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CLINICAL STUDY

Changing profile of infective endocarditis during a 20-year observation period

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ABSTRACT
BACKGROUND: Infective endocarditis (IE) is most often caused by bacteria.
OBJECTIVES: The aim of this work is the research of the dynamics of the clinical laboratory and instrumental methods of the diagnostics during the period of two decades.
METHODS: The data of 241 patients with infective endocarditis (IE) who were treated at the State Clinical Hospital named after Botkin S.P. was included in the research. 121 patients were observed from 2011 till 2020 (the first group) and 120 patients – from 1997 to 2004 (the second test group). These data included age and social structure of pathology, peculiarities of clinical picture, laboratory, and instrumental methods of research, as well as the outcome of the disease. We studied the concentrations of procalcitonin and presepsin in patients hospitalized after 2011. We observed pathomorphism of the modern IE.
RESULTS: To discover the bacteriological origin of the disease, we found the diagnostic evaluation of inflammation, procalcitonin, and presepsin activities, using C-reactive protein, important. We observed decrease in the number of general and hospital deaths.
CONCLUSIONS: The knowledge of the IE peculiarities during the IE progression is essential for timely diagnosis and more accurate pathology prediction *(Fig. 5, Ref. 38)*. Text in PDF *www.elis.sk*
KEY WORDS: infectious endocarditis, valve apparatus disease, thromboembolic complications, immunocomplex complications, procalcitonin, presepsin.

Introduction

Infective endocarditis (IE) is most often caused by bacteria. The infection penetrates the valves of the heart, the endocardium around foreign bodies, the parietal endocardium, the endothelium of large adjacent vessels, and systemic internal organ involvement is observed.

Since 2000, there has been a marked increase in morbidity worldwide, the clinical picture has varied greatly, and, despite new opportunities in diagnosis and treatment, the prognosis is poor and mortality is high (1, 2).

From 1970 to 2000, the annual incidence of IE in the world averaged from 5 to 7 cases per 100,000 person-years (3). Since the year 2000, its frequency has doubled or tripled, and averaged 10 to 15 cases per 100,000 person-years (4–6).

After 2000, IE had become more common in elderly patients and in young, intravenous drug abusers. An increase in the number of hospitalisations of drug addicts with IE, especially in the age group from 15 to 34 years old, was seen (7). Risk factors for IE also include degenerative valve disease, heart and vascular surgery, intravenous catheters and implanted cardiac devices, immunosuppressive conditions, and diabetes mellitus. Even modern cardiac surgery techniques, such as implantation of a transcatheter valve prosthesis, may be associated with a higher incidence of prosthetic IE (8–10). Rheumatic heart disease remains a predisposing factor for IE in people from low-income countries, while in high-income countries, IE is much less common and continues to decline (11).

Modification of risk factors contributed to expansion and change in the spectrum of microbial flora that can cause the disease. After 2000, S. aureus had been the leading cause of IE worldwide (12–14). Increase in the proportion of enterococcal (15, 16) and nosocomial (14, 17) IE was seen. When selecting antibiotic therapy, regional differences in the pathogens were observed (18).

Control of microbial growth remains complex, and the multistage process complicates the early diagnosis of the disease. According to the European Cardiology Society, negative blood culture occurs in 31 % of patients. In such cases, modern automated incubation systems are needed, and a continuous monitoring of blood culture is to be performed. To exclude fungal IE etiology, a serological test for atypical bacteria (genera Coxiella, Bartonella, Mycoplasma, Aspergillus etc.) followed by polymerase chain reaction is also advised.

Difficulties in early diagnosis of IE are largely associated with the polymorphism of the clinical picture. The typical manifesta-

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tions of IE are not always clearly expressed, and the first clinical signs may be nonspecific and may be distinct in variety. It is difficult to establish the diagnosis of prosthetic valve endocarditis in elderly patients, in the absence of positive data from bacteriological blood tests, and the presence of false positive or negative echocardiographic results (19–21). The frequency of detection of primary IE during surgery is still between 21 % and 30 %, reaching 38.2% at postmortem examination (22–24).

The IE disease is associated with significant treatment costs, disabilities, and mortality. In high-income countries, hospital mortality ranges from 17 % to 32 % (25–27), of which 40 % to 64 % is due to prosthetic valve endocarditis (25, 28). In France, In-hospital IE mortality reached 61 % during the COVID-19 pandemic versus 31 % in 2019, which was similar to European Infective Endocarditis Registry results (29).

In this regard, a diagnostic strategy is needed. On the one hand, it must be sensitive to various manifestations of the disease, and on the other, specific enough to exclude it. Thus, in 1994, based on a comprehensive analysis of echocardiography (EChoCG), clinical indicators, and the results of blood cultures and serological tests, the Duke criteria for diagnosis of IE were introduced. Later, the Duke criteria were modified; however, they still provide a low level of diagnosis, especially in the early stages of the disease (30). For example, 30 % of patients with prosthetic valve endocarditis do not have distinct EChoCG criteria (31, 32). Therefore, physicians need to use most recent knowledge of the new appearance of the 'old disease' to improve its diagnosis and prognosis.

The aim of this work was to study the dynamics of the clinical, laboratory, and instrumental diagnostic methods of IE during a 20-year observation period.

The objectives of the study were to establish the patterns of the modern course of IE on the basis of a retrospective and prospective analysis of the data from the examination of patients hospitalized in 1997–2004 and 2011–2020.

The work was carried out on a large clinical material, the results of a complex clinical, laboratory and instrumental study are presented, which made it possible to identify the features of the course of IE at the present stage.

Materials and methods

From 1997 to 2020, 241 patients with IE were treated at the City Clinical Hospital named after S.P. Botkin. We compared the results of 121 patients hospitalized between 2011 and 2020 (Group 1) with the results of 120 patients hospitalized between 1997 and 2004 (Group 2 (control)). All patients underwent a complex examination. To objectify the criteria of the diagnosis, we used the criteria proposed by D.T. Durak et al, from the Duke University Medical Center (DUKE-criteria).

We observed 155 men (64.3 %) and 86 women (35.7 %). Half of the patients were between 20 and 49 years old (53.5 % Cl 47.4 % to 59.5 %), and a quarter of the patients were between 60 and 89 years old (24.1 % Cl 19.2 % to 29.5 %).

The source of the infection was known in 66.0 % (Cl 60.0 % to 71.6 %) of the patients. The main cause of IE was intravenous drug use 19.6 % (Cl 15.1 % to 24.8 %), medical interference and manipulations 12.3 % (Cl 8.8 % to 16.8 %), and odontogenic sepsis 11.5 % (Cl 8.1 % to 15.8 %).

Primary IE (PIE) 52.3 % (Cl 46.2 % to 58.3 %) and secondary IE (SIE) 47.7 % (Cl 41.7 % to 53.8 %) were diagnosed with equal frequency. Sclerosis of the leaves resulted in SIE in 12.4 % patients (Cl 8.9 % to 16.8 %), rheumatism in 8.3 % (Cl 5.5 % to 12.0 %), inborn valvular disease of the heart in 5.0 % (Cl 2.9 % to 8.0 %) of patients. Myxomatous degeneration of the leaves of the mitral valve was diagnosed in 4,1 % (Cl 2.3 % to 7.0 %), double leaved aorta valve in 9.1 % (Cl 6.1 % to 13.0 %), IE of the artificial valve in 5.0 % (Cl 2.9% to 8.0 %).

All patients were treated with double antibacterial therapy, and when necessary, patients received triple antibacterial therapy (59.3 % (Cl 53.3 % to 65.2 %)). The medicine of the first appliance was the protected penicillin 29.0 % (Cl 23.8 % to 34.8 %), or octacillin 26.1 % (Cl 21.1 % to 31.7 %), vancomycine 24.1 % (Cl 19.2 % to 29.5 %), cephalosporins of the 3rd or 4th generation 40.7 % (Cl 34.8 % to 46.7 %), aminoglycosides 36.1 % (Cl 30.4 % to 42.1 %); of the second appliance – ftorchinolons of the third generation 47.3 (Cl 41.3 % to 53.4 %), rifampicin 19.5 %: (Cl 15.1 % to 24.6 %), carbophenems 27.8 % (Cl 22.6 % to 33.5 %). Lynezolid was also used 17.9 % (Cl 15.1 % to 21.5 %), daptomycin 14.6 % (Cl 12.6 % to 27.5 %), or fluconazole 44.1 % (Cl 38.0 % to 50.2 %).

54 (22.4 %) (Cl 17.7 % to 27.8 %) patients were discharged from hospital with a significant improvement, 67 (27.8 %) (Cl 22.6 % to 33.5 %) were transferred for surgical correction. The total death rate reached 30.3 % (Cl 24.9 to 36.1 %). 49 patients died in hospital 20.3 % (Cl 15.8 % to 25.5 %). Main reasons of hospital death were progressing, against the background of the septic process, cardiac insufficiency in 25.0 % (Cl 15.3 % to 37.3 %), meningoencephalitis in 22.9 % (Cl 13.6 to 35.0 %). For half a year, after their discharge from hospital, 24 more patients died (10.0 %) (Cl 6.8 % to 14.0 %), mainly against the background of the increasing cardiac insufficiency (70.8 %) (Cl 53.3 % to 84.4 %).

The special program included quantitative determination of procalcitonin (PCT) in blood plasma, using the BRAHMS TM PCT sensitive reagent kits on the KRYPTOR® immunofluorescence analyzer (ThermoFisher, Hennigsdorf, Germany) (normal values ≤ 0.05ng/mL), and presepsin (PSP) by chemiluminescent enzyme-linked immunosorbent assay using MAGTRATION technology on a PATHFAST analyzer (LSI Medience Corporation, Japan) (normal PSP values < 300 pg/mL).

We processed statistical data using the statistical software package IBM SPSS Statistics 23.0. We determined the type of distribution of quantitative characteristics visually (when building a histogram) or using the Kolmogorov-Smirnov criterion, or both. For description of the normal distribution of quantitative signs, we used the arithmetic mean (M) ± standard error of the mean (m). For description of the nonparametric distribution, instead of the value of the sign concentration, we used the logarithm of this concentration, the distribution of which was close to normal.

Qualitative indicators are presented in fractions (%), on an ordinal (points) scale or on the fact of the presence of a sign, or both. We tested the equality hypothesis of the average of two un-

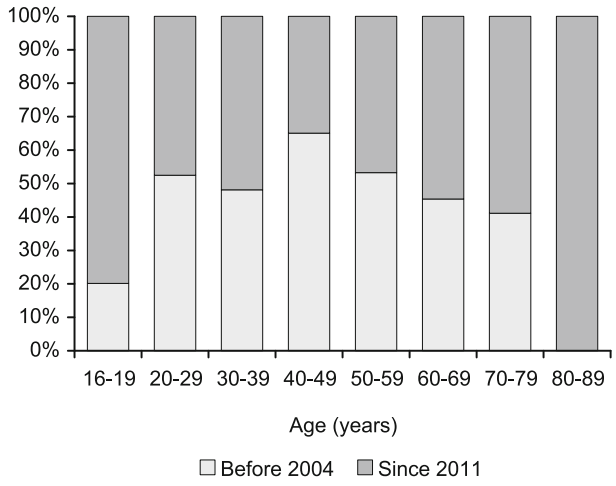

Fig. 1. Age distribution of patients.

related samples using the two-sample student t-test, adjusted to the statistically significant Levene test for homogeneity of variances in cases of normal distribution, and we used the Mann-Whitney U-test for non-parametric data distribution. To compare the average values of two related samples, we used the t-test for paired samples, and when we had a different distribution from the normal data distribution, we used the Wilcoxon test. We compared the frequency characteristics in independent samples using the Pearson criterion χ^2. We determined the difference in paired frequency characteristics (values before-after) using the McNemar test. We carried a correlation analysis of the data with the determination of the correlation coefficient (r). $p < 0.05$ level was regarded as a critical level of statistical significance of differences.

Results

Among the patients examined from 2011 through 2020, 61.2 % (Cl 52.7 % to 69.1 %) were men, and 38.8 % (Cl 30.9 % to 47.3 %) were women. Age ranged from 16 to 87 years, one third were elderly patients 28.9 % (Cl 21.8 % to 37.0 %), of which 4.1 % (Cl 1.8 % to 8.2 %) were over 80 years old. Compared with the data from the prior period (i.e., from 1997 to 2004), the number of observed men and women with IE did not change significantly, IE was diagnosed 1.5 times more often in patients over 60 years of age (Fig. 1).

Patients were admitted to the cardiology (44.6 % (Cl 36.4 % to 53.1 %)) and therapeutic (63.6 % (Cl 55.1 % to 71.4 %)) departments, and significantly more often to the intensive care unit: 19.8 % (13.8 % to 27.1 %) during the 2011–2020 period and 7.6 % (4.1 % to 12.9 %) ($p = 0.013$) from 1997 to 2004. Patients were more often referred to psychosomatic hospitals after 2011 due to rapidly increasing psychotic reactions.

At the prehospital stage, the modern IE diagnosis was made in 27.3 % (Cl 20.3 % to 35.2 %) of patients, which was twice more often compared with the 1997 to 2004 period (13.9 % (Cl 8.9 % to 20.6 %)) ($p = 0.028$). The diagnoses, requiring hospitalization, were pneumonia 19.0 % (Cl 13.1 % to 26.2 %), kidney pathology (pyelonephritis, glomerulonephritis, acute renal failure) 9.9 % (Cl 5.8 % to 15.7 %), stroke or brain abscess 8.3 % (Cl 4.6 % to 13.7 %), and foodborne toxicosis 4.1 % (Cl 1.8 % to 8.2 %). The condition was regarded as "unclear fever" in 6 patients 5.0 % (Cl 2.4 % to 9.4 %).

In the 2011–2020 period, a slight decrease in the number of PIE patients was noted, from 57.5 % (Cl 49.0 % to 65.7 %) to 47.1 % (Cl 38.8 % to 55.6 %), and, accordingly, an increase in the number of patients with SIE 42.5 % (Cl 34.3 % to 51.0 %) to 52.9 % (Cl 44.4 % to 61.2 %). However, the differences are not statistically significant.

After 2011, the number of SIE patients has risen on the background of atherosclerosis, from 7.5 % (Cl 4.1 % to 12.7 %) to 17.4 % (Cl 11.8 % to 24.4 %) ($p = 0.031$), i.e., increased more than twice, and four times on the background of myxomatous valve damage, from 1.7 % (Cl 0.5 % to 4.6 %) to 6.6 % (Cl 3.5 % to 11.6 %). Seven patients 5.8 % (Cl 2.9 % to 10.5 %) were diagnosed with prosthetic heart valves, and 3 patients were diagnosed with IE (2.5 %) (Cl 0.9 % to 5.8 %). The frequency of rheumatic defects was comparable between the two periods: 9.1 % (Cl 5.2 % to 14.7 %) and (8.3 %) (Cl 4.7 % to 13.8 %), respectively.

The source of infection was established in 64.5 % (Cl 56.1 % to 72.2 %) of patients. The intravenous route of various psychoactive substance administration prevailed (the proportion of drug addicts increased from 14.0 % (Cl 8.9 % to 20.8 %) in 1997 to 2004 to 24.8 % (Cl 18.1 % to 32.6 %) in 2011 to 2020) (Fig. 2a). We found odontogenic sepsis 7.4 % (Cl 4.0 % to 12.6 %) and foci of chronic infection 7.4 % (Cl 4.0 % to 12.6 %) less often than in

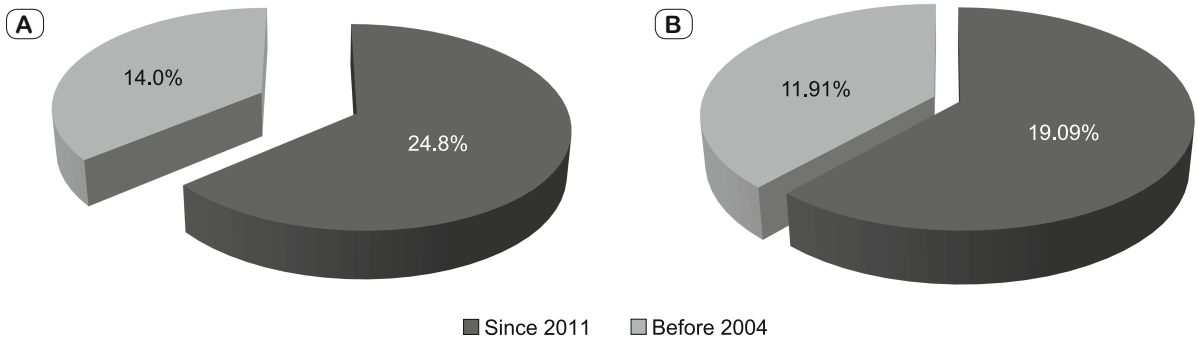

Fig. 2. A – drug addicts, B – surgical interventions.

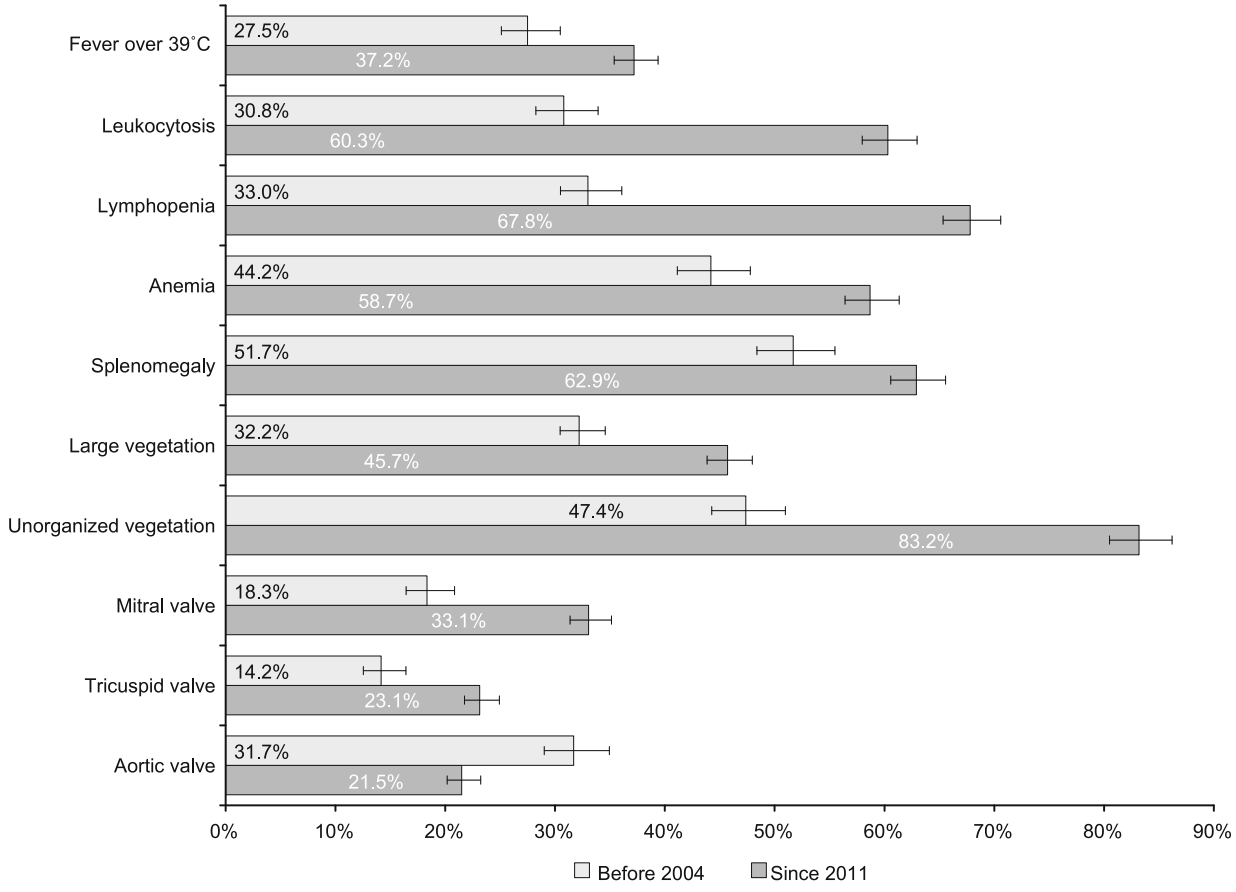

Fig. 3. Clinical manifestations of infective endocarditis.

the 1997 to 2004 period. In 19.1 % (Cl 15.2 % to 21.7 %) of the cases, IE development was associated with surgical interventions on the genitourinary system, gastrointestinal tract, cardiac devices implantation, or venous vessels catheterisation (Fig. 2).

In 95.8 % (Cl 91.7 % to 98.1 %) of the patients, fever was the main reason for asking for medical help. After 2011 hospitalisation with hectic fever was 1.5 times more often (37. 2 % Cl 29.3 % to 45.6 %) than in the patients during the 1997 to 2004 period (27.5 % Cl 20.5 % to 35.5 %) (Fig. 3).

Chills and profuse sweating accompanied 66.7 % (Cl 58.2 % to 74.3 %) of the patients; decreased body weight was observed in 56.8 % (Cl 47.9 % to 65.3 %) of the patients; and muscle and joint pain had 19.0 % (Cl 13.1 % to 26.2 %) of the patients. In 27 patients (22.3 %) (Cl 16.0 % to 29.9 %), changes on the skin (small-point or large hemorrhages on the trunk, extremities (13.2 %) (Cl 8.4 % to 19.6 %) or mucous membranes (petechiae in the oral cavity, on the conjunctiva (11.4 %) (Cl 5.2 % to 21.7 %)), or both, were seen. During the 1997 to 2004 period, skin hemorrhages were almost twice less common (13.3 %) (Cl 8.5 % to 19.8 %).

We observed a tendency towards growth of the level of leukocytes (from 9.17 ± 0.32 to 12.50 ± 0.60 × 109/L) ($p < 0.001$), SOE (from 33.08 ± 1.59 to 38.07 ± 1.71 mm/h) ($p = 0.034$), and immunoglobulin G (from 23.97 ± 1.53 to 39.0 ± 8.5 g-/L) ($p = 0.037$) in patients with IE from Group 1 (i.e. 2011–2020 period). We also registered a more pronounced decrease in the haemoglobin level (from 111.82 ± 2.28 to 103.62 ± 2.21 g/L) ($p = 0.001$), lymphocytes (from 24.57 ± 0.84 to 16.38 ± 0.84 %) ($p < 0.001$), and platelets (from 219.39 ± 6.95 to 206.77 ± 10.07 × 109/L) ($p = 0.043$) in the patients from Group 1. On admission, C-reactive protein value was increased in 100 % (97.0 % to 100.0 %) of IE patients and averaged 72.93 ± 6.05 mg/L (normal: 0 mg/L to 5 mg/L).

After 2011, the frequency of positive hemoculture has grown from 39 % (Cl 30.9 % to 47.5 %) to 67,8 % (Cl 59.5 % to 75.2 %) ($p = 0.009$). During the 2011–2020 period, we observed Staphylococcus aureus 22.3 % (Cl 16.0 % to 29.9 %) and polymicrobial highly virulent associations (combination of staphylococcal flora and Enterococcus, Streptococcus anginosus, Acinetobacter lwoffii) 15.0 % (Cl 12.4 % to 19.4 %) significantly more often than during the 1997 to 2004 period; Staphylococcus aureus 11.0 % (Cl 6.6 % to 17.1 %) ($p = 0.034$) and polymicrobial highly virulent associations 2.0 % (Cl 0.8 % to 3.1 %) ($p = 0.018$). We also observed Enterococcus spp. growth to occur twice more often: 9.9 % (Cl 5.8 % to 15.7 %) after 2011 versus (4.2 %) (Cl 1.9 % to 8.5 %), i.e. before 2004, and Streptococcus viridans were thrice less often (1.7 %) (Cl 0.5 % to 4.5 %) (2011–2020 period) versus (5.1 %) (Cl 2.4 % to 9.6 %) (1997 to 2004 period).

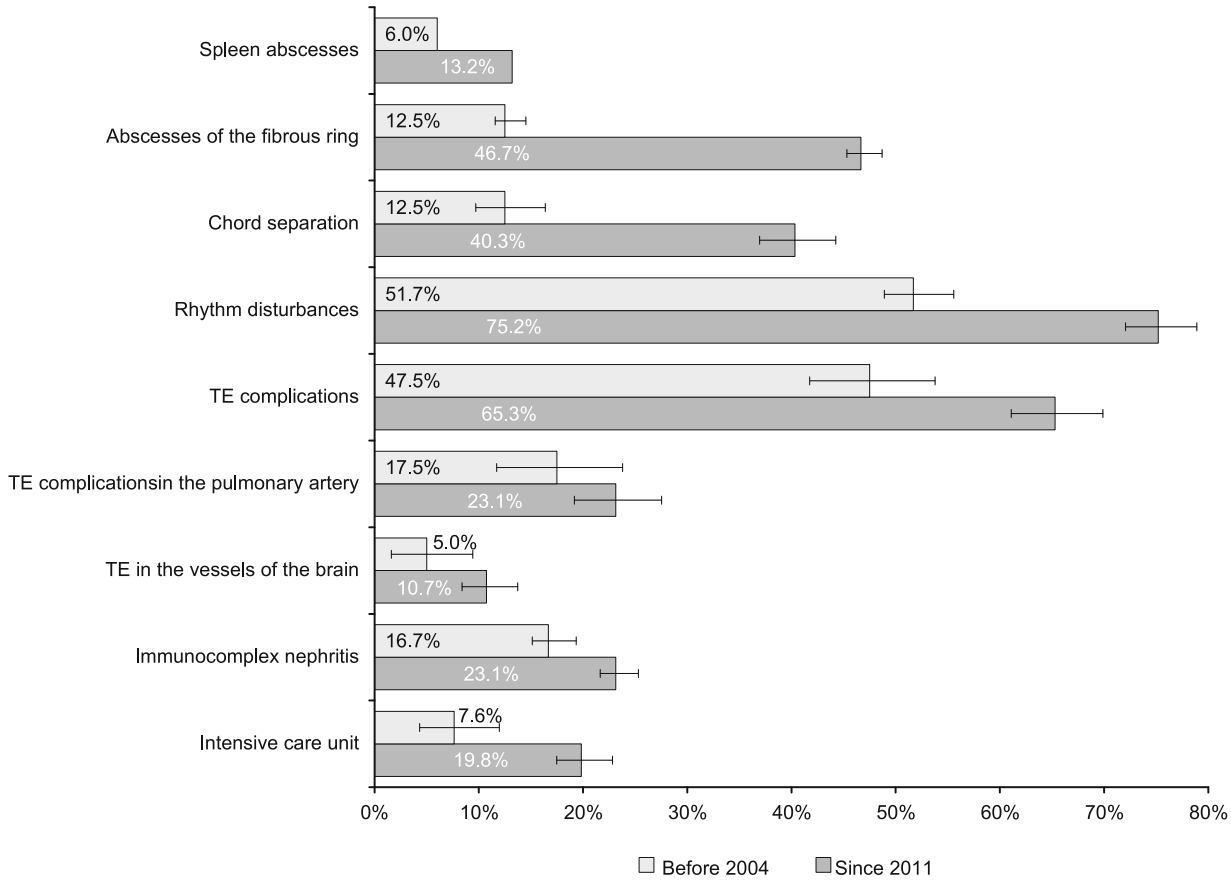

Fig. 4. Complication diagram.

In 67.7 % (Cl 65.7 % to 82.3 %) of the patients in the 2011–2020 period, we registered increased procalcitonin (PCT) level which averaged 1.00 ± 0.23 ng/mL (normal PCT values were ≤ 0.05 ng/mL). The evaluation of presepsin (PSP) made it possible to diagnose bacterial inflammation in 100 % of patients with PIE and in 82.8 % of patients with SIE in the 2011–2020 period. The PSP study allowed to verify the bacterial nature of inflammation in 31 % of patients with negative blood culture and in 21 % with discordant PCT indices.

97.5 % (Cl 94.2 % to 99.1 %) of patients from 2011–2020 period underwent EChoCG. In most patients (62.9 %) (Cl 53.9 % to 71.2 %), we observed large vegetations, the height of which exceeded 10 mm ($p = 0.041$). We also noted statistically significant differences in the degree of their organization: "fresh" thrombotic overlays on the valves were observed in 83.2 % (Cl 76.2 % to 88.7 %) patients of Group 1 versus 47.4 % (Cl 38.8 % to 56.1 %) patients in Group 2 ($p = 0.005$).

Compared with the data from the 1997 to 2004 period, the number of patients with mitral valve disease increased, from 18.3 % (Cl 12.6 % to 25.5 %) to 33.1 % (Cl 25.5 % to 41.3 %) ($p = 0.030$), isolated tricuspid insufficiency was diagnosed 1.6 times more often (23.1 %) (Cl 16.7 % to 30.8 %) versus 14.2 % (Cl 9.1 % to 20.7 %), respectively, the proportion of aortic heart defects decreased from 31.7 % (Cl 24.2 % to 39.9 %) to 21.5 % (Cl 15.2 % to 29.0 %) (Fig. 3). In 26 patients (21.5 %) (Cl 15.2 % to 29.0 %), two valves (mitral and aortic, mitral and tricuspid, mitral and pulmonary valve, aortic and tricuspid) were involved in the infection process, while in the 1997 to 2004 period, infection process was found in 41 (34.2 %) (Cl 26.5 % to 42.5 %) patients. We detected damage to the right heart with approximately equal frequency in both groups (29.8 %) (Cl 22.5 % to 37.9 %; Group 1) versus (26.7 %) (Cl 19.7 % to 34.6 %; Group 2).

Abscesses of the fibrous ring (46.7 %) (Cl 38.3 % to 55.2 %) ($p < 0.001$), valve leaf ruptures and chord separation (40.3 %) (Cl 32.2 % to 48.9 %) ($p < 0.001$), fistulas between the chambers of the heart (16.8 %) (Cl 11.3 % to 23.8 %) ($p = 0.007$) occurred significantly more often in the patients from the 2011–2020 period (Fig. 4).

According to abdominal ultrasound, hepatomegaly increased from 68.8 % (Cl 60.2 % to 76.5 %) to 79.7 % (Cl 72.2 % to 85.8 %), splenomegaly from 51,7 % (Cl 43.2 % to 60.1 %) to 62.9 % (Cl 54.4 % to 70.9 %) in the patients from the 2011–2020 period. We detected spleen abscesses twice as often (13.2 %) (Cl 8.4 % to 19.6 %) compared with the 1997 to 2004 period (6.0 %) (Cl 2.7 % to 11.7 %), respectively.

During the 2011 to 2020 period, more than two third of the patients (75.2 %) (Cl 67.4 % to 81.9 %) had various rhythm and

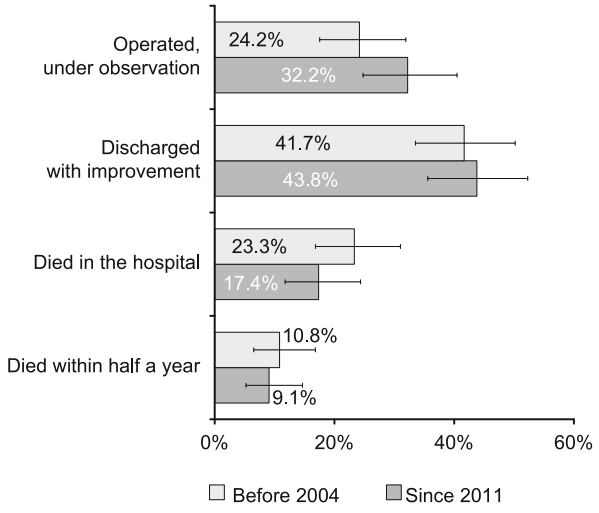

Fig. 5. Mortality.

conduction disturbances (p = 0.045). Frequent ventricular extrasystole or tachycardia (75.0 %), incomplete left bundle branch block (71.4 %), paroxysmal (64.7 %) or persistent (66.7 %) forms of atrial fibrillation predominated in the form of mono-arrhythmia or in combination with atrial and ventricular extrasystoles (66.7 %); rhythm from the A-V connection, atrial and ventricular extrasystole (66.7 %); atrial, ventricular extrasystole and A-V blockade of the II degree (50.0 %) predominated.

Thromboembolic complications (65.3 %) (Cl 57.0 % to 73.0 %) were revealed 1.5 times more often than in the 1997 to 2004 period (47.5 %) (Cl 39.1 % to 56.0 %), while the structure of the complications had somewhat changed. From 17.5 % (Cl 11.9 % to 24.6 %) to 23.1 % (Cl 16.7 % to 30.8 %), the number of thromboembolic complications in the pulmonary artery system increased with the development of heart attack pneumonia. The number of emboli in the vessels of the brain increased up to 10.7 % (Cl 6.5 % to 16.7 %). Spleen thromboembolic complications were observed in 5.8 % (Cl 2.9 % to 10.5 %), kidney vessel thromboembolism in 1.7 % (Cl 0.5 % to 4.5 %), lower-extremities vessels thromboembolism in 2.5 % (Cl 0.9 % to 5.8 %) of the examined patients. In 19.8 % (Cl 13.8 % to 27.1 %) of cases, multiple organ emboli were found: in the vessels of the lungs and peripheral arteries, lungs and spleen, brain and kidneys, brain, lungs, spleen, and kidneys.

In the structure of thromboembolic complications, the complications of pulmonary embolism were 35.4 % (Cl 26.1 % to 45.7 %), cerebral vessels – 16.5 % (Cl 10.0 % to 25.0 %), and spleen 8.9 % (Cl 4.5 % to 15.8 %). The damage of several vessel areas was observed in 30,4 % of the patients.

In 48.8 % (Cl 40.4 % to 57.2 %) of the patients, we observed immunocomplex complications. Immunocomplex nephritis prevailed (23.1 %) (Cl 16.7 % to 30.8 %); in 6 patients (5.0 %: Cl 2.4 % to 9.4 %), it was complicated by kidney failure and multiple changes (17, 4 %: Cl 11.8 % to 24.4 %), mainly represented by a combination of nephritis and vasculitis (11.6 %: Cl 7.1 % to 17.7 %). Vasculitis was diagnosed in 6.6 % (Cl 3.5 % to 11.6 %) of patients, and arthritis was diagnosed in 1.7 % (Cl 0.5 % to 4.5 %) of patients. During the 1997 to 2004 period, arthritis was significantly more frequent (6.7 %) (Cl 3.5 % to 11.6 %) (p = 0.050) (Fig. 4).

Almost all patients from both periods showed symptoms of cardiac insufficiency (98.3 %) (Cl 95.5 % to 99.5 %) (2011–2020 period) versus (97.5 %) (Cl 94.1 % to 99.1 %) (1997–2004 period). The majority were diagnosed with heart failure II functional class (37.2 %) (Cl 29.3 % to 45.6 %) (2011–2020 period) versus (33.3 %) (Cl 25.8 % to 41.7 %) (1997–2004 period), or III functional class (44.6 %) (Cl 36, 4 % to 53.1 %) (2011–2020 period) versus (35.0 %) (Cl 27.3 % to 43.4 %) (1997–2004 period).

During the 2011 to 2020 period, we observed a decrease in general mortality from 34.2 % (Cl 26.5 % to 42.5 %) to 26.4 % (Cl 19.6 % to 34.4 %), and hospital mortality from 23.3 % (Cl 16.8 % to 31.0 %) to 17.4 % (Cl 11.8 % to 24.4 %). The maximum mortality rate during the first two weeks of hospitalisation was 10.8 % (Cl 6.5 % to 16.8 %) (2011–2020 period) versus 13.2 % (Cl 8.4 % to 19.6 %) (1997–2004 period). Mortality was caused by septic process itself (32.1 %) (Cl 18.6 % to 48.7 %), or meningoencephalitis arising on its background (17.9 %) (Cl 8.3 % to 32. %), severe cardiac insufficiency (10.7 %) (Cl 4.0 % to 23.5 %), and pulmonary embolism (10.7 %) (Cl 4.0 % to 23.5 %). During the 1997 to 2004 period, most patients (70.0 %) (Cl 50.9 % to 84.6 %) died because of increasing heart failure. Another 9 (7.5 %) (Cl 4.1 % to 12.7 %) patients from Group 1 and 10 (8.3 %) (Cl 4.6 % to 13.7 %) patients from Group 2 died six months later. Most of these patients (75.0 %) (Cl 51.6 % to 90.1 %) of the 2011–2020 period and (63.6 %) (Cl 39.0 % to 83.3 %) of the 1997–2004 period died because of progressive heart failure (Fig. 5).

Discussion

This study is a comparative analysis of two time periods: 2011 to 2020 and 1997 to 2004. We aimed to map the causes for IE and how the disease has changed after 2000. As a result of our study, we can highlight features of the IE disease which are more representative for the present stage.

In our study, the length of the prehospital period has decreased. However, the correct diagnosis was made only in 27.3 % of the cases, which indicates the remaining lack of awareness of primary care doctors about the features of the disease and examination tactics with persistent fever.

We noticed a growing number of correct diagnoses at the outpatient clinic level, as well as a growing frequency of IE in senior citizens (9,7 % increase). The increase of medical interventions (7,7 % increase) and intravenous drug addiction (10.8 % increase) are among the causes of the IE.

The rate of activity of the infectious-toxic process was growing in the 2011–2020 period: we noted highly virulent (two-fold increase, p = 0.034) and mixed (increased 7 times, p = 0.018) flora, increase of the frequency of damaged mitral (14.8 % increase, p = 0.030) and tricuspidal (8.9 % increase) valves with the formation of large and non-organic vegetations on the leaves (35.8 %, p = 0.005). Disruption of the rhythm and conductivity (23.5 % increase, p = 0.045), thromboembolism into the system of the pul-

monary artery (5.8 % increase), and cardiac insufficiency (98.3 % of patients) were observed.

Over the past decade, microbiological diagnostics have changed and improved, which allows to identify the aetiology, antibiotic resistance, and sensitivity of IE pathogens. According to our data, positive blood culture began to be observed more often (67.8 %); however, in some cases, the etiology remains unknown. To solve this problem, it is advisable to perform qualitative bacteriological studies, apply, and use more widely methods based on mass spectrometry, serological testing, and polymerase chain reaction. Molecular methods have been used for a long time (33), but even today they are not always available. Of practical importance is the study of bacterial infection markers in cases of suspected IE. The performed comparative analysis of PCT and PSP concentrations at admission showed that PSP is a more sensitive IE marker, which is especially important for negative blood culture and discordant changes in PCT. However, these indicators reflect the state of various mechanisms of the immune response to a bacterial infection; therefore, their complex use is expedient for the timely verification of the bacterial nature of inflammation and the appointment of antibiotic therapy.

At present, typical IE pathogens are S. aureus, Str. viridans, S. gallolyticus (S. bovis), HACEK group, and community-acquired enterococci (34,35). However, most scientists stress a change in pathogens over the past decades. Thus, L. Slipczuk et al. (15) analysed 160 cases (27,083 patients) on the IE epidemiology. The authors found that the frequency of IE caused by staphylococcal flora increased from 18 % in the 1960s to 30 % in the 2000s, and streptococcal decreased from 27.4 % in the 1960s to 17.6 % in the 2000s. The number of enterococcal IEs increased. In our study, a similar picture was observed: S. aureus increased from 11 % to 22.3 %, Enterococcus spp. increased from 4.2 % to 9.9 %, and three-fold decrease was observed for Str. viridans (from 5.1 % to 1.7 %).

The change in the IE microbial landscape is largely due to the modification of risk factors. After 2000, significant changes in the provision of medical care is taking place, a large number of invasive procedures are carried out, antibacterial drugs are widely used, and the number of elderly patients and number of drug abusers increased (7, 8, 36). According to our data, an increase in the proportion of addicts up to 24.8 %, nosocomial IE up to 19.1 % was registered; IE was 1.5 times more often diagnosed in patients over 60 years of age (from 19.2 % to 28.9 %). The secondary form of the disease prevailed in the elderly, arising on the background of atherosclerotic or myxomatous lesions of the valve cusps, while PIE prevailed in young people.

The clinical picture of the disease has also changed. Infectious-toxic process increased, as evidenced by febrile and hectic fever (37.2 %), severe leukocytosis ($12.50 \pm 0.60 \times 10^9$/L) and accelerated SOE (38.07 ± 1.71 mm/h), hyperimmunoglobulinemia G (39.0 ± 8.5 g/L), significant increase in the C-reactive protein level (72.93 ± 6.05 mg/L), anaemia (103.62 ± 2.21 g/L). Most patients had splenomegaly (62.9 %), large (62.9 %) and poorly organised (83.2 %) vegetations on valve cusps, and abscesses of the fibrous ring (36.7 %).

The incidence of aortic valve disease continues to decline. According to Daniel D. Correa de Sa (2010), from the year 1975 to 1979 and from 2001to 2006, the aortic localisation of IE decreased from 69 % to 30 % (37). In our study, it was 21.5 %. After 2011, mitral (33.1 %) or tricuspid (23.1 %) valves defects have been more commonly observed. A tendency to a decrease in the number of cases of multivalvular lesions, which can be associated with the timeliness of surgical interventions, should be noted.

The severity of the disease increased in the 2011–2020 period: often patients were admitted to the intensive care unit (19.8 %), immunocomplexes were diagnosed in half of the patients (48.8 %), thromboembolism complications were observed in 65.3 %, rhythm and conduction disturbances were observed in 75.2 % of cases, and almost all of them had symptoms of circulatory failure (98.3 %). The high frequency of complications is explained by the late admission, prevalence of highly virulent pathogens, and an increase in the number of elderly patients with comorbid pathology. Literary data show a lower number of thromboembolisms (14); however, it is stressed that this may be due to an insufficiently complete examination of patients (38).

The results of our study indicate a decrease in overall (up to 26.4 %) and hospital (up to 17.4 %) mortality rate, which is primarily due to the expansion of indications for surgical treatment and improvement of surgical tactics. At the same time, since the 1960s, a significant decrease in nosocomial mortality has not occurred (15,36), which requires further study of the IE problem.

Conclusion

Time makes certain changes in the epidemiology, clinical manifestations, and frequency of various IE complications. The character of IE has changed, and its classical features appear less often. The causes that contribute to the development of IE (drug addiction, medical interference, and manipulations), the IE aetiology (the share of Staphylococcus and mixed flora has increased), the structure of the valve damage, the changed picture of the embolic complications, and the number of the right-sided forms of the disease have increased. The etiological confirmation of IE, the development of the methods allowing to diagnose the bacteriological nature of the inflammation in time and with the high probability of sensitivity and specification, which is the guarantee of the timely diagnostics, correction of the tactics of the control, and improvement of the prognosis of the pathology under consideration is though left still unsatisfactory.

Awareness of doctors about the features of the course of IE at the present stage, the possibilities of various methods of laboratory and instrumental diagnostics, a multidisciplinary approach to patient management will contribute to timely diagnosis and improvement of prognosis in this pathology.

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