

Original article

Childhood infective endocarditis in Khon Kaen University Hospital from 1992 to 2011

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Background: Infective endocarditis (IE) is an important cause of child morbidity and mortality, but the current burden of the disease in Thai children is unknown.

Objectives: To determine the current burden of IE in Thai children.

Patients and Methods: The records of all children aged <15 years admitted to Khon Kaen University Hospital from 1992 to 2011 were reviewed.

Results: Of 69,822 admissions, 56 patients fulfilled the modified Duke criteria for definite IE giving a rate of 0.8 cases per 1,000 admissions. Age at diagnosis was 7.9 ± 3.8 years (range, 8 days to 14.8 years). There was congenital heart disease in 38 (68%) patients, rheumatic heart disease (RHD) in 10 (18%), and no previous heart disease in 8 (14%). RHD was a less frequent underlying disease during the latter half (2002-2011) of the period studied (1/34 vs. 9/22, $P < 0.001$). Blood cultures were positive for pathogens in 34 (61%) patients with 11 cases of *Streptococcus viridians* and 8 cases of *Staphylococcus aureus* infections. Vegetations on echocardiography were present in 46 (82%) patients. For 8 embolic events, patients with large vegetations had a higher rate (4/6) than patients with small and no vegetations (4/50) ($P < 0.003$). In-hospital mortality was 11%. Eight patients with *S. aureus* infection had a higher mortality (5/8) than 26 patients (1/26) infected with other pathogens ($P < 0.001$).

Conclusion: The changing epidemiology of pediatric IE was toward fewer children with RHD. Mortality among children with IE was higher in those with *S. aureus* infection.

Keywords: Childhood, congenital heart disease, epidemiology, infective endocarditis, rheumatic heart disease, *Staphylococcus aureus*, *Streptococcus viridans*

Infective endocarditis (IE) is an infection of the endocardium that usually affects the heart valves [1]. It is a significant cause of morbidity and mortality in children and adolescents despite advances in the management and prophylaxis of the disease with antimicrobial agents [2-5]. Although IE is relatively uncommon in children compared with adults, accounting for 0.5–0.8 cases per 1,000 pediatric admissions [1-5], the incidence of pediatric IE is believed to be increasing [1]. This is due in part to improved survival among children who are at risk for IE, such as those with congenital heart disease (CHD) and hospitalized newborn infants [1-4]. Moreover,

increasing use of synthetic materials in children with heart diseases and frequent use of indwelling central venous catheters for the care of critically ill infants and children are supposed to increase the risk for development of IE [1-5].

Recent advances in echocardiography and microbiological techniques have enhanced the ability for early diagnosis and the proper management of IE [1]. Moreover, newer diagnostic guidelines, availability of newer antibiotics and advances in cardiovascular surgery have resulted in better survival outcomes of IE in developed countries [2-6].

However, reports regarding IE in children from developing countries [7], including Thailand are scarce [8-9]. The current burden of the disease in Thai children is unknown. The purpose of this study was to assess the epidemiology, clinical features,

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complications and mortality of IE in children admitted to Khon Kaen University (KKU) hospital in northeastern Thailand during the 20 years from 1992 to 2011.

Materials and methods

Setting

Thailand has a land area of 513,115 km² and is divided into 4 regions; central, northern, northeastern and southern regions. The population of the northeastern Thailand was approximately 20.9 million in 2002. KKU hospital, having approximately 1,100 beds, is located in the central area of Khon Kaen province in northeastern Thailand and is a teaching and tertiary referral center in this region [10, 11]. According to the 2002 census, the population of Khon Kaen province was approximately 1.7 million.

Diagnostic criteria

A diagnosis of definite IE was based on modified Duke criteria [12]. RHD was clinically diagnosed in children who had either mitral regurgitation or aortic regurgitation, or both. CHD was defined as a defect in the structure of the heart or great vessels that was present at birth.

Recurrence of IE was diagnosed if a second episode of IE occurred after treatment of an initial episode of IE. Recurrences included relapses and reinfections. Relapse was a repeat episode of IE caused by the same microorganism as the previous episode. Reinfection was an infection with a different microorganism [13].

Streptococci were defined as susceptible to penicillin if the minimum inhibitory concentration (MIC) was $<0.1 \mu\text{g/ml}$ and methicillin-resistant strains of staphylococci were identified as having an MIC to oxacillin of $>4 \mu\text{g/ml}$.

Stroke was defined as an acute neurological deficit of vascular etiology lasting more than 24 hours.

Study procedures

After this study was approved by the Human Research Ethics Committee, Khon Kaen University (approval number HE531036), we searched the hospital database using International Classification of Diseases 10th revision (ICD-10) for any patient younger than 15 years old diagnosed with IE from January 1, 1992 to December 31, 2011. In addition, the echocardiography record book in the Echocardiographic Laboratory of the hospital was checked for cases of IE. We reviewed all potential

cases to confirm that they met the modified Duke criteria for the diagnosis of definite IE [12]. The hospital records of all patients admitted with a diagnosis of definite IE were reviewed by two of the authors (WS and MP). In KKU hospital, infectious disease consultation is routinely performed for all patients diagnosed as having IE.

A data collection form was used to record clinical information, which was anonymized. Extracted variables included age, sex, previous dental procedures, cardiac lesions, prior cardiac surgery, history of rheumatic fever or rheumatic heart disease, central venous catheter use, clinical manifestations, blood culture results, echocardiographic findings, medical and surgical treatments, complications, outcomes and pathology reports. When available, all diagnostic studies were reviewed by the authors to confirm outcomes.

Statistical Analysis

Statistically significant differences were estimated using a chi-square test or Fisher's exact test and $P < 0.05$ was considered as significant.

Results

Epidemiology

Patient population

During the 20-year study period, there were 69,822 pediatric admissions and 56 patients met the modified Duke criteria for the diagnosis of definite IE. The cumulative rate of IE was 0.80 cases per 1,000 pediatric admissions. Distribution of cases by periods was as following: 22 cases per 28,277 admissions in 1992–2001, and 34 cases per 41,545 admissions in 2002–2011. No significant ($P = 0.853$) increasing incidence of IE patients was seen during the latter years of the study. According to the Thai Bureau of Census, there was an average of 426,700 children less than 15 years old living in Khon Kaen province in the study period, 1992 to 2011. KKU hospital was the only referral center for this disease in the study area and 20 of the 56 patients were the residents of Khon Kaen province. The average annual incidence rate of IE in Khon Kaen province was, therefore, 0.23 cases per year per 100,000 children below 15 years of age.

Of the 56 patients, 33 (59%) were boys and 23 (41%) were girls and the male-to-female ratio was therefore 1.4:1 ($P = 0.181$). The mean age at diagnosis was 7.9 ± 3.8 years with a range of 8 days to 14.8 years. Fifteen patients (27%) were under 5 years old and 2 (4%) of them were neonates (**Figure 1**).

Underlying heart disease

The most common underlying heart disease was CHD, which was found in 38 (68%) patients. RHD was the second common underlying heart disease, which was seen in 10 patients (18%). Eight patients (14%) had no underlying heart disease (**Figure 1** and **Table 1**). Among CHD, ventricular septal defect (VSD) and tetralogy of Fallot (TOF) were the most common underlying CHD in noncyanotic and cyanotic groups, respectively. Of the 10 patients with RHD, 6 (60%) patients had mitral regurgitation, and 4 (40%) patients had mitral and aortic regurgitation. Among 10 patients with RHD, 9 cases were found in the first half (1992–2001) of this study, and the only 1 case was found in the latter half (2002–2011) (**Figure 2**). Among 48 patients with underlying heart disease, 11 had received cardiac surgery (10 cases were

congenital heart surgery) before IE was diagnosed. Types of prior cardiac surgery were corrective surgery (7 patients), palliative shunt surgery (3 patients), and mitral valve repair for severe rheumatic mitral regurgitation (1 patient). Among the 10 patients with underlying CHD having postoperative IE, 4 were found in the first half (1992–2001) of this study, and 6 were found in the latter half (2002–2011). The median duration from the date of surgery to the time of diagnosis of IE was 14 days (range, 6 to 30 days). One patient with VSD had a history of one episode of IE before this admission. Among 8 patients with no previous heart disease, one patient was found to be human immunodeficiency virus-positive and one newborn patient had a central venous catheter inserted before the diagnosis of IE (**Table 1**).

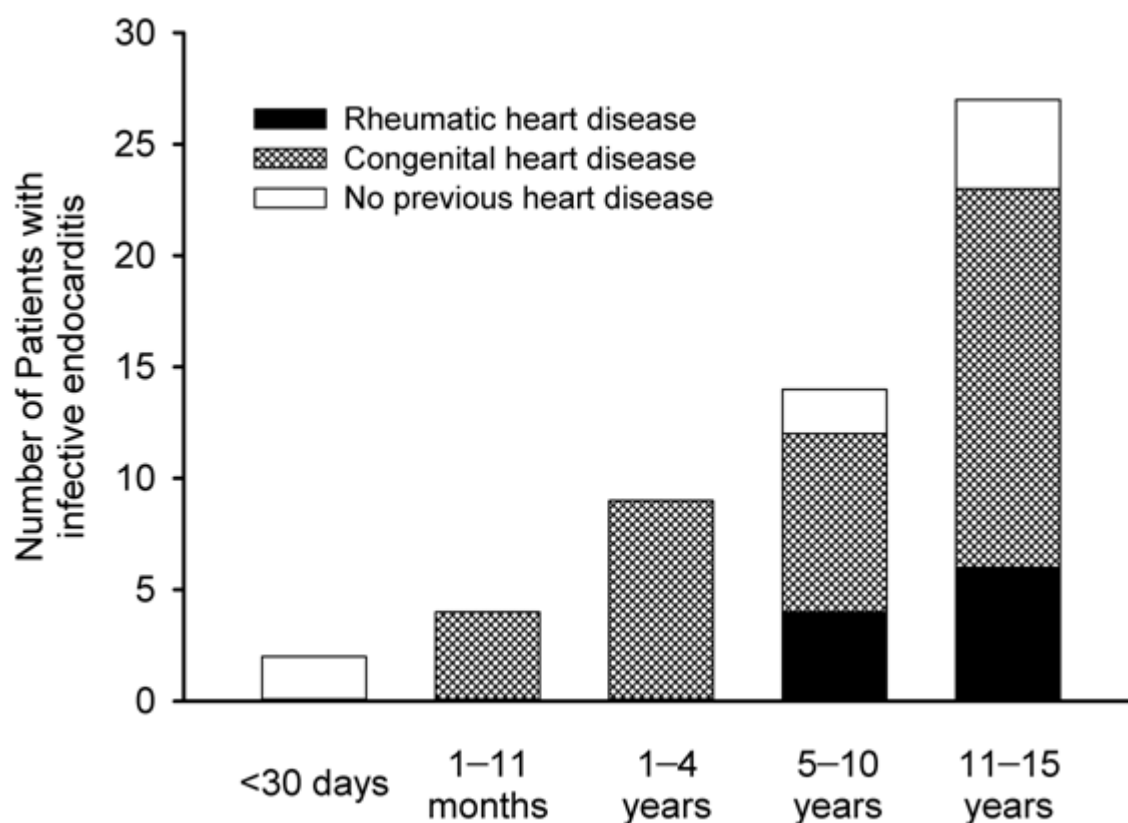


Figure 1. Age distribution and underlying heart diseases of children admitted with infective endocarditis in the Khon Kaen University hospital between 1992 and 2011

Table 1. Underlying heart diseases in 56 patients with infective endocarditis

Heart diseases	Number of patients (%)
1. Congenital heart disease (CHD)	38 (67.9%)
Noncyanotic CHD (24 patients)	
VSD	6
VSD + AR	2
VSD + PS	2
VSD + ruptured sinus of Valsalva	1
VSD + ASD secundum	2
ASD primum + MV cleft	1
AS	3
AS + AR	1
AR	1
MR	1
PDA	3
Cor triatriatum + PDA	1
Cyanotic CHD (14 patients)	
TOF	5
Single ventricle + PS	1
Tricuspid atresia + PA	2
TGA + ASD	1
TGA + VSD	1
Truncus arteriosus	1
TOF + PA	1
PA + PDA	2
2. Rheumatic heart disease	10 (17.8%)
3. No previous heart disease	8 (14.3%)

CHD = congenital heart disease, VSD = ventricular septal defect, AR = aortic regurgitation, PS = pulmonic stenosis, ASD = atrial septal defect, MV = mitral valve, AS = aortic stenosis, MR = mitral regurgitation, PDA = patent ductus arteriosus, TOF = tetralogy of Fallot, TGA = transposition of great arteries, PA = pulmonary atresia, DORV = double outlet right ventricle

Figure 2. Proportion of underlying heart diseases associated with childhood infective endocarditis (IE) in Khon Kaen University hospital from 1992 to 2011. Note that proportion of IE patients with underlying rheumatic heart disease was lower ($P < 0.001$) in the latter half (1/34 in 2002–2011) than in the first half (9/22 in 1992–2001) of this study.

Clinical features

Presentation

The common symptoms were fever in 55 (98%) patients, heart murmur in 49 (88%), tachycardia in 36 (64%), and tachypnea in 31 (55%) patients. These were followed by hepatomegaly (36%), cyanosis in patients with cyanotic CHD (25%), pallor (14%), hemiparesis or hemiplegia (13%), clubbing of fingers (11%), lung crepitation (9%), splenomegaly (9%), edema (5%), subconjunctival hemorrhage (5%), Osler nodes (5%), Janeway lesions (5%), orthopnea (4%), petechiae (4%), Roth spots (2%), and pleural rub (2%). Only one newborn patient, 8 days old, was diagnosed as having IE without fever. The duration from the onset of fever to the time of diagnosis of IE was 10 ± 3.8 days (range, 1–62 days) and was less than 14 days in 48 (86%) patients. The cardiac examination findings in children with IE mainly depended on the type of underlying heart diseases and also on the site of infection. In 3 children with cyanotic CHD who had undergone systemic-pulmonary artery shunt procedures, the type and the intensity of heart murmur remained unchanged after the occurrence of IE. In 7 of 8 patients who had no previous heart diseases, IE caused leaflet destruction resulted in regurgitant heart murmurs.

Pathogens

Twenty (36%) patients received antibiotic treatment before their IE admission. Blood cultures were performed for all patients on admission and were positive for pathogens in 34 (61%) patients. *Streptococcus viridans* was the most common pathogen found in 11 of 34 patients (32%). *Staphylococcus aureus* was found in 8 patients (24%) and was the only pathogen found in patients with no previous heart disease (Table 2 and Figure 3).

Echocardiography

Transthoracic echocardiography was performed for all patients, and vegetations were found in 46 (82%). Twenty-three (50%) patients had vegetation in the left heart, and 17 (37%) patients had vegetation in the right heart. Six (13%) patients had vegetations in both sides of the heart. A single vegetation was found in 31 (67%) patients and multiple vegetations were demonstrated in 15 (33%) patients. The sizes of vegetation varied from 2 to 14 mm in diameter. Six patients had large vegetations (>10 mm in diameter) and 40 patients had small vegetations (2–10 mm in diameter). Ten patients had no vegetation.

Table 2. Pathogens isolated from blood cultures in 34 patients and their relationship to the underlying heart diseases

Organisms	Underlying heart diseases			Total
	CHD (n = 38)	RHD (n = 10)	None (n = 8)	
<i>Streptococcus viridans</i>	8	3	0	11
Group D streptococci	3	0	0	3
Non-hemolytic streptococci	1	1	0	2
<i>Streptococcus pneumoniae</i>	2	0	0	2
<i>Staphylococcus aureus</i>	2	1	5	8
<i>Staphylococcus epidermidis</i>	3	0	0	3
<i>Haemophilus influenzae</i>	2	1	0	3
<i>Haemophilus parainfluenzae</i> *	1	0	0	1
<i>Candida albicans</i>	1	0	0	1
Total	23	6	5	34

CHD = congenital heart disease, RHD = rheumatic heart disease, None = no underlying heart disease, *HACEK (*Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Haemophilus paraphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*) organisms.

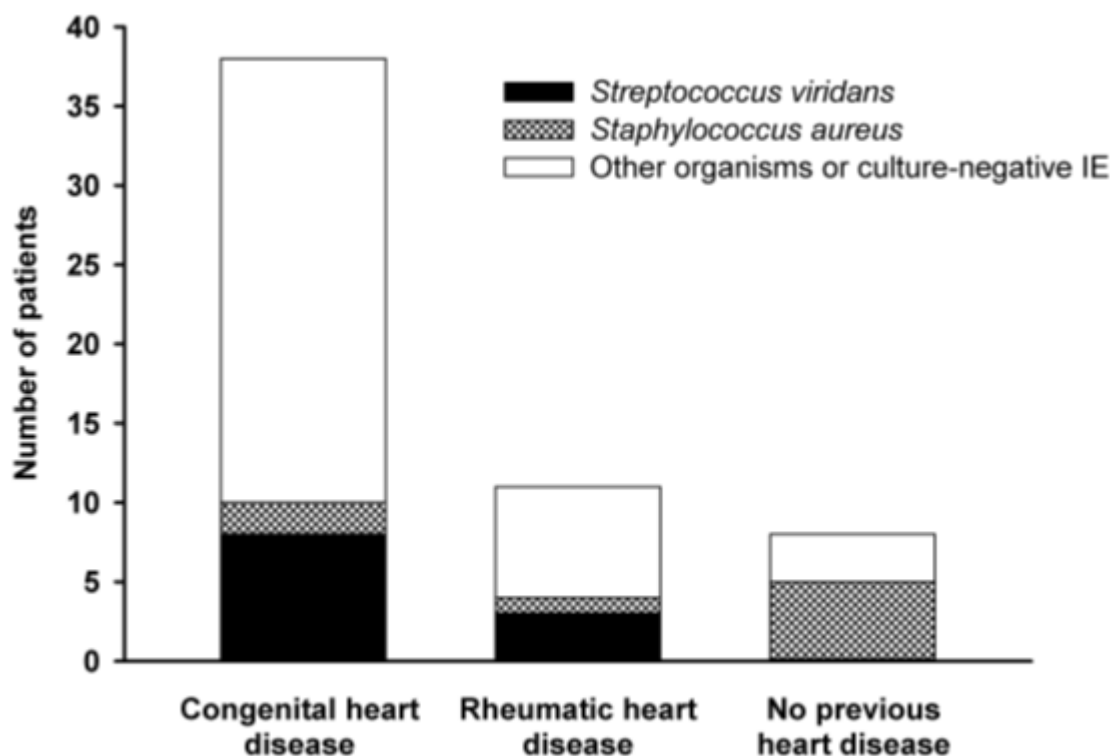


Figure 3. Relationship between underlying heart diseases and the causative pathogens for infective endocarditis (IE) in children admitted in Khon Kaen University hospital from 1992 to 2011.

Antibiotics

Intravenous antibiotics were administered to all patients and the course of treatment was 4–8 weeks. The types and durations of antibiotic treatments were selected according to the pathogens found, clinical presentations and complications of the patients. The most common antibiotics used were penicillin G sodium combined with aminoglycoside (32%). This was followed by cloxacillin plus aminoglycoside (18%), third generation cephalosporin (12%), penicillin G sodium (8%), cloxacillin (6%), ampicillin (4%), ampicillin plus aminoglycoside (4%), ampicillin plus third generation cephalosporin (4%), vancomycin plus aminoglycoside (4%), cloxacillin plus third generation cephalosporin (2%), vancomycin (2%), vancomycin plus third generation cephalosporin (2%), and amphotericin B (2%).

Surgical treatments

Of these 56 patients, 6 (10.7%) underwent surgery as a part of the treatment regimen for IE. The most common indication for surgery was severe valvular insufficiency and congestive heart failure (4 patients). Of these 4 patients, one patient also had evidence of concomitant left ventricular dysfunction. Septic

embolization was the surgical indication in 2 patients. The types of surgical treatments were vegetation removal in 4 cases, mitral valve repair in 1 case and aortic valve replacement in 1 patient. *S. aureus* was the most common pathogen found in 3 (50%) of the 6 patients who had surgical treatments. There was no surgical mortality.

Outcomes

Complications

The median duration of hospitalization was 38 days (range, 8 to 97 days). Thirty nine (70%) of 56 patients had complications. Cardiovascular complications were the leading cause of complications in this study. Congestive heart failure was the most common complication occurring in 15 patients. Central nervous system complications included brain abscess and stroke (Table 3). Eight embolic events were found in 8 patients. Of the occurring 8 embolic events, 6 patients with large vegetations (>10 mm in diameter) had a higher rate of embolic events (4/6) than the rate of the 50 patients with small (2–10 mm in diameter), and no vegetations (4/50) (4/6 vs. 4/50, $P < 0.003$).

Table 3. Complications seen in the childhood infective endocarditis patients

Complications	Number of patients
Cardiovascular complications	
Congestive heart failure	15
Pericardial effusion	1
Mycotic aneurysm	2
Neurologic complications	
Brain abscess	5
Stroke	5
Renal complication	
Impairment of renal function	2
Embolism	
Cerebral emboli	5
Peripheral (leg) emboli	2
Pulmonary emboli	1
Other complication	
Osteomyelitis	1

Mortality

In this study, the in-hospital mortality rate of childhood IE was 6/56 (11%). *S. aureus* was the causative organism in 5 (83%) of 6 patients who died. The in-hospital mortality rate was extremely high in patients with *S. aureus* infection (5/8) compared with that in patients infected with other pathogens (1/26) (5/8 vs. 1/26, $P < 0.001$) (Table 4).

Follow-up

Of the 50 survivors, 40 (80%) patients came for follow-up visits with the average follow-up duration of 65 ± 53 (range, 12–188, median, 68) months. Two patients had recurrences of IE. One patient had a recurrence which was a relapse. The recurrence of the other patient was a reinfection.

Discussion

The cumulative prevalence rate of childhood IE in KKU hospital between 1992 and 2011 was 0.8 cases per 1,000 pediatric admissions, which was lower than 4 cases of adult IE per 1,000 admissions in KKU hospital from 1990 to 1999 ($P < 0.001$) [14]. In this study, CHD was the underlying heart disease in 38 (68%) patients with IE, RHD was underlying in 10 (18%) patients with IE, and no previous heart disease was found in 8 (14%) patients. By comparison with a previous multicenter study of 37 Thai children with IE from 1973 to 1978, the present study of 56 children from northeastern Thailand with IE from 1992 to 2011 had the percentage of patients with RHD falling from 41% to 18%, and the percentage of patients with no

previous heart disease rising from 0 to 14% [9]. Moreover, the present study confirmed that RHD was the underlying heart disease in significantly ($P < 0.001$) fewer patients during the latter half of the study period (2002–2011) than during the first half (1992–2001) (Figure 2). These findings suggest that RHD is becoming less frequent as the underlying heart disease for childhood IE in northeastern Thailand. Related to this, the prevalence of RHD is declining in this community [11]. Conversely, there is a move toward a higher proportion of childhood IE with no underlying heart disease in northeastern Thailand.

CHD and RHD were the major underlying heart diseases of the childhood IE in this study and were seen in 48 (86%) patients. VSD and TOF were commonly found among CHD and mitral regurgitation was the major cardiac lesion among RHD. In children with underlying heart disease including CHD and RHD, the abnormal high-velocity jet stream of blood can damage the endothelium or endocardium. Thrombogenesis occurring at the damaged endothelium or endocardium results in the formation of nonbacterial thrombotic endocarditis (NBTE) [1, 6, 13]. Synthetic materials used for the treatment of CHD or indwelling catheters can also cause direct damage to the endothelium or endocardium resulting in the formation of NBTE [1]. Bacteremia or fungemia, in sufficient numbers, can adhere to the NBTE lesion and platelets with fibrin are further deposited over the organisms, leading to the enlargement of the vegetation. The organisms trapped within the vegetation are protected from phagocytic cells and

Table 4. Summary of patients with infective endocarditis who died

Patient No.	Age/ Sex	Interval from onset of symptom to diagnosis of IE (days)	Previous heart diseases	Blood culture results	Echocardiographic findings/complications (days from onset of symptom)	Antibiotics/surgical treatment	Cause of death and interval from diagnosis of IE to death (days)
1	2 m/M	4	Post-operation of correction of TGA with VSD	<i>S. aureus</i> (MRSA)	Pulmonary valve vegetation 6 mm (4)	Vancomycin	Pulmonary emboli (8)*
2	14 y/F	3	RHD	<i>S. aureus</i>	Aortic valve vegetation 14 mm (3)/subconjunctival hemorrhage, Osler node, and Janeway lesion (3) and mycotic aneurysm (7)	Cloxacillin	Cerebral emboli (25)*
3	10 y/F	4	No	<i>S. aureus</i>	Mitral valve vegetation 12 mm (4)/Janeway lesion (4), pustule (4), multiple brain abscess (18)	Cloxacillin	Cerebral emboli (10), Brain edema (18)*
4	2 y/M	30	TOF with PA [‡]	<i>S. viridans</i>	Aortic valve vegetation 6 mm and tricuspid valve vegetation 2 mm (30)/brain abscess (43)	PGS and gentamicin	Brain edema (43) [‡]
5	8 d/M	8	Single ventricle with PS	<i>S. aureus</i> (MRSA)	RVOT vegetation 3 mm/hemothorax complication from central shunt operation (41)	Vancomycin and amikacin	Massive hemothorax (41) [‡]
6	9 y/F	6	No	<i>S. aureus</i>	Aortic valve vegetation 11 mm (6)/CHF (8)	Cloxacillin and gentamicin	Cerebral emboli (7), CHF (8)*

M = male, F = female, IE = infective endocarditis, Previous heart disease = underlying heart disease, TGA = transposition of the great arteries, TOF = Tetralogy of Fallot, PS = pulmonary stenosis, PA = pulmonary atresia, VSD = ventricular septal defect, *S. aureus* = *Staphylococcus aureus*, *S. viridans* = *Streptococcus viridans*, RHD = rheumatic heart disease, MRSA = methicillin resistant *S. aureus*, PGS = penicillin G sodium, RVOT = right ventricular outflow tract, CHF = congestive heart failure
^{*}Without autopsy, [‡]With autopsy, [‡]DiGeorge syndrome with chromosomal abnormality of 22q11.2 deletion

other host defense mechanisms. The combination of endothelial damage and bacteremia or fungemia is a critical etiology of IE [1, 6, 13]. Advances in the understanding of the pathogenesis of IE may be useful in the prevention and treatment of this disease.

The majority of organisms causing IE in this study were gram-positive cocci (85%) and this finding is in accordance with findings in other studies [2-6]. Considerable data support the hypothesis that the interactions of gram-positive cocci with platelets and the capacity of these organism to resist the host defense properties of platelets are pivotal in the occurrence and persistence of IE [1, 15].

IE as a result of *S. aureus* infection has been reported to be associated with a poor prognosis [1-5]. This association was confirmed in the present study because *S. aureus* was involved in 5 of 6 deaths in this cohort. This is because the highly virulent nature of *S. aureus* and these children with IE as a result of *S. aureus* infections are more likely to present with significantly severe involvements [1-5].

In this study, the size of vegetations detected by echocardiography was shown to have an association with embolic events. This is consistent with previous studies showing that the presence of large vegetations (>10 mm in diameter) was associated with higher rates of embolic events [8, 16]. A study in adult patients found that the presence of large vegetations was also associated with an increased in-hospital mortality rate [16].

Recommendations for IE prophylaxis is suggesting for patients with the highest risk for adverse outcomes from IE [6]. In this study, most of the patients with CHD had cardiac lesions for which IE prophylaxis was recommended, and IE occurred among patients for whom IE prophylaxis was not given.

This retrospective study design with a relatively small sample size in a single center may be at risk of patient selection bias and was not designed to assess the efficacy of IE prophylaxis. There were no data related to antecedent procedures or compliance with prophylaxis in this study population.

Conclusion

The epidemiology of pediatric IE in northeastern Thailand continues to change. The changing epidemiology of pediatric IE was toward a lower proportion of children with RHD and higher proportion of children without underlying heart disease. Mortality among patients with IE was higher in those with *S.*

aureus infection. These findings should be considered at the time of decision-making in the diagnosis and treatment for childhood IE in developing countries.

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The authors have no conflicts of interest to report.

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