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Article

Trend in Infective Endocarditis in Bulgaria—Characteristics and Outcome, 17-Years, Single Center Experience

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Abstract: Background: Infective endocarditis (IE) remains a difficult disease to diagnose and treat, with a persistently high mortality rate. There is a lack of recent data on IE in Bulgaria over the last decades. **Methods:** The study is retrospective, single centered, includes 270 patients diagnosed with IE, for the period 2005 - 2021. We compared the two periods 2005-2015 (n=119) and 2016-2021 (n=151) to find the characteristics changes. **Results:** The median age was 65 (23) years and 65.5% (177) were male. In the second period, there is a significant increase in age from 62 (29) to 67 (22), (p=0.023); Charlson comorbidities index (CCI) from 3 (3) to 4 (4), (p=0.000); cases with chronic kidney diseases (CKD) from 12.6% (15) to 36.9% (55), (p=0.001); coronary arterial diseases (CAD) from 16.85% (20) to 29.1% (44), (p=0.018); atrial fibrillation (AF) from 10.9% (13) to 23.8% (36), (p=0.006). Injection fraction decreased significantly in the second period from 63 (14) to 59 (15), (p=0.000). Almost half of the patients 45.6% (123) had no known predisposing cardiac condition and 46.3 (125) had an unknown port of entry. IE was community-acquired in 173 (64.1%), healthcare-associated in 26.7% (72), and injection drug use related IE in 9.3% (25). The study population included 67.8% (183) native valve IE, 31.5% (85) prosthetic IE, and 0.74% (2) intracardiac device-related IE. The hemoculture were positive in 59.6%, and the most frequent pathogenic agent was *Staphylococcus* - 33.3 % (*aureus* - 16.5 % and *coagulase negative* - 16.8 %). Only 20% of patients underwent early surgery. The all-cause 30 days mortality rate was 24.8%. There is no significant difference between the two periods in terms of the characteristics listed above. **Conclusion:** The profile of IE in Bulgaria has changed with increasing age and comorbidity, changing predisposing cardiac conditions and entry door. The most common pathogen was the *Staphylococcus* group. The 30 day mortality rate remains high.

Keywords: infective endocarditis; current profile; mortality

1. Introduction

Infective endocarditis (IE) was first described more than 4 centuries ago, but it remains a major challenge for physicians. Sir William Osler called it "malignant endocarditis" in a lecture to the Royal College of Physicians in London in 1885 (1,2). Even then, he noted that few diseases present so many difficulties in diagnosis as malignant endocarditis, and that some of these difficulties are practically insurmountable.

IE is a changing disease in which, despite modern imaging and microbiological techniques, there are often serious difficulties and delays in diagnosis (3). Improvements in medical and surgical treatment in recent decades have not altered the mortality and serious complication rates. The

mortality remains high, up to 30 % (4,5). The challenges associated with infective endocarditis are greater than ever due to the changing profile of the disease, both on the patient side and on the microbiological pathogen side. Characteristics of IE change over time and depend on geographical and socioeconomic level of the country. In recent decades there has been an increase in the patients' age, comorbidity, Staphylococcus etiology and health care-related IE. There is a shift in predisposing factors with an increase in the cases of degenerative valvular involvement, valve prostheses, indwelling catheters and implanted cardiac devices, intravenous drug users while cases due to rheumatic heart disease are becoming less common in developed countries (4–6).

Knowing the current profile of patients with IE helps to ensure timely and accurate diagnosis, which is key to initiating appropriate treatment. Equally important is early risk stratification for complications and death. Early identification of high-risk patients would change the therapeutic approach to a more aggressive one, especially when deciding on surgical treatment. This is associated with a reduction in in-hospital mortality and an improvement in the long-term prognosis of patients (7–9).

There are no data for Bulgaria for the last few decades. Up-to-date IE data for Europe are available from EURO-ENDO, but Bulgaria is not included in this register. We aim to describe the characteristics of IE and its changes over the 17 years period.

2. Material and Method

The study is retrospective, single-centered, including 270 patients with a diagnosis of IE, according to the modified Duke criteria, treated at the University Hospital "St. Georgi", in the city of Plovdiv for the period January 2005 – December 2021. We compared the two periods 2005-2015 (n=119) and 2016-2021 (n=151) to find the characteristics changes. The hospital capacity is 1500 beds, and the cardiology clinic is a reference center for the treatment of IE for a large part of southern Bulgaria. The medical records of treated patients with codes I33, I38, and I39 for the described period were used. Variables studied included demographics, risk group, presence of predisposing heart disease, comorbidities, Charlson comorbidity index (CCI) (10), entry gate, predictors for transient bacteremia, clinical, echocardiographic findings, causative organisms, complications, and clinical outcome.

3. Definition and Classification of IE

The diagnosis was defined as definite IE or possible IE according to the modified Duke criteria (11). Surgical treatment of IE was defined as early when the surgery was done during antibiotic treatment. Valvular involvement of IE is determined based on findings from echocardiography, other imaging studies, cardiac surgery, or in some cases by clinical presentation. Episodes of IE were categorised by mode of acquisition as follows: community-acquired IE (CAIE), healthcare-associated IE (HAIE), and intravenous drug-use associated IE (IDUIE). These categories are mutually exclusive. IE was defined as HAIE according to the following criteria: (1) occurrence of IE >48 hours after hospital admission or within 6 months after hospital discharge for ≥ 2 days; (2) IE developed within 6 months after a significant invasive procedure performed during hospitalisation or in an outpatient setting; (3) extensive outpatient healthcare contacts, defined as receiving wound care or intravenous treatment within 1 month before the onset of IE; or (4) stay in a clinic-home to receive similar care. IE occurring on a prosthetic valve within 12 months of surgery is defined as prosthetic valve early endocarditis (PVIE) and is classified as HAIE. Patients with a recent (within 1 month) or longer history of intravenous drug use were classified as IDUIE. Patients with no medical history and no history of injecting drug use were classified as CAIE. IE following dental treatment is considered to be CAIE if there is no other healthcare contact. The presence of septic emboli and an extracardiac focus of infection was defined as a focus of infection detected by imaging or based on typical clinical presentation. Complications were diagnosed according to the established diagnostic criteria and recommendations.

4. Statistical Methods

Quantitative data are presented as arithmetic mean±standard deviation (mean±SD) or median and interquartile range (median (IQR)) according to the type of distribution of the variables (Kolmogorov-Smirnov test). Categorical variables were summarized using absolute (n) and relative (%) magnitudes. Man-Whitney test for in-dependent samples was used to compare quantitative variables between two groups. A z-test was used to compare the relative shares of categorical variables between the studied groups. A p-value<0.05 (two-tailed test) was considered statistically significant for all tests. Statistical analysis was performed using SPSS, version 26.0 (IBM corp., NY, USA).

5. Results

Of all 270 patients, 75.9% (n=205) had definite IE, with 65% (n=133) of them having two major criteria and 35% (n=72) having one major and three minor criteria. There were 24.1% (n=65) diagnosed with possible IE, 95% (n=62) of them with one major and one minor criterion and three with three minor criteria. The patients’ baseline characteristics are shown in Table 1. The median age was 65 (23) and the patients were significantly older in the second time period (67 (22) vs 62 (29), p=0.023). We found an increasing number of cases per year in the second period. The median time from symptom onset to hospitalization was 30 (40) days, with no difference between the two periods. Almost half of the patients are at low risk, 33% at high risk and should receive IE prophylaxis. Native valve IE was prevalent - 66.7%, prosthetic IE was 32.6% and CDRIE was 0.74%. The entry door was unknown in almost half of the cases (46.3%) and the most common gateway was manipulation/procedures (16.3%), followed by dental procedures (11.1%), intravenous drug users (8.9%) and hemodialysis (4.8%). We found an increase in cases with manipulations/procedures and hemodialysis in the second period, without significant differences. The most common cardiac predisposition was prosthetic heart valves (28.2%) and almost half of the patients (45.6%) had no known cardiac disease. According to the mode of acquisition, we found community acquired IE in 64.1%, health care related IE in 26.7% and intravenous drug use related IE in 9.3%, with no significant difference between the two periods.

Table 1. Baseline characteristics.

Variables	2005 – 2021 G0 n=270	2005 – 2015 G1 n=119	2016 – 2021 G2 n=151	p value
Age in yrs., X ± SD	60.86 ±16.83	58.13 ± 17.71	63.01± 15.84	0.023†
median (IQR)	65 (23)	62.0 (29.0)	67 (22)	
Gender – male, n (%)	177 (65.6)	79 (66.4)	98 (64.9)	0.7968*
Time symptoms-hospitalization, median (IQR)	30 (40)	30 (46)	30 (40)	0.932†
Previous AB treatment	142 (52.6)	59 (49.6)	82 (54.3)	0.443*
Risk groups, n (%)				
Low	136 (50.4)	55 (46.2)	81 (53.6)	0.227*
Moderate	44 (16.3)	24 (20.2)	20 (13.2)	0.122*
High	90 (33.3)	40 (33.6)	50 (33.1)	0.931*
Type of valves, n (%)				
Native IE	180 (66.7)	77 (64.7)	103 (68.2)	0.629*
Prosthetic IE	88 (32.6)	41 (34.4)	47 (31.1)	0.567*
Late prosthetic	9 (3.3)	6 (5.0)	3 (2.0)	0.172*
Early prosthetic	79 (29.3)	35 (29.4)	44 (29.1)	0.957*
CDRIE	2 (0.7)	1 (0.8)	1 (0.7)	0.061*
Entry door, n (%)				
Unknown	125 (46.3)	57 (47.9)	68 (45)	0.635*
Manipulation/procedures	44 (16.3)	15 (12.6)	29 (19.2)	0.145*
Dental	30 (11.1)	14 (11.8)	16 (10.6)	0.756*

I.v. drug users	24 (8.9)	13 (10.9)	11 (7.3)	0.302*
Hemodialysis	13 (4.8)	3 (2.5)	10 (6.6)	0.117*
Skin	10 (3.7)	2 (1.7)	8 (5.3)	0.120*
Urogenital	9 (3.3)	3 (2.5)	6 (4.0)	0.496*
Gastrointestinal	5 (1.9)	5 (4.2)	0 (0)	0.011*
Respirators	5 (1.9)	5 (4.2)	0 (0)	0.011*
Ear Nose Throat	4 (1.5)	2 (1.7)	2 (1.3)	0.787*
Others	1 (0.4)	(0)	1 (0.7)	0.361*
Predisposing heart conditions, n (%)				
Prosthetic valve	76 (28.2)	33 (27.7)	43 (28.5)	0.899*
Past IE	20 (7.4)	10 (8.4)	10 (6.6)	0.575*
Past IE prosthetic	14 (5.2)	7 (5.9)	7(4.6)	0.632*
Past IE native valves	6 (2.2)	3 (2.5)	3 (2.0)	0.782*
Rheumatic heart disease	11 (4.0)	7 (5.9)	4 (2.6)	0.172*
Congenital heart disease	2 (0.7)	1(0.8)	1 (0.7)	0.924*
Degenerative valve	19 (7.0)	8 (6.7)	11 (7.3)	0.848*
Bicuspid Ao valve	11 (4.1)	5 (4.2)	6 (4.0)	0.934*
Mitral valve prolapse	8 (3.0)	4 (3.4)	4 (2.6)	0.734*
Without	123 (45.6)	51 (42.9)	72 (47.7)	0.432*
Type of acquisition				
Community acquired IE	173 (64.1)	75 (63.0)	98 (64.9)	0.747*
Health care-associated IE	72 (26.7)	29 (24.4)	43 (28.5)	0.350*
Intravenous drug use-related IE	25 (9.3)	15 (12.6)	10 (6.6)	0.091*

*z-test; †Mann-Whitney U Test; AB – antibiotic; CDRIE - cardiac device related IE.

We found a wide range of comorbidities and a significant increase in CCI in the second period from 3(3) to 4(4), p=0.000 (Table 2.). The most common comorbidities were arterial hypertension (63.3%), chronic heart failure (45.9%), previous cardiac surgery (35.2%), chronic kidney disease (CKD) (25.9%), coronary artery disease (CAD) (23.7%), diabetes (18.9%) and atrial fibrillation (AF) (18.1%). We reported significant increases in the second period for CKD from 12.6% to 36.9%, p=0.001; CAD from 16.8% to 29.1%, p=0.018; AF from 10.9% to 23.8%, p=0.006 (Table 2).

The most common clinical presentations were fever 97.4%, anemia 92.5%, heart murmur 66.2%, splenomegaly 18.1% and skin disorders 5.5%. We found a significant increase in cases with anemia in the second period (from 88.9% to 95.4%, p=0.044).

The 30-day mortality was 24.8%, with no significant change between periods. Early surgery was 20%, with an increase in the second period from 16.8% to 22.5%, with no significant difference. The most common complications were acute heart failure (47.5%), worsening kidney function (41.1%), embolism (20.7%), stroke (11.1%) and septic shock (8.5%) (Table 2.).

Table 2. Comorbidities, clinical symptoms and complications.

Variables	2005 – 2021 G0 n=270	2005 – 2015 G1 n=119	2016 – 2021 G2 n=151	p value
Comorbidity				
CCI, median (IQR)	3 (3)	3 (3)	4 (4)	0.000†
AH	171 (63.3)	69 (58.0)	102 (67.5)	0.108*
CHF	124 (45.9)	61 (51.3)	63 (41.7)	0.279*
Heart surgery	95 (35.2)	43 (36.1)	52 (34.4)	0.772*
CKD	70 (25.9)	15 (12.6)	55 (36.9)	0.001*

CAD	64 (23.7)	20 (16.8)	44 (29.1)	0.018*
Diabetes	51 (18.9)	19 (16.0)	32 (21.2)	0.279*
Atrial fibrillation	49 (18.1)	13 (10.9)	36 (23.8)	0.006*
Past stroke	40 (14.8)	16 (13.4)	24 (15.9)	0.566*
Gastrointestinal	32 (11.1)	13 (10.9)	19 (12.6)	0.668*
Malignancy	30 (11.1)	11 (9.2)	19 (12.6)	0.377*
COPD	21 (7.8)	6 (15.0)	15 (10.0)	0.213*
Hemodialysis	14 (5.2)	3 (2.5)	11 (7.3)	0.077*
Chronic liver disease	13 (4.8)	7 (5.9)	6 (4.0)	0.470*
Systemic disease	4 (1.5)	1 (0.8)	3 (2.0)	0.416*
Clinical symptoms				
Fever	263 (97.4)	115 (96.6)	148 (98)	0.474*
Anemia	248 (92.5)	104 (88.9)	144 (95.4)	0.044*
Cardiac murmur	178 (66.2)	77 (64.7)	101 (67.3)	0.654*
Splenomegaly	49 (18.1)	25 (21.0)	24 (15.9)	0.280*
Skin disorders	14 (5.5)	9 (7.6)	5 (3.3)	0.114*
Complications				
Outcome 30 days- died, n (%)	67 (24.8)	30 (25.2)	37 (24.5)	0.895*
Early surgery, n (%)	54 (20.0)	20 (16.8)	34 (22.5)	0.245*
AHF	128 (47.5)	58 (48.7)	70 (46.4)	0.707*
Septic shock	23 (8.5)	11 (9.2)	12 (7.9)	0.703*
Stroke	30 (11.1)	11 (9.2)	19 (12.6)	0.377*
Embolism	56 (20.7)	24 (21.0)	31 (20.5)	0.920*
Brain	29 (51.7)	11 (45.8)	18 (58)	0.369*
Lang	5 (8.9)	0 (0.0)	5 (16.1)	-
Spleen	10 (17.9)	4 (16.7)	6 (19.4)	0.800*
Skin	7 (12.5)	6 (25)	1 (3.22)	0.016*
Musculoskeletal	2 (3.57)	2 (8.3)	0 (0.0)	-
Combine	3 (5.4)	2 (8.3)	1 (3.2)	0.408*
Worsening kidney function	111 (41.1)	43 (36.1)	68 (45.0)	0.140*

*z-test; †Mann-Whitney U Test; CCI- Charlson Comorbidity index; AH – Arterial hypertension; CHF – Chronic heart failure; CKD – Chronic kidney diseases; CAD – Coronary arterial diseases; COPD – Chronic obstructive pulmonary diseases; AHF- Acute heart failure.

Transthoracic echocardiography was performed in 100% of patients, transesophageal echocardiography – in 35.9% of them (Table 3). We found vegetation in 83.7% (n=226), perianular abscess – 3% (n=8), chordal rupture – 3.3% (n=5), valve obstruction – 11.9% (n=32). The distribution of valvular regurgitation according to severity was as follows: mild/moderate: AV – 29.3%; MV – 23.7%; TV – 6%. Severe regurgitation: AV – 24.8%; MV – 19.3%; TV – 7.4%.

Single-valve IE (SIE) was found in 82.6% (n=223), multivalvular IE (MIE) in 16.66% (n=45) and CDRIE in 0.74% (n=2). The most frequently affected valve was aortic (AV) (44.8%, n=121), followed by mitral valve (MV) (27.8%, n=75) and tricuspid valve (TV) (9.62% (n=26). We had one case (0.37%) with pulmonary valve IE. Of the MIE, the most common was AV-MV IE – 13.7% (n=37) (Table 3). There was no triple- or quadruple-valve endocarditis in our series. We found vegetation in 83.7% and significantly increase the cases with vegetation 10-15 mm in the second period (from 5.9% to 20.5%, p = 0.001*. We also found a significant decrease in EF in the second period from 63% (14) to 59% (15), (p=0.000†).

Table 3. Echocardiogram findings.

Variables	2005 – 2021 G0 n=270	2005 – 2015 G1 n=119	2016 – 2021 G2 n=151	p value
TTE	270 (100)	119 (100)	151(100)	N/A
TTE + TOE	97 (35.9)	42 (35.3)	55 (36.4)	0.8516*
Valve location, n (%)				
AV	121 (44.8)	55 (46.2)	66 (43.7)	0.682*
MV	74 (27.4)	29 (24.4)	45 (29.8)	0.323*
TV	26 (9.6)	11 (9.2)	15 (9.9)	0.846*
PV	1 (0.4)	0 (0.0)	1 (0.7)	0.361*
Bivalve IE	45 (16.7)	23 (19.3)	22 (14.6)	0.304*
AV - MV	37 (13.7)	20 (16.8)	17 (11.3)	0.192*
AV - TV	4 (1.5)	1 (0.8)	3 (2.0)	0.416*
MV - TV	4 (1.5)	2 (1.7)	2 (1.3)	0.787*
CDRIE	2 (0.74)	1 (0.8)	1 (0.66)	0.693*
Vegetations, n (%)	226 (83.7)	95 (79.8)	131 (86.8)	0.122*
< 10 mm	153 (56.7)	77 (64.7)	76 (50.3)	0.018*
10-15 mm	38 (14.1)	7 (5.9)	31 (20.5)	0.001*
> 15 mm	35 (13.0)	11 (9.2)	24 (15.9)	0.104*
Perivalvular abscess, n (%)	8 (3.0)	3 (2.5)	5 (3.3)	0.670*
Chordal rupture, n (%)	5 (3.3)	1 (0.7)	4 (2.6)	0.239*
EF %. медиана (IQR)	60 (14)	63 (14)	59 (15)	0.000†
Valve obstruction, n (%)	32 (11.9)	13 (10.9)	19 (12.6)	0.668*
Aortic regurgitation, n (%)	146 (54)	66 (60.0)	80 (53.0)	0.250*
Mild - moderate	79 (29.3)	32 (26.8)	44 (29.2)	0.663*
Severe	67 (24.8)	34 (28.5)	36 (23.9)	0.392*
Mitral regurgitation, n (%)	115 (42.6)	52 (43.7)	63 (41.7)	0.775*
Mild - moderate	64 (23.7)	29 (24.3)	35 (23.2)	0.833*
Severe	51 (18.9)	23 (19.3)	28 (18.5)	0.868*
Tricuspid regurgitation, n (%)	36 (13.3)	14 (11.8)	22 (14.6)	0.502*
Mild - moderate	16 (6.0)	6 (5.0)	10 (6.6)	0.579*
Severe	20 (7.4)	8 (6.8)	12 (7.9)	0.732*

*z-test; †Mann-Whitney U Test; TTE – transthoracic echocardiography; TOE – transesophageal echocardiography; AV – aortic valve; MV – mitral valve; TV – tricuspid valve; CDRIE – cardiac device related IE; EF – injection fraction.

We had 41.1% negative blood cultures and the most common pathogens were *Staphylococci* (33%) - *Staphylococcus aureus* 16.3% and *Staphylococcus CoNS* 16.7% . We found *Enterococci* in 9.3%, *Streptococci* in 7.7%, *Gram negative, non HASEK* in 7.0%, with no difference between two periods. Only other *Streptococci* decreased significantly in the second period from 3.4% to 0%, p= 0.022 (Table 4.).

Table 4. Microbiological agent.

Microbiological agent n (%)	2005 – 2021 G0 n=270	2005 – 2015 G1 n=119	2016 – 2021 G2 n=151	p-value*
Negative hemoculture	111 (41.1)	48 (40.3)	63 (41.8)	0.803
<i>Staphylococci</i>	89 (33.0)	39 (32.8)	50 (33.1)	0.958
<i>Staphylococcus aureus</i>	44 (16.3)	16 (13.5)	28 (18.5)	0.269
<i>Staphylococcus CoNS</i>	45 (16.7)	23 (19.3)	22 (14,6)	0.303
<i>Streptococci</i>	21 (7.7)	12 (10.1)	9 (6.0)	0.212
<i>Streptococcus viridans</i>	9 (3.4)	6 (5.0)	3 (2.1)	0.190

<i>Streptococcus beta-hemolyticus</i>	2 (0.7)	0 (0.0)	2 (1.3)	0.212
<i>Streptococcus alfa hemolyticus</i>	6 (2.2)	2 (1.7)	4 (2.6)	0.617
<i>Streptococci -δpyzu</i>	4 (1.5)	4 (3.4)	0 (0.0)	0.022
<i>Enterococci</i>	25 (9.3)	9 (7.6)	16 (10.5)	0.413
<i>Enterococcus species</i>	1 (0.4)	0 (0.0)	1 (0.65)	0.378
<i>Enterococcus faecalis</i>	23 (8.5)	9 (7.6)	14 (9.2)	0.639
<i>Enterococcus durans</i>	1 (0.4)	0 (0.0)	1 (0.65)	0.378
<i>Gram negative (non HASEK)</i>	19 (7.0)	8 (6.7)	11 (7.3)	0.848
<i>Pseudomonas aeruginosa</i>	2 (0.7)	0 (0.0)	2 (1.3)	0.212
<i>Escherichia coli</i>	9 (3.3)	3 (2.5)	6 (4.0)	0.496
<i>Enterobacter cloacae</i>	1 (0.4)	1 (0.8)	0 (0.0)	0.271
<i>Klebsiella pneumoniae</i>	3 (1.1)	2 (1.7)	1 (0.65)	0.414
<i>Serratia marcescens</i>	4 (1.5)	2 (1.7)	2 (1.3)	0.887
<i>Others</i>	5 (1.9)	3 (2.5)	2 (1.3)	0.465
<i>Candida spp</i>	3 (1.1)	3 (2.5)	0 (0.0)	0.051
<i>Erysipelothrix rhusiopathiae</i>	1 (0.4)	0 (0.0)	1 (0.65)	0.378
<i>Brevibacterium casei</i>	1 (0.4)	0 (0.0)	1 (0.65)	0.378

z – test*; CoNS – Coagulase-Negative Staphylococcus; non HACEK – (Hemophilus species, Actinobacillus, Cardiobacterium, Eikenella, or Kingella).

6. Discussion

The average age of patients with IE has increased significantly in recent decades. In our study, the average age of patients was 65 years. Recent data from other economically developed countries are similar: EURO-ENDO - mean age was 59.25 ± 18.03 years (12), France - 69 years (6) , Japan - 69.1 years (13), Canada - 56 years (14), Spain - 61.8 years (15), Portugal - 68.3 years (16), Netherlands - 67.5 years (17), South Korea - 56 years (18). In the subgroup analysis, a statistically significant increase in age was found in the second period - 67 years compared to 62 years, over a period of 6 years. Age is an important characteristic as it is associated with increased comorbidity, a greater proportion of patients with IE, healthcare-related difficulties, treatment difficulties and a greater proportion of patients with an unfavorable outcome.

In the total study sample, 65.6% were men. Data from other studies from different time periods and geographical locations are similar. The male predominance, about 2/3 of IE cases, has not changed historically. The gender distribution is also independent of the geographical and socio-economic status of the countries.

The distribution of patients by risk groups in the total sample of our study shows that 33.3% are at high risk, 16.3% at intermediate risk and 50.4% at low risk. No significant differences were observed in the subgroup analysis. The high-risk group included patients with prosthetic valve IE (PVIE), patients with past IE and a very low percentage of cyanotic uncorrected congenital heart diseases. In our sample, the majority were PVIE (28.2%) and experienced IE (7.4%), with 5.2% having experienced prosthetic valve IE. In comparison, the high risk in EURO-ENDO is 37% (5); India - 45.6% (19); Africa - 29.1% (20); Portugal - 38% (21). The latest recommendations of the ESC (9), AHA (American Heart Association), JHF (Japanese Heart Foundation), etc. recommend IE prophylaxis only for high-risk groups. The reduction in the number of cases with a dental entry door and the reduction in the proportion of streptococci as causative agents worldwide are arguments in favor of restricting IE prophylaxis. In our study, 2/3 of patients with IE did not receive prophylaxis. These data are likely to be relevant to further discussion of the effect of restrictions on the prevention of IE.

Predisposing cardiac conditions are an important part of the pathogenesis of IE. Their spectrum and distribution have changed significantly in recent decades, with significant differences in geographical and socioeconomic status between countries. In the past, the most common predisposing conditions were rheumatic heart disease and congenital heart disorders, which continue to be the most common in under- and medium-developed countries - India, Iran, Pakistan,

Vietnam. In our results, the largest proportion of patients without previous heart disease is 45.6%. It has been shown that 30-40% of degenerative valve lesions are of unknown etiology (22). According to our data, the most common predisposing factor is the presence of a prosthetic heart valve - 28.2%. These data are similar to those in European and other economically developed countries, where PVIE cases are increasing. In comparison, PVIE cases in ICE-PCS were 21% (4); France - 25% (6); Euro Heart Survey - 26% (23); EURO-ENDO - 30% (5).

The port of entry was unknown in almost 1/2 (46.3%) of patients in our study. Data from a study in Romania are similar - 34% (24). Donova found an unknown port of entry in 68.6% (25). This was followed by manipulation/procedure - 13.3%; dental - 11.1%; i.v. drug addiction - 8.9%; hemodialysis - 4.8%. The remaining categories - skin, genitourinary, gastrointestinal, respiratory, ear-nose-throat and others - are represented by less than 5%. Data from EURO-ENDO are similar, with gastrointestinal gateways accounting for 6.3%, urogenital - 4.5% and i.v. drug dependence - 6.9%. The dental route is of particular interest in the context of IE prevention restrictions. A high proportion of patients with a dental portal was reported in a meta-analysis for Africa - 28.3%, with an underlying predisposing cardiac condition of rheumatic heart disease (20). Our data are close to those of EURO-ENDO - 9.8%, where they reported a decrease in cases with a dental portal. For comparison, in the Euro Heart Survey it is 15% (23); French Registry - 20.6% (6); ICE-PCS 17% (4). These data correlate with a decrease in the proportion of *Streptococcus* as the causative agent. The largest proportion of cases are gateway cases due to manipulation/procedure, reflecting a global increase in *Staphylococcus* as the causative agent and the increasing proportion of healthcare-associated IE.

The most common clinical symptoms in our study were: fever - 97.4%; anemia - 92.5%; heart murmur - 66.2%. Splenomegaly was seen in 18.1%. Skin changes were found in 5.5%. We reported a statistically significant increase in the proportion of anemia in G2 compared to G1 ($p=0.0436^*$). This led to a statistically significant increase in CKD patients in G2. We observed a decrease in cases with splenomegaly and skin changes in G2 compared to G1, without statistical significance. The data from our study are comparable to those from EURO-ENDO and other studies from the last 5 years. Most patients in recent decades have few of the classic clinical findings traditionally associated with IE, which is a modern trend. For example, in the 1960s and 1970s, 11-23% of patients with IE had Osler's nodes and 20-44% had splenomegaly (8). In recent decades, a significant decrease in cases with typical skin changes (immunological and embolic) has been observed. In another study from 2014 (26), Servy et al. found skin changes in 11.9% of 497 patients. These were: purpura - 8%; Osler's nodes - 2.7%; Janeway lesions - 1.6%; conjunctival haemorrhages - 0.6%.

In our sample, TEE was performed in 35.9% of patients. The data for Canada are similar - 29.4% (14) TEE was performed more frequently in Japan - 73.3% (13); Latin America - 59.6% (27), ICE-PCS - 59% (4); EURO - ENDO - 58.1% (5) Iran - 54.4% (28). TEE was performed significantly less frequently in India - 18.1% (19). However, we found a high percentage of vegetations - 83.7%. TEE is known to be difficult to perform in patients with severe or critical illness. TEE is the gold standard in the diagnosis of IE, especially in cases of PVIE and CDRIE, and its wider use is recommended.

We found valvular vegetations in 83.7% and this result is comparable with other studies. According to our data, the most frequently affected valve is the aortic valve. Data from EURO-ENDO, Latin America and Canada are similar. In the remaining studies, mitral valve involvement is the most common. The high percentage of tricuspid valve involvement found in India - 30.2%, Iran - 20.7% and Canada - 15%. This is due to the widespread use of intravenous drug addiction as a predisposing factor in these countries.

Regarding the size of valve vegetations, the highest proportion is found in those smaller than 10 mm - 56.7%, and in the subgroup analysis we find a statistically significant increase in vegetations with a size of 10-15 mm in G2 (20.5%) compared to G1 (5.9%). This is associated with an increase in cases of *staphylococcal* IE. Correspondingly, vegetations smaller than 10 mm decreased significantly in G2 compared to G1. A higher proportion of vegetations over 10 mm was found in Canada - 44.6%; India - 10-30 mm - 38.7% and over 30 mm - 21.6%; Romania - over 10 mm 42.8%; Vietnam - 10-15 mm 31.2%; over 15 mm - 7.4%. Vegetations greater than 10 mm are associated with a higher risk of embolism and are an indication for early surgical intervention to prevent embolism (9).

Left ventricular ejection fraction (EF) is an indicator of left ventricular systolic function. In our study for EF, a statistically significant difference was found in the subgroup analysis, with a lower EF for G2 (U=6680.00; $p=0.000†$) compared to G1. This was the result of a significantly higher proportion of patients with CAD and atrial fibrillation, as well as the higher CCI in G2.

The distribution of severity of regurgitation was similar to other studies. We found a perivalvular abscess in 3% of patients. The incidence of this complication varies between studies: Vietnam - 28.8% (29); Africa - 17.7% (20); Turkey - 15.6% (30); ICI-PCS - 14% (4); EURO-ENDO - 13.9% (5); Latin America - 12.7% (27); India - 1% (19). Another rare complication of IE - chordal rupture - occurs in 3.3%. A very high percentage of this complication was reported in Turkey - 10.9%(30) and Vietnam - 30.3%(31).

The microbiological results in our sample are comparable with changes and trends over the last decades. The leading cause of IE are *staphylococci*, with a decrease in the proportion of *streptococci* and an increase in the proportion of *enterococci* and *gram-negative (GNB)* microorganisms. This is directly related to the increase in the proportion of healthcare-associated IE, intravenous drug-associated IE and the decrease in the incidence of dental entry door. Our data show the largest proportion for *Staphylococci* - 33.3%, followed by *Enterococci* - 9.4%, *Streptococci* - 7.8% and *GNB non HASEK* - 7.1%. These data are comparable to those reported in almost all current studies. For EURO-ENDO - 44.1% for *Staphylococci*, 15.8% for *Enterococci*, 12.3% for *Streptococci*, 3.5% for *GNB non HASEK* (5). For ICI-PCS, the data were 42% for *Staphylococci*, 10% for *Enterococci* and 31% for *Streptococci* (4). For France - 43.9% for *Staphylococci*, 44.6% for *Enterococci* and *Streptococci* together, for *GNB non HASEK* - 9.1% (6). The relatively higher proportion of *streptococci* is probably due to the fact that these two studies are older - 2009 and 2011. Data for Latin America are 53.8% for *Staphylococci*, 9.3% for *Enterococci*, 26.7% for *Streptococci*, 2.8% for *GNB non HASEK*; Africa - 41.3% for *Staphylococci*, 9.1% for *Enterococci*, 34% for *Streptococci*, 10.6% for *GNB non HASEK*. An exception is the data from South Korea, where the largest proportion of *Streptococci* is 35.1%, followed by 23.4% for *Staphylococci* and 8.6% for *Enterococci* (18). The proportion of negative blood cultures varies widely (10-52%) and is mainly associated with previous long-term antibiotic treatment. Our data showed negative blood cultures in 40.4% and previous antibiotic treatment in 52.6% of patients. In comparison, a higher proportion of negative blood cultures were found in Iran - 56%, Pakistan - 54%, Portugal - 52% and Africa - 51.4%. The fewest cases of negative blood cultures were observed in Japan - 5%, ICI-PCS - 10%, Canada - 18%, EURO-ENDO - 21%, Latin America - 24% and South Korea - 26.3%. Our data are close to those of France - 35.8% and India - 36%. Cases of true culture-negative IE, for which specific serological and polymerase chain reaction (PCR) tests are required, should also be considered. In up to 60% of these cases, the pathogen can be isolated (32).

In our study, the highest rate was community-acquired IE - 64.1%, followed by healthcare-associated IE - 26.7% and intravenous drug-induced IE (IVN-IE) - 9.3%. We found no significant differences in the subgroup analysis, but there was an increase in the incidence of healthcare-associated IE from 24.4% to 28.5% in G2 compared to G1. The results are similar in EURO-ENDO - 65.65%, 32.96% and 6.9%, respectively. The current trend worldwide, especially in economically developed countries, is to increase the proportion of IE related to health care. This is the result of an ageing population, improvements in health care, technological advances in medicine and an increase in the average age of IE patients.

In-hospital complications are an important feature of patients with IE and are directly related to the outcome of the disease. According to our data, in-hospital mortality up to 30 days is 24.8%, which is comparable to data worldwide. Data from studies and meta-analyses with large numbers of patients show in-hospital mortality of around 20-25%. Relatively lower mortality rates are reported by South Korea - 14.6%, India - 17%, EUR-ENDO - 17.1%, ICE-PCS - 18%. For the first two countries, this is probably due to a lower mean age and correspondingly lower patient comorbidity. For the other two registries, the high rate of early surgery is noteworthy - 51.2% and 48%, respectively. The highest in-hospital mortality was reported for Iran - 34.1% in a relatively small study (28). It can be seen that acute heart failure is the most common complication, with the exception of India. There, the average age is low - 34.1 ± 13.7 years - and there is low comorbidity due to a high percentage of IV

drug dependence - 35.7% and congenital heart disease - 21.6% as predisposing conditions. The high proportion of patients with impaired kidney function can be explained by a higher proportion of patients with CKD, worsened renal function as a result of antibiotic treatment, immunological changes as well as circulatory and systemic disorders in acute heart failure and septic shock. The rates of embolic events and septic shock in our study were similar to those in EURO-ENDO. Acute neurological complications occur in 20-40% of patients with IE (33). The incidence of acute neurological complications in our study is similar to that in Portugal, Iran, India and Africa. A significantly higher proportion is found in EURO-ENDO. It is likely that the more frequent use of CT and MRI increases the diagnosis of acute neurological complications.

Early surgery is a protective indicator and failure to perform early surgery when indicated is a strong predictor of in-hospital death (EURO-ENDO, Latin America, Japan) (5). In our sample, early surgery was performed in 20% of cases in G0, with an increase from 16% to 22.5% in G2 compared with G1, without statistical significance. In comparison, the highest percentage of early surgery was performed in South Korea - 65.2% (18); followed by Iran - 57.6% (28) ; Romania - 51.7%(24); EURO-ENDO - 51.2% (5); Africa - 49.1 (20); Canada - 48% (14); ICE - PCS 48% (4); France - 45% (6). Fewest patients were treated with early surgery in India - 13.1% (19) and Portugal - 13.2% (16); Japan - 17.2% (13); Russia - 17% (34). Refractory heart failure, septic shock (persistent infection) and prevention of embolism are established indications for early surgery by ECS (2023) (9).

Conclusion: The profile of IE in Bulgaria has changed with increasing age and comorbidity, changing predisposing cardiac conditions and entry door. The most common pathogen was the Staphylococcus group. The in-hospital mortality rate remains high.

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