Contemporary Epidemiology and Prognosis of Health Care–Associated Infective Endocarditis

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Background. The aim of this study was to describe the characteristics of health care–associated infective endocarditis (HAIE) and to establish the risk factors for mortality.

Methods. We conducted a prospective, observational cohort study. HAIE was defined according to the following conditions: (1) symptom onset >48 h after hospitalization or within 6 months after hospital discharge; or (2) ambulatory manipulations causing endocarditis.

Results. Eighty-three episodes of HAIE (accounting for 28.4% of all cases of endocarditis) were diagnosed. Compared with patients with community-acquired endocarditis, patients with HAIE were older (median age ± standard deviation, 65.3 ± 16.4 years vs. 57.8 ± 17.0 years; $P = .001$), were in poorer health before disease onset (Charlson index, 2.5 ± 2.3 vs. 1.7 ± 2.1; $P = .006$), had more staphylococcal (55.4% vs. 28.3% of cases) and enterococcal infections (22.9% vs. 7.7% of cases; $P < .005$), underwent fewer surgeries (22.9% vs. 45.9% of cases; $P < .005$), and experienced a higher rate of in-hospital (45.8% vs. 22.0%) and 1-year mortality (59.5% vs. 29.6%; $P < .005$). In the HAIE cohort, independent predictors of in-hospital death were stroke (odds ratio [OR], 8.95; 95% confidence interval [CI], 2.04–39.31; $P = .004$), congestive heart failure (OR, 5.48; 95% CI, 1.77–17.03; $P = .003$), surgery indicated but not performed (OR, 3.74; 95% CI, 1.22–11.45; $P = .021$), and enterococcal infection (OR, 0.18; 95% CI, 0.04–0.78; $P = .022$). Independent predictors of 1-year mortality were surgery indicated but not performed (OR, 7.81; 95% CI, 2.06–29.67; $P = .003$), acute renal failure (OR, 7.18; 95% CI, 1.32–39.18; $P = .023$), and enterococcal infection (OR, 0.18; 95% CI, 0.04–0.81; $P = .026$). For the series overall (292 episodes), HAIE was an independent predictor of in-hospital (OR, 2.83; 95% CI, 1.34–5.98; $P = .007$) and 1-year mortality (OR, 2.59; 95% CI, 1.25–5.39; $P = .011$).

Conclusions. HAIE is an important health problem associated with considerable mortality. New strategies to prevent HAIE should be assessed.

Despite improvements in the diagnosis and surgical treatment of infective endocarditis (IE), this disease continues to be associated with high rates of morbidity and mortality [1–3]. This is a consequence of changes in the epidemiology of IE that have been observed during the past few years [4]. The classic concept of viridans group streptococcal IE involving a rheumatic valve resulting from a dental infection or manipulation has now almost disappeared in developed countries [5, 6]. At the same time, the increasing number of patients with a prosthetic valve or long-term central venous catheter, both of which are well-recognized risk factors for the development of IE, has led to an increasing rate of health care–associated IE (HAIE) [4]. In this scenario, most of the microorganisms isolated are *Staphylococcus* species [7].

The few existing studies that describe the characteristics of nosocomial IE have reported rates of 7.7%–21.5% of all IE cases [8–10]. However, these studies underestimate the true magnitude of the problem. Patients who are highly dependent on the health care system, such as those who are receiving ambulatory hemodialysis treatment, and who acquire IE secondary to catheter-related bacteremia are often erroneously classified as having community-acquired IE (CAIE), rather than nosohusial IE (i.e., HAIE).

The aims of this study were as follows: (1) to describe

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the epidemiology, clinical characteristics, and prognosis of HAIE; (2) to compare the characteristics of HAIE with those CAIE; and (3) to establish the independent risk factors for HAIE-related in-hospital and 1-year mortality.

PATIENTS AND METHODS

Patients and settings. This prospective, observational cohort study was performed at Vall d'Hebron Hospital, which is a 1000-bed teaching hospital in Barcelona, Spain, that includes all major medical and surgical departments and a referral center for cardiac surgery. All consecutive adult patients (≥18 years of age) with a diagnosis of definite or possible IE [11] who were treated at our center from January 2000 through December 2007 were enrolled in the study. Patients were identified from our Infectious Diseases Department database, the Microbiology Department blood culture registry, and the echocardiography laboratory. All interventions were performed by the same medical staff team during the entire study period.

Patients who were referred for surgery from another center at completion of antimicrobial treatment, patients with noninvasive endocarditis, and patients with pacemaker infection and no evidence of endocardial involvement were excluded from the study.

Data collection. Demographic, clinical, diagnostic, treatment, and follow-up data were obtained by detailed chart abstraction with use of standardized reporting forms and were entered into a Microsoft Access 2000 database created specifically for the purpose of this study.

Definitions. IE was defined as HAIE according to the following criteria: (1) onset of symptoms >48 h after hospitalization with no evidence of IE at the time of hospital admission or within 6 months after hospital discharge [9] (designated nosocomial IE) or (2) diagnostic or therapeutic manipulations in the ambulatory setting within 6 months before symptom onset (designated nosohusial IE), including long-term central venous catheter use; autologous or prosthetic arteriovenous fistula for hemodialysis; invasive intravascular techniques (cardiac catheterization, pacemaker insertion, and other intravascular devices); urologic, gynecologic, or digestive procedures; and acupuncture.

Catheter-related bacteremia is defined elsewhere [12]. Long-term central venous catheter–related bacteremia was diagnosed by means of simultaneous quantitative blood cultures.

The Charlson index [13] at hospital admission was used to stratify patients with respect to overall comorbidity. The presence of diabetes mellitus, hemodialysis, neoplasm, or any heart disease at hospital admission was recorded.

The EuroSCORE [14] was calculated for all patients with an indication for surgery. Cardiac surgery was indicated according to the American Heart Association guidelines [15]. For patients with an indication for surgery but for whom surgery was not performed, the main reason for this decision was recorded. Only cardiac surgery performed during hospitalization was taken into consideration.

IE complications were defined as the development of any of the following conditions: (1) persistent fever (present 7 days after the start of treatment), (2) congestive heart failure (new condition or worsening of a known previous condition), (3) intracardiac abscess (diagnosed by echocardiography or during surgery), (4) new conduction abnormality, (5) stroke, (6) systemic embolism other than stroke, and (7) acute renal failure (defined as a 50% increase in the baseline creatinine concentration).

In-hospital mortality was defined as death from any cause during hospitalization. Related mortality was defined as death secondary to sepsis or complications of IE, as described above. The 1-year cumulative mortality was defined as death from any cause within 1 year after hospital discharge.

Patients were evaluated in the outpatient clinic on days 30, 90, and 365 after hospital discharge. Blood samples were obtained for culture 2 days after completion of antimicrobial treatment and 30 and 90 days after hospital discharge. Echocardiographic examination was performed at the end of treatment and at least once again during the first year of follow-up.

Statistical analysis. Quantitative variables are reported as means and standard deviations, median values and ranges, or median values and interquartile ranges. The χ^2 test (or Fisher's exact test, when appropriate) was used to compare the distribution of categorical variables, and the Student's *t* test was used for continuous variables. Differences were considered to be statistically significant at a *P* value of <.05. For the multivariate analysis, the effects on in-hospital and 1-year mortality of variables that were determined to be clinically and statistically significant in the univariate analysis ($P < .1$) were analyzed by logistic regression. Only patients with at least 1 year of follow-up were included in the 1-year mortality analysis. Statistical analyses were performed with Microsoft SPSS-PC+, version 12.0 (SPSS).

RESULTS

Two hundred ninety-two episodes of IE in 289 patients were treated at our hospital during the study period. Eighty-three cases in 83 patients (28.4% of all cases of IE) were classified as HAIE. Sixty-seven cases (80.7%) were nosocomial infections, and 16 cases (19.3%) were nosohusial infections. Seventy-one patients (85.5%) were classified as presenting with definite IE according to the modified Duke criteria [11].

Source of infection. It was possible to establish the source of infection (other than hospital admission within the previous 6 months) in 63 (75.9%) of the 83 cases of HAIE. The most important sources of infection were catheter-related bacteremia (33 cases; 39.8%), cardiac surgery (10 cases; 12.0%), and ar-

teriovenous fistula for hemodialysis (8 cases; 9.6%) (table 1). In detail, patients who underwent urologic and colonoscopic manipulations (most of whom had enterococcal IE) developed bacteremia <12 h after the procedure. For patients with cardiac catheterization and pacemaker implantation (most of whom had IE due to coagulase-negative staphylococci), the onset of symptoms was <1 month after the procedure (which was always described as difficult). In the case that was associated with acupuncture, the patient developed local signs of infection on the skin 3 weeks before the onset of other symptoms. Finally, 1 patient presented with early infection of the ostium of the gastrostomy tube and cultures that were persistently positive for *Candida albicans;* this patient developed IE due to the same microorganism 2 weeks later.

In table 2, the characteristics of patients with HAIE who had a known source of infection are compared with those of patients for whom a hospital admission within the previous 6 months was the only risk factor for IE. Detailed data on cases of nosohusial HAIE are shown in table 3.

Predisposing cardiac factors. Forty (48.2%) of the patients with HAIE had a cardiac factor that predisposed them for IE. Of these 40 patients, 24 (28.9% of all patients with HAIE) had a prosthetic valve; 2 of these 24 patients had IE episodes that involved both native and prosthetic valves. Sixteen (19.3%) of 83 patients had a predisposing factor other than a prosthetic valve, including 14 patients with valvular disease and 2 patients with congenital heart disease.

Etiology. *Staphylococcus aureus* was the most frequently isolated microorganism (28 cases; 33.7%), followed by *Enterococcus* species (19 cases; 22.9%) and coagulase-negative staphylococci (18 cases; 21.7%) (table 4).

Cardiac involvement. The mitral valve alone was affected in 36 (43.4%) of 83 cases, the aortic valve alone was affected in 26 (31.3%), 2 valves were affected in 10 (12.0%), an unknown number of valves were affected in 5 (6.0%), the tricuspid valve alone was affected in 3 (3.6%), a pacemaker lead and the endocardial wall in 2 (2.4%), and the pulmonary valve and pacemaker lead in 1 (1.2%).

Surgery. Nineteen (22.9%) of 83 patients underwent surgery during the active phase of infection. However, 29 patients with an indication for surgery did not undergo valve replacement. Four of these patients died before surgery could be performed, and in the 25 remaining patients, surgery was rejected because of the high associated risk. The median EuroSCORE for these high-risk patients was 13 points (interquartile range, 9.5–15.5; range, 5–21). Overall, 20 of 29 patients died during hospitalization (69.0%); the 1-year cumulative mortality was 85.2%.

Outcome. Seventy-one patients (85.5%) experienced at least 1 complication during hospitalization. Of these patients, 39 (47.0% of all patients with HAIE) experienced congestive heart failure, 23 (27.7%) experienced systemic embolism other than stroke, 19 (22.9%) experienced acute renal failure, 16 (19.3%) experienced stroke, 13 (15.7%) experienced persistent fever, 9 (10.8%) experienced a new conduction abnormality episode, and 8 (9.6%) experienced intracardiac abscess. Thirty-nine patients (47.0%) experienced >1 complication.

Thirty-eight patients (45.8%) died during hospitalization. Of

Table 1. Source of infection in 83 cases of health care–associated infective endocarditis.

Variable	No. (%) of cases (n = 83)
Hospital admission within the previous 6 months	20 (24.1)
Venous catheter[a]	33 (39.8)
Cardiac surgery (valve replacement within the previous 2 months)	10 (12.0)
Arteriovenous fistula for hemodialysis	8 (9.6)
Urologic manipulation[b]	5 (6.0)
Colonoscopy	2 (2.4)
Cardiac catheterization	2 (2.4)
Pacemaker implantation	1 (1.2)
Acupuncture	1 (1.2)
Gastrostomy	1 (1.2)

[a] Includes 13 cases of peripheral venous catheter–related bacteremia (9 due to *Staphylococcus aureus,* 2 due to *Enterococcus faecalis,* 1 due to *Enterobacter cloacae,* and 1 due to *Candida glabrata*); 8 cases of short-term central venous catheter–related bacteremia (4 due to *E. faecalis,* 2 due to *Staphylococcus epidermidis,* 1 due to *S. aureus,* and 1 due to *Pseudomonas aeruginosa*); and 12 cases of long-term central venous catheter–related bacteremia (5 due to *S. aureus,* 3 due to *E. faecalis,* 2 due to *Staphylococcus hominis,* 1 due to *S. epidermidis,* and 1 due to *Enterobacter aerogenes*).

[b] Includes 4 cases with urinary catheterization and 1 case with cystoscopic examination following urinary tract infection.

Table 2. Comparison between 63 patients with health care–associated infective endocarditis (HAIE) with a known source of infection and 20 patients with HAIE whose only risk factor for infective endocarditis was hospital admission within the previous 6 months.

Variable	Hospital admission within previous 6 months (n = 20)	Known source of infection (n = 63)	OR (95% CI)	P
Age, years	66.5 ± 17.6	65.0 ± 16.2	1.02 (0.99–1.05)	.260
Female sex	10 (50.0)	34 (54.0)	0.85 (0.31–2.33)	.757
Charlson index, mean value ± SD	2.2 ± 2.2	2.6 ± 2.2	1.24 (0.99–1.55)	.057
Diabetes mellitus	3 (15.0)	16 (25.4)	0.52 (0.13–2.00)	.341
Hemodialysis	…	16 (25.4)	NA	<.005
Neoplasm	3 (15.0)	11 (17.5)	0.83 (0.21–3.35)	.798
Prosthetic valve involvement	5 (25.0)	19 (30.2)	1.30 (0.41–4.08)	0.658
Aortic valve involvement only	3 (15.0)	22 (34.9)	0.33 (0.09–1.25)	.102
Mitral valve involvement only	11 (55.0)	25 (39.7)	1.86 (0.67–5.13)	.232
Staphylococcus aureus infection	4 (20.0)	24 (38.1)	0.41 (0.12–1.36)	.144
Coagulase-negative staphylococcal infection	7 (35.0)	11 (17.5)	2.55 (0.83–7.85)	.104
Enterococcal infection	3 (15.0)	16 (25.4)	0.52 (0.13–2.00)	.341
Other etiology	6 (30.0)	13 (20.6)	1.05 (1.00–1.10)	.031
Moderate-to-severe aortic regurgitation	7 (35.0)	20 (31.7)	1.16 (0.40–3.35)	.787
Moderate-to-severe mitral regurgitation	11 (55.0)	26 (41.3)	1.74 (0.63–4.79)	.285
Vegetation diameter, mean mm ± SD	16.9 ± 11.8	12.0 ± 5.9	1.08 (1.00–1.16)	.066
Paravalvular complication	8 (40.0)	20 (31.7)	1.43 (0.51–4.06)	.498
Left ventricular ejection fraction, mean value ± SD	59.2 ± 8.6	60.9 ± 10.6	0.98 (0.92–1.05)	.601
Pulmonary arterial blood pressure, mean mm Hg ± SD	60.8 ± 18.6	47.6 ± 14.43	1.05 (1.00–1.10)	.031
Indication for surgery	9 (45.0)	20 (31.7)	2.73 (0.88–8.41)	.081
EuroSCORE[a], mean value ± SD	12.0 ± 3.0	11.3 ± 3.9	1.17 (0.96–1.44)	.127
Surgery performed	6 (30.0)	13 (20.6)	1.65 (0.53–5.13)	.388
Any complication	17 (85.0)	54 (85.7)	0.94 (0.23–3.89)	.937
Persistent fever	3 (15.0)	10 (15.9)	0.94 (0.23–3.80)	.925
Congestive heart failure	13 (65.0)	26 (41.3)	2.64 (0.93–7.53)	.069
Intracardiac abscess	2 (10.0)	6 (9.5)	1.06 (0.20–5.70)	.950
Conduction abnormality	3 (15.0)	6 (9.5)	1.68 (0.38–7.42)	.496
Stroke	4 (20.0)	12 (19.0)	1.03 (0.30–3.76)	.925
Sistemic embolism other than stroke	3 (15.0)	20 (31.7)	0.38 (0.10–1.45)	.155
Acute renal failure	4 (20.0)	15 (23.8)	0.80 (0.23–2.76)	.724
In-hospital mortality	10 (50.0)	28 (44.4)	1.25 (0.46–3.42)	.664
One-year mortality	12 (63.2)	32 (58.2)	1.23 (0.42–3.61)	.704

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Includes only patients with an indication for surgery.

these, 32 (84.2%) experienced HAIE-related in-hospital deaths, including 15 deaths from congestive heart failure, 7 from stroke, 4 from septic shock (all in patients with episodes of HAIE due to *S. aureus*), 2 immediately after surgery, 1 from multiorgan failure, 1 during valve replacement surgery, 1 from pulmonary thromboembolism, and 1 sudden death (table 5). The 1-year mortality among patients with 1 year of follow-up was 59.5% (44 patients died). In addition, there were 6 in-hospital deaths that were not related to HAIE.

Patients who died during hospitalization included 16 (57.1%) of 28 patients with HAIE due to *S. aureus* (7 [87.5%] of 8 patients with infection due to methicillin-resistant *S. aureus* and 9 [45%] of 20 patients with infection due to methicillin-susceptible *S. aureus*), 5 (55.6%) of 9 patients with HAIE due to *Streptococcus viridans*, 8 (44.4%) of 18 patients with HAIE due to coagulase-negative staphylococci, and 5 (26.3%) of 19 with HAIE due to *Enterococcus* species.

Comparison between HAIE and CAIE. In table 6, the characteristics of patients with HAIE are compared with the characteristics of patients with IE that was not health care related. Most cases of HAIE involved mitral valves and occurred among elderly individuals in poor general condition; men and women were equally affected. Compared with patients who had CAIE, patients with HAIE were transferred less often from another facility; had more infections that were due to *S. aureus, Enterococcus* species, and coagulase-negative staphylococci; under-

Table 3. Characteristics of 16 patients with cases of nosohusial infective endocarditis.

Patient	Sex	Age, years	Charlson index	Etiology	Valve affected	Predisposing cardiac factor	Source of infection	Surgery	Outcome[a]
1	Male	52	4	*Staphylococcus epidermidis*	Mitral	None	AVF	Yes	Death
2	Male	77	2	*Staphylococus sanguis* II	Mitral	Severe mitral regurgitation	Cardiac catheterization	No[b]	Death
3	Male	52	9	MSSA	Mitral	None	AVF	No	Survival
4	Male	52	2	MSSA	Mitral	None	AVF	No	Survival
5	Female	66	2	MRSA	Mitral	None	PVC; MRSA bacteremia	No	Survival
6	Female	66	4	*Enterococcus faecalis*	Mitral	None	PVC; *E. faecalis* bacteremia	No	Survival
7	Female	87	2	*S. epidermidis*	Tricuspid	Aortic stenosis and regurgitation	PVC; *S. epidermidis* bacteremia	No	Death
8	Male	73	0	*E. faecalis*	Aortic	None	PUC; *E. faecalis* UI	Yes	Survival
9	Male	45	7	MSSA	Unknown	None	PVC; MSSA bacteremia	No	Survival
10	Female	77	5	*E. faecalis*	Aortic	None	PVC; *E. faecalis* bacteremia	No	Survival
11	Male	75	2	*S. epidermidis*	Aortic	None	AVF	Yes	Survival
12	Male	83	7	*S. epidermidis*	Aortic	None	AVF	No[b]	Death
13	Female	86	4	MSSA	Mitral	None	PVC; MSSA bacteremia	No	Survival
14	Female	81	5	*Staphylococcus hominis*	Unknown	None	PVC; *S. hominis* bacteremia	No	Death
15	Female	24	0	*Staphylococcus lugdunensis* and *S. epidermidis*	Aortic and ISD	Aortic regurgitation and ISD	Acupuncture	Yes	Survival
16	Male	75	5	MRSA	Aortic	None	AVF	No	Death

NOTE. AVF, arteriovenous fistula for hemodialysis; ISD, interventricular septal defect; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus;* PUC, permanent urinary catheter; PVC, permanent vascular catheter; UI, urinary tract infection.

[a] In-hospital outcome.

[b] Surgery indicated but not performed because of high risk.

Table 4. Microorganisms causing health care–associated infective endocarditis.

Variable	No. (%) of cases (n = 83)
Staphylococcus aureus	
Overall	28 (33.7)
MSSA	20
MRSA	8
Enterococcus species	
Overall	19 (22.9)
Enterococcus facealis	17
Enterococcus faecium	1
Enterococcus durans	1
CoNS	
Overall	18 (21.7)
Staphylococcus epidermidis	14
Staphylococcus hominis	2
Staphylococcus lugdunensis and *S. epidermidis*	1
Unidentified CoNS	1
Viridans group streptococci	
Overall	9 (10.8)
Streptococcus mitis	2
Unidentified viridans group streptococci	2
Streptococcus anginosus	2
Streptococcus gordonii	1
Streptococcus sanguis II	1
Streptococcus mutans	1
Other	
Overall	7 (8.4)
Pseudomonas aeruginosa	1
Enterobacter cloacae	1
Enterobacter aerogenes	1
Unidentified gram-positive microorganism	1
Candida albicans	1
Candida tropicalis	1
Candida glabrata	1
Negative blood culture result	2 (2.4)

NOTE. CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

went surgery during hospitalization less often (although with a higher median presurgery risk, as determined by EuroSCORE); and had higher in-hospital and 1-year mortality.

Predictors of outcome. In the univariate analysis, the factors associated with in-hospital death in patients with HAIE were diabetes mellitus, enterococcal infection, vegetation diameter, pulmonary arterial blood pressure, indication for surgery, surgery indicated but not performed (SINP), development of any complication, congestive heart failure, stroke, acute renal failure, and duration of intensive care unit stay (table 7). For the multivariate logistic regression analysis, we included only stroke, congestive heart failure, SINP, and enterococcal infection, which were the most clinically significant variables in the analysis. These variables remained independently associated with in-hospital mortality.

Similarly, factors associated with death at 1 year in patients with HAIE were Charlson index, enterococcal infection, moderate-to-severe aortic regurgitation, elevated pulmonary arterial blood pressure, indication for surgery, SINP, development of any complication, congestive heart failure, stroke, and acute renal failure (table 8). Enterococcal infection, SINP, congestive heart failure, stroke, and acute renal failure were included in the multivariate logistic regression analysis, in which SINP, acute renal failure, and enterococal infection remained independently associated with 1-year mortality. Finally, when the whole series was examined with use of multivariate analysis, HAIE was an independent risk factor for both in-hospital (OR, 2.83; 95% CI, 1.34–5.98; $P = .007$) and 1-year mortality (OR, 2.59; 95% CI, 1.25–5.39; $P = .011$).

DISCUSSION

Previous studies have reported that nosocomial IE accounts for up to 21.5% of all IE cases [8–10]. However, these studies have some limitations, including the use of retrospective, rather than contemporary, series [8,9] and the failure to include nosohusial episodes [8–10]. Our study describes the epidemiology and prognosis of HAIE (including cases of nosohusial IE) in a contemporary, prospective cohort of patients. With use of this broader definition, we found that HAIE represented almost 30% of all episodes of IE, reflecting current changes in the epidemiology of this disease in developed countries. The fact that this study was conducted in a single hospital by the same team of medical personnel throughout the study period conferred homogeneity on the medical decisions and interventions and, therefore, conferred homgeneity on the results.

Advances in diagnostic and therapeutic techniques have improved the quality of life of many patients, particularly by avoiding hospitalization for certain procedures. However, patients who are not hospitalized are exposed to the same risk of bacteremia as patients who are hospitalized, as was well demonstrated in most of the nosohusial episodes in our series. We did not classify cases of IE that occurred after oral manipulations as cases of nosohusial infection, because although we treated 5 episodes of IE that began within 2 weeks after dental extraction, it is difficult to know whether these cases were, in fact, attributable to the dental extraction or were secondary to routine daily activities. Moreover, the characteristics of this small subgroup of patients were similar to the characteristics of those in the CAIE group, with whom they were classified.

On the basis of incidence and etiology data from patients with IE that manifested during the 6-month period after hospital discharge, Ben-Ami et al. [9] suggested that the definition of HAIE should be broadened to include these episodes. Pre-

Table 5. Characteristics of 32 patients with health care–associated infective endocarditis (HAIE) who died during hospitalization.

Patient	Sex	Age, years	Charlson index	Etiology	Source of infection	Valve affected	Surgery	Cause of death	Time from initiation of treatment to death, days
1	Male	79	8	MRSA	Previous hospitalization	Aortic (P) and mitral (N)	No[a]	CHF (present at diagnosis)	1
2	Male	66	NA	*Enterococcus faecalis*	PVC-related sepsis	Mitral (P)	No	CHF (present at diagnosis)	50
3	Female	78	5	*Streptococcus viridans*	Previous hospitalization	Aortic (P)	No[a]	CHF (started 18 days after initiation of therapy)	25
4	Male	45	1	*E. faecalis*	PVC-related sepsis	Aortic (N) and mitral (N)	Yes	CHF (present at diagnosis)	20
5	Female	84	2	MSSA	Peripheral catheter–related sepsis	Aortic (N) and mitral (N)	No[a]	CHF (started 12 days after initiation of therapy)	23
6	Male	70	2	MSSA	Peripheral catheter–related sepsis	Mitral (N)	Yes	CHF (present at diagnosis)	11
7	Female	87	2	*Staphylococcus epidermidis*	PVC-related sepsis	Tricuspid (N)	No	CHF (hyperhydration; started 3 days after initiation of therapy)	42
8	Male	52	4	*S. epidermidis*	AVF	Mitral (N)	Yes	CHF (present at diagnosis)	10
9	Male	76	2	*Staphylococus sanguis* II	Cardiac catheterization	Mitral (N)	No[a]	Cerebral hemorrhage (mycotic aneurysm)	9
10	Female	46	0	MRSA	Early prosthetic; surgery	Mitral (P) and tricuspid (N)	Yes	Cerebellum hemorrhage	8
11	Female	65	7	MSSA	PVC-related sepsis	Mitral (N)	No[a]	Ischemic stroke (Glasgow 7)	15
12	Male	65	2	MSSA	Cardiac catheterization	Unknown (N)	No	Ischemic stroke, aspiration (Glasgow 10)	15
13	Female	81	5	*Staphylococcus hominis*	PVC	Aortic (N)	No	Ischemic stroke (Glasgow 3)	11
14	Female	75	2	MSSA	Early prosthetic; surgery	Aortic (P)	No[a]	Septic shock due to mediastinitis	5
15	Female	66	0	MSSA	Early prosthetic; surgery	Mitral (P)	No[a]	Septic shock due to mediastinitis	6
16	Male	74	1	MSSA	Early prosthetic; surgery	Aortic (P)	Yes	Septic shock due to mediastinitis	2
17	Female	76	2	MRSA	Early prosthetic; surgery	Mitral (P)	Yes	Septic shock	1
18	Female	50	0	*Pseudomonas aeruginosa*	PVC-related sepsis	Aortic (N) and mitral (N)	No	Multiorgan failure	6
19	Female	61	0	Gram-positive microorganism	Early prosthetic; surgery	Aortic (P)	Yes	Death during surgery	1
20	Male	82	2	*Enterococcus durans*	Previous hospitalization	Aortic (N)	Yes	Death immediately after surgery	12
21	Male	75	5	MRSA	AVF	Aortic (N)	No	Ischemic stroke (Glasgow 6)	1
22	Female	61	1	*E. faecalis*	CVC-related sepsis	Mitral (P)	No[a]	Cerebral hemorrhage	4
23	Female	83	2	*E. faecalis*	Peripheral catheter-related sepsis	Mitral (N)	No[a]	CHF (present at diagnosis)	15
24	Male	80	7	*S. epidermidis*	Previous hospitalization	Aortic (N)	No	CHF (started 68 days after initiation of therapy)	76
25	Female	91	1	*S. viridans*	Previous hospitalization	Mitral (N)	No[a]	CHF (present at diagnosis)	53
26	Male	56	3	*Streptococcus gordonii*	Previous hospitalization	Mitral (P)	No[a]	CHF (started 7 days after initiation of therapy)	7
27	Female	78	6	MRSA	Previous hospitalization	Mitral (N)	No	Sudden death	13
28	Female	70	3	*S. epidermidis*	Previous hospitalization	Mitral (N)	No[a]	CHF (present at diagnosis)	30
29	Female	67	3	MSSA	Previous hospitalization	Mitral (N)	No[a]	Pulmonary thromboembolism	20
30	Female	67	0	*Streptococcus anginosus*	Previous hospitalization	Unknown (N)	No	CHF (started 6 days after initiation of therapy)	6
31	Female	68	1	MSSA	Previous hospitalization	Unknown (P)	No[a]	CHF (present at diagnosis)	17
32	Male	21	1	*S. epidermidis*	Early prosthetic; surgery	Tricuspid (P) and pulmonic (P)	Yes	Death immediately after surgery	20

NOTE. AVF, arteriovenous fistula for hemodialysis; CHF, congestive heart failure; CVC, short-term central venous catheter; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; N, native; NA, not available; P, prosthetic; PVC, permanent venous catheter.

[a] Surgery indicated but not performed because of high risk.

Table 6. Univariate comparison between patients with health care–associated infective endocarditis (HAIE) and patients with community-acquired infective endocarditis (CAIE) episodes.

Variable	HAIE group (n = 83)	CAIE group (n = 209)	OR (95% CI)	P
Age, median years ± SD	65.3 ± 16.4	57.8 ± 17.0	1.03 (1.01–1.05)	.001
Female sex	44 (53.0)	57 (27.3)	3.01 (1.78–5.10)	<.005
Transferred from another health care center	18 (21.7)	87 (41.6)	0.39 (0.22–0.70)	.002
Charlson index, mean value ± SD	2.5 ± 2.3	1.7 ± 2.1	1.17 (1.05–1.31)	.006
Diabetes mellitus	19 (22.9)	30 (14.4)	1.77 (0.93–3.37)	.081
Hemodialysis	16 (19.3)	…	NA	<.005
Neoplasm	14 (16.9)	23 (11.0)	1.64 (0.80–3.37)	.177
HIV infection	3 (3.6)	14 (6.7)	0.52 (0.15–1.87)	.318
Prosthetic valve	24 (28.9)	38 (18.2)	1.83 (1.01–3.30)	.045
Affected valve				
Aortic alone	26 (31.3)	94 (45.0)	0.56 (0.33–0.96)	.034
Mitral alone	36 (43.4)	59 (28.2)	1.95 (1.15–3.30)	.013
Other	21 (25.3)	56 (26.8)	0.93 (0.52–1.66)	.794
Etiology				
Staphylococcus aureus	28 (33.7)	43 (20.6)	1.97 (1.12–3.46)	.019
MRSA	8/28 (28.6)	3/43 (7.0)	5.33 (1.28–22.32)	.022
Viridans group streptococci	9 (10.8)	56 (26.9)	0.33 (0.16–0.71)	.004
Enterococcus species	19 (22.9)	16 (7.7)	3.58 (1.74–7.38)	.001
Coagulase-negative staphylococci	18 (21.7)	16 (7.7)	3.34 (1.61–6.93)	.001
Streptococcus bovis	…	19 (9.1)	NA	.003
Negative culture results	2 (2.4)	14 (6.7)	0.34 (0.76–1.55)	.164
Streptococcus agalactiae	…	13 (6.2)	NA	.023
HACEK group	…	6 (2.5)	NA	.188
Other	7 (8.4)	26 (12.4)	0.65 (0.17 –1.56)	.332
Moderate-to-severe mitral regurgitation	37 (44.6)	84 (40.2)	0.84 (0.50–1.40)	.493
Moderate-to-severe aortic regurgitation	27 (32.5)	84 (40.2)	1.39 (0.82–2.38)	.225
Surgical procedure during hospitalization	19 (22.9)	96 (45.9)	0.35 (0.20–0.62)	<.005
EuroSCORE[a], mean value ± SD	11.6 ± 3.6	9.0 ± 3.7	1.20 (1.09–1.34)	<.005
Complication				
Any	71 (85.5)	172 (82.7)	1.24 (0.61–2.52)	.56
Congestive heart failure	39 (47.0)	94 (45.2)	1.08 (0.65–1.79)	.781
Systemic embolism other than stroke	23 (27.7)	71 (34.1)	0.74 (0.42–1.29)	.291
Acute renal failure	19 (22.9)	61 (29.3)	0.72 (0.40–1.29)	.268
Stroke	16 (19.3)	38 (18.3)	1.07 (0.56–2.04)	.842
Intracardiac abscess	8 (9.9)	40 (19.2)	0.46 (0.21–1.03)	.060
Conduction abnormality	9 (10.8)	28 (13.6)	0.77 (0.35–1.72)	.528
Persistent fever	13 (15.7)	26 (12.5)	1.30 (0.63–2.67)	.475
Intensive care unit stay, mean days ± SD	10.7 ± 28.2	7.8 ± 16.2	1.01 (1.00–1.02)	.271
In-hospital mortality	38 (45.8)	46 (22.0)	3.00 (1.74–5.14)	<.005
One-year mortality[b]	44 (59.5)	55 (29.6)	3.41 (1.95–5.98)	<.005

NOTE. Data are no. (%) of patients, unless otherwise indicated. HACEK, *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella;* MRSA, methicillin-resistant *S. aureus;* NA, not applicable.

[a] Includes only patients with an indication for surgery.

[b] Includes only patients with at least 1 year of follow-up.

vious analyses of our series showed that patients with HAIE defined according to this broadened definition were similar to patients with HAIE defined according to the most conservative definition (i.e., only including cases of IE that occurred 1–2 months after hospital discharge), even with respect to etiology and mortality, and were significantly different from patients with CAIE (data not shown). On the basis of these results, we decided to adopt the classification proposed by Ben-Ami et al.

Table 7. Association between characteristics of patients with health care–associated infective endocarditis (HAIE) and in-hospital death.

Variable	Patients who died (n = 38)	Patients who survived (n = 45)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	P	OR (95% CI)	P
Age, mean years ± SD	68.4 ± 14.6	62.8 ± 17.5	1.02 (1.00–1.05)	.125	…	…
Charlson index, mean value ± SD	2.89 ± 2.40	2.16 ± 2.21	1.51 (0.95–1.39)	.151	…	…
Diabetes mellitus	12 (31.6)	7 (15.6)	2.51 (0.87–7.21)	.089	…	…
Prosthetic valve	14 (36.8)	10 (22.2)	2.04 (0.78–5.35)	.147	…	…
Etiology						
Staphylococcus aureus	16 (42.1)	12 (26.7)	2.00 (0.80–5.03)	.141	…	…
Coagulase-negative staphylococci	8 (21.1)	10 (22.2)	0.93 (0.33–2.67)	.898	…	…
Viridans group streptococci	5 (13.2)	4 (8.9)	1.55 (0.39–6.25)	.535	…	…
Enterococcus species	5 (13.2)	14 (31.1)	0.34 (0.11–1.04)	.059	0.18 (0.04–0.78)	.022
Other microorganism	4 (10.5)	5 (11.1)	0.94 (0.23–3.79)	.932	…	…
Moderate-to-severe aortic regurgitation	9 (23.7)	18 (40.0)	0.47 (0.18–1.21)	.117	…	…
Vegetation diameter, mean mm ± SD	16.0 ± 9.6	11.6 ± 6.4	1.08 (1.00–1.17)	.056	…	…
Pulmonary arterial blood pressure, mean mm Hg ± SD	60.0 ± 18.9	48.3 ± 14.9	1.04 (1.00–1.09)	.060	…	…
Indication for surgery	29 (76.3)	19 (42.2)	4.41 (1.70–11.44)	.002	…	…
EuroSCORE[a], mean value ± SD	12.3 ± 3.9	10.6 ± 3.0	1.15 (0.96–1.38)	.129	…	…
Surgery indicated but not performed	20 (52.6)	9 (20.5)	4.32 (1.64–11.41)	.003	3.74 (1.22–11.45)	.021
Complication						
Any	37 (97.4)	34 (75.6)	11.97 (1.47–97.70)	.020	…	…
Congestive heart failure	25 (65.8)	14 (31.1)	4.26 (1.70–10.69)	.002	5.48 (1.77–17.03)	.003
Stroke	12 (31.6)	4 (8.9)	4.73 (1.38–16.24)	.014	8.95 (2.04–39.31)	.004
Acute renal failure	15 (39.5)	4 (8.9)	6.69 (1.98–25.54)	.002	…	…
Intensive care unit stay, mean days ± SD	19.4 ± 37.9	3.3 ± 12.4	1.03 (1.00–1.06)	.044	…	…

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Includes only patients with an indication for surgery.

[9], although the link between some cases of viridans group IE and health care could be questioned. Thus, further studies should validate our definition of HAIE.

The source of infection was attributed to manipulation of a vascular access in 41 cases. This illustrates that catheterization is an important cause of HAIE and explains the high rate of infection due to staphylococci and enterococci. These findings are not surprising, because the risk of endocarditis associated with catheter-related bacteremia due to *S. aureus* and *Enterococcus* species is well recognized [16, 17]. Nevertheless, these data are a cause for concern and indicate the need to improve the care provided to patients with all types of vascular accesses, because HAIE is potentially avoidable and has considerable associated mortality [18].

There were 4 episodes of HAIE secondary to persistent bacteremia in mediastinitis after cardiac surgery (3 due to *S. aureus* and 1 due to *Staphylococcus epidermidis*). Early debridement of any deep wound infection would potentially avoid persistent bacteremia and, therefore, decrease the risk of endocarditis [19].

There were fewer patients who were transferred from another center in the HAIE group than there were in the CAIE group. This could be explained by the fact that a tertiary teaching center performs a great number of ambulatory procedures (e.g., hemodialysis and chemotherapy infusion) that place patients at risk for bacteremia.

The microorganism that was isolated most often in both the HAIE group and the CAIE group was *Staphylococcus* species, as has been described by other authors [7], which indicates the changing epidemiology of this disease. There was a higher rate of MRSA infection in the HAIE group than in the CAIE group, as expected. Moreover, most patients with HAIE due to MRSA died, a fact that indicates the difficulty of treating these cases. In our study, enterococcal IE was associated with a lower rate of in-hospital and 1-year mortality. This is not surprising, because a previous study has demonstrated that enterococcal IE is associated with a lower risk of embolism and lower mortality than staphylococcal IE [20].

HAIE affects elderly men and women in poor general condition. This comorbid status leads to close contact with the health system and a subsequent increased risk of acquiring bacteremia and IE; it also influences the attitude of physicians attending these patients. It is worth mentioning that 29 (60.4%) of 48 patients with HAIE who had an indication for surgery did not undergo valve replacement during hospitalization be-

Table 8. Association between characteristics of patients with health care–associated infective endocarditis (HAIE) and 1-year mortality.

Variable	Patients who died (n = 44)	Patients who survived (n = 30)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	P	OR (95% CI)	P
Age, mean years ± SD	67.2 ± 15.6	62.8 ± 17.1	1.02 (0.99–1.05)	.260	…	…
Charlson index, mean value ± SD	2.9 ± 2.5	1.8 ± 2.1	1.24 (0.99–1.55)	.057	…	…
Diabetes mellitus	13 (29.5)	4 (13.3)	2.73 (0.79–9.38)	.112	…	…
Etiology						
Staphylococcus aureus	18 (40.9)	10 (33.3)	1.39 (0.53–3.65)	.510	…	…
Coagulase-negative staphylococci	10 (22.7)	6 (20.0)	1.18 (0.38–3.68)	.780	…	…
Viridans group streptococci	6 (13.6)	3 (10.0)	1.42 (0.33–6.19)	.640	…	…
Enterococcus species	4 (9.1)	10 (33.3)	0.20 (0.06–0.72)	.014	0.18 (0.04–0.81)	.026
Other microorganism	6 (13.6)	1 (3.3)	3.72 (0.41–33.56)	.242	…	…
Moderate-to-severe aortic regurgitation	11 (25.0)	14 (46.7)	0.38 (0.14–1.03)	.056	…	…
Pulmonary arterial blood pressure, median mm Hg ± SD	58.1 ± 19.3	46.6 ± 12.9	1.05 (1.00–1.10)	.055	…	…
Indication for surgery	33 (75.0)	11 (36.7)	5.18 (1.89–14.21)	.001	…	…
EuroSCORE[a], mean value ± SD	12.1 ± 3.8	10.2 ± 3.3	1.17 (0.96–1.44)	.127	…	…
Surgery indicated but not performed	23 (52.3)	4 (13.3)	7.12 (2.13–23.81)	.001	7.81 (2.06–29.67)	.003
Complication						
Any	40 (90.9)	22 (73.3)	3.64 (0.98–13.45)	.053	…	…
Congestive heart failure	26 (59.1)	10 (33.3)	2.89 (1.10–7.61)	.032	…	…
Stroke	12 (27.3)	3 (10.0)	3.38 (0.86–13.21)	.081	…	…
Acute renal failure	15 (34.1)	2 (6.7)	7.24 (1.51–34.60)	.013	7.18 (1.32–39.18)	.023
ICU stay, mean days ± SD	16.8 ± 35.8	3.93 ± 14.73	1.02 (0.99–1.06)	.117	…	…

NOTE. Data are no. (%) of patients, unless otherwise indicated. ICU, intensive care unit.

[a] Includes only patients with an indication for surgery.

cause of a high surgical risk, and this was an independent risk factor for in-hospital and 1-year mortality. Moreover, mortality was higher in the HAIE group than in the CAIE group. Although there were no differences between the HAIE and CAIE groups with respect to the incidence or type of complications (indicating that IE is a severe disease regardless of the source of acquisition), in the multivariate analysis of the whole series (292 episodes), HAIE was an independent risk factor for in-hospital and 1-year mortality.

Only 26 (31.3%) of our 83 patients with HAIE were potential candidates for antimicrobial prophylaxis (24 patients with prosthetic valve endocarditis and 2 patients with congenital heart disease). Nevertheless, only a small or negligible percentage of IE episodes could have been prevented by administration of antimicrobial prophylaxis. Therefore, routine antimicrobial prophylaxis administered before most invasive procedures is no longer considered to be appropriate [21]. The maintenance of proper aseptic measures before and during invasive procedures is probably much more important than a generalized use of prophylactic antimicrobials.

This study has several limitations. It is subject to the referral bias of a large tertiary teaching center. The high rate of HAIE in the series implied a high rate of *S. aureus* infection. Extrapolation of the results to other community hospitals should be done with caution. Detection of IE in hospitalized patients requires a high index of suspicion and routine practice of transesophageal echocardiography in patients with bacteremia (in particular, in patients with infections caused by gram-positive microorganisms) [16,22]. Taking into account the high mortality associated with HAIE, it is possible that some HAIE episodes that occurred during the study period may not have been diagnosed. Finally, some episodes of viridans group IE could have been unintentionally misclassified.

In conclusion, this study reveals that HAIE is an important health problem that affects elderly men and women in poor general condition equally. The infection is mainly caused by staphylococci and enterococci and is associated with considerable in-hospital and 1-year mortality. Maximizing prophylactic measures during the insertion and manipulation of venous catheters and, in general, maintaining aseptic measures before and during any invasive procedures could reduce the rate of this devastating infection.

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References

1. López-Dupla M, Hernández S, Olona M, et al. Clinical characteristics and outcome of infective endocarditis in individuals of the general population managed at a teaching hospital without cardiac surgery facilities: study of 120 cases. Rev Esp Cardiol **2006**; 59:1131–9.
2. Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. JAMA **2007**; 297:1354–61.
3. Thuny F, Avierinos JF, Tribouilloy C, et al. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentric study. Eur Heart J **2007**; 28: 1155–61.
4. Prendergast BD. The changing face of infective endocarditis. Heart **2006**; 92:879–85.
5. Moreillon P, Que YA. Infective endocarditis. Lancet **2004**; 363:139–49.
6. Mylonakis E, Carlderwood SB. Infective endocarditis in adults. N Engl J Med **2001**; 345:1318–30.
7. Fowler VG, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. JAMA **2005**; 293:3012–21.
8. Martín-Dávila P, Fortún J, Navas E, et al. Nosocomial endocarditis in a tertiary hospital: an increasing trend in native valve cases. Chest **2005**; 128:772–9.
9. Ben-Ami R, Giladi M, Carmeli Y, Orni-Wasserlauf R, Siegman-Igra Y. Hospital-acquired infective endocarditis: should the definition be broadened? Clin Infect Dis **2004**; 38:843–50.
10. Giannitsioti E, Skiadas I, Antoniadou A, et al. Nosocomial vs. community-acquired infective endocarditis in Greece: changing epidemiological profile and mortality risk. Clin Microbiol Infect **2007**; 13: 763–9.
11. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis **2000**; 30:633–8.
12. Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. Lancet Infect Dis **2007**; 7:645–57.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis **1987**; 40:373–83.
14. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg **1999**; 16:9–13.
15. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Disease Society of America. Circulation **2005**; 111:394–434.
16. Pigrau C, Rodríguez D, Planes AM, et al. Management of catheter-related *Staphylococcus aureus* bacteremia: when may sonographic study be unnecessary? Eur J Clin Microbiol Infect Dis **2003**; 22:713–9.
17. Fernández-Guerrero ML, Herrero L, Bellver M, Gadea I, Roblas RF, de Górgolas M. Nosocomial enterococcal endocarditis: a serious hazard for hospitalized patients with enterococcal bacteraemia. J Intern Med **2002**; 252:510–5.
18. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infection. Am J Infect Control **2002**; 30:476–89.
19. Diez C, Koch D, Kuss O, Silber RE, Friedrich I, Boergermann J. Risk factors for mediastinitis after cardiac surgery: a retrospective analysis of 1700 patients. J Cardiothorac Surg **2007**; 2:23–30.
20. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation **2007**; 116:1736–54.
21. McDonald JR, Olaison L, Anderson DS, et al. Enterococcal endocarditis: 107 cases from the international collaboration on endocarditis merged database. Am J Med **2005**; 118:759–66.
22. Fowler VG, Justice A, Moore C, et al. Risk factors for hematogenous complications of intravascular catheter–associated *Staphylococcus aureus* bacteremia. Clin Infect Dis **2005**; 40:695–703.