Current Profile of Infective Endocarditis in Japan

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Despite advances in diagnosis and treatment, the high mortality of infective endocarditis (IE) has not changed in almost 25 years.¹ To improve the treatment strategy for IE, it is essential to realize the current status of the disease. In this issue of the Journal, Nakatani et al report the current status of IE in Japan, based on a nation-wide survey, the Cardiac Disease REgistration – Infective Endocarditis (CADRE-IE).² Their report should be used as a basis for evidence-based treatment in this country. To accentuate the clinical profile of IE in Japan, this editorial compares their results with the recent, large-scale reports from Western countries: a population-based survey from France (the Association pour l'Etude et la Prévention de l'Endocardite Infectieuse study, AEPEI) Study,³ a nation-wide inpatient database (Nationwide Inpatient Sample, NIS) from the United States,⁴ and an international prospective cohort study from 25 countries in north and south America and Europe (the International Collabora-

tion on Endocarditis-Pro prospective Cohort Study, ICE-PCS).¹

Article p1558

Background of IE Patients

Mean and median age of the patients in CADRE-IE was 59.5 and 61 years, respectively, and more than 200 were aged between 61 and 80 years. The age distribution were almost similar among this and 3 other large-scale studies (Table), indicating that IE mostly occurs in the older population. The mean age in the NIS data from the USA rose from 58.6 to 60.8 years between 1998 and 2009, and the incidence of IE in all age groups older than 50 years increased while that in younger populations was stable.⁴ These trends may be related to the increasing elderly population in industrialized countries, which is most remarkable in Japan. The increased number of patients receiving prosthetic valves might be associated with higher

Table. Clinical Profile of IE Reported in Large-Scale Studies

	CADRE ²	JCS Committee ⁶	AEPEI ³	ICE-PCS ¹	NIS ⁴
Nationality	Japan	Japan	France	International	USA
Enrolment (year)	2007–2009	2000–2001	1999	2000–2005	1998–2009
No. of cases	513	817	390	2,759	382,153
Age (mean, years)	59.5	55	59.5	57.9 (median)	59.7
Male (%)	62.4	63.6	71	68.1	57.7
Predisposition (%)					
Known heart disease	68.8	82.1	53	–	25.4
Valvular heart disease	55.9	65	31	53	–
Congenital heart disease	4.4	9.1	1	12	–
Pacemaker/ICD	–	2.6	7	11	–
Prosthetic valve	–	11.7	16	21	15.5*
History of IE	3.5	–	9	8	–
Hemodialysis	7.4	–	–	8	4.4
Drug abuse	2.2	–	5.6	10	7.8
Outcome (%)					
Hospital stay (days)	56.6	–	47	–	15.3
Heart failure	43	–	34	32	–
Intracranial complications	30	–	–	31	10.8
Extracerebral emboli	21	–	32.3	23	–
Valve surgery	61	–	49.7	48	9.6
In-hospital death	11	–	16.6	18	14.5

*Data include prosthetic valves, pacemakers and ICD.

IE, infective endocarditis; ICD, implantable cardioverter-defibrillator; –, data not available.

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Figure. Comparison of the spectrum of causative microorganisms in the recent large-scale studies.

rate of IE in elderly population.⁵

There is a striking difference in the cardiac and noncardiac predisposing conditions among countries. A high incidence of underlying cardiac disease (82%) was observed in CADRE-IE, as well as in the prior report by the Japanese Circulation Society's (JCS) committee for guidelines.⁶ The incidence of predisposing heart disease was only 53% in France according to the AEPEI report, and 55% in ICE-PCS, with 74.6% in NIS (Table). Valvular heart disease was the leading cause in all these reports. It is not clear why underlying heart disease was so frequent in CADRE-IE compared with the others. It could be a characteristic of IE in Japan, but it might be a result of the limitation of that study. Only cardiologists certified by JCS could register to CADRE, and they might have found underlying cardiac disease more frequently than participants of other population-based studies.

The rate of drug users was distinctively lower (2.2%) in CADRE-IE, compared with 5.6% in AEPEI, 7.8% in NIS, and 10% in ICE-PCS. Hopefully, the lower rate demonstrates that Japanese society is wholesome, but it might be related to the selection bias. Drug abuse correlates with social and economic background. Patients in CADRE-IE were admitted to institutes specializing in cardiovascular disease, to which patients with a complex background might be less likely to be admitted. These disparate patient backgrounds might be associated with the spectrum of microorganisms and outcomes.

Causative Microorganisms

In CADRE-IE, AEPEI and ICE-PCS, *Streptococcus* sp. was the most common causative microorganisms followed by staphylococci. On the other hand, staphylococci surpassed streptococci in NIS (Figure). Another report from ICE-PCS showed that the leading microorganism in older patients (>65 years) was *Staphylococcus aureus*, with a higher rate of methicillin-

resistance *S. aureus* (MRSA).⁷ During the last 2 decades of the 20th century, an increase in staphylococci and relative decrease in streptococci as the causative microorganisms were observed in Japan,⁶ as in other countries. The rate of staphylococci infection in CADRE-IE was higher than in the prior study on IE in Japan conducted between 1971 and 1978.⁸ No distinctive difference in microorganism distribution was observed among CADRE-IE, AEPEI, and ICE-PCS. MRSA accounted for 35.7% of staphylococci cases in CADRE-IE, and for 53.3% in NIS.

The high incidence of streptococci infection was related to the predisposing conditions and infection route. Oral disease and dental procedures were the major predisposition and portal of infection in CADRE-IE, as well as in AEPEI. Although good dental hygiene is obviously important for the prevention of IE, the effectiveness of prophylactic antibiotics is not fully determined. The guidelines for IE prevention from the American Heart Association were updated in 2007, and it recommend limited use of antibiotic prophylaxis for dental procedures only in patients at higher risk of developing IE.⁹ Subanalysis of the NIS database reported no perceivable increase in *Streptococcus viridans*-related IE after publication of the 2007 guidelines.¹⁰

Treatment and Outcomes

Remarkable differences between CARDRE-IE and other reports were found in the treatment and clinical outcomes, possibly because of differences in the healthcare systems. Mean length of hospital stay was 56.6 days, which was longer than in AEPEI (47 days). In NIS, it was far shorter, 15.3 days. Valve surgery was frequently (61%) performed in CARDRE-IE, but in only 9.6% of patients in NIS. Proudly, CADRE-IE demonstrated a lower rate of in-hospital mortality (11%) than other reports. It is not clear whether the better survival rate

might be attributed solely to longer hospital stay and a higher rate of surgery. A different spectrum of causative microorganisms might be associated with the risk of in-hospital death. *Staphylococcus aureus* infection was associated with an increased risk of in-hospital death, and *Streptococcal viridans* infection with a decreased risk.^{1,11} Most of the attending hospitals in CADRE-IE were high-standard institutes with a cardiology division, and that might be related to better outcomes.

Conclusions

As roughly outlined, CADRE-IE had (1) a higher incidence of dental disease as predisposition, (2) streptococci as the leading causative microorganism, and (3) longer hospital stay, higher rate of surgical treatment and lower in-hospital death rate. These characteristics might match the “classical” picture of IE. A drastic change in the pathologic profile of IE was mainly observed in the USA, and the change seems to be relatively slow in European countries. The current report was a cross-sectional study with a limited number of subjects, and might not be suitable for the assessment of temporal changes in IE profile. It could not provide information on the fundamental statistics of IE, such as prevalence in Japan. A long-term, population-based survey is required for the accurate picture of IE in today’s Japan.

Disclosures

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References

1. Murdoch D, Corey G, Hoen B, Miró J, Fowler V, Bayer A, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: The International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med* 2009; **169**: 463–473.
2. Nakatani S, Mitsutake K, Ohara T, Kokubo Y, Yamamoto H, Hanai S; the CADRE investigators. Recent picture of infective endocarditis in Japan: Lessons from Cardiac Disease Registration (CADRE-IE). *Circ J* 2013; **77**: 1558–1564.
3. Hoen B, Alla F, Selton-Suty C, Béguinot I, Bouvet A, Briançon S, et al. Changing profile of infective endocarditis: Results of a 1-year survey in France. *JAMA* 2002; **288**: 75–81.
4. Bor D, Woolhandler S, Nardin R, Brusch J, Himmelstein D. Infective endocarditis in the U.S., 1998–2009: A nationwide study. *PLoS One* 2013; **8**: 10.
5. Okamura H, Yamaguchi A, Nagano H, Itoh S, Morita H, Naito K, et al. Mid-term outcomes after aortic valve replacement with the 17-mm St. Jude Medical Regent valve. *Circ J* 2012; **76**: 365–371.
6. Nakatani S, Mitsutake K, Hozumi T, Yoshikawa J, Akiyama M, Yoshida K, et al. Current characteristics of infective endocarditis in Japan: An analysis of 848 cases in 2000 and 2001. *Circ J* 2003; **67**: 901–905.
7. Durante-Mangoni E, Bradley S, Selton-Suty C, Tripodi M, Barsic B, Bouza E, et al. Current features of infective endocarditis in elderly patients: Results of the International Collaboration on Endocarditis Prospective Cohort Study. *Arch Intern Med* 2008; **168**: 2095–2103.
8. Katsu M. Present situation around infective endocarditis. *Nippon Ishikai Zasshi (J Jpn Med Assoc)* 1980; **84**: 869–886.
9. Wilson W, Taubert K, Gewitz M, Lockhart P, Baddour L, Levison M, et al. Prevention of infective endocarditis: Guidelines from the American Heart Association: A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; **116**: 1736–1754.
10. Desimone D, Tleyjeh I, Correa D, Anavekar N, Lahr B, Sohail M, et al. Incidence of infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American Heart Association’s endocarditis prevention guidelines. *Circulation* 2012; **126**: 60–64.
11. Cabell C, Jollis J, Peterson G, Corey G, Anderson D, Sexton D, et al. Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med* 2002; **162**: 90–94.