

# Infective endocarditis in children: A 5 year experience from Al-Zahra Hospital, Isfahan, Iran

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## Abstract

**Background:** Considering that there are no regional published data regarding the epidemiologic findings of infective endocarditis (IE) in children, in this study we reviewed the epidemiologic and clinical features and treatment and outcome of children diagnosed with IE at Al-Zahra hospital over a 5-year period.

**Materials and Methods:** In this retrospective study, medical records of patients (<18 years old) admitted from March 2006 to March 2011 in Al-Zahra Hospital (Pediatrics Infectious or Cardiology Departments) reviewed. The medical files reviewed regarding demographic, clinical, diagnostic (laboratory, microbiological and echocardiographic details) and treatment and outcome details. Obtained data were recorded in a questionnaire. The diagnosis of IE was determined based on Duke criteria.

**Results:** In this study, 17 patients fulfill the Duke criteria for definite or the possible IE. The most common causes of IE was non-cyanotic heart disease (ventricular septal defect and AS; 64.8%). From cyanotic hearth disease, Tetralogy of Fallot (TOF) was the most frequent causes (11.8%). In this study, 41% of patients with IE aged < 2 years and 70% aged < 6 years. In this study, 76.5% of patients had a history of congenital heart disease or cardiac surgery. Blood cultures were positive in 10 patients (58.8%). Coagulase-negative staphylococci (23.5%) and *Staphylococcus aureus* (11.7%) were the most common organisms that cause IE.

**Conclusion:** It seems that in order to provide a regional comprehensive guideline for appropriate management and prevention of IE related complications further advanced studies with larger sample size and evaluation is recommended.

**Key Words:** Congenital heart disease, infective endocarditis, pediatric

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## INTRODUCTION

Infective endocarditis (IE) with an estimated rate

of 0.34-0.64 cases per 100,000/year considered as an uncommon disease in childhood.<sup>[1]</sup> The higher rate of morbidity and mortality due to its long-term parenteral antibiotic treatment and related complication made it as a serious disease in children.<sup>[2,3]</sup>

Though the incidence rate of the disease was not changed over the past 40 years, but the distribution of its etiologies has been changed significantly.<sup>[1]</sup> The incidence of IE is less common in children than adults and it tends to occur in children with congenital heart disease (CHD).<sup>[4]</sup>

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Rheumatic heart disease as a predisposing heart disease, which was once the common cause of IE, is now considered as a rare condition associated with IE, especially in developed countries. In contrast, CHD are the underlying cause of IE in most of the pediatrics cases. Advanced medical and surgical management including cardiac procedures, early intervention and proper antibiotic use are the causes of this feature.<sup>[5]</sup>

Moreover, the rate of IE is high in premature neonates without underlying heart disease due to frequent use of chronic indwelling catheters and long-term hospitalization.<sup>[6]</sup>

Evidences indicated that the rate of IE related complications and mortality is still high among patients with CHD in spite of developments in prevention and diagnosis of IE and medical and surgical management of acute IE.<sup>[7,8]</sup>

It seems that in order to prevent and manage IE properly specially in pediatrics patients a comprehensive guideline should be established in each region based on a large cohort of patients.

Considering that there are no regional published data regarding the epidemiologic findings of IE in children and the fact that recent studies have indicated that the characteristics of IE including the organisms causing IE and affected age groups are changing, so in this study we reviewed the epidemiologic and clinical features and treatment and outcome of children diagnosed with IE at Al-Zahra hospital over a 5-year period.

## MATERIALS AND METHODS

In this retrospective study, medical records of patients (<18 years old) admitted from March 2006 to March 2011 in Al-Zahra Hospital (Pediatrics Infectious or Cardiology Departments) were reviewed.

The study was approved by the Medical Ethics Committee of Isfahan University of Medical Sciences.

The medical files were reviewed regarding demographic, clinical, diagnostic (laboratory, microbiological and echocardiographic details) and treatment and outcome details. Obtained data were recorded in a questionnaire. The diagnosis of IE was determined based on Duke criteria. According to Duke criteria a definitive clinical diagnosis is made based on the presence of 2 major criteria, 1 major criterion and 3 minor criteria, or by 5 minor criteria. A possible clinical diagnosis is made based on the presence of 1 major criterion and 1 minor criteria or by 3 minor criteria.<sup>[9]</sup>

Demographic data consist of age, sex, underlying heart disease, past medical history including previous palliative or corrective surgery for cardiac disease, CHD and surgery for complications of IE, predisposing conditions for bacteremia, complications, outcome and treatments.

Clinical data consist of information regarding the sign and symptoms of patients at the time of admission.

Laboratory data consist of complete blood count (leukocytosis), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and microscopic hematuria.

Microbiological data consist of all blood cultures used to evaluate IE obtained by the Microbiology Laboratory of the Al-Zahra Hospital and processed by using Automated Bactec 9240.

Echocardiographic data consist of transthoracic echocardiography (TTE) performed to determine the location of vegetation, type of valve infected and cardiac complications.

Obtained data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

In this study, 24 patients were admitted with the diagnosis of IE from which 17 included for the study and reminder 6 patients were excluded because they did not fulfill the Duke criteria not for definite nor for the possible IE.

The characteristics of patients diagnosed with IE including demographic, clinical, diagnostic (laboratory, microbiological and echocardiographic details) and treatment and outcome details are presented in Tables 1 and 2.

## DISCUSSION

In this study, the epidemiologic and clinical features and outcome of 17 children diagnosed with IE at Al-Zahra hospital over a 5-year period was reviewed. The findings of our study indicated that IE in this studied population resembles the features of developed countries. The most common underlying risk factor in our studied children with IE was CHD.

The most common causes of IE were non-cyanotic heart disease. From cyanotic hearth disease, TOF was the most frequent causes. The results were similar to the reported data of Lertsapcharoen *et al.* in Thailand and some other studies.<sup>[10,11]</sup> As reported by many studies

**Table 1: Demographic and clinical presentations of patients with IE**

Variables	Number (%)
Demographics (years old)	
Age (mean±SD)	6.31±4.73
<2	7 (41.2)
2-6	5 (29.4)
7-12	3 (17.6)
13-18 years old	2 (11.8)
Sex	
Male	9 (53.0)
Female	8 (47)
Underlying heart disease	
VSD	7 (41.2)
AS	4 (23.6)
TOF	2 (11.8)
PA	1 (5.9)
MS	1 (5.9)
Single LV	2 (11.8)
Others	4 (23.6)
Past medical history	
Previous palliative or corrective surgery	12 (70.6)
Surgery for complications of IE	1 (5.9)
Clinical presentation (sign and symptoms)	
Fever	12 (70.6)
Malaise	14 (82.4)
Arthralgia	4 (23.6)
Myalgia	3 (17.6)
Headache	4 (23.6)
Splenomegaly	6 (35.4)
Neurologic findings	10 (58.9)
Cardiac murmur	5 (29.4)
Petechia	4 (23.6)
Metastatic infection	2 (11.8)
Outcome	
Mortality	1 (5.9)

SD: Standard deviation, IE: Infective endocarditis, VSD: Ventricular septal defect, TOF: Tetralogy of fallot, PA: Pulmonary atresia, MS: Mitral stenosis, AS: Aortic stenosis, LV: Left ventricle

by improving the survival of CHD and also treatment of rheumatic heart disease in children the causative factors of IE is changed and the feature of the disease in most but not all of developing countries is also changed to that reported in developed countries.<sup>[12,13]</sup>

In this study, 76.5% of patients had a history of CHD or cardiac surgery. The rate was similar to many studies in pediatrics patients with IE. It indicated that likewise other studies world-wide the most common etiology for IE in pediatrics is CHD.<sup>[1,14]</sup>

In this study, the diagnosis of IE was performed using Duke criteria. Though many studies have confirmed the utility of this criteria in this regard, but others reported the limitation of these criteria in diagnosing IE in patients with negative blood culture.<sup>[15,16]</sup> Some studies evaluated the utility of other minor factors

**Table 2: Laboratory and echocardiographic findings of patients with IE**

Variables	Number (%)
Laboratory	
ESR >20	11 (64.7)
CRP positive	12 (70.6)
RF positive	2 (11.8)
Microscopic hematuria	8 (47)
Leukocytosis	13 (76.5)
Microbiological	
Positive culture	10 (58.8)
<i>Staphylococcus aureus</i>	2 (11.8)
Coagulase-negative staphylococci	4 (23.6)
HACEK organisms	1 (5.8)
<i>E. coli</i>	1 (5.8)
Pseudomonas	1 (5.8)
Fungal	1 (5.8)
Negative culture	7 (41.2)
Echocardiographic	
Vegetation	12 (70.6)
Aortic	4 (34)
Mitral	2 (16.5)
Tricuspid	2 (16.5)
VSD patch	2 (16.5)
RA	2 (16.5)

HACEK: *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* species, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RF: Rheumatoid factor, IE: Infective endocarditis, VSD: Ventricular septal defect, *E. coli*: *Escherichia coli*, RA: Rheumatoid arthritis

that improve the sensitivity of Duke criteria Piere *et al.* have reported that inclusion of some factors as minor criteria such as splenomegaly, petechiae or purpuric rashes, microscopic hematuria and a high CRP value > 100 mg/L would improve the sensitivity of the criteria specially in patients with fever.<sup>[17]</sup>

Though factors such as Leukocytosis, high CRP, high ESR and microscopic hematuria were evaluated in our studied patients with IE, but for considering these factors as minor criteria more studies with larger sample size is needed.

Moreover, it seems that as mentioned by other studies using of echocardiography especially transthoracic ones in the evaluation of children with a clinical suspicious of endocarditis (positive Duke criteria) consider as a sensitive method in diagnosing of IE. In this study, both the mentioned methods have been used similar to Liew *et al.* in Singapore.<sup>[11]</sup>

The utility of Echocardiography and especially TTE in the diagnosis of IE have reported in many studies. The sensitivity of TTE was reported to be 81% in this regard.<sup>[18]</sup> In this study, 70.5% of patients had valvular vegetations.

In this study, 41% of patients with IE aged < 2 years and 70% aged < 6 years. The results are similar to recent studies in pediatrics IE. Pereira *et al.* in Brazil indicated that 50% of their studied cases were newborns and infants.<sup>[17]</sup> Some pediatric cardiology units have reported that the incidence of IE among children under two years is increasing mostly due to increased survival of children with CHD that underwent surgery.<sup>[19,20]</sup>

Another explanation for the higher rate of IE in children aged < 2 years is that development and maturation of the immune system in children less than 2 years old has not completed yet so this group of children are at risk for bacteremia. Before developing any case of endocarditis the presence of bacteremia is necessary. Hence, the occurrence of IE is more common in this age group of children.

Sex distribution in children with IE was not significantly different in our studied population. The finding was in accordance with previous studies.<sup>[2]</sup> Some studies observed male predominance due to the increased risk of CHD in males.<sup>[21-23]</sup>

The most frequent clinical presentations in the studied patients with IE in this study were fever and malaise. The finding was similar to previous reported studies.<sup>[2,17]</sup>

Leukocytosis is noted in less than 50% of patients. In our studied population, 76.5% have leukocytosis.<sup>[2]</sup>

A positive rheumatoid factor is observed in 40-50% of patients with endocarditis of more than 6 weeks' duration.<sup>[2]</sup> In the current study, two cases (11.8%) were positive for rheumatoid factor.

Though CRP is a non-specific variable in the diagnosis of IE, but it properly could be used during treatment and follow-up period for monitoring the outcome of the disease.<sup>[2]</sup> In this study, 70.6% of patients were positive for CRP (most of them 3+).

Evidences indicated that in almost all patients with IE, the ESR is elevated.<sup>[2]</sup> In this review 64.7% of the patients have high ESR (>20).

In a study in Yemen, Khaled *et al.* indicated that high ESR as minor criteria improved the diagnostic possibilities and using empirical antibiotic therapy improves the outcome.<sup>[24]</sup>

Blood cultures were positive in 10 patients (58.8%). Coagulase-negative staphylococci (23.5%) and *Staphylococcus aureus* (11.7%) were the most common organisms that causes IE in studied patients. Several

studies have studied the role of different organisms in IE, accordingly Gram-positive organisms, particularly alpha-hemolytic streptococci (*Streptococcus viridans*), *S. aureus* and coagulase-negative staphylococci, are the most common offenders. *S. aureus* is the most common cause of acute bacterial endocarditis.<sup>[11-13]</sup>

Recent microbiological studies showed that the rate of IE due to infections by *Streptococcus viridians* is decreased and the rate of IE due to staphylococcal infections is increased.<sup>[25]</sup> Our results demonstrated that staphylococcal infections were the most common cause of IE in our pediatrics population with IE. However in contrast to many studies Coagulase-negative staphylococci was more prevalent than *S. aureus*, the most frequent isolated microorganism in children with IE. The results were similar to that reported by Khan *et al.* in Pakistan.<sup>[26]</sup>

Isolation of Coagulase-negative staphylococci may be due to skin contamination, but some studies reported that it is the leading cause of IE in patients with prosthetic valves endocarditis especially in those with fever, CHD, splenomegaly, vegetations and abscesses.<sup>[26,27]</sup> However for obtaining more conclusive results more studies with larger sample size and isolation of patients with normal and prosthetic valves endocarditis is recommended.

The prevalence of culture-negative endocarditis is reported to be 2.5-31% in different studies and it considered as an important clinical entity.<sup>[9]</sup>

Possible factors responsible for this type of IE are previous antibiotic therapy, lack of optimal conventional culture techniques, lack of advanced investigation techniques for rare microorganisms and inappropriate specimen collection specially in pediatrics patients.<sup>[28]</sup> In the current study this rate was 41%. Hence, it seems that the rate is high. It was similar to the results of some studies in both developed and developing countries.<sup>[29-31]</sup> Therefore, others have reported a lower rate of culture-negative endocarditis.<sup>[21,32]</sup>

It may be due to that sufficient blood for blood cultures may not obtained from the pediatric patients. It is recommended to use special procedures or reducing the mentioned limitations in this regard.

The overall mortality rate for endocarditis in pediatric patients is approximately 16-25%. Improved general health-care, improved dental care, early treatment and antibiotic prophylaxis have decreased the mortality rate. Mortality is mostly due to secondary congestive heart failure CHF or to the complications of systemic emboli, which was lower than that reported.

Heart failure with acute, severe aortic insufficiency is associated with high mortality rates.<sup>[2]</sup>

In this study, the mortality rate was 5.8%, which was lower than that reported. It was similar to the results of Johnson *et al.*<sup>[33]</sup>

The limitation of this study was that the complications of IE were not recorded completely so it was not reported in this review. Though, the mortality rate was low, but it seems that mentioned data would be helpful.

## CONCLUSION

In conclusion, IE is a rare infection in children, which occurs mainly in patients with CHD. Alternations reported by many studies world-wide regarding the organisms involved as causative agents and age distribution is demonstrated in our community also. It seems that in order to provide a regional comprehensive guideline for appropriate management and prevention of IE related complications further advanced studies and evaluation with larger sample size is recommended.

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