CONGENITAL HEART DISEASE

Infective endocarditis in congenital heart disease: Japanese national collaboration study

K Niwa, M Nakazawa, S Tateno, M Yoshinaga, M Terai

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See end of article for authors' affiliations

Correspondence to: Dr K Niwa, Department of Paediatrics, Chiba Cardiovascular Centre, 575 Tsurumai, Ichihara, Chiba 290-0512 Japan; kniwa@aol.com

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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)[1–6] 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[7] and CHD constitutes the major substrate for IE in both children and adults.[8–14] 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.[9–12 15 16] Accordingly, there is a dearth of practical and current data of IE from a large cohort of paediatric and adult patients with CHD.[8]

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

- Pathological findings (necropsy and surgery): site and size of vegetation, periannular extension of abscess, prosthetic material infection, and systemic emboli
- Complications: whether complications were observed (complications were increased valvar regurgitation, cardiac failure, cerebral or systemic embolisation, arrhythmia, periannular extension of abscess, prosthetic valve dysfunction, glomerular nephritis or renal failure, and mycotic aneurysm)
- Management: choice, dose, and duration of antibiotics, and interval between diagnosis and initiation of antibiotics; whether complications, anticardiac failure regimens, antiarrhythmic medication, and neurosurgery for mycotic aneurysm were managed; and timing, indication, surgical method, and mortality of cardiac surgery after IE
- Mortality: whether the patient was alive or dead and cause of death; among 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).

Statistical analysis

Data were expressed as mean (SD) with range, the number and percentage, or the number of answers as a percentage of total number of answers. When a question had no response or when an answer was unclear, those data were not counted. Available data from participating hospitals were analysed with StatView J-5.0 PPC (SAS Institute Inc, Cary, North Carolina, USA). Discrete variables were analysed by χ^2 test. Continuous data were compared between subgroups by two sample t test or the Wilcoxon rank sum test wherever 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 reparative 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 with previous cardiac surgery, IE developed perioperatively.

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).

Diagnosis of IE

Blood samples were cultured 3.5 (range 1–18) times for each patient. The mean (SD) interval between initial blood culturing and initiation of antibiotics was 90.8 (150) hours (range 0–720 hours).

Transoesophageal echocardiography (TOE) was performed in 30 of 228 (13.2%) patients and 23 of them were adults. IE findings were positive in 167 of 235 (71.1%) patients: vegetations, 145 (61.7%); enhanced intensity of endocardium, 127 (54.0%); perforations of valve leaflet, 17 (7.2%); and periannular extension of abscess, 14 (6.0%). Mean (SD) vegetation size was 11.1 (6.7) mm (range 1–39 mm). Vegetation size in patients with systemic embolisation (n = 26) was 11.5 (6.5) mm (range 1–27 mm), which was similar to the size in patients without systemic embolisation (10.9 (6.3) mm (range 1–39 mm)). In six patients, vegetations of 6 mm were identified by pathological examinations but were not found by echocardiographic study. Vegetation was detected in 39 of 67 (58.2%) patients with a size of 11.1 mm in adults, which was similar to the size in paediatric patients (106 of 170 (62.4%), 11.1 mm, p = 0.2).

Prosthetic material infection

Prosthetic material was infected in 26 of 136 (19.1%) patients: prosthetic valve, four; right ventricular outflow conduit, 10; right ventricular outflow patch, two; ventricular septal defect patch, six; Blalock-Taussig shunt, two; pulmonary artery banding, one; and ventriculoatrial shunt, one.

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 antiarrhythmic medication and a pacemaker was implanted in one patient with complete atrioventricular block. Patients with periannular 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.

Table 1 Diagnoses of underlying congenital heart disease

Diagnosis	Total (n = 216)	Non-operated (n = 97)	Repaired (n = 75)	Palliated (n = 44)
VSD, VSD + ASD or PDA	81 (37.5%)	65	VSD closure: 16	0
Tetralogy of Fallot with/without pulmonary atresia	39 (18.1%)*	3	Rastelli: 11, ICR: 8	Unifocalisation: 4, AP shunt: 13
Single ventricle (heterotaxia)	19 (8.8%)	3	TCPC: 2, Fontan: 2	AP shunt: 10, PAB: 2
Double outlet right ventricle	16 (7.4%)	0	Rastelli: 2, Fontan: 3, ICR: 3	AP shunt: 6, PAB: 2
Mitral stenosis/regurgitation	15 (6.9%)	12	MVR: 1, MVP: 2	
Aortic stenosis/regurgitation (bicuspid aortic valve)	11 (5.1%)	7	Ross: 1, AVR: 1, AVP: 2	
Complete TGA	8 (3.7%)	0	Rastelli: 5, Jatane: 1	AP shunt: 2
COA, COA VSD	6 (2.8%)	0	VSD closure: 4	SCLF: 2
AVSD	6 (2.8%)	2	AVSD closure, MVP: 3	AP shunt: 1
Corrected TGA	5 (2.3%)	0	Rastelli: 2; TVR: 1, VSD closure: 1	AP shunt: 1
ASD	2 (0.9%)	1	Closure: 1	
PDA	2 (0.9%)	2		
Truncus arteriosus communis	2 (0.9%)	0	Rastelli: 2	
Valsalva aneurysm	2 (0.9%)	2		
Ebstein's disease	1 (0.5%)	0	TVP: 1	
HLHS	1 (0.5%)	0		Norwood: 1

*Tetralogy of Fallot and pulmonary atresia: 22.
AP, aortopulmonary; ASD, atrial septal defect; AVP, aortic valvoplasty; AVR, aortic valve replacement; AVSD, atrioventricular septal defect; COA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; ICR, intracardiac repair; MVP, mitral valvoplasty; MVR, mitral valve replacement; PAB, pulmonary artery banding; PDA, patent ductus arteriosus; SCLF, subclavian flap; TCPC, total cavopulmonary connection; TGA, transposition of the great arteries; TVR, tricuspid valve repair; VSD, ventricular septal defect.

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 235 patients) penicillins in 147 (63%), cephems in 81 (35%), aminoglycosides in 84 (36%), carbapenems in 43(18%), vancomycin in 29 (12%), oxacephems in nine (4%), tetracyclines in nine (4%), fosfomycin in seven (3%), fluconazole in five (2.1%), clindamycin in four (2%), and chloramphenicol in one (0.4%).

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 not been completed) in 63 of 239 (26.4%) at 37.2 (34.8) days (range 0–180 days) of illness and in healed 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. Table 6 lists indications for cardiac surgery.

Table 2 Conditions and procedures associated with infective endocarditis

Conditions and procedures	Number (n = 78)
Invasive dental procedures	29 (37.2%)
Cardiovascular surgery	20 (25.6%)
Pneumonia	11 (14.1%)
Invasive otolaryngeal procedures	5 (6.4%)
Unexpected trauma	4 (5.1%)
Atopic dermatitis	4 (5.1%)
Central venous catheter	2 (2.6%)
Catheter intervention	1 (1.3%)
Meningitis	1 (1.3%)
Piercings	1 (1.3%)

Mortality

Total mortality was 21 of 239(8.8%). Fourteen of 176 (8.0%) patients who received medical treatment alone (n = 176) died. None of 40 (0%) patients who had surgery (n = 40) after IE had healed died. Seven of 63 (11.1%) patients who had surgery (n = 63) during active IE died, which was similar to mortality with medical treatment alone (p = 0.2).

The mortality among paediatric patients (16 of 170 (9.4%)) was similar to that of adults (five of 69 (7.2%), p = 0.6). Three of the 12 patients with prosthetic material infection died: one with medical treatment alone and two others who underwent surgery during acute IE.

Causes of death

The causes of death in 21 patients were surgery in seven, cardiac failure in six (including two with cerebral embolisation), IE unresponsive to antimicrobials in six, pneumonia in one, and renal failure in one.

DISCUSSION

Clinical features of IE in 239 patients—170 paediatric and 69 adults—with CHD are established. The incidence of IE in

Table 3 Causative microorganisms

Organism	Number (n = 201)*
Streptococcus species	100 (49.8%)
α Streptococcus	87 (43.3%)
Pneumonia	11 (5.5%)
β Streptococcus	2 (1.0%)
Staphylococcus species	74 (36.8%)
S aureus	64 (31.8%)
MRSA	15 (7.5%)
S epidermidis	10 (5.0%)
MRSE	4 (2.0%)
Haemophilus species	9 (4.5%)
Candida species	5 (2.5%)
Pseudomonas	4 (2%)
Others†	9 (4.5%)

*Unknown causative microorganism: 38; †*Granulicatella* species 3, *Micrococcus* species 1, *Moraxella* species 1, *Gamella* species 1, enterococci 1, bacillus 1, anaerobic species 1.
MRSA, methicillin resistant *Staphylococcus aureus*; MRSE, methicillin resistant *Staphylococcus epidermidis*.

Table 4 Complications

Complications	Number (n = 116, multiple answers)
Increased valvar regurgitation	73 (30.5%)
Cardiac failure	56 (23.4)
Systemic emboli	48 (20.1)
Stroke	25 (10.5%)
Systemic abscess formation	12 (5%)
Arrhythmia development	13 (5.4%)
Periannular extension of abscess	11 (4.6%)
Intracranial haemorrhage	7 (2.9%)
Prosthetic valve dysfunction	4 (1.7%)
Glomerulonephritis/renal failure	4 (1.7%)
Mycotic aneurysm	3 (1.3%)

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.[8–15] Morris[14] reported that the highest risk for IE was found in children who have 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 reports[2 16–18] 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.[2 9 10 15 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.[9 10] 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 reportedly tetralogy of Fallot or an aortopulmonary shunt.[2 9] In this study, aortopulmonary shunt, extraconduit repair, 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.[2 16] 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.[15 16] In this study, four of 11 patients with previous aortic valve surgery developed IE.

Table 5 Empirical antimicrobial treatment

Antibiotics	Number (n = 235)
Penicillins alone	54 (23%)
Penicillins plus aminoglycosides	50 (21%)
Penicillins plus others*	30 (13%)
Cephems alone	29 (12%)
Cephems plus aminoglycosides	8 (3.4%)
Cephems plus others†	15 (6%)
Carbapenems alone	9 (4%)
Carbapenems plus others‡	7 (3%)
Vancomycin alone	4 (1.7%)
Vancomycin plus carbapenems	6 (2.6%)
Vancomycin plus others§	17 (7%)
Oxacephems	4 (1.7%)
Antifungal agents (fluconazole)	2 (0.8%)

*Cephems, aminoglycosides, carbapenems, clindamycin, or tetracyclines; †carbapenems, fosfomycin, aminoglycosides, or tetracyclines; ‡aminoglycosides, oxacephems, fosfomycin, clindamycin, or tetracyclines; §aminoglycosides, cephems, tetracyclines, or carbapenems.

It is reported that drug misuse is often associated with IE in adults in the USA and Europe,[1] but there were no patients associated with drug abuse in this study or in a recent nationwide survey of IE in adults in Japan.[13]

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.[1]. 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.[8] 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.[20] In adults with CHD in this study, left sided IE was more frequent than right

Table 6 Indications of surgery in active infective endocarditis

Indication	Number (n = 63, multiple answers)
Vegetation: possible future development of systemic embolisation/status after systemic embolisation	37 (52.4%)
Cardiac failure unresponsive to medical treatment	20 (31.7%)
Prosthetic material infection	14 (20.3%)
Periannular extension of abscess	11 (17.5%)
Persistent bacteraemia despite appropriate medical treatment	5 (7.9%)
Arrhythmia	2 (2.9%)
Others	4 (5.8%)

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.[2 9] 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,[2 9] 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%).[1 9 10] 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.[20 21] 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.[2 8 19 22] 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.[3] 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.[8 9]

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[23] 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%[21] and the rate dropped to 60% when antibiotics were used before blood culturing.[24] 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.[21] Prosthetic valve IE is common and usually results in valve replacement in adults.[3] Extension of IE beyond the valve annulus predicts higher mortality with more frequent development of cardiac failure and the need for cardiac surgery.[3] 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.[25] Neurological signs and symptoms are often associated with *S aureus* infection and are reported in 20% of children with IE.[18] 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.[3 26] 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.[3 27] 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.[3] 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.[3–6] 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.[21] The recently reported mortality among paediatric patients with IE is about 10%,[9 19 21] 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,[3] and surgery as an adjunct to medical treatment was recognised as more effective than medical treatment alone.[3 26–32] 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.[29–32] 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[30] requiring replacement.[10 19] 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

Most cardiologists in Japan use the Duke criteria for diagnosing IE, but some in the participating institutions had no uniform criteria[8] 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 adults 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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Authors' affiliations

K Niwa, S Tateno, Chiba Cardiovascular Centre, Chiba, Japan
M Nakazawa, Tokyo Women's Medical University, Tokyo, Japan
M Yoshinaga, Kagoshima University, Kagoshima, Japan
M Terai, Chiba University, Chiba, Japan

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