

An evaluation of risk factors, clinical features, and follow-up findings of patients with infective endocarditis

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Abstract

Aim: Infective endocarditis (IE) is a serious infection of the endocardial layer of the heart and the endothelial layer of the aorta, which usually is caused by bacteria or fungal microorganisms, requiring early diagnosis and treatment. Congenital heart diseases (CHD) and acquired valvular diseases are risk factors for IE. Advances in life-saving medical interventions such as intensive care, immunosuppressive treatments and the more frequent use of implanted prosthetic materials have increased the risk of IE.

The aim of this retrospective study is to evaluate the underlying risk factors, clinical and laboratory findings, microbiological profiles, treatments, and follow-up of patients diagnosed with IE in our clinic.

Material and Methods: In this retrospective study, risk factors, clinical features, laboratory findings, microbiological characteristics, echocardiographic features and medical treatment results and complications of 7 patients who admitted to Inonu University Faculty of Medicine Pediatric Cardiology Department a diagnosed with IE, between 2013-2019 were evaluated.

Results: Seven patients who were diagnosed with IE were detected from the hospital data system. When the predisposing causes were examined, we found that 3 patients had mitral insufficiency due to rheumatic heart disease, and 3 patients had CHD. None of our patients had a history of intervention before infective endocarditis. Bacteria grew in blood cultures of all patients. The most grown microorganisms were Staphylococci. Surgical treatment, valve repair or replacement therapy, was applied to three patients. A patient, who had aortic coarctation and mycotic aneurysm developing based on infective endarteritis, died on the 5th day due to aneurysm rupture while waiting for surgery under antibiotic pressure.

Conclusion: Despite advancing treatment modalities, the mortality rate is about 25%, which is still too high. The most common bacterial infections that cause IE are Streptococci and Staphylococcal infections. Since mortality and morbidity rates are too high in IE, in case of suspicion, necessary laboratory tests and blood cultures should be taken, and treatment should be started immediately.

Keywords: Child; congenital; endocarditis; heart defects

INTRODUCTION

Infective endocarditis (IE) is a serious infection of the endocardial layer of the heart and the endothelial layer of the aorta that usually caused by bacterial or fungal microorganisms and it requires early diagnosis and treatment (1). Congenital heart disease (CHD) and acquired valvular diseases are risk factors for IE. The morbidity and mortality rates are high, due to difficulties in diagnosis and treatment (1). Despite advanced treatment methods, mortality rate is high as 25% (2). Streptococcal infections are the most common cause of IE (3). The following most common causes are coagulase-negative staphylococci and *Staphylococcus aureus* (4).

Since the incidence of rheumatic heart disease (RHD) has decreased in developed countries, it has still predisposing condition for IE, in children in developing countries.

Although advances in surgical and medical treatment increase the life expectancy of children with complex congenital heart disease, the frequency of infective endocarditis has increased due to prosthetic materials (5). Developments in life-saving medical interventions such as intensive care and immunosuppressive treatments and the widespread use of prosthetic materials used in heart surgeries have also increased the risk of IE (6-7).

The aim of this retrospective study is to evaluate the underlying risk factors, clinical and laboratory findings, microbiological factors, treatments, follow-up and prognosis of patients who were diagnosed with IE in the pediatric cardiology clinic of Inonu University Medical Faculty between 2013 and 2019. In this study, we presented the laboratory and clinical characteristics of 7 patients presenting with IE as a case series.

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MATERIALS and METHODS

In this study cross sectional study, patients selected for this study who admitted to the Department of Pediatric Cardiology at Inonu University Faculty of Medicine between 2013 and 2019 and diagnosed with IE according to modified Duke criteria (8) were included in the study. The risk factors, clinical features, laboratory findings, microbiological characteristics, medical treatment results and echocardiographic features of the patients were analyzed retrospectively. In this descriptive study, categorical datas were presented with numbers and percentages, while numerical data were summarized with average, smallest and largest values. Our study was conducted in accordance with the principles stated in the Declaration of Helsinki by obtaining the consent of the patients and ethical approval was obtained from the ethics committee of Inonu University. Ethics committee approval were obtained with the session of Inonu University Scientific Research and Publication Ethics Board dated 26.01.2021 and the decision numbered 2021/1499.

RESULTS

Seven patients diagnosed with IE according to the modified Duke criteria among 67356 patients who register to our hospital between 2013-2019 were included in the study. The IE incidence of our hospital was found to be approximately 10.3 per 100,000. Three of the patients were female (42.8%) and 4 were male (57.2%). The mean age of the patients were 9.6 years (3-16 years). When the patients were evaluated in terms of predisposing factors for IE, it was found that 3 (42.8%) of the patients had underlying congenital heart disease. There was no history of dental intervention or any similar intervention before infective endocarditis. Congenital heart diseases detected in the patients included coarctation of aorta (CoA), ventricular septal defect (VSD), operated transposition of great artery (TGA), and residual VSD. In addition, 3 patients had been followed up for RHD. One of these patients with RHD had undergone mitral valve replacement due to mitral valve insufficiency. One patient had ventriculo atrial shunt due to meningomyelocele and hydrocephalus. Two of the patients were referred from another center for liver transplantation due to liver failure.

Medical history of patients showed that they were generally applied with nonspecific complaints including fever, tremor, fatigue, chest pain, shortness of breath, palpitations, cough, and joint pain. Fever and fatigue were present in all 7 patients (100%), cough, shortness of breath and palpitation in 4 patients (57%), and joint pain was present in 2 patients (28%). In addition, vomiting, diarrhea, and body rash were present in the patients, more rarely. It was found that fever persisted in some patients for a long period up to 15-20 days before admission. In physical examination, tachycardia was present in all patients and marked murmur was present in 6 patients (85%). In general, murmurs were 3-4 / 6 in severity and accompanied by tremor. Signs of heart failure were detected in 5 (71%) patients. The complaints and physical

examination findings of the patients at admission are shown in Table 1.

On laboratory examination, white blood cell and CRP elevation were detected in all patients (Table 2). Liver enzymes were found to be elevated particularly in patients who were followed up for liver failure (AST: 4145 U / L, ALT: 2141U / L, LDH: 4387U / L).

Table 1. The complaints and physical examination findings of the patients at admission

Symptoms and Findings	N (7)	%
Fever	7	100
Chough	4	57
Shortness of breath	4	57
Palpitations	4	57
Joint pain	2	28
Murmur	6	85
Heart failure	5	71
Hepatomegaly	3	43
Splenomegaly	3	43
Splinter hemorrhage	1	14
Petechiae	1	14
Rheumatoid Factor	1	14
Hematuria	1	14

Microorganisms grew in blood cultures of all patients. Staphylococcus aureus was detected in three patients, Staphylococcus epidermidis was detected in two patients, Streptococcus viridans in one patient, and Abiotrophia defectiva in one patient. Meropenem, vancomycin, amikacin, cefazolin, teicoplanin were administered as antibiotic treatment for at least six weeks in appropriate combination.

The clinical and laboratory data of the patients are summarized in Table 2.

On the Echocardiographic examination of the patients, mycotic aneurysm with a diameter of 3.4 cm after the coarctation level was detected in one patient who was followed up for coarctation of aorta (Figure 1). A vegetation with a diameter of 11x12 mm was detected in the distal of the pulmonary artery valve in the patient who followed up for VSD. Mitral valve anterior leaflet perforation and related 3rd degree mitral insufficiency, and 2nd degree tricuspid insufficiency were detected in one of the 2 patients who were followed up due to mitral valve insufficiency due to rheumatic heart disease and perforation in the posterior leaflet of the mitral valve, 3-4th degree mitral insufficiency in the mitral valve, and 12x12 mm vegetation was detected in another patient. Mitral bioprosthetic valve separation and valve dysfunction, 3-4th degree mitral insufficiency, 3rd degree atrial insufficiency, and 2nd degree tricuspid insufficiency were detected in the patient who was followed up for bioprosthetic mitral valve replacement due to RHD. Vegetation was detected at the tip of the

shunt in the patient who had ventriculoatrial shunt due to hydrocephalus. There was no finding in favor of IE in the patient who was followed up for Nikaidoh surgery due to TGA, VSD, and ASD.

One patient, who was followed up for CoA and mycotic aneurysm, died on the 5th day of his hospitalization. Surgical treatment was performed in three patients who were followed up due to RHD and mitral valve perforation. It was observed that the vegetation completely disappeared

due to septic emboli in the ECHO performed on the 2nd day of the treatment in the patient who had vegetation distal to the VSD pulmonary artery valve. Diffuse micro abscess in the lungs were detected in the chest radiography of the patient. The treatment of the patient was completed in 8 weeks. The patient was followed up for meningomyelocele, hydrocephalus, and ventriculoatrial shunt, and the patient's shunt was changed by neurosurgery after 6 weeks of treatment.

Table 2. The complaints and physical examination findings of the patients at admission

Age (year)/gender	Risk Factor	ECHO	WBC (/mm ³)	CRP (mg/dl)	Culture	Treatment /Duration
15/Female	CoA	Mycotic aneurysm	29.7	12.9	Staf. Epidermitis	Vancomycin, meropenem/exitus on 5 th day
7/Male	Op.TGA, VSD, ASD	-	17	2.04	Strep. Viridans	Vancomycin, amikacin/6weeks
3/Male	VSD	11x12 mm vegetation	9.4	16.3	Staf. Aureus	Sefazolin, amikacin/8 weeks
16/Female	RHD	Mitral valve perforation	18.9	6.69	Abiotrophia Defectiva	Meropenem, teicoplanin/10 weeks Valve repairment
6/Male	RHD Bioprosthetic valve	Mitral valve perforation, valve disfunction	14.3	3.94	Staf. Epidermitis	Vancomycin, amikacin Valve replacement
13/Male	RHD	Mitral valve perforation 12x12 mm vegetation	13.5	72.2	Staf. Aureus	Vancomycin, amikacin/7weeks Valve repairment
6/Female	Hydrosephalia Ventriculoatrial shunt	Vegetation at the tip of shunt	9.4	16.3	Staf. Aureus	Meropenem, teicoplanin/6 weeks Shunt revision

CoA: Aort Coarctation, TGA: Transposition of the great arteries, RHD: Rheumatic Heart Disease, VSD: Ventricular Septal Defect, ASD: Atrial septal defect



Figure 1. Coarctation of aorta and mycotic aneurism immediately inferior of coarctation

DISCUSSION

Infective endocarditis (IE) is a serious infection of the endocardial layer of the heart and the endothelial layer

of the aorta, which usually develops due to bacterial and fungal microorganisms. It requires early diagnosis and treatment. Infective endocarditis is a less common disease in children compared to adult patients, but incidence of it has been increasing in recent years (9). Although advances in surgical and medical treatment increase the life expectancy of children with complex congenital heart disease, the frequency of infective endocarditis has increased due to prosthetic materials. In a multi-center study conducted in the United States between 2003 and 2010, the annual incidence was reported to be 5-12 per 100,000 (10). Despite advances in diagnostic methods, advances in antibiotic treatments, and advances in surgical techniques, morbidity and mortality of IE is still high. The incidence of IE appears to be similar between pediatric and adult patients. In epidemiological studies conducted in developed countries, the prevalence of IE is estimated as 1.5-11.6 / 100 000 (11). In our study, the incidence of IE was found as 10.3 per 100000, and it was consistent with the literature.

In developed countries, IE due to rheumatic valvular diseases have decreased significantly. On the other hand, the incidence of IE that develops due to the underlying congenital heart disease has increased seriously. In the study of Johnson et al., in which they reviewed 60 years of data of patients followed in the Mayo clinic, it was determined that the rate of RHD that predisposes to IE decreased. In the same study, the incidence of CHD was reported to be 75% (12).

The risk factors for IE may vary between countries and between regions. In a study conducted in Our Country, performed by Tavli et al., they were reported that 3 of 28 patients they followed up had RHD and 25 had CHD (13). In another study, they were reported that none of the 11 patients followed-up had RHD, and 10 patients had the underlying CHD (14).

However, RHD still continues to be a high-risk factor for IE in developing countries. In a study conducted in Tunisia, RHD was reported to be a high-risk factor for IE (15). Again, in a multicenter study conducted on adult patients, in Our Country, RHD was reported to continue to be a high-risk factor for IE (16).

High-risk conditions for IE were identified as cyanotic congenital heart diseases, prosthetic valves, operated cardiac anomalies with residual pathologies, and patients within the first 6 months after the operation, with or without residual pathology. In a retrospective study, conducted by Rushani et al., on 136 pediatric patients diagnosed with IE and CHD which have high-risk CHDs for the development of IE were cyanotic CHD, endocardial cushion defect, and left heart lesions, respectively (17). Compared to adult patients, there is no significant difference in terms of risk factors. In studies conducted with adult patients, patients with valvular heart disease, congenital heart disease and intracardiac foreign bodies, intravenous drug users, using central venous catheters for chronic hemodialysis, solid organ and hematopoietic stem cell transplantation were identified as high-risk patients (18).

Therefore, prophylaxis should recommend before the interventions for patients who have previous IE, patients with prosthetic valves (biological and mechanical, surgical and transcatheter implanted), patients treated by using with prosthetic material or conduits, and uncorrected cyanotic heart disease (19).

In our study, 7 patients, who were diagnosed with IE, followed up and treated in our hospital for 6 years period, were included. We detected that the underlying cause was RHD in 3 (42.8%) patients and CHD in 3 (42.8%) patients. One of our patients had been followed up for operated TGA, one for VSD, and one for CoA. The rates of RHD and CHD were equal in our patients.

Clinically, IE patients are classified as acute or subacute. Patients presenting with subacute IE present with subfebrile fever, weakness, chronic fatigue, muscle pain and weight loss that last for days and weeks. Acute IE usually presents with high fever and rapid clinical deterioration if not treated. It is recommended that

IE should be considered in patients who present with unexplained fever, heart failure, while changes in the character and severity of the murmur, symptoms of heart failure or sepsis, and those with underlying cardiac pathologies including CHD, prosthetic valve, or RHD (2,20).

Therefore, the use of modified Duke criteria by considering clinical suspicion and risk factors, enables early diagnosis of IE in children with suspected IE, and early treatment can be initiated. Our patients who admitted to our hospital were diagnosed and their treatments were planned, in line with these criteria.

In the literature, it has been reported that, streptococci and staphylococci are still highly detected in blood culture in patients with or without CHD (3,6,8,11,21). In addition, when compared with adult patients, the most common microorganisms causing IE are staphylococcus aureus, streptococci, coagulase-negative staphylococci and enterococci. (22). We detected growth in the blood culture of all our patients. Staphylococci grew in 5 (71%) of the patients, streptococcus viridians in one patient, and Abiotrophia Defectiva grew in one patient. The diagnosis of our patients were made by transthoracic echocardiography (ECHO), except for one patient.

In patients presenting with IE findings, initiating appropriate antibiotic therapy after cultures are taken without delay significantly reduces mortality and morbidity. For this reason, empirical treatment should start with appropriate combinations of meropenem, amikacin, gentamicin, teicoplanin, vancomycin and antibiotic treatments were revised according to the culture results. The treatment period was at least 6 weeks and prolonged was up to 10 weeks depending on the underlying disease. In addition to antibiotic therapy, mitral valve repair or replacement was performed in 3 patients with mitral valve pathologies caused by RHD. In addition, shunt replacement was performed in one patient who had ventriculoarterial shunt due to hydrocephalus.

The mortality rate of IE is reported to be between 4 and 7% (11,23), however there are publications reporting that mortality can reach up to 25% in some series. One patient we followed up due to coarctation of aorta and mycotic aneurysm died on the 5th day of the treatment.

The most common complication associated with infective endocarditis is congestive heart failure (42-66%). CHF is the main determinant of prognosis and the most common indication for surgical intervention (24,25). The main cause of heart failure in IE is insufficiency due to mitral valve and aortic valve involvement (26). Septic embolisms from the infected heart valves or intracardiac devices are life-threatening complications seen in 20-50% of patients. The most important risk factor for embolism is the size (> 10 mm) and mobility of the vegetation, and the risk decreases with the initiation of antibiotic treatment (27,28). The most common embolic sites are pulmonary 28%, peripheral vascular-cutaneous 26%, cerebral 16%, kidney 10%, spleen, and intestines (4%). The most common

neurological complications associated with these embolia are stroke 16%, transient ischemic attack, intracerebral or subdural bleeding, seizure (11%), abscess formation (5%), hemiparesis (2%), meningitis, and toxic encephalopathy. These complications may be the first findings of IE or may occur later (29,30). Renal dysfunction can be seen in 6-30% of IE patients. This situation may be due to various factors including glomerulonephritis due to vasculitis or immune complexes, renal infarction due to embolism, toxicity due to medications, and renal failure due to toxicity caused by radio-opaque agents used for imaging. Although myocarditis, pericarditis and myocardial infarction are rarely seen in IE patients, the prevalence has been reported to be approximately 20% in autopsy series. Again, rhythm and conduction disorders, which are rarely seen during IE, which are poor prognostic factors and are associated with high mortality (30). Apart from these, rare complications such as perivalvular abscess, myocardial abscess, intracardiac fistula can also be seen.

Persistent or recurrent fever despite appropriate antibiotic therapy should suggest uncontrolled cardiac infections or metastatic suppurative complications. Despite the use of antibiotics, current the mortality rate is about 20-25%. The most common complication and cause of death is heart failure. In patients whom sudden and rapidly progressing heart failure is observed, ulceration, perforation, rupture of the chordae, and perforation in the septum should be considered, especially in the left heart valves.

Mycotic aneurysms due to endarteritis are caused by the spread of the infection to the intraluminal or vasa vasorum via septic arterial emboli or intimal vessels. These aneurysms are more likely to bleed and rupture because they are typically thin and fragile. Since 80% of these aneurysms, which are usually located intracranially, are silent, imaging should be obtained when suspected. Intrathoracic and intraabdominal aneurysms generally remain silent until they rupture. The mechanism of mycotic aneurysms due to aortic coarctation is the same as endocarditis. Mycotic aneurysms usually occur in the aortic wall below the narrowed coarctation segment. The turbulent blood flow that occurs here and damaged to the aortic wall and then creates conditions for the development of endarteritis. Infection develops due to microorganisms involve here and leads to mycotic aneurysms (31). However, mycotic aneurysms due to CoA can be seen very rarely. In the literature, the reported cases have been defined as single cases (32,33). Patients can present with nonspecific symptoms or without symptoms (32,34). However, there is a consensus on the treatment that combines surgical treatment with antibiotic therapy (32,35). However, there is no consensus on the timing of the surgery and procedure to be used.

In patients with infective endocarditis, consensus is on surgical treatment. Surgical intervention is required in cases with uncontrollable local infection (abscess, pseudoaneurysm, fistula, growing vegetation), in the presence of endocarditis of natural or artificial aortic valve or mitral valve, in the presence of severe acute valve

regurgitation, obstruction or fistula causing pulmonary edema or cardiogenic shock, and in infections due to fungi or multiple resistant bacteria.

In addition, early surgical intervention is required in cases of persistence of blood culture positivity despite appropriate antibiotic treatment and in the presence of vegetations larger than 10 mm with continuing septic embolism despite appropriate antibiotic treatment in natural or artificial aortic valve endocarditis, and in patients with mobile vegetations which poses a large risk of embolization in a short time. (36,37).

CONCLUSION

Congenital heart disease or acquired structural heart disease continues to be risk factors for IE. The treatment and follow-up of IE is a long and challenging. Streptococci and staphylococcal infections are the common causes. IE should consider in patients with unexplained fever, heart failure, changes in the character and severity of the murmur, signs of heart failure or sepsis, and those with underlying cardiac pathologies including CHD, prosthetic valve, and RHD. The laboratory examinations should plan urgently blood culture should study and broad-spectrum bactericidal antibiotics should be initiated immediately due to high mortality. In addition to antibiotic treatment, appropriate treatment of complications should apply, and surgical treatment should be considered in the presence of treatment-resistant heart failure, aortic sinus rupture, mycotic aneurysms, recurrent embolic attacks, infection that cannot be controlled with antibiotics, prosthetic valve endocarditis, myocardial abscess, and fungal endocarditis. When necessary, further evaluations should plan without delay.

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