Clinical Characteristics and Outcome of Infective Endocarditis Involving Implantable Cardiac Devices

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Context Infection of implantable cardiac devices is an emerging disease with significant morbidity, mortality, and health care costs.

Objectives To describe the clinical characteristics and outcome of cardiac device infective endocarditis (CDIE) with attention to its health care association and to evaluate the association between device removal during index hospitalization and outcome.

Design, Setting, and Patients Prospective cohort study using data from the International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS), conducted June 2000 through August 2006 in 61 centers in 28 countries. Patients were hospitalized adults with definite endocarditis as defined by modified Duke endocarditis criteria.

Main Outcome Measures In-hospital and 1-year mortality.

Results CDIE was diagnosed in 177 (6.4% [95% CI, 5.5%-7.4%]) of a total cohort of 2760 patients with definite infective endocarditis. The clinical profile of CDIE included advanced patient age (median, 71.2 years [interquartile range, 59.8-77.6]); causation by staphylococci (62 [35.0% {95% CI, 28.0%-42.5%}] *Staphylococcus aureus* and 56 [31.6% {95% CI, 24.9%-39.0%}] coagulase-negative staphylococci); and a high prevalence of health care–associated infection (81 [45.8% {95% CI, 38.3%-53.4%}]). There was coexisting valve involvement in 66 (37.3% [95% CI, 30.2%-44.9%]) patients, predominantly tricuspid valve infection (43/177 [24.3%]), with associated higher mortality. In-hospital and 1-year mortality rates were 14.7% (26/177 [95% CI, 9.8%-20.8%]) and 23.2% (41/177 [95% CI, 17.2%-30.1%]), respectively. Proportional hazards regression analysis showed a survival benefit at 1 year for device removal during the initial hospitalization (28/141 patients [19.9%] who underwent device removal during the index hospitalization had died at 1 year, vs 13/34 [38.2%] who did not undergo device removal; hazard ratio, 0.42 [95% CI, 0.22-0.82]).

Conclusions Among patients with CDIE, the rate of concomitant valve infection is high, as is mortality, particularly if there is valve involvement. Early device removal is associated with improved survival at 1 year.

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CARDIAC ELECTRONIC DEVICES, including permanent pacemakers and implantable cardioverter-defibrillators (ICDs), are increasingly implanted worldwide, with estimates of more than 4.2 million patients with a permanent pacemaker or ICD implanted in the United States between 1993 and 2008.[1,2] Cardiac device infection is a serious, emerging disease with a 210% increase in incidence between 1993 and 2008.[1,3,4] In-hospital charges for this complication are estimated to be at least US $146 000 per case.[1,5,6] Cardiac device infective endocarditis (CDIE) in particular has a substantially higher mortality rate than cardiac device infection without endocarditis.[7]

The pathogenesis of CDIE usually involves skin contamination at the time of implantation or sometimes later from the generator site.[8,9] The majority of car-

diac device infections affect the subcutaneous generator pocket, with approximately 10% to 23% resulting in CDIE.[7,10] The incidence of CDIE has been reported as between 0.06% and 0.6% per year,[11,12] or 1.14 per 1000 device-years.[12] Risk factors include host factors, such as malnutrition, malignancy, diabetes mellitus, skin disorders, and use of corticosteroids and anticoagulants,[13] as well as procedural factors, such as type of device, prolonged duration, generator replacement, or catheter-related bloodstream or sternal infection.[3,8,11,12] The management of CDIE is complex and usually requires prolonged antibiotic therapy, percutaneous or surgical removal of the device, and possible device reimplantation.[3,8,14,15]

The objectives of this prospective, observational study were to describe the characteristics and outcome of CDIE with attention to health care–associated infection and to determine prognostic factors associated with in-hospital and 1-year mortality, particularly the association between device removal and outcome.

METHODS
International Collaboration on Endocarditis–Prospective Cohort Study

Data from the International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS) were used for this study. The background and inclusion criteria of this prospective, multicenter, international registry of infective endocarditis have been reported.[16-18]

Between June 2000 and September 2006, 3284 patients from 61 centers in 28 countries were enrolled. The ICE-PCS database is maintained at the Duke Clinical Research Institute, which is the data coordinating center for ICE studies. The ICE-PCS protocol was reviewed by institutional review boards and ethics committees at all sites, including Duke University; written informed consent was obtained from patients unless the requirement was waived by the boards and committees.

Patient Selection and Data Collection

Patients were identified prospectively using site-specific procedures to ensure consecutive enrollment.[17,18] Patients were enrolled in ICE-PCS if they met criteria for possible or definite infective endocarditis based on modified Duke criteria.[17,18] Only patients with definite infective endocarditis were included in the current study. To preserve the assumption of independence of observations, only the first episode of infective endocarditis recorded for an individual patient was used in the analysis.

The method of data collection for ICE-PCS has been previously reported.[16] Briefly, a standard case report form was used at all sites to collect data. The case report form included 275 variables and was developed by ICE according to standard definitions.[18] Data were collected during the index hospitalization and then entered at the coordinating center or by site investigators using an Internet-based data entry system. Clinical characteristics including demographics, comorbid conditions, preexisting valvular conditions, details regarding the current episode of infective endocarditis (including source of acquisition, microbiology and echocardiography findings, complications, management, and outcome) were collected. All sites were queried to obtain 1-year outcome data for survival, with use of national death indices, medical records, or patient contact, as available.

Outcome and Definitions

The outcomes of interest in this study were in-hospital and 1-year mortality. Definitions of the variables included in the ICE-PCS case report form have been reported.[16] Definite CDIE was clinically defined as valvular or lead vegetations detected by echocardiography or as meeting the Duke criteria for infective endocarditis.[19] Pathologic diagnostic criteria for definite infective endocarditis included microorganisms detected by culture or histology in a vegetation or by culture of a cardiac device lead.[7]

Health care–associated CDIE was defined as either nosocomial infection or nonnosocomial health care–associated infection.[20,21] Nosocomial infection was defined as infective endocarditis developing in a patient hospitalized for more than 48 hours prior to the onset of signs or symptoms consistent with infective endocarditis. Nonnosocomial, health care–associated infection was defined if signs or symptoms consistent with infective endocarditis developed before hospitalization in patients with extensive out-of-hospital contact with health care interventions, including (1) receipt of intravenous therapy, wound care, or specialized nursing care at home within the 30 days prior to the onset of CDIE; (2) visiting a hospital or hemodialysis clinic or receiving intravenous chemotherapy within the 30 days before the onset of CDIE; (3) hospitalization in an acute care hospital for 2 or more days in the 90 days before the onset of CDIE; or (4) residing in a nursing home or long-term care facility.[20,21] Community-acquired infective endocarditis was defined as signs or symptoms of infective endocarditis developing before hospitalization in a patient without extensive out-of-hospital contact with health care interventions or systems.[21]

Intravascular access devices were defined as an arterial venous fistula or an indwelling vascular catheter; a long-term indwelling central venous catheter was defined as a tunnelled, cuffed catheter or as a subcutaneous port catheter. An intravascular access device was presumed to be a possible source of infective endocarditis if it was present at the onset of symptoms of infective endocarditis. Persistent bacteremia was defined as previously reported.[19] Intracardiac abscess was defined as a thickened area or mass with a heterogeneous echogenic or echolucent appearance by echocardiography or as the presence of pus by direct visualization at the time of surgery.[22]

Statistical Analysis

Data are presented as medians (interquartile ranges) for continuous variables and as frequencies (percent-

ages) for categorical variables. Simple comparisons were made with the Wilcoxon rank-sum test or the χ^2 test as appropriate.

A generalized estimating equation method was used to determine if device removal is associated with in-hospital mortality among patients with CDIE. The method produces consistent parameter estimates while accounting for the correlation in outcomes of patients from the same hospital. The final parameter estimate is converted to an odds ratio (OR) with a corresponding 95% Wald CI. The relative risk (RR) and corresponding 95% CI were also computed. Removal or nonremoval of the cardiac device was analyzed for the end points, because it was hypothesized to be prognostically significant.

A proportional hazards regression model was used to determine if device removal is associated with survival among patients with CDIE. Survival curves were produced by plotting the estimated survival distribution obtained from the proportional hazards regression model, stratified by device removal. Survival times were censored at 1 year or date of last contact. The potential interaction between concomitant valve infection and cardiac device removal during index hospitalization was evaluated by comparing the survival for each pairwise combination of valve infection and cardiac device removal. Pairwise tests were performed, and results were adjusted for multiple comparisons using the Bonferroni method.

All tests were 2-sided, and statistical significance was determined at the .05 level. All statistical analyses were performed using SAS version 9.2.

RESULTS

Cardiac device infective endocarditis was diagnosed in 177 (6.4% [95% CI, 5.5%-7.4%]) of the total cohort of 2760 patients with definite infective endocarditis, including 152 (85.9% [95% CI, 79.9%-90.7%]) with a permanent pacemaker, 21 (11.9% [95% CI, 7.5%-17.6%]) with an ICD, and 4 (2.3% [95% CI, 0.6%-5.7%]) with device type not

specified. The geographic distribution of these cases was North America (n=43 patients), Europe (n=95), South America (n=15), and others, including Australia, Asia, the Middle East, and Africa (n=24).

The clinical characteristics of CDIE are shown in TABLE 1 and FIGURE 1. Patients were predominantly men (74.0% [95% CI, 66.9%-80.3%]), with a median age of 71.2 (interquartile range, 59.8-77.6) years; 27.1% (95% CI, 20.7%-34.3%) had diabetes mellitus. Blood cultures were positive in 149 patients (84.2% [95% CI, 78.0%-89.2%]), and isolates were predominantly staphylococcal (*Staphylococcus aureus*, 35.0% [95% CI, 28.0%-42.5%]; coagulase-negative staphylococci, 31.6% [95% CI, 24.9%-39.0%]). Vegetations were visualized by echocardiography in 159 patients (89.8% [95% CI, 84.4%-93.9%]), of whom 135 (76.3% [95% CI, 69.3%-82.3%]) had vegetation on a cardiac device lead.

Coexisting valve infection was found in 66 patients (37.3% [95% CI, 30.2%-44.9%]), with echocardiographic detection of valvular vegetations in 63. Vegetations involved a native valve in 57 patients (32.2% [95% CI, 25.4%-39.6%]) or a prosthetic valve in 9 (5.1% [95% CI, 2.4%-9.4%]). The distribution of valve involvement included the tricuspid (n=43), mitral (n=17), aortic (n=6), and pulmonic (n=1) valves. Concomitant valve infection with CDIE was associated with in-hospital mortality (OR, 3.31 [95% CI, 1.71-6.39]; *P*=.004; RR, 2.75 [95% CI, 1.30-5.83]).

Device and lead removal was performed during the index hospitalization in 141 of 177 patients (79.7% [95% CI, 73.0%-85.3%]), with a median delay of 12 days (interquartile range, 5-25 days) after admission; data on device removal were not available for 2 patients. Comparisons between patients who did and did not undergo device removal during the index hospitalization are shown in TABLE 2. These patient groups were similar for most characteristics, although patients who

underwent device removal had a lower percentage of positive blood cultures and lower rate of heart failure. Thirty of the 66 patients with concomitant valve infection (45.5% [95% CI, 33.1%-58.2%]) underwent valve surgery during the index hospitalization, representing 17.0% (95% CI, 11.7%-23.3%) of the overall CDIE cohort.

Twenty-six of the patients with CDIE (14.7% [95% CI, 9.8%-20.8%]) died during the index hospitalization, including 18 of 141 (12.8%) who underwent device removal and 8 of 34 (23.5%) who did not. Simple logistic regression analysis demonstrated that removal of the cardiac device was not associated with lower in-hospital mortality (OR, 0.47 [95% CI, 0.19-1.21]; *P*=.12; RR, 0.54 [95% CI, 0.26-1.14]).

Between hospital discharge and 1-year follow-up, 15 patients died and 10 were lost to follow-up. Overall, of the 177 patients with CDIE enrolled, 126 (71.2% [95% CI, 63.9%-77.7%]) were alive at 1 year, 41 (23.2% [95% CI, 17.2%-30.1%]) had died, and 10 (5.6% [95% CI, 2.7%-10.1%]) had been lost to follow-up. At 1 year, 28 of 141 (19.9% [95% CI, 13.6%-27.4%]) patients who underwent device removal during the index hospitalization had died, compared with 13 of 34 (38.2% [95% CI, 22.2%-56.4%]) who did not undergo device removal. FIGURE 2A shows survival as a function of device removal during index hospitalization, censored at 1 year or date of last contact. Device removal during the index hospitalization was associated with improved 1-year survival (hazard ratio, 0.42 [95% CI, 0.22-0.82]; *P*=.01; RR, 0.52 [95% CI, 0.30-0.89]). When survival at 1 year was stratified by presence of concomitant valve infection during initial hospitalization, the presence of concomitant valve infection was found to confer worse survival, regardless of device removal (Figure 2B). There was no evidence of significant interaction between concomitant valve infection and device removal.

Health care–associated infection was identified in 81 (45.8% [95% CI, 38.3%-53.4%]) patients with CDIE, includ-

Table 1. Characteristics of Study Patients and Cardiac Device Infective Endocarditis and Their Association With In-Hospital Mortality

Variable	CDIE Total (n = 177)	In-Hospital Survival (n = 151)	In-Hospital Death (n = 26)	Unadjusted OR (95% CI)	P Value
Age, median (IQR), y (OR per 10-y intervals)	71.2 (59.8-77.6)	72.2 (56.2-77.2)	71.0 (64.0-78.0)	1.47 (1.07-2.02)	.02
Men	131 (74.0)	112 (74.2)	19 (73.1)	1.05 (0.29-3.82)	.94
Fever >38°C	143 (80.7)	120 (7.4)	23 (88.5)	2.44 (0.62-9.58)	.20
Presentation <1 mo of symptoms	119 (67.2)	97 (64.2)	22 (84.6)	2.72 (0.97-7.61)	.06
Health care–associated infection	81 (45.8)	63 (41.7)	18 (69.2)	3.22 (1.52-6.80)	.002
Transferred from another hospital	77 (43.5)	70 (46.4)	7 (26.9)	0.44 (0.17-1.13)	.09
Device type (n = 173)					<.001
Pacemaker	152 (87.9)	130 (86.1)	22 (84.6)	0.72 (0.22-2.34)	.37
ICD	21 (12.1)	17 (11.2)	4 (15.4)	1.39 (0.43-4.52)	.53
Endocarditis type					
CDIE only	110 (62.1)	101 (67)	9 (34.6)	1 [Reference]	
CDIE + valve infection	66 (37.2)	49 (32.5)	17 (65.4)	3.31 (1.71-6.39)	.004
Native valve	57 (32.2)	42 (27.8)	15 (57.7)		
Prosthetic valve	9 (5.1)	7 (4.6)	2 (7.7)		
Geographic region					
North America	43 (24.3)	36 (23.8)	7 (26.9)	1 [Reference]	
Europe	95 (53.7)	82 (54.3)	13 (50.0)	0.72 (0.16-3.22)	.67
South America	15 (8.5)	13 (8.6)	2 (7.7)	0.73 (0.11-4.84)	.75
Other	24 (13.6)	20 (13.2)	4 (15.4)	0.86 (0.21-3.49)	.83
Diabetes mellitus	48 (27.1)	38 (25.1)	10 (38.5)	1.98 (1.11-3.53)	.02
Cancer	19 (10.7)	12 (7.9)	7 (26.9)	4.92 (1.78-13.62)	.002
Hemodialysis	11 (6.2)	6 (4.0)	5 (19.2)	5.25 (1.48-18.54)	.01
Microbiology					
Positive blood cultures	149 (84.2)	126 (83.4)	23 (88.5)	1.74 (0.69-4.38)	.24
Positive lead or vegetation culture	93 (52.5)	79 (52.3)	14 (53.8)	0.62 (0.03-11.83)	.40
Staphylococcus aureus	62 (35.0)	46 (30.5)	16 (61.5)	3.32 (1.95-5.64)	<.001
MRSA	26 (14.7)	18 (11.9)	8 (30.7)	3.54 (1.52-8.28)	.004
Coagulase-negative staphylococci	56 (31.6)	50 (33.1)	6 (23.1)	0.69 (0.33-1.45)	.33
Enterococcus	9 (5.1)	9 (6.0)	0		
Viridans streptococci	5 (2.8)	4 (2.6)	1 (3.8)	1.11 (0.04-27.92)	.95
Gram negative	8 (4.5)	8 (5.3)	0		
Echocardiography					
Vegetation on device lead	135 (76.3)	115 (76.2)	20 (76.9)	1.20 (0.49-2.92)	.69
Intracardiac abscess	4 (2.2)	2 (1.3)	2 (7.7)	5.34 (0.81-35.07)	.08
Any valvular vegetation	63 (36)	47 (31)	16 (62)	3.54 (1.50-8.38)	.05
Tricuspid valve vegetation	43 (24.3)	33 (2.2)	10 (38.4)	2.22 (1.14-4.32)	.02
New moderate or severe tricuspid regurgitation	24 (13.6)	21 (13.9)	3 (11.5)	0.77 (0.23-2.62)	.68
Complications					
Pulmonary embolism	17 (9.6)	14 (9.3)	3 (11.5)	1.03 (0.26-4.19)	.96
Systemic embolism	25 (14.1)	21 (13.9)	4 (15.4)	0.88 (0.36-2.15)	.78
Heart failure	27 (15.3)	19 (12.6)	8 (30.7)	3.11 (1.42-6.83)	.005
Persistent bacteremia	28 (15.8)	18 (11.9)	10 (38.5)	5.00 (2.12-11.77)	<.001
Treatment					
Device removal surgery during index hospitalization	141 (79.7)	123 (81.5)	18 (69.2)	0.48 (0.19-1.21)	.12
Concomitant valve surgery	30 (16.9)	23 (15.3)	7 (26.9)	1.81 (0.72-4.54)	.21

Abbreviations: CDIE, cardiac device infective endocarditis; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio.

ing 61 (34.5% [95% CI, 27.5%-42.0%]) with nosocomial and 20 (11.3% [95% CI, 7.0%-16.9%]) with nonnosocomial infections. Compared with community-acquired infections, health care–associated infections in patients with CDIE presented earlier, occurred more often in patients referred from other facilities, and were associated with intravascular access and hemodialysis (TABLE 3). Health care–associated CDIE also was more often caused by *S aureus* (49.4% [95% CI, 38.1%-60.7%]), particularly methicillin-resistant *S aureus* (MRSA) (25.9% [95% CI, 16.8%-36.9%]), and associated with persistent bacteremia (19.8% [95% CI, 11.7%-30.1%]) and increased in-hospital mortality (22.2% [95% CI, 13.7%-32.8%]).

Compared with staphylococcal endocarditis of native and prosthetic valves in patients without cardiac devices who were also enrolled in ICE-PCS, patients with CDIE were significantly older, more likely to be men, and more likely to have a delayed presentation (eTable, available at http://www.jama.com). Patients with CDIE also were more likely to have health care–associated infections and in particular to have undergone a recent device-related procedure. However, in-hospital mortality was lower in patients with CDIE (18.6% [95% CI, 12.1%-26.9%]), compared with in-hospital mortality of patients without cardiac devices who had native-valve (22.4% [95% CI, 19.4%-25.6%]) or prosthetic-valve (31.3% [95% CI, 25.2%-38.0%]) staphylococcal infective endocarditis (P=.01).

COMMENT

This study describes the clinical characteristics and outcome of CDIE in what is to our knowledge the largest prospective cohort of patients reported to date. Cardiac device infective endocarditis accounted for 6.4% of all cases of definite infective endocarditis. Compared with patients with infective endocarditis but with no cardiac devices in place, patients with CDIE were more likely to be male, older, and diabetic,

as shown in recent discharge data from the National Inpatient Sample.[1] The advanced age of patients with CDIE reflects the population likely to have indications for cardiac devices but also potential host factors, including exposure to other medical care, as predispositions to device-related infection. Along these lines, the etiology of CDIE was characterized by a predominance of staphylococci (coagulase-negative staphylococci and *S aureus*) as recently described by other investigators,[7,11,15,23,24] and health care–associated infection was identified in nearly half of patients with CDIE. The high percentage of patients with health care–associated CDIE reiterates the significant recent epidemiologic trend and prognostic influence on survival previously described in both native- and prosthetic-valve infective endocarditis.[16,25,26]

In addition to these host-related characteristics of CDIE, this study illustrates the high prevalence of associated acute and longer-term complications of this condition, including concomitant valve involvement (37.2%), heart failure (15.3%), and persistent bacteremia (15.8%) during the index hospitalization. Several of these complications were found to be associated with in-hospital and 1-year mortality in patients with CDIE. The high rates of mortality emphasize the need for improved preventive measures, including optimal skin decontamination and appropriate antibiotic administration at the time of cardiac device insertion or manipulation,[27] as well as careful attention to any invasive or intravascular procedures performed after device implantation.

A recent retrospective study evaluated risk factors for 6-month mortality in patients with cardiac device infection, including systemic infection in 113 patients.[28] Of note, only 51% of patients had positive blood cultures, and 23% had lead vegetation visualized (compared with 84% and 76%, respectively, in the present study). In the overall cohort of that study, mortality was associated with moderate or severe tricuspid regurgitation, abnormal right ventricular function, systemic emboli-

zation, and abnormal renal function.[28] Administrative data from the National Inpatient Sample also demonstrated associations between comorbid conditions (such as respiratory or renal conditions or heart failure) and in-hospital mortality of cardiac device infection.[1] Our study confirms the prognostic influence of concomitant cardiac conditions, specifically valve infection and heart failure, on mortality.

Current American Heart Association recommendations on infections of cardiovascular implantable electronic devices strongly support complete device and lead removal for all patients with definite infection as evidenced by valvular vegetations, lead vegetations, or both.[29] In a retrospective, single-

center study of 60 patients with CDIE, 95% underwent device removal, and the overall mortality rate was only 10% at 3 years.[30] However, only 4 patients (7%) had concomitant valve infection.[30]

In the present study of CDIE, device removal was performed in a similarly high percentage of cases, despite the older age of patients and the higher prevalence of comorbid conditions such as diabetes mellitus compared with other forms of staphylococcal infective endocarditis. Device removal was not associated with improved in-hospital survival but was associated with significantly higher 1-year survival. The lack of benefit for in-hospital mortality may be related to the total number of deaths in this study and

**Figure 1.** Distribution of Patients in Study by Clinical Characteristics and Device Removal Status
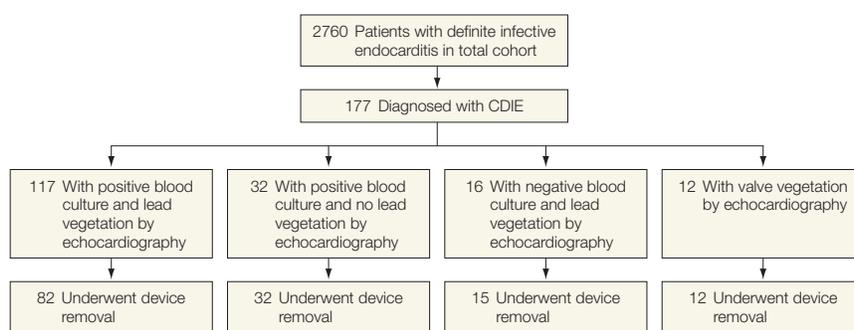
Device removal was performed during the index hospitalization.

Table 2. Characteristics of Patients With Cardiac Device Infective Endocarditis and With or Without Cardiac Device Removal During Hospitalization

Variable	Device Removal (n = 141)	No Device Removal (n = 34)	P Value
Age, median (IQR), y	70.1 (59.8-76.3)	70.4 (68.1-78.6)	.13
Diabetes mellitus	39 (27.7)	8 (23.5)	.76
Hemodialysis	9 (6.4)	2 (5.9)	.93
History of cancer	13 (9.2)	6 (17.7)	.14
Transferred from another hospital	61 (43.3)	16 (47.1)	.61
Positive blood cultures	114 (80.9)	34 (100)	.006
Staphylococcus aureus	47 (33.3)	15 (44.1)	.24
Coagulase-negative staphylococci	46 (32.6)	10 (29.4)	.72
Health care–associated infection	62 (44.0)	19 (55.9)	.21
Concomitant valve vegetation	54 (38.3)	9 (26.5)	.20
Heart failure	18 (12.8)	9 (26.5)	.03
Pulmonary embolism	14 (9.9)	2 (5.9)	.46
In-hospital mortality	18 (12.8)	8 (23.5)	.12
1-y mortality	28 (19.9)	13 (38.2)	.02

Abbreviation: IQR, interquartile range.

Figure 2. Outcome of Patients With Cardiac Device Infective Endocarditis (CDIE)
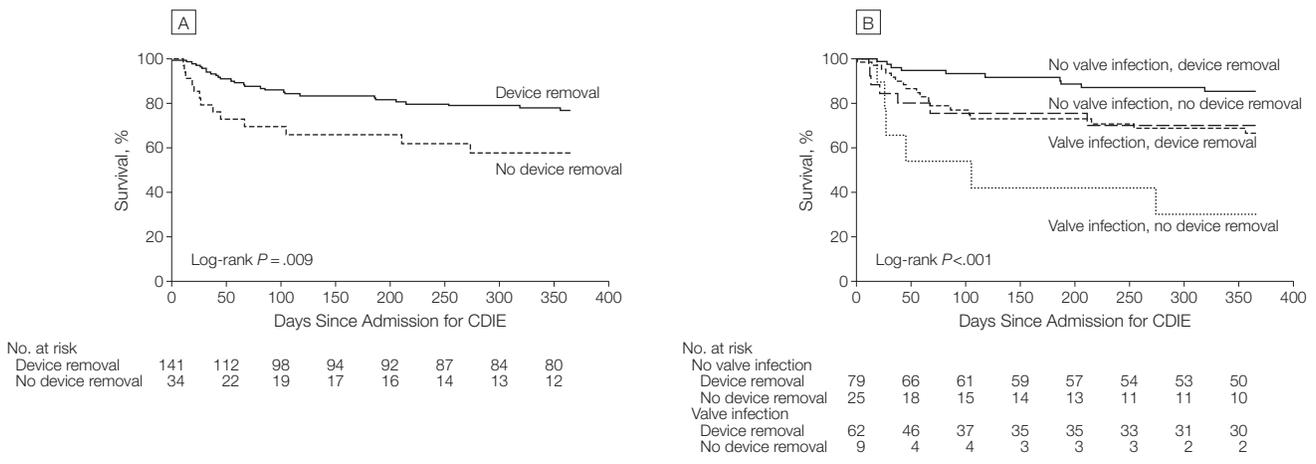
A, One-year survival related to device removal vs no removal during index hospitalization, with survival censored at 1 year or date of last contact. Data on device removal were not available for 2 patients. B, One-year survival stratified by presence of concomitant valve infection and device removal during index hospitalization, with survival censored at 1 year or date of last contact. Data on device removal were not available for 2 patients.

Table 3. Comparison of Patients With Health Care–Associated and Community-Acquired Cardiac Device Infective Endocarditis (CDIE)

Variable	Health Care–Associated CDIE (n = 81)	Community-Acquired CDIE (n = 96)	P Value
Age, median (IQR), y	68.2 (64.0-77.2)	72.2 (56.2-77.2)	.46
Men	61 (75.3)	70 (72.9)	.72
Presentation <1 mo of symptoms	65 (80.2)	55 (57.3)	.002
Transferred from another facility	45 (55.6)	32 (33.3)	.004
Diabetes mellitus	24 (29.6)	24 (25.0)	.43
Cancer	11 (13.5)	8 (8.3)	.25
Hemodialysis	8 (9.9)	3 (3.1)	.06
Staphylococcus aureus	40 (49.4)	22 (22.9)	<.001
MRSA[a]	21 (52.5)	5 (22.7)	.02
Coagulase-negative staphylococci	23 (28.4)	33 (34.4)	.39
Device removal surgery	62 (76.5)	79 (82.3)	.21
In-hospital mortality	18 (22.2)	8 (8.3)	.009
1-y mortality	30 (37.0)	19 (19.8)	<.001

Abbreviations: IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a] Denominators used to calculate percentages are 40 for health care–associated endocarditis and 22 for community-acquired endocarditis.

to insufficient statistical power to detect a significant difference. This delayed benefit of device removal also may be related to the operative risk of device removal in this older patient population. In addition, appropriate antibiotic therapy may mitigate short-term complications of CDIE but not prevent long-term complications or be curative of infection.

The presence of concomitant valve infection was associated with increased mortality at 1 year, regardless

of device removal. This finding suggests an important additional risk associated with CDIE and an influence on its outcome. Furthermore, only approximately half of patients with CDIE and concomitant valve infection underwent valve surgery, reflecting the anticipated operative risk in this older patient population with preexisting cardiac disease and potentially increasing the mortality rate associated with this complication. For patients with CDIE with or without concomitant

valve infection, a multidisciplinary approach to management involving specialists in cardiology, infectious disease, and cardiac surgery may optimize the use of surgical therapy and improve long-term outcome.

Health care–associated infection has been associated with poorer prognosis in both native- and prosthetic-valve infective endocarditis.[16,25] The results of the present study also confirmed an adverse effect of health care–associated infection in CDIE that was independent of S aureus infection. Interestingly, the percentage of infections attributable to coagulase-negative staphylococci was similar between health care–associated and community-acquired cases. The current definition of health care–associated infection has not been applied to cardiac device infections and may lack sensitivity, thus underestimating the prevalence of infections (such as those attributable to coagulase-negative staphylococci) associated with delayed presentations after remote implantation or other medical interventions. Although the ICE-PCS registry did not collect data regarding the time interval between cardiac device implantation and infection, recent (within 90 days) implantation would be included in the current, validated definition of

health care–associated infection, because the Prospective Evaluation of Pacemaker Lead Endocarditis study previously found that cardiac device infections are typically diagnosed within 2 months of device implantation.[10]

Compared with other forms of staphylococcal infective endocarditis, including prosthetic-valve endocarditis, patients with CDIE, as well as the subset with health care–associated CDIE, had a higher prevalence of MRSA infection. Because many experts continue to recommend a first-generation cephalosporin for prophylaxis at the time of device implantation, additional studies are needed to define the role for glycopeptides or other antistaphylococcal antibiotics to reduce the incidence of CDIE, particularly in geographic regions with higher rates of MRSA infection.

Although ICE-PCS was designed as a large, multinational, prospective registry of definite infective endocarditis, this study has certain limitations. This is an observational study involving centers with voluntary participation; thus, population sampling was not obtained, limiting any epidemiologic inferences. Specifically, because this cohort only included patients with CDIE, risk factors for developing CDIE could not be evaluated. Data on presence of device-pocket infection were not collected, so the relationship between pocket infection and CDIE could not be evaluated. The Mayo Clinic Cardiovascular Infections Study Group has reported that pocket-site infection was negatively associated with CDIE.[24] The effect of device removal on outcome may be confounded by selection and survival biases, as well as by the effect of other interventions such as valve surgery. Although device removal was documented, data regarding duration since device implantation, the means of removal (such as percutaneous or surgical), the incidence and timing of device reimplantation, and recurrence of infection after discharge were not collected. Patient enrollment in this registry was completed in 2006, and our cohort included a smaller percentage of

patients with ICDs than recently reported.[31] Patients with ICDs have an adverse cardiac risk profile that may affect outcome, yet the results of the present study are comparable with those of other CDIE cohorts with higher percentages of these devices.[31]

In conclusion, CDIE, similar to native- and prosthetic-valve endocarditis, is significantly influenced by health care interventions in its development, microbiology, and outcome. It is associated with a high rate of complications, especially concomitant valve infection, and results in high in-hospital and 1-year mortality rates, particularly if there is valve involvement. Device removal is associated with higher survival at 1 year. Given that numbers of cardiovascular implantable electronic devices placed are increasing rapidly, further studies on the prevention and treatment of this serious complication are needed.

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