



## Original Article

## Infectious Endocarditis in Pediatric Patients: Analysis of 19 Cases Presenting at a Medical Center

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**BACKGROUND/PURPOSE:** Infectious endocarditis (IE) is a rare, but potentially fatal disease in pediatric patients. In this study, we reviewed the symptoms and signs, etiology, laboratory findings and outcomes of IE patients over the past 10 years.

**METHODS:** Patients (< 18 years old) with definite IE according to the modified Duke criteria, or patients with positive pathological findings, between September 1998 and September 2008 were included in the study. The etiology, symptoms and signs, laboratory findings and outcomes were collected via chart review.

**RESULTS:** Nineteen cases (13 boys and 6 girls) ranging in age from 2.5 months to 18 years (mean = 7.98 years; median = 5 years) were included. Nine out of 17 cases (52.9%) had microscopic hematuria and two out of three (66.7%) cases showed elevated rheumatoid factor levels. Seventeen (89.5%) had fever and seven (36.8%) had major vessel embolic events. Blood cultures yielded *Staphylococcus aureus* in seven cases, and viridans *Streptococci* in two cases. The other three cases had *Pneumococcus*, *Pseudomonas aeruginosa* and *Candida albicans*. Two patients died and one was discharged in a critical condition. Two of the seven (28.6%) patients with a positive blood culture for *S. aureus* died, three (42.9%) had an embolic event and one (14.3%) had central nervous system complications (intracranial hemorrhage). The initial C-reactive protein levels in the blood culture-positive group were significantly higher than those in the blood culture-negative group ( $p=0.035$ ).

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**CONCLUSION:** *S. aureus* is one of the most common etiologies in IE patients, while viridans *Streptococcus* accounts for fewer cases than suggested by previous studies. IE caused by *S. aureus* seems to carry a higher risk of mortality, and embolic events are associated with increased mortality.

**KEYWORDS:** child, echocardiogram, etiology, infectious endocarditis, laboratory findings

## Introduction

Infectious endocarditis (IE) is a rare, but potentially fatal disease in pediatric patients. Most patients have underlying hemodynamic problems that predispose them to the risks of IE. Modified Duke criteria are commonly used for clinical diagnosis of IE.<sup>1</sup> Though *Streptococcus viridans* and *Staphylococcus aureus* are the main pathogens of the disease, other pathogens have also been isolated.<sup>2-4</sup> In this study we reviewed the symptoms and signs, etiologies, laboratory findings and outcomes of pediatric IE patients over the past 10 years and the initial white blood cell counts (WBC) and C-reactive protein (CRP) levels were recorded.

## Methods

Patients less than 18 years of age who fulfilled the criteria of definite IE according to the modified Duke criteria, or cases with positive pathological findings, from September 1998 to September 2008 were retrospectively included in the chart review study. Echocardiography findings were confirmed by experienced cardiologists (>10 years' experience), except for one case in which the sternum was left unapproximated. Data regarding etiology, general patient characteristics and underlying diseases, symptoms and signs, sites of vegetation, laboratory findings and outcomes were collected. The WBC counts and CRP levels (taken at first presentation at the hospital) of culture-positive and culture-negative patients and between *S. aureus* and non-*S. aureus* groups were compared using the Mann-Whitney *U* test and SPSS version 14.0 (SPSS, Chicago, IL, USA). Risk factors for mortality (e.g. neurological complications, gender, embolic events and IE pathogens) and embolic events (*S. aureus* infections) were investigated for statistical significance using Fisher's exact test. A *p* value <0.05 was considered statistically significant.

## Results

### General characteristics

In all, 19 cases (13 boys and 6 girls) were included in the study. All cases fulfilled the criteria of definite endocarditis according to the modified Duke criteria, or were pathologically confirmed. The age of the patients ranged from 2.5 months to 18 years (mean=7.98 years, median=5 years). The age and gender distributions are shown in Figure 1. Five cases (26.3%) were immunocompromised and without a previous history of heart disease. Of the 14 cases with congenital heart disease, 11 cases (78.6%) had undergone previous cardiac surgery and all had residual heart abnormalities with a turbulent flow. Of the 11 cases with congenital heart disease post-surgery, the time between the last operation and the onset of endocarditis ranged from 1 month to 12 years (mean=39.5 months; median=12 months) (Table 1). The most common sites of vegetation were the tricuspid valve (7 cases), the right ventricle (6 cases) and the mitral valve (4 cases). There was no obvious trend in the number of cases per year over the past 10 years (Figure 2) or seasonal changes (Figure 3).

### Findings on presentation

The major presenting symptoms and signs are summarized in Table 2. Seventeen patients (89.5%) had fever and

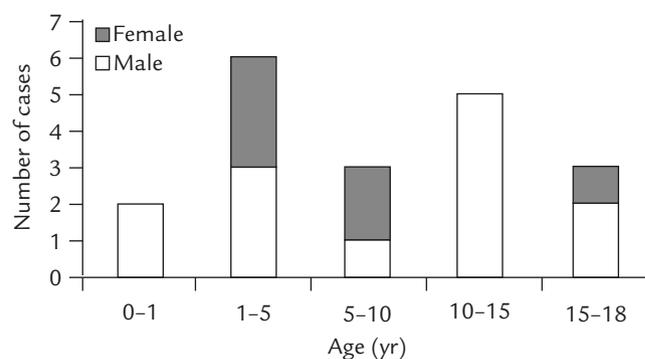
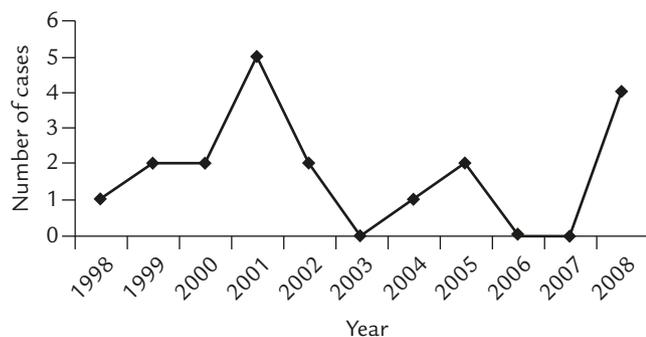


Figure 1. Age distribution of 19 patients with infectious endocarditis.

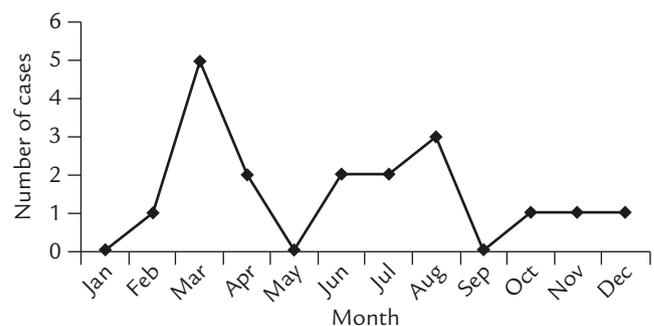
**Table 1.** The sites of vegetations, C-reactive protein levels at diagnosis of infectious endocarditis and blood culture results and duration between onset of infectious endocarditis and last operations

Case	Site of vegetations	Duration between IE and operation	Blood culture results	CRP at diagnosis of IE (mg/dL)
1	Poor visualization	9 mo	MRSA	9.81
2	RV, TV	7 yr	MSSA	24.91
3	TV	5 yr & 4 mo	<i>Viridan Streptococci</i>	2.58
4	PV	5 yr	-	5.27
5	MV	2 mo	-	0.06
6	LV, AV	1 mo	MRSA	21.29
7	-	1 mo	<i>Pseudomonas aeruginosa</i>	1.05
8	RV	11 yr	-	1.66
9	RV, RA	9 mo	-	0.58
10	RV, TV	5 yr	-	9.59
11	TV	1 yr	<i>Pneumococcus</i>	2.40
12	RV, AO, MV	-	MRSA	17.30
13	TV	-	MSSA	20.70
14	RV, VSD	-	<i>Viridan Streptococci</i>	0.30
15	RA	-	<i>Candida Albican</i>	18.20
16	TV	-	MSSA	1.60
17	MV, TV	-	MRSA	2.60
18	AV	-	-	0.01
19	MV	-	-	0.90

CRP=C-reactive protein; RV=right ventricle; LV=left ventricle; PV=pulmonary valve; AV=aortic valve; MV=mitral valve; TV=tricuspid valve; AO=aorta; RA=right atrium; VSD=ventricular septum defect; IE=infectious endocarditis; MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-sensitive *Staphylococcus aureus*.

**Figure 2.** The number of cases of infectious endocarditis (1998–2008).

17 (94.4%) had documented vegetations via echocardiogram (2 patients did not have an echocardiogram and were diagnosed with definite IE on the basis of culture results and 3 additional minor criteria). Fever and vegetations were the most common initial presentations. Of the 17 cases who had routine urine tests, nine (52.9%) had evidence of microscopic hematuria. Seven patients (36.8%) had major vessel embolic events (1 intracranial

**Figure 3.** The number of cases of infectious endocarditis each month (1998–2008).

hemorrhagic infarct, 1 brain abscess, 1 cerebral embolism, 1 ischemic bowel, and 3 pulmonary embolisms above the intermediate level). Three patients were tested for Rheumatic factor and two (66.7%) of them had elevated levels. Four patients (21.1%) had Janeway's lesions and one (5.3%) had ruptured chordae tendineae. Of the 16 cases who had a chest X ray, three (18.8%) had marked cardiomegaly. When the initial CRP levels in blood culture-positive and

**Table 2.** Presenting findings in 19 patients with infectious endocarditis<sup>a</sup>

Presenting findings	n (%)
TTE prove	17/18 (94.4)
Fever	17/19 (89.5)
Microscopic hematuria	9/17 (52.9)
Janeway's lesion	4/19 (21.1)
Pulmonary embolism	3/16 (18.8)
New cardiomegaly on plain films	3/19 (15.8)
Elevated RF levels	2/3 (66.7)
Acute renal failure	2/19 (10.5)
Shortness of breath	2/19 (10.5)
Brain infarct	1/19 (5.3)
Intracranial hemorrhage	1/19 (5.3)
Brain abscess	1/19 (5.3)
Bowel infarct	1/19 (5.3)
Rupture of cordae tendinae	1/19 (5.3)
Hepatitis	1/19 (5.3)
Syncope	1/19 (5.3)

<sup>a</sup>Data presented as number of positive cases/total number of cases studied (%). TTE=transthoracic echocardiogram; RF=rheumatoid factor.

blood culture-negative groups were compared, the blood culture-positive group (CRP=10.27±9.58 mg/dL) had significantly higher initial CRP levels than the culture-negative group (CRP=2.58±3.58;  $p=0.035$ ) (Table 1). However, there were no significant differences in the initial CRP levels and WBC counts between the *S. aureus* and non-*S. aureus* groups.

### Underlying conditions

All cases had either underlying heart disease or were immunocompromised. Postoperative congenital heart disease was the most common underlying condition (11/19; 57.9%). Five patients (26.3%) were immunocompromised (1 brain sarcoma with neutropenic fever, 2 osteomyelitis, 1 neonatal pneumonia and 1 toxic megacolon under total parenteral nutrition with a central venous line infection). Three patients had congenital heart disease without surgery (1 had a ventricular septal defect, 1 had severe mitral regurgitation with mitral valve prolapse, 1 patient with dental caries had transposition of the great arteries, with a single ventricle and atrium). Three patients had documented central line infections (1 brain sarcoma with

**Table 3.** Underlying conditions in 19 patients with infectious endocarditis

Case	Diagnosis before infectious endocarditis
1	TGA post total correction
2	DORV post correction
3	TGA post Rastelli procedure
4	TGA post Mustard procedure, caries
5	MR post annuloplasty
6	TGA post total correction
7	DORV post correction, central line infection
8	TGA post PAB, BAS+large VSD
9	TOF post total correction
10	TOF post total correction, caries
11	TGA post total correction
12	Brain sarcoma, neutropenic fever, central line infection
13	Osteomyelitis, cerebral palsy
14	VSD
15	Toxic megacolon with central line infection
16	Osteomyelitis, motorcycle accident
17	Neonatal pneumonia
18	TGA with single ventricle and atrium, caries
19	MR

PAB=pulmonary artery banding; BAS=balloon atrial septectomy; VSD=ventricular septal defect; TGA=transposition of great arteries; TOF=Tetralogy of Fallot; DORV=double outlet of right ventricle; MR=mitral regurgitation.

neutropenic fever, 1 toxic megacolon and 1 ventricular septal defect) and three had dental caries (1 Tetralogy of Fallot post-total correction, 1 transposition of the great arteries post-mustard operation and 1 single ventricle) (Table 3).

### Microbiological findings

Of the 19 cases that fulfilled the criteria of definite endocarditis according to the modified Duke criteria, 12 had positive blood culture results. Seven patients (36.8%) had *S. aureus* (4 methicillin-resistant *S. aureus* and 3 methicillin-sensitive *S. aureus*), two (10.5%) had viridans *Streptococci*, one (5.3%) had *Pneumococcus*, one (5.3%) had *Pseudomonas aeruginosa*, and one (5.3%) had *Candida albicans* (Table 4). The culture-negative patients were diagnosed with definite IE by echocardiogram and three additional minor criteria, except one patient in whom IE was diagnosed pathologically. Three out of seven culture-negative patients lived in rural areas, but no history of animal contact was documented and four of the seven culture-negative patients were referred

**Table 4.** Microbiology findings in 19 patients with infectious endocarditis

Microbiology findings	n (%)
Methicillin-resistant <i>Staphylococcus aureus</i>	4 (21.1)
Methicillin-sensitive <i>Staphylococcus aureus</i>	3 (15.8)
<i>Viridan streptococci</i>	2 (10.5)
<i>Pneumococcus</i>	1 (5.3)
<i>Pseudomonas aeruginosa</i>	1 (5.3)
<i>Candida albican</i>	1 (5.3)
Unknown	7 (36.8)

from other hospitals. Five immunocompromised patients all had positive blood cultures (2 methicillin-resistant *S. aureus*, 2 methicillin-sensitive *S. aureus* and 1 *Candida albicans*).

#### Patient outcomes

Two patients died and one was discharged in a critical condition, accounting for 15.8% of all cases included in the study. Two of the deceased patients (66.7%) were infected with *S. aureus* (1 methicillin-resistant and 1 methicillin-sensitive) and one had negative blood culture results. All had either a pulmonary embolism, intracranial hemorrhage or a brain abscess. IE caused by *S. aureus* was not a statistically significant risk factor for mortality ( $p=0.47$ ; Fisher's exact test). The three deceased patients were male, although male gender was not a statistically significant risk factor for mortality ( $p=0.517$ ; Fisher's exact test), and two had neurological complications, although neurological complications were not a statistically significant risk factor for mortality ( $p=0.051$ ; Fisher's exact test). One of the patients died of sepsis and multiple organ failure, and another died of sepsis and brain herniation. Three out of seven cases with *S. aureus* infection had embolic events, but *S. aureus* infection was not a statistically significant risk factor for embolic events ( $p=0.205$ ; Fisher's exact test). The embolic event rate was higher in the mortality group (100% vs. 25%;  $p=0.036$ , Fisher's exact test). One of the pulmonary embolisms was treated with antibiotics plus Coumadin and the result was favorable. The other two cases of pulmonary embolism were treated with antibiotics only and one death occurred. Three patients with IE underwent surgery with no mortality. None of the surviving patients has had a recurrence of definite IE to date.

## Discussion

The precise incidence of IE in pediatric patients is difficult to ascertain because case definitions have varied from decade to decade, between different authors, and between different medical centers.<sup>5</sup> In one report, 50–70% of children less than 2 years old had no obvious underlying cardiac disease.<sup>6</sup> However, two studies show that approximately 3/4 of patients with IE had a pre-existing structural cardiac abnormality, and another earlier study showed that rheumatic heart diseases accounted for 39% of heart abnormalities in IE.<sup>7–9</sup> In our study, 73.7% (14/17) of patients had a heart structural abnormality, but none had rheumatic heart disease or a previous history of IE. This is in contrast to other studies that show recurrence of endocarditis accounting for 2.5–9.0% of IE cases.<sup>10,11</sup> The reason that rheumatic heart disease was seen less frequently in our study of pediatric IE may be largely due to the use of penicillin for primary prevention and improved living conditions, which have resulted in less overcrowding and better hygiene, and consequent reductions in transmission of group A *Streptococci*.<sup>12</sup> Changes in the virulence of circulating group A *Streptococci* (i.e. a decrease in the prevalence of highly rheumatogenic *emm*-type group A *Streptococci*) have also accounted for much of the decline in the incidence of rheumatic fever, and approximately 95% of the reduction in the rate of death due to rheumatic fever during the 20<sup>th</sup> century in the United States occurred before 1960, probably because of reduced group A streptococcal transmission resulting from an improved housing infrastructure.<sup>13</sup> In Taiwan, the prevalence of rheumatic heart disease among school children was the highest in 1970 (1.42%) and in 1971 (1.26%), falling back to 0.39% in 1987. The prevalence suddenly rose to 0.7% in 1988, indicating a resurgence of rheumatic fever, followed by a steady decrease until 1997.<sup>14</sup> The fact that none of our patients had a recurrence of IE might reflect the fact that they are just too young or that this study was conducted with small patient numbers and the follow-ups were not long enough.

The International Collaboration on Endocarditis-Pro prospective Cohort Study identified the microbiological etiology in 1,779 patients from 39 medical centers in 16 countries with definite endocarditis according to the Duke criteria.<sup>15</sup> Overall, *Staphylococci* were the causal agent

in 744/1,779 (41.8%) of cases and *Streptococci* in 712 (40.0%). Eight percent of cases were culture-negative endocarditis and 1% were polymicrobial. However, a study conducted in Taiwan<sup>16</sup> showed that *S. aureus* (32%) and streptococcal species (61%) were the most common causative pathogens. Also, male gender, heart failure, neurologic complications, renal insufficiency, respiratory failure, shock and *Staphylococcus* spp. as the causative microorganism, were all independent predictors of in-hospital mortality. Neurological complications was also found to be associated with higher mortality in other studies conducted in Taiwan.<sup>17,18</sup> In our study, *Staphylococci* account for 36.8% and *Streptococci* for only 10% cases of endocarditis. Only embolic events were associated with higher mortality. In our study, four out of nine referred cases had culture-negative IE compared with three of 10 non-referred cases. However, this was not statically significant ( $p=0.65$ ); 36.8% were culture-negative IE, which is much higher than that reported in another study in Taiwan,<sup>19</sup> which may reflect the overuse of antibiotics in pediatric patients and an insufficient number of blood samples collected.

The proportion of IE cases without an etiologic diagnosis varies from country to country and between different centers in the same country. These variations reflect the local epidemiology of IE, the diagnostic criteria used, initiation of antibiotics in patients prior to obtaining blood cultures, and the diagnostic protocol used to establish an etiolog.<sup>20</sup> The incidence of culture-negative IE is higher in developing countries and tends to occur more often with prosthetic valves,<sup>21-29</sup> and mortality rates are similar between the culture-negative and culture-positive groups.<sup>29</sup> Cultures remain negative in 2-7% of patients with IE, even when the utmost care is taken to obtain the proper number and volume of blood cultures and patients with prior antibiotic treatment are excluded; the frequency of culture-negative IE is higher in patients who have already been treated with antibiotics.<sup>30</sup> Cultures can be negative in endocarditis patients for three major reasons: (1) previous administration of antimicrobial agents; (2) inadequate microbiological techniques; or (3) infection with highly fastidious bacteria or nonbacterial pathogens (e.g. fungi). The higher frequency of culture-negative IE seen in developing countries reflects the increased incidence of fastidious zoonotic agents (e.g. *Bartonella* spp., *Coxiella burnetii*, or *Brucella* spp.) that cause human

infections,<sup>23</sup> differences in microbiologic culture techniques, and the overuse of antibiotics without prescription in some countries.

The HACEK organisms (*Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) were thought to be the most common agents involved in culture-negative endocarditis. However, studies have found that the HACEK organisms can be isolated using current blood culture systems when incubated for at least 5 days.<sup>31,32</sup> The mean and median durations of detection of HACEK pathogens from blood cultures were found to be 3.4 and 3 days, respectively.<sup>33</sup> The most common causative agents of blood culture-negative IE are fastidious organisms (e.g. zoonotic agents and fungi) and streptococcal spp. in patients who have received previous antibiotic treatment. Perhaps studies should be conducted that include serological tests for *Coxiella burnetii*, *Bartonella* spp., *Chlamydomphila* spp., *Leionella* spp., and *Aspergillus* spp., using blood culture on shell vials and direct PCR amplification and lysis centrifugation<sup>33-35</sup> in cases of culture-negative IE to increase etiology yields. Another reason for the larger portion of culture-negative IE found in our study (36.8%), apart from antibiotic overuse, might be that an insufficient blood volume was collected. In one study, blood cultures inoculated with at least 5 mL of blood had a significantly higher detection rate for bacteremia than bottles inoculated with less than 5 mL of blood (92% vs. 69%).<sup>36</sup> A minimum of 0.5-5 mL of blood should be obtained from infants and children.<sup>37</sup>

In an analysis of native valve IE, 34% of patients had IE caused by *S. aureus*,<sup>38</sup> while in our study *S. aureus* accounted for 36.8%. Compared with patients with IE due to other organisms in a previous study,<sup>38</sup> patients with *S. aureus* IE were significantly more likely to die (20% vs. 12%), experience an embolic event (60% vs. 31%), or have a CNS event (20% vs. 13%). In our study, 28.6% of cases (2/7) with positive culture for *S. aureus* died, 42.9% (3/7) had an embolic event, and 14.2% (1/7) had a CNS complication (intracranial hemorrhage), whereas no deaths, embolic events, or CNS complications occurred in the culture-positive group that were caused by pathogens other than *S. aureus*. The risk of embolization tends to decline after the institution of effective antimicrobial therapy, and serious embolic events rarely occur in the several weeks after

such therapy is instituted.<sup>39-41</sup> In patients receiving appropriate antibiotic therapy, the incidence of stroke was 4.8/1,000 patient days in the first week of therapy, falling to 1.7/1,000 patient days in the second week, and continuing to fall with continued therapy.<sup>41</sup>

In conclusion, IE carries a risk of mortality of 15.8% and IE caused by *S. aureus* accounted for 67% of deaths in our study. IE caused by *S. aureus* may also carry a higher risk of embolic events. Embolic events were associated with higher mortality. The decreased frequency of IE caused by viridans *Streptococci* (only 10.5%) may reflect the overuse of antibiotics and an insufficient number of blood samples. Proper blood culture collection (enough blood samples) and judicious use of antibiotics may increase the yield of culture results. When culture-negative IE is encountered, blood culture on shell vials, direct PCR amplification, lysis centrifugation and serology tests may be considered to confirm an etiology.

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