Epidemiological Trends of Infective Endocarditis: A Population-Based Study in Olmsted County, Minnesota

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OBJECTIVE: To provide a contemporary profile of epidemiological trends of infective endocarditis (IE) in Olmsted County, Minnesota.

PATIENTS AND METHODS: This study consists of all definite or possible IE cases among adults in Olmsted County from January 1, 1970, through December 31, 2006. Cases were identified using resources of the Rochester Epidemiology Project.

RESULTS: We identified 150 cases of IE. The age- and sex-adjusted incidences of IE ranged from 5.0 to 7.9 cases per 100,000 person-years with an increasing trend over time differential with respect to sex (for interaction, $P=.02$); the age-adjusted incidence of IE increased significantly in women ($P=.006$) but not in men ($P=.79$). We observed an increasing temporal trend in the mean age at diagnosis ($P=.04$) and a decreasing trend in the proportion of cases with rheumatic heart disease as a predisposing condition ($P=.02$). There were no statistically significant temporal trends in the incidence of either *Staphylococcus aureus* or viridans group streptococcal IE. Data on infection site of acquisition were available for cases seen in 2001 and thereafter, with 50.0% designated as health care–associated, 42.5% community-acquired, and 7.5% nosocomial.

CONCLUSION: The incidence of IE among women increased from 1970 to 2006. Ongoing surveillance is warranted to determine whether the incidence change in women will be sustained. Subsequent analysis of infection site of acquisition and its impact on the epidemiology of IE are planned.

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Several factors have garnered attention in the new millennium that markedly affect the epidemiology of infective endocarditis (IE). These include an increase in the prevalence of health care exposure as a source of infection acquisition,^{1,2} an increasing incidence of bacteremia due to *Staphylococcus aureus*,³⁻⁵ a decreasing incidence of rheumatic carditis, and an older age at onset in developed countries. Although IE investigations have examined each of these factors, the studies were conducted in large teaching facilities and are subject to different biases that can affect epidemiological findings in IE.^{6,7} A recent systematic review⁸ found that evidence from well-planned, representative IE epidemiological surveys is scarce in many countries and that the available evidence from population-based studies does not support the contention that IE epidemiology is undergoing major changes.

Olmsted County, Minnesota, provides a unique opportunity to conduct population-based studies because

its population is stable and medical care is limited to a few local facilities. The long-established Rochester Epidemiology Project⁹ facilitates data collection and ensures detection of virtually all cases. Our group has previously described a population-based analysis of IE from Olmsted County that included cases seen between 1970 and 2000.¹⁰ In that surveillance study, we observed no important trend in the incidence of IE or the distribution of causative organisms. Because there are factors, as aforementioned, that have affected the epidemiology of IE in other geographic locations, we performed an updated and contemporary temporal trends analysis of the epidemiology of IE in Olmsted County to determine whether clinical features of the disease had changed in more recent years. In addition, we evaluated the site of infection acquisition of local IE cases (health care–associated, nosocomial, and community-acquired) because this characterization was not conducted in our previous survey.¹⁰ To our knowledge, no population-based investigation of the site of IE infection acquisition has previously been published.

PATIENTS AND METHODS

The unique characteristics of Olmsted County foster population-based studies and have been outlined previously.¹⁰ The Endocarditis Registry of the Division of Infectious Diseases was our primary resource for data collection, including baseline demographics and microbiology. In addition, the Rochester Epidemiologic Project database was

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used to ensure that all cases were included and to confirm each patient's residential status and mortality. In case of conflicting information, the patient's chart was reviewed. We identified all Olmsted County residents 18 years or older with possible or definitive endocarditis, as defined by modified Duke criteria,¹¹ between January 1, 1970, and December 31, 2006. We excluded patients who refused to provide consent to have their medical record reviewed for research purposes.

All cases of IE were entered by trained data coordinators at the IE registry and were reviewed by one or more infectious diseases consultants (J.M.S., W.R.W., L.M.B.) Comorbidity data were obtained by reviewing physicians' diagnoses and supporting data. We used the modified Charlson Comorbidity Index¹² to stratify patients' medical conditions. Infection site of acquisition was based on definitions described by Friedman et al.¹³ According to these criteria, patients were considered to have health care-associated infections if one of the following occurred before development of signs and symptoms of IE: received intravenous therapy at home; received wound care or specialized nursing care through a health care agency, family, or friends; self-administered intravenous medical therapy in the prior 30 days; examined at a hospital or hemodialysis clinic or received intravenous chemotherapy in the prior 30 days; hospitalized in an acute care hospital for 2 or more days in the 90 days before the infection; or resided in a nursing home or long-term care facility. Nosocomial acquisition of IE was defined by onset of signs and symptoms of IE in patients who had been hospitalized for 48 hours or longer.¹⁴

STATISTICAL ANALYSES

Descriptive statistics were used to summarize the cohort, including counts and percentages for categorical data and medians and interquartile ranges for continuous data. For calculating incidence rates, the adult population (≥ 18 years) of Olmsted County was considered at risk, with denominator age- and sex-specific person-years derived from decennial census figures. For post-2000 years, the denominator values were estimated using a projected annual growth rate of 1.9%. For IE rates, 95% confidence intervals were estimated on the assumption that the incidence rates follow a Poisson distribution. Rates were age- and sex-adjusted to the population of white people in the United States in 2000. Multivariable Poisson regression was used to examine temporal trends in the incidence of IE from 1970 to 2006, with the period grouped into 5-year intervals (except the last 2 intervals, which were each 6 years: 1995-2000 and 2001-2006) and fit as continuous, adjusted for age and sex. In addition, all pair-wise interactions among the 3 factors in the model were tested for significance. To evaluate a temporal trend in the proportion of various clinical characteristics

among incident cases, the Wilcoxon rank sum test was used. Spearman correlation was used to assess for a significant temporal association with age at diagnosis or Charlson Index score. All analyses were performed in SAS version 8 (SAS Institute, Cary, NC). The level of significance for all statistical tests was 2-sided, with $P < .05$.

RESULTS

We identified 150 cases of IE in Olmsted County adults. The age- and sex-adjusted and age-adjusted, sex-specific incidence rates of IE over different periods are shown in Figure 1. The age- and sex-adjusted incidence rates of IE ranged between 5.0 and 7.9 cases per 100,000 person-years. The interaction between sex and calendar time was significant, indicating a temporal trend in incidence that was differential with respect to sex ($P = .02$). In particular, incidence among men was relatively stable across the study period and ranged from 8.6 to 12.7 cases per 100,000 person-years ($P = .79$). In contrast, there was a significant increase in incidence among women, from 1.4 cases per 100,000 person-years at the beginning of the study period to 6.7 at the end of the period ($P = .006$).

The demographic and clinical characteristics of IE cases over time are reported in the Table. Among incident cases, there was a temporal trend of increasing age on presentation (Spearman correlation coefficient, 0.17; $P = .04$), with median age increasing from 46.5 years in 1980-1984 to 70.5 years in 2001-2006. There were also decreases in the proportions of cases affecting the aortic valve ($P = .01$) and rheumatic heart disease as a predisposing factor ($P = .02$) over time. From 1975-1979 to 2001-2006, the proportion of cases affecting the aortic valve decreased steadily from 69% to 30%, whereas the rate of rheumatic heart disease as a predisposing factor declined from 31%

FIGURE 1. Age-adjusted incidence of infective endocarditis over time; for trend in women, $P = .006$; for trend in men, $P = .79$.

TABLE. Clinical Features of Patients With IE, Stratified by Designated Periods^a

Variable	1970-1974 (n=12)	1975-1979 (n=13)	1980-1984 (n=14)	1985-1989 (n=19)	1990-1994 (n=21)	1995-2000 (n=31)	2001-2006 (n=40)	P value ^b
Age (y), median (IQR)	65.5 (56.0-79.5)	53.0 (34.0-80.0)	46.5 (34.0-41.0)	66.0 (41.0-76.0)	66.0 (49.0-80.0)	70.0 (54.0-83.0)	70.5 (54.5-82.5)	.04 ^c
Women	2 (17)	3 (23)	4 (29)	6 (32)	7 (33)	8 (26)	20 (50)	.02
Charlson Index, ^d median (IQR)			1.5 (0.0-3.0)	1.0 (0.0-3.0)	2.0 (1.0-5.0)	2.0 (0.0-3.0)	2.5 (1.0-6.0)	.08 ^c
Definitive IE by Duke criteria	6 (50)	13 (100)	13 (93)	18 (95)	20 (95)	26 (84)	36 (90)	.31
Underlying heart disease								
Rheumatic heart disease	2 (17)	4 (31)	3 (21)	2 (11)	0 (0)	3 (10)	2 (5)	.02
Congenital heart disease	1 (8)	0 (0)	3 (21)	1 (5)	1 (5)	3 (10)	2 (5)	.65
Bicuspid aortic valve	0 (0)	4 (31)	0 (0)	2 (11)	0 (0)	0 (0)	2 (5)	.15
Acquired valvular disease	3 (25)	4 (31)	1 (7)	0 (0)	3 (14)	2 (7)	7 (18)	.70
Mitral valve prolapse	1 (8)	0 (0)	1 (7)	5 (26)	8 (38)	3 (10)	7 (18)	.45
Previous IE	0 (0)	0 (0)	0 (0)	6 (32)	1 (5)	1 (3)	6 (15)	.23
Unknown (none)	6 (55)	2 (15)	4 (29)	5 (26)	2 (10)	14 (45)	16 (40)	.24
Prosthetic	0 (0)	1 (8)	2 (14)	8 (42)	6 (29)	9 (29)	7 (18)	.44
Valves involved								
Native	12 (100)	12 (92)	12 (86)	11 (58)	15 (71)	22 (71)	33 (83)	.44
Aortic (any)	5 (42)	9 (69)	8 (57)	9 (47)	8 (38)	10 (32)	12 (30)	.01
Mitral (any)	8 (67)	6 (46)	5 (36)	11 (58)	16 (76)	16 (52)	24 (60)	.62
Right-sided or bilateral	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (6)	2 (5)	.08
Unknown valve	0 (0)	0 (0)	2 (14)	1 (5)	0 (0)	6 (19)	0 (0)	.97
Organism								
Viridans group streptococci	6 (50)	5 (38)	6 (43)	10 (53)	7 (33)	14 (45)	12 (30)	.20
<i>Staphylococcus aureus</i>	3 (25)	4 (31)	3 (21)	4 (21)	8 (38)	6 (19)	12 (30)	.81
Coagulase-negative staphylococci	0 (0)	0 (0)	3 (21)	2 (11)	0 (0)	2 (6)	8 (20)	.06
<i>Enterococcus</i> species	0 (0)	0 (0)	1 (7)	1 (5)	2 (10)	3 (10)	3 (8)	.28
HACEK	0 (0)	1 (8)	0 (0)	1 (5)	1 (5)	2 (6)	1 (3)	.97
Non- <i>viridans</i> group streptococci	2 (17)	2 (15)	2 (14)	1 (5)	3 (14)	1 (3)	2 (5)	.09
Other organisms	0 (0)	0 (0)	1 (7)	1 (5)	0 (0)	3 (10)	1 (3)	.67
Culture-negative	1 (8)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)	.86
Outcomes								
Valve surgery, 42 d	0 (0)	3 (23)	3 (21)	4 (21)	2 (10)	5 (16)	7 (18)	.74
Valve surgery, 1 y	0 (0)	3 (23)	3 (21)	4 (21)	2 (10)	6 (19)	12 (30)	.09
6-mo mortality	4 (33)	3 (23)	2 (14)	4 (21)	7 (33)	9 (29)	11 (28)	.67
Cardiac abscess	0 (0)	2 (15)	1 (7)	4 (21)	1 (5)	4 (13)	2 (5)	.60
Other abscess	0 (0)	0 (0)	3 (21)	1 (5)	4 (19)	5 (16)	5 (13)	.26
Emboli	2 (17)	4 (31)	4 (29)	6 (32)	5 (24)	7 (23)	13 (33)	.60

^a Values are No. (%) unless indicated otherwise. HACEK = *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; IE = infective endocarditis; IQR = interquartile range.

^b P value from Wilcoxon rank sum test unless indicated otherwise.

^c P value via Spearman correlation test.

^d Charlson Comorbidity Index was not obtained before 1980.

to 5%. There were no significant temporal trends in the proportions of other predisposing conditions, including congenital heart disease, prosthetic valve, acquired valvular disease, or mitral valve prolapse.

Age- and sex-adjusted incidences of IE for different microorganisms are shown in Figure 2. There was not

a significant temporal trend in the incidence of either *S aureus* or viridans group streptococcal IE. Data regarding infection site of acquisition were obtained in cases seen between 2001 and 2006, of which 50% were health care-associated, 42.5% were community-acquired, and 7.5% were nosocomial infection.

FIGURE 2. Age- and sex-adjusted incidence of infective endocarditis over time based on microbial etiology; for trend in *Staphylococcus aureus* incidence, $P=.21$; for trend in viridans group streptococci, $P=.70$.

DISCUSSION

Although there has been a notion that the incidence of IE has increased in recent years, contemporary population-based data have been lacking to support this opinion. Findings presented herein support this notion, although this increase was limited to only the female population. Multiple factors can positively or negatively affect the incidence of IE.

Sex predilection as a risk factor for the development of IE is important because past studies have historically demonstrated a prevailing male predominance for the syndrome of IE. This observation has been due in part to the associated male sex predilection with intravenous recreational drug use, a risk factor associated with the development of IE that has been and remains distinctly uncommon among our local population. This, coupled with an assumed equal access to medical care for both sexes, could have affected the incidence of female sex among IE cases in more recent years considering the commonality of health care-associated and nosocomial exposure as infection sites of acquisition.

Durante-Mangoni et al,¹⁵ using resources of the International Collaboration on Endocarditis, demonstrated that the male predominance of IE decreased with aging. Increasing age is a well-recognized risk factor associated with the development of IE, and as populations in developing countries continue to age, an anticipated growth in the number of IE cases is expected. We think that an aging effect has been operative in Olmsted County and is reflected in the trend of increasing age among IE cases. Females have a higher life expectancy than males,¹⁶ and biologic sex differences decrease with age;

thus, both factors likely affected the sex distribution among local IE cases. There is a similar change in sex predisposition with age and in the development of atherosclerosis, a cardiovascular disease in which well-recognized hormone effects on endothelial cell function and platelet aggregation conceivably could also affect the likelihood of the development of IE.¹⁷ However, it remains to be seen whether this differential increase in IE incidence among females will persist over time or will regress to the mean.

A growing number of reports have demonstrated a major effect of infection site of acquisition on the epidemiology of IE, and this prompted us to evaluate the disease in a population-based survey that included contemporary cases. Although we think that health care exposure was more common among the more recently seen local cases, data regarding infection acquisition were not collected in our previous work, which included IE cases seen through 2000, to confirm this theory.

Recent investigations into the effect of health care exposure on the epidemiology of IE in large tertiary care institutions have gleaned meaningful findings. A study that included a retrospective, multinational cohort database demonstrated that, in more than one-third of patients who had native valve endocarditis and who did not inject drugs, endocarditis had health care-related infection acquisition. Similar to findings in our investigation, that study¹ and another investigation¹⁸ that included contemporary IE cases demonstrated a cohort that included a higher female prevalence than what has been historically described in most IE case series from large tertiary care facilities. Interestingly, neither of these studies addressed sex, per se, and the differences in sex distribution between health care-associated and community-acquired infection acquisition were striking. For example, among study patients who were seen between 2000 and 2007 at a 1000-bed teaching facility in Barcelona,¹⁸ only 27.3% of patients with community-acquired IE were female. In contrast, the female sex predilection was almost double (53%; $P<.005$) for patients with health care-associated infection acquisition. We could not evaluate the effect of infection site of acquisition on sex trends because these data were not collected before 2000 in the Olmsted County population. Nevertheless, it is intuitive that there was an increase in the number of cases with either health care-associated or nosocomial acquisition of IE during the past approximately 35 years, and this shift in infection site of acquisition influenced sex distribution.

Globally, an estimated 12 million people are affected by acute rheumatic fever and rheumatic heart disease. In contrast, rheumatic heart disease has markedly decreased in prevalence during the past several decades in developed countries. Recently, the striking differences in the estimated annual incidence of acute rheumatic fever in underde-

veloped countries (up to 150 cases per 100,000 population) vs that of developed countries, including the United States (<1 case per 100,000 population), has been highlighted.¹⁹ Our findings are concordant with this epidemiological observation, with a 6-fold decrease in its occurrence as a predisposing condition for IE.

Although we do not currently have an explanation for the observed finding of a decreasing proportion of local IE cases that involved the aortic valve, another study has cited a similar proportion of aortic valve involvement.²⁰

We observed no major change in the distribution of causative pathogens despite almost 60% of recent IE cases having either health care–associated or nosocomial exposure as the predominant site of IE acquisition. Of note, however, since its peak incidence between 1985 and 1989, the incidence of viridans group streptococcal IE has appeared to decrease and could be related to a significant decrease in the proportion of rheumatic heart disease as a predisposing condition. In the most recent period (2001–2006), the incidence of *S aureus* IE was higher than the incidence of viridans group streptococcal IE for the first time, although not statistically significant. It is tempting to speculate that in future years the incidence of local *S aureus* cases will increase considering the high proportion of nosocomial and health care–associated infections in the more recent cases. Therefore, continued monitoring of the local IE epidemiology is crucial. Considering that no statistical trend was observed for coagulase-negative staphylococcal IE, it is interesting to note the high incidence of IE due to this group of organisms among more recent cases; this is despite the fact that the proportion of prosthetic valve cases did not change significantly over time. Therefore, native valve IE due to these organisms also deserves close monitoring.

The Olmsted County population has a low prevalence of intravenous recreational drug users and predominantly consists of white people of middle socioeconomic class; thus, the findings in this population may not be applicable to all populations. Infective endocarditis is an uncommon syndrome, and because of the size of the population in Olmsted County, our sample size is relatively small. However, the homogeneous nature of the population limits external biases, and thus our observations reflect a pure assessment of the temporal trends of IE in a preserved population.

CONCLUSION

The epidemiology of IE changed significantly in Olmsted County. The incidence in women increased. Health care–associated and nosocomial sites of infection acquisition were

common in patients seen between 2001 and 2006. However, no temporal trends in the microbiology of IE were noted. Monitoring the local epidemiology of IE is necessary to determine whether the change in sex predilection continues and what effect, if any, that infection site of acquisition will have on all aspects of IE epidemiology.

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REFERENCES

- Benito N, Miro JM, de Lazzari E, et al. Health care-associated native valve endocarditis: importance of non-nosocomial acquisition. *Ann Intern Med.* 2009;150:586–594.
- Murdoch DR, Corey GR, Hoen B, et al; International Collaboration on Endocarditis-Prospective (ICE-PCS) Investigators. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Int Med.* 2009;169(5):463–473.
- Fowler VG Jr, Miro JM, Hoen B, et al. Staphylococcus aureus endocarditis: a consequence of medical progress [published correction appears in *JAMA.* 2005;294(8):900]. *JAMA.* 2005;293(24):3012–3021.
- Letaief A, Boughzala E, Kaabia N, et al. Epidemiology of infective endocarditis in Tunisia: a 10-year multicenter retrospective study. *Int J Infect Dis.* 2007;11:430–433.
- Krecki R, Drozd J, Ibata G, et al. Clinical profile, prognosis and treatment of patients with infective endocarditis—a 14-year follow-up study. *Pol Arch Med Wewn.* 2007;117:512–520.
- Tleyjeh IM, Steckelberg JM. Changing epidemiology of infective endocarditis. *Curr Infect Dis Rep.* 2006;8:265–270.
- Steckelberg JM, Melton LJ III, Ilstrup DM, Rouse MS, Wilson WR. Influence of referral bias on the apparent clinical spectrum of infective endocarditis. *Am J Med.* 1990;88:582–588.
- Tleyjeh IM, Abdel-Latif A, Rahbi H, et al. A systematic review of population-based studies of infective endocarditis. *Chest.* 2007;132:1025–1035.
- Melton LJ III. History of the Rochester Epidemiology Project. *Mayo Clin Proc.* 1996;71(3):266–274.
- Tleyjeh IM, Steckelberg JM, Murad HS, et al. Temporal trends in infective endocarditis: a population-based study in Olmsted County, Minnesota. *JAMA.* 2005;293:3022–3028.
- Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis.* 2000;30:633–638.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40:373–383.
- Friedman ND, Kaye KS, Stout JE, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med.* 2002;137:791–797.
- Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control.* 1988;16:128–140.
- Durante-Mangoni E, Bradley S, Selton-Suty C, 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.
- Arias E. United States life tables, 2004. *Natl Vital Stat Rep.* 2007;56:1–39.
- Tsang TS, Barnes ME, Gersh BJ, Hayes SN. Risks of coronary heart disease in women: current understanding and evolving concepts. *Mayo Clin Proc.* 2000;75(12):1289–1303.
- Fernandez-Hidalgo N, Almirante B, Tornos P, et al. Contemporary epidemiology and prognosis of health care-associated infective endocarditis. *Clin Infect Dis.* 2008;47:1287–1297.
- Rheumatic fever and rheumatic heart disease. *World Health Organ Tech Rep Ser.* 2004;923:1–122, back cover.
- Hoen B, Alla F, Selton-Suty C, et al. Changing profile of infective endocarditis: results of a 1-year survey in France. *JAMA.* 2002;288:75–81.