Infectious Endocarditis in the Elderly – Comparative Study of Clinical Features, Course and Outcomes

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In the context of the increased incidence of infectious endocarditis (IE) in the elderly, an assessment of clinical features of IE in elderly patients is still controversial.

Aim. To study the clinical features and outcomes of IE in patients aged ⩾65 years.

Material and methods. A comparative assessment of risk factors, etiology, clinical manifestations, outcomes was performed in 75 IE patients ⩾65 years old and in 356 IE patients <65 years old.

Results. In patients ⩾65 years old IE was more often associated with previous medical care (odds ratio [OR]=14.9; 95% confidence interval [95%CI] 8.6;25.9), infections and tumors of the genitourinary system or tumors of the gastrointestinal tract (OR=12.6; 95%CI 6.4;24.6); there were more concomitant oncological diseases (OR=66.2; 95%CI 19.3;226.8), diabetes mellitus (OR=9.9; 95%CI 4.5;22.1), chronic kidney disease (OR=27.0; 95%CI 13.6;53.3). In patients ⩾65 years old compared with non-drug users IE patients <65 years old (n=266), the incidence of enterococcal IE was higher (OR=3.3; 95%CI 1.4;7.9); the timing of IE diagnosis was longer – 60 (37;152) vs 30 (20;110) days (p<0.05); cardiac surgery was performed less often (8% vs 24.8%; p<0.05); in-hospital mortality was almost two-fold higher. However, with the exclusion from the mortality rate assessment of postmortem diagnosed IE cases in-hospital mortality in patients ⩾65 years old and patients <65 years old did not differ significantly (14.8% vs 12.2% in non-drug users <65 years old and 14.9% in drug-users IE).

Conclusion. Late diagnosis of IE and comorbidity, which limits the possibility of cardiac surgery, are the most important prognostic unfavorable features of IE in the elderly.

Keywords: infectious endocarditis, elderly, etiology, clinic, outcome.

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The epidemiology of infective endocarditis (IE) has been changing through the last decades, one of the most evident trends observed all over the world is the "ageing" of IE [1,2]. IE national registers in many countries report the most prominent morbidity rates increase in the senior age group with the peak in the age of 70-80 years [3-5]. In accordance with the many of the last decade studies the mean age of IE patients exceeds 65 years [6]. Such trend can be explained not only by the growth of the elderly people group in population but, in the first place, by more frequent invasive cardiac interventions in elderly people, increased lifetime in the presence of predisposing heart diseases and the high prevalence of degenerative valve diseases in the aged. At present the risk for IE development in the elderly is almost 5-time as higher as in general population [7].

Prospective studies of IE in the elderly reveal such characteristic features of the disease in elderly people as later diagnostics, frequent combination with other diseases typical of advanced age and higher mortality [8,9].

Aim of the study to estimate demographic characteristics of IE patients, the share of patients aged 65 years and older, followed up in different years, and also to evaluate features of IE clinical course and outcomes in patients ⩾65 years old in comparison with IE in patients under the age of 65 years.

Material and methods

A total of 431 consecutive cases of definite IE (in accordance with the modified Duke criteria [10,11]) diagnosed in two Moscow hospitals: the City clinical oncologic hospital №1 (1986-2018 years) and the First City clinical hospital named after N. I. Pirogov (2004-2007 years) were enrolled in the study. The study was conducted in accordance with the Helsinki Declaration. The study protocol was approved by the Pirogov Russian National Research Medical University Ethics Committee.

Transthoracic echocardiography (TTE); the ultrasound examination of kidneys, liver, spleen; blood microbiology testing; clinical and biochemical blood assays, urine analysis were conducted in all of the patients. Transesophageal echocardiography (TEE), computer tomography, magnetic resonance imaging were carried out when indicated. The diagnosis of IE was morphologically confirmed in 194 patients (in 104 people during surgical treatment and in 90 – during autopsy).

We estimated the demographic characteristics of IE patients, IE incidence rates in patients ⩾65 years old in different periods of follow up. The comparative evaluation of risk factors, predisposing heart conditions, etiology, clinical features and outcomes of IE in patients ⩾65 years old (n=75) and <65 years old (n=356, including 90 cases of IE in injection drug users and 266 cases unrelated to drug addiction) was also performed.

The SAS (Statistical Analysis System) statistics package was used for statistical treatment of the data with calculation of absolute frequencies, odds ratio (OR) and 95% confidence intervals (95%CI). Mean value (M), median (Me), standard deviation (SD) and interquartile range (25-75%) were calculated for quantitative indices. Comparative analysis was performed using Student's t-test, Fisher's χ^2 test, Wilcoxon's test in accordance with the distribution of the analyzed indices. Distinctions were regarded as statistically significant at *p* values of less than 0.05.

Results
Demographic and epidemiological characteristics of the IE patients enrolled in the study

Among the IE patients followed from 1986 to 2018 years (Table 1) 341 patients were not addicted to drugs, while 90 individuals used intravenous drugs during the 3-month period before the disease onset (IE of drug users).

Patients enrolled in the study were aged from 17 to 87 years (47.9±15.0). We have revealed no statistically significant distinctions at comparison of the mean age of the patients treated in different time periods (1986-1990, 1991-2000, 2001-2010 and 2011-2018 years). However the mean age of IE patients with no drug addiction (n=341) statistically significantly increased in 2011-2018 years as compared to 1986-1990 years, at that the percentage of the patients ⩾65 years old increased eightfold: from 7.4% to 60.8% (p<0.05; Table 1). A total of 75 subjects among patients with IE not related to drug addiction aged ⩾65 years. All the patients with IE due to drug addiction were young (21-42 years).

Table 1. Demographic and epidemiological characteristics of 431 IE patients, followed from 1986 to 2018 years

Years	IE in drug addicts			IE not related to drug abuse				Age, years
	n	Men, n(%)	Age, years	<65 years		≥65 years		
				n(%)	Men, n(%)	n(%)	Men, n(%)	
1985-1990 (n=81)	0	0		75 (92,6)	38 (50,7)	6 (7,4)	3 (50)	43,4±14
1991-2000 (n=108)	3	3 (100)	29,3±11	84 (80)	52 (61,9)	21 (20)*	11 (52,4)	51,4±14,7*
2001-2010 (n=125)	28	18 (64,3)	28,4±4,8	77 (79,4)	54 (70,1)	20 (20,6)*	10 (47,6)	51,4±14,0*
2011-2018 (n=117)	59	44 (74,6)	31,2±7,5	30 (51,7)	17 (56,7)	28 (48,3)*	14 (50)	60,8±15,8*
Total (n=431)	90	65 (72,2)	30,2±7,8	266 (78)	161 (60,5)	75 (22)	38 (50)	51,1±17,2

Data are presented as M±SD, unless indicated otherwise

*p<0.05 as compared to the similar index in 1985-1990 years

IE – infective endocarditis

Table 2. Conditions predisposing to IE in the examined 431 patients

Predisposing condition	IE in drug addicts	IE not related to drug addiction		
	(n=90)	<65 years (n=266)	≥65 years (n=75)	Total (n=431)
Predisposing heart diseases				
Non (primary IE), n (%)	70 (77.8)	135 (50.8)	30 (40)*	165 (48.4)†
Relapse of IE on the natural valve, n (%)	12 (13.3)	43 (16.1)	7 (9.3)	50 (14.7)
Acquired valvular heart disease, n (%):	0	44 (16.6)	7 (9.3)	51 (15.0)†
rheumatic		42 (15.8)	7 (9.3)	49 (14.4)†
other		2 (0.8)	0	2 (0.6)
Congenital heart disease, n (%):	0	18 (6.8)	1 (1.3)*	19 (5.6)†
non-cyanotic		16 (6.0)	1 (1.3)	17 (5)
cyanotic		2 (0.8)	0	2 (0.6)
MV prolapse, n (%)	0	3 (1.1)	1 (1.3)	4 (1.2)
MV myxomatous degeneration, n (%)	0	1 (0.4)	2 (2.6)	3 (0.9)
Valves calcification, n (%):	0	3 (1.2)	18 (23.9)*	21 (5.1)†
MVC		2 (0.8)	10 (13.3)*	12 (3.5)
CAS/AVC		1 (0.4)	8 (10.6)*	9 (2.6)
Valve replacement or plastics/IE relapse on the operated valve, n (%)	7 (7.8)/7 (7.8)	16 (6.0)/5 (1.9)	4 (5.3)/1(1.3)	20 (5.9)/6(1.7)
Pacemaker, n (%)	0	1 (0.4)	3 (4)	4 (1.2)
Coronary artery bypass grafting, n (%)	0	1 (0.4)	1 (1.3)	2 (0.6)
HCM, n (%)	0	1 (0.4)	0	1 (0.3)
Other, n (%)	1 (1.1)	0	1 (1.3)	1 (0.3)
A total, secondary IE, n (%)	20 (22.2)	131 (49.2)	45 (60)*	176 (51.6)†
Infection site of entry				
Intravenous drug use, n (%)	90 (100)	0	0	0†
Dental interventions, n (%)	0	21 (7.9)	9 (12)	30 (8.8)†
Medical invasive interventions, hospital admission during the last 6 months, n (%)	18 (20)	36 (13.5)	48 (64)*	84 (24.6)
Genitourinary system infection or cancer, n (%)	0	15 (5.6)	24(32)*	39 (11.4)†
Gastrointestinal tract cancer, n (%)	0	2 (0.7)	5 (6.7)*	7 (2.05)
Pyodermia, n (%)	6 (6.7)	9 (3.4)	2 (2.7)	11 (3.2)
Other, n (%)	1 (1.1)	20 (7.5)	3 (4)	23 (6.7)
Unascertained, n (%)	0 (0)	163 (61.3)	14 (18.7)*	177 (51.9)†

* p<0.05 as compared to incidence in IE patients under 65 years not addicted to drugs

† p<0.05 as compared to incidence in IE patients addicted to drugs

IE – infective endocarditis, CAS – calcific aortic stenosis, AVC – aortic valve calcification, MVC – mitral valve or annulus calcification, HCM – hypertrophic cardiomyopathy, MV – mitral valve

In the subgroup of aged IE patients, a number of men and women was almost equal, while among patients under 65 years old men prevailed (p>0.05).

Predisposing factors in aged IE patients: previous heart diseases and conditions contributing to endocardium contamination, comorbidity

IE was secondary in 60% of subjects ≥65 years old, while majority of the patients under 65 years had primary IE (50.8% of not related to drug addiction IE cases and 77.8% cases of IE in drug users; p<0.05; Table 2). The most frequent heart abnormality prior to IE in patients ≥65 years old was idiopathic valves calcification: mitral valve and annulus calcification, aortic valve calcification and calcific aortic stenosis (23.9%); rheumatic heart diseases were the background for IE in 9.3% of the cases and 1 patient (1.3%) had congenital atrial septal defect. Patients under 65 years old with IE not related to drug abuse on the contrary more often had underlying rheumatic and other acquired valve diseases, while preceding calcific valve lesions were very rare (1.2%). Incidence rates of both IE relapses and IE of prosthetic valves did not significantly differ in the studied subgroups of patients. Rare underlying heart abnormalities in patients with IE not related to drug abuse were the following: mitral valve prolapse (1.3% in patients ≥65 and 1.1% in those <65 years old), valve myxomatous degeneration (in 2.6% and 0.4% of the patients, respectively), permanent pacemaker (in 4% and 0.4%, respectively), coronary artery bypass graft surgery (in 1.3% and 0.4%, respectively; p>0.05 for all comparisons). In the case of IE related to drug abuse such predisposing conditions as previous episodes of IE and valve replacement took place, one patient had the history of a post-traumatic aortic aneurysm.

A probable site of entry for IE not related to drug addiction was more often identified in the patients ≥65 years old (81.3%) than in younger ones (38.7%; p<0.05). 64% of the IE patients ≥65 years old had undergone healthcare interventions during preceding 6 months, including cardiac surgery (5.3%) or in-hospital invasive diagnostic or treatment procedures (OR 14.9; 95%CI 8.6-25.9). IE in the elderly was more often related to infectious or oncologic diseases of the genitourinary system (32% as compared to 5.6% in the patients <65 years old;

Table 3. Comorbidity in IE patients (n=431)

Concomitant diseases	IE in drug addicts	IE not related to drug addiction		
	(n=90)	<65 years (n=266)	≥65 years (n=75)	Total (n=431)
CHF (before the present episode of IE), n (%)	10 (11.1)	89 (33.5)	38 (50.6)*	127 (37.2)†
CAD, n (%)	0	28 (10.5)	68 (90.1)*	96 (28.1)†
Diabetes mellitus, n (%)	0	11 (4.1)	18 (24)*	29 (8.5)†
Chronic urinary tract infection, CKD, n (%)	4 (4.4)	12 (4.5)	42 (56)*	54 (15.8)†
Cancers, n (%)	0	3 (1.1)	27 (36)*	30 (8.8)†
Viral hepatitis C, B; liver cirrhosis, n (%)	80 (88.8)	7 (2.6)	2 (2.6)	9 (2.6)†
HIV, n (%)	8 (8.8)	0	0	0†
Connective tissue disease, n (%)	0	4 (1.5)	0	4 (1.2)
COPD, bronchial asthma, n (%)	1 (1.1)	3 (1.1)	9 (12)*	12 (3.5)
Ulcerative colitis, n (%)	0	1 (0.4)	0	1 (0.3)
Alcohol abuse, n (%)	0	11 (4.1)	1 (1.3)	12 (3.5)
Chronic brain ischemia, n (%)	0	0	21 (28)*	21 (6.1)†
Other, n (%)	2 (2.2)	5 (1.9)	15 (20)	20 (5.9)
Charlson comorbidity index, scores (M±SD)	1.0 ±0.5	1.2 ±0.8	5.5 ±2.3*	2.1 ±1.0

* p<0.05 as compared to incidence in IE patients under 65 years not addicted to drugs

† p<0.05 as compared to incidence in IE patients addicted to drugs

IE – infective endocarditis, HIV –human immunodeficiency virus, CAD – coronary artery disease, CKD – chronic kidney disease, COPD – chronic obstructive pulmonary disease

Table 4. IE localization and etiology

Characteristics	IE in drug addicts	IE not related to drug addiction		
	(n=90)	<65 years (n=266)	≥65 years (n=75)	Total (n=431)
IE localization, n (%)				
Mitral valve	4 (4.4)	90 (33.8)	34 (45.3)	124 (36.4)†
Aortic valve	0	121 (45.4)	29 (38.7)	150 (44)†
Tricuspid valve	73 (81.1)	0	0	0†
Pulmonary artery valve	0	3 (1.1)	0	3 (0.9)
Mitral and aortic valves	6 (6.7)	47 (17.7)	7 (9.3)	54 (15.8)†
Aortic and tricuspid valves	1 (1.1)	0	1 (1.3)	1 (0.3)
Mitral and tricuspid valves	4 (4.4)	2 (0.8)	0	2 (0.6)
Tricuspid and pulmonary artery valves	2 (2.3)	0	0	0
Mural endocarditis	0	2 (0.8)	1 (1.3)	3 (0.9)†
Pacemaker electrodes in the right side of the heart	0	1 (0.4)	3 (4.0)*	4 (1.2)†
IE pathogens, n (%)				
Staphylococci:				
Aureus	73 (81.1)	37 (13.9)	11 (14.7)	48 (14.1)†
Coagulase-negative	0	11 (4.1)	0	11 (3.2)
Streptococci	4 (4.4)	37 (13.9)	14 (18.7)	51 (14.9)†
Enterococci	0	12 (4.5)	10 (13.3)*	22 (6.5)†
Other	2 (2.2)	16 (6.0)	2 (2.7)	18 (5.3)
Mixed flora	2 (2.2)	0	0	0
Negative hemoculture	9 (10.0)	153 (57.5)	38 (50.7)	191 (56.0)†

* p<0.05 as compared to incidence in IE patients under 65 years not addicted to drugs

† p<0.05 as compared to incidence in IE patients addicted to drugs

IE – infective endocarditis

p<0.05) and cancers of the gastrointestinal tract (6.7% as compared to 0.7% in the patients <65 years old; p<0.05). Incidence rates of preceding dental procedures, skin infections and infectious diseases of the respiratory system were not differed in ≥65- and <65-year-old non-drug users IE patients.

All the examined old patients with IE had more than 2 concomitant diseases (Table 3). They more often than younger patients suffered from diabetes mellitus (24% and 4.1%, respectively; OR 9.9; 95%CI 4.5-22.1), cancers (36% and 1.1%, respectively; OR 66.2; 95%CI 19.3-226.8) and chronic kidney diseases (56% and 4.5%, respectively; OR 27.0; 95%CI 13.6-53.3). These illnesses are considered to be the risk factors for poor prognosis in IE [12-14]. The most frequent oncologic diseases in the patients of old age were the following: lymphoproliferative disorders (8 patients), colon and rectal cancers (5 patients) and prostate cancer (5 patients); besides, breast cancer, uterine corpus and cervix car-

cinoma, lung cancer, gastric cancer and myeloma were also reported. Oncologic diseases were newly diagnosed in 2 subjects during IE treatment, two patients were on a chemotherapy due to an oncologic disease. In addition, frequent concomitant illnesses were the following: coronary artery disease (90.1%), chronic brain ischemia (28%), chronic heart failure (50.6%), chronic obstructive pulmonary disease (12%).

Clinical features of IE in aged patients

Mitral valve was the most frequent localization of IE in patients ≥65 years old (45.3% of the cases), aortic valve – in 38.7%, bivalvular endocarditis of mitral and aortic valves – in 9.3%, aortic and tricuspid valves – in 9.3%, pacemaker's electrodes – in 4% and left ventricle mural endocarditis in 1.3% of the cases (Table 4). IE patients <65 years old with no drug abuse more often revealed an affection of aortic than mitral valve, we also registered individual

cases of the combined vegetation localization on mitral and tricuspid valves and isolated pulmonary artery valve affection. However, except for the more seldom IE localization on pacemaker's electrodes in younger patients we have found no significant distinctions in vegetation localization rates between patients above and under 65 years old. Drug addicts more often revealed the right sided IE localization (isolated tricuspid valve – in 81.1%, tricuspid with pulmonary artery valves – in 2.3%), some patients had a combined affection of tricuspid valve and left sided valves (5.5%) and 11.1% of the patients were reported to have isolated left sided IE – all registered peculiarities statistically significantly differed from the vegetation localization in IE not related to drug abuse. Streptococci prevailed in the etiology of IE in patients ⩾65 years old (18.7%), *Staphylococcus aureus* caused the disease in 14.7% of the cases (in about half of the cases it was methicillin resistant – MRSA) and enterococci – in 13.3% (*Enterococcus faecalis* in all of the cases) (Table 4). In IE patients under 65 years with no drug addiction the most frequent causative organisms were the following: *Staphylococcus aureus* – 13.9% and coagulase negative staphylococci – 4.1%, streptococci – 13.9%, enterococci – 4.5% of the subjects. The only significant distinction in the etiology of IE not related to drug abuse between patients under and above 65 years was the higher incidence rate of enterococcal endocarditis in aged patients (OR 3.3; 95%CI 1.4-7.9), any other

statistically significant distinctions were absent. Drug addicts significantly more often than non-addicts presented with *Staphylococcus aureus* as the etiological factor (81.1%), they also less often revealed negative blood culture findings.

Median of the IE diagnostics duration amounted to 60 (37-152) days in patients ⩾65 years old, it was higher than in those <65 years old: 30 (20-110) days in IE not related to drug abuse (p<0.05) and 18.5 (10-28) days in drug users (p<0.05). 14 (18.7%) cases of IE in elderly patients were only diagnosed at autopsy study, a number of IE cases undiagnosed during lifetime in patients under 65 years was less: 21 (7.9%) – in non-drug addicts and 3 (3.3%) – in drug addicts (p<0.05). Under-diagnosis of IE in the elderly resulted from the insufficient informativeness capacity of TTE in 4 patients with calcification of aortic and mitral valves, overestimation of possibility of marantic (thrombotic) endocarditis in 1 oncologic patient with revealed valve vegetation, misinterpretation of fever by concomitant diseases. Late reference to doctor and admission to hospital in grave condition, severe comorbidity, long-term cancer screening at outpatient stage, wrong interpretation of IE extracardiac manifestations were the other causes of untimely diagnosis. Almost all elderly patients with late or postmortem diagnosed IE had 2-3 minor diagnostic criteria, but TTE examination and bacterial blood tests were not conducted despite long-term fever.

Table 5. Clinical manifestations of IE in the examined patients (n=431)

IE manifestations	IE in drug addicts	IE not related to drug addiction (n=431)	
	(n=90)	<65 years (n=266)	⩾65 years (n=75)
Fever >38°C, n (%)	90 (100)/90 (100)	266 (100)/220 (82.9)	71 (94.6)*/48 (65.2)*
Splenomegaly, n (%)	49 (54.4)	170 (69.9)	44 (58.7)
Anemia/severe anemia, n (%)	80 (88.8)/10 (11.1)	212 (79.7)/20 (7.5)	67 (89.3)/16 (21.3)*
Thromboembolism, n (%)	89 (98.9)	58 (21.8)	14 (18.7)
Vasculitis, n (%)	15 (15.5)	62 (23.3)	14 (18.7)
Kidney involvement/glomerulonephritis, n (%)	35 (38.9)/31 (34.4)	115 (43.2)/67 (25.2)	45 (60)*/16 (21.3)
Pyogenic spondylodiscitis, n (%)	0	1 (0.4)	3 (4)*
Septic arthritis, n (%)	2 (2.2)	2 (0.8)	0
Vegetation size, mm	10.6 (4.1;16.6)	7.0 (3.4;15.8)	10.6 (3.8;15.5)

Data are presented as Me (25-75%), unless indicated otherwise

*p<0.05 at incidence rates comparison in patients above and under 65 years with no drug addiction

IE – infective endocarditis

Clinical manifestations of IE are listed in Table 5. Patients ⩾65 years old revealed fever in 94.6% of the cases (less often, then younger patients [p<0.05]). Two patients with glomerular filtration rate (GFR) <30 ml/min and two patients with 2b stage of heart failure had no fever. Anemia was registered in 67 (89%) of aged patients, at that they significantly more often revealed severe anemia as compared to patients under 65 years old (21.3% vs 7.5% in IE subjects with no drug abuse and 11.1% – in drug addicts; p<0.05). Severe anemia was considered as iron-deficiency anemia of chronic disease in all cases with one exception. The absence of fever/high fever combined with severe anemia and years-long chronic heart failure due to concomitant coronary heart disease was the reason for IE late diagnosis in 10 patients ⩾65 years old. GFR<60 ml/min was registered in more than a half of the aged patients (significantly more often than in patients under 65), this was resulted from the concomitant chronic kidney disease, acute renal injury due to medical drug treatment, hemodynamic instability, thromboembolism of renal arteries or secondary glomerulonephritis (GN). At that GN incidence rate in aged patients amounted to 21.3% and was not differed significantly from that one in patients under 65 years. The pyogenic spondilodiscitus/osteomyelitis of vertebrae body was more often diagnosed in older patients than in younger ones (4% vs 0.4%, respectively; p<0.05). Incidence rates of thromboembolic events, splenomegaly, vasculitis, arthritis and mean valve vegetation size were not differed significantly in the elderly and in the group of non-drug users ⸲65 years old with IE. Drug users revealed the higher incidence rate of thromboembolic events due to septic embolic pneumonia in almost all cases of the right sided IE.

IE outcomes in patients ≥65 years old

Patients aged ⩾65 years had undergone IE surgical treatment significantly less often than those under 65 years (8% vs 24.8% in non-drug addicts and 28% in drug addicts; p<0.05 for both comparisons). In majority of the cases the reason for refusal of surgical treatment was the high operative risk due to concomitant diseases. In-hospital mortality accounted to 30.7% in IE patients ⩾65 years old, it was more than 1.5-times higher than in people under 65 years (non-drug addicts – 19.2%, p<0.05; OR 1.86, 95%CI 1.05-3.34, p<0.05; drug addicts – 17.8%; p<0.05). However when excluding post-mortem diagnosed IE cases from mortality rates estimation, the incidence rate of lethal outcomes in aged people amounted to 14.8%, which was not significantly differed from that one in IE patients under 65 years with no drug addiction (12.2%) and in drug addicts with IE (14.9%). This testifies that the untimely diagnosis of IE is the most significant reason for the disease poor outcome.

Discussion

According to our observation a number of IE cases in the elderly increased from 1986 to 2018 years and has almost doubled in the last decade, which is corresponding to the worldwide trend to IE "aging" [1,2].

Many trials suggest that IE in the aged had a number of unique features due to patients' age [9]. Old people more often suffer from diabetes mellitus, chronic kidney diseases, cancers, they also have many other illnesses which are frequently accompanied by bacteremia and require invasive medical interventions. In current times old people more often undergo cardiac surgery, implantation of pacemaker. Accordingly, IE in the elderly is more likely related to medical interventions, gastrointestinal tract cancers, inflammatory and oncologic diseases of the urinary tract. Colon and rectum cancers in line with genitourinary system diseases are regarded as the most important IE risk factors in old age [9,14]. Increased incidence of these predisposing factors seems to influence IE etiology [8]. Relatively higher incidence rates of IE caused by MRSA, coagulase negative staphylococci, enterococci and *Streptococcus bovis* were reported in elderly patients [9,10,15,16]. IE caused by each of these pathogens has some peculiar clinical signs, echocardiographic characteristics, complications and special aspects of surgical treatment necessity. The evaluation of epidemiologic factors in our group of patients proves higher association of IE in the elderly with healthcare interventions, gastrointestinal tract cancers, urine system inflammatory and oncologic diseases. In accordance with our data enterococcus caused IE in old patients almost three times as often

as in younger ones. So, epidemiologic factors and prevalent pathogens, but not the age, may to a great extent determine peculiarities of IE clinical course in old patients.

In accordance with the data of literature IE in the elderly is more often developed on prosthetic valves and pacemaker electrodes [9,15]. The significance of idiopathic valve calcification, including calcific aortic stenosis, as predisposing heart pathology in elderly people, having been underestimated for a long time, is in no doubt nowadays [9]. Our study demonstrated the calcification of aortic and mitral valves to be the most frequent preceding valve lesions in aged patients. Difficulties in the differentiation of valve calcification and vegetation and also in the detection of vegetation on valve prostheses and pacemaker electrodes during TTE are well known, that is why experts underscore the transesophageal echocardiography as more sensitive for IE diagnosis in elderly patients [9,10,11,15].

Elderly IE patients reveal feebly marked extracardiac signs; such symptoms as splenomegaly, immunogenic and thromboembolic manifestations (stroke, Osler nodes, Roth spots, glomerulonephritis and others) are less often [9]. In accordance with the E. Durante-Mangoni et al. data [9] the age above 65 years was independently associated with less incidence of thromboembolic events. In the opinion of some authors low embolic risk may be explained by a less size of valve vegetation in elderly patients [10]. We have found no such consistency: the incidence rate of thromboembolic events did not depend on the patients' age, so as the size of valve vegetation was not significantly differed in patients ⩾65 years old and younger ones. The incidence rate of secondary glomerulonephritis had also revealed no dependence on age, however vasculitis presented less often in elderly patients.

According to the literature and our data elderly IE patients were less often feverish, but more often presented with severe anemia, pyogenic spondylodiscitis and vertebrae osteomyelitis [17]. Consequently, early echocardiographic examination, TEE preferably, is recommended in elderly patients with the unspecified iron-deficient anemia of chronic disease (with increased ferritin level) and also in cases of pyogenic spondylodiscitis [17].

Majority of trials dealt with elderly patients, so as our study, reported of later IE diagnosis, less incidence of surgical treatment and higher mortality rates [9,10]. The estimation of reasons for poor IE prognosis in the aged is controversial. The following factors are supposed to contribute: more aggressive causative organisms; later IE diagnosis due to feebly marked clinical signs and difficulties in the differentiation of vegetation with valve calcification and marantic thromboendocarditis in the elderly; concomitant diseases considered as risk factors for IE poor outcome (diabetes mellitus, CKD, cancers); limitations in the antibiotics choice due to frequent kidneys dysfunction; refusal of surgical treatment due to high operative risk associated with age and comorbidity [7,9,10]. E. Durante-Mangoni et al. considered elderly age as the independent predictor of IE poor prognosis [9]. However, in accordance with our data in-hospital mortality rates in the groups of patients ⩾65 years old and younger ones were similar when excluding postmortem diagnosed IE cases. Consequently, we suppose that delayed diagnosis is the most significant factor contributing to IE poor prognosis in the elderly.

Nowadays reasonability of the considering IE in the elderly as a special form of the disease is debatable. The Guidelines of European Society of Cardiology (2009) included "IE in the elderly" in a number of special forms of infective endocarditis [10], but in the following revision of the document in 2015 this IE form was not mentioned as special [11]. We have found no any conceptual differences in non-related to drug addiction IE clinical course depending on age; clinical and epidemiological features revealed in patients ⩾65 years old have to be taken into account, but they are not sufficient to identify IE in elderly as a special form such as, for instance, IE in drug users.

Conclusion

Increase in IE morbidity rates in the elderly demand enhanced wariness of doctors for the improvement of the disease diagnostics in patients above 65 years old. TTE and microbiologic blood samples testing must be urgently performed in aged patients in the presence of 2-3 minor criteria of IE diagnosis (even if they may be explained by other diseases or fever is

absent) and also in the cases of the unspecified iron-deficient anemia of chronic disease and pyogenic spondylodiscitis. Detecting of a floating mass on valves in patients with valve calcification is suspicious in the respect of IE and dictates the necessity for TEE. Marantic thromboendocarditis is an exceedingly rare disease; it can be only diagnosed in elderly patients with cancers providing certain IE exclusion.

The treatment of IE in the elderly must be conducted in consistence with the general guidelines for IE management: antibiotics treatment regimens are used according to the sensitivity of an obtained pathogen, indications for surgical treatment are similar in old and younger patients. However, the high possibility of enterococcal etiology must be taken into account at the choice of empiric treatment in elderly patients with subacute IE before the results of microbiological testing receiving. Nephrotoxic antibiotics should be avoided in the treatment of IE in the aged and the regular control of GFR is necessary.

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References / Литература

1. Vatutin N.T., Taradin G.G., Tchaus E.A., Smirnova A.S. Infective endocarditis in elderly: from etiology to treatment and prevention. Russian Journal of Cardiology. 2016;(1):80-9 (In Russ.). [Ватутин Н.Т., Тарадин Г.Г., Чаус Е.А., Смирнова А.С. Инфекционный эндокардит у пожилых: от этиологических особенностей до лечения и профилактики. Российский Кардиологический Журнал. 2016;(1):80-9]. DOI:10.15829/1560-4071-2016-1-80-89.

2. Slipczuk L., Codolosa J.N., Davila C.D., et al. Infective endocarditis epidemiology over five decades: a systematic review. PLoS One. 2013;8(12):e82665. DOI:10.1371/journal.pone.0082665.

3. Sy R.W., Kritharides L. Health care exposure and age in infective endocarditis: results of a contemporary population-based profile of 1536 patients in Australia. Eur Heart J, 2010;31(15):1890-7. DOI:10.1093/eurheartj/ehq110.

4. Nakatani S., Mitsutake K., Ohara T., et al.; CADRE Investigators. Recent picture of infective endocarditis in Japan--lessons from Cardiac Disease Registration (CADRE-IE). Circ J. 2013;77(6):1558-64. DOI:10.1253/circj.CJ-12-1101.

5. Selton-Suty Ch., Célard M, Le Moing V., et al.; AEPEI Study Group.Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based survey. Clin Infect Dis. 2012;54(9):1230-9. DOI:10.1093/cid/cis199.

6. DeSimone D.C., Tleyjeh I.M., Correa de Sa D.D., et al. Temporal trends in infective endocarditis epidemiology from 2007 to 2013 in Olmsted County, MN. Am Heart J. 2015t;170(4):830-6. DOI:10.1016/j.ahj.2015.07.007.

7. Ursi M.P., Durante Mangoni E., Rajani R., et al.Infective Endocarditis in the Elderly: Diagnostic and Treatment Options. Drugs Aging. 2019;36(2):115-24. DOI:10.1007/s40266-018-0614-7.

8. Di Salvo G., Thuny F., Rosenberg V., et al. Endocarditis in the elderly: clinical, echocardiographic, and prognostic features. Eur Heart J. 2003;24(17):1576-83.DOI:10.1016/S0195-668X(03)00309-9.

9. Durante-Mangoni E., Bradley S, Selton-Suty C., et al.; International Collaboration on Endocarditis Prospective Cohort Study Group.Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study. Arch Intern Med. 2008;168(19):2095-103. DOI:10.1001/archinte.168.19.2095.

10. Habib G., Hoen B., Tornos P., et al.; ESC Committee for Practice Guidelines. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009) The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and by the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J. 2009;30(19):2369-413. DOI:10.1093/eurheartj/ehp285.

11. Habib G., Lancellotti P., Antunes M.J., et al.; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44):3075-128. DOI:10.1093/eurheartj/ehv319.

12. Buchholtz K., Larsen C.T., Hassager C., Bruun N.E. In infectious endocarditis patients mortality is highly related to kidney function at time of diagnosis: a prospective observational cohort study of 231 cases. Eur J Intern Med. 2009;20(4):407-10. DOI:10.1016/j.ejim.2008.12.017.

13. Kourany W.M., Miro J.M., Moreno A., et al. Influence of diabetes mellitus on the clinical manifestations and prognosis of infective endocarditis: a report from the International Collaboration on Endocarditis-Merged Database. Scand J Infect Dis. 2006;38(8):613-9. DOI:10.1080/00365540600617017.

14. Chipigina N.S., Karpova N.Y., Barsegyan V.A., Timofeev V.T. Infective endocarditis and malignant neoplasms: facts and hypotheses. The Clinician. 2018;12(1):17-24 (In Russ.) [Чипигина Н.С., Карпова Н.Ю., Барсегян В.А., Тимофеев В.Т. Инфекционный эндокардит и злокачественные новообразования: факты и гипотезы. Клиницист. 2018;12(1):17-24. DOI.10.17650/1818-8338-2018-12-1-17-24.

15. Cecchi E., Chirillo F., Castiglione A., et al. Clinical epidemiology in Italian Registry of Infective Endocarditis (RIEI): Focus on age, intravascular devices and enterococci. Int J Cardiol. 2015;190:151-6. DOI:10.1016/j.ijcard.2015.04.123.

16. Cahill T.J., Baddour L.M., Habib G., et al. Challenges in Infective Endocarditis. J Am Coll Cardiol. 2017;69(3):325-344. DOI:10.1016/j.jacc.2016.10.066.

17. Aguilar-Company J., Pigrau C., Fernández-Hidalgo N., et al. Native vertebral osteomyelitis in aged patients: distinctive features. An observational cohort study. Infection. 2018;46(5):679-86. DOI:10.1007/s15010-018-1177-6.

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