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ФАКТОРИ, ВЛИЯЕЩИ ВЪРХУ ИЗХОДА ПРИ ИНФЕКЦИОЗЕН ЕНДОКАРДИТ В ДЕТСКА ВЪЗРАСТ

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FACTORS INFLUENCING OUTCOME IN PEDIATRIC INFECTIVE ENDOCARDITIS

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Резюме. Инфекциозният ендокардит (ИЕ) е рядко заболяване в детска възраст и засяга предимно пациенти с вродени сърдечни малформации (ВСМ). Нашето проучване оценява връзката между времето до диагностициране на ИЕ и времето до операцията и клиничния изход за пациента. Средният период от първоначалната изява на симптомите до потвърждаването на диагнозата е 38 дни (3-180 дни). При 12 пациенти (60%) диагнозата е поставена рано (< 30 дни), докато при 8 случая (40%) диагнозата е поставена със закъснение (> 30 дни). 75% от пациентите със забавена диагноза са с предшестваща антибиотична терапия спрямо 58% от децата с ранна диагноза. Всичките 3 деца с летален изход са получавали предварителна антибиотична терапия, като в два от случаите диагнозата ИЕ е била ранна, а в един случай е била забавена. В заключение, емпиричната антибиотична терапия е свързана със забавяне на диагностицирането на инфекциозния ендокардит и колкото по-дълго е времето до операцията, толкова по-голям е рискът от неблагоприятен изход за пациента.

Ключови думи: инфекциозен ендокардит, вродени сърдечни дефекти, време до поставяне на диагнозата, време до операцията, изход

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Abstract Infective endocarditis (IE) is a rare entity in children and predominantly affects patients with congenital heart defects (CHD). Our study assesses the association between the time to diagnosis of IE and the time to surgery and outcome. The mean period from initial symptom presentation to diagnosis confirmation was 38 days (3-180 days). 12 patients (60%) had an early diagnosis (< 30 days), while in 8 cases (40%) the diagnosis was delayed (>30 days). 75% of the patients with a delayed diagnosis had received prior antibiotic therapy vs. 58% of the children with an early diagnosis. All 3 children with lethal outcomes had received prior antibiotic therapy, in two of the cases the diagnosis of IE was early, and in one case it was delayed. In conclusion, empiric antibiotic therapy is associated with a delayed diagnosis of infective endocarditis, and the longer the time to surgery the greater the risk for unfavorable patient outcome.

Key words& infective endocarditis, congenital heart defects, time to diagnosis, time to surgery, outcome

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Introduction

Infective endocarditis (IE) is a rare entity in children – frequency 0.43-0.69 cases in 100 000 patient-years [1, 2, 3] and predominantly affects patients with congenital heart defects (CHD) – native or surgically corrected. Diagnostic delays have a negative effect on patient outcomes, whereas timely surgery is associated with a better prognosis.

Aim

Our study aims to form a sample of patients aged < 18 years with CHD who were hospitalized and treated with IE for 14 years, and to assess how time to diagnosis and time to surgery influence their outcome.

Materials and methods

The study is retrospective and includes the data of 20 patients aged < 18 years with underlying CHD and IE treated at the National Heart Hospital - Sofia Pediatric Cardiology Department, 01.01.2009-31.12.2022. IE was diagnosed based on the modified Duke criteria [4, 5, 6]: major (isolation of typical microorganisms (Staphylococcus aureus, Enterococcus, Streptococcus viridans) from the blood culture and the visualization of valvular vegetations on the echocardiography) and minor (predisposing conditions, fever, and embolic phenomena - glomerulonephritis, Osler nodes, Roth spots, positive rheumatoid factor). The diagnosis of IE requires two major and one major and two additional criteria. We followed the patients for up to 14 years (9 months-14 years, mean 6.3).

Results

The demographic characteristics of the patients are presented in Table 1.

The clinical signs of IE are diverse (Table 2).

Table 1. Demographic characteristics of the patients

Characteristic	Number (%)
Age, (Mean ± SD)	3 months-7 years (9.12 ± 5.4)
< 1 year	1 (5%)
1-6 years	5 (25%)
7-12 years	7 (35%)
13-18 years	7 (35%)
Sex	
Male	12 (60%)
Female	8 (40%)
Underlying CHD	
Left ventricular outflow tract obstruction (subvalvular/valvular aortic stenosis/bicuspid aortic valve)	7 (35%)
Fallot tetralogy	5 (25%)
Atrioventricular septal defect	3 (15%)
Ventricular septal defect	2 (10%)
Mitral valve dysplasia	1 (5%)
Complex cardiac disease	2 (10%)

The leading symptom is malaise in 19 patients (95%); the second most common symptom was fever in 18 children (90%). In the remaining two cases (10%), the course of the disease was subacute, without a significant rise in body temperature. Eight patients (40%) had heart failure. Five children (25%) had gastrointes-

Table 2.Clinical symptoms in patients with IE

Patient	Fever	Malaise	Heart failure	Respiratory failure	Gastrointestinal sympt.	Embolic phenomena	Neurological symptoms
№1	+	-	-	+	+	-	+
№2	+	+	+	+	-	-	-
№3	+	+	+	-	+	-	-
№4	+	+	-	+	-	-	-
№5	+	+	+	-	-	-	+
№6	+	+	+	+	-	-	-
№7	+	+	-	-	-	-	+
№8	-	+	+	-	+	-	-
№9	+	+	-	-	+	-	-
№10	+	+	-	-	-	-	-
№11	+	+	-	-	-	+	+
№12	+	+	-	-	-	-	-
№13	+	+	+	-	-	-	-
№14	-	+	+	-	-	-	-
№15	+	+	-	-	-	-	-
№16	+	+	-	-	-	-	+
№17	+	+	+	-	+	-	-
№18	+	+	-	-	-	-	-
№19	+	+	-	-	-	-	-
№20	+	+	-	-	-	+	+

tinal symptoms, the same number of cases had neurological symptoms, four children (20%) had respiratory failure, and two patients had embolic phenomena.

All patients had increased inflammatory markers – in eight children, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and white blood cells (WBC) were elevated; in four cases – ESR and CRP, in 2 children – CRP and WBC, in 2 - only CRP, in 2 – only ESR, in one – only WBC, and in one – ESR and WBC.

In 5 cases (26%), the blood cultures remained negative, as four children had received antibiotic therapy, and the fifth child had positive serology for Chlamydia. In 4 cases, the blood culture was positive for Staphylococcus: Staphylococcus aureus (S. aureus) (n = 3), methicillin- resistant S. aureus (MRSA) in one patient, S. hominis (n = 1). In 4 children, Streptococcus was isolated from blood culture: S. sanguinis (n = 3), S. gordonii (n = 1). In six cases the blood culture was positive for Gram-negative bacteria: Enterobacter (n=1), Pseudomonas aeruginosa (n = 1). Kingella (n = 1), Klebsiella pneumoniae (n = 2), Serratia (n = 1). In one child (patient 9), mixed bacterial flora (Enterococcus faecalis and Candida tropicalis) was isolated from the blood culture.

In 7 patients with CHD and IE (32%) the heart defect was not corrected (Table 3).

Endocarditis developed after surgery in the remaining 13 patients (72%) with IE and underlying CHD. Their characteristics are presented in Table 4.

The mean period from initial symptom presentation to diagnosis confirmation was 38 days (3-180 days). Three children (15%) had hospital-acquired, and the remaining 17 (85%) had community-acquired IE. The time to diagnosis was ≤ 30 days from symptom onset in 12 patients (60%), while in 8 cases (40%) the diagnosis was delayed (> 30 days). 6 out of 8 patients (75%) with delayed diagnosis had received prior antibiotic therapy and 7 out of 12 children (58%) with early diagnosis had preceding antibacterial treatment. The blood cultures were positive in all cases with an early diagnosis whereas 20% of the patients with a late diagnosis had negative blood cultures. Out of the 4 patients without bacterial growth from blood cultures, 3 (75%) had received prior antibiotic treatment.

All patients were treated conservatively with antibiotics according to the guidelines [4]. In 12 children (5 with unoperated CHD and 7 after surgery), operative treatment was undertaken. The indications for surgery were uncontrollable heart failure, uncontrollable infection, and high embolic risk. The mean period between the diagnosis of IE and surgery was 33 days (4-90 days). Valve replacement was needed in 7 out of 12 operated children (58%) – AVR in three cases, MVR in one case, and biological pulmonary valve in three cases (valved conduit in two children).

IE relapse was reported in one case. Lethal outcome within 3 months of IE diagnosis was documented in three children, corresponding to a mortality rate of 15%. All children with lethal outcomes had received prior antibiotic therapy, in two of the cases the diagnosis of IE was early, and in one case it was delayed (> 30 days from symptom onset). In two children with lethal outcomes, the causative microorganism was Staphylococcus aureus (methicillin-resistant in one case), and the infection was community-acquired, while in one case IE was caused by a hospital-acquired Klebsiella pneumoniae strain. Both children with S. aureus IE died before surgery was undertaken, while the patient with Klebsiella pneumoniae IE underwent surgery 30 days after IE diagnosis, and died in the early postoperative period. It is noteworthy however that the child had a severe aortic valve stenosis which may have contributed to the unfavourable outcome.

Discussion

Our data confirm the low frequency of IE in children – < 2 cases/year in our clinic. Gupta et al. report an incidence of IE of 0.43/100 000 children [2], Mahony et al. – 0.84/100 000 patients < 18 years [3]. The mean age of the patients with IE in our cohort is 9.12 years, with a lower incidence of IE in children < 1 year (5%) and higher in older patients – 25% among the age group 1-6 years and 35% among the patients > 7 years. The results of Gupta et al. are similar – in their study, 56.2% of the patients with IE were aged ≥ 11 years, while 15.4% were aged ≤ 1 year. In our patient cohort, IE was more frequent among males compared to females – 60 vs. 40%, respectively. Luca et al. from Romania also report a higher frequency of IE by males – 33 cases vs. 21 cases by females [7]. In a study by Carceller et al. from Canada, 54% of the children with IE were males [8].

Our results confirm the critical role of an underlying heart disease in developing IE. This corresponds to the literature data reporting that the vast majority (50-70%) of the children with IE have CHD, which is the major predisposing factor [2, 3]. In the study of Mahony et al., almost 60% of the children with IE had underlying heart disease, and in the study of Gupta et al. – 53.5%.

The risk for IE in children with CHD is 75 times higher than the general population risk [9, 10]. The probability of IE depends greatly on the CHD type, as the malformations associated with higher risk are cyanotic CHD, left-sided heart defects, and atrioventricular septal defect (AVSD) [11, 12, 13]. Our data confirm these observations, as 35% of the children with CHD and IE have left-sided obstructive lesions, 25% – AVSD, and 15% – Fallot tetralogy. Regarding the localization of the vegetations, our results show that the left-sided heart structures are most often involved. These data are similar to the results of other authors (Luca et al., Ahmadi et al. [15]. Our patients' most often reported symptoms are malaise, fever, and cardiovascular manifestations. The results from the meta-analysis of Day et al. are similar – all children had cardiovascular symptoms, 83% had fever, and 61% had malaise.

Table 3. Characteristics of the patients with IE and unoperated CHD

Patient	Age at diagnosis of IE	Time to diagnosis (days)	Prior antibiotic treatment	CHD type	Microorganisms isolated from blood culture	Infection type	Localization of the vegetations	Time to surgery (days)	Therapeutic approach	Clinical outcome	Follow-up (years)
№ 1	2 y	30	No	TF	Streptococcucs sanguinis	CA	Tricuspid and pulmonary valve	10	Radical correction of the defect with the removal of the vegetations	Cured, no relapse	13
№ 2	3 m	25	Yes	Valvular AoSt and CoA	Klebsiella pneumoniae	HA	Left atrial roof	30	Resection of the coarctation and removal of the vegetations	Lethal outcome 21 days after surgery	N/A
№ 7	11 y	7	No	MV dysplasia	Kingella dentrificans	CA	Mitral valve	N/ A	Conservative treatment	Cure d, no relapse	9
№ 10	12 y	90	No	Subvalvular and valvular AoSt	Streptococcus gordonii	CA	Between the subaor tic membrane and the aortic valve, aortic valve	35	Removal of the vegetations and the subaortic membrane, AVR aith a mechanical valve	Cure d, no rela pse	1
№ 18	10 y	58	Yes	Subvalvular AoSt	Negative blood culture	CA	Left ventricular outflow tract	4	Removal of the subaortic membrane, AVR with a mechanical valve	Cure d, no rela pse	14
№ 19	14 y	38	Yes	Perimembranous VSD, partially closed by aneurysmal tissue from the septal tricuspid valve leaflet	Streptococcus sanguinis	CA	Aneurysmal tissue	90	Removal of the vegetations and VSD closure	Cure d, no rela pse	1
№ 20	17 y	40	Yes	Bicuspid AV	MRSA	CA	Aortic valve	N/ A	Conservative treatment	Lethal outcome before surgery	N/A

AVR – aortic valve replacement, CA – community-acquired, HA – hospital-acquired, MRSA – methicillin-resistant S. aureus, N/A – not applicable, VSD – ventricular septal defect

Table 4. Characteristics of the patients with IE after surgical correction of CHD

Patient	CHD type	Age at diagnosis of IE	Time to diagnosis	Prior antibiotic treatment	Type of surgery	Time between surgery and IE diagnosis	Micro organisms isolated from blood culture	Localization of the vegetations	Infection type	Therapeutic approach	Time to surgery (days)	Clinical outcome	Follow-up (years)
№ 3	Complete AVSD with spontaneous closure of the VSD	3 y	50	Yes	Radical correction	9 months	Negative blood cultures	Mitral valve	CA	Conservative treatment	N/A	Cured, no relapse	10
№ 4	TF with absent PV	5 y	60	Yes	Radical correction with a conduit RV-PA Contegra (Medtronic) 12 mm	5 years	Staphylococcus intermedius	Conduit	CA	Surgery – conduit replacement with Contegra 18 mm	53	Cured, no relapse	12
№ 5	Complete AVSD	9 y	18	Yes	Radical correction followed by MVR ATS (Medtronic) 27 mm	8 years	Pseudomonas aerugi nosa	RA and IVC ostium	HA	Conservative treatment	N/A	Cured, no relapse	11
№ 6	TF	1 y, 6 m	12	Yes	Radical correction with Contegra 14 mm	10 days	Klebsiella pneumoniae	VSD patch	HA	Conservative treatment	N/A	Cured,	9
№ 8	Subvalvular aortic stenosis, MV dysplasia	16 y	8	No	Surgery with subaortic stenosis removal and mitral valve plasty	14 years	Serratia	Mitral valve	CA	Conservative treatment	N/A	Cured, no relapse	1
№ 9	ASD, VSD, PDA	1 y 4 m	20	Yes	ASD, VSD plasty, PDA ligation	39 days	Enterococcus fecal, Candida tropicalis	TV, SVC orifice	CA	Surgical – removal of the vegetations, replay of the tricuspid valve	23	Cured, no relapse	10
№ 11	TF	8 y	16	Yes	Radical correction with Contegra 16 mm	4 years	S .aureus	Conduit RV/PA	CA	Conservative treatment – lethal outcome before surgery	N/A	Lethal outcome	N/A

ASD – atrial septal defect, AV – aortic valve, AoSt – aortic stenosis, AVSD – atrioventricular septal defect, CoA – coarctation of the aorta, IVC – inferior caval vein, MV – mitiral valve, PDA – patent arterial duct, PV – pulmonary valve, RA – right atrium, RV – right ventricle, TF – tetralogy of Fallot, TV – tricuspid valve, VSD – ventricular septal defect

Table 4. Continued

Patient	CHD type	Age at diagnosis of IE	Time to diagnosis	Prior antibiotic treatment	Type of surgery	Time between surgery and IE diagnosis	Micro organisms isolated from blood culture	Localization of the vegetations	Infection type	Therapeutic approach	Time to surgery (days)	Clinical outcome	Follow-up (years)
№ 12	Complete AVSD	10 y	20	Yes	Radical correction	5 years	Streptococcus sanguinis	MV	CA	Surgery – vegetation removal, MV plasty	30	Cured, no relapse	7
№ 13	AV stenosis	15 y	10	No	AVR Carbomedix 16 mm	Intraoperatively	Negative blood culture, positive serology for Chlamydia	Pannus area	CA	Replacement of the mechanical AV with MEDHALL - EASY – FIT 23 mm	N/A	IE relapse	
№ 14	TF	15 y	60	No	Radical correction at 9 m, 6 years later PV replacement (Hancock 21 mm)	13 years	Negative blood cultures	PV	CA	Biological PV replacement Hancock II 23 мм	25	Cured, no relapse	10
№ 15	AV stenosis	14 y	20	Yes	AVR ATS 22 mm	10 days	Staphylococcus hominis	Pannus area	CA	Conservative	N/A	Cured, no relapse	1
№ 16	Complete AVSD	17 y	180	Yes	Radical correction	16 years	Negative blood cultures (preceding antibiotic treatment)	Mitral valve	CA	Surgery – MVR (ATS 27 mm)	16	Cured, no relapse	1
№ 17	Complex CHD (D-TG, VSD, PV nosis)	15 y	3		Radical correction Rastelli type with Contegra 16 mm	10 years	S. aureus	Conduit RV/PA and AV	CA	Surgery – conduit replacement (Hancock 22 mm), removal of the vegetations and AV plasty	43	Cured, no relapse	1

ASD – atrial septal defect, AV – aortic valve, AoSt – aortic stenosis, AVSD – atrioventricular septal defect, CoA – coarctation of the aorta, IVC – inferior caval vein, MV – mitiral valve, PDA – patent arterial duct, PV – pulmonary valve, RA – right atrium, RV – right ventricle, TF – tetralogy of Fallot, TV – tricuspid valve, VSD – ventricular septal defect

It is worth mentioning that the diagnosis IE is often delayed, with a mean period between first symptom presentation and diagnosis confirmation of 43 days. The patients with an early diagnosis are those with acute symptoms who were timely referred to a pediatric cardiologist. The diagnosis is frequently delayed in cases with subacute or non-specific symptoms, and empiric antibiotic courses obscure symptoms.

Regarding the etiology of IE, our data are similar to those of other authors. In 5 cases (26%), the blood cultures remained negative. This is the so-called culture-negative endocarditis (CNE), which is most often due to preceding antibiotic treatment or infections with difficult- to-culture microorganisms, whose incidence varies from 8 to 36% [16, 17, 18]. For example, one of our patients with a negative blood culture had positive serology for Chlamydia, and three children had received antibiotic therapy before the blood culture was taken.

The leading bacterial pathogens in our cohort were the so-called “typical” microorganisms – most often Gram-positive bacteria. Four of the cases with IE were caused by Streptococci, and three were caused by Staphylococci. These data are similar to those reported by other authors [19].

Most patients with IE require surgery – all children with uncorrected CHD and almost two-thirds with operated CHD. In the study of Mahony et al., surgical treatment was necessary in 51% of the patients.

Hospital mortality from IE in our patient cohort is 15%. Carceller et al. report a mortality rate of 12.5%, Gupta et al. have found a mortality of 2.8%, Day et al. report a 5% mortality rate, and Ahmadi et al. report 5.6% mortality.

Conclusion

Infective endocarditis is a disease associated with significant morbidity and mortality, which affects most often patients with an underlying heart disease (operated or unoperated) and whose diagnosis is based on positive blood cultures and the visualization of vegetations on the echocardiography. It is crucial to exclude IE in cases of persistent fever in a child with a known heart disease. The prerequisites for a favorable patient outcome are the timely diagnosis, the early initiation of effective antibiotic therapy, and, when necessary – surgical treatment.

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