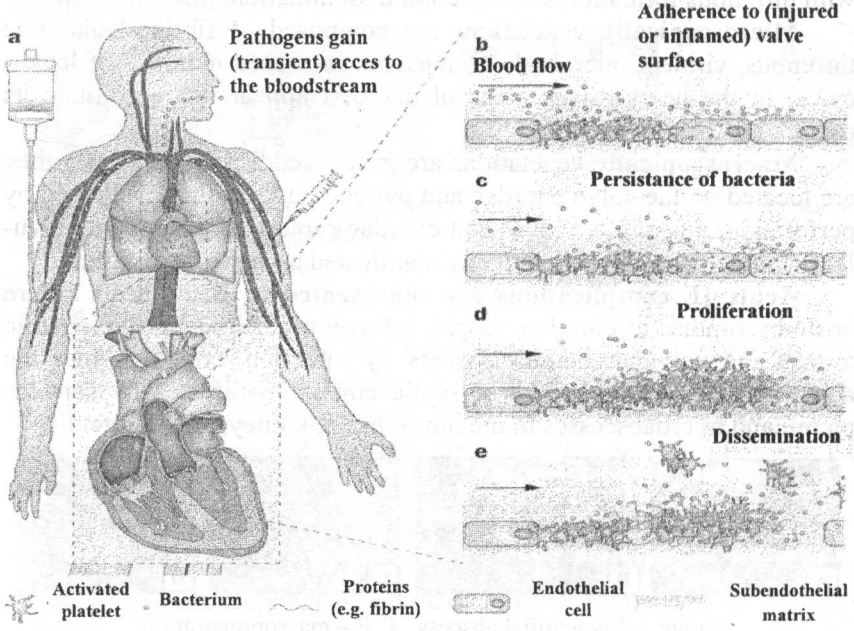


Image 6. Pathogeny of IE.

a – ways of the infection penetration: respiratory, intravenous, IVDU and urogenital; *b* – adhesion and bacterial colonization in blood flow on the endocardium of the intact cardiac valves, native or prosthetic; *c* – persistant bacteria with injury of endocardial integrity; *d* – endothelial proliferation with the formation of microbial vegetation; *e* – infection dissemination, and vegetations defragmentation with septic embolus migration in target organs.

5. Morphopathology

Pathomorphologically, two types of IE are distinguished: acute (ulcerous-vegetative) and subacute (vegetive) differentiated by clinical criteria, the degree of disease severity, and the presence of disease pathogenic virulent agents and preexisting cardiovascular diseases.

Acute ulcerous-vegetative IE is caused by several virulent pathogen agents: *staphylococci, Gram-negative bacilli* with acute manifested infectious outbreaks, accompanied by persistent bacteremia. Microbial aggressive trigger is responsible for native or prosthetic valve alteration with thrombus formation and infection dissemination.

Microscopically vegetations are composed of fibrino-leukocytic thrombus, virulent microbial colonies and increased numbers of leukocytes. In the heart valves areas of necrosis appear that facilitate its rupture and perforation.

Macroscopically vegetations are gray – reddish, bulky loose, they are located on the valve chordae and parietal endocardium, followed by perforation, ulceration, valves and chordae rupture to the advent valvular incompetence device, clinically manifested as acute heart failure.

Acute IE complications are represented by acute heart failure acute by rupture of chordae, valves, intraventricular septum, miocardic abcess and valvular annular abscess by infection extending into the adjacent myocardium, systemic septic emboli manifested by septicopiemii and microabscesses in the lungs, brain, kidney, spleen, etc.

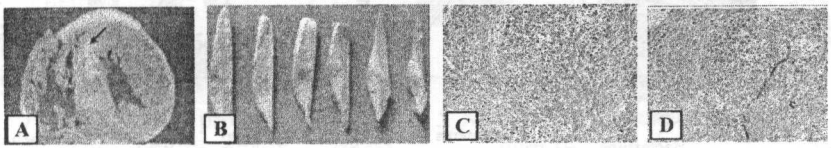


Image 7. Myocardial abscess. *A, B* – macropreparation; *C, D* – micropreparation.

Subacute vegetative IE is caused by low virulence organisms: *streptococci, fungi* originated in occult or latent infectious outbreaks (oral cavity, intestine, skin), accompanied by intermittent bacteremia. The infection spreads on valves previously damaged by rheumatic process, congenital or degenerative, previous cardiac surgery and intravenous drug abuse. Pathogenic, endothelial impairment leads to the formation of sterile fibrin – platelet thrombus, which can be colonized by microorganisms in transient bacteriemias.

Microscopically dense vegetations are composed of fibrin and platelet aggregates, a small number of leukocytes and neutrophils.

Macroscopically vegetations are gray – reddish highlight multiple polypoid, friable, arranged on the surface of valves, chordae, pillars and small vegetation grouped adjacent to the parietal endocardium. These usually do not cause valvular destructions and perforation.

Subacute IE complications: progressive heart failure with slow alteration of valvular apparatus, systemic embolism with cerebral and splenic infarctions, renal and focal glomerulonephritis in autoimmune complex deposition.

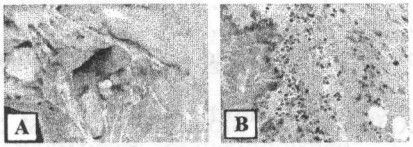


Image. 8. Thrombus-septical vegetation on MV: *A* – macropreparation; *B* – micropreparation.

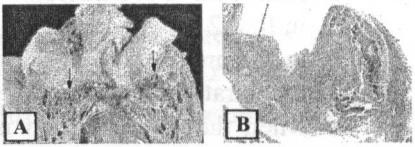


Image. 9. Multiple MV vegetation: *A* – macropreparation; *B* – micropreparation.

6. Classification

The old classification was based on the evolution of the process, defining acute, subacute and chronic IE forms [2, 11]. The actual classification is based on microbiology (etiology) of IE, activity of the process and recurrence, diagnostic status, pathogenic mechanism and anatomic location [28, 31].

I. We can differentiate Classification by certain criteria:

A. *Definite IE* – when endocardial involvement is evidenced (preferably by transesophageal EchoCG) during septicemia or systemic infection.

Definite IE can be:

a. *microbiologically positive,* when bacteremia is confirmed by 3 positive blood cultures with the same bacteria or in the presence of bacterial DNA (dezoxiribonucleinic acid). If the causative bacteria is determined, its name is included in the diagnosis, because it is important for clinical evolution, treatment and prognosis.

b. *microbiologically negative (with negative blood cultures)* when bacteremia is not confirmed, but endocardial involvement is evident. In cases of IE with negative blood cultures, serologic, histologic tests or

negative molecular investigations (PCR), IE with negative microbiology is diagnosed.

B. ***Suspected IE*** is established when there is a high level of clinical suspicion for IE, but at the moment of research, the endocardial involvement is not revealed and specific laboratory data are absent.

C. ***Possible IE*** is only a potential differential diagnosis in febrile patients. This is when diagnostic criteria for IE, Duke, revised in 1994 are of a special importance.

II. Classification by process activity:

A. ***Active IE*** is considered:

a. in first 2 months from the IE onset

b. in the presence of positive blood cultures and fever persistence, despite the duration of the disease

c. when the inflammation is confirmed by morphological test of tissue obtained during operation and/or positive blood cultures during operation and also before antibiotic therapy.

B. ***IE*** is considered to be ***cured,*** when there is a complete eradication of infection and a patient has a normal body temperature, normal ESR and negative blood cultures during 1 year after the treatment.

C. ***Relapsed IE:***

is diagnosed in case of recurrence of clinical signs and laboratory data (fever, positive blood cultures, increased ESR) which confirm an active infection from few weeks, and sometimes until 1 year from antibiotic treatment termination, the same agent with a profile of sensibility similar to the initial, being isolated in blood cultures.

D. ***Recurrent IE*** is a new episode of IE, which develops after clinical and bacteriologic recovery from in previous IE, it is caused by bacteria similar or different from the previous IE. IE which appears in 1 year after a surgical treatment of IE is considered *recurrent* and it is a severe complication with a high risk of mortality.

E. ***Persistent IE*** is considered when infection was never completely eliminated. The differentiation of these 2 types *(recurrent and persistent)* can be difficult or impossible with the exception of the case when recurrent IE is caused by a different microorganism determined in the previous episode.

III. Classification by infectious process location:

A. ***IE of intact valves (IE IV)*** – IE develops on intact valves.

B. ***IE of native valves (IE NV)*** – IE develops on native valves, injured by rheumatic process, congenital or degenerative.

C. ***IE of prosthetic valve (IE PV)*** is diagnosed when microbial or fungal infection is located on prosthetic valves.

a. *Precocious (nosocomial) IE of prosthetic valves (IE PV)* – infection of prosthetic valve during first 6 months after valve prosthesis.

b. *Late (community) IE of prosthetic valves (IE PV)* – infection of prosthetic valve minimum 6 months after valve prosthesis.

These 2 forms differ in causative bacteria and severity of the process.

D. ***IE of the left heart (EI LH)*** – IE with infectious process located on the mitral valve and/or aortic valve

E. ***IE of the right heart (IE RH)*** – IE with infectious process located on the tricuspid valve and/or on pulmonary artery valve.

IV. Classification according to duration from the onset of infectious process are distinguished:

A. ***Nosocomial IE:*** is considered when IE occurs after 72 h from the hospitalization, or during 6 months after discharge, when there is a link with the procedure made in the hospital. It represents 5–29% from total cases of IE and mortality in this group varies between 40–56%, most common agent being *Staphylococcus aureus.*

B. ***Community IE:*** IE which is not linked with hospital procedures.

V. According to age:

A. ***IE in new-borns*** – infection of endocardium in children under the age of 12 months.

B. ***IE in children*** – infection of endocardium in children aged 1–18.

C. ***IE in adults*** – infection of endocardium in patients aged 18–65.

D. ***IE in elderly*** – infection of endocardium in patients over 65 years.

Lately, an increased incidence of IE with blurred clinical picture and prognosis more reserved in comparison with other age groups in new-borns and in elderly has been noted.

VI. New clinical forms:

A. ***IE in IVDU:*** IE develops in IVDU. It affects predominantly the right heart, prevalence being 60 times more frequent than in the rest of the population.

B. IE in patients with hemodialysis.

C. ***IE in patients with intracardiac devices:*** IE develops in patients with pacemaker and implanted cardiac defibrillator.

ANAMNESIS

IE should be suspected in patients with pre-existing heart disease (mitral valve prolapse with significant regurgitation, congenital heart disease, rheumatic and degenerative valve disease, hypertrophic cardiomyopathy, patients with prosthetic valve endocarditis in anamnesis), unexplained fever for at least one week or subfebrility in elderly and in case of fever in intravenous drug users [8, 19].

Recent surgery, diagnostic or therapeutic manipulations known as a result of bacteremia and anamnestic comorbidities are also of significant importance [12, 18].

1. Criteria for cases with a high degree of suspicion for IE

- Sepsis of unknown origin.
- Newly appeared valvular lesion / regurgitation murmur.
- Embolic events of unknown origin (cerebral infarction or renal disease, etc.).
- Hematuria, glomerulonephritis and suspected renal infarction.
- Fever with:
  - Intracardiac prostheses, pacemakers, intracardiac defibrillator
  - Predisposing conditions for IE in the high risk group.
  - Recently occurred ventricular arrhythmias or conducting disorders.
  - The first manifestations of heart failure.
  - Positive blood cultures (if the detected organism is typical for native and prosthetic valve IE).
  - Skin manifestations (Osler nodes, Janeway lesions) or ophthalmic manifestations (Roth spots).
  - Rapidly changing multifocal lung infiltrates (IE of the right heart).
  - Peripheral abscesses (renal, spleen, bone marrow) of unknown origin.

Factors that should be taked into consideration:

- character, values and duration of fever, conditions of occurrence;
- cardiac and extracardiac signs (cerebral, renal, ocular manifestation) recently appeared;
- assessment of the preexisting heart disease probability;
- patient`s age, comorbidities;
- evaluation of procedures performed in the last 6 months.

2. Risk factors

According to published data risk factors for IE development are divided into 3 categories: predisposing heart diseases, morbid circumstances for entering pathogenic flora and diseases associated with the immune suppression condition.

A. Predisposing heart diseases.

- IE history
- prosthetic valves
- cardiac heart disease
  - Fallot tetralogy
  - Inter ventricular septum defect
  - bicuspid aortic valve
  - coarctation of the aorta
  - persistent ductus arteriosus
  - mitral valve prolapse
- acquired valvulopathy
  - rheumatic
  - degenerative
- hypertrophic cardiomyopathy.

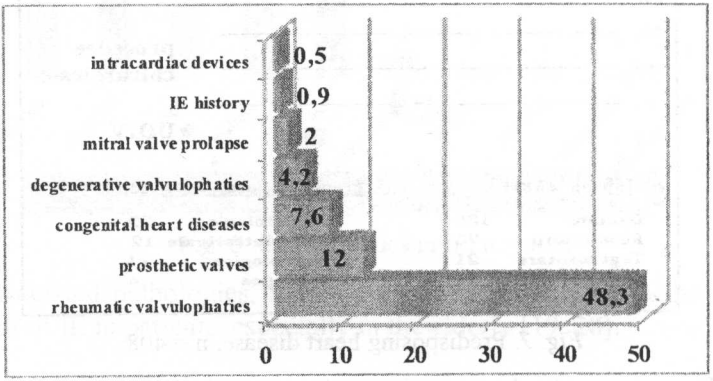


Fig. 6. Predisposing heart disease, n = 408.

During the last century the most common cardiac disease predisposing to the development of IE was considered rheumatismal valvulopathy – 40–60%. Today, in Western countries, degenerative valvular disease, prosthetic heart valves, mitral valve prolapse with significant regurgitation have replaced rheumatismal cardiopathies, which assume 6–23% [19, 26].

B. The gateway for bacteremia

- tooth extraction
- gingivitis
- failure to oral hygiene
- skin infections
- respiratory infections
- combustion
- polytrauma
- intravenous drug use
- wide range of invasive procedures:
  - intravenous catheters
  - hemodialysis
  - heart surgery
    - prosthetic valves
    - intracardiac pacemaker and defibrillator implants.

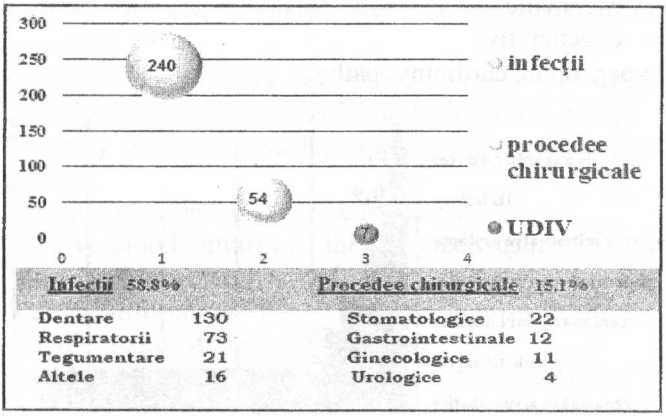


Fig. 7. Predisposing heart disease, n = 408.

The gateway for bacteremia can be recognized in 70–85% of cases of IE, the most common being dental in 25%, gastrointestinal in 10%, cutaneous in 7%, urogenital in 4% and nosocomial in 7–29% of cases [29, 27]. Therapeutic surgical maneuvers (extractions or dental procedures, incisions) may cause significant bacteremia [22, 30]. Non-sterile intravenous injection is a common source of bacteremia in IVDU [5, 20].

C. Comorbidities (diseases associated with IE)

- cirrhosis
- hepatitis
- diabetes
- systemic diseases
- tuberculosis
- cancer
- alcoholism
- syphilis
- HIV AIDS
- mental retardation.

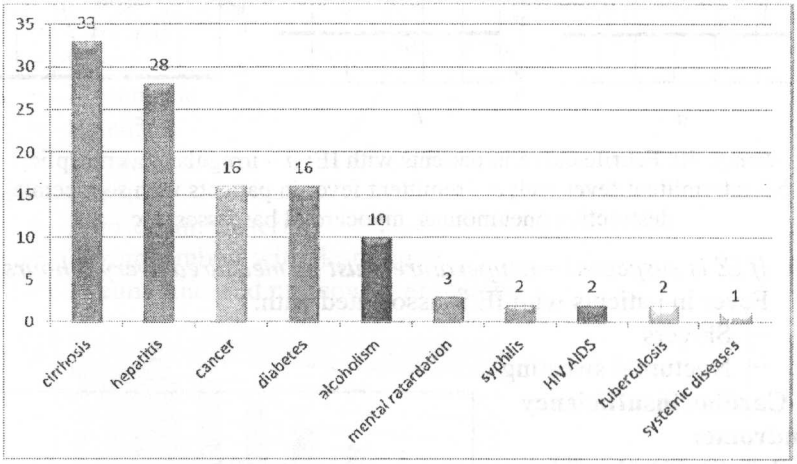


Fig. 8. Comorbidities in IE, n = 408.

Associated pathologies, immunosuppression can lead to the development of IE in patients, especially in the elderly [19, 28].

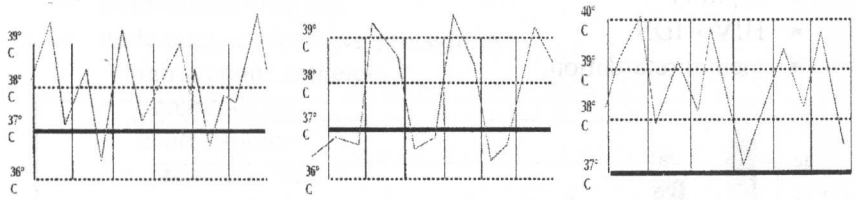
CLINICAL MANIFESTATIONS IN IE

1. Clinical manifestations

Clinical manifestations of patients with IE are not pathognomonic to the disease and are divided in 4 syndromes:

I. Toxico-infectious syndrome:

Hectic fever, undulating or subfebrility (in elderly, in immune compromised persons, in patients with congestive heart failure, with renal failure).



a *b* *c*

Image 10. Febrile curve in patients with IE: *a* – irregular fever, septic; *b* – intermittent fever and; *c* – remittent fever in patients with septicemia, destructive pneumonias, myocardial bascesses, etc.

If IE is suspected – temperature must be measured every 3 hours

Fever in patients with IE is associated with:

- Shivers
- Nocturnal sweating

II. Cardiac insufficiency syndrome:

- Palpitations
- Inspiratory dyspnea
- Fatigue

III. General alteration syndrome:

- Headache
- Myalgia
- Arthralgia
- Low dorsalgia
- Asthenia
- Loss of appetite
- Weight loss

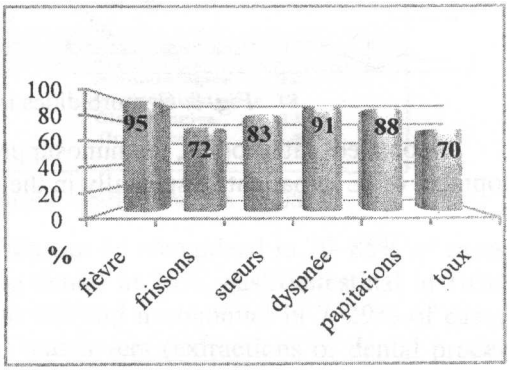


Fig. 9. Toxico-infectious syndrome and cardiac failure in EI, n=408.

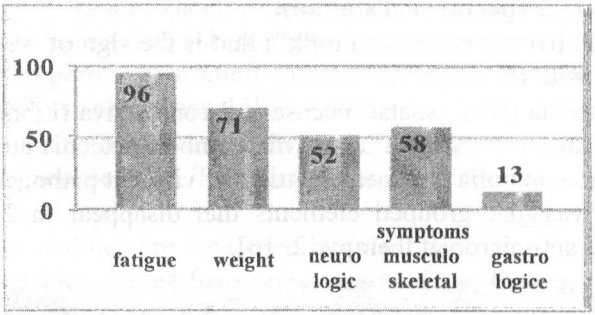


Fig. 10. General alteration syndrome.

IV. Emboli at the onset of the disease and during evolution of IE:

- Cerebral
- Renal
- Mesenteric
- Splenic
- Retinal
- Coronary
- Inferior limb arteries
- Thrombemboli with destructive
- Pneumonias and pulmonary abscesses.

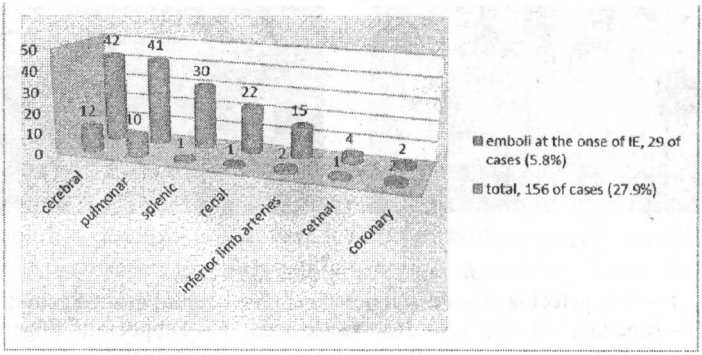


Fig. 11. IE, tromboembolic syndrome.

2. Physical examination in IE

In a patient with IE, the skin and mucous membranes should be examined carefully to detect stigmate, peripheral element suggestive of the diagnosis of IE in 50–90% of patients in the past, and in 14–36% of patients currently [19, 31].

Skin signs (peripheral stigma):

- skin palor ("coffe with milk") that is the sign of severe anemia in patients with IE.
- petechia (skin, palatal mucosa and conjunctiva (Libman-Luchin)) is detected in 10–15% of patients. Microemboli-petechia are manifestations of microembolia teguments caused by virulent pathogens. It is presented by vascular grouped elements that disappear in 2–3 days of appropriate antimicrobial therapy [2, 16].

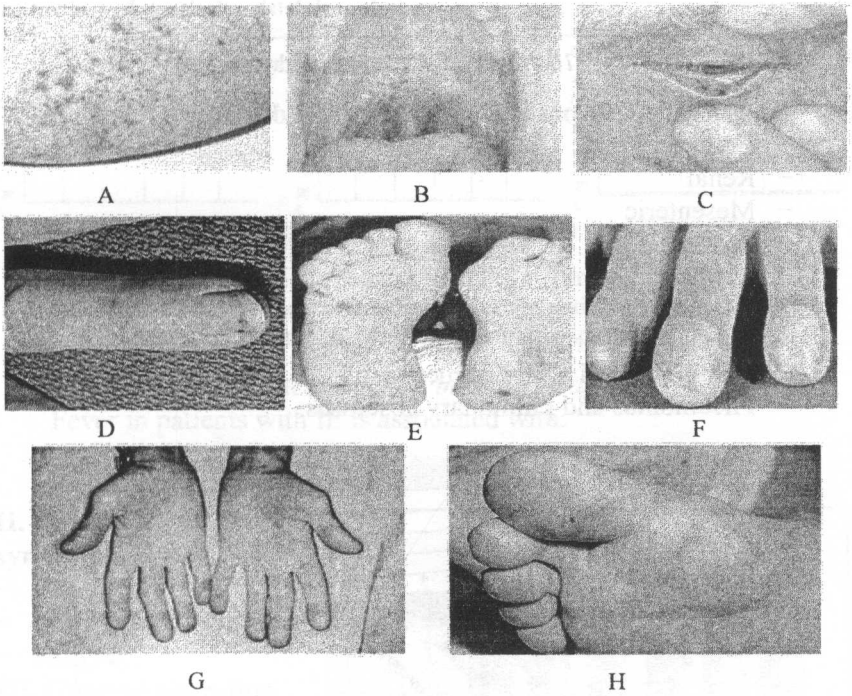


Image 11. Peripheral stigma.
A – Skin petechia; *B* – Palatal petechia; *C* – Conjunctival petechia; *D* – Bleeding "on chip"; *E* – Janeway lesions; *F* – Hippocratic fingers; *G, H* – Osler nodules.

- subungual linear bleeding "splinter", similar to those produced by traumatic penetration of some chips, proximal unrelated to the edge of the nail. They are manifestations of insidious IE in 20% of patients [19].

• Janeway lesions (hemorrhagic macular lesions, painless, which appear on the palms and soles), these are the manifestations of septic vasculitis with perivascular microabscess formation. It is detected in 5% of patients with staphylococcal IE [14, 25].

• hippocratic fingers are observed in 6–10% of patients with streptococcal IE diagnosed late. They disappear after complete eradication of infection [14, 31].

• Osler nodules are small red nodules, the size of a pea, on the finger pads, which persist for some hours or days. They are manifestations of necrotizing vasculitis of small vessels mediated immunologically with perivascular inflammation.

B. Hemodynamic parameters:

• frequency of heart contractions. Often tachycardia is caused by the toxic-infective syndrome and heart failure. After the beginning of appropriate antimicrobial therapy the cardiac contraction frequency returns to normal [2, 19].

• low diastolic blood pressure indicates severe aortic regurgitation that is manifested in IE by the aortic valve affecting [31].

C. Stetoacustic changes:

Heart sounds and murmurs regurgitation changing caused by valve damage:

– appearance of new murmurs.
– modification of preexisting murmurs.

Heart murmurs are present in 85–95% of patients with IE, excepting the early period of the disease or in intravenous drug users (tricuspid valve damage). In case the patient has predisposing cardiac pathology (rheumatic valvular, congenital, degenerative, hypertrophic cardiomyopathy), anemia and fever. It is important to specify modification of preexisting murmurs especially when progressing heart failure is caused by valve perforation and rupture of chordae [30].

D. Extracardiac signs:

• Musculoskeletal manifestations: myalgia and arthralgia detected in 40–50% of patients with IE and aseptic arthritis develops in 5–9% of patients, back pain occurs rarely [19].

- Ocular manifestations:
  - optic neuritis
  - Roth spots in 2–3% of cases (retinal microinfartion with hemorrhages, exudates with oval pale flocs clear in center) [2, 28].

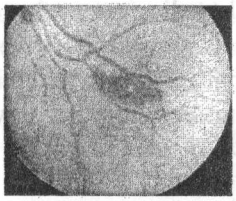


Image 12. Roth patches.

- Gastrointestinal manifestations: moderate splenomegaly in 30–50% of cases, hepatomegaly and rarely pain in the epigastrium [31].
- Neurological manifestations: headache, paresthesia, plegias, hemiparesis, motor aphasia depending on severity of IE and its complications [24, 26].
- Renal manifestations: in 15–19% of cases symptoms of renal failure due to renal embolias and diffuse glomerulonephritis are detected [19].
- Manifestations of embolic episodes are described in 11–40% of patients with IE. Femoral artery embolism causing violent pain in the lower limbs, cerebrovascular accident presented by the symptoms that are dependent on neurologic artery embolisms. Lien infarction is manifested by pain in the left upper quadrant, renal infarction with lumbar pain and hematuria. Mezenterial embolism may simulate acute abdomen. Coronary embolism develops acute myocardial infarction and retinal embolism causes blindness [7, 25].

DIAGNOSIS OF INFECTIOUS ENDOCARDITIS

At present the diagnostic of IE is difficult due to the modification of etiologic spectrum, increased incidence of negative hemocultures, resistance of pathogens to antimicrobial conditions, "ageing" of the disease and multiple comorbidities.

1. The Duke criteria for diagnosis of infectious endocarditis

The diagnostic criteria of infectious endocarditis were developed by Duke and revised by Durack in 1994. They are 2 main criteria to make an accurate diagnosis of IE: positive blood cultures with identical microorganisms in three separate samples and demonstration of the affection of endocardium by involvement by echographic examination (EchoCG) [15]. American Heart Association (AHA) recommends the use of Duke criteria as the primary tool for the assessment of a patient with suspected IE (*Table 1*), especially when blood cultures are negative [28].

Tabel 1

The Duke diagnostic criteria of IE revised in 1994

The main criteria	Positive blood cultures with:	1. Microorganisms typical for IE from 3 separate blood cultures	*Streptococcus viridians*, *Streptococcus bovis*, Bacteria from HACEK group
			Staphylococcus aureus, *Enterococcus* in absence of a primary source *Coxiella burnetti* (only positive blood culture)
		2. Persistent positive blood cultures, with bacteria that can cause IE	Blood cultures with 12 h between
			3 or more positive blood cultures with at least 1 h between the first and last sample
	Evidence of endocardial involvement	Echocardiography	• Vegetations (presence of oscillating intracardiac masses located on: – cardiac valves – on supporting structures – the way of regurgitant flow – on prosthesis • Annular abscesses • New dehiscences on valve prosthesis
		New regurgitation murmur or change in preexisting murmur	

Minor criteria	Cardiac predispozing conditions for IE or IVDU
	Fever over 38°C
	Vascular phenomena: • Arterial emboli, pulmonary septic infarcts; micotic aneurisms; intracranial haemorrhages; • Janeway lesions
	Immunologic phenomena: glomerulonephritis, Osler nodules, Roth patches, presence of rheumatic factor
	PCR > 100 mg/l, splenomegaly
	"Hippocratic" fingers recently appeared

According to revised diagnostic criteria of IE, Duke 1994, these 2 main criteria for determination of the final diagnosis of IE are considered to be positive blood cultures with identical microorganisms from 3 separate cultures and evidence of endocardial involvement on echocardiography (EchoCG).

Note: IE can be suspected in case of biologic inflammatory syndrome, thrombocytopenia, normochromic anemia, signs of renal lesions, positive immunological tests and new cardiac murmurs.

2. Differential diagnosis

In patients with unexplained fever changes in auscultation (heart murmurs), negative blood cultures and absence of echocardiographic signs characteristic of IE it is important to make a differential diagnosis with:

- acute rheumatic fever in children and the young
- thromboembolism of the pulmonary artery.

In febrile patients with absence of changes in organic auscultation (heart murmurs), it is necessary to suggest pathologies arising from febrile syndrome:

- sepsis
- tuberculosis
- cancer
- infectious diseases
- hematologic diseases
- systemic diseases
- osteomyelitis
- purulent processes.

In febrile patients with systemic embolisms and the absence of positive blood cultures it is necessary to exclude:

- cardiac myxoma
- Libman-Sacks endocarditis.

Patients with or without fever, with negative blood cultures, "doubtful" data on echocardiography must be assessed clinically, as there are false positive EcoCG changes (noninfectious intracardiac thrombus, endocardial tumors, such as papillar fibroelastomas, filiform tumors, noninfectious vegetations in Libman-Sacks endocarditis, Behcet's disease, heart carcinoid, acute rheumatic fever) [18].

3. Examples of clinical diagnosis

- Infectious endocarditis in active form, caused by *Streptococcus viridans*. Rheumatic heart disease. Moderate mitral stenosis. III degree mitral valve insufficiency. III degree tricuspid valve insufficiency. Chronic atrial fibrillation. HF III NYHA. Multiple periodontal dental caries.
- Nosocomial infectious mitral valve endocarditis in active form, caused by *Enterococcus faecalis*. III degree mitral valve insufficiency. HF II NYHA. Condition after transurethral prostatectomy (12.01.09).
- Infectious endocarditis, recurrence (II episode) of aortic valve prosthesis (05.2005) caused by *Staphylococcus epidermidis*. Dehiscence of the prosthesis. III degree aortic prothesised valve insufficiency. HF III NYHA.
- Infectious endocarditis of the right heart (massive vegetations on the tricuspid valve), active, caused by *Staphylococcus aureus*. IV degree tricuspid valve insufficiency. HF III NYHA. Bilateral multifocal septic pneumonia with destruction. Intravenous drug user.
- Infectious endocarditis in active form with negative blood cultures, relapse. Congenital heart disease. Bicuspid aortic valve. II degree aortic valve insufficiency. Annular myocardial abscess. HF II NYHA. Acute cerebrovascular accident in the left media cerebralis artery with mild right hemiparesis from 14.03.09.
- Late infective endocarditis of the mitral valve prosthesis (2007), with negative blood cultures. HF I NYHA.

IE COMPLICATIONS

1. Embolic complications may occur at the onset of the disease, during treatment or after therapy. They always have a life-threatening effect and require emergency treatment:

- Cerebral emboli due to microemboli, with or without formation of microabscesses usually involve the middle cerebral artery system and occur more frequently in IE caused by staphylococcus.
- Emboli in large arteries (femoral arteries) are often the result of fungal IE with large friable vegetations.
- Pulmonary embolism is common in drug addicts with right heart IE and left heart IE patients with left-right shunts.
- Renal, spleen, mesenteric, retinal and coronary artery embolism in patients with left heart IE with aortic valve damage.

2. Cardiac complications with high mortality risk.

- Congestive heart failure develops more frequently in IE affecting the aortic valve, caused by perforation of native or prosthetic valve cusps, mitral chordate rupture, fistulas or prosthetic dehiscence.
- Annular myocardial abscess in IE PV and aortic IE NV located in the membranous septum and the atrioventricular node, conduction disturbances are common consequences of this complication.
- Miocarditis with myocardial papillary muscle rupture is the consequence of myocardial abscess and regional necrosis caused by coronary embolism.

3. Neurological complications

- Ischemic strokes caused by cerebral embolism in IE affecting the aortic valve.
- Mycotic aneurysms are rare complications resulting from septic embolization of vasa vasorum, localized mainly in the point of arterial bifurcation.
- Intracranial aneurysms with signs of meningeal irritation.
- Intraventricular or subarachnoid hemorrhage.

4. Renal complications with the development of acute renal failure (ARF) have a particularly negative prognosis in patients with IENV and IEPV non-staphylococcal.

- Rapidly progressing glomerulonephritis (GMN) may be the first manifestation of previously unidentified IE. GMN caused by immune complex is the most likely form.
- ARF may be caused by:
  - Hemodynamic instability, severe septic syndrome, polyorganic failure
  - - Renal infarction and systemic embolism
  - Toxicity caused by long-term antibiotic therapy with aminoglycosides, vancomycin and penicillin.

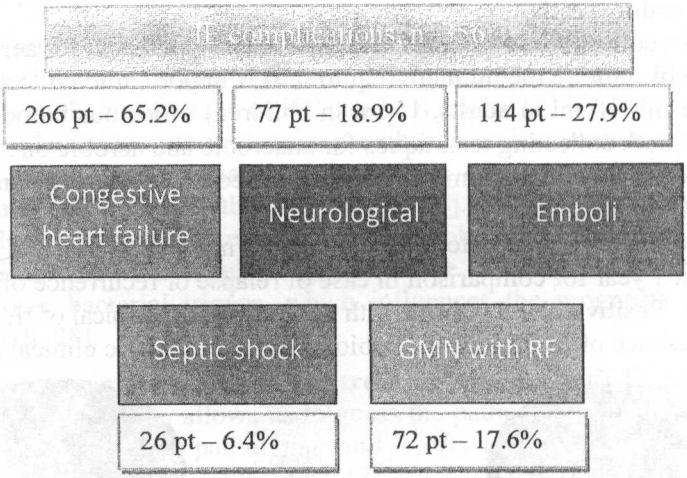


Fig. 12. Complications of IE, n = 356.

LABORATORY INVESTIGATIONS

Patients with IE should have:

- Investigations administered according to IE diagnostic criteria;
- Routine investigations;
- Supplementary investigations, specified by special indications (in complications of IE).

1. Investigations administered according to IE diagnostic criteria:

A. Examination of blood cultures in patients suspected of infectious endocarditis

To collect blood samples two test-tubes 50 ml each, for aerobic and anaerobic culture medium are required. It is important to collect not less than 5 ml (10 ml in adults, 15 ml in children) of venous blood. Should be use both collecting techniques for anaerobic and aerobic ones.

Making sowing from the valves excised during surgery and septic emboli is mandatory.

Microorganisms detected positive HC must be stored and kept for at least 1 year for comparison in case of relapse or recurrence of IE.

a. **Positive blood culture** with microorganisms typical of IE suggests the presence of IE defined microbiologically in specific clinical picture.

Fig. 13. Positive blood cultures, colonies of streptococcus, staphylococcus and enterococcus.

- The following should be taken into consideration: blood culture collection technique, prior administration of antibiotics.
- The lowest inhibitory concentration to chose antibiotic the most suitable one is determined.
- Suspicion of IE requires three or more HC in the first 24 hours.
- A single culture should be taken from each vein.
- HC should be taken separately with the interval at least 30-60 min, to show continuing bacteremia.

- If the initiation of antibiotic treatment is urgent at least 3 blood cultures every 3 hours are collected.
- If the patient is administered antibiotics for a short period of time, new blood cultures are taken at least 3 days after the treatment.
- Blood cultures may remain negative 6-7 days after a long-term treatment with antibiotic.
- HC should be made regularly during the treatment, HC becomes negative after several days of therapy.
- HC should be made in 2 and 4 weeks after the therapy because it detects a lot of relapses.

b. **Causes can that lead to negative blood cultures:**

Blood culture is the fundamental laboratory test to confirm the diagnosis of IE, but 22-45% of HC can be negative [2, 19, 28, 31]. This can be explained by intermittent or paucibacterian bacteremia, microorganisms that require special growth medium or serum sampling after the initiation of therapy with antibiotics [9, 28]. Patients with IE and negative HC are treated with empirical antimicrobial regimens and require the modification of treatment regimens more frequently than patients with known bacterial trigger, which influences the prognosis of the disease [19, 28].

c. **Approximate etiologic spectrum in patients with IE and negative blood cultures** allows us to guess the pathogen by means of the substrate of preceeding pathologies and is very important for choice of an appropriate antibacterial therapy [18].

Table 2

Etiologic spectrum in patients with IE and negative blood cultures

Epidemiological features	Microorganisms
IVDU	*Staphylococcus aureus, Coagulase-negative Staphylococci, Streptococcus ß-hemolytic; Fungi; Gram-negative bacilli; Pseudomonas aeruginosa*; Polimicrobial
I/v catheter	*Staphylococcus aureus, Coagulase-negative Staphylococci, Gram-negative bacilli, Corynebacteria, Fungi;*
Urogenital disorders, infections, manipulations, including pregnancy, childbirth and abortion	*Enterococci; Streptococci group B; Listeria; Gram-negative bacilli; Neiseria gonorrhea;*

Skin infections	*Staphylococcus aureus; Streptococcus ß-hemolytic;*
Poor oral hygiene, dental procedures	*Streptococci group viridians "oral streptococci"; Gemelia; HACEK;*
Alcoholism, cirrhosis	*Bartonela, Listeria, Streptococcus pneumonia, ß-hemolytic streptococcus;;*
Burns	*Staphylococcus aureus, gram-negative bacilli, Pseudomonas, fungi*
Diabetes mellitus	*Staphylococcus aureus, Streptococcus ß-hemolytic, streptococcus pneumonia;*
Valvular plasty, early period (≤ 6 months)	*Streptococcus ß-hemolytic; Staphylococcus aureus; Coagulase-negative Staphylococci; Fungi; Corynebacteria; Legionella;*
Valvular plasty (>6 months)	*Coagulase-negative Staphylococci; Staphylococcus aureus; Streptococci group; Enterococci; Fungi; Corynebacteria;*
Contact with pets (cat/dog)	*Bartonela; Pasteurella;*
Contact with contaminated milk or infected pets	*Brucella; Coxiela;*
Pediculosis	*Bartonela;*
AIDS	*Salmonella, Streptococcus pneumonia, Staphylococcus aureus;*
Pneumonia, meningitis	*Streptococcus pneumonia*
Organ Transplant	*Staphylococcus aureus, fungi (especially Candida) Enterococci;*
Gastrointestinal lesions	*Streptococci, Enterococci, Clostridia*

B. Echocardiography in patients with suspected IE

Each patient suspected of IE of native valve should be examined by transthoracic echocardiography (TTE) [9, 18, 28]. High quality TTE with negative results in the presence of low clinical suspicion, denies the diagnosis of IE, other causes should be sought for negative TTE with high clinical suspicion requires transesophageal echocardiography (TEE) [9, 28].

TEE is performed in: negative TTE but high clinical suspicion, in all patients with IE of prosthetic valve, in patients with complications (fistula, abscess, perforation of the valve), suspected of vegetation, after surgery for active IE, in patients with IE of the right heart, in patients with abscesses around the fibrous annulus (Class I, level A) [9, 18, 21, 28].

If TEE is negative but clinical suspicion remains, TEE is repeated in a week. The negative result of repeated TEE has a negative prognosed impact in 95–97% of cases.

The presence in EchoCG exam of: vegetation, heart abscess or fistula around the fibrous annulus and emerging prosthesis dehiscence is the 2nd major criterion for IE [18, 28].

TEE is more sensitive than TTE in detecting vegetations, especially on the prosthetic valve and abscesses. TEE can detect vegetation of 1–1.5 mm, while the smallest size detected by the TTE is 2–3 mm. EchoCG can not differentiate vegetation of active IE and healed IE. EchoCG should be considered in association with clinical picture, as there are false positives EchoCG changes (uninfected intracardiac thrombus, endocardial tumors, papillary fibroblastoma, filiform tumors, uninfected vegetations in Libman-Sacks endocarditis, Behcet's disease, carcinoid heart disease, acute rheumatic fever) [9,18].

The study revealed, vegetations in 77.7% of patients, with the predominance of aortic valve damage in 51.2%, followed by 36.7% of the mitral one. Tricuspid valves (11.3%) and pulmonary artery valve (1.2%) were affected by IE. In 18.1% of cases other echocardiography changes were diagnosed: rupture of cords and valve, cardiac abscesses, fistulas around prosthetic valve. The data are shown in figure 14.

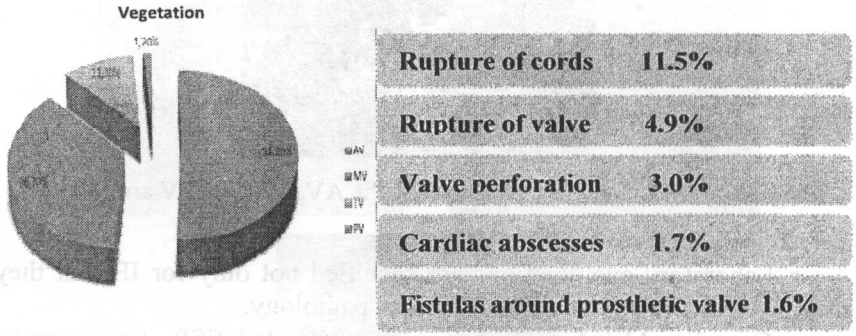


Fig. 14. Echocardiography changes in patients with IE
Echocardiography images of patients from the study.

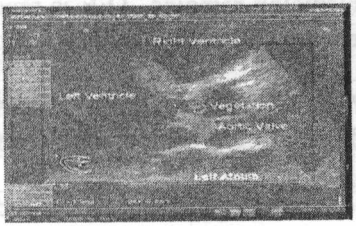


Image 13. EchoCG of patient R., 67 years, with nosocomial IE, enterococcal etiology, AV (vegetation – 11 mm).

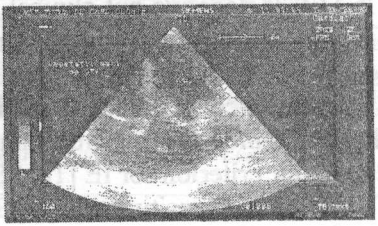


Image 14. EchoCG of patient Z. 23 years, with IE of the right heart, staphylococcal etiology, massive vegetation on the TV.

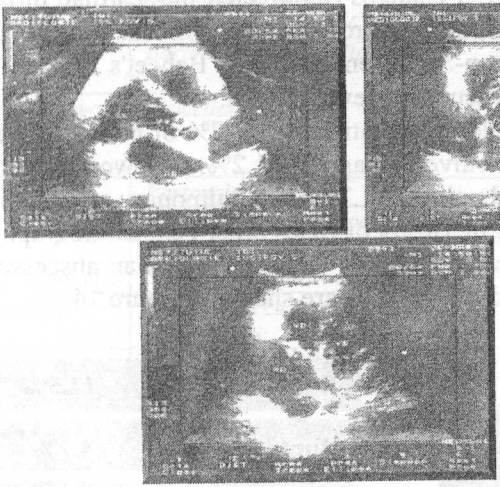


Image 15. EchoCG patient O., 24 years: the AV, MV and TV are affected.

2. Required routine investigations

- Laboratory examinations are specified not only for IE, but they may be characteristic of other infectious pathology.
- Complete blood count (anemia, accelerated ESR, leukocytosis: neutrophilic ±, monocytosis ±).
- Urine examination (pathologic urinary sediment (microhematuria ±, proteinuria ±, cilindrurie).
- General protein (dysproteinemia + , hyper - γ - globulinemie).
- Urea, creatinine (elevated in renal failure).
- Rheumatoid factor.

- C-reactive protein.
- Circulating immune complexes.
- Serology for rickettsial (*Coxiella burnetii), Chlamydia (Chlamydia psittaci, Chlamydia pneumonia and Chlamydia trachomatis), Brucella, Bartonella and spirochete (Spirillum minus)* – these serological tests are done in case of clinical suspicion but blood cultures in 7 days after sampling are negative.
- Polymerase chain reaction demonstrating bacterial DNA is made in patients with negative HC and it is made compulsorily in all patients undergoing cardiac surgery.

A. Radiography of the chest in patients with IE:

Chest Radiography is informative in identifying:

- progression of rheumatic heart disease in patients with IE.
- heart failure progression.
- radiological signs of pulmonary embolism in patients with left heart IE on the background of congenital heart disease with left-right shunts.
- fluoroscopic examination can determine valvular prosthesis dysfunction in patients with prosthetic valve.
- multifocal destructive pneumonia, lung abscess, radiological signs of pulmonary embolism in IVDU with right heart IE.

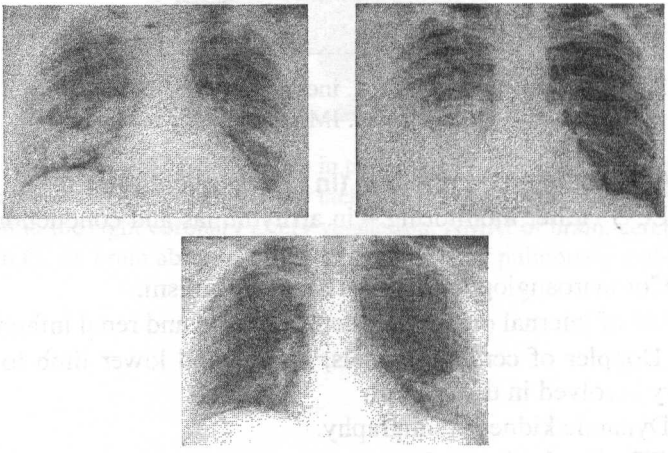


Image 16. Chest X-ray of IVDU patient Z., 23 years with right heart IE. Multiple infiltration and signs of destruction.

B. ECG examination in patients with IE:

There are no ECG suggestive changes, but we must assess disturbances caused by rheumatic heart disease or congenital disease in clinical picture, depending on the process duration, degree of activity and impaired endocardium and myocardium: LV/RV hypertrophy, atrial hypertrophy, atrial fibrillation, atrial flutter, left bundle branch block and/or as Hiss bundle – in rheumatic heart disease and congenital disease; second and third degree of atrioventricular block (first 3 days after dehiscence of the prosthesis, or abscess around fibrous annulus), ECG changes in myocardial ischemia caused by coronary embolism [9,18, 28].

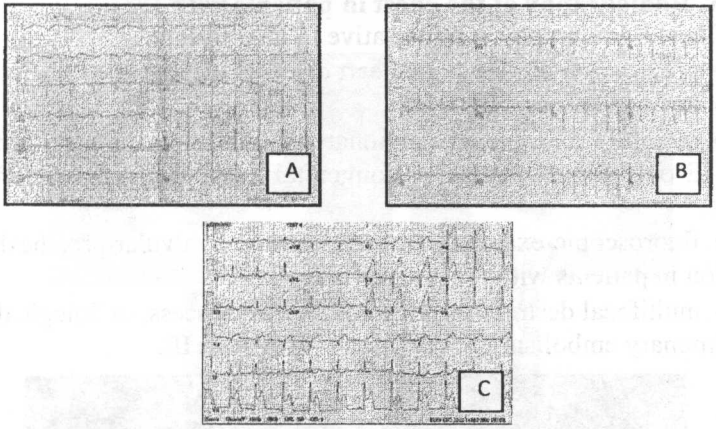


Image 17. ECG in patients with IE. A. incomplete right bundle branch block of Hiss, B. Myocarditis, C. IMA previously extended.

3. Additional investigations (in IE complications)

- ECG Holter monitoring – in arrhythmias and conduction disturbances.
- Coronaroangiography in coronary embolism.
- US of internal organs – to detect splenic and renal infarcts.
- Doppler of cerebral vessels, kidney and lower limb to specify the artery involved in the process.
- Dynamic kidney scintigraphy.
- CT of brain, internal organs – in the case of cerebral, renal, mesenteric, splenic embolisms.

- NMRI of brain – mycotic aneurysm, intracranial aneurysms, cerebral septic emboli.

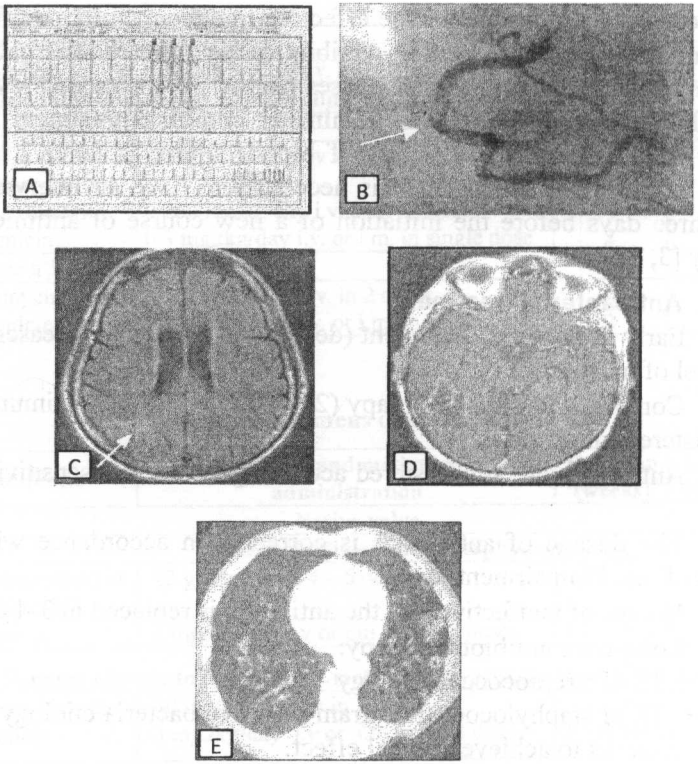


Image 18. Additional investigations in patients with EI. *A.* Holter ECG monitor: paroxysms of supraventricular tachycardia. *B.* coronary angiography. Embolism in the right coronary artery vegetation. NMRI of brain: cerebral embolism *C., D.* brain abscess, *E.* CT of lungs - septic pulmonary emboli.

TREATMENT OF PATIENTS WITH IE

Necessary conditions for the effective treatment: full, qualified investigation made in time [9, 28]. Antibiotics are initiated after obtaining positive results, only in emergency cases (sepsis, severe valvular dysfunction, blocks, embolism) we can administer empirical treatment immediately after taking cultures [19]. If blood culture is taken after the course of antibiotic treatment it is necessary to have an interval of at least three days before the initiation of a new course of antimicrobial therapy [3, 18].

1. Antibacterial treatment

- Early initiation of treatment (delay of 2–8 weeks, increases twice the level of mortality).
- Combined antibiotic therapy (2–3 antibiotics) in maximum dose administered intravenously.
- Antibiotics are administered according to bacteria sensitivity and MIC.
- The dosage of antibiotics is corrected in accordance with the degree of renal impairment.
- In case of ineffectiveness the antibiotic is replaced in 3-4 days.
- Long-term antibiotic therapy:
  - IE of streptococcal etiology – 4 weeks.
  - IE of staphylococcal or gram-negative bacteria etiology – 6–8 weeks to achieve clinical effect.

Table 3

Therapy regimens in IE caused by streptococci of groups B and D

Antibiotic	The dose and method of administration	Duration (weeks)	Level of evidence
Penicillin-sensitive strains MIC < 0.125 mg/L			
Standart treatment			
Penicillin G#	12–18 mil. U/day i.v in 6 doses	4	IB
Benzylpenicillin or			
Amoxicillin or	100 – 200 mg/kg/day i.v. in 4 – 6 doses	4	IB
Ceftriaxone	2 gr/day i.v. or i.m. in single dose	4	IB
Two-week treatment			
Penicillin G#	12–18 mil. U/day i.v in 6 doses	2	IB
Benzylpenicillin or	100 – 200 mg/kg/day i.v. in 4 – 6 doses	2	IB
Amoxicillin or	2 gr/zi i.v. or i.m. in single dose	2	IB

Ceftriaxone with Gentamicin or Netilmicin	3 mg./kg/day i.v. or i.m. in single dose 4 – 5 mg/kg/day i.v. in single dose	2 2	IB IB
Patients allergic to beta-lactams			
Vancomycin	30 mg/kg/day i.v. în 2 doses	4	IC
Strains relatively resistant to penicillin (MIC 0.125 – 2 mg/L)			
Standart treatment			
Penicillin G# Benzylpenicillin or	24 mil. U/day i.v in 6 doses	4	IB
Amoxicillin with Gentamicin	200 mg/kg/day i.v. in 4 – 6 doses 3 mg./kg/day i.v. or i.m. in single dose	4 2	IB
Patients allergic to beta-lactams			
Vancomycin with Gentamicin	30 mg/kg/day i.v. in 2 doses 3 mg./kg/day i.v. or i.m. in single dose	4 2	IC

Table 4

Therapeutic regimens of streptococcal IE

Antibiotic	Dosage and method of administration	Duration (weeks)	Level of evidence
Native valve			
Methicillin-sensitive staphylococcus			
Flu (cloxacillin) or oxacillin with gentamicin	12 gr/day i.v in 4 – 6 doses 3 mg./kg/day i.v or i.m in 2 – 3 doses	4 – 6 3 – 5 days	IB
Patients allergic to penicillin or methicillin - resistant staphylococcus			
Vancomycin with gentamicin	30 mg/kg/day i.v in 2 doses 3 mg./kg/day i.v or i.m in 2 – 3 doses	4 – 6 3 – 5 days	IB
Prosthetic Heart Valves			
Methicillin-sensitive staphylococcus			
Flu (cloxacillin) or oxacillin with rifampin and gentamicin	12 gr/day i.v in 4 – 6 doses 1200 mg/day i.v or p.o in 2 doses 3 mg./kg/day i.v or i.m in 2 – 3 doses	≥ 6 ≥ 6 2	IB
Patients allergic to penicillin or methicillin-resistant staphylococcus			
Vancomycin with rifampicin and gentamicin	30 mg/kg/day i.v in 2 doses 1200 mg/day i.v or p.o in 2 doses 3 mg./kg/day i.v or i.m in 2 – 3 doses	≥ 6 ≥ 6 2	IB

Table 5

Therapeutic regimens of streptococcal IE

Antibiotic	Dosage and method of administration	Duration (weeks)	Level of evidence
Beta-lactams and gentamicin susceptible strains			
amoxicillin with gentamicin	200 mg/kg/day i.v in 4 – 6 doses 3 mg./kg/day i.v or i.m in 2 – 3 doses	**4 – 6** **4 – 6**	**IB**
or			
ampicillin with gentamicin	200 mg/kg/day i.v in 4 – 6 doses 3 mg./kg/day i.v or i.m in 2 – 3 doses	**4 – 6** **4 – 6**	**IB**
or			
vancomycin with gentamicin	30 mg/kg/day i.v in 2 doses 3 mg./kg/day i.v or i.m in 2 – 3 doses	**6** **6**	**IC**

Multi-resistance to aminoglycosides, b-lactams and vancomycin implies administration of alternative antibiotics:

1. Linezolid 2600 mg / day i.v. or p.o. within a 8-week period (IIa C)
2. Daptomicyn (Cubicin) – 6mg/kg/day i.v. perfusion induced for 30 min - 1 hour time, within 2–6 weeks (IIa W);
3. Imipenem (Thien Prepenem) (IIb C) 1gr/24 hour i.v. infusion induced within 1 hour time for 10–14 days.

Table 6

Recommended therapeutic regimens for empirical initial treatment of IE

Antibiotic	Dosage and method of administration	Duration (weeks)	Level of evidence
Native valves			
Ampicillin - Sulbactam or	12 gr/day i.v in 4 doses	**4 – 6**	**IIb C**
Amoxicillin - Clavulanic Acid	12 gr/day i.v in 4 doses	**4 – 6**	**IIb C**
with gentamicin	3 mg./kg/day i.v or i.m in 2 – 3 doses	**4 – 6**	
For b – lactams non-tolerant patients			
vancomycin with	30 mg/kg/day i.v in 2 doses	**4 – 6**	**IIb C**
gentamicin with	3 mg./kg/day i.v or i.m in 2 – 3 doses	**4 – 6**	
ciprofloxacin	1000 mg/day p.o in 2 doses or 800 mg/day i.v in 2 doses	**4 – 6**	

Prosthetic heart valves (early, <12 months after surgery)			
vancomycin with gentamicin with rifampicin	30 mg/kg/day i.v in 2 doses 3 mg./kg/day i.v or i.m in 2–3 doses 1200 mg/day i.v or p.o in 2 doses	6 2 2	IIb C
Prosthetic valves (latem > 12 months after surgery)			
The same treatment as in native valves			

2. Management of embolic complications in IE

- Early effective antimicrobial therapy prevents the development of embolic events.
- If patients with prosthetic heart use oral anticoagulants for long periods, these are substituted with heparin immediately after the diagnosis of IE.
- After embolic complication, there a higher risk for recurrences.
- After a cerebral embolism there is no contraindication for surgery to prevent recurrences, if it is performed early (within 72 hours) and cerebral haemorrhage was excluded by CT immediately after surgery. If the surgery was not performed within this period, it is delayed for 3–4 weeks [18].

3. Clinical monitoring and assessment of efficacy of treatment

- Daily examination and strict clinical management of the patient.
- Thermometry (fever is a very important and useful criteria in revealing IE development).
- In patients with uncomplicated development, fever becomes normal in 5–10 days. If fever persists for more than 10 days, the possible causes must be excluded.
- Blood tests for the assessment of infection and renal function.
- Suspected infectious complications require repeated blood cultures, EchoCG, ECG.
- Repeated clinical examinations to assess dynamic changes in heart murmurs and blood pressure, signs of heart failure and embolic phenomena of the brain, lungs, skin and lien.
- Repeated abdominal ultrasound examinations and eventually CT and NMRI to exclude splenic and renal abscesses.
- Medical examination of ophthalmologist is recommended in order to detect Roth spots.
- Laboratory findings:

– CRP is the most reliable criteria for the assessment of the therapeutic efficiency. Its values usually decrease within 1–2 weeks but remain slightly elevated within 4–6 weeks. The persistence of high CRP values should be interpreted as a sign of inadequate infection control resulting in heart and other septic complications.

– ESR is not informative to assess the evolution of disease since high values may persist within several weeks despite a good therapeutic response.

– Leukocytes count becomes normal within the first 2 weeks. Persistence of leucocytosis also indicates the presence of an acute process.

– A prolonged treatment with high doses of group β-lactams antibiotics may inhibit granulopoiesis and cause neutropenia.

– Repeated test for creatine levels to detect renal failure, which is a common complication of IE or a side effect due to vancomycin and gentamicin treatment [18].

- EchoCG will be repeated:

– If paravalvular abscesses and valvular damage are suspected.

– When the antibiotic treatment is completed the place and condition of valvular damage is recorded in order to detect a recurrent infection or late IE recurrence [18].

Table 7

Possible causes of persistent fever in patients with IE

Complications	
	Inadequate antibacterial therapy
Cardiac	myocardial abscess paravalvular abscess Large valve vegetations
Renal	glomerulonephritis bacteriuria
Neurologic	cerebral embolism mycotic aneurysm Meningitis
Pulmonary	pulmonary embolism exudative pleuresy
Other	embolisms: • splenic • articular • vertebral Infected venous catheters Allergy to antibiotics

4. Surgical treatment

A. Indications for surgery in native valve IE, in active phase

Despite the high operative mortality in surgical treatment of prosthetic valves the overall benefit of surgery vs. medical treatment I/IIA and level of evidence B and C was demonstrated [9, 28].

- Acute aortic or mitral regurgitation and acute heart failure.
- Progressive perivalvular infection (local uncontrolled infection).
- Evidence of abscess, false aneurysm, abnormal communication (fistula, rupture of one or more valves), conduction abnormalities, myocarditis, or other signs of local infection spread.
- Infections caused by microorganisms with inappropriate response to antimicrobial therapy and high level of resistance, and gram-negative bacillus (*fungi, Brucella, Coxiella*, etc.).
- If valve vegetations grow in size despite the administered treatment or "kissing vegetations" persist on the mitral valve then an early surgery is performed.
- In the presence of vegetations larger than 20 mm on the tricuspid valve after recurrent pulmonary embolisms [9, 18, 28].

B. Indications for surgical treatment in prosthetic valve IE, in active phase

- Early prosthetic valve IE (less than 12 months after surgery).
- Late prosthetic valve IE complicated by prosthesis dysfunction including significant perivalvular fistulas or obstructions, persistent positive blood cultures, abscess formation, conduction abnormalities and large vegetations, particularly ones caused by *Staphylococcus* [9, 18, 28].

After the surgery, a complete course of antibiotic treatment is administered, irrespectively of the duration of treatment preceeding the intervention.

5. Special therapeutic strategies

A. Right-sided cord IE:

- In these patients the treatment is conservative.
- In IVDU the causative agent is MRSA in approximately 60-70% of cases.
- Tricuspid valve is affected in more than 70% of the cases.
- The used antibiotic range should necessarily include typical causative agent (*Staphylococcus aureus*).

- IVDU who are predisposed to cardiac lesions or left-sided cord process are administered addiotionally an antistreptococcal antibiotic therapy.
- Recurrent pulmonary infiltrates are not indications for surgery.
- Pulmonary valve should be saved as much as possible, but if necessary it is substituted by a pulmonary homograft.
- High level of morbidity after reprosthesis may often occur in patients with bad habits, which may lead to reinfection or perivalvular abscess. In patients with increased pulmonary pressure, valvular excision may be associated with postsurgical right-sided heart failure after multiple pulmonary embolisms [18, 28].

B. IE Permanent implantable pacemaker or intra cardiac defibrillator

- Antimicrobial treatment of infections of permanently implanted pacemaker or cardiac defibrillator is based upon blood cultures and antibiotic susceptibility results.
- In most cases the duration of treatment lasts from 4 to 6 weeks.
- The removal of pacemaker or cardiac defibrillator and excision of all infected lesions is recommended on the level of the tricuspid valve, right atrium and free right ventricular wall.
- The infection is eliminated before a new permanent system is implanted [18, 28].

C. IE during pregnancy

- Acute IE does not imply an absolute indication for abortion. Acute heart failure due to tricuspid regurgitation is not improve hemodynamically with pregnancy termination. A pregnant woman should be treated even if there is an increased risk of foetal death. In severe cases, the decision is taken after an individual discussion with the patient
- The diagnosis of IE is made and the disease is treated the same way as in the absence of pregnancy
- Antibiotic therapy for pregnant women should be modified and adjusted according to the term of gestation. β-lactam antibiotics (benzylpenicillin, ampicillin, amoxicillin) are of choice and can be used without complications for mather and fetus. Cephalosporins and macrolides can also be administered during pregnancy because they have not

proved any embryotoxic and teratogenic effects. Aminoglycosides are administered only on special indications because of potential toxic risk for the eighth cranial nerve of the foetus. The of vancomycin is controversial use due to ototoxicity and nephrotoxicity for fetus

- Administration of such antifungal drug as amphotericin B does not cause teratogenic effects, whereas fluconazole is teratogenic depending on the dose (over 150 mg/day).
- Loop diuretics should be used with caution.
- In life threatening situations the surgery along with CS (Caesarean Section) is performed in specialized health centres where the patient can be safely transferred to [9, 18, 28].

PROPHYLAXIS OF IE

Correlation between the pre-Existing heart disease, bacteraemia, and IE onset was first recognized in 1923 [9]. The relationship between transient bacteraemia (commonly *Streptococcus viridans* after dental extractions) and IE in patients with rheumatic heart lesions was noted in 1944 and laid the foundation of using antibiotics to prevent IE in patients following tooth extractions or other procedures that may cause bacteraemia [9, 18, 28]. But the introduction of these measures has not significantly reduced its incidence. The reported causes are as follows:

- Bacteremia may occur not necessarily in major interventions (dental extraction, tonsillectomy, bronchoscopies), but also during daily basic routine activities such as tooth brushing. Sometimes, upper respiratory infections may also lead to acute bacteremia [9, 28].
- The inefficiency of antibiotic therapy in cases of severe bacteraemia. This does not imply a complete therapeutic failure, as the used doses are not of bactericidal effect, but prevents the adhesion of microorganisms to the endocardium or artificial valves.

The main concept of antibiotic prophylaxis consists of the administration of antibiotics before the bacteremia onset in order to reduce the ability of adhesion and multiplication of microorganisms [18].

1. Risk groups

I group – minor risk of IE development. Prophylaxis is not required

It includes almost healthy people / some heart disorders with minor risk of IE development:

- ischemic heart disease;
- patients with coronary bypass;
- atrial septum defect;
- closed ventricular septum defect;
- isolated pulmonary stenosis;
- Ebstein anomaly;
- Fontan and Mustard procedures;
- patients with cardiac murmurs in the absence of detected echocardiography changes;
- mitral valve prolapse without regurgitation and calcification;
- patients with cardiac pacemaker and defibrillator.

II group – patients with high risk of IE development. Prophylaxis is preferable:

- acquired valvular lesions;
- mitral valve prolapse with marked regurgitation and myxomatous degeneration;
- hypertrophic cardiomyopathy;
- non-cyanogenic congenital defects such as coarctation of aorta and presence of ductus arteriosus (except for secondary atrial septum defect).

III group – patients with very high risk of IE development. Mandatory prophylaxis is required:

- prosthetic valve;
- previous IE history;
- cyanotic heart disease (Fallot Tetralogy);
- artificial systemic/pulmonary communications.

2. Noncardiac risk factors

I. Nonbacterial thrombotic vegetations.

Microorganisms adhere easier to the endocardial surface in the presence of recently formed platelet-rich thrombi [18]. Thrombogenesis is caused by blood hypercoagulability that develops due to comorbidities persistence:

- liver cirrhosis;
- hepatocarcinoma;
- leukemia;
- inflammatory bowel disease;
- systemic lupus erythematosus;
- steroid medication.

II. Immune pathologies

- defective antibody (i.e. steroid medication-induced)
- cellular defects.

III. Immunosuppressive effects on the body:

- lesions with increased permeability of mucous membranes thereof:
  - chronic inflammatory bowel disease;
- capillary reduced clearance:
  - arteriovenous fistulae;
- chronic hemodialysis.

IV. Bacteremia:

- skin conditions;
- burns;
- trophic ulcers in diabetes;
- polytraumas;
- dental disorders;
- IVDU.

V. Aggressive colonization of the bowel with streptococcus bovis biotype I.

3. Predisposing heart diseases causing risks of EI development which require mandatory antibacterial prophylaxis

Table 8

Predisposing heart disease requiring antibacterial prophylaxis

High-risk Patients	Moderate-risk patients
• Prosthetic heart valves • Cyanotic congenital cardiomyopathy • Anamnestic IE • Pulmonary systemic palliative groovings	• Obtained valvular cardiomyopathy, • Noncyanotic congenital cardiomyopathy (including bicuspid aortic valve), except for atrial septal defect. • MV prolapse with significant regurgitation • Hypertrophic cardiomyopathy
Mandatory Prophylaxis	

4. Diagnostic and therapeutic procedures predisposing to IE development, requiring prophylaxis in high-and moderate-risk patients.

Table 9

Diagnostic procedures requiring IE prophylaxis

Diagnostic Interventions	Therapeutic and surgical interventions
• Rigid bronchoscopy procedure • Cystoscopy (urethral catheterization) • Urinary tract and prostate biopsy	• Dental procedures: – Tooth extraction, – Periodontal surgery, – Tartar removal – Dental plaques removal, – duct cleaning • ENT procedures: – tonsillectomy – adenoidectomy

	• Gastrointestinal procedures: – Gastrointestinal polypectomy, – Oesophageal dilatation, – Sclerotherapy for esophageal varices, – Endoscopic retrograde cholangiopancreatography with bile duct obstructions • Urogenital procedures: – Transurethral resection of the prostate, – Lithotripsy, – Urethral dilation, – Cystoscopy

5. Antibacterial prophylaxis regimen in patients at risk of IE development.

Table 10

Antibacterial medication and prophylactic regimens

For dental, oral, esophageal or upper respiratory tract interventions		
Condition	**Medication**	**Regimen**
Standard Prophylaxis	Amoxicillin	Adults: 2.0 g.; Children: 50 mg/kg p.o. 30min-1 hour before the procedure onset
Failure to oral antibiotic administration	Amoxicillin or Ampicillin	Adults: 2.0g; Children: 50 mg/kg i.v. 30min-1 hour before the procedure onset
Allergy to penicillin	Clindamycin or	Adults: 600 mg;Children: 20 mg/kg p.o. 1 hour before the procedure onset
	Azithromycin/ Carithromycin	Adults: 500 mg;Children: 15 mg/kg p.o. 1 hour before the procedure onset
Allergy to penicillin and failure to oral antibiotic administration	Clindamycin	Adults: 600 mg; Children: 20 mg/kg i.v. 30min before the procedure onset
Gastrointestinal and urogenital procedures		
For dental, oral, esophageal or upper respiratory tract interventions		
Condition	**Medication**	**Regimen**
High-risk patients without penicillin allergy	Ampicillin / Amoxicillin + Gentamicin and Ampicillin / Amoxicillin	Adults: 2.0 g i.v; Children 50mg/kg. 1.5 mg/kg. I.V 30 min – 1 hour before intervention, 1.0g per os in 6 hours after intervention

Moderate-risk patients without penicillin allergy	Ampicillin / Amoxicillin amoxicillin	Adults: 2.0 g i/v; Children: 50 mg/kg I.V 30 min – 1 hour before intervention, and 2.0 p.o. In 1 hour after intervention
High-risk patients allergic to penicillin	vancomycin + Gentamicin	Adults: 1.0g ; Children: 20 mg/kg; 1,5 mg/kg I.V or I.M 1-2 hours before intervention
Moderate-risk patients allergic to penicillin	Vancomycin	Adults: 1.0g ; Children: 20 mg/kg i.v or i.m 1-2 hours before intervention

The total dosage for children should not exceed the adult dosage

Note: *Generation III Cephalosporins, Clindamycin or vancomycin (for Staphylococcus aureus meticilinrezistent) are drugs of choice in patients undergoing heart surgery or procedures involving infected tissues.

* Cephalosporins are not administered in cases of acute hypersensitivity response to penicillin (rash, angioneurotrophic swelling, anaphylaxis).

IE PROGNOSIS

Untreated infectious endocarditis is a fatal disease. A 2-4-week delay of treatment may double the mortality rate. IE caused by Streptococcus viridans is treated in 90% of cases if an appropriate antimicrobial therapy is adimistered. Relapse of IE occurs usually within the first two months after the completion of antibacterial treatment, being more frequent in EI caused by *Staphylococcus aureus*, *Enterococcus faecalis* and fungi. Intravenous drug abuse may by the strongest predictor of IE recurrence.

1. IE Mortality tendency

Infectious endocarditis used to be a fatal disease until the use of antibiotics gave hope for a favourable prognosis in the early '40s of the last century reducing mortality rates by 40–50%. With the advent of valve surgery there has been achieved a significant progress in the management of IE and patient's life quality. In the XXI century, in case of late diagnosis or delayed therapeutic measures, mortality rate still remains at a high level: 16–20% for common IE and 24–50% for nosocomial IE. The mortality rate varies due to its causative agent, severity of complications and associated comorbidities. Death occurs most commonly due to hemodynamic deterioration or cerebral complications.

2. Factors of reserved prognosis

I. Characteristics of the patient

- Old age
- IE valvular prosthesis
- Insulin-dependent diabetes
- Comorbidities (altered general condition, cardiovascular disease, pulmonary or renal concomitance)

II. IE complications

- heart failure
- renal failure
- strokes

- septic shock
- annular complications

III. Microorganisms
- *Staphylococcus aureus*
- *fungi*
- *Gram-negative bacilli*

IV. Echocardiography
- annular complications
- severe left-sided valvular regurgitation
- lowered left-ventricular ejection fraction
- pulmonary hypertension
- heavy vegetations
- severe prosthetic dysfunction
- premature closure of the mitral valve and other signs of increased diastolic pressure.

3. Predictors of in-hospital mortality in IE

Despite all modern achievements in early diagnosis and appropriate treatment of patients with IE, the mortality rate still remains high. The studies made on this subject found out mortality predictors in patients with this severe pathology (Table 11) [24].

Table 11

Predictors of in-hospital mortality in EI

Variables	Hazard Correlation (95% CI)	p
age (increases with every 10 years of aging)	1.45 (1.37- 1.54)	< 0.0001
males	0.91 (0.75 – 1.11)	0.36
diabetes	1.14 (0.89 – 1.45)	0.30
chronic renal failure	1.45 (1.13 – 1.86)	0.004
nosocomial infections	1.62 (1.34 – 1.96)	0.0001
prosthetic valve infection	1.05 (0.80 – 1.38)	0.71
***Staphylococcus aureus* infection**	1.72 (1.37 – 2.15)	0.0001
enterococcal infection	0.82 (0.60 –1.13)	0.22
streptococcal infection	0.75 (0.57 –0.99)	0.046
heart failure	1.89 (1.53 –2.35)	0.0001
severe embolic events	1.69 (1.28 –2.22)	0.0001
valvular surgery	0.67 (0.5 – 0.9)	0.008

4. Causes of death in IE

Still nowadays, infectious endocarditis is an acute pathology evolving severe systemic complications, sometimes irreversible, resulting in high levels of mortality, 16–20% for community IE and 24–50% for nosocomial IE. The main causes of death in patients with IE are: progressive heart failure, septic shock polyorganic failure, embolic syndrome, renal and liver failure etc. [24, 28]. The results of the our studies are shown in figure 22.

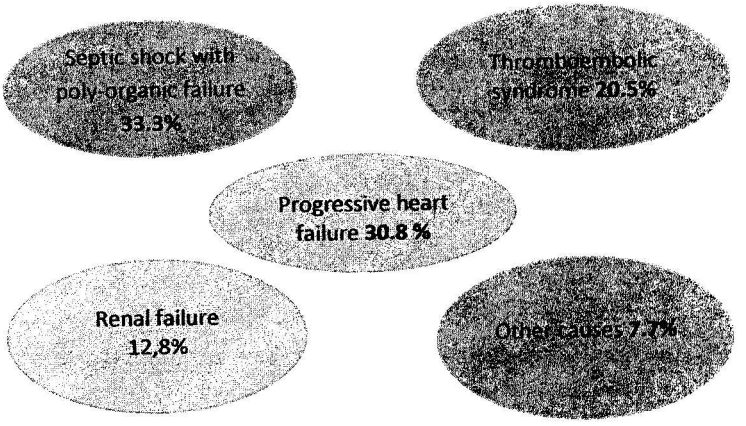


Fig. 15. Causes of death in IE, n = 78.

TESTS

1. SC. Streptococcal methicillin-resistant infectious endocarditis is treated exclusively with:
   A. penicillin G
   B. ceftriaxone
   C. vancomycin
   D. gentamicin
   E. amoxicillin.

2. MC Microbial graft in IE is placed on:
   A. native valves
   B. Eustachian valve
   C. the ileocecal valve
   D. prosthetic valve
   E. ventricular septal defect.

3. CM The major criteria for diagnosis of infective endocarditis are:
   A. fever $\geq$ 38 C
   B. fever $\leq$ 38 C
   C. positive blood culture taken from three peripheral veins
   D. positive blood culture taken from a single sample
   E. the presence of vegetation on echocardiography.

4. MC Note the essential clinical manifestations of infectious endocarditis:
   A. diarrhea
   B. vomiting
   C. chills
   D. increased sweating
   E. fever.

5. MC The right-sided IE may cause the following complications:
   A. septic pneumonia
   B. destructive multi-focal pneumonia
   C. cerebral embolism
   D. coronary embolism
   E. pulmonary abscess.

6. MC Tick embolic complications specific for left-sided IE :
   A. renal emboli
   B. cerebral embolism

C. splenic embolism
D. coronary embolism
E. pulmonary abscess.

7. MC Infective endocarditis is considered to be active:
   A. in the first two months of the IE onset
   B. in the presence of positive blood cultures and persistent fever
   C. in the evidence of endocardial inflammation due to morphological examination
   D. in the evidence of pathogenic agent in positive blood cultures
   E. in the evidence of pathogenic agents in nasopharyngeal smears.

8. MC Infective endocarditis is described as being:
   A. infectious
   B. with vegetative lesions on native valves
   C. dehiscence of prosthesis
   D. positive blood cultures
   E. positive nasopharyngeal smears.

9. MC IE affects:
   A. native valves
   B. mechanical prosthetic valves
   C. biological prosthetic valves
   D. intact valves
   E. ileocecal valves.

10. SC Tick the predominant infectious agent of prosthetic IE:
   A. *Streprococcus virdans*
   B. *Streptococcus bovis*
   C. *Enterococcus faecalis*
   D. *Staphiylococcus epidermidis*
   E. *Staphiylococcus aureus.*

11. SC Tick the predominant IE agent in intravenous drug users:
   A. *Staphylococcus epidermidis*
   B. *Staphylococcus aureus*
   C. *Streprococcus virdans*
   D. *Streptococcus bovis*
   E. *Enterococcus faecalis.*

12. SC Tick the predominant IE agent in patients who do not follow dental hygiene:
    A. *Streprococcus virdans*
    B. *Streptococcus bovis*
    C. *Enterococcus faecalis*
    D. *Staphiylococcus epidermidis*
    E. *Staphiylococcus aureus.*

13. MC Tick the scientists who did research in the field of infectious endocarditis:
    A. E. Libman
    B. W. Osler
    C. H. Schottmuller
    D. L. Nikolaev
    E. V. Socoteanu.

14. MC The treatment of infectious endocarditis includes the following medications:
    A. antibiotics
    B. antifungal
    C. cardiac glucosides
    D. anticoagulants
    E. beta-blockers.

15. SC Tick the treatment dose and method of administration of daptomycin in patients with IE caused by *Staphylococcus aureus*:
    A. 500 mg / day intravenous infusion
    B. 1gr/day intravenous bolus
    C. 3 g / day per os
    D. 1 g / day per os
    E. 500 mg / day in four doses intramuscularly.

16. SC Tick the treatment dose of vancomycin in patients with IE caused by methicillin-resistant staphylococci:
    A. 500 mg / day intravenous infusion
    B. 1 g / day intravenous infusion
    C. 1.5 or 2 g / day in 2 doses intravenous infusion
    D. 500 mg / day intravenous bolus
    E. 1 g / day intravenous bolus.

17. MC Staphylococcal methicillin - resistant IE is treated with:
    A. penicillin G
    B. daptomycin
    C. vancomycin
    D. gentamicin
    E. amoxacillin.

18. MC Tick the IE complications:
    A. glomerulonephritis
    B. embolisms
    C. heart failure
    D. torticolism
    E. toxic hepatitis.

19. MC The major criteria for diagnosis of infective endocarditis are:
    A. fever $\geq 38°C$
    B. myocardial abscess on echocardiography
    C. positive blood culture taken from three peripheral veins
    D. dehiscence of prosthesis on echocardiography
    E. the presence of vegetation on echocardiography.

20. MC Mandatory IE prophylaxis is admiistered to patients with:
    A. mitral valve prolapse
    B. ischemic cardiomyopathy
    C. hypertrophic cardiomyopathy
    D. prosthetic heart valves
    E. early incidence of Infective endocarditis.

21. MC Infective endocarditis is considered active in the following cases:
    A. in the first two months of the IE onset
    B. in the presence of positive blood cultures and persistent fever regardless of disease duration
    C. in the evidence of endocardial inflammation at morphological examination
    D. in the evidence of pathogenic agent by positive blood cultures
    E. in the evidence of pathogenic agent by nasopharyngeal smears.

22. MC Choose the correct statements for early prosthesis IE:
    A. staphylococcs and streptococcs are the predominant infectious agents
    B. embolic complications lead to a high percentage of incidence and death

C. it develops within 6 months after prosthesis
D. it is called community -associated endocarditis
E. it is also called nosocomial endocarditis.

23. MC Surgical treatment of IE is indicated for:
A. fungal endocarditis
B. streptococcal endocarditis
C. IE aggravated by myocardial abscess
D. IE aggravated by glomerulonephritis
E. infection resistant to antibacterial therapy.

24. MC Minor criteria for diagnosis of IE are:
A. fever $\geq$ 38°C
B. positive blood culture in one peripheral veins
C. prosthesis dehiscence in echocardiography
D. evidence of vegetation in echocardiography
E. predisposing cardiac factors.

25. MC The Duke minor criteria for the diagnosis of endocarditis are:
A. fever $\geq$ 38°C
B. Janeway lesions
C. positive blood culture in three peripheral veins
D. Osler nodules
E. the presence of vegetation on echocardiography.

26. MC The Duke minor criteria for the diagnosis of IE are:
A. fever $\geq$ 38°C
B. positive rheumatoid factor
C. positive blood culture in three peripheral veins
D. Roth spots
E. the presence of vegetation on echocardiography.

27.MC Choose the correct statements for late prosthesis endocarditis:
A. Staphylococci and streptococci are the predominant infectious agents
B. embolic complications lead to a high percentage of incidence and death
C. it develops within more than 1 year after prosthetic
D. it is called community-associated endocarditis
E. it is also called nosocomial endocarditis.

28.MC Tick the new forms of infectious endocarditis:

A. infective endocarditis of intracardiac devices
B. infective endocarditis in adolescents
C. infective endocarditis in elderly
D. infective endocarditis in intravenous drug users
E. infective endocarditis in addicts.

29.MC Choose the predisposing cardiac factors for developing infectious endocarditis:

A. bicuspid aortic valve
B. mitral stenosis
C. ventricular septal defect
D. arterial hypertension
E. mitral valve prolapse.

30. MC Tick the sources of infection in IE:

A. infections
B. tooth extractions
C. hemodialysis
D. poor dental hygiene
E. old age.

31.MC Infectious endocarditis is considered cured in case of:

A. final elimination of infection
B. normal body temperature
C. normal range of ESR and negative blood cultures within 1 year after of the treatment completion
D. normal range of ESR and negative blood cultures within 1 month after the treatment completion
E. normal range of ESR and negative blood cultures within 6 months after the treatment completion.

CORRECT ANSWERS

1. Pretest

1. B
2. E
3. C
4. D
5. C
6. E
7. B

2. Tests

1. C
2. A, B, D, E
3. C, E
4. C, D, E
5. A, B, E
6. A, B, C, D
7. A, B, C, D
8. A, B, C, D
9. A, B, C, D
10. E
11. B
12. A
13. A, B, C
14. A, B, C, E
15. A
16. C
17. B, C
18. A, B, C, E
19. B, C, D, E
20. C, D, E
21. A, B, C, D
22. A, B, C, E
23. A, C, E
24. A, B, D, E
25. A, B, D
26. A, B, D
27. C, D
28. A, C, D
29. A, B, C, E
30. A, B, C, D
31. A, B, C

3. Clinical cases: Correct answer

Clinical case No. 1

Diagnosis: right-sided infectious endocarditis, active period, unidentified etiology with large vegetations on the tricuspid valve. IVDU. HF II NYHA.

Mandatory additional investigations: 3 peripheral vein blood cultures taken when the patient is in high fever; C-reactive protein;

Principles of treatment: bed rest, maximal doses of antibacterial therapy according to the antibiotic sensitivity (II-III generation cephalosporins i.v. combined with fluoroquinolone i.v.; initially before the blood culture results, administration of vancomycin 2 gr./day i.v.

infusion in 2 doses and Gentamicin 240 mg/day I.V. in 0.9% NaCl infusion – 10 ml in 3 doses) antifungal treatments .

Clinical case no. 2

Diagnosis: Infectious endocarditis of the mitral prosthesis (early), in active period, unidentified etiology with vegetations on the mitral prosthesis. Condition after prosthetis of mitral valve and tricuspid valve annuloplasty (year, month). HF II NYHA. Iron deficiency anaemia.

Mandatory additional Investigations: 3 peripheral vein blood culture taken when the patient is in a high fever; C-reactive protein; prothrombin.

Principles of treatment: bed rest, maximal doses of antibacterial therapy according to the antibioticogram (II-III generation cephalosporins i.v. combined with a macrolide i.v.; initially before the blood culture results, administration of vancomycin 2 gr./day i.v. infusion in 2 doses and Gentamicin 240 mg/day I.V. in 0.9% NaCl infusion – 0 ml in 3 doses) antifungal treatments; indirect anticoagulants under cautious prothrombin control. Iron medications.

Bibliography

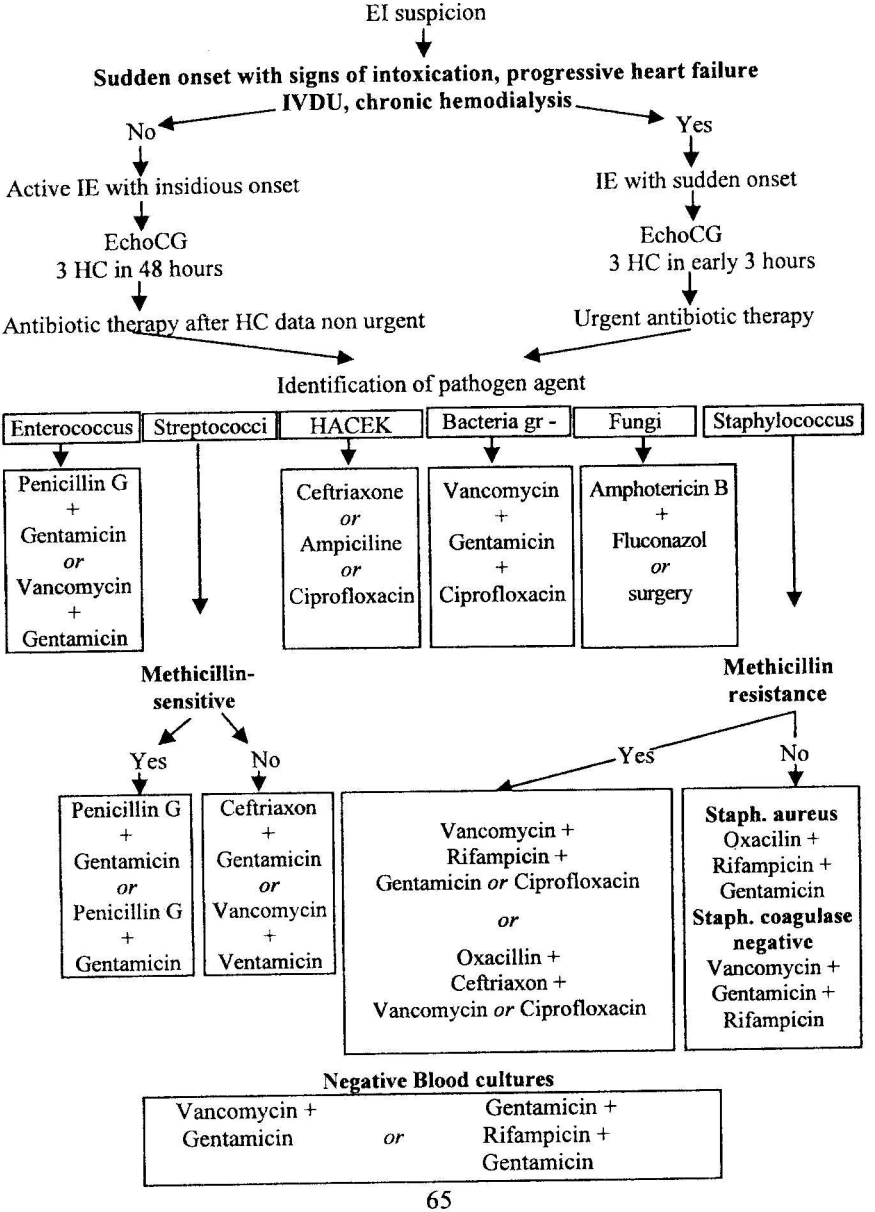
1. Anguera I., Miro J., Vilacosta I. et all. *Aorto-cavitary fistulous tract formation in infective endocarditis: clinical and echocardiographic features of 76 cases and risk factors for mortality.* Europ Heart J 2005; 26: 288.
2. Babiuc Constantin, Dumbrava Vlada-Tatiana. *Medicina internă.* Vol I, Chișinău, 2007, p. 324-354.
3. Baddour L., Wilson W., Bayer A., Fowler Jr V., Bolger A., Levison M. et al. *Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications.* Circulation. 2005;111: e394–e434.
4. Dickerman S., Abrutyn E., Barsic B. et al. *The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS).* Am Heart J 2007; 154:1086.
5. Engemann J., Sexton D. *Infective endocarditis in injection drug users.* Up To Date, 2007.
6. Fowler V., Miro J., Hoen B., Cabell C., Abrutyn E., Rubinstein E. et al. *Staphylococcus aureus endocarditis: a consequence of medical progress.* JAMA. 2005; 293:3012-21.
7. Grabowski M., Hryniewiecki T., Janas J., Stępińska J. *Clinically overt and silent cerebral embolism in the course of infective endocarditis.* J Neurol. 2011; 258(6):1133-9.
8. Hill E., Herigers P. et al. *Infective endocarditis: chaging epidemiology and predictors of 6 month mortality: a prospectiv cohort study.* Europ Heart J 2007, 28 (2): 196-203.
9. Habib G., Hoen B., Tornos P., Thuny F., Prendergast B., Vilacosta I. et al. *Guidelines on the prevention, diagnosis, and treatment of infective endocarditis.* Eur Heart J. 2009; 30:2369-413.
10. Hoen Bruno, Duval Xavier. *Infective Endocarditis.* The new England Journal of Medicine: 368: 15 April 11, 2013, p. 1425-1433.
11. Moreillon P., Que Y.A. *Infective endocarditis.* Lancet 2004; 363 p. 139-149.
12. Murdoch D., Corey G., Hoen B., Miró J., Fowler V., Bayer A. et al. *Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis.* Prospective Cohort Study. Arch Intern Med. 2009; 169:463-73.
13. Musci M., Siniawski H., Pasic M., Grauhan O., Weng Y., Meyer R., Yankah C., Hetzer R.. *Surgical treatment of right-sided active infective endocarditis with or without involvement of the left heart: 20-year single center experience.* Europ. J. Cardiothoracal Surg. 2007; 32:118–125.

14. Selma Guler, Abdullah Sokmen, Bulent Mese, Orhan Bozoglan. *Infective endocarditis developing serious multiple complications.* BMJ, Case Reports 2013; 10.1136.
15. Sexton Daniel J., Corey G. Ralph. *Infective endocarditis: Historical and Duke criteria.* Up To Date, 2008.
16. Spelman Denis, Sexton Daniel J. *Complications and outcome of infective endocarditis.* Up To Date. 2008.
17. Ştirbul A., Grejdieru A., Mazur M. *Protocolul Clinic Naţional „Endocardita infecţioasă la adult".* Chişinău, 2009.
18. Ştirbul A., Grejdieru A., Mazur M. *Protocolul Clinic Naţional „Endocardita infecţioasă la adult reactualizat".* 2011.
19. Ştirbul A., Grejdieru A., Mazur M. ş. a. *Endocardita infecţioasă, profilul clinic, prezentare şi evoluţie.* În: „Buletinul Academiei de Ştiinţe a Moldovei" nr. 4 (18). Chişinău, 2008, p. 90-96.
20. Ştirbul A., Grejdieru A., Mazur M. ş. a. *Endocardita infecţioasă a cordului drept, profilul şi caracteristica clinică.* În: „Buletinul Academiei de Ştiinţe a Moldovei" nr. 4 (18). Chişinău, 2008, p.97-101.
21. Thuny F., Di Salvo G., Belliard O., Avierinos J., Pergola V., Rosenberg V., Casalta J., Gouvernet J., Derumeaux G., Iarussi D., Ambrosi P., Calabro R., Riberi A., Collart F., Metras D., Lepidi H., Raoult D., Harle J., Weiller P., Cohen A., Habib G. *Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study.* Circulation 2005; p.112: p.69-75.
22. Tornos P., Iung B., Permanyer-Miralda G., Baron G., Delahaye F., Gohlke-Barwolf C., Butchart E., Ravaud P., Vahanian A. *Infective endocarditis in Europe: lessons from the Euro heart survey.* Heart 2005; 91: p.571-575.
23. Varona Jose F., Juan M. Guerra. *Tricuspid Valve Endocarditis in a Nonadicted pacients Withoud Predisponding Myocardiopathy.* Revista Espaniola de Cardiologia; 2004; 57; ps 993-996.
24. Wallace S., Walton B., Kharbanda R. et al. *Mortality from infective endocarditis: clinical predictors of outcome.* Heart 2002; 88:53.
25. Wang C., Lee C., Chan C., Chen H. *Splenic infarction and abcess complicaiting infective endocarditis.* Am J Emerg Med. 2009; 1532-8171.
26. Wang A., Athan E., Pappas P. et al. *Contemporany clinical profile and outcome of prosthetic valve endocaridits.* JAMA 2007; 297:1354.
27. Ward M., Boehm K. *Pacemaker Related Infective Endocarditis from Staphylococcus Lugdunensis: A Case Report.* Case Reports in Critical Care Volume 2013 (2013), Article ID 180401, pag. 3.

28. Wilson W., Taubert K., Gewitz M. et al. *Prevention of infective endocarditis: guidelines from the American Heart Association: a guidelines from the American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group* // Circulation, 2007, 116, p.1736-1754.
29. Zafer Isilac, Onur Sinan, Murat Yalqn. *An unusual case of* infective endocarditis*: annulus vegetation.* BMJ Case Reports 2013; 10.1136.
30. Шустваль Н.Ф., Дмитренко В.М., Екимова Н.А., Калюжный В.А *Инфекционный эндокардит у инъекционных наркоманов. Обновление рекомендаций по профилактике инфекционного эндокардита у пациентов с клапанными пороками сердца.* 2008.
31. Романенко В.В., Романенко З.В. *Пороки сердца: этиология, патогенез, диагностика, лечение.* (Учебное пособие). Минск: ИВЦ Минфина, 2012, с.429-483.

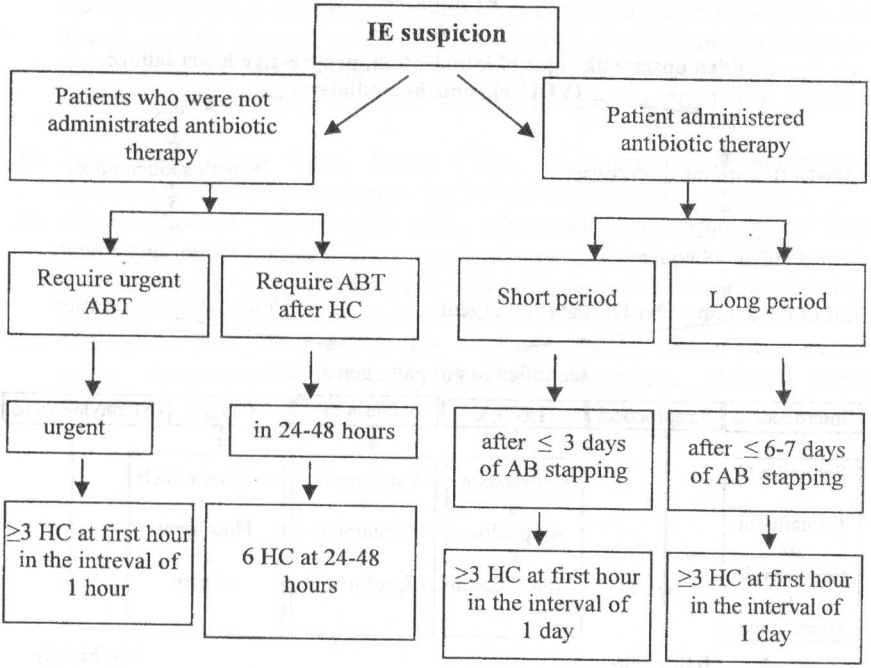
Annex 1

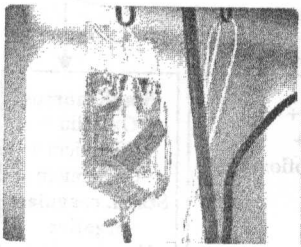
General algorithm of management for patients with suspected IE

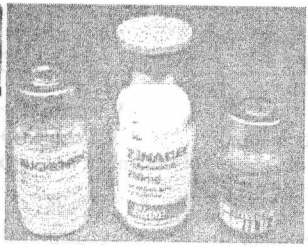


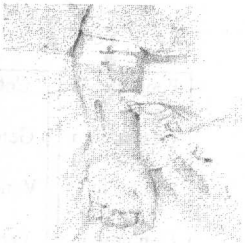
Annex 2

Algorithm of examination of blood cultures in patients suspected of IE

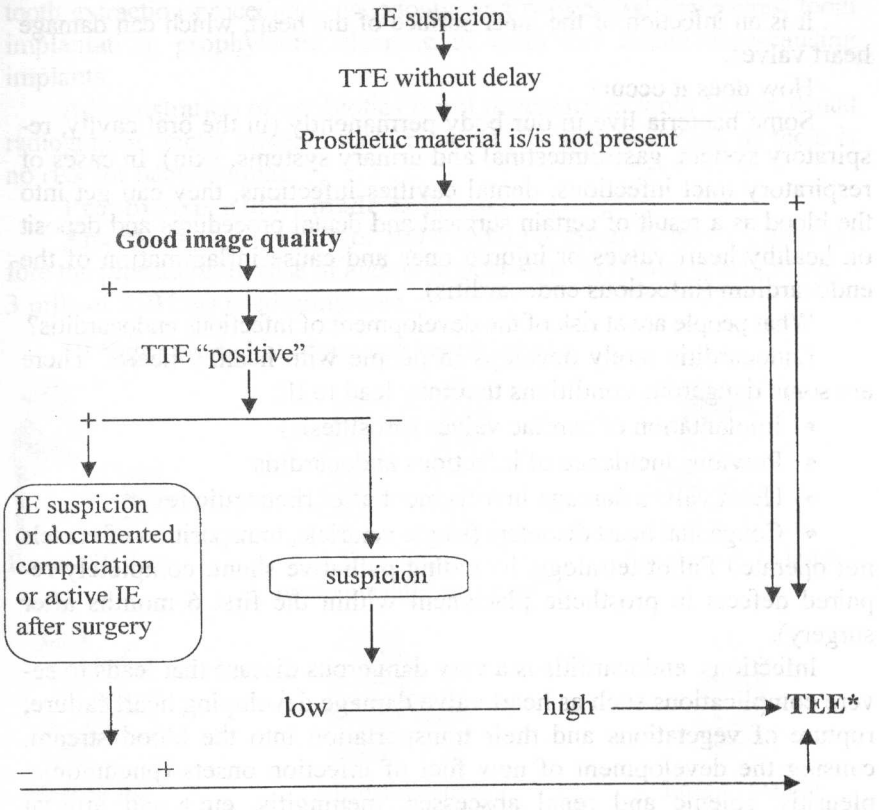




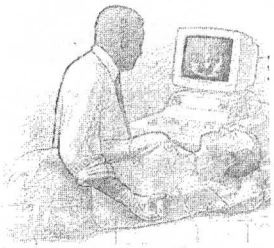




Echocardiographic examination algorithm (TTE and TOE) in suspected IE



Note: * If TEE is negative but clinical suspicion is still high, TOE is repeated again in 48 hours and 7 days.



Annex 4

Guide du patient pour la prophylaxie de l'EI

What is infectious endocarditis?

It is an infection of the inner surface of the heart, which can damage heart valves.

How does it occur?

Some bacteria live in our body permanently (in the oral cavity, respiratory system, gastrointestinal and urinary systems, skin). In cases of respiratory tract infections, dental cavities infections, they can get into the blood as a result of certain surgical and dental procedures and deposit on healthy heart valves or injured ones and cause inflammation of the endocardium (infectious endocarditis).

What people are at risk of the development of infectious endocarditis?

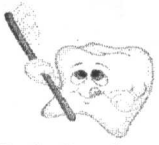
Endocarditis rarely develops in people with healthy hearts. There are some dangerous conditions that may lead to IE:

- Implantation of cardiac valves (prosthesis)
- Previous incidence of infectious endocarditis
- Heart valves damage involvement after rheumatic fever
- Congenital heart disorders (single ventricle, transposition of vessels, not operated Fallot tetralogy, including palliative shunt; completely repaired defects in prosthetic placement within the first 6 months after surgery).

Infectious endocarditis is a very dangerous disease that leads to severe complications such as heart valve damage developing heart failure; rupture of vegetations and their transportation into the blood stream, causing the development of new foci of infection onsets (pneumonia, pleuritis, splenic and renal abscesses, meningitis, etc.) and arterial thrombosis (i.e. brain = stroke, eye = blindness, heart = heart attack).

Preventive measures.

Dental Hygiene is of major importance in IE prevention!



Daily Brushin

Decayed teeth treatment

Immediate consultation if suspected signs appear

Patients at risk of the development of infectious endocarditis may protect the endocardium against bacteria if they are administered antibiotics according to the following scheme before the dental procedures: tooth extraction procedures, endodontic and periodontal procedures, tooth implantation, prophylactic cleaning of teeth and hemorrhage-causing implants.

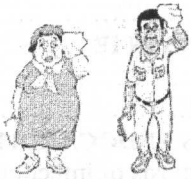
Administration of antibiotics is not necessary in tooth filling, dental radiography, dental bracing, tooth removal, fluoride treatment, as there is no risk for bacteraemia.

Prophylaxis will be made as follows

Amoxicillin 2 g – 4 pills of 500 mg p.o.) is given 30 min – 1 hour before the procedure. In case of allergy to penicillin: Erythromycin (750 mg – 3 pills of 250 mg) is administered.

!!! Signs that should arouse suspicions:

Fever >10 days



Sweating predominantly nocturnal

Sore muscles / joints

Heartbeats

Breathlessness

Loss of weight

Dizziness

Loss of appetite

Weakness

Immediately consult your Family doctor or a cardiologist!

Contents