Valvular Heart Disease

Age-Dependent Profile of Left-Sided Infective Endocarditis
A 3-Center Experience

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Background—The influence of age on the main epidemiological, clinical, echocardiographic, microbiological, and prognostic features of patients with infective endocarditis remains unknown. We present the series with the largest numbers and range of ages of subjects to date that analyzes the influence of age on the main characteristics of patients with isolated left-sided infective endocarditis. Furthermore, this series is the first one in which patients have been distributed according to age quartile.

Methods and Results—A total of 600 episodes of left-sided endocarditis consecutively diagnosed in 3 tertiary centers were stratified into age-specific quartiles and 107 variables compared between the different groups. With increasing age, the percentage of women, previous heart disease, predisposing disease (diabetes mellitus and cancer), and infection by enterococci and Streptococcus bovis also increased. Valvular insufficiency and perforation and Staphylococcus aureus infection were more common in younger patients. The therapeutic approach differed depending on patient age because of the growing proportion of older patients who only received medical treatment. Clinical course and hospital prognosis were worse in the older patients because of increased surgical mortality among them.

Conclusions—Increasing age is associated with less valvular impairment (insufficiency and perforation), a more favorable microbiological profile, and increased surgical mortality among adults with left-sided infective endocarditis. (Circulation. 2010;121:892-897.)

Key Words: aging ■ endocarditis ■ endocardium ■ prognosis

Infective endocarditis is a disease with a grim prognosis, especially when the left side of the heart is affected. A progressively aging population in developed countries and the fact that infective endocarditis more commonly affects older people1–4 make us speculate that there will be a steady increase in the incidence of this disease in the near future.

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The influence of age on the profile of left-sided infective endocarditis remains unknown. Prior studies may have reflected different demographics and focused on variable outcomes6–17; they were also limited by small numbers of patients.6–16 Furthermore, they employed arbitrary age-specific cutoff points that were determined a posteriori.6–17 The aim of the present study was to analyze the influence of patient age at the time of diagnosis on the epidemiological, clinical, echocardiographic, microbiological, and prognostic profile of left-sided infective endocarditis. We did so by distributing patients homogeneously by age in quartiles.

Methods

Patients included in the analysis come from 3 university-affiliated tertiary care hospitals, which are referral centers for their regions on infective endocarditis. All of them had been working together on infective endocarditis with the use of standardized protocols, uniform data collection, and diagnostic and therapeutic criteria from the beginning of the study.

From 1996 to 2008, 770 episodes of infective endocarditis were diagnosed in 736 patients older than 14 years; Duke criteria were applied until 200218 and modified Duke criteria thereafter.19 Of these episodes, 600 were left-sided (78%) and make up the study group. We excluded from the analysis those episodes of right-sided endocarditis (n=96), those affecting permanent intracardiac devices (pacemakers and implantable cardioverter-defibrillators) (n=40), and 34 episodes with no echocardiographic evidence of endocarditis because they have completely different clinical and microbiological aspects and outcome compared with left-sided endocarditis.

A total of 107 variables were prospectively recorded for each episode analyzed (see the Appendix in the online-only Data Supplement). An echocardiogram was obtained in all cases of suspected endocarditis, and the patients were monitored until a definite diagnosis was made. All participating hospitals followed a standardized protocol under which all patients underwent at least 1 physical...
examination, ECG, chest x-ray, urinalysis, 3 blood cultures, and transthoracic and transesophageal echocardiogram. If blood cultures were negative after 72 hours, specific serological tests were conducted to detect Chlamydia, Brucella, Q fever, Legionella, and Mycoplasma.

Heart failure was defined according to established criteria,20 and acute kidney failure was defined as the presence of a serum creatinine ≥2 mg/dL in patients without previous diagnosis of chronic renal insufficiency. Systemic emboli were diagnosed by the clinical investigators who took care of these patients. The diagnosis was made on the basis of clinical signs and/or data derived from radiological procedures (eg, tomography, echocardiography, arteriography, magnetic resonance imaging). Cutaneous manifestations of endocarditis were not considered systemic embolisms because their pathogenesis is still questionable, and they do not contribute to morbidity and mortality. Surgery was considered urgent when this was performed before antibiotic treatment had ended. Surgical indications were agreed on by consensus by the researchers before the study began and included heart failure refractory to medical treatment, fungal endocarditis, recurrent embolism with persistent vegetations in the echocardiogram, and uncontrolled infection, defined as persistent bacteremia or fever persisting for >7 days despite appropriate antibiotic treatment, once other foci of infection had been ruled out. Surgery was defined as elective when it was performed after antibiotic treatment had ended. The clinical criteria to operate or not were the same in all groups. When a patient meeting the surgical criteria did not undergo surgery, the reason was either because the patient rejected the intervention, surgical risk was too high, or the patient was too fragile. In all cases, the final decision was made by a multidisciplinary team of cardiologists, cardiac surgeons, microbiologists, and specialists in infective diseases. Early prosthetic valve endocarditis was defined as occurring <1 year after surgery.21 Echocardiographic definitions of vegetation, abscess, pseudoaneurysm, and fistula have been described in previous works.22 Vegetations were measured in various planes at the point in the cardiac cycle in which the vegetation appeared the largest. The greatest diameter and the greatest area by planimetry were recorded. In cases of multiple vegetations, the largest vegetation was measured. Moderate or severe new valvular regurgitation was also recorded as echocardiogram, magnetic resonance imaging). Cutaneous manifestations of infective endocarditis. We considered as possible sites of entry the infection those situations or procedures performed within 2 months before the beginning of the symptoms related to endocarditis that are associated with risk of bacteremia (cardiac surgery and infection of intravascular catheters).

Statistical Analysis
A total of 600 episodes of left-sided infective endocarditis were stratified into age-specific quartiles at the time of diagnosis. The age-specific quartile cutoff points are shown in Figure 1. Continuous variables are expressed as mean±SD or median and interquartile range, and discrete variables are expressed as absolute value (n) and percentage. Differences in the categorical variables for increasing age groups were assessed with the use of the χ² test for trend. For continuous variables, ANOVA with linear polynomial contrast for trend was used. Normal distribution was verified with the

Kolmogorov-Smirnov test. A P value <.01 was used as a cutoff for statistical significance. Data were analyzed with the use of the SPSS V 15.0 software package (SPSS, Chicago, Ill).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
The distribution of the patients was quite homogeneous between the 3 hospitals, at 37%, 33%, and 30%, as well as in main epidemiological and echocardiographic characteristics, management (surgery and medical treatment), and outcome (data not shown). The microbiological profile only differed in the percentage of patients with Staphylococcus aureus infection (15%, 26%, and 14%), but there were no differences in the proportion of those with methicillin-resistant S aureus.

Epidemiological, Clinical, Radiological, and Analytical Variables
A total of 35 epidemiological, clinical, radiological, and analytical variables were compared between different age groups. The most relevant results of this analysis are shown in Table 1.

There were age-related increases in the proportion of women, nosocomial endocarditis, patients with previous heart disease, and some predisposing conditions that increase the risk of endocarditis (diabetes mellitus and cancer).23 Clinical characteristics at admission were similar in all age groups, except for cutaneous lesions and splenomegaly, whose frequency decreases with age. There were no differences among groups in the suspected port of entry of the infection.

Cardiomegaly and pleural effusion at chest x-ray were more frequent with increasing age. No statistically significant differences were found in the 14 analytical and 3 ECG variables analyzed.

Microbiological Variables
A total of 15 microbiological variables were compared between age groups. The most relevant findings are shown in Figure 2. There were no statistically significant differences in the percentages of gram-negative bacilli, anaerobic bacteria, HACEK group, other streptococci, polymicrobial infection, fungi, negative blood cultures, and other microorganisms or in the percentage of patients with positive blood cultures at admission. It is noteworthy that the percentage of methicillin-resistant S aureus increased with age (8%, 19%, 18%, 33%; P=0.020).

Echocardiographic Variables
A total of 16 echocardiographic variables were compared between different age groups. The most important results of this analysis are shown in Table 2. In native valve endocarditis, mitral valve endocarditis steadily increases with age and aortic valve endocarditis decreases, whereas in prosthetic valve endocarditis, there is a steady decrease in aortic mechanical valve endocarditis.

Prognostic Differences
A total of 21 outcome-related variables during hospital stay were compared between the different age groups. The most remarkable results of this analysis are shown in Table 3. During the clinical course, and as the age of patients increased, there was an
increase in heart failure and kidney failure rates. Similarly, differences were observed in therapeutic management, and hospital mortality: Younger patients underwent surgical intervention more frequently and their hospital prognosis was better, whereas mortality rates among patients who underwent urgent and elective surgical intervention increased with age. There were no statistically significant differences in the causes of mortality (septic shock, heart failure, multiorgan failure, impossibility of disconnection from the extracorporeal circulation, and others) between groups (P=0.62)

**Discussion**

This study presents the series with the largest numbers and range of ages of subjects to date that analyzes the influence of age on the most relevant variables in isolated left-sided infective endocarditis. Our study is unique in 2 ways. First, previous studies have set arbitrary age limits without considering any preestablished criterion. To avoid this important limitation, we stratified our population into age quartiles. Second, we have limited the analysis to patients with left-sided endocarditis. Right-sided and device-related endocarditis affect a very specific population, and these forms have a more benign prognosis. Thus, these forms of endocarditis must be analyzed separately; otherwise, results would be biased. Patients were consecutively included in 3 tertiary hospitals with similar characteristics, and uniform criteria were applied relative to the definition of endocarditis and its complications. All patients underwent transesophageal echo-

| Table 1. Comparison of Epidemiological, Clinical, and Radiological Variables |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | Total (n=546)   | Q1 (<50 y) (n=147) | Q2 (50–63 y) (n=153) | Q3 (64–72 y) (n=152) | Q4 (>72 y) (n=148) |
| Men, n (%)                     | 386 (64)        | 111 (76)         | 99 (65)          | 103 (68)         | 73 (49)         | <0.001          |
| Modified Duke criteria, definitive, n (%) | 570 (95)        | 140 (95)         | 149 (97)         | 143 (94)         | 138 (94)        | 0.344           |
| Nosocomial, n (%)              | 172 (29)        | 26 (18)          | 42 (28)          | 49 (33)          | 55 (37)         | <0.001          |
| Previous heart disease, n (%)  | 427 (72)        | 90 (62)          | 106 (70)         | 112 (75)         | 119 (82)        | <0.001          |
| Rheumatic                       | 55 (9)          | 18 (12)          | 9 (6)            | 16 (11)          | 12 (8)          | 0.477           |
| Congenital                      | 30 (5)          | 22 (15)          | 6 (4)            | 2 (1)            | 0 (0)           | <0.001          |
| Prosthetic                      | 243 (41)        | 39 (27)          | 66 (44)          | 72 (48)          | 66 (45)         | 0.001           |
| Degenerative                    | 69 (12)         | 3 (2)            | 17 (11)          | 18 (12)          | 31 (21)         | <0.001          |
| Diabetes mellitus, n (%)        | 124 (21)        | 8 (5)            | 30 (20)          | 43 (28)          | 43 (29)         | <0.001          |
| History of cancer, n (%)        | 48 (8)          | 4 (3)            | 9 (6)            | 16 (11)          | 19 (13)         | <0.001          |
| Prosthetic valve endocarditis, n (%) | 237 (40)        | 38 (26)          | 65 (42)          | 72 (47)          | 62 (42)         | 0.003           |
| Early prosthetic valve endocarditis | 88 (15)        | 15 (10)          | 23 (35)          | 26 (36)          | 24 (39)         | 0.965           |

**Figure 2. Comparison of microbiological variables. Q indicates quartile.**
cardiogram, and indications for urgent surgery were agreed on by consensus among the researchers. Thus, our study group is a homogeneous series of patients with left-sided infective endocarditis that is representative of the population seen in these types of hospitals.

During recent decades, the demographic characteristics of patients with infective endocarditis have undergone a profound change. In the 1950s, the most frequently affected members were those aged 20 to 30 years, and only 5% lived beyond 60 years.24 Today, the proportion of patients aged >60

### Table 2. Comparison of Transesophageal Echocardiographic Variables

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Q1 (&lt;50 y) (n=147)</th>
<th>Q2 (50–63 y) (n=153)</th>
<th>Q3 (64–72 y) (n=152)</th>
<th>Q4 (&gt;72 y) (n=148)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetations, n (%)</td>
<td>496 (84)</td>
<td>129 (88)</td>
<td>123 (83)</td>
<td>122 (82)</td>
<td>122 (84)</td>
<td>0.328</td>
</tr>
<tr>
<td>Vegetation cross-sectional area, cm²</td>
<td>1.2±1.2</td>
<td>1.2±1.2</td>
<td>1.2±1.3</td>
<td>1.0±0.9</td>
<td>1.5±1.3</td>
<td>0.424</td>
</tr>
<tr>
<td>Maximal vegetation diameter, cm²</td>
<td>1.4±0.8</td>
<td>1.5±0.8</td>
<td>1.5±0.9</td>
<td>1.2±0.6</td>
<td>1.5±0.9</td>
<td>0.499</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, mean±SD, %</td>
<td>62±12</td>
<td>62±11</td>
<td>65±12</td>
<td>59±12</td>
<td>62±11</td>
<td>0.416</td>
</tr>
<tr>
<td>Pulmonary hypertension, n (%)</td>
<td>245 (41)</td>
<td>50 (34)</td>
<td>55 (36)</td>
<td>68 (45)</td>
<td>72 (49)</td>
<td>0.003</td>
</tr>
<tr>
<td>Moderate or severe new valvular regurgitation, n (%)</td>
<td>413 (70)</td>
<td>113 (77)</td>
<td>109 (72)</td>
<td>100 (68)</td>
<td>91 (62)</td>
<td>0.002</td>
</tr>
<tr>
<td>Perivalvular complications, n (%)</td>
<td>166 (28)</td>
<td>47 (32)</td>
<td>44 (29)</td>
<td>39 (26)</td>
<td>36 (25)</td>
<td>0.123</td>
</tr>
<tr>
<td>Valvular perforation, n (%)</td>
<td>83 (14)</td>
<td>31 (21)</td>
<td>26 (17)</td>
<td>15 (10)</td>
<td>11 (8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 3. Differences in Prognosis and Clinical Course

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Q1 (&lt;50 y) (n=147)</th>
<th>Q2 (50–63 y) (n=153)</th>
<th>Q3 (64–72 y) (n=152)</th>
<th>Q4 (&gt;72 y) (n=148)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure, n (%)</td>
<td>341 (57)</td>
<td>70 (48)</td>
<td>86 (56)</td>
<td>98 (64)</td>
<td>b87 (59)</td>
<td>0.022</td>
</tr>
<tr>
<td>Persistent infection, n (%)</td>
<td>207 (35)</td>
<td>52 (36)</td>
<td>50 (33)</td>
<td>57 (37)</td>
<td>48 (32)</td>
<td>0.753</td>
</tr>
<tr>
<td>Septic shock, n (%)</td>
<td>85 (14)</td>
<td>20 (14)</td>
<td>19 (12)</td>
<td>22 (14)</td>
<td>24 (16)</td>
<td>0.483</td>
</tr>
<tr>
<td>Systemic embolism, n (%)</td>
<td>174 (29)</td>
<td>49 (33)</td>
<td>48 (31)</td>
<td>42 (28)</td>
<td>35 (24)</td>
<td>0.053</td>
</tr>
<tr>
<td>Acute stroke, n (%)</td>
<td>128 (21)</td>
<td>29 (20)</td>
<td>38 (25)</td>
<td>35 (23)</td>
<td>26 (18)</td>
<td>0.577</td>
</tr>
<tr>
<td>Splenomegaly, n (%)</td>
<td>60 (10)</td>
<td>24 (16)</td>
<td>14 (9)</td>
<td>14 (9)</td>
<td>8 (5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Kidney failure, n (%)</td>
<td>220 (37)</td>
<td>34 (23)</td>
<td>57 (37)</td>
<td>70 (46)</td>
<td>59 (40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cutaneous lesions, n (%)</td>
<td>72 (12)</td>
<td>26 (18)</td>
<td>22 (14)</td>
<td>14 (9)</td>
<td>10 (7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hematuria, n (%)</td>
<td>282 (47)</td>
<td>58 (39)</td>
<td>67 (43)</td>
<td>79 (52)</td>
<td>78 (53)</td>
<td>0.009</td>
</tr>
<tr>
<td>Hospital stay, mean (SD), d</td>
<td>44±28</td>
<td>37±24</td>
<td>46±29</td>
<td>47±29</td>
<td>44±28</td>
<td>0.059</td>
</tr>
<tr>
<td>Therapeutic treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical treatment</td>
<td>251 (42)</td>
<td>48 (33)</td>
<td>45 (29)</td>
<td>70 (46)</td>
<td>88 (60)</td>
<td></td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>349 (58)</td>
<td>99 (67)</td>
<td>108 (71)</td>
<td>82 (54)</td>
<td>60 (40)</td>
<td></td>
</tr>
</tbody>
</table>

### Q indicates quartile.

*There were 600 episodes of endocarditis, and in 98 of them, 2 valves were affected.
†Total native valves=440: Q1, 127; Q2, 110; Q3, 100; Q4, 103.
‡Total prosthetic valves=258: Q1, 44; Q2, 70; Q3, 78; Q4, 66.
years has increased dramatically, and the steady increase of the elderly in Western countries suggests that this trend will continue. Our series is similar to that reported in other studies conducted during the current decade, indicating a greater prevalence of infective endocarditis that peaks among those aged between 70 and 80 years.

Several studies have analyzed the influence of age on infective endocarditis. It should be emphasized that there are marked differences in the results of these studies, which are related to the different age-specific cutoff points established, the varying baseline characteristics of the patients analyzed, and the different protocols reported. These differences include crucial aspects when the influence of age on infective endocarditis is analyzed, such as whether the therapeutic approach is different depending on the age of the patients and whether increasing age is associated with higher mortality, aspects that thus far remain controversial. The microbiological findings also differed, although, as a general rule, *S. aureus* and gram-negative microorganisms were more frequently found in young patients, and *Streptococcus bovis* and enterococci were more frequent in the elderly.

Many of the findings in older adults were expected. These include a higher percentage of patients with previous heart disease, comprising mainly prosthetic and degenerative valves, higher rates of nosocomial endocarditis and predisposing diseases (diabetes mellitus and cancer), a higher proportion of patients with prosthetic valve endocarditis, and lower percentages of intravenous drug use and HIV infection. All these aspects are so dependent on age that the reported numbers of infections cannot be used to understand the effects of patient age on these infections. Nonetheless, we have found specific age-related trends not reported thus far that merit further analysis.

The percentage of endocarditis in women increased with age, especially in the upper quartile, which may be related to the greater life expectancy of women (in our country, 59% of people aged >70 years are women) and to the greater rates of nosocomial endocarditis, rheumatic heart disease, prosthetic endocarditis, and diabetes mellitus among the women included in our series.

Moreover, we have observed echocardiographic differences in relation to age. The use of transesophageal echocardiography in all the patients and the large number of echocardiographic variables analyzed may explain, at least in part, this finding not previously seen in other investigations. The percentage of patients with valvular insufficiency or perforation was higher in younger patients, which may have been caused by greater rates of *S. aureus* infection. Furthermore, the percentage of native mitral valve endocarditis increases with age, as was seen in a recent study, which may account for the facts that rheumatic mitral disease is present in all age groups and degenerative mitral disease increases with age. The most relevant microbiological findings are the age-related increase in *S. bovis* and enterococci infection and the decrease in *S. aureus*. *S. bovis* endocarditis in elderly patients and its association with gastrointestinal lesions have been described previously. Infections due to enterococci are commonly caused by gastrointestinal and genitourinary procedures and are hospital-acquired infections in a high proportion of patients (51% in our series). The percentage of methicillin-resistant *S. aureus* increases with age, probably as a result of the increasing proportion of nosocomial endocarditis with age.

The therapeutic management of our patients differed according to their age; thus, the percentage of patients who underwent urgent or elective surgery decreased with increasing age. Several reasons may account for this finding: the lower percentage of valvular impairment (insufficiency, perforation), the lower rate of endocarditis due to *S. aureus*, and greater comorbidity among these patients that leads to rejection for surgery due to the high risk involved. In fact, the percentage of patients with surgical indications who were rejected for surgery in our group increased significantly with age (23%, 24%, 38%, 50%; *P*<0.001).

An increase in mortality was observed with increasing age, which was probably related to the trend toward increase in mortality among older patients who underwent urgent and elective surgery. However, there were no differences in mortality between patients who received medical treatment. Age has been identified as a predictor of mortality in cardiac surgery, and is always included as an independent variable when risk in cardiac surgery is calculated. Although our findings suggest that this can also be applied to patients with infective endocarditis, well-designed studies to specifically address this issue are needed.

One possible limitation of our study is the lack of inclusion of pediatric patients with left-sided endocarditis because none of the participating participants was competent to take care of these patients. If they had been analyzed, our results would probably remain applicable because the incidence of pediatric endocarditis is very low, and the main characteristics of this entity do not differ substantially from those of adults. Nevertheless, our results can only be applied to adult patients with left-sided endocarditis.

**Conclusions**

Our study, in which patients were stratified into age-specific quartiles, suggests that increasing age at the time of diagnosing left-sided infective endocarditis is associated with less valvular impairment (insufficiency and perforation), a more favorable microbiological profile, and increased surgical mortality.

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**Disclosures**

None.

**References**


11. Robbins N, DeMaria A, Miller MH. Infective endocarditis in elderly subjects to date that analyzes the influence of age on the main characteristics of patients with isolated left-sided infective endocarditis and the first one in which patients have been homogeneous distributed by their age rather than in an arbitrary way. *J Diabetes Complications.* 2007;21:403–406.


**CLINICAL PERSPECTIVE**

Given the demographic shifts that have occurred in infective endocarditis during the last decades, especially the increasing number of episodes in elderly patients, it is pertinent to investigate the age-related clinical impact in the presentation, course, and response to therapy in patients with infective endocarditis. Thus far, studies addressing this issue have established arbitrary cutoff points of age. This study represents the series with the largest numbers and range of ages of subjects to date that analyzes the influence of age on the main characteristics of patients with isolated left-sided infective endocarditis and the first one in which patients have been homogeneous distributed by their age rather than in an arbitrary way. We divided 600 episodes of endocarditis into quartiles of age and compared a total of 107 variables between the 4 groups. We found differences in the clinical presentation, demographics, and echocardiographic and microbiological characteristics as well as in the management and outcome between groups according to age. Because the prevalence of endocarditis in the elderly is increasing, the information herein presented about the impact of age on the clinical profile of endocarditis suggests how changes in the characteristics of endocarditis might evolve in the future.
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Appendix: all variables analyzed. (* variables mentioned in the table and/or text)

**Epidemiologic:** sex*, definite infective endocarditis*, nosocomial*, previous infective endocarditis, chronic renal failure, diabetes*, cancer*, chronic anemia, immunosuppressive state, immunosuppressive treatment, colagenopathy, HIV*, IDU*, previous heart disease: rheumatic*, degenerative*, congenital*, mixoid, hypertrophic myocardiopathy, prosthetic valve endocarditis*, early-onset prosthetic valve endocarditis*, possible port of entry of the infection (previous surgery*, infective intravascular catheter*)

**Clinical:** NYHA functional status, fever at admission (temperature \( \geq 38^\circ\text{C} \)), fever before admission, antibiotic treatment before admission, dyspnea, chills, new murmur, ischemic stroke, haemorrhagic stroke, acute development of symptoms, type of cutaneous manifestations (Janeway lesions, splinter haemorrhages, petechiae, Osler nodes).

**Analytical:** serum creatinine, BUN, hemoglobin, hematocrit, globular sedimentation rate, thrombocytopenia, white cells blood count, leucocytosis, AST, ALT, GGT, sodium, potassium, LDH, proteinuria).

**Electrocardiographic:** atrioventricular block, right and left bundle branch block; echocardiographic; abscess, fistula, pseudoaneurysms, valvular estenosis, prosthetic dehiscence.

**Echocardiographic:** vegetations*, vegetation cross sectional area*, maximal vegetation diameter*, left ventricular ejection fraction*, pulmonary hypertension*, moderate or severe new valvular regurgitation*, perivalvular complications*, valvular perforation*, endocarditis location* (native [mitral, aortic], prosthetic [aortic mechanical valve, mitral mechanical valve, aortic tissue valve, mitral tissue valve]