Infective endocarditis is a serious septic disease that can be life-threatening unless effective therapy under the correct diagnosis is instituted. Although there have been many developments and improvements in diagnostic and therapeutic methods, clinical diagnosis of infective endocarditis is sometimes difficult and the annual incidence and the morbidity and mortality are still relatively high. Reputable guidelines are desirable for the effective prevention, detection and treatment of infective endocarditis. The American Heart Association has published guidelines, but to date none have been formulated in Japan. Therefore, the Japanese Circulation Society took the initiative and appointed a committee, which decided that recent information on the characteristics and clinical presentation of infective endocarditis in Japan was required for the formulation of the guidelines. A similar survey study had been performed before in Japan, in 1980, so a questionnaire about infective endocarditis in the past 2 years was sent to hospitals throughout Japan that specialize in cardiovascular diseases and the resulting data are presented.

Methods

The committee compiled a simple questionnaire of the

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nfective endocarditis is a serious septic disease that can be life-threatening unless effective therapy under the correct diagnosis is instituted. Although there have been many developments and improvements in diagnostic and therapeutic methods, clinical diagnosis of infective endocarditis is sometimes difficult and the annual incidence and the morbidity and mortality are still relatively high. Reputable guidelines are desirable for the effective prevention, detection and treatment of infective endocarditis. The American Heart Association has published guidelines but to date none have been formulated in Japan. Therefore, the Japanese Circulation Society took the initiative and appointed a committee, which decided that recent information on the characteristics and clinical presentation of infective endocarditis in Japan was required for the formulation of the guidelines. A similar survey study had been performed before in Japan, in 1980 so a questionnaire about infective endocarditis in the past 2 years was sent to hospitals throughout Japan that specialize in cardiovascular diseases and the resulting data are presented.

Key Words: Antibiotics; Endocarditis; Guidelines; Microorganism; Questionnaire; Survey

Fig 1. Questionnaire.
clinical and microbiologic data from patients with infective endocarditis, including the patient’s characteristics, causative microorganisms and whether they were sensitive or resistant to the antibiotics (Fig 1). Eligible patients were those who were diagnosed with infective endocarditis in 2000 and 2001, based on clinical, echocardiographic and microbiologic findings.

Participating Hospitals

We sent the questionnaire to 817 hospitals that are authorized as a cardiovascular disease specialty institution by the Japanese Circulation Society.

Results

Collection of Questionnaires

We received 277 responses (848 cases) to the questionnaire (33.9%); 31 hospitals had not had any cases of infective endocarditis in 2000 and 2001, based on clinical, echocardiographic and microbiologic findings.

Clinical Characteristics

There were 517 men and 296 women, excluding the omitted cases, and their ages ranged from 0 to 99 years old (mean, 55±18 years), but most were in their 50’s or 60’s (Fig 2). Approximately 20% of the patients (180 of 817) were older than 70 years. Underlying cardiac disorders were valvular heart disease in 531 (65.0%), congenital heart disease in 74 (9.1%) and pacemaker implantation in 21 (2.6%) (Fig 3). In 146 cases (17.9%), infective endocarditis occurred without any predisposing cardiac disorder. More than 70% of cases had no history of cardiac surgery. Of the 148 cases with a history of cardiac surgery, 100 cases had undergone valve replacement and only 8 cases had undergone valve repair.

Predisposing Extracardiac Conditions or Procedures Relating to Infective Endocarditis

More than half of the patients (53.9%) developed infective endocarditis of unknown origin without any predisposing extracardiac conditions or prior invasive procedures and the next most common condition was post dental procedures (18.0%). There were 5 cases of atopic dermatitis and infective endocarditis.

Causative Microorganisms

From the 817 cases, 697 microorganisms were isolated (Table 1), which is a positive rate of blood culture of approximately 80%, although some cases may have been infected with more than 2 microorganisms. The most common microorganism was gram-positive cocci, the majority of which were streptococcus species (n=345, 49.5%) and staphylococcus species (n=221, 31.7%). Methicillin resistant Staphylococcus aureus (MRSA) was found in 51 cases (7.3%). Gram-negative bacilli were found in 41 cases only (5.9%).

Relationship Between Microorganisms and Predisposing Conditions

In both Streptococcus viridans (S. viridans) and Staphylococcus aureus (S. aureus) infections, the main predisposing condition was unknown. The second leading condition was post dental procedures and oral hygiene related conditions in S. viridans infections (35.7%) and vascular catheterization, including pacemaker implantation, in S. aureus infections (17.9%) (Fig 4). Next to vascular catheterization,

Table 1 Causative Microorganisms

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococci</td>
<td>221</td>
</tr>
<tr>
<td>S. aureus</td>
<td>145</td>
</tr>
<tr>
<td>MSSA</td>
<td>88</td>
</tr>
<tr>
<td>MRSA</td>
<td>51</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
</tr>
<tr>
<td>CNS</td>
<td>76</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>31</td>
</tr>
<tr>
<td>Others</td>
<td>45</td>
</tr>
<tr>
<td>Streptococci</td>
<td>345</td>
</tr>
<tr>
<td>S. viridans</td>
<td>269</td>
</tr>
<tr>
<td>Others</td>
<td>76</td>
</tr>
<tr>
<td>Enterococci</td>
<td>58</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>49</td>
</tr>
<tr>
<td>Enterococcus sp.</td>
<td>9</td>
</tr>
<tr>
<td>Others</td>
<td>25</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>41</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
</tr>
<tr>
<td>E. coli</td>
<td>7</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>5</td>
</tr>
<tr>
<td>Haemophilus sp.</td>
<td>6</td>
</tr>
<tr>
<td>Pseudomonas sp.</td>
<td>6</td>
</tr>
<tr>
<td>Others</td>
<td>17</td>
</tr>
<tr>
<td>Fungi</td>
<td>7</td>
</tr>
<tr>
<td>Candida sp.</td>
<td>6</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
</tbody>
</table>

MSSA, methicillin sensitive Staphylococcus aureus; MRSA, methicillin resistant Staphylococcus aureus; CNS, coagulase-negative staphylococcus.
4.4\% of cases with S. aureus infection developed infective endocarditis after a dental procedure.

**Antibiotics Sensitivity**

Of the 345 streptococcus species, 269 (77.9\%) were in the S. viridans group. Because the effectiveness of penicillin G on this group is quite important clinically, we investigated 182 cases of S. viridans for which sensitivity to penicillin G was clearly shown in the questionnaire: 170 cases (93.4\%) were sensitive to penicillin G, but it should be noted that 12 (6.6\%) were resistant.

All MRSAs were sensitive to vancomycin. None of the gram-negative bacilli was multi-drug resistant.

**Discussion**

A nationwide questionnaire was conducted to survey the present situation regarding infective endocarditis in Japan. Responses were obtained from nearly 300 hospitals, providing data from which the recent trend of the disease could be determined.

**Comparison With Previous Studies**

Other studies in Japan have described the trend of infective endocarditis in a community hospital\(^7\) or in patients with congenital heart disease\(^8\). In 1980, Katsu performed a nationwide questionnaire survey in Japan that was similar to the present study\(^6\) and a comparison of the results of the 2 studies should show any changes in the epidemiology of infective endocarditis. Katsu collected 906 microorganisms from all over Japan, whereas the present study analyzed 848 cases. Interestingly, his patients were mostly aged in their 20s and 30s, but those in our study were in their 50s or 60s. Approximately 60\% of the patients in the United States in the late 1960s were aged 50 years and over\(^\(_{10–11}\)\) so our present age distribution is similar to that in the United States 40 years previously.

More than half of the patients in the present study (53.9\%) and more than 70\% of the patients in Katsu’s study\(^6\) had developed infective endocarditis without any predisposing extracardiac conditions or prior invasive procedure. In both studies the leading invasive procedure was a dental procedure (18.0\% vs 11.7\%, present study vs Katsu, respectively), which suggests that prophylactic treatments are not working effectively. Of the patients with infective endocarditis and a history of cardiovascular surgery, there were 6.8\% in the previous study\(^6\) and 18.1\% in the present study, which may simply reflect the fact that cases undergoing cardiac surgery have increased recently compared with 20 years ago. Of note, there were 5 cases of atopic dermatitis and infective endocarditis in the present study. Although there is little direct evidence of a relationship between dermatitis and endocarditis\(^{12}\), attention should be paid to this finding because the number of patients with atopic dermatitis has increased recently.

In Katsu’s study, 679 microorganisms were isolated from 668 cases (73.7\%) and 56.7\% were streptococcus species and 14.6\% were staphylococcus species\(^8\) However, in a survey in the United States between 1974 and 1977, streptococcus species comprised 25.8\% and staphylococcus species were 35.1\% and that trend was confirmed in a recent series in the United States\(^{13}\). In the present study, 697 microorganisms were isolated and the most common were streptococcus species (49.5\%) and staphylococcus species (31.7\%). Fig.5 shows a comparison of the spectrum of microorganisms in the United States (1974–77) and in Japan (1971–78; 2001–02) and it can be seen that the recent trend in Japan reflects that of the US 30 years ago.

**Underlying Disease**

In the present study, the leading underlying cardiac disorder was valvular heart disease and the second was congenital heart disease, which is in accord with the results from other reports\(^2,4\). There were 21 patients (2.6\%) with infective endocarditis who had undergone pacemaker implantation and although pacemaker implantation has been classified as a negligible-risk category for infective endocarditis by the American Heart Association\(^4\), we may reconsider the necessity of prophylaxis for such patients. It should be noted that more than 17\% of all cases developed infective endocarditis without any predisposing cardiac disorders, but it is not certain whether those patients had undiagnosed disorders or were truly without any underlying disorders. It seems that the incidence of infective endocarditis in patients without predisposing cardiac disorders has been increasing\(^{14,15}\) and this fact should alert us to the possibility of infective endocarditis in a patient who comes in with fever of unknown origin even if there is not a baseline cardiac disease.

Most of the patients in the present study did not have a history of cardiac surgery. Considering the recent trend in valvular heart disease, this suggests the importance of non-
surgical mitral valve prolapse and bicuspid aortic valve as the potential site of infective endocarditis. Only a small number of cases had infective endocarditis after valve repair, which is consistent with the previous observation that valve repair is more resistant to infection than valve replacement.16

Antibiotics
We made the questionnaire as simple as possible in order to increase the rate of return. Thus, we did not ask for details of the antibiotics used to treat infective endocarditis and so the best treatment for each microorganism cannot be provided from the present results. We found that most cases of S. viridans (93.4%) were still sensitive to penicillin G, as in previous reports, but 6.6% were resistant and clinicians should continue to be alert to an increase in resistant streptococci. Likewise, although all MRSAs were sensitive to vancomycin and none of the Gram-negative bacilli were multi-drug resistant, the emergence of drug-resistant microorganisms is a possibility in the future.

Clinical Impact
The characteristics of a disease can change over time because of the development of the new diagnostic technology and therapies, so clinicians need to have the current facts. We believe there is not another report that more clearly shows the actual circumstances of infective endocarditis in Japan than this and the information obtained from the survey was very helpful for developing the guidelines for the prevention, diagnosis and management of infective endocarditis and its complications. Infective endocarditis can be fatal without effective therapy and it is the committee's hope that the guidelines become an indispensable tool for all clinicians.

Acknowledgment
We thank Ms Noriko Ochi for her assistance with the preparation of the manuscript.

References

Appendix
We thank the following institutions for sending back the questionnaires. Because of limited space, only 1 doctor from each institution is listed.

Akita Medical Center: K. Kadowaki; Akita University School of Medicine: M. Miura; Asahikawa Medical College: K. Kikuchi; Asahikawa Red Cross Hospital: T. Nishimiya; Ayab City Hospital: H. Kohno; Cardiovascular Hospital of Central Japan: T. Iwasaki; Chiba Rosai Hospital: M. Yamauchi; Chidorigahashi Hospital: S. Abe; Chigasaki Municipal Hospital: M. Nakamura; Chuubu-Rosai Hospital: M. Nanki; Chubo Hospital: K. Kagaya; Daido Hospital: T. Tajima; Daiyo-cho National Health Insurance Hospital: T. Kakio; Dokkyo University Koshigaya Hospital: S. Kobayashi; Dokkyo University School of Medicine: M. Takahashi; Ebina General Higashi Hospital: S. Iwahara; Fujisawa City Hospital: T. Usui; Fujita Health University School of Medicine: A. Uemura; Fukaya Red Cross Hospital: O. Uchida; Fukui Cardiovascular Center: M. Ohnaka; Fukui Prefectural Hospital: T. Saga; Fukuoka Medical Center for Adults: F. Ohshima; Fukuoka Memorial Hospital: H. Fujiwara; Fukushu postal Service Agency Hospital: M. Nozaki; Fukutaka University Chikushu Hospital: H. Miura; Fukuzaki Cardiovascular Hospital: S. Hida; Fukuzaki Cardiovascular Hospital: H. Ichinose; Fujuyama National Hospital: T. Kajikawa; Funabashi Futaba Hospital: O. Morizuki; Funabashi Municipal Medical Center: S. Ozawa; Gifu Prefectural Tajimi Hospital: T. Yoshida; Gifu University School of Medicine: K. Nishigaki; Gunma University School of Medicine: M. Kurabayashi; Hagiwara Central Hospital: K. Hiyanuma; Hamamatsu Medical Center: C. Takana; Hamamatsu University School of Medicine: K. Yamazaki; Hemanomachi Hospital: Y. Maruoka; Harasanshin Hospital: Y. Taira; Hata Kenmin Hospital: T. Yabe; Hidaka Hospital: S. Tanaka; Higashimatsuyama Municipal Hospital: Y. Suzuki; Higashiosaka-city General Hospital: Y. Kijima; Himemachi Cardiovascular Center: A. Takarada; Hitaraka City Hospital: T. Matsubara; Hiroshima General Hospital: T. Fujii; Hiroshima Prefectural Hospital: M. Okamoto; Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital: S. Kaseda; Hokkaido Keiaikai Minami Ichijo Hospital: M. Goto; Hokkaido University Graduate School of Medicine: A. Kitahara; Hoshi General Hospital: Y. Seino; Hoshiku Cardiovascular Hospital: T. Iwasaki; Ichinomiya Municipal Hospital: T. Shibata; Inada-Noborito Hospital: M. Koh; Ishikireiseki Hospital: K. Yoshimura; Ishinokai Yae General Hospital: K. Tanaka; Itabashi Chuo Medical Center: T. Tamura; Iwaki Kyoritsu General Hospital: T. Ichihara; Iwakuni National Hospital: D. Saito; Iwamizawa Rosai Hospital: H. Sakai; Iwate Medical University Memorial Heart Center: M. Nasu; Izumi Municipal Hospital: M. Nishimoto; Japanese Red Cross Kumamoto Hospital: Y. Ogata; Japanese Red Cross Medical Center: T. Aoyagi; Japanese Red Cross Nagasaki Atomic Bomb Hospital: Y. Ueda; Jichi Medical School Omiya Medical Center: K. Tsuchi; Jichi Medical School: O. Mizuno; Jikei University Daioke Hospital: K. Takasawa; Kaisei University Hospital: T. Shimizu; JR Hiroshima Hospital: A. Hiraoka; JSDF Central Hospital: Y. Tanaka; Juntendo Izunagakoen Hospital: S. Kojima; Juntendo University School of Medicine: H. Daido; Juntendo Urayasu Hospital: M. Arima; Kagawa Prefectural Central Hospital: K. Takeda; Kagoshima City Hospital: K. Toyama; Kagoshima Seiko City Hospital: K. Wawatari; Kagoshima University School of Medicine: C. Tei; Kameda General Hospital: T. Ohara; Kamo Hospital: M. Tsuzuki; Kanagawa Cardiovascular and Respiratory Center: Y. Shimotani; Kanazawa National Hospital: T. Saeki; Kansai Electric Power Hospital: K. Miwa; Kasumigaura National Hospital: T. Hayashi; Kawaguchi General Medical Center: T. Ohba; Kawan Yamanashi Hospital: Y. Sugimura; Kawasaki Medical School: K. Yoshida; Kawasaki Saiwai Hospital: A. Miyamato; Keio University School of Medicine: S. Iwanaga; Kidô Hospital: T. Miyajima; Kimitsu Chuo Hospital: T. Himi; Kihan National Hospital: H. Akagi; Kinoi Obayashi Hospital: M. Ino; Kinki Central Hospital: K. Takatsugi; Kinki University Nara Hospital: R. Hattori; Kishiwada City Hospital: M. Matsuda; Kitakyushu Municipal
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