Clinical Presentation, Etiology, and Outcome of Infective Endocarditis in the 21st Century

The International Collaboration on Endocarditis–Prospective Cohort Study

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Background: We sought to provide a contemporary picture of the presentation, etiology, and outcome of infective endocarditis (IE) in a large patient cohort from multiple locations worldwide.

Methods: Prospective cohort study of 2781 adults with definite IE who were admitted to 58 hospitals in 25 countries from June 1, 2000, through September 1, 2005.

Results: The median age of the cohort was 57.9 (interquartile range, 43.2-71.8) years, and 72.1% had native valve IE. Most patients (77.0%) presented early in the disease (<30 days) with few of the classic clinical hallmarks of IE. Recent health care exposure was found in one-quarter of patients. *Staphylococcus aureus* was the most common pathogen (31.2%). The mitral (41.1%) and aortic (37.6%) valves were infected most commonly. The following complications were common: stroke (16.9%), embolization other than stroke (22.6%), heart failure (32.3%), and intracardiac abscess (14.4%). Surgical therapy was common (48.2%), and in-hospital mortality remained high (17.7%). Prosthetic valve involvement (odds ratio, 1.47; 95% confidence interval, 1.13-1.90), increasing age (1.30; 1.17-1.46 per 10-year interval), pulmonary edema (1.79; 1.39-2.30), *S aureus* infection (1.54; 1.14-2.08), coagulase-negative staphylococcal infection (1.50; 1.07-2.10), mitral valve vegetation (1.34; 1.06-1.68), and paravalvular complications (2.25; 1.64-3.09) were associated with an increased risk of in-hospital death, whereas viridans streptococcal infection (0.52; 0.33-0.81) and surgery (0.61; 0.44-0.83) were associated with a decreased risk.

Conclusions: In the early 21st century, IE is more often an acute disease, characterized by a high rate of *S aureus* infection. Mortality remains relatively high.

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INFECTIVE ENDOCARDITIS (IE) IS A disease characterized by high morbidity and mortality. Although first described in the mid-16th century, the Gulstonian lectures by Osler[1-3] to the Royal College of Physicians in 1885 created the impetus for the systematic study of IE. Beginning in the early 1900s, investigators have frequently reported on the manifestations of this disease.[4-11] However, despite advances during the past century in diagnosis,[12] medical therapy,[13] and surgical treatment,[14,15] mortality rates have not changed substantially in the past 25 years.[5,9,16-18] The current in-hospital mortality rate for patients with IE is 15% to 20%,[5,16] with 1-year mortality approaching 40%.[16,18,19] This is in stark contrast to sustained and ongoing improvements observed in other cardiovascular diseases such as myocardial infarction.[20]

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Unfortunately, definitive studies of IE have been limited by its relative infrequency, a problem compounded by the wide range of causative organisms, at-risk populations, and underlying risk factors for infection. Most studies have consisted of case reports or single-center studies that limit the scope and statistical power necessary for definitive conclusions. Moreover, the lack of multinational studies has prevented an understanding of how geographic differences in patient characteristics and disease management affect outcome in patients with IE.

A prospective multicenter approach is essential for addressing the limitations associated with prior investigations of IE and, importantly, for examining therapeutic choices in a definitive way. Therefore, the

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Group Information: The ICE-PCS Investigators are listed on pages 470-471.

Table 1. Definition of IE According to the Modified Duke Criteria[a]

Definite IE
Pathologic criteria
Microorganisms demonstrated by results of cultures or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen
Pathologic lesions, vegetation, or intracardiac abscess confirmed by results of histologic examination showing active endocarditis
Clinical criteria
2 Major criteria
1 Major criterion and 3 minor criteria
5 Minor criteria
Possible IE
1 Major criterion and 1 minor criterion
3 Minor criteria
Rejected
Firm alternate diagnosis explaining evidence of IE
Resolution of IE syndrome with antibiotic therapy for ≤4 d
No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 d
Does not meet criteria for possible IE
Definition of Terms Used in the Modified Duke Criteria for IE Diagnosis
Major criteria
Blood culture findings positive for IE
Typical microorganisms consistent with IE from 2 separate blood cultures
Viridans streptococci, *Streptococcus bovis*, HACEK group, or *Staphylococcus aureus*
Community-acquired enterococci, in the absence of a primary focus
Microorganisms consistent with IE from persistently positive blood culture findings, defined as:
≥2 positive culture findings of blood samples drawn >12 h apart
3 or most of ≥4 separate culture findings of blood (with first and last sample drawn ≥1 h apart)
Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800
Evidence of endocardial involvement
Echocardiographic findings positive for IE (TEE recommended in patients with prosthetic valves, rated at least possible IE by clinical criteria or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation
Abscess
New partial dehiscence of prosthetic valve (including new valvular regurgitation; worsening or changing of preexisting murmur not sufficient)
Minor criteria
Predisposition, predisposing heart condition, or intravenous drug use
Fever, temperature >38°C
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
Microbiological evidence: positive blood culture finding but does not meet a major criterion[b] or serologic evidence of active infection with organism consistent with IE
Echocardiographic minor criteria eliminated

Abbreviations: HACEK, bacteria consisting of *Haemophilus* species, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species; IE, infective endocarditis; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a] Adapted with permission from Li et al[22] (©2000 by the Infectious Diseases Society of America).

[b] Excludes single positive culture findings for coagulase-negative staphylococci and organisms that do not cause endocarditis.

International Collaboration on Endocarditis (ICE) was established to facilitate a multinational, multicenter approach to the study of IE. From this collaboration, the ICE–Prospective Cohort Study (ICE-PCS) was designed to assess the current characteristics of patients with IE. In this study, we describe this large cohort of patients, with particular emphasis on the current clinical presentation, microbial etiology, and outcomes of patients with IE.

METHODS

THE ICE-PCS

The ICE began in June 1999. The ICE investigators later developed the ICE-PCS.[21] Enrollment in ICE-PCS began on June 1, 2000, and for the purposes of this study was closed on September 1, 2005; the present study includes data from 58 sites in 25 countries.

All patients 18 years or older with IE from sites that met criteria for participation were included in the study. Sites had to meet the following criteria: (1) minimum enrollment of 12 cases per year in a center with access to cardiac surgery; (2) patient identification procedures in place to ensure consecutive enrollment and to minimize ascertainment bias[21]; (3) high-quality data, including query resolution; and (4) institutional review board and/or ethics committee approval or waiver based on local standards.

The ICE-PCS database is maintained at the Duke Clinical Research Institute, which serves as the coordinating center for the ICE studies, with institutional review board approval from Duke University School of Medicine.

Table 2. Baseline Characteristics and Predisposing Conditions in 2781 Patients With Definite Endocarditis[a]

	Total Cohort	Patients Admitted Directly to Study Sites Only[b]	Region				*P* Value for the Difference in Regions
			North America	South America	Europe	Other	
Baseline characteristics							
Age, median (IQR), y	57.9 (43.2-71.8)	59.8 (44.2-73.1)	52.9 (44.1-66.4)	56.8 (40.3-70.4)	61.4 (45.1-72.7)	58.0 (40.5-72.9)	<.001
Male	1889/2777 (68)	1045/1556 (67)	388/596 (65)	179/254 (70)	873/1212 (72)	449/715 (63)	<.001
First sign to admission <1 mo	2088/2711 (77)	1201/1529 (79)	496/582 (85)	166/244 (68)	896/1174 (76)	530/711 (75)	<.001
Hemodialysis	220/2777 (8)	130/1556 (8)	124/596 (21)	20/254 (8)	49/1210 (4)	27/717 (4)	<.001
Diabetes mellitus	447/2764 (16)	261/1550 (17)	158/592 (27)	25/253 (10)	169/1207 (14)	95/712 (13)	<.001
HIV positive	58/2748 (2)	41/1540 (3)	16/594 (3)	4/236 (2)	33/1211 (3)	5/707 (0.7)	.02
Cancer	230/2772 (8)	160/1553 (10)	52/596 (9)	15/251 (6)	101/1210 (8)	62/715 (9)	.56
IE type							.05
Native valve	1901/2636 (72)	1048/1471 (71)	411/573 (72)	167/246 (68)	860/1166 (74)	463/651 (71)	
Prosthetic valve	563/2636 (21)	321/1471 (22)	116/573 (20)	66/246 (27)	227/1166 (20)	154/651 (24)	
Pacemaker/ICD	172/2636 (7)	102/1471 (7)	46/573 (8)	13/246 (5)	79/1166 (7)	34/651 (5)	
Predisposing conditions							
Current IV drug use	268/2746 (10)	157/1540 (10)	93/587 (16)	1/249 (0.4)	113/1203 (9)	61/707 (9)	<.001
Previous IE	222/2780 (8)	138/1557 (9)	66/596 (11)	26/254 (10)	84/1213 (7)	46/717 (6)	.003
Invasive procedure within 60 d	690/2581 (27)	392/1463 (27)	162/508 (32)	64/247 (26)	289/1145 (25)	175/681 (26)	.03
Chronic IV access	244/2763 (9)	142/1548 (9)	148/595 (25)	12/251 (5)	56/1205 (5)	28/712 (4)	<.001
Endocavitary device							
Pacemaker	262/2752 (10)	146/1540 (9)	55/595 (9)	23/252 (9)	137/1191 (12)	47/714 (7)	.005
ICD	27/2720 (1)	15/1521 (1)	16/593 (3)	0/249 (0)	8/1172 (0.7)	3/706 (0.4)	<.001
Congenital heart disease	311/2656 (12)	167/1481 (11)	62/582 (11)	53/244 (22)	111/1156 (10)	85/674 (13)	<.001
Native valve predisposition	884/2761 (32)	538/1547 (35)	147/596 (25)	93/252 (37)	370/1201 (31)	274/712 (38)	<.001

Abbreviations: HIV, human immunodeficiency virus; ICD, implantable cardioverter defibrillator; IE, infective endocarditis; IQR, interquartile range; IV, intravenous.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. Only percentages less than 1% are carried to the first decimal place.

[b] Excludes patients transferred to study hospitals from other health care facilities.

PATIENT SELECTION

Patients were prospectively identified at each site to ensure consecutive enrollment.[21] A total of 3284 patients were enrolled into ICE-PCS, of whom 2781 had definite IE by the modified Duke criteria (**Table 1**).[22] The 2781 patients with definite IE were included in this analysis.

DATA COLLECTION

A case report form of 275 variables was developed by the ICE group according to standard definitions.[21,23,24] Data were collected prospectively by site investigators during the index hospitalization and were then sent to the coordinating center for data entry or were entered directly by the site investigators through a secure Internet data entry system. Queries were developed on critical variables and were distributed to the sites for reconciliation. Once complete, the reconciled queries were returned to the coordinating center for final data entry.

DEFINITIONS

Definitions of the variables included in the ICE-PCS case report form have been reported in detail elsewhere.[23] Community-acquired IE was defined as IE diagnosed at the time of admission (or within 48 hours of admission) in a patient who did not fulfill the criteria for health care–associated infection. Health care–associated IE was defined as nosocomial IE or nonnosocomial health care–associated IE. Nosocomial IE was defined as IE that developed in a patient who was hospitalized for more than 48 hours before the onset of signs or symptoms consistent with IE. Nonnosocomial health care–associated IE was defined as IE diagnosed within 48 hours of admission in an outpatient with extensive health care contact as reflected by any of the following criteria: (1) receipt of intravenous therapy, wound care, or specialized nursing care at home within the 30 days before the onset of IE; (2) attendance at a hospital or hemodialysis clinic or receipt of intravenous chemotherapy within the 30 days before the onset of IE; (3) hospitalization in an acute care hospital for 2 or more days in the 90 days before the onset of IE; or (4) residence in a nursing home or long-term care facility. In an effort to group centers according to geographic similarities, regions were defined as follows: North America (10 sites from the United States), South America (8 sites from Brazil, Argentina, and Chile), Europe (22 sites from Croatia, France, Germany, Italy, the Netherlands, Spain, Sweden, Ireland, Romania, Russia, Slovenia, and the United Kingdom), and other (18 sites from Australia, Israel, India, Lebanon, Malaysia, New Zealand, Singapore, Thailand, and South Africa).

STATISTICAL ANALYSES

Continuous variables are presented as medians with 25th and 75th percentiles. Categorical variables are presented as frequencies and percentages of the specified group. Univariable comparisons were made with the χ^2 test or Kruskal-Wallis test as appropriate. To account for the possibility that patients referred to study hospitals from other health care facilities may represent a different population than those who were admitted directly, data from the latter group only were analyzed separately where indicated.

We used a generalized estimating equation method to determine factors associated with in-hospital mortality. Age, sex, transfer from another health care facility, and variables found to have a univariable association with in-hospital mortality ($P<.10$) were entered into the final exploratory model. The generalized estimating equation method produces consistent parameter estimates that measure the association between in-hospital death and the baseline covariates while accounting for the correlation in outcomes of patients from the same hospital. Likelihood ratio tests were used to compare models with and without interaction terms. Final parameter estimates were converted to odds ratios with cor-

responding 95% Wald confidence intervals. The model was validated using the bootstrap procedure. Some 200 estimates were obtained by fitting the generalized estimating equation model to 200 data sets obtained by randomly selecting 2781 observations with replacement from the actual data. Bootstrap estimates were computed by averaging the 200 parameter estimates, and bootstrap confidence intervals were computed sorting the parameter estimates in ascending order and selecting the 5th estimate for the lower confidence limit and the 195th estimate for the upper confidence limit.

Statistical analyses were performed using commercially available software (STATA, version 8.2; StataCorp, College Station, Texas).

RESULTS

Patients were enrolled in ICE-PCS from the following regions: North America (n=597 [21.5%]), South America (n=254 [9.1%]), Europe (n=1213 [43.6%]), and other (n=717 [25.8%]). Baseline characteristics and predisposing factors are shown in **Table 2**. The median age of the cohort was 57.9 (mean, 56.5; interquartile range, 43.2-71.8) years. Most of the patients in the cohort (72.1%) had native valve IE, and most patients (77.0%) were admitted within 1 month of the initial signs of illness. The most common underlying condition was diabetes mellitus (16.2%), but 9.9% of the South American patients had diabetes, compared with 26.7% of North American patients. Similarly, less than 5% of patients from outside North America were receiving hemodialysis, compared with 20.8% of North American patients.

Predisposing conditions were common in patients with definite IE (Table 2). Although intravenous drug use remains important (9.8%), the most common predisposing conditions were related to valvular heart disease. Degenerative valve disease (eg, significant mitral [43.3%] and/or aortic [26.3%] valve regurgitation) was the most frequent native valve predisposing factor. In contrast, rheumatic heart disease was uncommon; only 92 patients (3.3%) had rheumatic mitral valve disease. Valvular predisposing conditions also included the presence of a prosthetic valve in 618 patients (22.2%).

Chronic intravenous access was as common as intravenous drug use in the overall cohort; 148 of 244 patients (60.7%) in this study with chronic intravenous access were from North America (Table 2).

Clinical and laboratory findings on admission are presented in **Table 3**. The classic signs that are often considered diagnostic for IE were infrequent.

In 2756 of the 2781 patients (99.1%), blood samples were cultured to determine the causative microorganism. Of the 310 patients (11.1%) with negative blood culture yields, 192 (61.9%) had received antibiotics within 7 days of the blood culture. In addition to blood culture information, serologic tests and valve cultures were performed in a minority of cases. Of the 2781 patients, 277 (10.0%) had cultures and serologic tests that were negative for IE.

Table 3. Clinical and Laboratory Findings on Admission in 2781 Patients With Definite Endocarditis and Historical Comparisons

Findings	No. (%) of Patients
Fever, temperature >38°C	2322/2428 (96)
Splinter hemorrhages	213/2655 (8)
Osler nodes	77/2648 (3)
Janeway lesions	123/2650 (5)
Roth spots	50/2649 (2)
Vascular embolic event	456/2665 (17)
Conjunctival hemorrhage	122/2655 (5)
Splenomegaly	284/2662 (11)
New murmur	1068/2232 (48)
Worsening of old murmur	359/1787 (20)
Elevated ESR	1611/2645 (61)
Elevated C-reactive protein level	1632/2650 (62)
Elevated rheumatoid factor	138/2549 (5)
Hematuria	666/2587 (26)

Abbreviation: ESR, erythrocyte sedimentation rate.

Table 4. Microbiologic Etiology by Region in 2781 Patients With Definite Endocarditis

	No. (%) of Patients[a]						
			Region				
Cause of Endocarditis	Total Cohort (N=2781)	Patients Admitted Directly to Study Sites Only[b] (n=1558)	North America (n=597)	South America (n=254)	Europe (n=1213)	Other (n=717)	*P* Value for the Difference Between Regions
Staphylococcus aureus	**869** (31)	487 (31)	256 (43)	43 (17)	339 (28)	231 (32)	<.001
Coagulase-negative staphylococcus	**304** (11)	161 (10)	69 (12)	18 (7)	156 (13)	61 (9)	.005
Viridans group streptococci	**483** (17)	288 (19)	54 (9)	66 (26)	198 (16)	165 (23)	<.001
Streptococcus bovis	**165** (6)	101 (7)	9 (2)	17 (7)	116 (10)	23 (3)	<.001
Other streptococci	**162** (6)	101 (7)	38 (6)	16 (6)	66 (5)	42 (6)	.86
Enterococcus species	**283** (10)	158 (10)	78 (13)	21 (8)	111 (9)	73 (10)	.05
HACEK	**44** (2)	26 (2)	2 (0.3)	6 (2)	19 (2)	17 (2)	.02
Fungi/yeast	**45** (2)	25 (2)	20 (3)	3 (1)	13 (1)	9 (1)	.002
Polymicrobial	**28** (1)	23 (2)	8 (1)	1 (0.4)	13 (1)	6 (0.8)	.60
Negative culture findings	**277** (10)	122 (8)	41 (7)	51 (20)	123 (10)	62 (9)	<.001
Other	**121** (4)	66 (4)	22 (4)	12 (5)	59 (5)	28 (4)	.61

Abbreviation: HACEK, bacteria consisting of *Haemophilus* species, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species.

[a] Only percentages less than 1% are carried to the first decimal place.

[b] Excludes patients transferred to study hospitals from other health care facilities.

Table 5. Microbiologic Etiology by IE Type in 2781 Patients With Definite Endocarditis

Cause of Endocarditis	No. (%) of Patients[a]			
	Native Valve IE		Intracardiac Device IE	
	Drug Abusers (n=237)	Not Drug Abusers (n=1644)	PVIE (n=563)	Other Devices (n=172)[b]
Staphylococcus aureus	160 (68)	457 (28)	129 (23)	60 (35)
Coagulase-negative staphylococcus	7 (3)	148 (9)	95 (17)	45 (26)
Viridans group streptococci	24 (10)	345 (21)	70 (12)	14 (8)
Streptococcus bovis	3 (1)	119 (7)	29 (5)	5 (3)
Other streptococci	5 (2)	118 (7)	26 (5)	7 (4)
Enterococcus species	11 (5)	179 (11)	70 (12)	10 (6)
HACEK	0 (0)	30 (2)	13 (2)	1 (0.5)
Fungi/yeast	3 (1)	16 (1)	23 (4)	2 (1)
Polymicrobial	6 (3)	16 (1)	5 (0.8)	0 (0)
Negative culture findings	12 (5)	154 (9)	65 (12)	18 (11)
Other	6 (3)	62 (4)	38 (7)	10 (6)
Surgical therapy	89/234 (38)[c]	784/1639 (48)	274/561 (49)	104/172 (61)
In-hospital mortality	23/236 (10)[c]	281/1643 (17)	131/561 (23)	17/172 (10)

Abbreviations: HACEK, bacteria consisting of *Haemophilus* species, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species; IE, infective endocarditis; PVIE, prosthetic valve IE.

[a] Only percentages less than 1% are carried to the first decimal place.

[b] Including pacemakers and implantable cardioverter defibrillators.

[c] For pure right-sided IE only, 23 of 107 patients (21.5%) underwent surgical therapy and 6 of 108 (5.6%) died in the hospital.

The causative microorganisms isolated from blood cultures are shown in **Table 4**. Gram-positive organisms were predominant (81.5%), with *Staphylococcus aureus* accounting for 31.2% of all infections. *Staphylococcus aureus* was also the most common organism in each major risk group, including intravenous drug users and those with intracardiac devices (**Table 5**). Positive serologic tests for *Coxiella burnetii* were reported for 27 patients (17 from Europe, 2 from North America, 1 from South America, and 7 from other regions), but only 9 were reported to have reciprocal antibody titers of more than 800. Similarly, 22 patients had positive serologic tests for *Bartonella* species (18 from Europe, 1 from South America, and 3 from other regions), but only 3 were reported to have reciprocal antibody titers of more than 800. One case of infection was due to *Tropheryma whippelii*.

Staphylococcus aureus was the most common organism in 3 of 4 regions, whereas viridans group streptococci were the most common organisms isolated from patients in South America. The frequency of *Streptococcus bovis*–associated IE was much higher in Europe and South America compared with the other regions, and IE due to the group of bacteria consisting of *Haemophilus* species, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species (HACEK bacteria) was relatively uncommon in North America. Most of the *C burnetii* and *Bartonella* infections were from Europe.

The location of acquisition was determined in 94.5% of patients; community acquisition (71.5%) was more common than nosocomial (13.7%) or nonnosocomial (9.3%) health care–associated IE in the total cohort (**Figure**). North America had a much higher proportion of health care–associated infections (38.1%) compared with other regions, mainly owing to a larger proportion with nonnosocomial health care–associated IE.

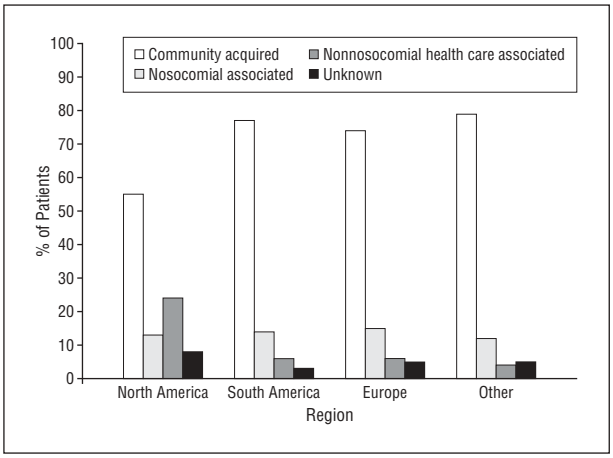

Figure. Geographic comparison of location of acquisition in 2781 patients with definite endocarditis.

The microbial causes of IE varied with location of acquisition, with a higher proportion who had staphylococcal IE and a lower proportion who had viridans streptococcal IE among those with health care–associated IE. Among patients with community-acquired infection, 34.3% had staphylococcal IE and 22.7% had viridans streptococcal IE, whereas the corresponding figures for nosocomial infection were 69.8% and 0.8%, respectively, and for nonnosocomial health care–associated infection were 67.4% and 4.3%, respectively.

Echocardiography was used in most patients (99.2%). More than one-half (59.0%) of the patients had undergone transthoracic and transesophageal echocardiography. Of the 2781 patients, 87.1% had echocardiographic evidence of vegetation, whereas new, significant valvular regurgitation was discovered in 63.8% of patients. Abscess was the most common paravalvular complication (14.4% of patients), whereas

Table 6. Vegetation Findings, Complications, Treatment, and Outcome in 2781 Patients With Definite Endocarditis

	No. (%) of Patients[a]						
			Region				
	Total Cohort	Patients Admitted Directly to Study Sites Only[b]	North America	South America	Europe	Other	*P* Value for the Difference Between Regions
Vegetation present	2406/2764 (87)	1325/1545 (86)	530/594 (89)	223/254 (88)	1041/1201 (87)	612/715 (86)	.26
AV	1031/2741 (38)	524/1535 (34)	198/593 (33)	117/252 (46)	460/1189 (39)	256/707 (36)	.003
MV	1125/2740 (41)	640/1534 (42)	253/593 (43)	103/252 (41)	474/1188 (40)	295/707 (42)	.70
TV	323/2741 (12)	177/1534 (12)	107/593 (18)	18/252 (7)	129/1189 (11)	69/707 (10)	<.001
PV	29/2739 (1)	11/1534 (0.7)	8/593 (1)	5/252 (2)	7/1187 (0.6)	9/707 (1)	.15
Complications							
Stroke	462/2727 (17)	225/1528 (15)	118/595 (20)	37/252 (15)	199/1169 (17)	108/711 (15)	.11
Embolization, nonstroke	611/2709 (23)	324/1524 (21)	139/587 (24)	46/251 (18)	295/1163 (25)	131/708 (19)	.002
CHF	876/2713 (32)	414/1527 (27)	207/591 (35)	97/249 (39)	383/1162 (33)	189/711 (27)	<.001
Intracardiac abscess	389/2707 (14)	176/1522 (12)	101/590 (17)	48/250 (19)	156/1157 (13)	84/710 (12)	.005
Persistent positive blood culture	251/2699 (9)	131/1515 (9)	124/586 (21)	7/250 (3)	82/1153 (7)	38/710 (5)	<.001
New conduction abnormality	217/2695 (8)	100/1511 (7)	70/591 (12)	25/250 (10)	72/1152 (6)	50/702 (7)	<.001
Treatment/outcome							
Surgical therapy	1335/2769 (48)	574/1549 (37)	268/595 (45)	141/252 (56)	613/1210 (51)	313/712 (44)	.001
In-hospital mortality	490/2774 (18)	274/1555 (18)	108/596 (18)	43/254 (17)	231/1210 (19)	108/714 (15)	.17

Abbreviations: AV, aortic valve; CHF, congestive heart failure; PV, pulmonic valve; MV, mitral valve; TV, tricuspid valve.
[a] Only percentages less than 1% are carried to the first decimal place.
[b] Excludes patients transferred to study hospitals from other health care facilities.

34.1% of patients with prosthetic valve IE had evidence of a prosthetic valve complication such as dehiscence or new paravalvular regurgitation.

Congestive heart failure was the most common complication in all regions (**Table 6**). In general, the highest complication rates occurred in North America and Europe.

There were also geographic differences in treatment and outcome, although the magnitude of this variation was not large (Table 6). Surgical treatment was common for the entire cohort (48.2%), and in-hospital mortality was 17.7%. **Table 7** shows the results of the regression modeling for in-hospital mortality with the estimates from bootstrap validation. The following variables were independently associated with an increased risk of in-hospital death: involvement of a prosthetic valve, increasing age, radiographic pulmonary edema, *S aureus* infection, coagulase-negative staphylococcus infection, presence of mitral valve vegetation, and paravalvular complications. Variables independently associated with a decreased risk of in-hospital death were elevated erythrocyte sedimentation rate (ESR), infection with a viridans group streptococcus, and surgery during the current IE episode. The estimates obtained by bootstrap validation were similar to those of the original model and support the validity of this model. Differences between models were noted for the following 4 variables: diabetes mellitus, health care–associated acquisition, coagulase-negative staphylococcus infection, and presence of a mitral valve vegetation.

Of the total cohort of patients with definite IE, 1174 (42.2%) had been transferred to a study hospital from another health care facility. Analysis of the data after excluding these patients revealed few differences from analysis of the whole cohort (Tables 2, 4, and 6). Notable differences were that transferred patients were more likely to undergo surgery (63.4% of transferred patients vs 37.1% of nontransferred patients [$P<.001$]) and were more likely to have congestive heart failure as a complication (39.3% vs 27.1% [$P<.001$]). In-hospital mortality (18%) and microbial etiology were similar for both groups of patients.

COMMENT

Despite more than a century of study and recent advances in diagnosis and treatment, IE remains an incompletely understood disease with high morbidity and mortality. Textbook descriptions of the clinical features and epidemiology of IE are still largely based on data obtained several decades ago. Lack of progress is partly related to the fundamental difficulty in studying this type of disease. By necessity, most studies are derived from case reports or small case series from single sites, with few large cohort studies or randomized trials. A shift in approach is necessary to further the understanding of endocarditis and to definitively study therapeutic choices. The ICE-PCS represents a new effort in broadening our understanding of endocarditis. To our knowledge, this study is by far the largest prospective cohort study of IE to date. The size of the cohort coupled with the multinational perspective has enabled several important observations to be made.

CHANGES IN PATIENT CHARACTERISTICS OF IE

Our findings reveal that, in much of the world, IE is no longer a subacute or chronic disease occurring primarily in younger patients with rheumatic valvular abnormalities. In contrast, most patients in this investigation presented early and demonstrated few of the classic clinical findings traditionally associated with IE. For example, in the 1960s and 1970s, Osler nodes were recorded in 11% to 23% and splenomegaly in 20% to 44% of patients with IE.[9,10,25,26] In our study, predisposing valvular conditions were common but were primarily owing to the presence of degenerative valve disease or a prosthetic valve rather than rheumatic heart disease. Forty years ago, approximately 50% of cases of IE in the United States were superimposed on preexisting rheumatic le-

Table 7. Results of Multivariable Regression Modeling of Associations With In-Hospital Death in 2781 Patients With Definite Endocarditis

Variable[a]	Original Model		Bootstrap Model[c]
	OR[b] (95% CI)	*P* Value	OR[b] (95% CI)
Age in 10-y intervals	1.30 (1.17-1.46)	<.001	1.23 (1.14-1.31)
Male sex	0.99 (0.74-1.34)	.97	1.02 (0.79-1.25)
Transferred from another health care facility	0.97 (0.74-1.29)	.85	1.17 (0.92-1.42)
Prosthetic valve endocarditis	1.47 (1.13-1.90)	.004	1.34 (1.05-1.70)
Hemodialysis	1.06 (0.73-1.53)	.76	1.01 (0.65-1.42)
Diabetes mellitus	1.28 (0.88-1.86)	.20	*1.45 (1.08-1.85)*
Intravenous drug use	0.93 (0.51-1.70)	.82	0.81 (0.47-1.24)
Cancer	1.04 (0.65-1.67)	.86	1.23 (0.80-1.70)
Other chronic illness	1.36 (0.95-1.95)	.10	1.28 (0.99-1.61)
Invasive procedure	0.96 (0.66-1.39)	.82	0.94 (0.73-1.18)
Congenital heart disease	1.22 (0.74-2.02)	.44	1.18 (0.75-1.61)
Elevated ERS	0.57 (0.44-0.73)	<.001	0.59 (0.47-0.72)
Radiographic pulmonary edema	1.79 (1.39-2.30)	<.001	2.03 (1.56-2.53)
Health care–associated acquisition	1.30 (0.85-1.98)	.23	*1.32 (1.02-1.69)*
Staphylococcus aureus–associated IE	1.54 (1.14-2.08)	.005	1.72 (1.31-2.18)
Coagulase-negative staphylococci–associated IE	1.50 (1.07-2.10)	.02	*1.36 (0.93-1.87)*
Viridans group streptococci–associated IE	0.52 (0.33-0.81)	.004	0.52 (0.35-0.71)
Mitral valve vegetation	1.34 (1.06-1.68)	.01	*1.20 (0.93-1.45)*
Paravalvular complications	2.25 (1.64-3.09)	<.001	2.00 (1.57-2.49)
Surgery during this episode	0.61 (0.44-0.83)	.002	*0.56 (0.44-0.69)*

Abbreviations: CI, confidence interval; ERS, erythrocyte sedimentation rate; IE, infectious endocarditis; OR, odds ratio.
[a] Includes all dichotomous variables except for age.
[b] Adjusted for all other variables in the model.
[c] Italicized values indicate differences between the original and bootstrap models.

sions,[27] compared with less than 5% in the present study. Prosthetic valve endocarditis was present in one-fifth of our patients, as discussed in detail elsewhere.[24]

An emerging population at risk for IE consists of patients with health care–associated infections. Overall, IE was attributed to a health care–related exposure in nearly 25% of the patients. These findings confirm those of recent reports from small single-center studies[16,28] and provide evidence that these population changes are occurring in many regions of the world. The health care setting will continue to gain importance in relation to complications such as IE, mainly owing to aging societies that rely on increasingly invasive medical care.[29,30]

Our analysis has provided evidence of geographic differences for several important characteristics in patients with IE. For example, although the overall IE population characteristics were influenced by contact with health care services and medical interventions, this specific finding was not observed in the centers from South America. In addition, the association between health care–associated IE was most striking in North America.

CHANGES IN MICROBIOLOGIC CHARACTERISTICS OF IE

Another observation arising from this investigation is the shift in the microbiologic characteristics of IE. *Staphylococcus aureus* is now the most common cause of IE in much of the world, confirming several recent investigations[5,16,31] and the earlier findings of the ICE-PCS.[23] This shift is due in part to the global presence of risk factors for *S aureus*–associated IE (eg, intravenous drug use, health care contact, and invasive procedures). Given the growing antimicrobial resistance of *S aureus*,[32] including to vancomycin,[33-35] the importance of this pathogen as a potentially lethal infection is cause for concern.

We also noted a substantially higher prevalence of *S bovis*–associated IE in Europe, that HACEK-associated IE was relatively uncommon in North America, and that most cases of Q fever and *Bartonella*-associated IE came from Europe. Whether these findings reflect differences in patient characteristics, regional health care access, diagnostic bias, or other factors remains to be determined. For IE due to microorganisms that are difficult to culture, geographic differences may, at least partially, reflect variation in the threshold for performing additional diagnostic tests. This may be the case for Q fever and *Bartonella*-associated IE, which often rely on serologic and/or nucleic acid amplification tests for diagnosis.[36] However, it is also clear that there are geographic differences in the incidence of these 2 infections.[37]

These changes in the patients and pathogens have important implications for the diagnosis and management of IE. For example, new risk groups have been identified that necessitate careful diagnostic attention in the presence of fever and bacteremia. In addition, the acute nature of IE in the modern era may require an accelerated evaluation strategy that provides the opportunity for early diagnosis and treatment decisions in patients at high risk for complications and death.

IN-HOSPITAL MORTALITY

We have found several factors that were independently associated with in-hospital mortality. Some of these factors, such as increasing age, presence of pulmonary edema,

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and paravalvular complications, were not surprising. In addition, prosthetic valve IE and staphylococcal IE were also associated with an increased risk of in-hospital death, whereas there was a decreased risk associated with viridans streptococcal IE. An elevated ESR was associated with a decreased risk of death, although the reason for this is unclear. Elevated ESR may be associated with more chronic infection, thereby signifying a more chronic clinical course. We have found that early surgery may be critical in improving survival in patients with definite IE. This finding adds detail to recent reports supporting early surgical intervention[38,39] and adds credence to the practice of a combined medical and surgical approach from admission for patients with IE, specifically in those with congestive heart failure and prosthetic valve infections. Our finding that nearly 50% of patients had surgery indicates that the threshold for early surgical treatment has lowered.

STUDY LIMITATIONS

This is an observational study of patients from centers with a particular interest in IE. These hospitals are typically referral centers with cardiac surgical programs. Consequently, the study population is unlikely to be a true population-based sample, thereby limiting epidemiologic inferences. This potential selection bias may be less evident in some sites (eg, New Zealand), where most cases of IE within the catchment area would be eligible for enrollment in the study. It might be expected that patients transferred from other health care facilities would represent a different population than those who presented directly to study hospitals. In particular, the former group may have more complicated disease and greater indications for surgery. However, when the 2 groups were compared, patients transferred from other facilities had characteristics similar to those presenting directly to study hospitals, with notable exceptions being that a larger proportion of the former group underwent surgery during their initial hospitalization and had congestive heart failure as a complication. Consequently, we believe it is important to present data from both groups of patients and that exclusion of referred patients may create a greater selection bias.

Although study sites spanned all non-Antarctic continents, there was a heavy weighting toward wealthy countries in Europe, North America, and Australasia, with few sites in Asia and Africa. There would undoubtedly be greater geographic differences in patient and microbiologic characteristics of IE if sampling was able to more

closely resemble the global population distribution. The study lacked long-term follow-up of patients, thereby limiting the ability to analyze outcome beyond initial hospitalization. The precise timing of all complications was not recorded and may affect the ability to determine the clinical significance of some findings.

CONCLUSIONS

Infective endocarditis remains a serious and deadly disease despite recent advances in diagnosis and treatment. Of particular note, IE has shifted to a disease in which the presentation is more acute than previously described and, throughout much of the world, is characterized by a high rate of *S aureus* infection in patients with previous health care exposure. More care must be taken to effectively treat all patients with *S aureus* bacteremia and to identify patients with high potential for complications.[40] We have documented geographic differences in the presentation, microbial etiology, treatment, and outcome of patients with IE. In addition, we have found initial evidence that early surgery may be important in improving patient outcomes. Because nearly 50% of patients with IE undergo surgery, early identification of surgical indications may improve mortality. More research also needs to focus on stroke prevention (eg, surgical therapy for vegetations), the identification of the most effective therapy (eg, the role of new antibiotics and combination treatment), and understanding reasons for the high prevalence of *S bovis*–associated IE in Europe and the near absence of HACEK-associated IE in North America.

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