

Infective endocarditis in childhood: a seven-year experience

W K Liew, T H Tan, K Y Wong

ABSTRACT

Introduction: The epidemiology, clinical features, treatment and outcomes of infective endocarditis (IE) are reviewed.

Methods: A retrospective descriptive study was performed involving patients treated for IE at a paediatric tertiary centre in Singapore, between May 1997 and April 2004. Duke criteria were used to retrospectively evaluate the diagnosis of IE in these cases. Data analysis was performed using SPSS for Windows.

Results: There were a total of 27 children with IE in the seven-year study period. Of these, 24 (88.9 percent) had congenital heart disease, one had rheumatic valvular heart disease and two had normal anatomy. Fever (81.5 percent) was the primary presenting symptom, while splenomegaly (40.7 percent) and septic spots (22.2 percent) were the most common physical findings. C-reactive protein was raised in all cases with a mean of 100.1 mg/L. Blood cultures were positive in 77.8 percent of cases and the most common organism identified was *Viridans Streptococcus* species (25.9 percent). Vegetations were detected on echocardiography in 55.5 percent of cases. According to the Duke criteria, 48.1 percent of our patients fulfilled the clinical diagnosis of definite IE and 51.9 percent had possible IE. The median duration of parenteral antibiotics was 31 days. Major complications were seen in seven (25.9 percent) patients, of whom five had either left heart vegetations or a right-to-left shunt physiology.

Conclusion: IE is an uncommon infection in childhood and occurs primarily in patients with congenital heart disease. Rheumatic heart disease is rarely a predisposing cause in our local children. Early diagnosis of IE is challenging and depends on a high index of suspicion. Useful clues include the presence of splenomegaly, septic emboli, microscopic haematuria and high C-reactive protein level greater than 100 mg/L. The Duke

criteria for the diagnosis of IE are relevant locally, but if modified with an expanded list of minor criteria including the above useful clues, may increase the sensitivity of diagnosing definite IE. The presence of left-sided heart vegetations is a strong predictor of complications and must be treated aggressively.

Keywords: endocarditis, heart disease, infection, outcome, treatment

Singapore Med J 2004 Vol 45(11):525-529

INTRODUCTION

Infective endocarditis (IE) in children is an uncommon infection. Its importance lies in the significant morbidity and mortality associated with the disease, the need for prolonged parenteral antibiotic treatment and the potential complications from embolic and immunological phenomenon. IE occurs less commonly in children than in adults, and tends to occur in children with congenital heart disease (CHD)^(1,2). Early diagnosis and regular follow-up of CHD, as well as the use of antibiotic prophylaxis prior to invasive procedures, have greatly reduced the incidence of IE among these children. As there are no published data on IE in local children, we reviewed the epidemiology, clinical features, treatment and outcomes of IE at a single paediatric centre in Singapore.

METHODS

All records of children (≤ 17 years old) with IE, diagnosed between May 1997 and April 2004 in our hospital, were collected and analysed retrospectively. The patients were identified using our hospital's cardiology database and discharge diagnosis codes. The demographic details, clinical, microbiological and echocardiography data, treatment and outcomes were reviewed. Duke criteria⁽³⁾ was used to retrospectively evaluate the diagnosis of IE in these cases. Data analysis was performed using SPSS for Windows version 9.0 (SPSS Inc., Chicago, Illinois, USA).

Department of
Paediatric Medicine
KK Women's and
Children's Hospital
100 Bukit Timah Road
Singapore 229899

W K Liew, MBBS,
MRCPCH
Registrar

T H Tan, MBBS,
MMed, MRCP
Consultant,
Cardiology Service

K Y Wong, MBBS,
MMed, FAMS
Senior Consultant
and Head, Cardiology
Service

Correspondence to:
Dr Liew Woei Kang
Tel: (65) 6394 1127
Fax: (65) 6394 1114
Email: Liew.Woei.Kang
@kkh.com.sg

Table I. Underlying cardiac disease.

Disease		No disease
Cyanotic	12	2 ⁺
FT	6	
Complex CHD	3	
TGA	1	
PA/IVS	1	
PAVSD	1	
Acyanotic	13	
VSD	7	
CoA	2	
MV dysplasia	2*	
MVPR	1	
RHD	1	

CHD:congenital heart disease; CoA:coarctation of aorta; CONS:coagulase negative *Staphylococcus*; FT:Falot's tetralogy; MV: mitral valve; MVPR:mitral valve prolapse with regurgitation; TGA:transposition of great arteries; PA/IVS:pulmonary atresia with intact ventricular septum; PAVSD:pulmonary atresia with ventricular septal defect; RHD:rheumatic heart disease; VSD:ventricular septal defect.* not diagnosed prior to IE. ⁺ varicella with *Staphylococcus aureus* septicaemia; neonate with CONS septicaemia

Table II. Causative organisms in IE.

Organism	KKH (n=27)
Viridans group streptococci	7 (25.9%)
MSSA	3 (11.1%)
MRSA	2 (7.4%)
CONS	2 (7.4%)
<i>Streptococcus pneumoniae</i>	2 (7.4%)
Group A <i>Streptococcus</i>	1 (3.7%)
Group B <i>Streptococcus</i>	1 (3.7%)
HACEK	1 (3.7%)
<i>Aspergillus</i> species	1 (3.7%)
Culture-negative	5 (18.5%)

CONS: coagulase- negative *Staphylococcus*; HACEK: *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensitive *Staphylococcus aureus*.

RESULTS

During the seven-year study period, 27 patients were diagnosed with IE. The mean age of the patients was 8 years (range 10 days to 15.8 years), with an almost equal distribution between both genders. There was a slight preponderance of Malay (25.9% versus population norm of 14%) patients, which is consistent with the higher percentage of Malay patients admitted to our hospital.

The majority (88.9%) of the patients have an underlying CHD, with an equal distribution of cyanotic

and acyanotic conditions. Only one patient had a history of rheumatic valvular heart disease. There were two patients without underlying heart defects, namely: a neonate with central catheter-associated septicaemia and a child with varicella and secondary skin infection with *Staphylococcus aureus* septicaemia (Table I).

Fever (81.5%) was the most common presenting symptom. Fifty-four percent of the febrile patients had fever ≤ 7 days at the time of admission. Of the five afebrile patients, four were infants <6 months old. Other significant symptoms include cough (25.9%), shortness of breath (22.2%), chest pain (11.1%), increasing cyanosis (11.1%) and lower limb swelling (3.7%). Eleven percent of patients reported a new-onset rash (petechiae or vasculitic). Non-specific complaints of lethargy, myalgia, loss of appetite or poor feeding were observed in 29.6% of patients.

There was a history of antecedent invasive procedure in 11 (40.7%) patients. Nine patients had antibiotic prophylaxis in the perioperative period, seven had cardiothoracic surgery six months prior to the IE episode, and two had general surgery done one month prior. The two remaining patients did not have antibiotic prophylaxis: one had a dental procedure and the other had multiple attempts of insertion of a central line because of difficult venous access.

Six (22.2%) patients presented with acute cardiorespiratory compromise, whereas the remaining patients had a more indolent course. Classical signs of IE, such as Janeway lesions and splinter haemorrhages, were present in only one patient each. There was no patient with Roth's spots or Osler's nodes. Three (11.1%) patients had new cardiac murmurs detected. Other significant physical findings included the presence of petechiae or purpuric rashes (22.2%), splenomegaly (40.7%), dental caries (11.1%), pneumonia (11.1%) and joint swellings (7.4%).

Significant investigations included raised total white counts and the absolute neutrophil counts, with a median of $15.7 \times 10^9/L$ (normal range, $5 - 13.5 \times 10^9/L$) and $9.8 \times 10^9/L$ (normal range, $1.5 - 8.0 \times 10^9/L$), respectively. The median platelet count was $205 \times 10^9/L$ (normal range, $150 - 450 \times 10^9/L$). It is of interest to note that 33.3% of patients had thrombocytopenia (platelet count, $<150 \times 10^9/L$). The C-reactive protein (CRP) level was raised in all patients, with a mean of 100.1mg/L (normal range, $0 - 9.9 \text{mg/L}$). In fact, 40.7% of patients had a CRP value $>100 \text{mg/L}$. Microscopic haematuria was present in five (18.5%) patients; this was transient in four patients, but persisted for two months in the remaining patient.

Blood cultures were positive in 77.8% of patients and the distribution of organism is shown in Table II. The patient with *Aspergillus* species IE required

Table III. Duke criteria for the diagnosis of IE⁽³⁾.

Definite IE	
Pathological criteria	
1. Micro-organisms: demonstrated by culture or histology in a vegetation, a vegetation that has embolised, or an intracardiac abscess, or	
2. Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis	
Clinical criteria as defined below	
1. Two major criteria or	
2. One major criterion and three minor criteria or	
3. Five minor criteria	
Possible IE	
Findings consistent with IE that fall short of "definite", but not "rejected"	
Rejected	
1. Firm alternative diagnosis for manifestations of endocarditis, or	
2. Resolution of manifestations of endocarditis with antibiotic therapy for less than 4 days, or	
3. No pathological evidence of IE at surgery or autopsy after antibiotic therapy for <4 days	
Clinical Criteria	
Major criteria	
1. Positive blood culture for IE	
2. Evidence of endocardial involvement	
Minor criteria	
1. Predisposition: predisposing heart condition or intravenous drug use	
2. Fever: temperature >38°C	
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages and Janeway lesions	
4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth's spots, and rheumatoid factor	
5. Microbiological evidence: positive blood culture, but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE	
6. Echocardiographic findings: consistent with IE, but do not meet a major criterion as noted above	

IE: infective endocarditis

replacement of the destroyed conduit valve and the organism was identified from the excised tissue cultures. Two-dimensional echocardiography revealed cardiac vegetations in 14 (51.9%) patients. Seven patients had right-heart vegetations, and seven patients had left-heart vegetations or a right-to-left shunt physiology. Duke criteria, proposed by Durack et al⁽³⁾ (Table III), was used to evaluate the diagnosis of IE in these cases retrospectively. In our series, 48.1% of patients met the above definition of definite IE and 51.9% of patients had possible IE.

Treatment was instituted and completed in all except two patients who died of overwhelming septicaemia. The median duration of intravenous antibiotics was 31 days (range, 21 to 200 days; mean, 44 days), when the two fatalities were excluded. Three patients received outpatient intravenous antibiotics after an initial inpatient stay. There were two patients who had a prolonged course of treatment. One was a premature infant with a large ventricular septal defect with persistent methicillin-resistant *Staphylococcus aureus* (MRSA) infective endocarditis.

Table IV: Complications of IE.

Complication	No. of patients
Major	
Death	2
Cerebral vascular accident (CVA)	3*
Transient ischaemic attack	1
Gangrene of the foot	1*
Pulmonary embolism	1#
Minor	
Transient ischaemic bowel	1
Acute nephritic syndrome	1
Pneumonia	3

* One patient had both CVA and gangrene of the foot

Patient had destruction of conduit homograft valve requiring redo Rastelli operation

He was successfully treated with intravenous vancomycin and linezolid for 88 days initially and another 112 days subsequently, with an interval of two months between the recurrence of positive blood

cultures. The second patient developed *Aspergillus* endocarditis six months after a Rastelli procedure with pulmonary homograft insertion for pulmonary atresia. She was treated with intravenous amphotericin for six weeks, oral voriconazole for the following eight weeks and is currently on itraconazole maintenance treatment.

Seven (25.9%) patients had major complications (Table IV), despite having started treatment with appropriate intravenous antibiotics. Two patients died of septic shock with multi-organ failure, secondary to Group B *Streptococcus* and methicillin-resistant *Staphylococcus epidermidis* septicaemia, respectively. Two patients had a cerebral vascular accident (CVA), one had both CVA and gangrene of the foot, one had a transient ischaemic attack, and one had pulmonary embolism. These events occurred at a mean of 11.4 days (range, 2 to 34 days) after initiation of treatment. Of these seven patients, three had left-sided heart vegetations and two of them had cyanotic CHD with right-to-left shunt physiology.

DISCUSSION

IE is an uncommon infection and accounted for a hospitalisation rate of 0.24 per 1000 paediatric admissions per year in our hospital. In the past seven years, a mean of 3.9 patients were treated per year. Our incidence of IE is similar to the other major studies⁽⁴⁻⁶⁾ published. The epidemiology of our IE patients resembles that of developed countries⁽¹⁾, with the majority of patients having CHD as the underlying risk factor. This is in contrast to the developing countries^(7,8) that have a higher incidence of rheumatic heart disease. Early diagnosis of IE remains challenging even today, and often depends on a high index of clinical suspicion. In our series, most patients had short fever durations, were not toxic-looking and have no classical stigmata of IE such as Osler's nodes, Janeway lesions, splinter haemorrhages, or Roth's spots.

Using the Duke criteria (Table III), 48.1% of our patients had definite IE while 51.9% had possible IE. Though the Duke criteria have been widely used for the diagnosis of IE, it has also been shown by some authors to perform badly in blood culture-negative endocarditis^(9,10). Various authors have suggested modifications to the Duke criteria to improve its sensitivity^(9,11). In our series, we found that splenomegaly, septic emboli to the skin (petechiae or purpuric rashes), microscopic haematuria and a high CRP value >100mg/L were important diagnostic clues of IE in a susceptible patient with fever. If these findings are included in the minor criteria, this would increase our clinically definite IE yield from 48.1% to 62.9%.

The rate of culture-negative endocarditis varies with different studies, ranging from 2.5% to 31%⁽¹¹⁾. In our series, five (18.5%) patients had negative blood cultures; Of these, three had prior antibiotics treatment. Fastidious pathogens, such as the *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae* (HACEK) were also not routinely requested for in the past. In addition, drawing sufficient blood for blood cultures may sometimes be a problem in paediatric patients. New recommendations to exclude rare infections include performing serology testing for Bartonella, Chlamydia, and Coxiella species antibodies, and sending any pathological specimen (such as excised valve or embolus) to be analysed by microscopy, culture, histology and relevant polymerase chain reaction^(9,11).

Our treatment regime consists of dual intravenous antibiotics for synergistic effect. Our first-line antibiotic combination is intravenous penicillin G and gentamicin, with further adjustment depending on the blood culture organism and sensitivities, as well as the clinical response of the patient. The intravenous antibiotics are given for at least 21 fever-free days before they are stopped. The total duration of antibiotics is further fine-tuned for each patient according to the risk group, results of repeat blood cultures and echocardiography findings.

The major complications in seven (25.9%) patients occurred at a mean of 11.4 days, despite initiating appropriate intravenous antibiotic treatment. Three of them had left-sided heart vegetations and two of them had cyanotic CHD with right-to-left shunt physiology. As noted in other reports⁽¹⁾, the presence of left-sided heart vegetations is a major risk factor for complications and extra vigilance is required in this group of patients.

In conclusion, IE is an uncommon infection in childhood and occurs primarily in patients with CHD. Rheumatic heart disease is rarely a predisposing cause in our local children. Early diagnosis of IE is challenging and depends on a high index of suspicion. Useful clues include the presence of splenomegaly, septic emboli, microscopic haematuria and high CRP (>100mg/L). The Duke criteria for the diagnosis of IE are relevant locally, but if modified with an expanded list of minor criteria including the above useful clues, may increase the sensitivity of diagnosing definite IE. The presence of left-sided heart vegetations or cyanotic heart disease with right-to-left shunt is a predictor of complications and must be treated aggressively.

REFERENCES

1. Ferrieri P, Gewitz MH, Gerber MA, Newburger JW, Dajani AS, Shulman ST, et al. Unique features of infective endocarditis in childhood. *Pediatrics* 2002; 109:931-43.
2. Fisher MC. Changing risk factors for pediatric infective endocarditis. *Curr Infect Dis Rep* 2001; 3:333-6.
3. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med* 1994; 96:200-9.
4. Johnson DH, Rosenthal A, Nadas AS. A forty-year review of bacterial endocarditis in infancy and childhood. *Circulation* 1975; 51:581-8.
5. Martin JM, Neches WH, Wald ER. Infective endocarditis: 35 years of experience at a children's hospital. *Clin Infect Dis* 1997; 24:669-75.
6. Stockheim JA, Chadwick EG, Kessler S, Amer A, Abdel-Haq W, Dajani AS, et al. Are the Duke criteria superior to Beth Israel criteria for diagnosis of infective endocarditis in children? *Clin Infect Dis* 1998; 27:1451-6.
7. Bitar FF, Jawdi RA, Dbaibo GS, Yunis KA, Gharzeddine W, Obeid M. Paediatric infective endocarditis: 19-year experience at a tertiary care hospital in a developing country. *Acta Paediatr* 2000; 89:427-30.
8. Dhawan A, Grover A, Marwaha RK, Khattri HN, Anand ID, Kumar L, et al. Infective endocarditis in children: profile in a developing country. *Ann Trop Paediatr* 1993; 13:189-94.
9. Lamas CC, Eykyn SJ. Blood culture negative endocarditis: analysis of 63 cases presenting over 25 years. *Heart* 2003; 89:258-62.
10. Habib A, Derumeaux. Value and limitations of the Duke criteria for the diagnosis of infective endocarditis. *J Am Coll Cardiol* 1999; 33:2023-9.
11. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000; 30:633-8.



THE CHINESE UNIVERSITY OF HONG KONG

Applications are invited for:

Department of Anatomical and Cellular Pathology

Associate Professor/Assistant Professor (clinical)

(Ref. 04/120(673)/2) (closing date: December 6, 2004)

The Department is looking for a suitable and qualified pathologist with a subspecialty interest in lymphoreticular pathology, GI pathology, neuropathology or other areas of surgical pathology. Applicants should have a medical qualification (approved for registration with The Medical Council of Hong Kong) and possess MRCPPath, FRCPA, FRCPC, FHKAM (Pathology) or American Board Certification. Applicants for Associate Professorship should also have a substantial record of teaching and research. Working experience in East Asian countries and commitment towards the region will be advantages. The appointee will join the Department (equipped with excellent facilities for basic and clinical research), and teams of dedicated pathologists, clinicians and scientists. Appointment will initially be made on a fixed-term contract basis for one to two years, renewable subject to mutual agreement. Information about the Department can be found at <http://www.acp.cuhk.edu.hk>. For enquiries about the post, please write to Professor H.K. Ng at hkng@cuhk.edu.hk.

Salary and Fringe Benefits

Salary will be highly competitive, commensurate with qualifications and experience. The University offers a comprehensive fringe benefit package including a contract-end gratuity for an appointment of two years, plus a monthly fixed-sum cash allowance and a housing subsidy for the eligible appointee.

Further information about the University and the general terms of service for teaching appointees is available at <http://www.cuhk.edu.hk/personnel>. The terms mentioned herein are for reference only and are subject to revision by the University.

Application Procedure

Please send full resume, copies of academic credentials, a publication list and/or abstracts of selected published papers, together with names, addresses and fax numbers/e-mail addresses of three referees to whom applicants' consent has been given for their providing references (unless otherwise specified), to the Personnel Office, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong (Fax: (852) 2603 6852) on or before **December 6, 2004**. The Personal Information Collection Statement will be provided upon request. Please quote the reference number and mark 'Application - Confidential' on cover.

[Note: The University reserves the right not to fill the post or to fill the post by invitation.]