Causative Organism Influences Clinical Profile and Outcome of Infective Endocarditis in Pediatric Patients and Adults With Congenital Heart Disease

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Background Studies on microorganisms in a large cohort of patients with congenital heart disease (CHD) and infective endocarditis (IE) are rare. Using a nationwide survey, the relationship between causative microorganisms and clinical profiles in patients with CHD and IE was investigated.

Methods and Results Data from 188 patients with CHD (pediatric patients (n=113), mean age, 6.2±4.9 years; adult patients (n=75), mean age 28.4±13.4 years) and IE from 60 institutions were analyzed. Causative microorganisms were *Streptococcus* species (94:50.0%), *Staphylococcus* species (68:36.2%), *Haemophilus* species (9:4.8%), *Candida* (5:2.7%), *Pseudomonas* species (4:2.1%) and other unclassified microorganisms (8:4.3%). Staphylococcal IE was observed significantly higher in perioperative IE (11/16), in cyanotic patients (32/73) and patients younger than 1 year old (11/16). Streptococcal IE was observed significantly higher in acyanotic patients (64/109) and patients aged 16 years or older (48/75). Total mortality was 20/188 (10.6%) and was high for candidial (2/5; 40%) and pseudomonal IE (2/4; 50%). Mortality was highly associated with younger age, especially infants (5/16), and methicillin-resistant staphylococcal IE (6/15).

Conclusions The causative microorganisms are significantly related to the clinical profile and outcome in patients with IE and CHD. These results form the basis for selecting appropriate antibiotics for prevention and management. (Circ J 2005; 69: 1266–1270)

Key Words: Children; Congenital heart disease; Infective endocarditis; Microorganisms

Infective endocarditis (IE) still has high mortality and is associated with serious complications in patients with congenital heart disease (CHD), despite of advances in antimicrobial treatment.¹ An increased incidence of staphylococcal IE, especially that caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in children with CHD, has been reported.² The causative organism and antimicrobial treatment modify the clinical course and prognosis of IE in patients with CHD, but data from a large cohort are scarce. The present study used a large clinical database to determine the relationship between causative organisms and clinical profile/outcome of patients with CHD and IE in order to provide a basis for selecting the appropriate antibiotics for prevention and management of IE in pediatric and adult patients with CHD, as well as establishing proper guidelines for management.

Methods

Members of the Japanese Society of Pediatrics Cardiology and Cardiac Surgery in 66 institutions registered 239 pediatric and adult patients with CHD and IE diagnosed by clinical, echocardiographic and microbiologic findings during a 5-year period (1997–2001). The causative organism was identified in 201 patients, CHD was identified in 188 patients, and 13 pediatric patients with no detectable cardiac disease were excluded from the study. The relationships between causative microorganisms and clinical profile/outcome were analyzed in the 188 patients, who comprised 107 males and 81 females, with an age range from 14 days to 63 years (mean, 15.1±14.3 years; pediatric patients (n=113), mean age, 6.2±4.9 years and adult patients (n=75), mean age 28.4±13.4). The data included causative organism, age, diagnosis of CHD, surgical history, source of infection, complications and mortality. There were 73 patients (38.8%) with cyanotic CHD, which included tetralogy of Fallot (TOF) in 34 (non-repaired: 17), double outlet right ventricle (DORV) in 14 (non-repaired: 9), single ventricle (heterotaxia) in 14 (non-repaired: 13), complete transposition of the great arteries (TGA) in 8 (non-repaired: 1), truncus arteriosus communis in 2 (non-repaired: 0), and hypoplastic left heart syndrome in 1 (non-repaired: 1). There were 109 patients (58.0%) with acyanotic CHD, which included ventricular septal defect (VSD) in 69 (non-repaired: 57), mitral stenosis/regurgitation in 14 (non-re-

(Received April 6, 2005; revised manuscript received July 4, 2005; accepted July 7, 2005)

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paired: 12), aortic stenosis/regurgitation in 8 (non-repaired: 5), coarctation of the aorta in 5 (non-repaired: 1), congenitally corrected TGA in 4 (non-repaired: 1), atrioventricular septal defect in 3 (non-repaired: 2), atrial septal defect (ASD) in 2 (non-repaired: 0), patent ductus arteriosus in 2 (non-repaired: 2), sinus of Valsalva aneurysm in 1 (non-repaired: 0), and Ebstein's anomaly 1 (non-repaired: 0). Two patients with ASD had an infected ASD patch during the postoperative period.

Age-Related Subgroups

For analysis of relation between age distribution and causative organisms, we divided the 188 patients into 5 subgroups based on differences in dental development: (1) neonates or infants, (2) 1–5 years, (3) 6–11 years, (4) 12–15 years, and (5) 16 years or older.

Statistical Analysis

Statistical analysis was performed with the software StatView, SAS Institute Inc (Cary, NC, USA). Numerical data are expressed as mean±SD and either range or number. Discrete variables were analyzed by chi-square test. Continuous data were analyzed across the groups by Kruskal-Wallis test and when significant differences were found ($p<0.05$), pair-wise comparisons were performed using a two-sample t-test. A p -value <0.05 was considered significant. If a survey question was unanswered or the answer was unclear, those data were not counted.

Results

Causative Microorganisms (Table 1)

Streptococcus ($n=94$; 50.0%) and Staphylococcus species ($n=68$, 36.2%) were the commonest pathogens; 58 of 94 species in streptococcal IE (63.7%) were in the mitis group, and 57 of 68 species in staphylococcal IE (83.8%) was Staphylococcus aureus (*S. aureus*), with MRSA ac-

Table 1 Causative Microorganism in 188 Cases of Congenital Heart Disease

Microorganism	No. of cases (%)
<i>Streptococcus</i> spp.	94 (50.0)
Mitis group	58
Anginosus group	3
Pyogenis group	1
Salivarius group	1
Mutant group	1
Unclassified	30
<i>Staphylococcus</i> spp.	68 (36.2)
<i>Staphylococcus aureus</i>	57
<i>Staphylococcus epidermidis</i>	9
<i>Staphylococcus hominis</i>	1
<i>Staphylococcus capitis</i>	1
<i>Haemophilus</i> spp.	9 (4.8)
<i>Candida</i> spp.	5 (2.7)
<i>Pseudomonas</i> spp.	4 (2.1)
Others	8 (4.3)
<i>Granulicatella</i> spp.	2
<i>Bacillus</i> spp.	1
<i>Micrococcus</i> spp.	1
<i>Moraxella</i> spp.	1
<i>Gamella</i> spp.	1
<i>Enterococcus</i> spp.	1
Anaerobes	1

counting for 15 (26.3%) of 57 *S. aureus* strains. The remaining pathogens were *Haemophilus* ($n=9$, 4.8%), *Candida* ($n=5$, 2.7%), and *Pseudomonas* ($n=4$, 2.1%).

Relationship Between Age and Causative Microorganisms (Table 2)

The patient's age at the onset of IE was available for 188 patients: 16 (8.5%) in the subgroup of neonates or infants (neonates: $n=2$, infants: $n=14$), 39 (20.7%) in the subgroup of 1–5 years, 37 (19.7%) in the subgroup of 6–11 years, 21 (11.2%) in the subgroup of 12–15 years, and 75 (39.9%) in the subgroup of 16 years or older. Streptococcus species

Table 2 Age Groups and Causative Microorganisms

Microorganism	Age group					Total
	Neonates and infants	1–5 years	6–11 years	12–15 years	≥16 years	
<i>Streptococcus</i> spp.	2	22	16	6	48	94
<i>Staphylococcus</i> spp.	11	7	17	13	20	68
<i>Haemophilus</i> spp.	1	5	0	0	3	9
<i>Candida</i> spp.	1	1	0	2	1	5
<i>Pseudomonas</i> spp.	1	1	2	0	0	4
Others	0	3	2	0	3	8
Total	16	39	37	21	75	188

Table 3 Diagnosis of CHD and Causative Microorganisms

Microorganism	Type of CHD									Total	
	Cyanotic CHD (n=73)					Acyanotic CHD (n=109)					Unknown
	TOF	DORV	Heterotaxia	TGA	Other	VSD	MS/MR	AS/AR	Other		
<i>Streptococcus</i> spp.	12 (8)	6 (4)	7 (7)	3 (0)	0 (0)	43 (38)	6 (5)	5 (3)	10 (4)	2	94
<i>Staphylococcus</i> spp.	16 (5)	6 (5)	3 (3)	4 (0)	3 (1)	20 (16)	7 (7)	1 (1)	5 (1)	3	68
<i>Haemophilus</i> spp.	3 (3)	1 (0)	2 (1)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0	9
<i>Candida</i> spp.	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	1	5
<i>Pseudomonas</i> spp.	1 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)	0	4
Others	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	5 (2)	0 (0)	1 (1)	0 (0)	0	8
Total	34 (17)	14 (9)	14 (13)	8 (1)	3 (1)	69 (57)	14 (12)	8 (5)	18 (6)	6	188

CHD, congenital heart disease; TOF, tetralogy of Fallot; DORV, double outlet right ventricle; TGA, transposition of the great arteries; VSD, ventricular septal defect; MS/MR, mitral valve stenosis/regurgitation; AS/AR, aortic valve stenosis/regurgitation. Results in parentheses are cases of previous cardiac surgery.

Table 4 Source of Infection and Causative Microorganisms

Microorganism	Predisposing condition									Total
	Dental procedure	Cardiac surgery	Pneumonia	Otolaryngeal procedure	Unexpected trauma	Atopic dermatitis	URTI	Other	Unknown	
<i>Streptococcus</i> spp.	17	1	4	2	1	0	1	2	66	94
<i>Staphylococcus</i> spp.	3	7	1	1	1	2	1	5	47	68
<i>Haemophilus</i> spp.	0	0	0	1	1	0	0	1	6	9
<i>Candida</i> spp.	0	3	0	0	0	0	0	1	1	5
<i>Pseudomonas</i> spp.	0	0	0	0	0	0	0	0	4	4
Others	3	0	0	0	0	0	0	0	5	8
Total	23	11	5	4	3	2	2	9	129	188

URTI, upper respiratory tract infection.

Table 5 History of Cardiac Surgery and Causative Microorganisms

Microorganism	Surgical status				Total
	Unrepaired	Palliative	Post-repair	Unknown	
<i>Streptococcus</i> spp.	52	17 (1)	23 (0)	2	94 (1)
<i>Staphylococcus</i> spp.	27	12 (2)	28 (9)	1	68 (11)
<i>Haemophilus</i> spp.	1	6 (0)	2 (0)	0	9 (0)
<i>Candida</i> spp.	1	0 (0)	4 (3)	0	5 (3)
<i>Pseudomonas</i> spp.	0	1 (0)	3 (0)	0	4 (0)
Others	3	2 (1)	3 (0)	0	8 (1)
Total	84	38 (4)	63 (12)	3	188 (16)

Results in parenthesis are no. of cases of perioperative infection.

Table 6 Site of Infection and Causative Microorganisms

Microorganism	Site of infection											Total
	TV	MV	AV	PV	AV + MV	PV + TV	AV + MV + TV	Conduit	Artificial patch	Other	Unknown	
<i>Streptococcus</i> spp.	16 (1)	15 (0)	6 (0)	4 (1)	3 (0)	0	1 (0)	1	1	13	34	94
<i>Staphylococcus</i> spp.	9 (0)	9 (0)	5 (0)	1 (0)	0	1 (0)	0	4	6	15	18	68
<i>Haemophilus</i> spp.	1 (0)	0	0	0	0	0	0	0	1	1	6	9
<i>Candida</i> spp.	1 (1)	1 (0)	0	1 (0)	0	0	0	2	0	0	0	5
<i>Pseudomonas</i> spp.	1 (0)	0	0	0	0	0	0	1	0	1	1	4
Others	1 (0)	1 (0)	2 (0)	0	0	0	0	0	1	1	2	8
Total	29 (2)	26 (0)	13 (0)	6 (1)	3 (0)	1 (0)	1 (0)	8	9	31	61	188

TV, tricuspid valve; MV, mitral valve; AV, aortic valve; PV, pulmonary valve. Results in parentheses are no. of infected prosthetic valves.

were more frequent than *Staphylococcus* species (48/94 vs 20/68, $p < 0.05$) in patients aged 16 years or older, whereas in the neonate and infant subgroup, *Staphylococcus* species were more frequent (11/68 vs 2/94, $p < 0.05$). *Pseudomonas* species were observed only in children under 11 years of age.

Relationship Between Diagnosis of CHD and Causative Microorganisms (Table 3)

The main causes of cyanotic CHD were TOF, DORV and heterotaxia, whereas VSD was the main cause of acyanotic CHD. In 13 of 14 (92.9%) cyanotic patients with heterotaxia, and in 57 of 69 (82.6%) acyanotic patients with VSD, IE developed in the case of non-repair or palliative surgery. In patients with cyanotic CHD, *Staphylococcus* species (32/68, 47.1%) were more frequent than *Streptococcus* species (28/94, 29.8%) ($p < 0.05$), whereas in patients with acyanotic CHD, *Streptococcus* species (64/94, 68.1%) were more frequent (33/68, 48.5%) ($p < 0.05$).

Source of Infection (Table 4)

The likely source of infection was identified in 59 patients (31.4%). The preceding factor of IE was determined in 28 of 94 patients with streptococcal IE (dental procedure

(17/28, 60.7%); pneumonia (4/28, 14.3%)), and in 21 of 68 of patients with staphylococcal IE (cardiac surgery (7/21, 33.3%); dental procedure (3/21, 14.3%); atopic dermatitis (2/21, 9.5%)).

Cardiac Surgery and Causative Microorganisms (Table 5)

Streptococcus species were isolated in 52 of 84 patients (61.9%) without previous cardiac surgery and *Staphylococcus* species in 27 (32.1%). IE developed in 101 patients with previous cardiac surgery, including 38 with palliative surgery, of whom 16 (15.8%) developed IE perioperatively.

Site of Infection and Causative Microorganisms (Table 6)

Atrioventricular valves were the most commonly affected sites. The tricuspid valve was affected in 31 patients (16.5%) and the mitral valve in 30 patients (16.0%). In 5 of these 61 patients, 2 or 3 valves were infected, and 3 of 85 infected valves (3.5%) from 79 patients were prosthetic valves. The incidence of infected artificial materials such as conduits and patches was high (10/68, 14.7%) in staphylococcal IE compared with streptococcal IE (2/94, 2.1%) ($p < 0.05$).

Table 7 Complications and Causative Microorganisms

	Vegetation	Valvular regurgitation	Cardiac failure	Arrhythmias	CNS embolism	Other embolism	Abscess	Aneurysm
<i>Streptococcus</i> spp.	54	32	22	6	9	8	5	2
<i>Staphylococcus</i> spp.	41	19	12	4	4	7	4	0
<i>Haemophilus</i> spp.	1	3	1	0	0	0	0	1
<i>Candida</i> spp.	5	1	1	0	0	1	0	0
<i>Pseudomonas</i> spp.	3	1	0	0	0	1	0	0
Others	5	2	2	0	0	0	0	0
Total	109	58	38	10	13	17	9	3
	(58.0%)	(30.9%)	(20.2%)	(5.3%)	(6.9%)	(9.0%)	(4.8%)	(1.6%)

CNS, central nervous system.

Table 8 Cases of Fatal IE

Case no.	Age	Diagnosis of CHD	Cardiac surgical status	Antibiotics administered before diagnosis of IE	Microorganism
1	1Y	TOF	Palliative	+	<i>Streptococcus mitis</i>
2	9Y	AS/AR	No	+	<i>Streptococcus mitis</i>
3	22Y	Others	No	—	<i>Streptococcus mitis</i>
4	3Y	DORV	Palliative	—	<i>Streptococcus oralis</i>
5	0Y7M	Heterotaxia	Palliative	—	<i>Streptococcus pneumoniae</i>
6	9Y	TOF	No	+	<i>Staphylococcus aureus</i>
7	10Y	VSD	No	+	<i>Staphylococcus aureus</i>
8	13Y	DORV	Post-repair	+	<i>Staphylococcus aureus</i>
9	21Y	Unknown	No	—	<i>Staphylococcus aureus</i>
10	23Y	VSD	Post-repair	+	<i>Staphylococcus aureus</i>
11	0Y2M	ECD	Post-repair	+	<i>Staphylococcus aureus</i> (MRSA)
12	0Y2M	TGA	Post-repair	+	<i>Staphylococcus aureus</i> (MRSA)
13	0Y4M	VSD	Post-repair	—	<i>Staphylococcus aureus</i> (MRSA)
14	12Y	DORV	Post-repair	+	<i>Staphylococcus aureus</i> (MRSA)
15	21Y	TOF	Palliative	+	<i>Staphylococcus aureus</i> (MRSA)
16	25Y	VSD	No	—	<i>Staphylococcus aureus</i> (MRSA)
17	0Y10M	MS/MR	Post-repair	+	<i>Pseudomonas aeruginosa</i>
18	1Y	Heterotaxia	Palliative	+	<i>Pseudomonas aeruginosa</i>
19	13Y	DORV	Post-repair	+	<i>Candida</i> spp.
20	25Y	TOF	Palliative	+	<i>Candida</i> spp.

IE, infective endocarditis; CHD, congenital heart disease; Y, years; TOF, tetralogy of Fallot; AS/AR, aortic valve stenosis/regurgitation; M, months; DORV, double-outlet right ventricle; VSD, ventricular septal defect; ECD, endocardial cushion defect; TGA, complete transposition of the great arteries; MS/MR, mitral valve stenosis/regurgitation.

Complications and Causative Microorganisms (Table 7)

Complications were common (126/188=67.0%) and there was no significant difference in the incidence of complications among the different causative species. The incidence of vegetations was very low (1/9, 11.1%) with IE caused by *Haemophilus* species compared with the other species ($p<0.05$).

Fatal IE (Table 8)

Twenty patients (10.6%) died of IE at a mean age of 10.5 years (2 months to 25 years). Mortality was highest in patients less than 1 year of age (5/16, 31.3%) compared with the other subgroups; 7.7% (3/39) in 1–5 years, 8.1% (3/37) in 6–11 years, 14.3% (3/21) in 12–15 years and 8.0% (6/75) in 16 years or older. Fourteen deaths were in patients (70.0%) who had undergone cardiac surgery, 11 of whom were given prophylactic antibiotics before the onset of IE. *S. aureus* was isolated from 11 of the 20 dead patients (55.0%) including 7 with MRSA, whereas *Streptococcus mitis* was the causative pathogen only in 3 of the fatal cases (15.0%). The overall mortality was higher for *S. aureus* (11/57, 19.3%) than for the *Streptococcus* species (5/94, 5.3%, $p<0.05$). Although *Candida* and *Pseudomonas* species were rare, the mortality was high for both: *Candida* (2/5, 40.0%) and *Pseudomonas* (2/4, 50.0%). *Candida* species were primarily isolated from fatal cases with long-

term intravenous antibiotic treatment.

Discussion

The causative microorganism significantly influences the clinical profile and course in CHD patients with IE. The present results will help in matching the causative organism with the clinical manifestation, and therefore in the selection of the correct antibiotics for prevention and management.

Microorganisms

In this study, *Streptococcus* and *Staphylococcus* species were the most commonly isolated of the causative organisms for IE, and the *Streptococcus mitis* group was the most frequent. Nakatani et al in Japan recently described the annual trend of IE in 817 adults with various cardiovascular diseases, including 9.1% who had CHD, and they isolated 697 microorganisms (85%), with 50% *Streptococcus* species and 32% *Staphylococcus* species.⁵ In a UK survey of IE in adults with cardiovascular disease, including 27% with CHD, conducted between 1987 and 1996, *Streptococcus* species comprised 49% and *Staphylococcus* species comprised 26%.⁶ In contrast, a US study reported that *Staphylococcus* species caused 50% of all episodes of IE in pediatric patients, followed by *Streptococcus* species

in 22%.¹ The results of the present study are similar to those in previous reports from Japan and the UK studies, but different from the US study, and the discrepancy may be related to patient age, type of CHD and type of preventive measures. The incidence of staphylococcal IE was higher in patients with cyanotic CHD than in those with acyanotic CHD. In the US study, 51% of the CHD patients were cyanotic CHD vs 39% in our study. There was a significant difference between staphylococcal IE and streptococcal IE in mean age: 12.8 and 17.6 years, respectively. In patients under 1 year of age, the prevalence of staphylococcal IE was significantly higher than that of streptococcal IE (16.2% vs 2.1%). Furthermore, 81.8% of the *S. aureus* strains cultured from these patients were MRSA.

Predisposing Factors for IE

In this study, the leading predisposing risk factor was dental procedures. The American Heart Association recommends antibiotic prophylaxis for dental procedures in patients with most types of CHD, excluding simple ASD and repaired simple CHD without postoperative residua beyond 6 months postoperatively.⁷ In our study, 53.7% of patients with CHD had undergone cardiac surgery, and perioperative IE was observed in 8.5%, an incidence similar to previous reports.^{1,10} Cardiac surgery was the second most frequent predisposing risk factor, and *Staphylococcus* species were the major pathogen. Atopic dermatitis was a frequent predisposing risk factor for staphylococcal IE. Although there are only a few case reports of IE associated with atopic dermatitis,^{11,12} the incidence of atopic dermatitis in Japan is rapidly increasing, a warning that prophylactic measures should be taken to prevent IE.

Infected Sites

The infected valve differed markedly between IE patients with CHD and without CHD. The aortic valve was the most commonly affected site in IE patients without CHD,⁶ whereas the tricuspid and mitral valves were the most common affected sites in those with CHD. The incidence of prosthetic valve IE in patients with CHD was lower than in the adult cohort,¹³ and infection of artificial materials, such as conduits and patches, mainly occurred with staphylococcal IE.

Morbidity and Mortality

Despite remarkable developments and improvements in the treatment of IE, morbidity and mortality remain high,^{4,15} as high as 10.0% in the present study. IE caused by MRSA had the highest mortality, followed by *Candida* and *Pseudomonas*, even though the latter are rare pathogens. These organisms are typically hospital-acquired, nosocomial pathogens that have been increasingly observed in patients with IE since the 1980s. *S. aureus* has been recognized as an important pathogen since the 1970s, and recently MRSA and coagulase-negative staphylococci have increased in prevalence.^{13,16} There has also been an increased incidence of fungal endocarditis,¹⁷ reflecting the longer duration of broad-spectrum antimicrobial therapy in seriously ill patients. Novel therapies against nosocomial pathogens are needed to improve patient outcome.

Conclusions

The causative microorganism is significantly related to the clinical profile and outcome of IE. Staphylococcal IE is

frequent in perioperative patients less than 1 year of age, in patients with cyanotic CHD, and in older patients with atopic dermatitis, whereas streptococcal IE is frequent in patients aged 16 years or more, with acyanotic CHD and without previous cardiac surgery.

Acknowledgments

This work was supported in part by the fund from the Japanese Society of Pediatric Cardiology and Cardiac Surgery Joint Working Groups for Guidelines for Prophylaxis, Diagnosis and Management of Infective Endocarditis in Patients with Congenital Heart Disease.

We gratefully acknowledge the assistance of members of the Japanese Society of Pediatric Cardiology and Cardiac Surgery Joint Working Groups for Guidelines for Prophylaxis, Diagnosis and Management of Infective Endocarditis in Patients with Congenital Heart Disease: Shigeyuki Echigo, MD, Taku Fujiwara, DDS, Kazumi Kubota, DDS, Tomiaki Murakami, MD, Fukiko Ichida, MD, Kunitaka Joo, MD, Noriyuki Haneda, MD, Takashi Higaki, MD, Hiroshi Suzuki, MD, Hideki Uemura, MD and Hiroyuki Fukushima, MD in the collecting data and in particular, the assistance of Atsuko Niwa, MD, in preparing the manuscript and analyzing the data. We gratefully acknowledge Joseph K Perloff, MD, for assessing the manuscript.

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