Clinical Investigation

Changing Profile of Infective Endocarditis:

A Clinicopathologic Study of 220 Patients in a Single Medical Center from 1998 through 2009

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The epidemiologic profile of infective endocarditis has changed substantially over the past few years, especially in industrialized countries. Our study evaluates the clinical and pathologic characteristics of infective endocarditis patients treated by cardiac surgery in China during a 12-year period.

We retrospectively evaluated 220 surgically treated infective endocarditis patients and analyzed their changes from the beginning of 1998 through 2009. The mean age of the patients increased from 36.9 to 42.7 years during those 12 years (P=0.036). The chief predisposing disease was congenital heart disease (32.8%), rather than rheumatic heart disease (13.2%); this rate did not change significantly during the 12 years. The prevalent congenital lesion was bicuspid aortic valve, the rate of which (55.6%) increased significantly over the 3 time intervals studied (P=0.016). The frequency of infective endocarditis after nondental surgical and nonsurgical intervention was significantly greater (23.3%) during 1998 through 2001, compared with the 2 intervals that followed (9%; P=0.019). Streptococcus viridans *was the most frequent causative agent overall (25.6%). Forty-seven of the 220 patients (21.4%) carried the clinical diagnosis of some other form of heart disease before surgery, but at surgery they were found to have infective endocarditis as the fundamental disease process. Of 47 patients, 33 (70.2%) had either very small or no vegetations but had focal necrosis and inflammation of valve tissue that supported the diagnosis of infective endocarditis.* ***(Tex Heart Inst J 2014;41(5):491-8)***

Key words: *Clinicopathology; endocarditis, infective; heart defects, congenital; heart valves/abnormalities; mitral valve prolapse; prosthesis-related infections; retrospective studies; rheumatic heart disease; staphylococcal infections; streptococcal infections*

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The epidemiologic profile of infective endocarditis (IE) has changed substantially over the past few years, especially in industrialized countries.[1] The risk factors, causative microorganisms, and the mean age of the patients with IE have also changed in developed countries.[1-3] However, this trend is not obvious in some developing countries, such as Tunisia and other African states.[4,5]

Because only a few studies regarding changes in the clinical presentation or the natural course of IE have application to China, we have attempted to evaluate the clinical presentations and outcomes of IE patients who were surgically treated in our largest national cardiovascular disease referral center over the course of 12 years.

Patients and Methods

We retrospectively examined the cases of all surgically treated IE patients in Fuwai Cardiovascular Hospital from the beginning of 1998 through the end of 2009. This hospital is the main referral center for severe and complicated cardiovascular diseases in China. Cases of endocarditis were included in this study if they met the modified Duke criteria for endocarditis: vegetations attached to the endocardial structure or to implanted intracardiac material; or abscess or some other morphologic feature characteristic of endocarditis, such as perforation, fistula, valve aneurysm, and dehiscence of a prosthetic valve.[6] Before surgery, clinical diagnosis of definite IE or possible IE was made in accordance with the modified Duke criteria.[7] Acute IE is characterized by an acute onset and fulminant course, and it is often accompanied by the sequelae of endocarditis, including spleen embolism, periannular abscess, and cardiogenic and septic shock. Subacute IE typically presents with subtle constitutional symptoms and often is not diagnosed until it has been present for months.

The indications for surgical treatment were severe valvular dysfunction in the presence of heart failure, abscess or perivalvular extension, large vegetations at high risk

of embolization (or recurrent embolization during antibiotic treatment), and failure of conservative medical treatment.

Patient Data. For each surgically treated IE patient, we collected data on age, sex, clinical symptoms, predisposing heart diseases, pathologic findings, microbiologic data, surgical treatment, complications, and outcomes. These data were then analyzed generally or individually at 4-year intervals over the course of 12 years, to reveal clinicopathologic changes. This study was approved by our institutional ethics committee.

Pathologic Examination. Surgically resected specimens were fixed in 10% formalin and embedded in paraffin. Sections were cut for hematoxylin–eosin, gram, and periodic acid–Schiff (PAS) stains. Gram and PAS stains were performed for detecting the bacteria and the fungi, respectively.

Statistical Analysis. Data are shown as mean ± SD or as number and percentage. The trend of patient age during different periods was tested with the polynomial contrast procedure. The change-over-time trend of categorical variables—including percentages of involved valves, underlying diseases, organisms, and the rate of missed diagnosis—were tested by the χ^2 test and linear-by-linear association. Actual *P* values were calculated in the event of small frequencies. A value of $P < 0.05$ was considered significant. Statistical analysis was performed with the use of SPSS 16.0 for Windows (IBM Corporation; Armonk, NY).

Results

Changes in Clinical Characteristics over Every 4-Year Period

A total of 620 patients fulfilled the modified Duke criteria for IE over this 12-year study period, during which 400 patients were medically treated and 220 were surgically treated. Of these 220 surgically treated IE patients, 153 were male and 67 were female, with a mean age of 39.1 ± 13.8 years (range, 3–75 yr). Only surgically treated IE patients were included in this study.

In order to divide these 12 years equally, we chose to analyze change at 4-year intervals (1998–2001, 2002–2005, and 2006–2009). When changes were analyzed at these intervals, the highest proportion of IE was seen in young patients (ages 19–39 yr) during 1998–2001. The proportions of young and middle-aged (40–69 yr) patients were almost equal during 2002–2005. Middle-aged patients became the highest proportion during 2006–2009 ($P < 0.001$). The average age of patients increased significantly from 36.9 ± 13.6 years during 1998–2001 to 42.7 ± 13.1 years during 2006–2009 ($P = 0.036$) (Table I).

Before surgery, 23 patients (10.5%) were diagnosed with acute IE. The mean time between the onset of signs or symptoms and treatment was 18 days (range, 1–30 d). Of the 23 patients, 12 had complications that included acute heart failure (5), acute renal failure (1), periannular abscess (3), aortic aneurysm rupture (2), and neurologic problems (1). One hundred fifty patients (68.2%) had subacute IE, with a mean time between onset and treatment of 3.3 months (range, 0.5–24 mo). Before surgery, 47 patients (21.4%) carried the clinical diagnosis of rheumatic or degenerative valve disease, but at surgery they were found to have IE as the fundamental disease process.

Preoperatively, evidence of embolization was clinically apparent in 12 of the 220 patients (5.5%).

Distribution of Infected Valves

The proportions of aortic valve involvement alone and mitral valve involvement alone were seen, respectively, in 91 (41.4%) and 79 (35.9%) of the patients. More than 2 valves were affected in 21 (9.6%) of the patients. Three patients with tricuspid valve involvement and 4 patients with pulmonary valve involvement had congenital heart disease (CHD): ventricular septal defect (VSD) (5), tetralogy of Fallot (1), and bicuspid pulmonary valve (1). The remaining 7 patients (3.2%) had prosthetic valve IE, which included the involvement of both mechanical (6) and bioprosthetic (1) valves. When analyzed separately, the proportion of aortic valve IE did not change significantly during the 3 time periods (43.3%, 41.9%, and 40.4%, respectively; $P = 0.755$). By contrast, the proportion of mitral valve IE increased over time (23.3%, 34.9%, and 40.4%, respectively); however, these changes did not attain significance ($P = 0.093$) (Table I).

Underlying Heart Diseases

In the current study, 72 of the patients (32.7%) had CHD, although the rate decreased slightly over the 3 time periods (43.4%, 33.8%, and 28.9%, respectively; $P = 0.142$). The average age of these patients was 34.3 years. Specifically, bicuspid aortic valve (BAV) was the most frequent anomaly (55.6% of patients with CHD), and it increased from 53.8% and 34.5% to 76.7% over the 3 time intervals ($P = 0.016$). Of all the 114 patients who had aortic valve involvement, either alone or in union with other valve involvement, 40 (35.1%) had BAV. Ventricular septal defect was another prominent risk factor in CHD-associated IE cases: it accounted for 27.8% overall and for 38.5%, 34.5%, and 16.7% of those cases, respectively, over the 3 time periods ($P = 0.094$). Five patients (6.9%) had patent ductus arteriosus, 4 (5.6%) had subaortic stenosis, 1 (1.4%) had double-outlet right ventricle accompanied by bicuspid pulmonary valve, 1 (1.4%) had bicuspid pulmonary valve, and 1 (1.4%) had Marfan syndrome.

Forty patients (18.2%) had preexisting mitral valve prolapse, a rate that did not change significantly during the 3 monitored time intervals (6.7%, 22.1%, and

TABLE I. Characteristics of 220 Surgically Treated Infective Endocarditis Patients Analyzed at 4-Year Intervals over a 12-Year Period

Variable	1998–2001	2002–2005	2006–2009	Total	*P* Value
No. of patients	30	86	104	220	—
Sex					—
Male	21 (70)	54 (62.8)	78 (75)	153 (71.1)	—
Female	9 (30)	32 (37.2)	26 (25)	67 (28.9)	—
Mean age (yr)	36.9 ± 13.6	35.4 ± 13.7	42.7 ± 13.1	39.1 ± 13.8	0.036**
Affected valves					—
Aortic	13 (43.3)	36 (41.9)	42 (40.4)	91 (41.4)	0.755
Mitral	7 (23.3)	30 (34.9)	42 (40.4)	79 (35.9)	0.093
Tricuspid	0	2 (2.33)	1 (0.97)	3 (1.4)	—
Pulmonary	2 (6.7)	2 (2.3)	0	4 (1.8)	—
≥2 valves	2 (6.7)	8 (9.3)	11 (10.6)	21 (9.6)	—
Prosthetic valves	2 (6.7)	1 (1.2)	4 (3.9)	7 (3.2)	—
Other	4 (13.3)	7 (6.98)	4 (3.9)	15 (6.8)	—
Symptoms/signs					—
Fever	18 (60)	64 (74.4)	69 (66.4)	151 (68.7)	0.966
New heart murmur	2	0	2	4	—
Nonspecific	9 (30)	21 (24.4)	33 (31.7)	63 (28.6)	—
Underlying disease					—
RHD	3 (10)	13 (15.1)	13 (12.5)	29 (13.2)	0.945
CHD	13 (43.4)	29 (33.8)	30 (28.9)	72 (32.7)	0.142
BAV	7 (53.8)	10 (34.5)	23 (76.8)	40 (55.6)	0.016**
VSD	5 (38.3)	10 (34.5)	5 (16.7)	20 (27.8)	0.094
Other*	1 (8.3)	9 (31)	2 (7.7)	12 (17.9)	—
MVP	2 (6.7)	19 (22.1)	19 (18.3)	40 (18.2)	0.38
Nondental intervention	7 (23.3)	8 (9.3)	9 (8.7)	24 (10.9)	0.063
No risk factor	5 (16.7)	12 (14)	24 (23.1)	41 (18.6)	0.201
Missed diagnosis	10 (33.3)	14 (16.3)	23 (22.1)	47 (21.4)	0.513
Death	1 (3.4)	2 (2.3)	2 (2)	5 (2.3)	0.662

BAV = bicuspid aortic valve; CHD = congenital heart disease; MVP = mitral valve prolapse; RHD = rheumatic heart disease; VSD = ventricular septal defect

*Other includes patent ductus arteriosus, subaortic stenosis, double-outlet right ventricle accompanied by bicuspid pulmonary valve, bicuspid pulmonary valve, and Marfan syndrome.

**Increased over the course of the 4-year intervals.

Data are presented as mean ± SD or as number and percentage. $P < 0.05$ was considered statistically significant.

18.3%, respectively; $P = 0.38$). Of 110 patients with mitral valve involvement alone or in union with other valve involvement, 40 (36.4%) had mitral valve prolapse.

Recent procedures were identified as risk factors in 25 patients (11.4%). These included recent (within the past 6 mo) dental treatment in 1 patient and recent surgical or nonsurgical intervention of a nondental nature in 24 patients, including 10 patients with valve replacement, 2 with valvuloplasty, 4 with atrial septal defect or VSD repair (or both), and 1 each with coronary stent implantation, correction of complete transposition of great arteries, correction of partial endocardial cushion defect, correction of tetralogy of Fallot, aortic sinus aneurysm repair, radiofrequency ablation, pacemaker implantation, and septal myocardial chemical ablation. The frequency of nondental surgical or nonsurgical intervention did not change over the 3 periods of time ($P = 0.063$). However, when the latter 2 periods were combined, this frequency was significantly greater from 1998 through 2001: 7 of 30 patients (23.3%) underwent such intervention during this interval. From 2002 on, the frequency declined significantly: 17 of 190 patients (9%) from 2002 through 2009 ($P = 0.019$).

There were 29 patients (13.2%) who had rheumatic heart diseases, and the rate did not change significantly during the 3 time periods (10%, 15.1%, and 12.5%, respectively; $P = 0.945$). Coexistent systemic diseases were occasionally encountered: diabetes mellitus in only 2 patients, respiratory infection in 8 patients, and skin furunculosis in 1 patient. In our study, 41 patients

(18.6%) had no evidence of underlying structural heart disease or of a risk factor for IE. The rate underwent no significant change during the 3 time periods (16.7%, 14%, and 23.1%, respectively; P=0.201) (Table I, Fig. 1).

None of the 23 patients with acute IE had rheumatic valve disease, but 7 patients (30%) had experienced mitral valve prolapse with recent intervention, 8 (34.8%) had CHD, 1 had diabetes mellitus, 1 had respiratory infection, and 6 (26.1%) had no risk factors. No patient reported intravenous drug abuse, chronic alcoholism, or other causes of immunosuppression. Of all 150 patients with subacute IE, 15 (10%) had rheumatic valve disease; 32 (23.3%), prolapsed mitral valve; 12 (8%), recent intervention; 48 (32%), CHD; 9 (6%), internal noncardiac infection; and 34 (22.7%), no risk factors. In total, rheumatic valve disease and mitral valve prolapse were more frequent (10% and 23.3%) in cases of subacute IE than in those of acute IE. On the other hand, recent intervention was encountered more often in acute IE than in subacute IE (30% vs 8%; P=0.001). The frequency of CHD and "no risk factor" was not significantly different between acute and subacute IE (34.8% vs 32% and 26.1% vs 22.7%, respectively; P=0.791 and P=0.717).

Clinical and Laboratory Findings

Fever was the most frequent symptom (151 patients, 68.6%) and did not change significantly over the 3 time periods (60%, 73.8%, and 65.4%, respectively; P=0.966). The immunologic manifestations, including Osler nodes and Janeway lesions, were observed in 6 of the patients who had fever (4%); systemic arterial emboli were diagnosed in 4 of those 151 patients (2.7%); the sites of involvement included the central nervous system, coronary artery, spleen, and lower limb. Sixty-five of the overall group of 220 patients (29.5%) reported palpitation, dyspnea, and chest pain; new cardiac murmurs were found in 4 patients (1.8%).

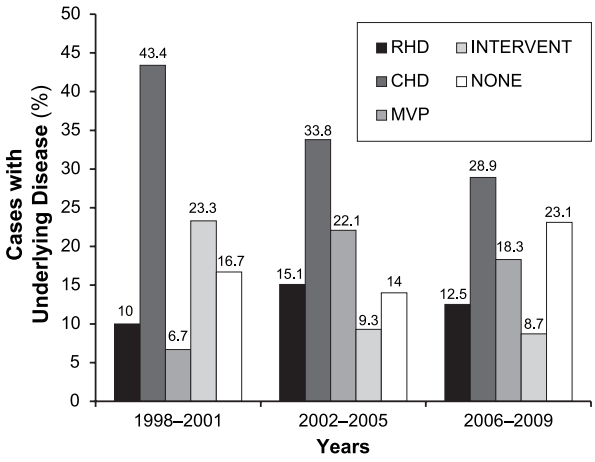

Fig. 1 *Graph shows the relative proportions of underlying heart diseases in cases of surgically treated infective endocarditis at 4-year intervals over a 12-year period.*

CHD = congenital heart disease; INTERVENT = recent intervention; MVP = mitral valve prolapse; NONE = no underlying heart disease; RHD = rheumatic heart disease

Transthoracic echocardiography (TTE) was performed in all patients, of whom 149 (67.7%) were found to have vegetations on the valves or patches.

Blood cultures were performed in 86 of the 220 surgical patients (39.1%). Sixteen of those 86 patients had acute IE, and 70 had subacute IE. The positive rate was 68.6% (59 patients). *Streptococcus* remained the chief causative agent of IE (35 of 86 patients, or 40.7%), of which *S. viridans* was identified in 22 (25.6%), unclassified *Streptococcus* in 8, *Enterococcus* in 2, Group D streptococcus in 2, and alpha-hemolytic streptococcus in 1. There was no significant change in the proportion of *S. viridans* infection during the 3 time periods (14.3%, 34.8%, and 24.5%, respectively; P=0.918). Staphylococci were identified in 13 of the 86 patients (15.1%): 6 of the 86 (7%) had *S. aureus*, 4 *S. epidermidis*, 1 *S. sciuri*, 1 a gram-negative staphylococcus, and 1 an unidentified staphylococcus. No *S. aureus* was identified from 1998 through 2005; the 6 cases were found from 2006 through 2009. The negative rate in blood cultures (31.4%, or 27 of the 86 patients), did not change significantly during the time periods (42.9%, 21.7%, and 32.7%, respectively; P=0.762) (Table II).

Acute Infective Endocarditis. Sixteen of the 23 patients with acute IE (69.6%) had blood drawn for culture. *S. aureus* was identified in 4, *S. epidermidis* in 2, other staphylococcus in 1, enterococcus in 1, gram-negative bacteria in 1, other bacteria in 2, and fungi in 1. *S. viridans* was identified in only 1 case. Three of the 16 (18.8%) had no identified organisms.

Subacute Infective Endocarditis. Of all 150 patients with subacute IE, 70 (46.7%) had blood drawn for culture. Streptococci were identified in 33 of the 70 (47.2%): *S. viridans* in 21 patients (30%), Group D streptococci in 2, and unclassified streptococci in 8. Staphylococci were identified in 6 of the 70 (8.6%): *S. aureus* in 2 (2.9%), *S. epidermidis* in 2, and other staphylococci in 2. Three patients had polymicrobial infections.

Negative blood cultures were encountered in 24 patients (34.3%). Overall, streptococci were more prevalent in subacute than in acute IE (47.2% vs 12.5%; P=0.012). Conversely, staphylococci were more prevalent in acute than in subacute IE (37.5% vs 8.6%; P=0.008). There was no significant difference between acute and subacute IE groups in regard to negative blood cultures (18.8% vs 34.3%; P=0.371). Valve specimens from 5 patients were sent for culture, but no microorganisms were identified in 4 of those.

Overview. From 1998 through 2009, a total of 620 patients fulfilled the modified Duke criteria: 220 of

TABLE II. Infecting Organisms in 86 Blood Cultures

Blood Culture Results	1998–2001	2002–2005	2006–2009	Total	*P* Value
Total organisms identified	8 (57.1)	18 (78.3)	33 (67.4)	59 (68.6)	—
Streptococci	4 (30.8)	13 (56.5)	18 (36.7)	35 (40.7)	—
S. viridans	2 (14.3)	8 (34.8)	12 (24.5)	22 (25.6)	0.918
Group D	—	1	1	2	—
Alpha-hemolytic	—	1	—	1	—
Enterococci	—	1	1	2	—
Unclassified	2	2	4	8	—
Staphylococci	2	1	10	13	—
S. aureus	0	0	6	6 (7)	—
S. epidermidis	2	—	2	4	—
S. sciuri	—	—	1	1	—
Gram-negative	—	—	1	1	—
Staphylococcus (NOS)	—	1	—	1	—
Fungi	1	—	—	1	—
Mycoplasma	1	—	—	1	—
Haemophilus influenzae	—	—	1	1	—
Two organisms	—	2	1	3	—
Other bacteria	—	2	2	4	—
Culture negative	6 (42.9)	5 (21.7)	16 (32.7)	27 (31.4)	0.762

NOS = not otherwise specified

Data are presented as number and percentage. $P < 0.05$ was considered statistically significant.

those were surgically treated, and the remaining 400 were medically treated. Blood cultures were performed in 420, which number included both medically and surgically treated patients. The positive rate was 53.6% with *S. viridans* as the chief causative agent of IE (34%, 210/620) in our total IE patient population—an overall rate that is similar to the *S. viridans* rate (25.6%) in our surgically treated IE patients.

Pathologic Findings

In 145 of the surgical patients (65.9%), the vegetations on the valves, on the atrial and ventricular endocardia, and on the aortic and pulmonary arterial intima were identified via microscopy. In 5 of those patients, bacterial colonies or fungal hyphae were found in the vegetations. In the remaining 75 patients (34.1%), no vegetations were found, but local necrosis, polymorphonuclear leukocyte infiltration, or granulation tissue was identified via microscopy. Sequelae occurred in 24 of the surgical patients (10.9%), including 12 with cusp ulceration or perforation, 4 with periprosthetic leak, 2 with rupture of aortic sinus aneurysm, 4 with infective vasculitis, and 1 with myocardial infarction due to coronary embolization.

Comparative Analysis between Clinical and Pathologic Diagnosis

Before surgery, infective endocarditis was diagnosed in 173 patients (78.6%): 154 (89%) were definite cases of IE and 19 (11%) were possible IE. Forty-seven of the 220 patients (21.4%) undergoing valve replacement had diagnoses of rheumatic valvulitis or degenerative valve disease before surgery but were found at surgery to have IE as the basic disease state. The rate of misdiagnosis did not change significantly over the 3 time periods (33.3%, 16.3%, and 22.1%, respectively; $P=0.513$). As determined by histopathology, 26 of the 47 patients had no vegetations and 7 had vegetations smaller than 2 mm (70.2%, 33/47), but all showed local necrosis, polymorphonuclear leukocyte infiltration, or granulation tissue. Four of the 47 (8.5%) patients with misdiagnoses had CHD: 3 cases of VSD and 1 of tetralogy of Fallot.

Outcomes

Of the 220 surgically treated IE patients, 204 (92.8%) underwent valve replacement: 185 received mechanical valves; 13, bioprosthetic valves; and 6, homografts. Eight (3.6%) underwent valve repair, and 8 (3.6%) underwent excision of vegetations (5 on ventricular defect patches, 1 in the pulmonary artery, 1 on a pacemaker lead, and 1 on the septum beneath the aortic valve).

Endocarditis recurred in 3 patients (1.4%): within 1 postoperative week in 1 patient, within 1 month in another, and within 8 months in the 3rd. All 3 patients had undergone replacement with mechanical prostheses.

Five patients died after surgery, which accounted for a 2.3% operative mortality rate: this included 3 patients with native-valve IE, 1 with infective vasculitis, and 1

with IE on the endocardium of the left atrium and the left ventricle. The causes of the 3 deaths were sepsis, heart failure, and myocardial infarction, respectively. The mortality rate did not change over the 3 time periods (3.4%, 2.3%, and 2%, respectively; P=0.662).

Discussion

In this analysis of 220 IE patients surgically treated over 12 years at the largest cardiovascular referral hospital in China, our data show that the average age of our patients (39.1 yr) was younger than the average in other developing countries.[8-10] In Western countries, the average age of such patients has shifted from 55 to 60 years in recent decades. This shift has been attributed to the dramatic decrease in the incidence of acute rheumatic disease and to increased lifespans that have given rise to more degenerative valvular lesions, to the placement of prosthetic valves, and to increased exposure to nosocomial bacteremia.[3]

In common with reports from developed countries, our study reveals a rising trend in degenerative valvular lesions (from 6.6% to 22.1% and 18.3%), such as mitral valve prolapse; these changes, however, did not attain statistical significance. Our overall rate of mitral valve prolapse was 36.4%, which is similar to that reported in other studies (28%–43%).[11,12] We should note that mitral valve prolapse was the risk factor for subacute IE, but not for acute IE. The risk factor for acute IE was recent surgical or nonsurgical intervention.

A factor that might account for the younger age of IE patients in our study is the higher-than-usual proportion of patients with CHD (32.8% of the total, with a mean age of 34.3 yr). In recent decades, the population of CHD patients who have survived to adulthood has increased markedly: even 8 years ago, it was estimated that more than 1.2 million Europeans had CHD.[13] Despite many advances in the management of these CHD patients, a variety of possible sequelae, such as IE, still occur frequently during long-term follow-up.[14] The incidence of IE ranges from 3 to 10 episodes per 100,000 person-years in the general population,[15] but the chance of IE in CHD patients is reported to be between 2% and 18%,[16-18] with minor male predominance.[14,19,20] In our current study, the frequency of IE associated with CHD was higher than that found in other reports. The reason for this wide frequency variation seems to vary in accordance with the cardiovascular defect. Lamas and Eykyn[21] have reported that IE is a well-recognized complication in CHD patients with BAV, occurring in 7% to 25% of cases. In our current patient population, BAV was the most frequent defect in our patients with CHD. Of all the involved aortic valves, 32.5% were bicuspid—a figure similar to that reported in another large study (38%), by Castonguay and colleagues.[12] Our findings also suggest that CHD was the chief risk factor for both acute and subacute IE.

Although the prognosis for IE is better in congenital than in acquired heart disease, the mortality rate still remains high (range, 4%–10%).[14,19,20] Furthermore, BAV patients with IE often have a high risk of complications. In one multicenter observational study,[22] half of the patients with BAV developed perivalvular abscess, and 72% of them needed early surgery (perioperative mortality rate, 8.3%). Bicuspid aortic valve with IE is a grave disease that requires preventive measures as specified by the 2009 IE guidelines.[15] Individuals with BAV need to be aware of the risk of developing IE; in the event of fever of unexplained origin, blood cultures should be performed.

A pooled analysis of 3,784 episodes of IE[1] showed that streptococci fell into 2nd place after staphylococci as the leading cause of IE. This shift might be due partly to recruitment referral bias in specialized centers, because the trend has not been seen in population-based epidemiologic surveys of IE.[23] The classical causative pattern persists in some studies. In Castonguay and colleagues' large 2013 study of native-valve endocarditis treated surgically,[12] streptococci were present in half of infections (51%) and staphylococci in over one quarter (29%). *S. viridans* was the most prevalent, in 28% of patients. In Tunisia,[4] most IE cases developed in patients with rheumatic valve disease as the most prevalent underlying heart disease and with streptococci as the most prevalent causative organism; up to 50% of the Tunisian patients had negative blood cultures.[4] Similarly, in our study, *S. viridans* was still the chief causative pathogen (25.6%), and only 12.8% of IE cases were caused by staphylococci (of which only 7% were *S. aureus*). Our findings also suggest that streptococci were the major causative pathogen in subacute IE, while acute IE was usually associated with staphylococcal infection. In our 620 consecutive cases of IE, blood cultures showed similar findings: *S. viridans* was the primary causative agent in surgically treated cases.

As was true in other series from developing countries,[9,10,24] the most characteristic finding in our study was the high rate of negative blood cultures (31.4%); the negative rate in industrialized countries, by contrast, has been reported at 5% to 15%.[25,8] The common causative factors involved in the high frequency of IE negative blood cultures (in the presence of infective endocarditis) include previous antibiotic therapy, the lack of optimal conventional culture techniques, and the failure of systematic investigation for rare and fastidious microorganisms.[3,26,27]

Confirmation by echocardiography is one of the major criteria for the diagnosis of IE. However, the sensitivity of echocardiography in the diagnosis of IE in patients with complex congenital cardiac malformations has been low. Di Filippo and colleagues[20] showed

that echocardiographic imaging was negative in 70% of IE patients who had complex CHD. Our own data showed that identification of vegetations by TTE was insensitive in comparison with histopathologic identification, especially when the vegetations were small (<2 mm) or already organized; moreover, IE can exist without vegetations. Difficulties in imaging shunts and conduits and in differentiating vegetations from dysplastic exuberant valves certainly decrease the usefulness of echocardiography in identifying IE in the presence of complex CHD. In such cases, careful comparison of valvular anatomy and function with previous records is helpful in detecting IE. Although transesophageal echocardiography (TEE) has been reported to be more sensitive than TTE in detecting vegetations as small as 1 to 1.5 mm,[28] Di Filippo and his colleagues[20] showed that TEE still failed to reveal vegetations in patients with complex cardiac anatomy. Diagnosis of IE should therefore rely on the Duke criteria, rather than on echocardiography alone, in patients who have complex cardiac conditions, conduits, and shunts.

The operative mortality rate was 2.3% in our series. This is similar to the rate reported by Kang and associates (3%),[29] but lower than those reported in other studies (12%–15%).[30,31] There are several possible explanations for the lower mortality rate in our study. First, the proportion of our patients with poor prognostic factors, such as moderate-to-severe congestive heart failure, altered mental status, and staphylococcal infection, was lower than that of previous studies. Second, the mortality rate in patients with native-valve IE (5.6%) tends to be much lower than that of patients with prosthetic-valve IE (13%).[32] In our study, the proportion of prosthetic-valve IE was quite low (only 5.8%).

Strengths and Limitations of the Study

Although the present work provides the opportunity to evaluate the profiling changes of a large number of surgically treated IE patients from a single institution, the possible influence of referral bias on our results cannot be fully excluded: only surgically treated IE patients were included, and the referral characteristics of our cardiovascular disease center might differ from those of other major centers.

Conclusion

The average ages and the underlying heart diseases of our IE patients in China's largest cardiovascular referral center changed over a 12-year period, but the affected valves, causative agents, and missed-diagnosis rates remained essentially the same.

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