Published in final edited form as:
Ann Intern Med. 2009 May 5; 150(9): 586–594.

Health Care–Associated Native Valve Endocarditis in Patients with no History of Injection Drug Use: Current Importance of Non-Nosocomial Acquisition

Dr Natividad Benito[0], **José M. Miró**[1,*], **Elisa de Lazzari**[1], **Christopher H Cabell**[2], **Ana del Río**[1], **Javier Altclas**[3], **Patrick Commerford**[4], **Francois Delahaye**[5], **Stefan Dragulescu**[6], **Helen Giamarellou**[7], **Gilbert Habib**[8], **Adeeba Kamarulzaman**[9], **A. Sampath Kumar**[10], **Francisco M. Nacinovich**[11], **Fredy Suter**[12], **Christophe Tribouilloy**[13], **K Venugopal**[14], **Asuncion Moreno**[1], **Vance G. Fowler Jr.**[2], and **the International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) Investigators**[15]

[0]Hospital de la Santa Creu i Sant Pau, University Autónoma of Barcelona, Barcelona (Spain)

[1]Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, (Spain)

[2]Duke University Medical Center, Durham, North Carolina (USA)

[3]Sanatorio Mitre, Buenos Aires, Argentina

[4]Hospital Groote Schuur, Cape Town, South Africa

[5]Hôpital Louis Pradel, Lyon, France

[6]Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

[7]Attikon University General Hospital, Athens, Greece

[8]Faculté de Médecine de Marseille, Marseille, France

[9]University of Malaya Medical Center, Kuala Lumpur, Malaysia

[10]All India Institute of Medical Sciences, New Deli, India

[11]Instituto Cardiovascular, Buenos Aires, Argentina

[12]Ospedali Riuniti di Bergamo, Bergamo, Italy

[13]South Hospital Amiens, Amiens, France

[14]Medical College Calicut, Kerala, India

Abstract

Background—The clinical profile and outcome of nosocomial and non-nosocomial health care–associated native valve endocarditis are not well defined.

[*]Address for correspondence and reprints: José M. Miró. Hospital Clinic Universitari. Helios-Villarroel Building - Desk no. 26. Villarroel, 170. 08036-Barcelona (Spain). Phone# 34-93-2275586/5400 (Ext. No. 2765). Fax# 34-93-4514438/5424. jmmiro@ub.edu.
[15]The ICE-PCS investigators are listed in the appendix.
Dr. Benito was working in Hospital Clínic-IDIBAPS when this paper was started; currently she is working in Hospital de la Santa Creu i Sant Pau, also in Barcelona (Spain)

Potential conflict of interest: Dr. Fowler has served as a consultant for Biosynexus, Cubist, Inhibitex, Merck, and Johnson & Johnson; received research grant support from Cubist, Inhibitex, Merck, Nabi, and Theravance, and is on speaker's bureau for Cubist and Pfizer. Dr. José M Miró has received honoraria for speaking or participating in Advisory Boards and/or research grants from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, (BMS) Chiron, Cubist, Novartis, Glaxo Smith Kline (GSK), Gilead Sciences, Oxford Immunotec, Pfizer, Roche and Theravance.

Objective—To describe the prevalence, clinical characteristics, and outcomes of nosocomial and non-nosocomial health care–associated native valve endocarditis.

Design—Prospective observational study.

Setting—61 hospitals in 28 countries.

Patients—Patients with definite native valve endocarditis and no history of injection drug use who were enrolled in the International Collaboration on Endocarditis–Prospective Cohort Study from June 2000 to August 2005.

Measurements—Characteristics of nosocomial and non-nosocomial health care–associated native valve endocarditis cases were described and compared with those cases acquired in the community.

Results—Health care–associated native valve endocarditis was present in 557 (34%) of 1622 patients with native valve endocarditis and no history of injection drug use (nosocomial native valve endocarditis 303 patients [54%]; non-nosocomial health care–associated native valve endocarditis 254 patients [46%]). *Staphylococcus aureus* was the most common cause of health care-associated native valve endocarditis (nosocomial native valve endocarditis, 47%; non-nosocomial health care–associated native valve endocarditis, 42%; p=0.3), with a notable proportion of methicillin-resistant *S. aureus* (nosocomial native valve endocarditis, 57%; non-nosocomial health care–associated native valve endocarditis, 41%; p=0.014). Patients with health care–associated native valve endocarditis had lower rates of cardiac surgery (41% health care–associated native valve endocarditis vs 51% community-acquired native valve endocarditis, p<0.001) and higher in-hospital mortality rates than patients with community-acquired native valve endocarditis (25% health care–associated native valve endocarditis vs. 13% community-acquired native valve endocarditis vs., p<0.001). Multivariable analysis confirmed a higher mortality associated with health care–associated native valve endocarditis (incidence risk ratio=1.20 (CI 95%, 1.03–1.61).

Limitations—This study involves tertiary hospitals with cardiac surgery programs. The results may not be generalized to patient populations receiving care in other types of facility.

Conclusions—More than one-third of all cases of native valve endocarditis in non-drug users involve contact with health care. *S. aureus* is the leading cause of health care–associated native valve endocarditis. Non-nosocomial health care–associated native valve endocarditis is common, especially in the US. Patients with health care-associated and community-acquired native valve endocarditis differ in their presentation, microbiology, and outcome. By contrast, patients with nosocomial and non-nosocomial healthcare-associated endocarditis are similar.

Keywords

infective endocarditis; healthcare-associated endocarditis; nosocomial endocarditis; non-nosocomial healthcare-associated endocarditis; community-acquired endocarditis; Staphylococcal aureus endocarditis; MRSA endocarditis; Coagulase-negative staphylococcal endocarditis; Surgery; Outcome

INTRODUCTION

Health care-associated bloodstream infections are an important and potentially lethal complication of medical care (1,2). Until recently, most health care-associated infections were acquired in the hospital (nosocomial health care acquired infection). Now, a new category of non-nosocomial health care-associated bloodstream infection has been recognized (3–9) and characterized (5, 7–10). The number of patients at risk for this newly defined infection category is growing, particularly in developed countries (11).

Infective endocarditis is one of the most dreaded complications of health care-associated bloodstream infections (12), but the characteristics of health care-associated endocarditis remain incompletely characterized. Health care-associated endocarditis comprises endocarditis acquired in the hospital (nosocomial) and endocarditis that develops outside the hospital (non-nosocomial) in patients with extensive health care contact (e.g. in day-care hospitals, dialysis centers, outpatient parenteral antibiotic therapy programs, and nursing homes). Much of the current understanding of health care associated endocarditis has been based on studies of nosocomial infection limited by small simple size and retrospective design (13–19), single-center experiences (13,14,17–19, 20), analyses that combine cases of native and prosthetic valve endocarditis (13–17, 20), and use of unvalidated case definitions (21,22). Less is known about the epidemiology and clinical profile of non-nosocomial health care-associated endocarditis because this group of patients has not previously been studied.

Using data from a large, contemporary, prospective, and international study of patients with endocarditis, the current investigation seeks to describe differences in the prevalence, epidemiology, clinical characteristics, and outcome of community and health care associated native valve endocarditis, and of nosocomial and non-nosocomial health care-associated native valve endocarditis. We exclude patients with prosthetic valve endocarditis from this description because prosthetic valve endocarditis has characteristics that distinguish it from native valve endocarditis (23).

METHODS

The International Collaboration on Endocarditis Prospective Cohort Study

We used data from the International Collaboration on Endocarditis Prospective Cohort Study (ICE–PCS) for this study. The ICE-PCS database was created in 1999 and enrollment began on January 1, 2000. The background and inclusion criteria of this prospective, multicenter, international registry of endocarditis have previously been reported (23, 24–28). From January 2000 to August 2005, patients with endocarditis from 61 centers in 28 countries were enrolled. Patients were prospectively identified using site-specific procedures to ensure consecutive enrollment (24). They were enrolled in ICE-PCS if they met criteria for possible or definite endocarditis based on modified Duke criteria (21,22). Geographic regions participating in ICE include the United States (10 sites), South America (9 sites), Australia/New Zealand (9 sites), Europe (25 sites), Asia/Middle East (7 sites) and Africa (1 site).

The method of data collection for ICE-PCS has also previously been reported (25). Briefly, a standard case report form was used at all sites to collect data. The form included 275 demographic and clinical variables and was developed by ICE investigators according to standard definitions (24). Data were collected during the index hospitalization and were then sent to the coordinating center for data entry or entered directly by site investigators using a secure Internet-based data entry system. If a patient had more than one hospitalization, only data from the first hospitalization were recorded.

The ICE–PCS database is maintained at the Duke Clinical Research Institute, which serves as the coordinating center for the ICE studies, with approval from the institutional review board. Local institutional review board or ethics committee approval are additionally required in each site.

Patient selection

All patients enrolled from 1 January 2000 to 31 August 31 2005 with definite native valve endocarditis criteria according to the modified Duke criteria (21,22), no history of injection drug use, and an identified place of acquisition were included in the present investigation.

Native valve endocarditis was defined as endocarditis involving native heart valves and not prosthetic heart valves or implanted endovascular devices. Patients with a pacemaker and/or implantable defibrillator could be included if they had evidence of valvular infection and no evidence of lead infection. Injection drug users were excluded because native valve endocarditis in this group of patients has specific characteristics that differentiate it from native valve endocarditis in non-injection drug users (29).

Definitions

Cases of native valve endocarditis were categorized as community-acquired or health care-associated, and as nosocomial or non-nosocomial health care-associated infection (5,23,25). Cases were considered community-acquired if they were diagnosed within 48 hours of admission, and if signs or symptoms consistent with infective endocarditis developed in a patient without extensive out-of-hospital contact with health care interventions or systems. Cases were considered nosocomial health care-associated if they occurred in a patient hospitalized for more than 48 hours prior to the onset of signs or symptoms consistent with infective endocarditis. Cases were considered non-nosocomial health care associated if they were diagnosed within 48 hours of admission, and if signs or symptoms consistent with infective endocarditis developed prior to hospitalization in patients with extensive out-of-hospital contact with health care interventions or systems, defined as: 1) receipt of intravenous therapy, wound care, or specialized nursing care at home within the 30 days prior to the onset of native valve endocarditis; 2) receipt of hemodialysis or intravenous chemotherapy in the 30 days before the onset of native valve endocarditis; 3) hospitalization for 2 or more days in the 90 days before the onset of native valve endocarditis; or 4) residence in a nursing home or long-term care facility (3).

Data on a range of demographic and clinical variables and on outcomes (eg need for surgery and complications) were collected using the ICE-PCS case report form as has been previously reported (23,25). We presumed that an intravascular catheter was a possible source of infection if it was present at the onset of endocarditis symptoms (23). We defined vascular evidence of endocarditis as vascular embolic events, conjunctival hemorrhages, or Janeway lesions (21). We defined immunologic evidence of infective endocarditis as the presence of Osler nodes or Roth spots (21). We defined persistent bacteremia by the criteria of Durack et al (21). We assessed in-hospital mortality only, although patients who were stabilized as inpatients and discharged to complete their initial course of antibiotics as outpatients were followed for mortality through their initial course of antibiotic therapy.

Statistical analyses

We summarize continuous variables with medians and interquartile ranges, and categorical variables with absolute frequencies and percents in relation to the total sample for that variable. Since some variable is affected by some missing values, total of patients in each variable may vary. We used the Wilcoxon rank sum and Chi-squared tests (or Fisher exact tests when appropriate) to evaluate group differences for continuous and categorical variables, respectively. A generalized estimating equation model (30) clustering on sites and with robust estimations of standard errors was used to identify factors independently associated with in-hospital mortality. Covariates for the final adjusted regression model were selected based on clinical judgment and statistical significance ($p<0.10$). Thus, all variables that have been associated with mortality in previous studies of endocarditis were included in the model (age, diabetes, infection with *S. aureus,* endocarditis complications including stroke, congestive heart failure and paravalvular abscess, receipt of cardiac surgery; and health care-related acquisition of infection. Patient gender was also included. Additionally, variables with p-value<0.1 in the univariable analysis were also considered. From this list of candidate variables, the following were selected for inclusion in the model

based on their clinical importance: presence of hemodialysis, cancer, or immunosuppressive therapy, persistent bacteremia, and new conduction abnormality. Covariate selection started from the saturated model and proceeded backward, reassessing at each step one by one all predictors left out of the model. Final parameter estimates were converted to incidence rate ratios (IRR) with corresponding 95% confidence interval (CI). The concordance index was used as a measure of fit of the multivariable model to the data. All tests were two-sided with a 95% confidence level. All analyses were performed using STATA software (StataCorp. 2005. Stata Statistical Software: Release 9.2. College Station, TX: Stata Corp LP).

Role of the Funding Source

The study did not receive funding.

RESULTS

Definite native valve endocarditis in non-injection drug users was diagnosed in 1622 patients: 1065 (66%) were community-acquired and 557 (34%) were health care-associated infection, and of patients with health care-associated infection, 303 (54%) were nosocomial and 254 (46%) were non-nosocomial infections. In the United States, the majority of cases were health care-associated (59%), 65% of which were non-nosocomial. Most cases in all other geographic regions were community acquired (Table 1).

Predisposing factors (Table 1)

More patients with health care-associated native valve endocarditis had diabetes mellitus, cancer, , or were taking chronic immunosuppressive therapy than patients with community-acquired infection. The same was true of patients with non-nosocomial compared to nosocomial health care-associated infection. Additionally, patients with non-nosocomial health care-associated infection were more often dependent on hemodialysis than patients with nosocomial infections. Compared to those with non-nosocomial health care associated infection, more patients with nosocomial infection had pre-existing valvular disease. An intravascular catheter was the presumed source of infection in more patients with non-nosocomial than nosocomial health care-associated endocarditis (54% v. 44%; p=0.022). Otherwise, more patients with nosocomial health care-associated infection had undergone a nondental invasive medical procedure (48% v. 35% of non-nosocomial cases; p=0.002).

Clinical and echocardiographic characteristics

Fever was the most common presenting feature in all categories of infection (Table 2). Fewer patients with health care-associated native valve endocarditis had other clinical evidence of endocarditis (e.g., splenomegaly, presence of a new cardiac murmur, or worsening of an old murmur), vascular or immunologic evidence of endocarditis, or evidence of systemic inflammation (elevated rheumatoid factor, elevated C-reactive protein, elevated sedimentation rate, or hematuria; $p<0.001$ for each characteristic) than patients with community-acquired native valve endocarditis.

The mitral valve was the most frequently involved valve in all categories of infection. Patients with health-care associated native valve endocarditis had less frequent involvement of the aortic valve and more frequent involvement of the tricuspid valve than patients with community acquired native valve endocarditis. No differences were observed between patients with nosocomial and non-nosocomial health-care associated endocarditis.

Microbiology (Table 3)

The microbiology of healthcare-associated and community-acquired native valve endocarditis differed significantly in our investigation. *Staphylococcus aureus* was the most

common cause of native valve endocarditis in patients with health care-associated infection, while viridans group streptococci were the most common cause of community-acquired native valve endocarditis (in patients with no history of injection drug use). Moreover, the rate of methicillin resistant *S. aureus* (MRSA) was higher among patients with health care-associated native valve endocarditis than among patients with community-acquired infection (47% v. 12%; p<0.001). Enterococci and coagulase negative staphylococci were also more common causes of endocarditis in patients with healthcare-associated infection than in patients with community-acquired infection. Although rates of *S. aureus*, enterococci, and coagulase-negative staphylococci were similar in patients with nosocomial and non-nosocomial healthcare associated endocarditis, rates of MRSA were higher among patients with hospital-acquired infections (57% v. 41%; p=0.014).

Complications and Outcome (Table 4)

Patients with health care-associated native valve endocarditis had higher rates of persistent bacteremia and mortality during the index hospitalization, but were less likely to receive cardiac surgery than patients with community-acquired infection. Patients with hospital-acquired endocarditis had more congestive heart failure than patients with non-nosocomial healthcare-associated endocarditis. No other significant differences in frequency of surgery, complications and outcome were noted between the two categories of healthcare-associated infection.

Non-nosocomial health care-associated native valve endocarditis in patients on hemodialysis vs. non-hemodialysis patients

Hemodialysis-dependent patients with non-nosocomial health care-associated native valve endocarditis were statistically significantly more likely to be from North America, to have diabetes mellitus, chronic indwelling central catheters, *S. aureus* infection, and persistent bacteremia, and less likely to have cancer and peripheral catheters than non-hemodialysis-dependent patients with non-nosocomial healthcare-associated infection (Appendix Table 1).

Risk factors for mortality of health care-associated native valve endocarditis

Risk factors for mortality are presented in Table 5. The adjusted estimation used 1464 cases of native valve endocarditis, as this was the largest sample with all the risk factors available (the percent of patients presenting missing values ranged between 0.1% to 3.2%). The factors evaluated for the adjusted models were age, gender, route of acquisition, hemodialysis, diabetes, cancer, chronic immunosuppressive therapy, *S. aureus*, paravalvular abscess, surgery, stroke, congestive heart failure, persistent positive blood culture, and new conduction abnormality. Characteristics independently associated with higher mortality among patients with native valve endocarditis were age ≥ 60 years (IRR=1.48; CI 1.23–1.79), diabetes (IRR=1.52; CI: 1.10–2.11), *S. aureus* etiology (IRR=1.57; CI: 1.24–1.99), health care acquisition of infection (IRR=1.29; 1.03–1.61), paravalvular abscess (IRR=1.53; CI: 1.16–2.01), congestive heart failure (IRR=2.53; CI: 2.04–3.14), and stroke (IRR=2.00; CI: 1.57–2.54). Cardiac surgery during the endocarditis episode was associated with lower rates of mortality (IRR=0.70; CI: 0.56–0.86).

DISCUSSION

Native valve endocarditis has been regarded as a disease of patients with community-associated bacteremia, mainly caused by viridans group streptococci. Several studies performed in different countries during last decades have suggested that the characteristics of endocarditis have changed (17, 32–37). An increase in the average age of patients, an increasing frequency of *S. aureus* and/or a decrease in viridans group streptococcal endocarditis, and new predisposing factors have been described in these studies (17, 31–37).

However, the role of the route of acquisition of endocarditis on these characteristics has not been assessed in detail.

More than one third of the patients with native valve endocarditis and no history of injection drug use in this large, contemporary, multinational cohort study acquired their endocarditis as a complication of healthcare. Almost half of these health care-associated infections were acquired outside of the hospital. This observation documents the emergence of health care contact as an important risk factor for the acquisition of native valve endocarditis, and updates our traditional understanding of native valve endocarditis as a primarily community-acquired infection. Patients with health care-associated infection were more likely to have comorbid conditions, to be infected with *S. aureus* –and particularly MRSA, to develop persistent bacteremia, and to die of their infection than patients with community-acquired infection. By contrast, patients with nosocomial and non-nosocomial healthcare-associated endocarditis were similar.

Infections have been traditionally classified as either nosocomial or community acquired (38). However, changes in health care systems in developed countries have shifted many health care services from hospitals to outpatient facilities. In this setting, non-nosocomial health care-associated infection is a recently described epidemiologic category (5, 7–10). Almost half of the patients (46%) with health care-associated native valve endocarditis in the current study acquired their infection outside of the hospital, a finding consistent with a previous report of health care-associated bacteremia (5). Interestingly, the prevalence of non-nosocomial health care-associated endocarditis in the current study differed by geographic region. In the USA, more than one-third of patients with native valve endocarditis and no history of injection drug had non-nosocomial health care-associated native valve endocarditis - more than twice the frequency of any other region represented in this study. This finding may be due in part to the growing importance of outpatient medical therapy and the rising number of hemodialysis patients in the US healthcare system (39,40). As these trends in demographics and healthcare access extend from the US to other regions of the world, the global importance of non-nosocomial health care-associated native valve endocarditis is likely to grow.

The present investigation also demonstrates that most cases of health care-associated native valve endocarditis – whether acquired inside or outside the hospital – are caused by *S. aureus*. In non-nosocomial health care-acquired Outside the hospital, it was more common in patients on hemodialysis than in non-hemodialysis patients. An alarming number of these cases are caused by MRSA. Almost half of the cases of health care-associated native valve endocarditis were caused by MRSA, far higher than previously reported (16,33,41–43). This finding has important implications for the empiric treatment and prognosis of suspected health care-associated native valve endocarditis. Given rising rates of antimicrobial resistance of *S. aureus*, these percentages are likely to grow (44–47). Enterococcus species were the second more common etiologic agent of health care-associated native valve endocarditis and was significantly higher than in community-acquired native valve endocarditis according to a recent study (48). By contrast, viridans group streptococci remain the most common cause of community-acquired infection in patients with no history of injection drug use. These findings underline the importance of taking into account the route of acquisition of native valve endocarditis when evaluating the etiology and possible temporal changes of a multifaceted disease such as endocarditis. In fact, the significant disparity between the microbial causes of endocarditis found in recent single-center studies could possibly be explained by different rates in the route of acquisition of native valve endocarditis (32–36, 49).

The clinical characteristics of health care-associated native valve endocarditis—lower prevalence of splenomegaly and less evidence of systemic inflammation—suggest a more acute course of infection than those of community-acquired native valve endocarditis. This finding agrees with the current understanding of the pathogenesis of healthcare-associated endocarditis and with previous reports (17–19, 37).

In agreement with previous studies, we found that advanced age, diabetes, infection with *S. aureus*, and endocarditis complications (stroke, congestive heart failure and paravalvular abscess) were associated with a higher mortality in patients with native valve endocarditis (12,15,18,37,50,51). The present investigation also confirms previous reports (14,16,17,23,25,48,52) suggesting a higher mortality rate in patients with health care-associated infection. How the health care-related acquisition of the infection could influence a patient's risk of death is not entirely clear. Health care-associated acquisition of endocarditis probably represent a composite of prognostic factors not completely identified in the multivariable analysis, that would include characteristics related to the virulence of causative organisms and host factors (23,48)

Multivariable analysis identified the receipt of cardiac surgery as an independent factor associated with survival in patients with native valve endocarditis. This finding agrees with some (53–56) but not all (37,57), previous reports. In our study, patients with health care-associated endocarditis underwent surgery less often than patients with community-acquired infection, despite more frequently exhibiting surgical indications (e.g., persistent bacteremia). This finding could be due in part to the larger burden of comorbidities – both acute and chronic- among patients with health care-associated native valve endocarditis. Additionally, referral bias must be considered, since higher-risk individuals with community-acquired native valve endocarditis would be transferred to a tertiary care center and they could have had higher rates of surgical intervention than patients with lower risk factors. More studies are needed to define more clearly the role, timing, and effect of surgery in native valve endocarditis.

Our investigation has limitations. First, this observational study primarily involves tertiary medical centers with cardiac surgery programs that have chosen to participate in the ICE-PCS. Therefore, our results may not be generalized to other patient populations receiving care in other facilities. Second, regional characterization was based only on data from participating medical centers, and our ability to make epidemiological inferences was limited by the absence of corresponding population samples for the study regions. Third, the end point of mortality was assessed at hospital discharge and, therefore, does not reflect health care-associated native valve outcome at a specific time after diagnosis. Finally, this study cannot establish the risk for endocarditis among in-hospital patients or patients with extensive preceding out-of-hospital health care contacts. However, clinicians should recognize that when outpatients with extensive health care contacts do develop endocarditis, they have similar risk factors for disease, etiologies, clinical presentation, and outcomes as those with hospital-acquired infection.

Despite these limitations, the current investigation reports several key findings. Health care-associated native valve endocarditis currently accounts for more than a third of all cases of native valve endocarditis in non-injection drug users throughout much of the world. *S. aureus* is the leading cause of health care-associated native valve endocarditis. Non-nosocomial health care-associated native valve endocarditis is common, especially in the US. Patients with health care-associated native valve endocarditis have a different profile from those with community-acquired native valve endocarditis. By contrast, nosocomial and non-nosocomial health care–associated native valve endocarditis share most epidemiologic, microbiologic, and prognostic characteristics. The growing frequency and high mortality

rate of health care-associated native valve endocarditis mean that preventive strategies should be managed carefully to help protect patients at risk of this potentially lethal infection.

Acknowledgments

Grant support information: This study was supported in part by the following grants: from the National Institutes of Health (grant no. R01-AI068804) (Dr Fowler), from the American Heart Association (grant no. 0455802U) (Dr. A. Wang), from the "Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, Spanish Network for the Research in Infectious Diseases (REIPI RD06/0008)", from the "Fundación Privada Máximo Soriano Jiménez, Barcelona, Spain" (grant supporting the Hospital Clínic Endocarditis database) (Dr. Miro). Dr. J.M. Miró was a recipient of a Research Grant from the "Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)" and the "Conselleria de Salut de la Generalitat de Catalunya, Barcelona (Spain)".

References

1. Wenzel RP, Edmond MB. The impact of hospital-acquired bloodstream infections. Emerg Infect Dis. 2001; 7:174–7. [PubMed: 11294700]
2. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: A three-year analysis. Clin Infect Dis. 1999; 29:239–44. [PubMed: 10476719]
3. Graham DR, Keldermans MM, Klemm LW, Semenza NJ, Shafer ML. Infectious complications among patients receiving home intravenous therapy with peripheral, central, or peripherally placed central venous catheters. Am J Med. 1991; 91:95S–100S. [PubMed: 1928199]
4. Morin CA, Hadler JL. Population-based incidence and characteristics of community-onset *Staphylococcus aureus* infections with bacteremia in 4 metropolitan Connecticut areas, 1998. J Infect Dis. 2001; 184:1029–34. [PubMed: 11574918]
5. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community acquired infections. Ann Intern Med. 2002; 137:791–7. [PubMed: 12435215]
6. Siegman-Igra Y, Fourer B, Orni-Wasserlauf R, Golan Y, Noy A, Schwartz D, et al. Reappraisal of community-acquired bacteremia: a proposal of a new classification for the spectrum of acquisition of bacteremia. Clin Infect Dis. 34:1431–9. [PubMed: 12015688]
7. Tacconelli E, Venkataraman L, Girolami PC, D'Agata EMC. Methicillin-resistant *Staphylococcus aureus* bacteremia diagnosed at hospital admission: distinguishing between community-acquired versus healthcare-associated strains. J Antimicrob Chemother. 2004; 53:474–9. [PubMed: 14762054]
8. Lesens O, Hansmann Y, Brannigan E, Hopkins S, Meyer P, O'Connel B, et al. Healthcare-associated *Staphylococcus aureus* bacteremia and the risk for methicillin resistance: is the Centers for Disease Control and Prevention definition for community-acquired bacteremia still appropriate? Infect Control Hosp Epidemiol. 2005; 26:204–9. [PubMed: 15756893]
9. Shorr AF, Tabak YP, Killian AD, Gupta V, Liu LZ, Kollef MH. Healthcare-associated bloodstream infection: a distinct entity? Insights from a large U.S database. Crit Care Med. 2006; 34:2588–95. [PubMed: 16915117]
10. Vallés J, Calbo E, Anoro E, Fontanals D, Xercavins M, Espejo E, et al. Bloodstream infections in adults: importance of healthcare-associated infections. J Infect. 2008; 56:27–34. [PubMed: 18022242]
11. Gasink LB, Lautenbach E. Prevention and treatment of health care-acquired infections. Med Clin North Am. 2008; 92:295–13. [PubMed: 18298980]
12. Giamarellou H. Nosocomial cardiac infections. J Hosp Infect. 2002; 50:91–105. [PubMed: 11846535]
13. Guce L, Pearce M. Hospital-acquired bacterial endocarditis. Arch Intern Med. 1963; 112:56–62. [PubMed: 13951518]
14. Friedland G, von Reyn F, Fevy B, Arbeit R, Dasse P, Crumpacker C. Nosocomial endocarditis. Infect Control. 1984; 5:284–8. [PubMed: 6564081]

15. Terpenning MS, Buggy B, Kauffman CA. Hospital-acquired infective endocarditis. Arch Intern Med. 1988; 148:1601–3. [PubMed: 3382305]

16. Chen S, Dwyer D, Sorrell T. A comparison of hospital and community-acquired infective endocarditis. Am J Cardiol. 1992; 70:1449–1603. [PubMed: 1442617]

17. Martín-Dávila P, Fortún J, Navas E, Cobo J, Jiménez-Mena M, Moya JL, et al. Nosocomial endocarditis in a tertiary hospital: an increasing trend in native valve cases. Chest. 2005; 128:772–9. [PubMed: 16100166]

18. Fernández-Guerrero M, Verdejo C, Azofra M, de Górgolas M. Hospital-acquired infectious endocarditis not associated with cardiac surgery: an emerging problem. Clin Infect Dis. 1995; 20:16–23. [PubMed: 7727642]

19. Lamas CC, Eykyn SJ. Hospital acquired native valve endocarditis: analysis of 22 cases presenting over 11 years. Heart. 1998; 79:442–7. [PubMed: 9659189]

20. Fernández-Hidalgo, Almirante B, Tornos P, Pigrau C, Sambola A, Igual A, Pahissa A. Contemporary epidemiology and prognosis of health care-associated infective endocarditis. Clin Infect Dis. 2008; 47:1278–97.

21. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med. 1994; 96:200–9. [PubMed: 8154507]

22. 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. [PubMed: 10770721]

23. Wang A, Athan E, Pappas PA, Fowler VG, Olaison L, Paré C, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. JAMA. 2007; 297:1354–61. [PubMed: 17392239]

24. Cabell CH, Abrutyn E. Progress toward a global understanding of infective endocarditis. Early lessons from the International Collaboration on Endocarditis investigation. Infect Dis Clin North Am. 2002; 16:255–72. [PubMed: 12092472]

25. Fowler VG, Miró JM, Hoen B, Cabell CH, Abrutyn E, Rubinstein E, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. From the International Collaboration on Endocarditis Prospective Cohort Study. JAMA. 2005; 293:3012–21. [PubMed: 15972563]

26. Morpeth S, Murdoch D, Cabell CH, Karchmer AW, Pappas P, Levine D, et al. Non-HACEK gram-negative bacillus endocarditis. Ann Intern Med. 2007; 18:147:829–35. [PubMed: 18087053]

27. Dickerman SA, Abrutyn E, Barsic B, Bouza E, Cecchi E, Moreno A, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). Am Heart J. 2007; 154:1086–94. [PubMed: 18035080]

28. Chu VH, Woods CW, Miro JM, Hoen B, Cabell CH, Pappas PA, et al. Emergence of coagulase-negative staphylococci as a cause of native valve endocarditis. Clin Infect Dis. 2008; 46:232–42. [PubMed: 18171255]

29. Miró JM, del Río A, Mestres CA. Infective endocarditis in intravenous drug abusers and HIV-1 infected patients. Infect Dis Clin N Am. 2002; 16:273–95.

30. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika. 1986; 73:13–22.

31. Mylonakis E, Calderwood SB. Infective endocarditis in adults. N Engl J Med. 2001; 345:1318–30. [PubMed: 11794152]

32. Bouza E, Menasalvas A, Muñoz P, Vasallo FJ, Moreno MM, García Fernández MA. Infective endocarditis: a prospective study at the end of the twentieth century – new predisposing conditions, new etiologic agents, and still a high mortality. Medicine (Baltimore). 2001; 80:298–307. [PubMed: 11552083]

33. Hoen B, Alla F, Selton-Suty C, et al. Changing profile of infective endocarditis: results of a 1-year survey in France. JAMA. 2002; 288:75–81. [PubMed: 12090865]

34. Cabell CH, Jollis JG, Peterson GE, et al. Changing patient characteristics and the effect on mortality in endocarditis. Arch Intern Med. 2002; 16:90–4. [PubMed: 11784225]

35. Moreillon P, Que Y. Infective endocarditis. Lancet. 2004; 363:139–49. [PubMed: 14726169]

36. Ferreiros E, Nacinovich F, Casabe JH, Modenesi JC, Swieszkowski S, Cortes C, et al. Epidemiologic, clinical, and microbiologic profile of infective endocarditis in Argentina: A

national survey. The Endocarditis Infecciosa en la Republica Argentina–2 (EIRA-2) Study. Am Heart J. 2006; 151:545–52. [PubMed: 16442929]

37. Hill EE, Herijgers P, Claus P, Vanderschueren S, Herregods MC, Peetermans WE. Infective endocarditis: changing epidemiology and predictors of 6-month mortality: a prospective cohort study. Eur Heart J. 2007; 28:196–203. [PubMed: 17158121]
38. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988:128–40. [PubMed: 2841893]
39. Gilleece A, Fenelon L. Increasing incidence of coagulase negative staphylococcal endocarditis. J Infection. 1998; 36:A22.
40. United States Renal Data System. Annual Data Report: Atlas of End-Stage Renal Disease. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD: 2008. URL: http://www.usrds.org/adr.htm
41. Sanabria TJ, Alpert JS, Goldberg R, Pape LA, Cheeseman SH. Increasing frequency of staphylococcal infective endocarditis. Experience at a university hospital, 1981 through 1988. Arch Intern Med. 1990; 150:1305–9. [PubMed: 2353863]
42. Gilleece A, Buckley A, Quigley P, Fenelon L. Infective endocarditis: evaluation of the Duke criteria and transesophageal echocardiography for the diagnosis of endocarditis. J Infection. 1998; 36:A10.
43. Naimi TS, LeDell KH, Como-Sabetti K, et al. Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. JAMA. 2003; 290:2976–84. [PubMed: 14665659]
44. Whitener CJ, Park SY, Browne FA, et al. Vancomycin-resistant *Staphylococcus aureus* in the absence of vancomycin exposure. Clin Infect Dis. 2004; 38:1049–55. [PubMed: 15095205]
45. Tenover FC, Weigel LM, Appelbaum PC, et al. Vancomycin-resistant *Staphylococcus aureus* isolate from a patient in Pennsylvania. Antimicrob Agents Chemother. 2004; 48:275–80. [PubMed: 14693550]
46. Chang S, Sievert DM, Hageman JC, et al. Vancomycin-Resistant *Staphylococcus aureus* Investigative Team. Infection with vancomycin-resistant *Staphylococcus aureus* containing the vanA resistance gene. N Engl J Med. 2003; 348:1342–7. [PubMed: 12672861]
47. Centers for Disease Control. Vancomycin-resistant *Staphylococcus aureus*–New York, 2004. MMWR Morb Mortal Wkly Rep. 2004; 23:322–3.
48. Fernández Guerrero ML, Goyenechea A, Verdejo C, Fernández Roblas R, de Górgolas M. Enterococcal endocarditis on native and prosthetic valves. A review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. Medicine. 2007; 86:366–77.
49. Tleyjeh IM, Steckelberg JM, Murad HS, Anavekar NS, Ghomrawi HM, Mirzoyev Z, et al. Temporal trends in infective endocarditis: a population-based study in Olmsted County, Minnesota. JAMA. 2005; 293:3022–8. [PubMed: 15972564]
50. Gilleece A, Fenelon L. Nosocomial infective endocarditis. J Hosp Infect. 2000; 46:83–8. [PubMed: 11049699]
51. Kourany WM, Miro JM, Moreno A, Corey GR, Pappas PA, Abrutyn E, et al. Influence of diabetes mellitus on the clinical manifestations and prognosis of infective endocarditis: A report from the International Collaboration on Endocarditis Merged Database. Scand J Infect Dis. 2006; 38:613–619. [PubMed: 16857604]
52. Ben-Ami R, Giladi M, Carmeli Y, Orni-Wasserlauf R, Siegman-Igra Y. Hospital-actquired infective endocarditis: should the definition be broadened? Clin Infect Dis. 2004; 38:843–50. [PubMed: 14999629]
53. Bishara J, Leibovici L, Gartman-Israel D, Sagie A, Kazakov A, Miroshnik E, et al. Long-term outcome of infective endocarditis: the impact of early surgical intervention. Clin Infect Dis. 2001; 33:1636–43. [PubMed: 11595978]
54. Vikram HR, Buenconsejo J, Hasbun R, Quagliarello VJ. Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis: a propensity analysis. JAMA. 2003; 290:3207–14. [PubMed: 14693873]

55. Mourvillier B, Trouillet JL, Timsit JF, Baudot J, Chastre J, Regnier B, et al. Infective endocarditis in the intensive care unit: clinical spectrum and prognostic factors in 228 consecutive patients. Intensive Care Med. 2004; 30:2046–52. [PubMed: 15372147]

56. Aksoy O, Sexton DJ, Wang A, Pappas PA, Kourany W, Chu V, et al. Early surgery in patients with infective endocarditis: a propensity score analysis. Clin Infect Dis. 2007; 44:364–72. [PubMed: 17205442]

57. Tleyjeh IM, Ghomrawi HMK, Steckelberg JM, Hoskin TL, Mirzoyev Z, Anaverkar NS, et al. The impact of valve surgery on 6-month mortality in left-sided infective endocarditis. Circulation. 2007; 115:1721–8. [PubMed: 17372170]

APPENDIX

Appendix Table 1

Clinical characteristics and outcomes of patients with non-nosocomial health care-associated native valve endocarditis in patients on hemodialysis vs. patients not on hemodialysis

	Non-hemodialysis (n=115)	Hemodialysis (n=138)	p value
Median age, years (IQR)	60 (42–71)	57(48–68)	0.79
Male	74 (64%)	83 (60%)	0.55
Region:			
- United States	44 (45%)	80 (65%)	< 0.001
- Europe	45 (52%)	28 (38%)	
- Australia/New Zealand	13 (45%)	16 (55%)	
- South America	4 (25%)	12 (75%)	
- Asia/Middle East	10 (83%)	2 (17%)	
Comorbid condition:			
- Diabetes mellitus	22 (19%)	55 (40%)	< 0.001
- Immunosuppressive therapy	26 (23%)	22 (16%)	0.178
- Cancer	31 (27%)	11 (8%)	< 0.001
Dental procedures	13 (14%)	7 (7%)	0.090
Other invasive procedures *	42 (41%)	36 (29%)	0.070
Intravascular access device present at the onset of symptoms:	70 (60%)	129 (93%)	<0.001
- Arterial-venous fistula for hemodialysis	2 (2%)	90 (66%)	<0.001
- Chronic central catheter	21 (18%)	58 (42%)	<0.001
- Short-term central catheter	12 (10%)	14 (10%)	0.96
- Peripherally inserted central catheter	8 (7%)	1 (1%)	0.007
- Peripheral catheter	36 (32%)	0 (0%)	<0.001
Echocardiographic findings:			
- Vegetations	103 (90%)	131 (95%)	0.107
▪ Mitral valve	51 (45%)	77 (56%)	0.081
▪ Aortic valve	43 (38%)	48 (35%)	0.62
▪ Tricuspid valve	18 (16%)	14 (10%)	0.179
▪ Pulmonary valve	0 (0%)	1 (1%)	0.363
- Paravalvular complications	16 (14%)	28 (20%)	0.174
Causative organisms			
- *Staphylococcus aureus*	41 (35%)	66 (48%)	0.045
•Methicillin resistant *S. aureus*	16 (40%)	25 (41%)	0.92

	Non-hemodialysis (n=115)	Hemodialysis (n=138)	p value
- Enterococci	19 (16%)	23 (17%)	0.95
- Coagulase-negative staphylococci	16 (14%)	23 (17%)	0.92
- Viridans group streptococci	19 (16%)	5 (4%)	0.150
- Other microorganisms	31 (27%)	21 (15%)	0.024
Outcomes			
- Surgery this episode	43 (37%)	53 (38%)	0.87
- Congestive heart failure	35 (32%)	41 (30%)	0.85
- Systemic embolization other than stroke	21 (19%)	29 (21%)	0.64
- Stroke	20 (18%)	31 (23%)	0.38
- Persistent bacteremia	12 (11%)	32 (24%)	0.009
- In-hospital mortality	20 (17%)	34 (25%)	0.151

* "Other invasive procedures" include any invasive procedure known to induce bacteremia performed 60 days before symptom onset, excluding dental manipulation.

International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) Investigators

David Gordon MBBS, PhD, Uma Devi MD (Flinders Medical Centre, Adelaide, Australia); Denis Spelman MD (Alfred Hospital, Melbourne, Australia); Jan T.M. van der Meer MD, PhD (University of Amsterdam, Amsterdam, Netherlands);Carol Kauffman MD, Suzanne Bradley MD, William Armstrong MD (Ann Arbor VA Medical Center, Ann Arbor, USA);Efthymia Giannitsioti MD, Helen Giamarellou MD, PhD (Attikon University General Hospital, Athens, Greece);Stamatios Lerakis MD (Emory University, Atlanta, USA);Ana del Rio MD PhD, Asuncion Moreno MD PhD, Carlos A. Mestres MD, PhD, Carlos Paré MD PhD, Cristina Garcia de la Maria PhD, Elisa De Lazzari MSs, Francesc Marco MD PhD, Jose M Gatell MD PhD, José M. Miró MD, PhD, Manuel Almela MD, Manuel Azqueta MD, Maria Jesús Jiménez-Expósito MD PhD, Natividad de Benito MD PhD, Noel Perez MD, Xavier Claramonte MD, Yolanda Armero MD, Carlos Cervera MD, Carlos Falces MD, Magda Heras, MD PhD (Hosp. Clinic – IDIBAPS, University of Barcelona, Barcelona, Spain);Benito Almirante MD, Nuria Fernandez-Hidalgo MD, Pablo Rodriguez de Vera MD, Pilar Tornos MD, Vicente Falcó MD, (Hospital Universitari Vall d'Hebron, Barcelona, Spain);Nisreen Sidani RN, MSN, Souha Kanj-Sharara MD, Zeina Kanafani MD, MS (American University of Beirut Medical Center, Beirut, Lebanon);Annibale Raglio MD, DTM&H, Antonio Goglio MD, Fabrizio Gnecchi MD, Fredy Suter MD, Grazia Valsecchi MD, Marco Rizzi MD, Veronica Ravasio MD (Ospedali Riuniti di Bergamo, Bergamo, Italy);Bruno Hoen MD, PhD, Catherine Chirouze MD, Efthymia Giannitsioti MD, Joel Leroy MD, Patrick Plesiat MD, Yvette Bernard MD (University Medical Center of Besançon, Besançon, France);Anna Casey, Peter Lambert BSc, PhD, DSc, Richard Watkin MBBS, Tom Elliott B.M., B.S., B.Med.Sci., PhD., D.Sc., (Queen Elizabeth Hospital, Birmingham, UK); John Baddley, MD, Mukesh Patel MD, William Dismukes MD (University of Alabama at Birmingham, Birmingham, USA);Angelo Pan MD, Giampiero Caros MD (Spedali Civili - Università di Brescia, Brescia, Italy);Amel Brahim Mathiron MD, Christophe Tribouilloy PhD, MD, Thomas Goissen MD (South Hospital Amiens, Bron Cedex, France);Armelle Delahaye, Francois Delahaye MD, MPH, Francois Vandenesch MD, PhD (Hopital Louis Pradel, Bron Cedex, France);Carla Vizzotti MD, Francisco M. Nacinovich MD, Marcelo Marin MD, Marcelo Trivi MD, Martin Lombardero MD (Instituto Cardiovascular, Buenos Aires, Argentina);Claudia Cortes MD,

José Horacio Casabé MD (Instituto de Cardiología y Cirugía Cardiovascular, Buenos Aires, Argentina);Javier Altclas MD, Silvia Kogan MD (Sanatorio Mitre, Buenos Aires, Argentina);Liliana Clara MD, Marisa Sanchez MD (Hospital Italiano, Buenos Aires, Argentina);Anita Commerford, Cass Hansa MD, Eduan Deetlefs MD, Mpiko Ntsekhe MD, Patrick Commerford MD (Groote Schuur Hospital, Cape Town, South Africa);Dannah Wray MD, MHS, Lisa L. Steed PhD, Preston Church MD, Robert Cantey MD (Medical University of South Carolina, Charleston, USA); Arthur Morris MD (Diagnostic MedLab, Auckland), David Holland MB, ChB, PhD (Middlemore Hospital, Auckland) David Murdoch MD, DTM&H, MSc, Stephen Chambers MD, MSc, (University of Otago, Christchurch and Christchurch Hospital, Christchurch, New Zealand); Kerry Read MB, ChB, (North Shore Hospital, Auckland, New Zealand); Nigel Raymond MB, ChB, (Wellington Hospital, Wellington, New Zealand); Selwyn Lang MB, ChB, (Middlemore Hospital, Auckland, New Zealand) Despina Kotsanas BSc, Tony M. Korman MD (Southern Health, Clayton, Australia);Gail Peterson MD, Paul M. Southern, Jr. MD (UT-Southwestern Medical Center, Dallas, USA);Manisha Shah MD, Roger Bedimo MD, MS (Dallas VA Medical Center, Dallas, USA);Arjun Reddy, Donald Levine MD, Gaurav Dhar MD (Wayne State University, Detroit, USA);Alanna Hanlon-Feeney, Margaret Hannan MD, BCh BAO, MSc, Sinead Kelly MD (Mater Hospitals, Dublin, Ireland);Andrew Wang MD, Christopher H. Cabell MD, MHS, Christopher W. Woods MD, MPH, Daniel J Sexton MD, G Ralph Corey MD, L. Barth Reller MD, Laura Drew RN, BSN, Tahaniyat Lalani MBBS, MHS, Vance G Fowler, Jr MD, MHS, Vivian H Chu MD, MHS (Duke University Medical Center, Durham, USA);Bahram Mazaheri PhD, Carl Neuerburg, Christoph Naber MD (University Essen, Essen, Germany);Eugene Athan MD, Margaret Henry BSc, PhD, Owen Harris MD (Barwon Health, Geelong, Australia);Eric Alestig MD, Lars Olaison MD, PhD, Lotta Wikstrom, Ulrika Snygg-Martin MD (Sahlgrenska Universitetssjukhuset/Östra, Goteborg, Sweden);Johnson Francis MD, DM, K Venugopal MD, DM, Lathi Nair MD, DM, Vinod Thomas MD, DM (Medical College Calicut, Kerla, India); Jaruwan Chaiworramukkun MD, Orathai Pachirat MD, Ploenchan Chetchotisakd MD, Tewan Suwanich, MD (Khon Kaen University, Khon Kaen, Thailand);Adeeba Kamarulzaman MBBS, Syahidah Syed Tamin MD (University of Malaya Medical Center, Kuala Lumpur, Malaysia);Manica Mueller Premru MD, PhD, Mateja Logar MD, PhD, Tatjana Lejko-Zupanc MD, PhD (Medical Center Ljublijana, Ljublijana, Slovenia);Christina Orezzi, John Klein MD (St. Thomas' Hospital, London, UK);Emilio Bouza MD, PhD, Mar Moreno MD, PhD, Marta Rodríguez-Créixems MD, PhD, Mercedes Marín MD, Miguel Fernández MD, Patricia Muñoz MD, PhD, Rocío Fernández, Victor Ramallo MD (Hospital General Universitario Gregorio Marañón, Madrid, Spain);Didier Raoult MD, PhD, Franck Thuny MD, Gilbert Habib MD, FACC, FESC, Jean-Paul Casalta MD, Pierre-Edouard Fournier MD (Faculté de Médecine de Marseille, Marseille, France);Natalia Chipigina PhD, Ozerecky Kirill MD, Tatiana Vinogradova MD, PhD, Vadim P. Kulichenko PhD (Russian Medical State University, Moscow, Russia); O.M. Butkevich PhD (Learning Medical Centre of Russian Presidential Affairs Government, Moscow, Russia);Christine Lion MD, Christine Selton-Suty MD, Francois Alla MD, PhD, Hélène Coyard, Thanh Doco-Lecompte MD (CHU Nancy-Brabois, Nancy, France);Diana Iarussi MD, Emanuele Durante-Mangoni MD, PhD, Enrico Ragone MD PhD, Giovanni Dialetto MD, Marie Françoise Tripodi MD, Riccardo Utili MD, Roberta Casillo MD PhD (II Università di Napoli, Naples, Italy);A. Sampath Kumar MD, Gautam Sharma MD (All India Institute of Medical Sciences, New Delhi, India);Stuart A. Dickerman MD (New York University Medical Center, New York, USA);Alan Street, Damon Peter Eisen MBBS, MD, Emma Sue McBryde MBBS, PhD, Leeanne Grigg (Royal Melbourne Hospital, Parkville, Australia);Elias Abrutyn MD (Drexel University College of Medicine, Philadelphia, USA);Christian Michelet MD, PhD, Pierre Tattevin MD, Pierre Yves Donnio PhD (Pontchaillou University, Rennes, France);Claudio Querido Fortes MD (Hospital Universitario Clementino Fraga Filho/UFRJ, Rio de Janeiro, Brazil);Jameela Edathodu, Mashael Al-Hegelan MD (King Faisal Specialist Hospital & Research Center,

Riyadh, Saudi Arabia);Bernat Font MD, Ignasi Anguera MD, PhD, Joan Raimon Guma MD (Hospitál de Sabadell, Sabedell, Spain);M Cereceda MD, Miguel J. Oyonarte MD, Rodrigo Montagna Mella Md (Hospital Clinico Universidad de Chile, Santiago, Chile);Patricia Garcia MD, Sandra Braun Jones MD (Hosp. Clínico Pont. Universidad Católica de Chile, Santiago, Chile);Auristela Isabel de Oliveira Ramos MD (Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil);Marcelo Goulart Paiva MD, Regina Aparecida de Medeiros Tranchesi MD (Hospital 9 de Julho, São Paulo, Brazil);Lok Ley Woon BSN, Luh-Nah Lum BSN, Ru-San Tan MBBS, (National Heart Centre, Singapore, Singapore);David Rees MD, Pam Kornecny MD, Richard Lawrence MD, Robyn Dever MD (St. George Hospital, Sydney, Australia);Jeffrey Post MD, Phillip Jones MD, Suzanne Ryan MHSc, (The University of New South Wales, Sydney, Australia);John Harkness MD, Michael Feneley MD (St. Vincent's, Sydney, Australia);Ethan Rubinstein MD, LL.B, Jacob Strahilewitz MD (Tel Aviv University School of Medicine, Tel Aviv, Israel);Adina Ionac MD, PhD, Cristian Mornos MD, Stefan Dragulescu MD, PhD (Victor Babes University of Medicine and Pharmacy, Timisoar, Romania); Davide Forno MD, Enrico Cecchi MD, Francesco De Rosa MD, Massimo Imazio MD, Rita Trinchero MD (Maria Vittoria Hospital, Torino, Italy);Franz Wiesbauer MD, Rainer Gattringer MD (Vienna General Hospital, Vienna, Austria);Ethan Rubinstein MD, LLB, Greg Deans MD (University of Manitoba, Winnipeg, Canada);Arjana Tambic Andrasevic MD, PhD, Bruno Barsic MD, PhD, Igor Klinar MD, Josip Vincelj MD, PhD, Suzana Bukovski MD, Vladimir Krajinovic MD (Univ. Hospital for Infectious Diseases, Zagreb, Croatia).

ICE Coordinating Center, Durham, USA

G Ralph Corey MD, Judy Stafford MS, Khaula Baloch BA, Thomas Redick MPH, Tina Harding RN, BSN, Vance G Fowler, Jr MD MHS, Vivian H Chu, MD, MHS

ICE Steering Committee

AW Karchmer MD, Arnie Bayer MD, Bruno Hoen MD, PhD, Christopher H Cabell, MD, MHS, Daniel J Sexton, MD, David T. Durack MD, D Phil, Ethan Rubinstein MD, LLB, G Ralph Corey MD, José M. Miró, MD, PhD, Lars Olaison MD, Phillipe Moreillon MD PhD, Susannah Eykyn MD, Vance G Fowler, Jr, MD, MHS, PhD, Vivian H Chu, MD, MHS

ICE Publications Committee

Andrew Wang MD, Arnie Bayer MD, A W Karchmer MD, Bruno Hoen MD, PhD, Christopher H Cabell, MD, MHS, David Murdoch MD, DTM&H, Eugene Athan MD, G Ralph Corey MD, MHS, José M. Miró, MD, PhD, Vance G Fowler, Jr, MD, MHS, Vivian H Chu, MD, MHS

Ann Intern Med. Author manuscript; available in PMC 2013 April 14.

Table 1

Comparison of demographic characteristics and predisposing factors of endocarditis in patients with health care-associated native valve endocarditis and those with community-acquired infection

	All NVE			Health care-associated NVE		
	Community-acquired (n=1065)	**Health care-associated (n=557)**	**p value**	**Nosocomial (n=303)**	**Non-nosocomial (n=254)**	**p value**
Median age, years (IQR)	58 (44–71)	63 (50–73)	< 0.001	66 (52–75)	58 (46–69)	< 0.001
Male	769/1063 (72%)	352/557 (63%)	< 0.001	195/303 (64%)	157/254 (62%)	0.001
Region:						
- United States	133/324 (41%)	191/324 (59%)	< 0.001	67/191(35%)	124/191 (65%)	< 0.001
- Europe	511/734 (70%)	223/734 (30%)		15/27 (56%)	12/27 (44%)	
- South America	120/164 (73%)	44/164 (27%)		28/44 (64%)	16/44 (36%)	
- Australia/New Zealand	249/318 (78%)	69/318 (22%)		40/69 (58%)	29/69 (42%)	
- Asia/Middle East	47/74 (64%)	27/74 (36%)		150/223 (67%)	73/223 (33%)	
Comorbid condition:						
- Hemodialysis	NA *	166/556 (63%)	NA *	28/302 (9%)	138/254 (54%)	< 0.001
- Diabetes mellitus	142/1064 (13%)	137/551 (25%)	< 0.001	60/301 (20%)	77/250 (31%)	0.003
- Cancer	74/1062(7%)	88/557 (16%)	< 0.001	46/303 (15%)	42/254 (17%)	0.66
- Immunosuppressive therapy	44/1057 (4%)	81/556 (15%)	< 0.001	33/303 (11%)	48/253 (19%)	0.007
Cardiac predisposing conditions:						
- Valvular disease †	404/1057 (38%)	187/552 (34%)	0.086	114/300 (38%)	73/252 (29%)	0.026
- History of congenital heart disease	8/949 (1%)	6/518 (1%)	0.42	5/284 (2%)	1/234 (0.4%)	0.158
- Previous IE episode	41/1065 (4%)	17//556 (3%)	0.55	10/302 (3%)	7/254 (3%)	0.71
Dental procedures	117/904 (13%)	37/436 (8%)	0.017	17/245 (7%)	20/191 (10%)	0.189
Other invasive procedures ‡	70/999 (7%) §	214/509 (42%)	<0.001	136/283 (48%) **	78/226 (35%) ††	0.002
Intravascular catheter present at the onset of symptoms:	NA ‡‡	271/557 (49%)	NA ‡‡	134/303 (44%)	137/254 (54%)	0.022
- Peripheral catheter	NA	102/548 (19%)	NA	66/298 (22%)	36/250 (14%)	0.020
- Short-term central catheter	NA	103/556 (19%)	NA	24/303 (8%)	79/253 (31%)	<0.001
- Chronic central catheter	NA	89/554 (16%)	NA	63/302 (21%)	26/252 (10%)	<0.001
- Peripherally inserted central catheter	NA	23/547 (4%)	NA	14/296 (5%)	9/251 (4%)	0.51

IE = infective endocarditis; IQR = interquartile ranges; NA= not applicable; NVE=native valve endocarditis

[*] Study definition of community-acquired infection excludes the possibility of having an intravascular catheter.

[†] "Valvular disease" refers to known underlying valvular heart disease (valve stenosis or regurgitation, usually related to rheumatic heart disease or degenerative lesions)

[‡] "Other invasive procedures" include any invasive procedure known to induce bacteremia performed 60 days before symptom onset, excluding dental manipulation. More than one procedure can have been performed to each patient

[§] Invasive procedures included: colonoscopy 17 (24%), urologic manipulations 12 (17%), esophagogastroduodenoscopy 11 (16%), other 30 (43%)

[**] Invasive procedures included: urologic manipulations 19 (14%), esophagogastroduodenoscopy 12 (9%), colonoscopy 9 (7%), cardiac catheterization 9 (7%), pacemarker implantacion 8 (6%), coronary artery bypass graft surgery 6 (4%), angiography (other than cardiac) 4 (3%), other 69 (51%)

[††] Invasive procedures included: colonoscopy 10 (13%), chronic central catheter insertion 9 (12%), arteriovenous fistula for hemodialysis 8 (10%), esophagogastroduodenoscopy 6 (8%), urologic manipulations 4 (5%), vascular surgery 3 (4%), other 38 (49%)

[‡‡] Study definition of community-acquired infection excludes the possibility of undergoing hemodialysis.

Table 2

Clinical and echocardiographic findings of patients with health care-associated native valve endocarditis and comparison with those with community-acquired endocarditis

	All NVE			Health care-associated NVE		
	Community-acquired (n=1065)	**Health care-associated (n=557)**	**p value**	**Nosocomial (n=303)**	**Non-nosocomial (n=254)**	**p value**
Clinical findings at presentation:						
- Fever	913/945 (96%)	461/489 (94%)	0.23	257/273 (94%)	204/216 (94%)	0.89
- New murmur or worsening of old murmur	609/881 (69%)	272/456 (60%)	0.001	137/250 (55%)	135/206 (66%)	0.020
- Vascular/immunologic evidence of endocarditis *	275/1028 (27%)	117/538 (22%)	0.030	62/289 (21%)	55/249 (22%)	0.86
- Splenomegaly	131/1027 (13%)	44/537 (8%)	0.007	27/288 (9%)	17/249 (7%)	0.28
Echocardiographic findings:						
Vegetations:	952/1058 (90%)	510/554 (92%)	0.173	276/301 (92%)	324/253 (92%)	0.73
- Mitral valve	503/1049 (48%)	277/547 (51%)	0.31	149/297 (50%)	128/250 (51%)	0.81
- Aortic valve	474/1049 (45%)	193/547 (35%)	<0.001	102/297 (34%)	91/250 (36%)	0.62
- Tricuspid valve	76/1048 (7%)	85/547 (16%)	<0.001	53/297 (18%)	32/250 (13%)	0.105
- Pulmonary valve	15/1048 (1%)	4/547 (1%)	0.22	3/297 (1%)	1/250 (0.4%)	0.40
Paravalvular complications †	245/1044 (23%)	107/545(20%)	0.081	63/293 (22%)	44/252 (17%)	0.23

NVE=native valve endocarditis

* Includes Osler nodes, Janeway lesions, Roth spots, conjunctival hemorrhage, or vascular embolic events.

† Paravalvular complications include abscess, valvular perforation, or cardiac fistula.

Table 3

Etiologic agents in patients with community-acquired and health care-associated native valve endocarditis

	All NVE			Health care-associated NVE		
	Community-acquired (n=1065)	**Health care-associated (n=557)**	**p value**	**Nosocomial (n=303)**	**Non-nosocomial (n=254)**	**p value**
Staphylococcus aureus	210 (20%)	248 (45%)	<0.001	141 (47%)	107 (42%)	0.30
• Methicillin-resistant *S. aureus*	25/210 (12%)	117/248 (47%)	<0.001	76/141 (57%)	41/107 (41%)	0.014
Enterococci	92 (9%)	84 (15%)	<0.001	42 (14%)	42 (17%)	0.38
Coagulase-negative staphylococci	67 (6%)	75 (13%)	<0.001	36 (12%)	39 (15%)	0.23
Viridans group streptococci	293 (28%)	47 (8%)	<0.001	33 (11%)	14 (6%)	0.023
Other microorganisms	285 [*] (27%) [‡]	103 (18%)	<0.001	37 (12%) [*]	36 (14%) [†]	0.27
No growth	118 (11%)	30 (5%)	<0.001	14 (5%)	16 (6%)	0.45

[*] Microorganisms included: *Streptococcus bovis* 8 (3%); yeast 6 (2%); anaerobes microorganisms 5 (2%); non-fermenter gram negative microorganisms 3 (1%); *Corynebacterium* spp. 2 (1%)

[†] Microorganisms included: *S. bovis* 7 (3%); anaerobes microorganisms 5 (2%); yeast 4 (2%); non-fermenter gram negative microorganisms 4 (2%); *Corynebacterium* spp. 4 (2%)

[‡] Microorganisms included: *S. bovis* 102 (10%); beta haemolyticus streptococci 58 (5%); HACEK organisms 27 (3%); *Streptococcus pneumoniae* 22 (2%); other streptococci 14 (1%); anaerobes microorganisms 10 (1%); nutritionally variant streptococci 7 (0.7%); *Gemella* spp. 7 (0.7%).

Table 4

Comparison of complications and outcome of patients with health care-associated and community-acquired native valve endocarditis

	All NVE			Health care-associated NVE		
	Community-acquired (n=1065)	**Health care-associated (n=557)**	**p value**	**Nosocomial (n=303)**	**Non-nosocomial (n=254)**	**p value**
Surgery	543/1063 (51%)	225/555 (41%)	<0.001	129/302 (43%)	96/253 (38%)	0.25
Complications and outcome						
• Congestive heart failure	354/1047 (34%)	197/539 (37%)	0.278	121/293 (41%)	76/246 (31%)	0.012
• Non CNS systemic embolization	253/1038 (24%)	115/542 (21%)	0.159	65/295 (22%)	50/247 (20%)	0.61
• Stroke	182/1045 (17%)	109/542 (20%)	0.188	58/296 (20%)	51/246 (21%)	0.74
• Persistent bacteremia	41/1034 (4%)	98/542 (18%)	<0.001	54/295 (18%)	44/247 (18%)	0.88
• Intracardiac abscess	134/1038 (13%)	63/539 (12%)	0.487	37/294 (13%)	26/245 (11%)	0.48
• New conduction abnormality	85/1035 (8%)	42/535 (8%)	0.80	19/291 (7%)	23/244 (9%)	0.22
In-hospital mortality	143/1065 (13%)	138/557 (25%)	<0.001	84/303 (28%)	54/254 (21%)	0.094

Table 5

Univariate and multivariate risk factors of mortality in patients with healthcare-associated and community-acquired native valve endocarditis

	Crude analysis		Adjusted analysis*	
	Incidence risk ratio (95% CI)	**p value**	**Incidence risk ratio (95% CI)**	**p value**
Route of acquisition:				
• Community	1		1	
• HCA NVE	1.75 (1.4; 2.19)	p<0.00	1.29 (1.03–1.61)	0.025
HCA NVE				
• Nosocomial	1.96 (1.54; 2.50)†	p<0.00		
• Non-nosocomial healthcare-associated	1.48 (1.09; 2.01)†	p<0.00		
Age (≥60 years)	1.84 (1.54–2.21)	<0.001	1.48 (1.23–1.78)	<0.001
Male	0.78 (59–1.04)	0.087		
Hemodialysis	1.62 (1.21–2.17)	<0.001		
Diabetes	1.89 (1.46–2.45)	<0.001	1.52 (1.10–2.11)	0.012
Cancer	1.49 (1.14–1.86)	0.004		
Immunosuppressive therapy	1.50 (1.21–1.86)	0.001		
Dental procedures	0.26 (0.14–0.50)	<0.001		
Other invasive procedures	1.77 (1.39–2.25)	<0.001		
S. aureus	1.98 (1.59–2.47)	<0.001	1.57 (1.24–1.99)	<0.001
Paravalvular abscess	1.51 (1.20–1.92)	0.001	1.53 (1.16–2.01)	0.002
Surgery	0.64 (0.50–0.83)	0.001	0.70 (0.56–0.86)	0.001
Stroke	2.25 (1.84–2.76)	<0.001	2.00 (1.57–2.54)	<0.001
Congestive heart failure	2.68 (2.16–3.31)	<0.001	2.53 (2.04–3.14)	<0.001
Persistent bacteremia	2.67 (2.15–2.31)	<0.001		
New conduction abnormality	1.49 (1.04–2.15)	0.031		

CI= confidence interval, HCA=health care-associated; NVE=native valve endocarditis

*Sample size for the adjusted estimates: 1464 cases of native valve endocarditis.

†The comparison between the IRR of mortality of non-nosocomial vs. nosocomial health care-associated native valve endocarditis produced a significance p-level of 0.07 (IRR=0.76; CI 0.57–1.02).