

## Risk Factors Associated with Endocarditis without Underlying Heart Disease

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Infective endocarditis (IE) pathogenesis has changed in the last decades and there is an increasing number of patients without predisposing heart condition. The aim of this study is to assess the clinical features of these non-drug addict patients affected with IE without underlying heart disease and to identify the potential risk factors. From 196 cases of IE, 49 (25% of the series) occurred in patients without underlying heart disease. A presumed portal of entry was identified in the majority (26 cases). The most frequent were digestive (6 cases), haemodialysis (6 cases) and central venous catheters (4 cases). Right heart valves were more often affected (29% vs 6%;  $P < .01$ ). The distribution of the causative microorganism showed a higher proportion of *Staphylococcus* (57% vs 30%). Despite a similar in-hospital complication rate and a similar need of surgery during the active phase, their prognosis is better than in those with underlying heart disease.

**Key words:** Endocarditis. Underlying heart disease.

### Factores de riesgo asociados a endocarditis sin cardiopatía predisponente

La patogenia de la endocarditis infecciosa (EI) ha cambiado en las últimas décadas, siendo cada vez mayor el número de casos sin cardiopatía predisponente. El objetivo de este trabajo es conocer las características de los pacientes no drogadictos afectados de EI sin cardiopatía predisponente e identificar los posibles factores de riesgo para la infección. De 196 casos de EI, 49 (25%) ocurrieron en pacientes sin cardiopatía predisponente. Se identificó en la mayoría (26 casos) un factor de riesgo para la infección, predominando las enfermedades digestivas (6 casos), hemodiálisis (6 casos) y catéteres venosos centrales (4 casos). La infección se localizó con mayor frecuencia en las válvulas derechas (29 frente a 6%;  $p < 0,01$ ), siendo el microorganismo más frecuente *Staphylococcus* spp. A pesar de una tasa de complicaciones y de necesidad de cirugía en la fase activa similares, el pronóstico de estos pacientes parece ser mejor que en aquellos con cardiopatía predisponente.

**Palabras clave:** Endocarditis. Cardiopatía predisponente.

## INTRODUCTION

The pathogenesis of infective endocarditis (IE) typically includes the formation of a sterile thrombus plaque over an endocardial lesion that is generally secondary to underlying heart disease (HD) (non-bacterial thrombotic endocarditis).<sup>1</sup> Social as well as medical changes that have occurred over the last decades have contributed to the changing pathology of this disease.<sup>2-5</sup> The incidence of endocarditis without underlying HD has changed for many reasons, such as

the disappearance of rheumatic HD, the increase in parenteral drug abuse, and the advent of immunosuppression, although the real scope of this change, with the exception of drug addiction, has not been studied.<sup>6</sup> We studied a prospective series of 196 patients with episodes of IE who were not addicted to intravenous drugs in our centers between 1987 and 1999 to evaluate the possible risk factors for infection and the differential characteristics of endocarditis without pre-existing HD.

## PATIENTS AND METHODS

This was a prospective study of all consecutive cases of patients with IE not addicted to intravenous drugs who had been diagnosed and treated in our centers between 1987 and 1999. For IE diagnosis, the criteria of Von Reyn et al<sup>7</sup> were used from 1987 to

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1994; these were subsequently replaced by the criteria of Durack et al<sup>8</sup> Parenteral drug-addicted patients were excluded from the study. The diagnosis of early prosthetic endocarditis was made when the episode occurred within 12 months following cardiac surgery, and late prosthetic endocarditis when it occurred more than a year after surgery. Mortality was considered nosocomial if it occurred during the 6 weeks after diagnosis

### Statistical analysis

All qualitative variables are expressed in percentages and quantitative values by mean $\pm$ 1 standard deviation. The differences between the distinct patient groups were evaluated by Fisher's exact t test for the qualitative variables and Student's t test for the quantitative data. A value of  $P<.05$  was considered significant.

### RESULTS

The median age of the 196 patients was 47 years ( $\pm 19$  years), and 65% were men. In 133 cases (68%), the IE was of a native valve and of a prosthetic valve in the remaining 63 (30 early and 33 late). The causative microorganism was most frequently *Staphylococcus* (37%) and *Streptococcus* (34%), although no microorganism could be identified in 10% of the cases. Fifteen (8%) patients had experienced 1 or more previous episodes of endocarditis, and 13 patients had a new episode of prosthetic valve IE. Of the 133 native valve IE cases, 49 occurred in patients with underlying HD (37% of IE in native valves and 25% of the total). Of these 49 patients, 35 (71%) had

the infection in the left side of the heart and 14 in the right. The incidence of IE without underlying HD in the study group increased from 15% between 1987 and 1991 to 29% between 1992 and 1999 ( $P<.05$ ). In 26 (53%) of these 49 patients possible causative factors were disease of the digestive tract (6 patients: 3 with cirrhosis, 2 with ulcerative colitis, and 1 with adenocarcinoma of the colon), chronic renal insufficiency on dialysis (6 patients), permanent implanted pacemakers (5 patients), central venous catheters (4 patients), severe psoriasis (2 patients), HIV infection in a non drug-addicted patient (1 patient), cutaneous abscesses (1 patient), and sideroblastic anemia (1 patient). The infection was localized to the right side of the heart more frequently in patients without underlying HD than those with the disease (29% as opposed to 6%, respectively,  $P<.01$ ) (Table 1). The causative microorganism was more frequently *Staphylococcus* in patients without underlying HD and *streptococcus* in patients with HD ( $P<.05$ ) (Table 1). We found a higher prevalence of chronic renal insufficiency with dialysis in patients without underlying HD than those with HD (12% as opposed to 1%, respectively;  $P<.05$ ) (Table 2). An echocardiogram was performed on all patients, and bacterial growth was found in 86% of patients with HD as opposed to 96% of patients without HD (no significant difference). Cardiac and non-cardiac complications during the active phase of the disease were the same in both endocarditis subtypes (75% of patients without HD and 77% of patients with HD). The need for surgery in the active phase of the disease was almost the same for both subgroups (49% vs 50%, respectively; nonsignificant). The predominant indication for surgery was failure to control infection

TABLE 1. General characteristics in 196 cases of infective endocarditis in nondrug-addicted patients

	Without heart disease, No.=49 (%)	With heart disease, No.=147 (%)	P
Age, y	43 $\pm$ 21	49 $\pm$ 19	NS
Sex, m	31 (64)	101 (69)	NS
Underlying heart disease			
Prosthetic implant	–	64 (43)	
Rheumatic	–	51 (35)	
Congenital	–	12 (8)	
Degenerative	–	20 (14)	
Location			0.01
Mitral	18 (37)	69 (47)	
Aortic	17 (34)	69 (47)	
Other	14 (29)	9 (6)	
Type of germ			0.05
Coagulase-positive <i>Staphylococcus</i>	24 (48)	30 (20)	
Coagulase-negative <i>Staphylococcus</i>	4 (8)	14 (10)	
<i>Streptococcus viridians</i>	4 (8)	41 (28)	
Enterococcus	7 (14)	13 (9)	
Nonidentified	2 (4)	19 (13)	

TABLE 2. Risk factors identified in 196 patients with infective endocarditis

	Without underlying heart disease, No.=49(%)	With underlying heart disease, No.=147 (%)	P
Immunosuppressive therapy	–	–	–
Chronic renal insufficiency	6 (12)	2 (1)	< 0,05
Diabetes mellitus	5 (10)	10 (7)	NS
Cancer	1 (2)	2 (1)	NS
Cutaneous illnesses	2 (4)	1 (1)	NS
Collagen disease	–	1 (1)	NS
Severe COPD	2 (4)	8 (5)	NS

COPD indicates chronic obstructive pulmonary disease.

with antibiotic treatment in the group without heart disease (HD) and severe cardiac insufficiency secondary to valve or prosthetic failure in the group with HD. Patients without HD had a lower nonsocomial mortality rate (5 of 49 patients [10%] as opposed to 32 of 147 patients[22%];  $P<.05$ ). There was no difference in the mortality rate in patients without underlying heart disease regarding the location of the infection (3 patients [9%] with left endocarditis vs 2 patients [14%] with right endocarditis). Of the patients with right endocarditis who died (2), 1 had a pacemaker and died of malignant ventricular arrhythmia immediately postsurgery and the other had an infection related to manipulation of a central venous catheter.

## DISCUSSION

The risk of developing an episode of IE depends on factors related to the affected patient and to specific dental, surgical, and therapeutic procedures that cause transient bacteremias of microorganisms commonly associated with IE. The predisposing factors (considered minor clinical criterion in the Duke<sup>8</sup> model) include, in addition to intravenous drug addiction, valvular lesions of both the native valve (of congenital, rheumatic, or degenerative origin) and the prosthetic valve (biological or mechanical). The literature, on the other hand, describes numerous risk factors, such as poor dental hygiene, chronic alcoholism, and diseases which cause immunological changes such as systemic lupus erythematosus, diabetes mellitus, renal insufficiency, cancer, or chronic inflammatory intestinal disease.<sup>1,2</sup> The number of IE cases with no previous underlying valvular HD varies in published studies (from 3% to 58%).<sup>3-5,7-12</sup> This range could, in part, be due to a disparity among patient selection criteria, such as whether or not patients had prostheses, were intravenous drug addicts, or who were children were included. Recent studies show the toll on IE patients without underlying HD tends to be higher,<sup>4,3-16</sup> surpassing mitral valve prolapse (the second most prevalent group), in total

nonprosthetic endocarditis.<sup>5</sup> This increase has only been explained by the decrease in the incidence of rheumatic HD, (during our 13-year study the incidence of rheumatic HD was unchanged), but is probably also due to the greater incidence of risk-associated factors such as diabetes mellitus, chronic inflammatory intestinal disease, and chronic renal insufficiency.<sup>17</sup> Of all the risk factors studied in our series, only chronic renal insufficiency with dialysis was significantly more frequent in patients without HD, and we were unable to differentiate whether the risk factor was chronic renal insufficiency, an immunosuppressive disease, *per se*, or dialysis creating a risk of infection by microorganisms of cutaneous origin. The cutaneous lesions and venous catheters are also risk factors for episodes caused by microorganism that are typically cutaneous (*S aureus*, *S coagulasa-negative*, *Streptococcus* groups A and B, and *erysipelothrux*)<sup>17</sup>. In our series, 5 patients had permanent pacemakers, 4 had central venous catheters, 2 had been diagnosed with severe psoriasis, and 1 had a cutaneous abscess. In all these patients, *Staphylococcus* was identified in blood cultures; therefore, the greater prevalence of *Staphylococcus* infection in patients without HD (57% as opposed to 30%) was probably related to the infection's cutaneous origin. This data concurs with another study,<sup>3</sup> in which IE was caused by *Staphylococcus* in 40% of patients without HD, as opposed to 26% of patients with HD. The localization of infection to the right side of the heart with greater frequency in patients without HD may be related to the above possible risk factors, fundamentally pacemakers and central venous catheters (9 of the 14 cases of right endocarditis). The greater benefit of echocardiogram in patients without HD may be due, in part, to a greater right localization of the infection and, on the other hand, to the fact that the group of patients with HD included those with prosthetic IE. In addition, the absence of cardiac lesions and the evidence of microorganism growth on echocardiogram, are nearly indispensable for the diagnosis of endocarditis, which supposes a baseline skew. The prognosis for endocarditis without

underlying HD is better, including for the subgroup with left endocarditis. This improved prognosis may be attributed at least in part to the fact that patients with prosthetic endocarditis are included in the group with endocarditis with underlying HD, and this illness is known to have a worse prognosis. Nevertheless, as we noted in a previous study,<sup>10</sup> we found no difference in the mortality rate between the group with native valve endocarditis with HD and the group with prosthetic endocarditis (22% in both subgroups) due to the low mortality rate of patients with late prosthetic endocarditis (8%), which is greater than in patients with native valve endocarditis.

In conclusion, chronic renal insufficiency, digestive disease, and the use of venous catheters are the most frequent risk factors for the development of infective endocarditis in patients without underlying HD. In spite of the complication rate and the need for surgery in the similar active phase of the disease, the prognosis for these patients appears to be better.

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