Infective endocarditis in congenital heart disease: Japanese national collaboration study

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Objective: To provide pure cohorts of paediatric and adult patients with congenital heart disease (CHD) and infective endocarditis (IE) for making future guidelines.

Design: Japanese nationwide survey.

Setting: 66 Japanese institutions.

Patients: 170 children, mean (SD) age 7.4 (5.7) years (range 14 days to 17 years), and 69 adults, age 32.5 (14.1) years (range 18–69) who developed IE between 1997 and 2001 (one in 240 admissions with CHD).

Main outcome measures: Clinical presentation of IE.

Results: 119 patients including 88 with cyanotic CHD had previous cardiac surgery. Procedures preceding IE were dental (12%) followed by cardiovascular surgery (8%). Sites of infection were left sided in 46% and right sided in 51%. Vegetation with diameter of 11 mm was documented in 151 (63%). Frequent complications were embolic events (stroke 11%, other emboli 20%) and cardiac failure (23%). The most common microorganisms were streptococci (50%) and staphylococci (37%) with methicillin resistant Staphylococcus aureus in 7.5%. Empirical treatments were penicillins (alone or with other antibiotics 57%) followed by cephems (22%) and vancomycin (11%). Surgery during active IE was common (26%), with vegetation (45%) and heart failure (29%) as the most frequent indications. Mortality was 8.8%: 8.0% among patients who received medical treatment alone and 11.1% among those with active IE who underwent surgery. The causes of death (n = 21) were surgery (7), infection (7), cardiac failure (6), and renal failure (1).

Conclusions: Because of a recent increase in the incidence of IE and high mortality and complication rate, it is mandatory to establish well formulated recommendations for management of IE in paediatric and adult patients with CHD based on a large cohort. Results of this nationwide multicentre database should be helpful in establishing guidelines.

Published guidelines used worldwide for infective endocarditis (IE) address mainly adults with acquired cardiac disorders. Cardiologists have not had access to formulated guidelines for IE in paediatric and adult patients with congenital heart disease (CHD) based on data from a pure large cohort. Increasing numbers of patients with CHD have now reached adulthood and CHD constitutes the major substrate for IE in both children and adults. Because relatively few cases of CHD and IE are seen in any one institution, authors have tended to report the issue of IE by combining their clinical experience over several decades. Accordingly, there is a dearth of practical and current data of IE from a large cohort of paediatric and adult patients with CHD.

This study aimed at clarifying recent information on the clinical presentation of IE in a nationwide survey in Japan for the formulation of the guidelines in paediatric and adult patients with CHD.

METHODS

Information regarding the history, demographics, prophylaxis, diagnosis, and management of IE in 239 patients with a mean (SD) age of 14.7 (14.5) years (range 14 days to 69 years) from January 1997 to December 2001 was obtained from 66 institutional databases and analysed at the Chiba Cardiovascular Centre, Chiba, Japan. The 239 patients comprised 170 children (147 with CHD and 23 without apparent underlying heart disease), aged 7.4 (5.7) years (range 14 days to 17 years), and 69 adults with CHD, aged 32.5 (14.1) years (range 18–69 years). Admissions with CHD during the five year period were 50 985 with a prevalence of IE of 0.42% (212 of 50 985 or one in 240) (excluding two institutions with four patients with CHD in which the total number of admissions was unknown).

Collection of data regarding IE

The following data regarding IE were solicited.

- Demographic data: age, sex, diagnosis of CHD, previous cardiac surgery (repair or palliative), residual lesion after repair and history of recurrent IE; in patients with previous cardiac surgery, whether IE was perioperative (perioperative was defined as the onset of IE within six months after surgery)
- Prophylaxis: whether IE prophylaxis was undertaken; the procedures and conditions requiring IE prophylactic in terms of choice, dose, duration
- Bacteriology: the causative microorganism; whether antibiotics were administered before blood was cultured and, if blood was cultured, the number of cultures for each patient and whether the culture was positive or negative
- Echocardiographic findings: site and size of vegetation, enhanced intensity of endocardium, perforation of valvar leaflet, and periannular extension of abscess

Abbreviations: CHD, congenital heart disease; IE, infective endocarditis; MRSA, methicillin resistant Staphylococcus aureus; TOE, transoesophageal echocardiography
Continuous data were compared between subgroups by two appropriate. When p < 0.05, the data were defined as significant.

RESULTS

Demographic data
The male to female ratio was 143:96. Of the population of 239, 20 (8.4%) were infants aged 5.1 (3.3) months (range 14 days to 10 months). Table 1 lists the diagnoses of CHD. No patients had rheumatic heart disease. Previous reparative or palliative cardiac surgery was undertaken in 119 patients with CHD (119 of 216 (55.1%), 75 with reoperative surgery and 44 with palliative surgery) including 88 with cyanotic CHD. A residual defect after repair was observed in 55 of 75 (73.3%) patients. IE recurred in 21 of 229 (9.2%) patients: once in 10, twice in two, three times in two, and four or more times in two. In 28 of 119 (23.5%) patients who died, whether they were treated with drugs alone, underwent surgery during active IE (before a full course of antibiotics had been completed), or underwent surgery with healed IE (after a full course of antibiotics had been completed).

Prophylaxis
In 78 of 234 (33.3%) patients, conditions and procedures associated with IE were identified (table 2). In 22 of 78 (28.2%), prophylactic antibiotic regimens were administered intravenously (14 patients) or orally (eight patients). In nine of 14 patients with intravenous prophylaxis, methicillin resistant Staphylococcus aureus (MRSA) (n = 7) or Candida albicans (n = 2) was the causative microorganism. In eight patients with oral prophylaxis, streptococci were found in three and staphylococci in four. No patients used injected drugs.

Site of infection
The site of infection was identified (175 of 239 of patients (73.2%)) more often in paediatric patients (127 of 170 (74.7%)) than in adults (48 of 69 (69.6%), p = 0.1). Left sided IE was observed in 81 of 175 (46.3%) patients: mitral valve, 44 (25.1%); aortic valve, 26 (14.9%); both the mitral and aortic valves, five (2.9%); left atrium, two (1.1%); left ventricular outflow tract, two (1.1%); and ascending aorta, arch, or both, six (3.4%). Right sided IE was observed in 89 of 175 (50.9%) patients: tricuspid valve, 37 (21.1%); ventricular septal defect, 19 (10.8%); right ventricle, 12 (6.9%); right ventricular outflow tract conduit, 10 (5.7%); pulmonary valve, nine (5.1%); pulmonary artery, four (2.2%); left carotid vein, one (0.5%); and atrial septal closure suture, one (0.5%). IE in both right and left ventricles was observed in four (2.3%) and Blalock-Taussig shunt in two (1.1%). In adults, the prevalence of left sided IE (29 of 48 (60.4%)) was higher than that of right sided IE (21 of 52 (40.4%)). In 23 children without underlying structural heart disease, sites of infection were mitral valve, 15; aortic valve, five; both mitral and aortic valve, two; and tricuspid valve, one (IE due to central venous catheter insertion).

Bacteriology
Causative microorganisms were identified in 201 of 239 (84.1%) patients (table 3).

Complications
Complications were observed in 116 of 239 (48.5%) patients after a mean (SD) of 29 (42) days (range 0–180 days) of illness (table 4). In 19 of 25 of patients with cerebral emboli, IE was associated with S aureus. In 37 of 48 of patients with embolisation, sites of vegetation were identified as the mitral valve in 10, aortic valve in seven, tricuspid valve in six, pulmonary valve in three, right ventricular outflow tract in four, atrial and mitral valves in one, conduit in one, right ventricle and mitral valve in one, pulmonary artery in one, left atrium in one, atrial, mitral, and tricuspid valves in one, and aortic arch in one. Thirteen patients received antiarhythm medication and a pacemaker was implanted in one patient with complete atroventricular block. Patients with perianular extension of the abscess did not manifest heart block. Medication for cardiac failure was administered to 57 patients. One child underwent neurosurgery for a mycotic aneurysm.
Antimicrobial treatment

Table 5 shows empirical antimicrobial treatment (n = 235). Antibiotics were started at 18.5 (33.3) days (range 0–240 days) of illness, which was within seven days in 104 of 203 (51.2%) patients. The duration of antibiotics administration was 29.7 (16) days (range 1–70 days). Antibiotics and antifungal agents were (n = 420) in 203 patients) penicillins was 29.7 (16) days (range 1–70 days). Antibiotics and antifungal agents were (n = 420) for 235 patients) penicillins was 29.7 (16) days (range 1–70 days). Antibiotics and antifungal agents were (n = 420) in 203 patients) penicillins was 29.7 (16) days (range 1–70 days).

Cardiac surgery

Cardiovascular surgery for IE was performed in 103 of 239 (43.1%) patients. This was during active IE (full course of antibiotics had been completed) in 40 of 239 (16.7%) patients at 301 (456) days (range 30 days to 49 months) of illness. In 12 of 26 of patients with prosthetic material infection, cardiac surgery was undertaken during active IE (full course of antibiotics had been completed) in 40 of 239 (16.7%) patients at 301 (456) days (range 30 days to 49 months) of illness. In 12 of 26 of patients with prosthetic material infection, cardiac surgery was undertaken during active IE (full course of antibiotics had been completed) in 40 of 239 (16.7%) patients at 301 (456) days (range 30 days to 49 months) of illness. In 12 of 26 of patients with prosthetic material infection, cardiac surgery was undertaken during active IE (full course of antibiotics had been completed) in 40 of 239 (16.7%) patients at 301 (456) days (range 30 days to 49 months) of illness. In 12 of 26 of patients with prosthetic material infection, cardiac surgery was undertaken during active IE (full course of antibiotics had been completed) in 40 of 239 (16.7%) patients at 301 (456) days (range 30 days to 49 months) of illness. In 12 of 26 of patients with prosthetic material infection, cardiac surgery was undertaken during active IE (full course of antibiotics had been completed) in 40 of 239 (16.7%) patients at 301 (456) days (range 30 days to 49 months) of illness. In 12 of 26 of patients with prosthetic material infection, cardiac surgery was undertaken during active IE (full course of antibiotics had been completed) in 40 of 239 (16.7%) patients at 301 (456) days (range 30 days to 49 months) of illness. In 12 of 26 of patients with prosthetic material infection, cardiac surgery was undertaken during active IE (full course of antibiotics had been completed) in 40 of 239 (16.7%) patients at 301 (456) days (range 30 days to 49 months) of illness.
patients with CHD is increasing, especially in infants and adults with previous cardiac surgery. Despite recent developments in prevention and diagnosis of IE and medical and surgical management of acute IE, complication rates and mortality are still too high. Because of the high mortality caused by IE among patients with CHD (8.8%) it is mandatory to establish formulated recommendations for the medical and surgical management of paediatric patients and adults with IE and CHD based on a large database. Results of this nationwide multicentre database should be helpful in achieving this goal.

**Demographic data**

The prevalence of IE in patients with CHD has been increasing.12–15 Morris14 reported that the highest risk for IE was found in children who had had repair or palliation of cyanotic CHD. In this study, the prevalence of IE, especially in infants and adults with CHD and repaired or palliated cyanotic CHD is high. An increased prevalence of perioperative IE in infants reflects the recent strategy of early cardiovascular repair in neonates and infants with complex CHD. Indeed, the proportion of patients with previous surgery is high (about 50% in published reports16–18 and 55% in our study). IE in adults with CHD has been increasing along with the increasing number of patients with CHD reaching adulthood.12–14

**Diagnosis of CHD and cardiac conditions associated with IE**

Ventricular septal defect, patent ductus arteriosus, aortic valve abnormalities, and tetralogy of Fallot are reported to be common underlying conditions for IE.19 In this study, ventricular septal defect was the most frequent underlying condition with patent ductus arteriosus and aortic abnormalities lower than in previous reports.18 Instead, cyanotic CHD, such as tetralogy of Fallot, single ventricle with or without heterotaxia, double outlet right ventricle, and transposition of the great arteries (38%) were more frequent. The most common lesion to develop IE after surgery is reported to be tetralogy of Fallot or an aortopulmonary shunt.20–22 In this study, aortopulmonary shunt, extracardiac conduit, and prosthetic material were frequent lesions.

Corrective surgery usually eliminates the risk for IE in patients with left to right shunts such as ventricular septal defect or persistent ductus arteriosus.23 In this study we observed residual defect in 82% of 75 patients with repaired defects. Close observation of residual lesions in patients after repair is therefore very important for prevention of IE. The risk of IE in patients with repaired defects with aortic stenosis is high regardless of residual haemodynamic defect.24 In this study, four of 11 patients with previous aortic valve surgery developed IE.

### Table 4 Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Number (n = 116, multiple answers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased valvar regurgitation</td>
<td>73 (30.5%)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>56 (23.4)</td>
</tr>
<tr>
<td>Systemic emboli</td>
<td>48 (20.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>25 (10.9%)</td>
</tr>
<tr>
<td>Systemic abscess formation</td>
<td>5 (2.2%)</td>
</tr>
<tr>
<td>Arrhythmia development</td>
<td>13 (5.4%)</td>
</tr>
<tr>
<td>Perianuillar extension of abscess</td>
<td>11 (4.6%)</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>7 (2.9%)</td>
</tr>
<tr>
<td>Prosthetic valve dysfunction</td>
<td>4 (1.7%)</td>
</tr>
<tr>
<td>Glomerulonephritis/renal failure</td>
<td>4 (1.7%)</td>
</tr>
<tr>
<td>Mycotic aneurysm</td>
<td>3 (1.3%)</td>
</tr>
</tbody>
</table>

### Table 5 Empirical antimicrobial treatment

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Number (n = 235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins alone</td>
<td>54 (23%)</td>
</tr>
<tr>
<td>Penicillins plus aminoglycosides</td>
<td>50 (21%)</td>
</tr>
<tr>
<td>Penicillins plus others*</td>
<td>50 (21%)</td>
</tr>
<tr>
<td>Cephalosporins alone</td>
<td>29 (12%)</td>
</tr>
<tr>
<td>Cephalosporins plus aminoglycosides</td>
<td>8 (3.4%)</td>
</tr>
<tr>
<td>Cephalosporins plus others*</td>
<td>15 (6%)</td>
</tr>
<tr>
<td>Carbapenems alone</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Carbapenems plus others*</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Vancomycin alone</td>
<td>4 (1.7%)</td>
</tr>
<tr>
<td>Vancomycin plus carbapenems</td>
<td>6 (2.6%)</td>
</tr>
<tr>
<td>Vancomycin plus others*</td>
<td>17 (7%)</td>
</tr>
<tr>
<td>Oxacephems</td>
<td>4 (1.7%)</td>
</tr>
<tr>
<td>Antifungal agents (Fluconnaize)</td>
<td>2 (0.8%)</td>
</tr>
</tbody>
</table>

*Cephalosporins, aminoglycosides, clindamycin, or tetracyclines;†Carapenems, fosfomycin, aminglycosides, or tetracyclines;‡Vancomycins, oxacephems, fosfomycin, clindamycin, or tetracyclines;§Vancomycins, cephems, tetracyclines, or carbapenems.

It is reported that drug misuse is often associated with IE in adults in the USA and Europe,2 but there were no patients associated with drug abuse in this study or in a recent nationwide survey of IE in adults in Japan.10

**Prophylaxis**

Significant bacteraemia is defined by the American Heart Association as organisms commonly associated with IE and attributable to identifiable procedures such as dental, oral, and respiratory tract procedures.1 In our study, the most frequent procedure associated with IE was dental followed by cardiac surgery. Otolaryngeal procedures, pneumonia, and atopic dermatitis were also important predisposing causes or conditions for IE in patients with CHD.13

Prophylaxis is recommended for patients who undergo open heart surgery and should be aimed primarily against S. aureus and coagulase negative staphylococci, for which a first generation cephalosporin or vancomycin is thought to be a reasonable choice.3 In this study, seven of 11 patients developed perioperative IE associated with MRSA or fungus resistant to the first choice antibiotics, cephalosporins. Most surgeons, as reported recently, used cephalosporins as first choice perioperative prophylactic agents. The choice of perioperative antibiotics should be tailored according to patient conditions and institutional circumstances.

**Site of IE**

In children with CHD, right sided IE is reported to be more frequent than left sided, but in adults mainly with acquired heart disease, left sided IE is more prevalent.16 In adults with CHD in this study, left sided IE was more frequent than right
sided IE. Right sided lesions susceptible to IE were common in CHD. About 10% of reported paediatric patients and IE have no underlying structural heart disease and the site of IE was usually the aortic or mitral valve associated with S. aureus bacteraemia. In this study, 23 children (13.8% of the paediatric patients) developed IE without structural heart disease and the site of IE was a left sided cardiac lesion in all except one. The results were similar to previous reports, but about half of the cases were associated with streptococcal bacteraemia.

Microorganism

The organisms that cause IE in children most often are Gram positive cocci (32–43%). With the increasing frequency of cardiac surgery in patients with complex CHD in which prosthetic materials are used, the incidence of infection with staphylococci, Gram negative bacilli, and fungi has been increasing. In this study, Gram positive cocci, especially Streptococcus species (50%) and Staphylococcus species (37%), were the most frequent microorganism followed by Haemophilus (4.5%) and Candida species (2.5%). In Staphylococcus species, S. aureus (with 24% MRSA) was the most frequent microorganism.

Echocardiography

Transthoracic echocardiography is more likely to identify vegetations in patients with normal anatomy or isolated valvar pathology than in complex cyanotic CHD as a result of interference in complex cyanotic CHD by arterial grafts, conduits, and valves. The low detection rate (62%) of vegetation by echocardiography in both paediatric and adult patients in this study may be attributable to our higher prevalence of post-surgical patients with complex CHD with prosthetic materials.

In this study, TOE was used in only a small number of patients, especially in adults. TOE is superior to transthoracic echocardiography in detecting vegetations in the adult cohort. However, this was not a study of the usefulness of TOE in paediatric cohorts. Paediatric patients usually have a much better echo window than do adults.

Blood culture

Two to three sets of blood cultures over a 24 hour period is thought to be adequate in most cases in children with IE and blood samples were cultured 3.5 times for each patient in this study. The positive rate of pathogens grown in blood culture was reported to be 68–98% and the rate dropped to 60% when antibiotics were used before blood culturing. In this study, blood cultures were positive for pathogens in 86% of the patients despite the high incidence of prior administration of antibiotics (69% of the patients; most of these were administered orally) before blood culturing.

Complications

Cardiac failure, usually accompanied by valve regurgitation, is one of the most important predictive factors for mortality of IE. Prosthetic valve IE is common and usually results in valve replacement in adults. Extension of IE beyond the valve annulus predicts higher mortality with more frequent development of cardiac failure and the need for cardiac surgery. In this study, cardiac failure worsened because of IE in 21% of patients. Periannular extension of the abscess was observed in only 5% and prosthetic valve IE was observed in 1.7%, which is consistent with previous reports on paediatric patients with IE. Neurological signs and symptoms are often associated with S. aureus infection and are reported in 20% of children with IE. In this study, cerebral emboli were observed in 11% of the patients and 76% were associated with S. aureus infection.

Because the likelihood of cure with antibiotics alone is decreased, surgical intervention is often required. A potentially life threatening complication is the development of IE in a surgically created shunt or conduit in patients with complex CHD. In this study, prosthetic material was infected in 26 of 120 patients with previous surgery (22%) and 12 required urgent cardiac surgery that resulted in three deaths.

Vegetation of 10 mm or greater is a predictive sign of embolisation, especially a mitral valve vegetation. In this study, the size of vegetation was 11 mm and systemic embolisation was observed in 20% of the patients: 55% of the embolisations were cerebral. Vegetation size in patients with embolisation (n = 26) in this study was 11.5 (6.5) mm; a similar number of patients did not have embolisation. The most frequent site of vegetation that resulted in embolisation is reported to be the mitral valve but in this study in patients with CHD, the aortic and tricuspid valves were also frequent foci for embolisation. Mycotic aneurysms are uncommon complications of IE and are very rare, especially in children. In this study, mycotic aneurysm was observed in two adults, and one child required neurosurgery. The development of new atrioventricular or bundle branch block is a frequent sequela of periannular extension of the abscess in adults. In this study, no patients with conduction defects had periannular extension of the abscess.

Medical management of IE

For empirical infection, penicillins alone or penicillins combined with aminoglycosides are widely recommended. In this study, penicillins (alone or combined with aminoglycosides) were most often used antibiotics for this purpose (57%), but about 20% of the physicians preferred cephems and 12% preferred vancomycin (or a combination of others).

Mortality and cardiac surgery in patients with active IE

The prognosis of children with IE depends on many factors, such as severity of underlying cardiac lesion, presence of prosthetic materials, type of infecting organism, and duration of illness before diagnosis. Mortality among paediatric patients with CHD and IE is reported to be lower than among adults with acquired heart disease. The recently reported mortality among paediatric patients with IE is about 10%, which is similar to our mortality (9.4%) and higher than that of adults with CHD (7.2%).

The incidence of reinfection of newly implanted valves in patients with active IE has been estimated at 2–3% in adult patients, and surgery as an adjunct to medical treatment was recognised as more effective than medical treatment alone. In this study, 26% of the patients underwent cardiac surgery during active IE with no recurrence but with higher mortality than with medical treatment alone. The risk factors for death were not measured in this study; however, this relatively higher mortality among patients with surgery in the acute phase may be attributable to differences in factors such as the timing of the operation, severity of cardiac disease, rate of complication, or differences in microorganisms between these two subgroups.

Indications for surgery in active IE are uncontrollable cardiac failure or infection, an episode of embolisation, fungal IE, perivalvar abscess, and prosthetic materials, such as prosthetic valve, conduit, aortopulmonary bypass graft, or patch infection. The most frequent indication for surgery in this study was a vegetation likely to develop systemic embolisation or the status after systemic embolisation and heart failure. The current practice of cardiac surgery for CHD is the frequent use of prosthetic material in a variety of cardiac locations. A high mortality has been reported among
patients with IE with infected prosthetic materials requiring replacement. In this study, infected prosthetic material was surgically removed from 17 patients with a resultant mortality of 12%.

Because of the recent increase in the incidence and the high mortality from IE (8.8%), it is mandatory to establish formulated recommendations for the medical and surgical management of IE in paediatric and adult patients with CHD based on a large database.

Limitations

Many cardiologists in Japan use the Duke criteria for diagnosing IE, but some in the participating institutions had no uniform criteria and the diagnosis of IE in the reported cases was not validated. Our patients had a large age range from infants and children to adults with CHD. Many cardiologists participated in this study; therefore, these factors may cause a bias in the analysis of the clinical profile of IE in Japanese patients with CHD.

Conclusions

Precise features of IE in 239 paediatric and adult patients with CHD are clarified. An increasing number of patients, especially infants and adults with cyanotic CHD and previous surgery, are developing IE. Despite recent advances in diagnosis and treatment, mortality and the rate of complications, such as cardiac failure and systemic embolisation, are high. To reduce mortality and morbidity in patients with CHD and IE, it is necessary to establish guidelines for IE prevention and management based on a large cohort of patients. The nationwide multicentre database was designed to meet this need, and the results should be helpful in establishing guidelines for IE in CHD.

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REFERENCES
