Recent Picture of Infective Endocarditis in Japan
– Lessons From Cardiac Disease Registration (CADRE-IE) –
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Background: It is important to manage a potentially fatal disease such as infective endocarditis (IE) based on evidence and guidelines for treatment published by academic societies. To clarify the current status of IE in Japan, we conducted a nationwide survey of IE (CArdiac Disease REgistration-Infective Endocarditis [CADRE-IE]).

Methods and Results: We collected data on every aspect of IE using web-based survey. Only a Japanese Circulation Society-certified cardiologists who had managed a case of IE could register the patient when the outcome was known. There were 513 cases (320 men, 193 women) from 114 institutions. The median age was 61 years and more than 80% of the patients had underlying cardiac diseases. The majority was valvular heart disease, in which mitral regurgitation was a leading cause. Most of the patients had some predisposing factors, among which, decayed teeth or periodontitis was a leading factor. Streptococci were found in approximately 52% and staphylococci were found in 32% in positive-culture cases. Methicillin-resistant Staphylococcus aureus was found in 7.5%. Congestive heart failure was found in 43% and intracranial complications were found in 31%. Most of the patients were discharged (65%) but in-hospital death occurred in 11%.

Conclusions: IE is still a lethal disease affecting older patients. The information obtained from the survey should be very helpful for physicians. (Circ J 2013; 77: 1558–1564)

Key Words: Echocardiography; Endocarditis; Infection

Infective endocarditis (IE) can be life-threatening unless early diagnosis is made and effective therapy is started. It is important to manage a potentially fatal disease such as IE based on evidence and guidelines for treatment published by academic societies. The Japanese Circulation Society has published “Guidelines for Prevention and Management of Infective Endocarditis” in 2003 and a revised version in 2008. Both sets of guidelines were based on our previous nationwide survey performed in 2000 and 2001. Because both the concept and treatment have advanced, it is important to know the present status of IE in Japan.

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The importance of a nationwide disease registry is beyond question. It will deepen our understanding about a disease itself, its occurrence, prognosis and effective treatment, thereby establishing treatment strategy and guidelines for diagnosis and treatment. However, there have been few such registries especially in the field of cardiology. Thus, we intended to establish a registry system with a grant from National Cardiovascular Center (18A-1) and the help of the Japanese Circulation Society, named CArdiac Disease REgistration (CADRE), CADRE is web-based registration system and only cardiologists certified by the Society can register. As the first entry disease, we choose IE and collected data from March 2007 to May 2009 from all over Japan (CADRE-IE). Here, we present the data to inform the present status of the disease.

Methods

Web-Based Questionnaire
In this nationwide survey, we intended to collect data on every aspect of IE. Therefore, the questionnaire covered the basic cardiac conditions, predisposing factors, results of blood culture, echocardiographic findings, treatments and outcome. In some questions, such as basic cardiac conditions and the location of vegetations, multiple answers were allowed to under-
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Registration through the Internet should be done with caution to secure personal information. In the present system, we placed the server in the Department of Information at the National Cerebral and Cardiovascular Center (formerly, National Cardiovascular Center) where the security of the database was highly guaranteed.6,7 The study was conducted in accordance with the Declaration of Helsinki, and was approved by the ethics committee of the National Cerebral and Cardiovascular Center.

Participating Physicians
A Japanese Circulation Society-certified cardiologist who experienced a case of IE could register the patient in CADRE when the outcome was known. IE was diagnosed according to the Duke criteria.8 The cardiologist used his or her username and a password that had been obtained in advance to enter the registration site. Only anonymous data were registered.

Results

Clinical Characteristics
There were 513 cases (320 men, 193 women) from 114 institutions in Japan. Age ranged from 1 to 97 years, with a mean of 59.5±17.5 years and median of 61 years (Figure 1). Approximately 40% of the patients were admitted to a hospital within 2 weeks of onset. However, 39 cases (7.6%) were admitted 3 months from the onset. The duration of hospital stay ranged from 1 to 329 days, with a mean of 56.6±41.0 days. When we excluded patients who died or were transferred to other hospitals for further treatment or rehabilitation, the duration was 60.9±36.9 days.

Figure 1. Age and sex distributions.

Figure 2. Basic cardiac conditions. VHD, valvular heart disease; CHD, congenital heart disease; CM, cardiomyopathy; CAD, coronary artery disease; PM/ICD, pacemaker or implantable cardioverter-defibrillator implantation.
Cardiomyopathy was found in 10 cases, of which there were 6 cases of hypertrophic obstructive cardiomyopathy (6 cases).

Basic Cardiac Conditions
Of the 513 cases, underlying cardiac disease was found in 353 and not in 78. Thus, if we exclude cases of unclear origin (n=82), 82% had underlying cardiac disease, the majority of which was valvular heart disease (287 cases), including 100 post-surgical cases (Figure 2). Among the valvular heart diseases, mitral regurgitation was the leading cause (145 cases) and aortic regurgitation was the second leading cause (76 cases) (Figure 3). Mitral valve prolapse was involved in 55 cases and bicuspid aortic valve was involved in 24 cases. Of the post-surgical cases, two-thirds developed IE more than 6 months after surgery. Congenital heart disease was found in 23 cases, among which there were 18 cases of a major ventricular septal defect. Cardiomyopathy was found in 10 cases, of which there were 6 cases of hypertrophic obstructive cardiomyopathy (6 cases).

Table 1. Predisposing Background of Japanese Patient With Infective Endocarditis

| With a predisposing background | n (%) |
|-------------------------------|-------|
| Decayed teeth/periodontitis    | 126 (31.0) |
| Indwelling catheter           | 27 (6.6) |
| Intravenous drug user         | 9 (2.2) |
| Steroid user                  | 22 (5.4) |
| Atopic dermatitis             | 5 (1.2) |
| Hemodialysis                  | 30 (7.4) |
| Diabetes mellitus             | 53 (13.0) |
| Hyperlipidemia                | 18 (4.4) |
| Hypertension                  | 55 (13.5) |
| History of infective endocarditis | 18 (4.4) |
| Other                         | 93 (22.9) |
| Without a predisposing background | 85 (20.9) |
| Unknown                       | 106 |

Only patients with and without a predisposing background were used for percentage calculation.

Table 2. Causative Microorganisms in Japanese Patient With Infective Endocarditis

| Gram-positive bacteria         | n (%) |
|-------------------------------|-------|
| Staphylococcus aureus         | 84 (21.0) |
| MSSA                          | 54 (13.5) |
| MRSA                          | 30 (7.5) |
| CNS                           | 45 (11.3) |
| Streptococci                  | 207 (51.9) |
| Viridans group streptococci   | 133 (33.3) |
| Streptococcus bovis           | 7 (1.8) |
| Others                        | 67 (16.8) |
| Enterococci                   | 39 (9.8) |
| Other                         | 6 (1.6) |

| Gram-negative bacteria        | n (%) |
|-------------------------------|-------|
| Escherichia coli              | 8 (2.0) |
| HACEK                         | 3 (0.8) |
| Others                        | 17 (4.3) |
| Fungi/yeast                   | 5 (1.3) |
| Other                         | 4 (1.0) |

Values are n (%).
MSSA, methicillin-sensitive Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus; CNS, coagulase-negative Staphylococcus; HACEK, bacteria consisting of Haemophilus species, Aggregatibacter (formerly Actinobacillus) actinomycetemcomitans, Cardiobacterium hominis, Eikenella corroden, and Kingella species.

Table 3. Echocardiographic Findings in Japanese Patient With Infective Endocarditis

| Echocardiographic finding       | n (%) |
|-------------------------------|-------|
| Vegetation                     | 456 (89.2) |
| Mitral valve                   | 302 (69.0) |
| Aortic valve                   | 170 (33.3) |
| Tricuspid valve                | 18 (3.5) |
| Pulmonic valve                 | 4 (0.8) |
| Pacemaker lead                 | 9 (1.8) |
| Other                          | 15 (2.9) |
| Abscess                        | 44 (8.6) |
| Mitral ring                    | 11 (2.2) |
| Aortic ring                    | 32 (6.3) |
| Tricuspid ring                 | 3 (0.6) |
| Ventricular septum             | 3 (0.6) |
| Valve perforation              | 75 (14.7) |
| Mitral valve                   | 41 (8.0) |
| Aortic valve                   | 38 (7.4) |
| Tricuspid valve                | 0 (0.0) |
| Valvular regurgitation         | 372 (72.8) |
| Newly occurred                 | 196 (38.4) |
| Worsened                       | 176 (34.4) |
| Intracardiac shunt             | 28 (5.5) |
| Newly occurred                 | 13 (2.5) |
| Worsened                       | 15 (2.9) |
| Other findings                 | 49 (9.6) |
| No findings                    | 17 (3.3) |
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Some predisposing factors were seen in 322 cases, but a significant number of patients either did not have those factors (85 cases) or definite factors could not be identified (106 cases). Among such factors, decayed teeth or periodontitis was a leading factor (Table 1). There were 5 cases of atopic dermatitis and 9 cases of intravenous drug use; 18 patients had a prior history of IE.

Possible Route for Infection
In 38% of the patients (196 cases), a possible route for infection was identified. More than 60% of the patients suffered from IE without an apparent route. Among those with identified routes, dental treatment was the major invasive procedure (81 cases, 41%) and included cavity treatment in 61, dental extraction in 13 and scaling in 5. Intravenous drug injection could be related in 12, gastrointestinal procedures in 12 and urological procedures in 7. There were 8 cases (1.6%) of IE after endoscopic procedure (7 gastroscopy, 1 transesophageal echocardiography). On the question of whether antibiotics was used or not during an invasive procedure, approximately one-third did, one-third did not and it was unclear in the remaining one-third.

Blood Culture
Blood culture was performed in almost all patients (Table 2): 399 positive cases and 99 negative cases. Streptococci were found in approximately 52% and staphylococci were found in 32%. Methicillin-resistant Staphylococcus aureus (MRSA) was found in 30 cases (7.5%). Fungus was found in only 5 cases.

Echocardiography
Echocardiography was performed in 511 cases (Table 3) and a vegetation was found in 456 cases, mostly on the mitral valve (302 cases). Ring abscess was found in 44 cases, mainly on the aortic annulus (32 cases). There were 17 cases (3.3%) with no significant findings on echocardiography.

Complications
Congestive heart failure was found in 43% and intracranial complications were found in 31%. Of the total patients, 21% showed cerebral infarction and 9% showed cerebral hemorrhage. Approximately 21% (109 cases) presented extra-cerebral embolization: 40 cases in the spleen and 34 in the kidney. Myocardial infarction because of embolization occurred in 3 cases.

Antibiotics
Antibiotic sensitivity test was performed in 386 cases and sensitivities are shown in Figure 4. The most frequently tested antibiotics were ampicillin (ABPC), benzylpenicillin (PCG), vancomycin (VCM) and clindamycin (CLDM). When asked which were the effective and ineffective antibiotics based on the physician’s experience, the most popular and effective an-
According to the age distribution, more than 200 patients were aged between 61 and 80 years. Therefore, IE now affects older patients in Japan as is the case in other industrialized nations. This may be related to the increasing proportion of elderly subjects in the general population, their high prevalence of degenerative valve disease and a decrease in rheumatic heart disease in younger subjects.

The rates of diabetes mellitus and hypertension in the patients (10% and 11%, respectively) may be explained by this age distribution and not be specific to IE.

There are some predisposing cardiac conditions that increase susceptibility to IE such as prosthetic heart valves, mitral valve prolapse and bicuspid aortic valve. In the present survey, one-third of the patients had no definite structural heart disease, which is slightly less than in the previous reports. Recent improvements in the easy of using echocardiography, including transesophageal echocardiography, may have enhanced diagnostic capability, resulting in less frequency of idiopathic IE. Among the valvular heart diseases, mitral valve prolapse was involved in 55 cases and bicuspid aortic valve in 24 cases, comprising 15% of the IE cases in the present survey.

Recent guidelines from the European Society of Cardiology and American Heart Association recommend limiting prophylactic antibiotics prior to invasive procedures to patients with a high risk of IE such as those with a prosthetic valve or cyanotic congenital heart disease. Prophylaxis is not recommended for patients undergoing dental treatment, surgery, or other invasive procedures.

**Patients’ Backgrounds**

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mitral valve prolapse or bicuspid aortic valve based on a lack of scientific evidence of efficacy.\textsuperscript{5,14} Although investigation of the effectiveness of prophylactic antibiotics was beyond our scope, we should note that not a few patients with these native valve diseases had IE.

In the present survey, 63\% had apparent predisposing factors and in patients with and without predisposing factors, 31\% had decayed teeth or periodontitis, strongly suggesting the importance of oral hygiene.\textsuperscript{5,14} Among the known routes for infection, dental treatment, ranging from scaling to dental extraction, was the most common. In the guidelines from the United States and Europe, dental procedures with the highest risk involve manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa.\textsuperscript{5,14} We should determine if prophylactic antibiotics are really effective in which patients and for which dental procedures in the future studies.

It is surprising that 8 patients had IE after endoscopic procedures. In the recent guidelines, antibiotic prophylaxis solely to prevent IE is not recommended for gastrointestinal tract procedures (Class III).\textsuperscript{5,14} However, we may consider prophylaxis in patients with specific conditions who are scheduled to have endoscopic procedures.

### Diagnosis

We found a quite similar bacteria spectrum in the present survey and in our previous survey in 2000–2001 (streptococci, 51.9\% vs. 49.5\%; staphylococci, 32.3\% vs. 31.7\%; MRSA, 7.5\% vs. 7.3\% for the present survey vs. previous survey, respectively).\textsuperscript{5} Sensitivity for each bacterium was not investigated, but overall sensitivity for PCG was 73\% and 98\% for VCM. As shown in Figure 4, the sensitivity of CLDM seemed to be checked often and sensitivity was 73\%, but as shown in Figure 5, it was not used in most cases, possibly because in the Japanese guidelines CLDM is recommended as prophylactic antibiotic for patients with penicillin allergy.\textsuperscript{2}

Echocardiography was successful in detecting structural abnormalities in most cases. However, 17 cases showed no abnormalities suggestive of IE. We know that the sensitivity of transthoracic echocardiography in detecting vegetations ranges from 40\% to 63\% and that of transesophageal echocardiography from 90\% to 100\%.\textsuperscript{15} It was unclear whether transesophageal echocardiography was performed in each case in the present survey, but it should be noted that approximately 3\% of the patients were reported to have “normal or unchanged” echocardiograms. The reason is unclear, but there are several possibilities. Simple temporal dissociation between clinical symptoms and structural destruction is 1 possibility. Second, the size of a vegetation may have been too small to be detected by echocardiography. Third, vegetations may have disappeared by the time of echocardiographic examination because of systemic embolism. Echocardiography plays a pivotal role in the diagnosis of IE as demonstrated in the Duke criteria.\textsuperscript{16} We should recognize the possibility of a “normal or unchanged” echocardiogram in a patient with IE and repeat transthoracic/transesophageal echocardiography at 7–10 days after the initial examination if the clinical suspicion remains, or even earlier in cases with virulent organisms such as \textit{Staph. aureus} or fungi.\textsuperscript{2,4,5}

### Treatment and Outcome

Different from the previous survey in which we asked only about sensitive and resistant antibiotics to the causative bacteria,\textsuperscript{3} we asked about effective and ineffective antibiotics in the present survey. Thus, we found that GM was used in approximately 40\%, PCG in 30\% and ABPC in 20\%. GM is probably used along with PCG or ABPC. This is consistent with the fact that streptococci were the most common bacteria in the present survey.

Surgical treatment was selected in 61\%, which was more frequent than the result reported from the International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) (48\%).\textsuperscript{12} This may indicate an lower threshold for early surgery in Japan. In-hospital mortality was 11\%, which was lower than the ICE-PCS result (17.7\%).\textsuperscript{12} Although the benefit of early surgery is still controversial,\textsuperscript{12,16–20} a tendency for earlier surgery may explain the better outcome. In the ICE-PCS, the main pathogen was \textit{Staph. aureus}, whereas in the present survey it was streptococci. This difference may also explain the lower mortality.

### Study Limitations

CADRE is a web-based registration of cardiac disease aiming at inventory survey all over Japan. With the present survey, we believe important features and facts regarding IE have been clarified. However, CADRE is not a complete enumeration of all patients in Japan. Only certified cardiologists mostly working in mid- to large-scale hospitals could register to help guarantee the data quality, but may create a selection bias. Therefore, the present results may show only part of the disease spectrum. We have to make efforts to collect data from all patients suffering IE in Japan.

We only present the numerical data regarding patients’ characteristics. Because of the nature of the present survey, we did not perform any statistical analysis.

### Conclusions

We conducted a nationwide survey of IE and found that it is still a lethal disease affecting older patients. Approximately 20\% of the patients had no definite structural heart disease. Decayed teeth or periodontitis was a leading predisposing factor. The bacterial spectrum has not changed significantly compared with 2000 and 2001, and the most popular and effective antibiotics were GM and PCG. The information obtained from the survey should be very helpful in clinical practice.

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### Disclosures

None.

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