Changing Patient Characteristics and the Effect on Mortality in Endocarditis

Christopher H. Cabell, MD; James G. Jollis, MD; Gail E. Peterson, MD; G. Ralph Corey, MD; Deverick J. Anderson, MD; Daniel J. Sexton, MD; Christopher W. Woods, MD; L. Barth Reller, MD; Thomas Ryan, MD; Vance G. Fowler, Jr, MD, MHS

Background: Limited data exist on recent demographic and microbiological changes in infective endocarditis (IE) and the impact of these changes on patient survival.

Methods: Data were collected from all patients with definite or possible IE at Duke University Medical Center, Durham, NC, from 1993 to 1999. Logistic regression analysis was used to identify demographic and microbiological changes that occurred in patients with IE over the study period. The impact of these changes on survival was evaluated using Cox proportional hazards modeling.

Results: Among the 329 study patients, rates of hemodialysis dependence, immunosuppression, and *Staphylococcus aureus* infection increased during the study period ($P=.04$, $P=.008$, and $P<.001$, respectively), while rates of infection due to viridans group streptococci decreased ($P=.007$). Hemodialysis was independently associated with *S aureus* infection (odds ratio, 3.1; 95% confidence interval, 1.6-5.9). Patients with *S aureus* IE had a higher 1-year mortality rate (43.9% vs 32.5%; $P=.04$) that persisted after adjustment for other illness severity characteristics (hazard ratio, 1.5; 95% confidence interval, 1.03-2.3).

Conclusions: The demographic and microbiological characteristics of IE at our institution have changed over the past decade in ways that suggest a link between medical practice and IE characteristics. *Staphylococcus aureus* has emerged as a dominant cause of IE, and is an independent predictor of mortality. These findings identify clinical settings that may warrant closer surveillance and more aggressive measures in the identification and prevention of endocarditis.

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HISTORICALLY, infective endocarditis (IE) was predominantly a disease of patients with preexisting valvular abnormalities and community-associated bacteremia. Streptococcal species accounted for 60% to 80% of all cases, and most patients had rheumatic heart disease.[1,2] Over the past 20 years, significant changes in the demographic characteristics of IE have occurred. For example, the prevalence of rheumatic heart disease has decreased,[3-5] while the prevalence of chronically ill patients receiving intensive and invasive care has increased.[6-8]

Approximately 20 years ago, leaders in IE research suggested that the preceding demographic changes would have a dramatic impact on the manifestations and outcomes of IE.[4,9] Specifically, increased use of invasive procedures (eg, surgical procedures, central intravenous catheters, hemodialysis) and steadily rising rates of nosocomial bacteremia were cited as factors that could increase the frequency of endocarditis.[9] In addition, advances in echocardiography and the use of validated diagnostic criteria have enhanced the ability of clinicians to diagnose endocarditis.[10-15] Although descriptive studies on the epidemiology of IE in the 1980s and 1990s have been published,[16-24] there are limited data available to understand the relationships between changing characteristics and outcomes in endocarditis.

We studied all patients with definite or possible IE seen at Duke University Medical Center, Durham, NC, from 1993 to 1999 in an effort to identify changes in demographic and microbiological characteristics in patients with endocarditis. In addition, we sought to classify relationships between demographic characteristics and microbiological etiologies and determine effects on survival.

From the Department of Medicine, Duke University School of Medicine (Drs Cabell, Jollis, Peterson, Corey, Anderson, Sexton, Woods, Reller, Ryan, and Fowler), Duke Clinical Research Institute (Drs Cabell and Jollis), and Durham Veterans Administration Medical Center (Dr Peterson), Durham, NC.

PATIENTS AND METHODS

PATIENT SELECTION

The study received institutional review board approval. Patients were identified in 3 ways: (1) a member of the endocarditis service screened patients admitted to Duke University Medical Center between January 1, 1993, and December 31, 1999, and who underwent an echocardiogram for evaluation of suspected IE; (2) referral to the infectious disease service for the evaluation of IE; and (3) referral to the cardiology service for evaluation of IE. To preserve the statistical assumption of independence of observations, only the initial episode of endocarditis for each patient was included in the study. All patients with definite or possible IE as determined by the Duke criteria[10] were enrolled in this study. Data were collected from each patient's medical record and clinical course. Immune suppression was defined as having received more than 30 days of systemic corticosteroid therapy ($\geq$10 mg/d of prednisone or equivalent drug) or other immunosuppressive therapy (eg, organ transplantation or cancer chemotherapy).

ECHOCARDIOGRAPHIC ASSESSMENT

Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) were performed as previously described.[25,26] Images for TTE and TEE were recorded on ½-in super VHS (vertical helix scan) videotape and in digital loop display format (EchoNet; Heartlab Inc, Westerly, RI, or EnConcert; Agilent Technologies Inc, Andover, Mass). A cardiologist member of the endocarditis team, specifically trained in echocardiography, interpreted echocardiograms for research purposes. The cardiologist interpreting echocardiograms was not part of the clinical care team and was blinded to clinical information for each patient. Echocardiographic findings of IE such as vegetations, oscillation, myocardial abscess, and prosthetic valve dehiscence were defined as previously described.[10,25,26]

MICROBIOLOGICAL ASSESSMENT

All blood cultures received from patients enrolled in this study were routinely processed in the clinical microbiology laboratory and incubated in an automated monitoring system for a minimum of 5 days. Duration of incubation was extended (up to 14 days) when requested by the clinical team. Identification of gram-positive organisms and yeasts was performed using standard microbiological methods. Most gram-negative organisms were evaluated using an automated identification system (MicroScan Walkaway; Dade MicroScan, Inc, West Sacramento, Calif).

FOLLOW-UP

Survival data were obtained on all patients by assessing the medical record to determine dates of clinic visits, admissions, and deaths at Duke Medical Center. To determine survival after hospitalization, a national death index search was performed for those patients without documentation of death in the hospital system.

STATISTICAL ANALYSES

Descriptive statistics are presented as percentages for discrete variables. Continuous variables are presented as mean$\pm$SD. Discrete variables were compared with the χ^2 test. Logistic regression was used to determine independent predictors of *Staphylococcus aureus* infection as well as the relationship between a later year of diagnosis and a particular characteristic. Independent predictors of mortality were determined with Cox proportional hazards models. A 2-sided *P* value of less than .05 was considered significant for all statistical tests. All statistical analyses were done with the use of the Statistical Analysis System, version 6.1 (SAS Institute Inc, Cary, NC).

RESULTS

DEMOGRAPHIC CHARACTERISTICS

During the study period, 1855 patients were screened; 375 patients met criteria for definite or possible IE and were entered into the endocarditis database. Forty patients had multiple episodes of IE (2 episodes in 36 patients, 3 episodes in 3 patients, and 5 episodes in 1 patient). Only the first episode of IE was used for these 40 patients. Of the 329 patients enrolled in this study, 185 (56.2%) had definite IE (**Table 1**). The mean age was 57 years and the male-female ratio was 1.2:1. Diabetes and hemodialysis were more common than intravenous drug abuse and human immunodeficiency virus infection. Sixty-three percent of patients were transferred from outside facilities.

ORGANISM FREQUENCIES

Forty percent (132/329) of the patients were infected with *S aureus* (Table 1). Of these 132, 79 (60%) were infected with methicillin-susceptible strains, accounting for 24% of the total cases. Patients with methicillin-resistant *S aureus* IE accounted for 40% (53/132) of patients with *S aureus* infection and 16% of the total cases. Coagulase-negative staphylococci, viridans group streptococci, and enterococci were less common. Other organisms classically associated with IE, such as *Strepococcus bovis*, were rare.

DEMOGRAPHIC AND ORGANISM CHANGES DURING THE 1990s

Demographic and microbiological characteristics were studied to determine if significant changes in these characteristics occurred over the study period (**Table 2**). The frequency of patients with hemodialysis dependence, immunosuppression, and *S aureus* infection all increased significantly during the study period (*P*=.04, *P*=.008, and *P*<.001, respectively). In addition, the frequency of viridans group streptococci infecting patients with IE decreased during the same interval (*P*=.007) (**Figure**).

PREDICTORS OF *S AUREUS*

Multivariable logistic regression analysis was used to determine which demographic characteristics were predictive of *S aureus* infection (**Table 3**). Characteristics that increased during the 1990s (hemodialysis and immunosuppression) were combined with clinically important characteristics that might be related to infectious etiologies. These clinical characteristics included year of diagnosis, prosthetic valve IE, age, sex, Duke diagnostic classification[10] (possible or definite), diagnosis of diabetes mellitus, transfer from referring hospital, and presence of myocardial abscess. Hemodialysis and year of diagnosis were independently predictive of *S aureus* infection (*P*<.001 for both), while patients with prosthetic valve involvement were half as likely to be infected with *S aureus* (*P*=.03).

ECHOCARDIOGRAPHIC FINDINGS

Echocardiographic findings were also analyzed over the decade of the 1990s. There were no echocardiographic findings that showed a significant change over the study period. Overall, 86% of patients underwent both TTE and TEE. In most patients who had both studies, TEE was the most diagnostic.

MORTALITY AT 30 DAYS AND 1 YEAR

At 30 days, 16.4% of patients had died, and the mortality rate at 1 year was 37.1% (**Table 4**). When stratified by *S aureus* infection, there was a trend toward higher mortality at 30 days for those patients infected with *S aureus* (18.9% vs 14.7%; *P*=.31). At 1 year, the mortality for patients with IE infected with *S aureus* was significantly higher than for those without *S aureus* infection (43.9% vs 32.5%; *P*=.04). Those patients with methicillin-resistant *S aureus* IE had a particularly high mortality at 1 year compared with patients with IE due to other pathogens (49.1% vs 34.8%; *P*=.05).

A multivariable Cox proportional hazards model was used to determine which patient characteristics were independently predictive of survival at 1 year. Variables included in the model were those found to change over the study period (*S aureus* infection, hemodialysis, and immunosuppression) and important characteristics that might affect survival (age, year of diagnosis, hemodialysis, immunosuppression, surgical therapy, and prosthetic valve infection). *Staphylococcus aureus* infection, immunosuppression, and age were the only independent predictors of mortality. Patients with endocarditis caused by *S aureus* had a 1.5-fold increase in the risk of death over 1 year (hazard ratio [HR], 1.5; 95% confidence interval [CI], 1.03-2.3). Patients with IE and immunosuppression had a similar increase in the risk of death over 1 year (HR, 1.7; 95% CI, 1.01-2.8). Finally, age at the time of diagnosis was also independently related to an increase in the risk of death (HR, 1.02; 95% CI, 1.01-1.04).

COMMENT

This investigation of a large cohort of patients with well-characterized endocarditis has identified important relationships between changing characteristics and the effect of these changes on survival. The results of this investigation yielded several key observations.

Table 1. Demographic and Organism Characteristics of 329 Patients With Endocarditis*

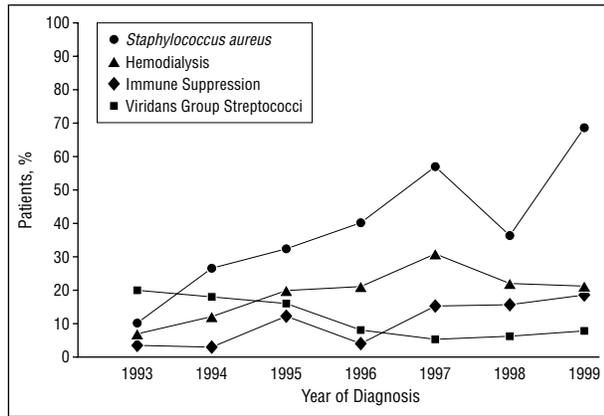| Characteristic	Finding
Demographic features	
Age, mean ± SD, y	56.7 ± 16.1
Male	176 (53.5)
Race	
White	180 (57.7)
African American	123 (38.5)
Other	26 (7.9)
Definite infective endocarditis	185 (56.2)
Hemodialysis	67 (20.4)
Diabetes	90 (27.4)
Intravenous drug abuse	26 (7.9)
Human immunodeficiency virus positive	21 (6.4)
Cancer	38 (11.6)
Immune suppression	37 (11.2)
Transfer	206 (62.6)
Prosthetic valve	90 (30.1)
Organism frequencies	
Staphylococcus aureus	132 (40.1)
Coagulase-negative staphylococci	31 (9.4)
Viridans group streptococci	35 (10.6)
Enterococci	33 (10.0)
Streptococcus bovis	8 (2.4)
Candida species	5 (1.3)
HACEK†	3 (0.8)
No growth	34 (10.3)
Other	48 (14.6)

*Unless otherwise indicated, data are given as absolute number (percentage).

†HACEK indicates *Haemophilus aphrophilus, Haemophilus parainfluenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens*, or *Kingella kingae*.

Table 2. Time Trend Analysis for Changing Characteristics*

Characteristic	1993 (n = 30)	1994 (n = 34)	1995 (n = 56)	1996 (n = 50)	1997 (n = 58)	1998 (n = 63)	1999 (n = 38)	*P* Value (for Trend)
Hemodialysis	2 (6.7)	4 (11.8)	11 (19.6)	10 (20.0)	18 (31.0)	14 (22.2)	8 (21.0)	.04
Immune suppression	1 (3.3)	1 (2.9)	7 (12.5)	2 (4.0)	9 (15.5)	10 (15.9)	7 (18.3)	.008
Staphylococcus aureus	3 (10.0)	9 (26.5)	18 (32.1)	20 (40.0)	33 (56.9)	23 (36.5)	26 (68.4)	<.001
Viridans group streptococci	6 (20.0)	6 (17.7)	9 (16.1)	4 (8.0)	3 (5.2)	4 (6.4)	3 (7.9)	.007

*Data are represented as absolute number (percentage).

Changing characteristics from 1993 to 1999 of 329 patients with infective endocarditis.

CHANGE IN DEMOGRAPHIC CHARACTERISTICS

The demographic characteristics of patients with endocarditis have changed over the last decade. Patients diagnosed with IE later in the decade were more likely to have recently undergone intensive and/or invasive medical care. The primary manifestation of this change was an increase in the frequency of patients undergoing hemodialysis or immunosuppressive therapy later in the decade. These findings are consistent with previous studies documenting an increase in the number of patients receiving hemodialysis[8] and immunosuppressive therapy,[27,28] and suggest that aggressively treated patients represent an emerging population at risk for IE. Other recent cohort investigations also underscore the importance of medical instrumentation as a risk factor for IE. For example, in one recent report, 21 of 22 cases of nosocomial IE occurred as a consequence of a medical or surgical procedure.[29]

CHANGES IN MICROBIOLOGICAL CHARACTERISTICS OF IE

During the 1990s, changes also occurred in the proportions of specific pathogens causing IE. By the end of the decade, *S aureus* was the single most common cause of IE at our institution, accounting for nearly 40% of all patients with IE. During the same period, IE caused by viridans group streptococci became less common. The increasing importance of *S aureus* as a cause of IE in our patients is consistent with other studies showing increases in the overall rates of *S aureus* bacteremia[30] and related infections such as vertebral osteomyelitis[31] and IE.[32-36]

RELATIONSHIP BETWEEN DEMOGRAPHIC AND MICROBIOLOGICAL CHARACTERISTICS

In this study we found a parallel increase in the frequency of patients undergoing hemodialysis and/or immune suppression and those infected with *S aureus*. The association between these comorbid conditions and *S aureus* IE may be due to several factors. First, patients undergoing immunosuppressive therapy and those undergoing hemodialysis are highly susceptible to bacterial infections, including *S aureus*.[37] This susceptibility may be due in part to both the underlying disease and its treatment. The susceptibility is also related to the method by which the treatment is delivered: specifically, intravenous catheters.

Studies have shown a strong relationship between immune suppression, vascular catheters, and hospital-acquired infections.[6,7] Intravascular devices are important risk factors for *S aureus* bacteremia and IE.[34,38] In this study, hemodialysis was independently predictive of *S aureus* infection, which was 3 times as likely to occur in hemodialysis patients than in those not undergoing hemodialysis.

IMPACT OF CHANGING CHARACTERISTICS ON SURVIVAL

Patient outcome was also related to demographic and microbiological changes. Consistent with previous reports,[32-36] patients with *S aureus* IE experienced a significantly higher unadjusted and adjusted 1-year mortality than patients with IE due to other pathogens. If the proportion of cases caused by *S aureus* continues to increase, this finding may have important implications on overall IE mortality rates.

STUDY LIMITATIONS

This study has several limitations. Although uniform data collection methods were used, ascertainment bias may have been present. For instance, our screening mechanism identified only those patients referred to the echocardiography laboratory, the infectious disease service,

or the cardiology service for the evaluation of IE. It is possible that time trends in referral for echocardiography or consultation may have affected our results. In addition, our patients were hospitalized at a large tertiary care medical center, and most of these patients transferred from another hospital. Thus, the frequency, type, and severity of IE in our institution were likely to differ from IE encountered in a community hospital setting.

CONCLUSIONS

The demographic and microbiological characteristics of IE at our institution have changed over the past decade, which suggests a link between medical practice and IE characteristics. *Staphylococcus aureus* infection has emerged as a dominant cause of IE, and is an independent predictor of mortality. These findings identify clinical settings that may warrant closer surveillance and more aggressive measures to identify and prevent endocarditis. Future investigations, ideally in the form of prospective, multicenter collaborations, will be necessary to more precisely characterize the impact of changes in medical practice on the clinical spectrum of endocarditis.

Corresponding author and reprints: Christopher H. Cabell, MD, Duke University Medical Center, Box 31020, Durham, NC 27710 (e-mail: chris.cabell@duke.edu).

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