An eBook on Cardiology

Chapter 2

Clinical Approach to Infective Endocarditis

Loredana Faraldi MD*

Grande Ospedale Metropolitano Niguarda, Milano, Italy

Email: loredana.faraldi@ospedaleniguarda.it

1. Introduction

Few diseases present greater difficulties in the way of diagnosis then are malignant endocarditis, difficulties which in many cases are practically insurmountable. It is no disparagement to the many skilled physicians who have put their cases upon record to say that, in fully one-half the diagnosis was made post mortem. (William Osler 1885).

More than 100 years after Osler's affirmation, the diagnosis and management of endocarditis remain a great challenge for the clinicians even today; in fact, its mortality is around 20% at 30 days [1] and 30% at 1 year [2], with a percentage that can vary depending on the population studied. Right endocarditis, which accounts for 5% - 10% of all cases, is characterized by lower mortality (about 7%), but can increase over a longer period in the case of patients who are chronic intravenous drug users. Its incidence increased in the United States from 9.3/100,000 people per year in 1998 to 15/100,000 people per year in 2011[3], due to widespread drug use. Depending on the location of the infection, endocarditis can be distinguished in:

• Left-sided native valve IE (NVE)

• Left-sided prosthetic valve IE (PVE): – Early PVE: 1 year after valve surgery

• Right-sided IE

• Device-related IE (permanent pacemaker or cardioverter-defibrillator) [4].

2. Epidemiology

In recent years, there has been a significant change in the epidemiology of this subtle disease, with a strong modification of the spectrum of patients and the microorganisms involved,

which makes its management even more complicated today in the face of new imaging technologies and antibiotic therapies. The population involved has become increasingly elderly, due to the global increase in the average age of survival [5,6] (**Figure 1** and **Figure 2**), with an increasing number of patients carrying implanted intracardiac devices such as permanent pacemakers (PPM) and implantable cardioverter defibrillators (ICD), valve prostheses, and an increasing number of patients with congenital heart diseases who survive in adulthood thanks to the improvement in medical and surgical cardiological treatments.

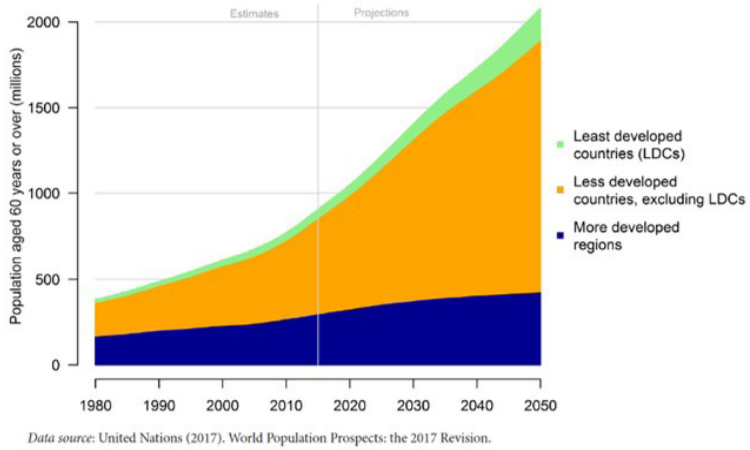


Figure 1: The number of persons aged 60 years or over by development group, from 1980 to 2050. Data source: United Nations (2017), World Population Ageing 2017. Highlights (2017).

In the last 20 years, prosthetic valve endocarditis has increased to the point that it now accounts for 20 percent of all infectious endocarditis [1,7] and a high in-hospital mortality rate of 20-40% has been reported in PVE as well as in infections of cardiac implantable electronic devices (CIEDs). The general increase in the average age of the population has meant that most patients potentially have a higher frailty score and a greater number of risk factors including chronic diseases such as chronic kidney diseases requiring dialysis, cancer, and diabetes. The older population also has increased contact to the healthcare system with a greater risk of contracting infections even from resistant microorganisms [5].

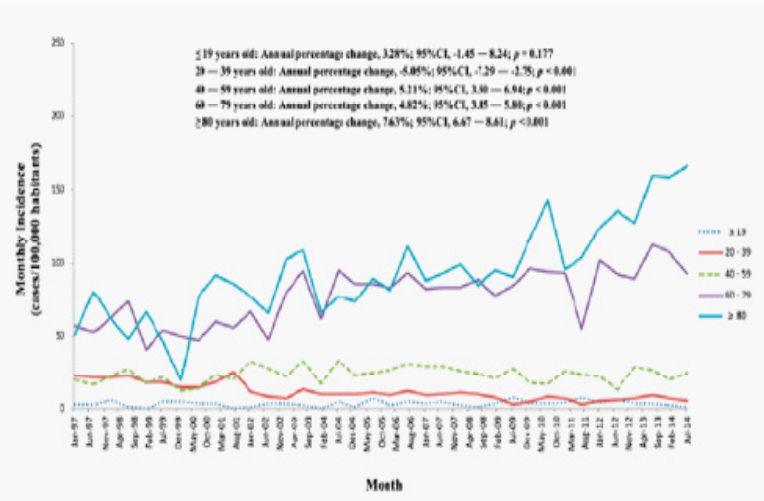


Figure 2: Incidents of IE according to gender (a) and age groups (b) from 1997 to 2014 in Spain is shown in the graph. [5] From: Christian Ortega-Loubon, María Fe Muñoz-Moreno et al. Nosocomial Vs. Community-Acquired Infective Endocarditis in Spain: Location, Trends, Clinical Presentation, Etiology, and Survival in the 21st Century. J. Clin. Med. 2019,8, 1755, 1–15. doi: 10.3390/jcm8101755

Another aspect to consider is the increase in the prevalence of drug abuse (DA); IVDAs (intravenous drug abusers) are usually affected by right-sided IE that accounts for 5-10% of IE cases. From a recent study published by Kadri, Wilner et al. on the trend of endocarditis associated with intravenous drug abuse in the USA from 2002 to 2016, there is a significant increase in the drug addict population and related IE: out of a total population of 455,404,161 hospitalized patients, the incidence of IE has increased from 18/10000 in 2002 to 29/10000 in 2016 and the incidence of drug abuse-related IE increased from 48 per 10000 in 2002 to 79 per 10000 in 2016 [8] (**Figure 3**).

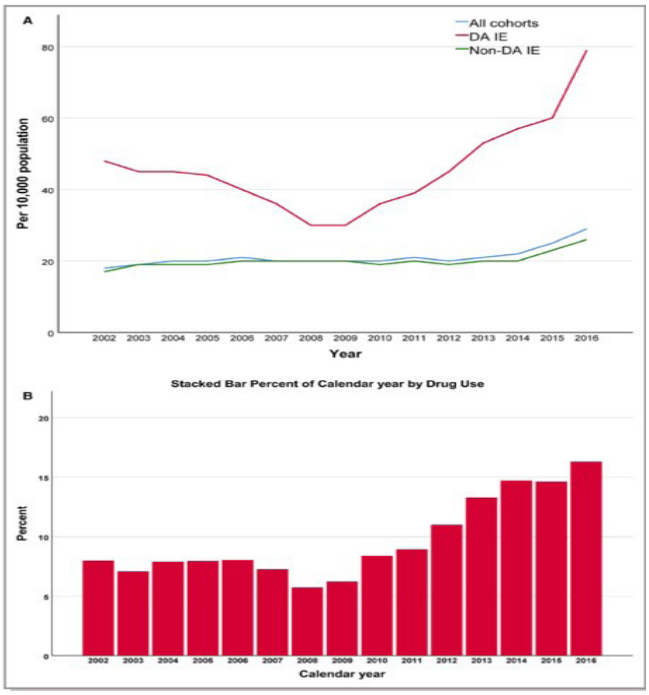


Figure 3: National trends of incidence rate of drug-abuse related IE vs non-drug-abuse-related IE (A) and prevalence ratio of drug abuse in patients with IE (B) [8] From: Amer N. Kadri; Bryan Wilner et al. Geographic Trends, Patient Characteristics, and Outcomes of Infective Endocarditis Associated With Drug Abuse in the United States From 2002 to 2016. J Am Heart Assoc. 2019:8:e012969. DOI: 10.1161/JAHA.119.012969.

Consensually to the spectrum of patients, the microbiological spectrum responsible for the infection has also changed, with a clear emergence of *Staphylococcus aureus* (26% - 33% of all cases, depending on the studies) and *Enterococci* (10.5%), and a reduction in *Streptococci viridans* (from 30% to 18.5%) [2,9,10], due to an increase in healthcare contact, use of intravenous drugs and invasive procedures, also thanks to the reduction of rheumatic heart disease in the most developed countries. Factors associated with the increase in in-hospital mortality are: infection of prosthetic valve, advanced age, pulmonary oedema, mitral vegetations, perivalvular complications, *Staphylococcus aureus* endocarditis and *coagulase-negative staphylococci*.

3. Diagnosis

Diagnosis can sometimes be very difficult due to the sub acute and subtle presentation of the disease with nonspecific symptoms, so it could be confused with other pathologies, such as rheumatoid arthritis, tumors, autoimmune diseases and other types of infections [4], but it should be performed as soon as possible to start early empirical antibiotic therapy

and identify patients who are at greater risk of developing complications and could benefit from early surgery. In the diagnostic process, blood cultures and echocardiography (TTE, transthoracic echocardiography and TEE, transesophageal echocardiography) are the masters which, however, can sometimes be negative even in the presence of active IE, thus giving false negatives. In 1994, Durack et al. proposed a series of standardized diagnostic criteria to facilitate the diagnosis of IE, subsequently recognized as Duke Criteria that was modified in 2000 and even more recently in 2015 to increase sensitivity of the method [11–13]. Duke's modified criteria (**Table 1** and **Table 2**) allow stratifying patients with suspicion of IE into three categories: certain, possible and rejected and has a high sensitivity (80%) and specificity in the diagnosis of endocarditis but despite being very useful in correct diagnosis, it doesn't replace clinical judgment. Especially in the case of prosthetic valves and implanted devices, sensitivity and specificity are significantly reduced, therefore, latest ESC guidelines have added some items to Duke's criteria to increase sensitivity in this group of patients for whom further investigations including cardiac CT, MRI, F-FDG-PET / CT should be considered. These Imaging investigations could in fact demonstrate cardiac involvement that the TTE or TEE has not shown. That's why these have been included in the latest ESC guidelines among the major criteria. In recent studies [14,15] hole body CT, cerebral MRI and F-FDG PET / CT or radiolabeled leukocytes SPECT / CT have been proved useful in highlighting clinically silent embolic phenomena affecting other organs and demonstrating the embolic phenomena, even if only for imaging, is one of Duke's modified minor criteria.

Table 1: Modified Duke criteria for IE diagnosis. Adapted from Li et al. [11]

A.	**DEFINITIVE IE**
1.	Pathological criteria
●	Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen
●	Pathologic lesion; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis
2.	Clinical criteria
●	2 major criteria or
●	1 major criteria + 3 minor criteria or
●	5 minor criteria
B.	**POSSIBLE IE**
●	1 major criteria + 1 minor criteria or
●	3 minor criteria
C.	**REJECTED**
3.	Firm alternate diagnosis explaining evidence of infective endocarditis or
4.	Resolution of IE syndrome with antibiotic therapy for ≤ 4 days; or
5.	No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤ 4 days; or
6.	Does not meet criteria for possible IE

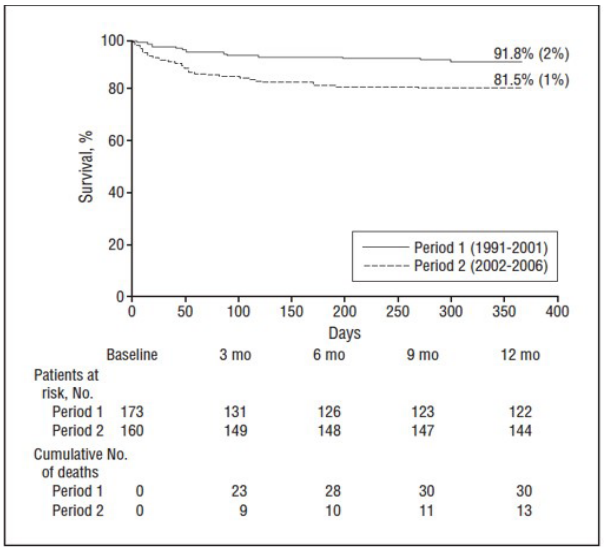
According to Duke's modified criteria, the diagnosis of IE is:

• Certain if they are met
– 2 major criteria or
– 1 major criterion + 3 minor criteria or
– 5 minor criteria;
• Possible if they are met
– 1 major criterion + 2 minor criteria or
– 3 minor criteria;
• Rejected

Table 2: Definition of terms used in the proposed modified Duke criteria for the diagnosis of IE, with modifications by 2015 ESC guidelines shown in boldface. Adapted from 2015 ESC Guidelines [12]

A.	**MAJOR CRITERIA**
1)	**Blood culture positive for IE**
●	Typical microorganisms consistent with IE from 2 separate blood cultures: *Viridans streptococci, Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or Community-acquired enterococci, in the absence of a primary focus; or
●	Microorganisms consistent with IE from persistently positive blood cultures: ≥2 positive cultures of blood samples drawn 112 h apart; or All of 3 or a majority of >4 separate cultures of blood (with first and last sample drawn at least 1 h apart); or
●	Single positive blood culture for *Coxiella burnetii* or anti-phase I IgG antibody titre > 1:800
2)	**Imaging positive for endocardial involvement**
●	Echocardiogram positive for IE: Vegetation; Abscess or pseudoaneurysm or intracardiac fistula; Valvular perforation or aneurysm; New partial dehiscence of prosthetic valve
●	New valvular regurgitation
●	**Abnormal activity around the site of prosthetic valve implantation detected by F-FDG PET/CT (only if the prosthesis was implanted for > 3 months) or radiolabeled leukocytes SPECT/CT**
●	**Definitive Para-valvular lesions by cardiac CT**
B.	**MINOR CRITERIA**
1)	Predisposition, predisposing heart condition or injection drug use
2)	Fever, temperature > 38 C°
3)	Vascular phenomena **(including those detected by imaging only)**: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway lesions
4)	Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
5)	Microbiological evidence: positive blood culture but it does not meet a major criterion as noted above or serological evidence of active infection with organisms consistent with IE.

If the diagnosis does not meet the criteria according to Duke's modified criteria and strong clinical suspicion remains then echocardiography and blood cultures should be repeated a few days apart. The management of endocarditis is therefore multidisciplinary and the result of a single test can't confirm diagnosis: for a correct classification of the IE, integration between clinical characteristics, microbiological results and imaging investigations is necessary (echocardiography, CT, MRI, PET). Hence the opportunity to create an endocarditis team [12,16–20]: a team that consists of different specialists who can work together and are able to integrate the different information in order to program a shared and effective diagnostic and therapeutic path; such team can take care not only of the intra hospital course but also of post-discharge follow-up; the endocarditis team should have a cardiologist (echocardiography specialist), cardiac surgeon, anaesthesiologist, microbiologist, infectious disease specialist, radiologist experienced in the aforementioned imaging, neurologist and neurosurgeon. This strategy is also recommended in the latest European guidelines: 2015 ESC Guidelines for the Management of Infective Endocarditis [12], and American, 2014 AHA / ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary [17]. The policy adopted in a French centre to use a task force in the management of IE has led to a clear reduction in the one-year mortality of patients when treated in this way as compared to patients traditionally treated in previous years: 1-year mortality has decreased significantly between the two groups from 18.5% (period 1) to 8.2% (from period 2) (**Figure 4**).



	Baseline	3 mo	6 mo	9 mo	12 mo
Patients at risk, No.					
Period 1	173	131	126	123	122
Period 2	160	149	148	147	144
Cumulative No. of deaths					
Period 1	0	23	28	30	30
Period 2	0	9	10	11	13

Figure 4: Kaplan-Meier curve related to survival according to the period of IE management. - From: Elisabeth Botelho-Nevers, Franck Thuny et al. Dramatic Reduction in Infective Endocarditis-Related Mortality With a Management-Based Approach. Arch Intern Med. 2009; 169(14): 1290–1298

The diagnostic path of IE can therefore be schematized in a series of steps to follow:

• Anamnestic collection and classification of risk factors.

• Clinical examination (collection of signs and symptoms).

• Performing blood cultures (Class 1, Level of Evidence A) + laboratory tests to check the severity of sepsis + ECG + serological tests or particular culture media for blood cultures in

case of initial negativity of the blood cultures but persistence of clinical suspicion of IE.

• Echocardiography, TTE or TEE performed as appropriate, (Class 1, Level of Evidence A) in case of positive blood culture or strong clinical suspicion of IE regardless of blood culture.

• Integration of all information and comparison with the Duke criteria.

• Execution of further diagnostic investigations (CT, MRI, F-FDG PET / CT, SPECT / CT) in case of negativity of blood cultures but persistence of a clinical suspicion, especially in the case of prosthetic valve.

4. Clinical History

Much attention must be paid to the collection of the patient's clinical history, in order to have first stratification of risk and then identification of those patients who could be more susceptible to develop Endocarditis: presence of prosthetic valve or other implanted Devices, valvular diseases, previous endocarditis, congenital heart diseases, recent dental surgery, intravenous drug abuse, chronic dialysis, diabetes [22] and recent access to hospital facilities or residence in long-term medical facilities (e.g. residence for the elderly). **Table 3** shows the main risk factors related to the development of endocarditis. Infective endocarditis should be considered in anyone with sepsis of unknown origin, or fever in the presence of risk factors.

Table 3: Risk Factors [1, 9]

Cardiac factors
● Bicuspid aortic valve
● Valvular diseases (e.g. rheumatic valve disease, mitral valve prolapse, degenerative)
● Congenital heart diseases
● Prior infective endocarditis
● Patients with implanted cardiac devices (permanent pacemakers / implantable cardioverter-defibrillator)
● Prosthetic heart valves.
Comorbidities
● Intravenous drug use
● Chronic kidney disease (particularly dialysis patients)
● Chronic liver disease
● Malignancy
● Advanced age
● Corticosteroid use
● Poorly controlled diabetes
● Indwelling line for venous access
● Immuno-compromised state (including HIV infection).
● Skin Infection
● Oral hygiene or dental pathology

5. Clinical Presentation

The clinical presentation can be very subtle. Fever is the almost constant clinical sign, present in up to 90% patients and can be accompanied, in a lesser percentage, by chills, night sweats, tiredness, generalized hyposthenia, loss of appetite, weight loss, abdominal pain, back pain, myalgia, arthralgias and hematuria: some of these symptoms are related to the extracardiac embolization of vegetation towards bones, kidneys and muscles; up to 25% of patients may present embolic phenomena at the first observation that can involve systemic organs such as brain (stroke, TIA, haemorrhage, with focal neurological signs, headache, vomiting and altered mental state), spleen, kidneys and bones (spondylodiscitis, back or lower back pain). Cutaneous manifestation can also be present such as petechiae to the extremities (Janeway lesions, Osler nodes actually now rare, or mucocutaneous localizations, for example micro-haemorrhages to the eyelids, or to the retina - Roth spots, **Figure 5**);embolic phenomena to the lungs with pulmonary infarcts, pneumonia, pleural effusion, and pneumothorax (cough, dyspnoea, chest pain) may be present in case of right IE (particularly frequent in IVDA addicts).

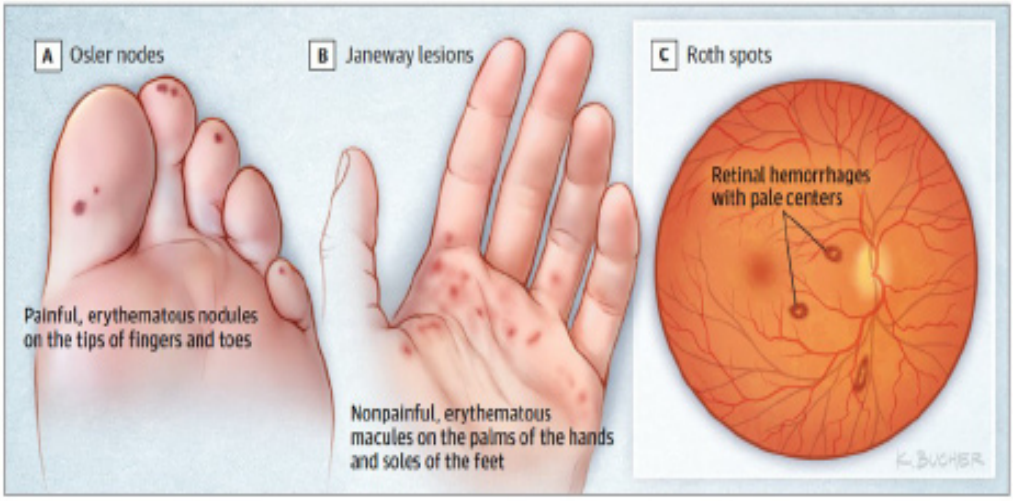


Figure 5: Classic but uncommon signs of Infective Endocarditis: A (Osler nodes present as painful and erythematous nodules on the tips of the fingers and toes); B (Janeway lesions present as painless erythematous macules on the palms of the hands and soles of the feet); C (Roth spots are haemorrhages with pale centres on the retina). From: AndrewWang, Jeffrey G. Gaca, Vivian H. Chu. Management Considerations in Infective Endocarditis. A review. JAMA. 2018 Jul 3;320(1):72-83. doi: 10.1001/jama.2018.7596.

In these patients, the presence of cardiac murmurs (new onset or increased number as compared to the previous ones), risk factors for IE and embolic phenomena strongly suspect the potential presence of an IE and must push the clinician to perform a series of blood cultures confirming the suspect. Patients with acute mitral or aortic insufficiency, secondary to IE, often present pulmonary oedema, hypotension and cardiogenic shock.

6. Investigation

6.1. Laboratory Features

Laboratory tests (leukocytosis, increase in PCR or PCT, increase in rheumatoid factor, lactate, hyperbilirubinemia, thrombocytopenia, creatinine movement, hematuria ...) have a low

positive predictive value, reflecting in most cases a general picture of sepsis and inflammation, and none of them is specific for the diagnosis of IE; despite this, these can be of great help in understanding the severity of sepsis and organ damage related to the IE (SOFA score). In the case of certain negative results of the culture tests (also excluding slow-growing germs and fungi) and suspicion of non-infectious endocarditis, antinuclear antibodies, anti-cardiolipin antibodies and anti beta2 glycoprotein 1 should be tested [12]. The execution of an initial ECG is mandatory given the possible occurrence of alterations of the rhythm for especially advanced heart block, in case of complications of IE affecting the aortic valve ring and the membranous interventricular septum: a change of the ECG during the hospitalization of a patient with certain IE must always lead to suspicion of the onset of complications and requires further confirmatory diagnostic tests (TEE) and consultation with cardiac surgeon to rule out any surgical emergencies.

6.2. Microbiological Investigations

In the suspicion of IE, positive blood cultures with echocardiography are vital in the diagnosis of the IE and provide the identification and antibiotic susceptibility of the microorganisms. Bacteraemia in endocarditis is continuous and therefore blood sampling doesn't need to be performed during high fever; at least 2^2 or 3^{12} blood culture sets, possibly from peripheral vein and from different sites (Class 1, Level of Evidence A) each containing 10 ml of blood must be taken in absolute asepsis before the start of empirical antibiotic therapy, both for the search for aerobic and anaerobic microorganisms. Complete identification is routinely achieved within 2 -3 days but may require longer time for fastidious or atypical organisms. Once the organism and its antibiotic susceptibility are known, it is possible to shift from empiric to specific therapy and repeat the blood cultures after 72 hours to check the appropriateness of the therapy. In 80 - 90% of cases, IE is due to Gram positive cocci: in developed countries the most responsible agent of IE is *Staphylococcus aureus* (up to about 30% of IEs) that often causes serious complications that require urgent surgery and is responsible for development of resistant strains, followed by *Streptococci* (36%), that is still the leading cause of IE in countries with low economic development and *Enterococci* (10%) [16,23]. For up to 30% cases, blood cultures can be negative at 72 hours: the negative results of the cultures may be due to previous or ongoing antibiotic therapy during blood sampling; in this case the therapy should be stopped and the blood cultures must be repeated at intervals of about 48 hours. Another possibility is that the IE is due to slow-growing fastidious microorganisms (usually intracellular bacteria) or fungi: in this case, if the suspicion of IE persists then blood cultures should be placed in particular culture media to search for *Brucella* spp, *Legionella pneumophila*, *Bartonella* spp, *Mycoplasma pneumoniae*, *Aspergillus* spp, and other specific investigations such as serological tests to search for *Coxiella burnetii* (Q fever) and the search for HACEK microorganisms that colonize the oropharynx (*Haemophilus aphrophilus,*

Actinobacillus actinomycetecomitans, Cardiobacterium hominis, Eikenella corrodens, and *Kingella kingae*) and are responsible for approximately 3% of the IE should also be performed as well as PCR research of *Tropheryma whipplei*, *Bartonella* spp, and Fungi, such as *Candida s*pp, *Aspergillus*. **Table 4** shows the microorganisms mostly responsible for IE from a French population-based cohort of 497 patients [16].

Table 4: Proportion of cases of infective endocarditis caused by different microorganisms from a French population-based cohort of 497 patients (Adapted from: Thomas J C et al.Infective endocarditis. Lancet 2016; 387: 882–93)

Staphylococci □ *Staphylococcus aureus*: 26·6% □ Coagulase-negative staphylococci: 9·7%
Streptococci and Enterococci □ Oral streptococci: 18·7% □ Non-oral streptococci: 17·5% □ Enterococci: 10·5% □ Other: 1·6% □ Oral streptococci: 18·7% □ Non-oral streptococci: 17·5%
HACEK (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenellacorrodens, Kingella*) microorganisms 1·2%
***Candida* species** 1·2%
Other* 6·0%
Polymicrobial (≥2 microorganisms) 1·8%
No microorganism identified 5·2%
*Includes small numbers of Enterobacteriaceae, *Propionibacterium acnes, Pseudomonas aeruginosa, Lactobacillus* spp, *Corynebacterium* spp, *Coxiella burnetii, Bartonella quintana, Tropheryma whipplei, Gordonia bronchialis, Bacillus* spp, *Erysipelothrix rhusiopathiae, Neisseria elongata, Moraxella catarrhalis, Veillonella* spp, *Listeria monocytogenes, Acinetobact erursingii,Campylobacter fetus, Francisella tularensis* and *Catabacter hongkongensi.*

6.3. Imaging Techniques

The main diagnostic investigation of IE Imaging is echocardiography, which not only provides the diagnosis of IE but allows, according to the acquired images, to reveal the characteristics of the IE and the presence of complications allowing a more targeted surgical planning. The echocardiographic diagnosis of IE is based on the demonstration of the presence of at least one of the following (**Figure 6** and **Figure 7**):

– Vegetations: oscillating or non-oscillating intracardiac masses, attached to the valves or endocardial structures and visible along the regurgitation jet or to implanted endocardial

structures;

– Abscesses: perivalvular areas thickened and not homogeneous, with an echo-dense or echo lucent appearance;

– Pseudoaneurysms: perivalvular, echo-free and pulsatile areas, with a detectable colour-Doppler flow;

– Dehiscence of valve prosthesis: perivalvular regurgitations, with or without rocking motion of the prosthesis.

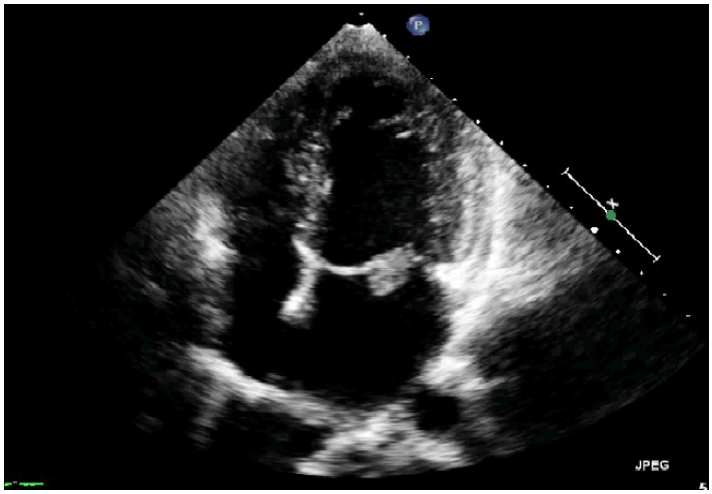


Figure 6: TTE: IE on the mitral valve.

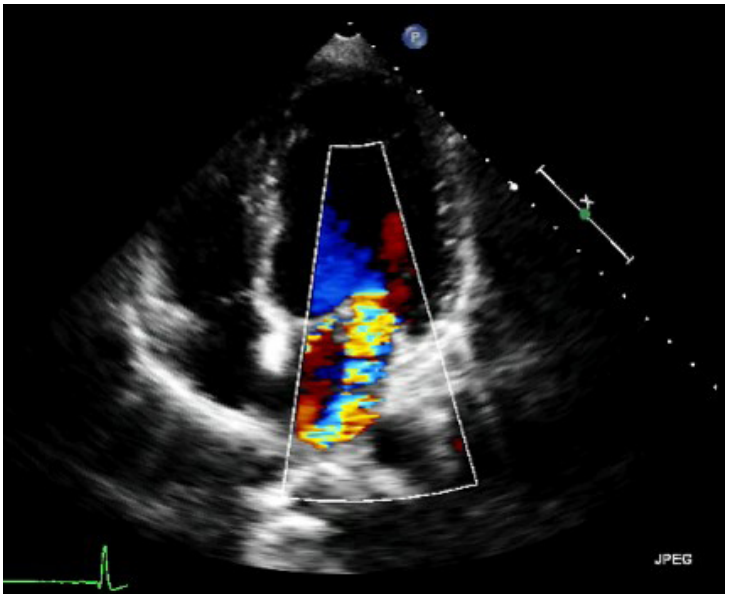


Figure 7: TTE: severe mitral regurgitation due to IE.

The sensitivity of the TTE for the diagnosis of IE on native valves varies between 50% and 90% and between 40% -70% on prosthetic valves, that of the TEE is 96% for the native ones while 85% -92% for prosthetic valves. The specificity is around 92% for both methods [12,24]. The literature agrees with the use of TTE as a first investigation step, not only for the evaluation of the valves and the characteristics of the vegetations, but also for the evaluation of the proper heart functioning that accounts the evaluation of left ventricular function,of the hemodynamic severity of the valve lesions and evaluation of the right heart with study of the pulmonary pressures. The use of the TEE is recommended in the case of:

– Non-diagnostic TTE in patients with suspected IE due to non-optimal thoracic acoustic window, which prevents correct interpretation of the images obtained by the TTE (e.g. ventilated patients in ICU, obese, COPD, previous thoracic or cardiovascular operations) or difficult interpretation of the images due to pre-existing valve alteration (e.g. calcifications) (Class I, Level of Evidence B);

– Negative results of TTE but persisting strong clinical suspicion for IE (Class I, Level of Evidence B);

– Negative results of TTE but persistence of positive blood cultures despite adequate antibiotic therapy (uncontrolled infection);

– Suspicion of valve complications not demonstrated at TTE (e.g. perivalvular abscesses, valve dehiscence, pseudoaneurysms) or suspicion of the appearance of new intracardiac complications, despite the fact that the TEE has already been performed and has tested positive for IE (Class I, Level of Evidence B);

– Patients with prosthetic heart valves or implantable cardiac defibrillator (ICD) / pacing leads and suspicion of IE (Class I, Level of Evidence B);

– *S. aureus* bacteraemia of unknown origin (Class IIa, Level of Evidence B);

– TEE negative results but persisting clinical suspicion of IE and a clinical change: in this case the examination will be repeated after 3 - 5 days or less (Class I, Level of Evidence B);

– Intraoperative control during repair / replacement of the valve for IE (Class I, Level of Evidence B) [12,25,26].

6.3.2. Radiological Investigations

In recent years, some radiological studies have been increasingly conducted for the identification of embolic complications related to IE[15] and endocardial lesions, to be added among the modified Duke criteria in the latest 2015 ESC guidelines: the identification of endocardial lesion with cardiac CT and the detection of abnormal activity around a valve prosthesis through FDG PET / CT or radiolabeled leukocytes SPECT / CT have been included among Duke's major criteria with echocardiography [12]. This type of investigation is proposed when both the TTE and the TEE have not been able to spot the presence of IE and its complications [25] but a strong suspicion of IE continues to persist (especially in the case of valve prostheses, in which the sensitivity of the TEE is between 85-92%). Coronary CT angiography can also provide an assessment of the coronary circulation for surgery to correct complications related to IE. F-FDG PET / CT or radiolabeled leukocytes SPECT / CT can also be used for the identification of even clinically silent embolic foci.

In a recent multicentre retrospective study conducted in Denmark by Holle et al., out of 178 cases of IE, the use of F- FDG PET / CT allowed to identify undetected embolic foci in 35% cases, to change therapeutic strategy in 10% cases and to reveal undiscovered cancers in 2% cases [14] (**Figure 8**).

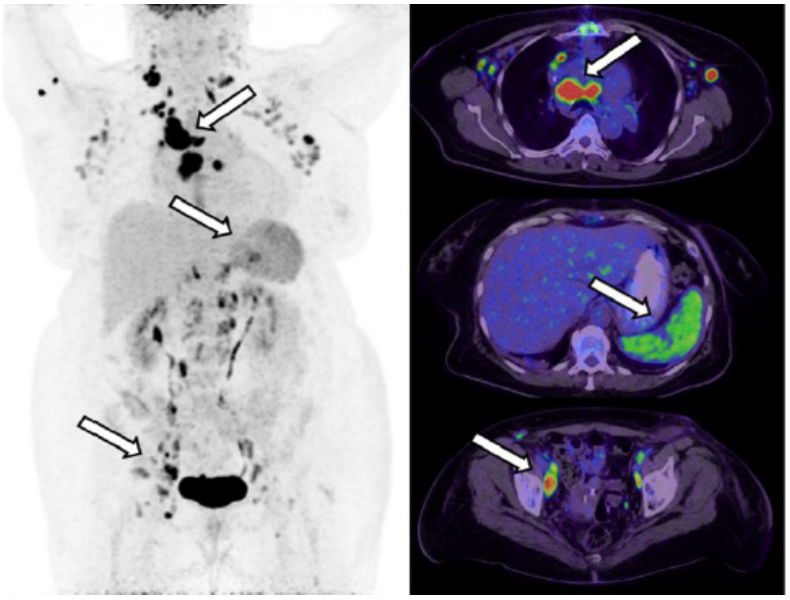


Figure 8: New PET/CT findings in an IE patient. The PET positive areas highlighted with arrows, were newly discovered diffuse large B-cell lymphoma [14]. From: Sarah Louise Kjølhede Holle, Malene Højgaard Andersen et al. Clinical usefulness of FDG-PET/CT for identification of abnormal extra-cardiac foci in patients with infective endocarditis. The International Journal of Cardiovascular Imaging. https://doi.org/10.1007/s10554-020-01787-8.

The use of complete body CT and cerebral MRI can improve the identification of even clinically silent embolic vascular phenomena and demonstration of the embolic events through imaging is among the minor modified Duke criteria (**Figure 9**).

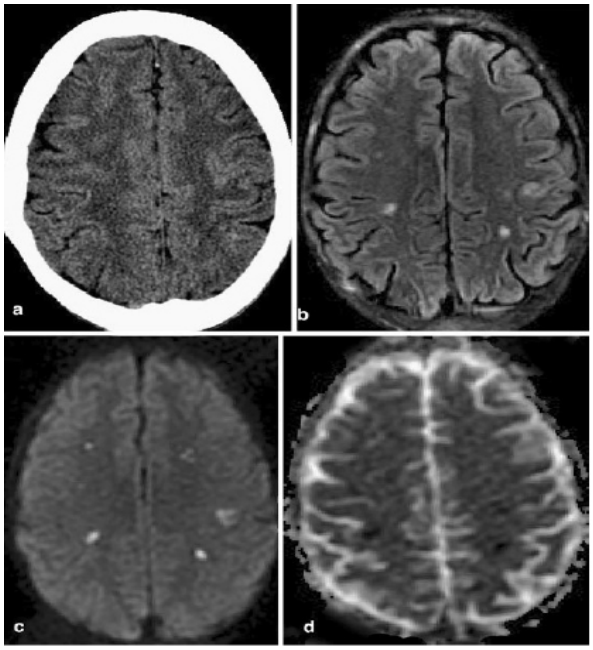


Figure 9: Emboli's stroke. Mitral valve *S.aureus* endocarditis with embolic cerebral infarctions is demonstrated. a (non-contrast CT demonstrates a vague hypo-density in the right parietal region), b (FLAIR), c (diffusion), d (ADC mapping from MRI reveals multiple bilateral foci of signal abnormality). Findings represent embolic infarcts. From [27]: Teran W. Colen, Martin Gunn et al. Radiologic manifestations of extracardiac complications of infective endocarditis. Eur Radiol. 2008; 18: 2433– 2445. DOI: 10.1007/s00330-008-1037-3.

7. Antibiotic Therapy

Antimicrobial therapy is the cornerstone of IE treatment and its main goal is to eradicate the infection. In the suspicion of IE, empirical antibiotic therapy should be started immediately after blood culture sampling and descaled as soon as the microorganism responsible and its antibiotic susceptibility are recognized to reduce the risk of resistance that may develop in case of prolonged use. Therapy should be prolonged to completely sterilize the infected valve and bactericidal antibiotics are more effective than bacteriostatic antibiotics. The combination of bactericidal antibiotics is preferred over monotherapy and the duration of antibiotic therapy must be quite long: 2-6 weeks for native valves (NVE) and at least 6 weeks for prosthetic valves (PVE) due to the difficulty in eradicating the microorganisms present in the vegetation and in the biofilms (e.g. in PVE) and due to the low bactericidal activity of some antibiotics such as beta- lactams and vancomycin: one of the characteristics of the IE is represented by the high bacterial concentration at the site of infection (vegetation and biofilm) that makes it difficult to eradicate the infection itself because high doses of antibiotics should be used. Due to these bacterial growth characteristics, the minimum inhibitory concentration (MIC) of antibiotics at the site of infection could be far greater than that tested in vitro and the particular conformation of the vegetation covered with layers of platelets and fibrin creates a real barrier while making it difficult for antibiotics to penetrate the action site. Furthermore, some microorganisms often develop tolerance to antibiotics, therefore, if the therapy is not prolonged after a certain period from the suspension of antibiotics, a regrowth of microorganisms and an incorrect eradication of the infection may occur [12,25]. The duration of the therapy is intended as starting from the first blood culture negative for IE, in those cases in which the blood cultures were initially positive: for this reason it would be indicated to take 2 sets of blood cultures every 24 or 48 hours from the start of antibiotic therapy until the blood culture is not negative, so as to begin counting the weeks of therapy from the first negative found.

During selection of the initial empirical therapy, several factors must be taken into account, including:

– The community or nosocomial origin of the IE

– Knowledge of one's own hospital and ward microbiological epidemiology, antibiotic resistance and the possible presence of uncommon Gram negative microorganisms [28]

– Whether the infection involves a native or prosthetic valve

– Whether the patient has received previous antibiotic treatments.

Given the greater involvement of Gram positive cocci in positive results of blood culture, empirical therapy will also have to cover this type of microorganisms. Below is the empirical

antibiotic therapy scheme (**Table 5**) recommended by the 2015 ESCG Guidelines, but the evaluation and collaboration of the microbiologist and infectious disease specialist (in the perspective of the Endocarditis team) is strongly recommended.

Table 5: Empirical treatment for IE in acute severely ill patients (Adapted from 2015 ESC Guidelines)

Antibiotic	Dosage and route	Class	Level
Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis			
Ampicillin with (Flu)cloxacillin or oxacillin with Gentamicin	12 g/day i.v. in 4–6 doses 12 g/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 1dose	IIa	C
Vancomycin* with Gentamicin* *Serum concentration and renal function should be monitored	30–60 mg/kg/day i.v. in 2–3 doses 3 mg/kg/day i.v. or i.m. in 1 Dose	IIb	C
Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis			
Vancomycin* with Gentamicin* with Rifampin *Serum concentration and renal function should be monitored	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 1 dose 900–1200 mg i.v. or orally in 2 or 3 divided doses	IIb	C

Once the results of the first blood cultures have been obtained, based on the type of isolation and antibiotic susceptibility, antibiotic therapy will be descaled to a targeted therapy. In more than 30% cases, endocarditis is due to *Staphylococcus aureus* responsible for more destructive and complicated IE (valve flap perforations, embolizations ...) and in this case three factors must be taken into account:

1. If *S. aureus* is MSSA or MRSA,

2. If the IE is right or left,

3. If the valve is native or prosthetic.

In fact, in case of MSSA infection on an uncomplicated right native valve and with vegetation less than 20 mm, the therapy can also last for 2 weeks and can be superimposed on that of the left IE on a native valve. In the case of native valve even if left, the use of aminoglycoside is no longer recommended due to its nephrotoxic effect and the drug mostly used is Flucloxacillin or Oxacillin (12 g / day in 4-6 doses) in case of MSSA for 4-6 weeks, and

Vancomycin (dose to reach a daily concentration of 15 - 20 mg / kg) or Daptomycin (high dose 10 mg / kg / day or more according to the 2015 ESC guidelines and 8 mg / kg / day according to the 2014 AHA Guidelines) [10,12] . In the case of MRSA: recent studies have shown the non-inferiority of Daptomycin as compared to Vancomycin in *S. aureus* bacteraemia [29], recommending its use always in association with other antibiotics to reduce the chances of resistance. In case of prosthetic valve IE, mortality increases to over 45% and often requires early surgical treatment of valve replacement: medical treatment is more aggressive and justifies the additional use of beta-lactams for at least 6 weeks, of aminoglycoside for two weeks and of rifampicin, the latter inserted 3-5 days after the start of a targeted therapy and once the sterilization of blood cultures has been completed then used for a duration of at least 6 weeks.

8. Complications and Their Management: The Surgical Approach

Surgery, whose main objective is the eradication of infection and the reconstruction of cardiac anatomy, is indicated in 40-50% of cases of EI and plays a predominant role in the management of complications related to IE. The dilemma still present today is represented by the optimal timing of surgery: the decision to proceed with surgery early when antibiotic therapy is ongoing, is much discussed and takes into consideration various factors including patient comorbidity, presence of cardiac and extracardiac complications that increase the risk of surgery (for example cerebral haemorrhages). On the one hand presence of all these factors increases the intrinsic surgical risk, on the other hand the delay in surgery increases the risk of spreading the infection to cardiac structures with greater rearrangement and subsequent greater difficulty with surgical repair thus increasing the risk of developing peripheral complications, embolism, progression of organ damage, hence ultimately increased mortality [6,12,24,25]. The decision on the best surgical timing therefore derives from the careful study of each individual clinical case in collaboration with the other members of the Endocarditis team. On the other hand, more and more studies have recently shown the benefit, in certain cases, of early surgery. A recent meta-analysis by Liang and colleagues found that early surgery compared to late surgery appears to be associated with lower intra-hospital and long-term mortality, especially for native valves [30]. Early surgery is defined as surgery "during initial hospitalization independent of completion of a full therapeutic course of antibiotics." The main surgical indications (of both the ESC guidelines and the AHA guidelines) are (**Table 6**):

1. Heart failure due to valve dysfunction,

2. Uncontrolled infection despite adequate medical therapy,

3. Prevention of embolic events.

Table 6: Indications for surgery in infective endocarditis according to the 2014 AHA/ACC and the 2015 ESC guidelines. NVE = native valve endocarditis; PVE = prosthetic valve endocarditis; HF = heart failure. Adapted from: Mahbub Jamil, Ibrahim Sultan et al. Infective endocarditis: trends, surgical outcomes, and controversies [2]. Journal of Thoracic Disease 2019; 11(11):4875-4885 | http://dx.doi.org/10.21037/jtd.2019.10.45

2014 ACC/AHA Guidelines for early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) [17]	**2015 ESC Guidelines** for management of infective endocarditis [12]	
	Left sided NVE	Timing of surgery
Heart failure due to valve dysfunction	1. Heart failure - Refractory cardiogenic shock or pulmonary edema caused by aortic or mitral NVE or PVE with severe acute regurgitation, obstruction or fistula	Emergency
	- Symptoms of HF or echocardiographic signs of poor haemodinamic tolerance	Urgent
- Heart block, annular or aortic abscess or destructive penetrating lesions	2. Uncontrolled infection - Locally uncontrolled infection (ex. fistula or abscesses)	Urgent
- Left-sided IE caused by *Staphylococcus aureus,* fungi or other highly resistant organisms	- Fungi or multiresistent organism	Urgent/elective
- Persisting infection (persistent bacteremia or fevers) longer than 5 days despite appropriate antibiotic therapy	- Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci	Urgent
- PVE and relapsing infection	- PVE caused by staphylococci or non-HACEK gram-negative bacteria	Urgent/elective
- Recurrent emboli and persistent vegetations despite appropriate antibiotic therapy	3. Prevention of embolism - Aortic or mitral NVE or PVE with persistent vegetations > 10 mm after one or more embolic episode despite appropriate antibiotic therapy	Urgent
- NVE with mobile vegetations > 10 mm with or without clinical evidence of embolic phenomenon	- Aortic or mitral NVE with vegetations > 10 mm with severe valve stenosis or regurgitation and low operative risk	Urgent
	- Aortic or mitral NVE or PVE caused by very large isolated vegetations > 30 mm	Urgent
	- Aortic or mitral NVE or PVE caused by large isolated vegetations > 15 mm and no other indication for surgery	Urgent

1. Heart failure is the most frequent complication of IE as well as the most common indication for surgery; it occurs in about 40-60% of native IEs and more frequently when IE affects the aortic valve and is the most important factor indicating in-hospital, 6-month and 1-year mortality. Heart failure can be linked to several circumstances: perforation of the valve flap, rupture of the tendon cord, acute valvular insufficiency of a high degree that is unresponsive to medical therapy and valve obstruction. In case of pulmonary oedema and cardiogenic shock refractory to medical therapy, surgery should be performed in an emergency regardless of the infectious state and ongoing antibiotics therapy.

2. Uncontrolled infection is characterized by a persistent fever and positive blood cultures

despite 7-10 days of therapy, once extracardiac abscesses have been excluded (cerebral, vertebral, splenic, renal): blood cultures and echocardiography should therefore be repeated to reassess the characteristics of the vegetation and check the appearance of new cardiac complications as well as radiological investigations such as CT, MRI, FDG PET / CT, SPECT should be performed to look for extracardiac embolic foci [4]. In this case, the infection often continues to be sustained by the perivalvular spread of the infection with the onset of paravalvular abscesses (30-40% of all EIs) especially in the aortic valve [24], pseudoaneurysms, fistulas, more frequent in PVE prosthetic valves and mostly due to *S. aureus* infection. The appearance of heart block or changes in rhythm on the ECG should lead one to suspect the evolution of an IE towards complications of this type. The presence of paravalvular complications of this kind significantly increases the risk of intra-hospital death and therefore early diagnosis is extremely important to indicate need for surgery as soon as possible [12,24,25]. Other causes of uncontrolled infection may be inadequate antibiotic therapy, the appearance of new antibiotic resistance and fungal infections.

3. Embolic phenomena occurs in about 40-50% of IE and are more frequent in the case of vegetations> 10 mm in length, mobile and supported by *S. Aureus* and more likely occur before the start or during the first 2 weeks of antibiotic therapy: their incidence after the first 2 weeks of antibiotic is reduced. Most of them therefore occur even before the diagnosis of IE itself. They can occur both in the systemic organs (starting on the left side) and in the pulmonary circle (starting on the right side). Many embolic episodes are asymptomatic and are only revealed by radiological investigations. Small splenic ischemia or involving other abdominal parenchymatous organs or bone (spondylodiscitis) hardly requires surgery but sometimes they can develop abscesses and in the case of uncontrolled infection, the opportunity of surgery or to drain the abscess should be considered [31]. Of all the embolic phenomena, the one that deserves a separate discussion and that certainly represents the greatest challenge for the surgeon is cerebral embolism, which affects about 15- 30% of all EIs[12]and can cause small clinically silent ischemic areas, real strokes up to cerebral haemorrhage with an increase in mortality and sequelae. In this case, a careful multidisciplinary assessment of the risk-benefit ratio is required, on a case-by-case basis that also involves the neurologist and neurosurgeon specialist. The cardiac surgery, due to the need for heparinization, exposes the patient to an increased risk of hemorrhagic transformation of an ischemic stroke or to a worsening of a previous cerebral haemorrhage. In the case of cerebral haemorrhage several studies [12,25,31] have shown that the delay of surgery with respect to the cerebral hemorrhagic event is associated with a lower worsening of brain conditions: for this reason the latest European guidelines of the Cardiology Society recommend to wait at least one month after the bleeding event before performing a cardiac surgery (Class IIa, Level B). In the case of ischemic event, the risk of surgery depends upon the size and severity of the stroke: if the ischemic event is silent or minor without haemorrhage and with a persistent risk of further embolization in the patient with few

comorbidities, then an early surgery would be recommended (Class I, Level B). Fifteen to 25% of IE patients develop mycotic aneurysms that most often occur in sub acute IE. Aneurysms are often multiple and may involve any vessel but they mostly occur in the CNS, sinuses of Valsalva, abdominal aorta and superior mesenteric artery[27]. The last (2016) AATS guidelines for surgical treatment of Infective endocarditis although similar are not identical to the ACC / AHA recommendations: the main disagreement relates to the level of aggressiveness and definition of early surgery and they conclude that once a surgical indication is evident, surgery must not be delayed. In patients with NVE, waiting for heart failure symptoms in patient with severe valve regurgitation and vegetations does not offer any benefit and they also recommend urgent or even emergency surgery (emergency or within 48 hours) in patients with left sided NVE or PVE who exhibit mobile vegetations greater than 10 mm in length with clinical evidence of embolic phenomenon despite appropriate antibiotic therapy [19].

9. Prognosis

In-hospital mortality varies from 15% to 30% depending on the studies [1,7] and is influenced by:

- Patient related factors (advanced age, IE on prosthetic valves, diabetes, IRC, immuno-suppression, other chronic diseases);

- Presence of cardiac and / or extracardiac complications related to IE (embolic phenomena, septic shock, heart failure);

- Kind of isolated microorganism (*Staphylococcus aureus*, Fungi, non HACEK Gram negative bacilli);

- Echocardiographic features (large vegetations, pulmonary hypertension, periannular complications, severe left valve failure, severe prosthetic valve failure, significant reduction in left ventricular ejection fraction, increase in left diastolic pressure).

B-type natriuretic peptide has potential use in the diagnosis and monitoring of HF in IE. Elevated levels of both cardiac troponins and B-type natriuretic peptide are associated with adverse outcomes in IE. Moderate to severe HF is the most important indicator of in-hospital, 6-month and 1-year mortality together with the impossibility of being able to undergo surgery for excessive surgical risk, although the surgical indication.

10. Conclusion

Infective endocarditis is associated with significant morbidity and mortality despite improvements in diagnostics and microbiological techniques. Establishing an early diagnosis with involvement of a multidisciplinary team (Endocarditis Team) and prompt surgical

intervention can improve patient outcomes. A particular attention should be pointed to the management of specific situations in which the diagnosis could be more difficult: PVE, CIEDs, and IE in drug abusers.

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