Risk Factors Associated with Endocarditis without Underlying Heart Disease

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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). Social as well as medical changes that have occurred over the last decades have contributed to the changing pathology of this disease. 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. 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 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 were used from 1987 to
1994; these were subsequently replaced by the criteria of Durack et al.\textsuperscript{8} 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±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 (±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 *Staphyloccus* 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 |
|-------------------------------------------------|-------------------------------------------------|-----|
| Age, y                                          | Without heart disease, No.=`49 (%)              | With heart disease, No.=`147 (%)              | P   |
| Sex, m                                          | 43±21                                           | 49±19                                       | NS  |
| Underlying heart disease                        | 31 (64)                                         | 101 (69)                                   | NS  |
| 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 *Staphylococcus*              | 24 (48)                                         | 30 (20)                                    |     |
| Coagulase-negative *Staphylococcus*              | 4 (8)                                           | 14 (10)                                    |     |
| *Streptococcus* viridans                        | 4 (8)                                           | 41 (28)                                    |     |
| Enterococcus                                    | 7 (14)                                          | 13 (9)                                     |     |
| Nonidentified                                   | 2 (4)                                           | 19 (13)                                    |     |
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\(^4\)
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.\(^1,2\) The number of IE
cases with no previous underlying valvular HD varies
in published studies (from 3% to 58%).\(^3,5,7-12\) 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,\(^3,5-16\) surpassing mitral valve
prolapse (the second most prevalent group), in total
nonprosthetic endocarditis.\(^5\) 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.\(^1,7\) 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 \(erysipelo-thrix\))\(^7\). 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,\(^3\) 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

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

<table>
<thead>
<tr>
<th>Without underlying heart disease, No.=49(%)</th>
<th>With underlying heart disease, No.=147 (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressive therapy</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>6 (12)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (10)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Cutaneous illnesses</td>
<td>2 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Collagen disease</td>
<td>–</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Severe COPD</td>
<td>2 (4)</td>
<td>8 (5)</td>
</tr>
</tbody>
</table>

COPD indicates chronic obstructive pulmonary disease.
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, 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.

REFERENCES