

Long-term outcome of patients with non-operated prosthetic valve infective endocarditis: is relapse the main issue?

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Abstract

In non-operated prosthetic valve endocarditis (PVE), long term outcome is largely unknown. We report the follow-up of 129 non-operated patients with PVE alive at discharge. At one year, the mortality rate was 24%, relapses and reinfection were rare (5% each). Enterococcal PVE was associated with a higher risk of relapse.

Key-words:

Infective endocarditis – Prosthetic valve – Relapse – Surgery

Text

INTRODUCTION

Prosthetic valve endocarditis (PVE) is associated with a well-known high in-hospital mortality rate (20-30%) [1,2]. However, the late outcome could also represent a major concern considering that the mortality in the year following discharge ranges from 10 to 20% [1,3]. Although surgery is generally considered the best option when PVE causes severe prosthetic dysfunction or heart failure, some studies indicate that early valve replacement may not always lead to better outcome in patients with PVE [1,3]. Therefore, both European (ESC) and American (IDSA) guidelines indicate that surgery for PVE should follow the general principles outlined for native valve endocarditis (NVE) [4,5] and surgery was performed in only 50% of patients with PVE in the International Collaboration on Endocarditis-Pro prospective Cohort Study, a similar rate as for patients with NVE [1,2].

However, there are very limited data regarding the long-term outcome in PVE patients who do not undergo surgical treatment. Considering that the affected population, microbiological epidemiology and management of IE have evolved these last years, this data should also be updated to reflect the current prognosis of these patients [1]. Because studies are rare and mainly focused on the intra-hospital prognosis of these patients [2], the rate of relapse and reinfection after medical treatment has been completed is unknown in this particular population.

The objective of our study is therefore to describe the outcomes of non-operated PVE patients focusing on the risks of relapse, reinfection and mortality.

MATERIAL AND METHODS

An observational cohort study of definite or possible endocarditis according to the Duke criteria was designed in 3 French referent centers: Bordeaux, Nantes and Rennes University Hospitals. Adult patients with PVE confirmed by endocarditis team and managed without surgical treatment from January 2013 to December 2017 were included. Patients were excluded if they had cardiovascular implantable electronic devices (CIED), if the infection was due to obligate intracellular bacteria and if they died during the antibiotic therapy of IE (6 weeks).

Primary endpoints were infection relapse, reinfection and mortality during the year following the diagnosis of IE. Two types of recurrence are distinguishable: relapse and reinfection [4]. Relapse was defined as an additional episode of IE caused by the same microorganism with the same antibiotic susceptibility test. Reinfection was defined as an additional episode of IE caused by a different microorganism after the initial episode.

Clinical, microbiological, radiological data and surgical indications (endocarditis team decision) were obtained from a review of the patients' medical records. The patients surviving the initial treatment or their physicians were contacted one year after the diagnosis to obtain follow-up data: this included reinfection, relapse or death. The study was approved by the local ethics committee. Patients were informed of the study in accordance with French legal standards.

Data analysis was performed using the R software (v3.2.2). Estimates of frequencies and medians were calculated for categorical and continuous variables respectively. Bivariate analyses were performed using Student-t test and Fisher test with a standard significance level of $p < 0.05$.

RESULTS

We screened 1,316 consecutive patients with infective endocarditis confirmed by endocarditis team (supplementary figure 1): the reasons for exclusion were NVE (861 cases), PVE with surgical treatment or death before the end of the curative treatment (219 cases), presence of a CIED (100 cases) and infection due to obligate intracellular parasite (7 cases). Finally, 129 PVE patients meeting inclusion criteria were included. Table 1 shows clinical and laboratory findings of the population. The median age was 77 years (25th–75th percentile, 69-84 years). The median Charlson comorbidity index was 6 (25th–75th percentile, 4-8). Organisms included streptococci (43%), staphylococci (23%), enterococci (18%). Eighty-four patients had biological valves (65.1%), 26 patients had mechanical valves (20.2%) and 19 patients had transcatheter aortic valve replacement (14.7%). A history of endocarditis was reported in 22 of the 129 patients (17.1%). Embolic events occurred in 66 patients (51.2%) mostly in the central nervous system (25.6%, 33/129). Seventy-three patients (56.6%) had no surgery despite a standard indication, 55 patients (44%) had comorbidities or high surgical risk documented as the reason for conservative management and one patient declined surgical treatment due to personal preference.

Follow-up was achieved in all patients included. We observed 14 recurrences of PVE including 7 relapses and 7 reinfections. Four relapses were due to *E. faecalis* (39, 263, 301 and 353 days after the first episode), one to *S. aureus* (22 days), one to *S. gallolyticus* (208 days) and one to *S. maltophilia* (38 days). In bivariate analysis, enterococcal PVE was the only factor associated with a higher risk of relapse compared to other pathogens (respectively 17.4% versus 2.8%, OR=7.1; CI95% 1.1-52.1; p=.02). Of the 22 patients who had a previous history of endocarditis, 4 had a recurrence (18.2%) and 2 had a relapse (9.1%).

In the 129 patients, the one-year mortality rate was 24% (31/129) and was lower in patients without surgical indication than in patients with indication but non-operated because of comorbidities (16.4% vs 33.9%, p=.02). In bivariate analysis, factors associated with one-year mortality were perivalvular complications (p=.002) and embolic lesions (p=.02) at baseline. Estimated overall mortality was not significantly different between patients with *Staphylococcus aureus* PVE versus others pathogens (21.1% vs 24.5%; p=.74).

DISCUSSION

The current recommendations suggest that PVE patients with no surgical treatment require close follow-up because of the risk of late events [4] but recent data are lacking. To the best of our knowledge, our series provides the most detailed description of relapse, reinfection and mortality in non-operated PVE patients.

Studies on recurrence in IE are rare and confusion between relapse and reinfection is frequent [6,7]. Some studies suggest that relapse rate in PVE may be higher than in NVE [8]. Despite the inclusion of patients expected to have a high risk of relapse in our study (PVE, no surgery, co-morbidities [4]), relapse was uncommon (5.4%). When comparing our current results with those previously reported, we found the same relapse rate as in recent studies ranging from 5.6% to 6.5% [9,10]. Interestingly, we confirm that *Enterococcus* is associated with a significantly higher risk of relapse. These results are consistent with the study of Iversen *et al.* where 6.2% of patients with enterococcal IE (NVE/PVE, operated or not) relapsed (6/97) versus 1.3% with other pathogen (4/303) [10].

In our study, the reinfection rate was relatively low possibly due to a follow-up limited to one year. In the study of Mansur *et al.* where 420 patients with IE were included (80 with PVE, mean follow-up of 6.1 years), 11.4% of patients had reinfection [8]. Unlike relapse risk factors, the factors of reinfection are well studied and are the same as those of first episode: presence of a mechanical valve, age, male sex, history of IE, intravenous drug use, chronic dialysis [4,8]. In a meta-analysis of 32 studies by Mihos *et al.* recurrence between operated and non-operated patients with PVE was not different (RR 0.38 CI95% (0.12-1.23)) contrary to the 30-day mortality which was higher among patients with non-operated PVE (25% versus 34%; RR, 0.73; 95% CI, 0.64–0.82; I^2 , 42%; $p < .001$) [11]. However, recurrence data were only available for 58 non-operated patients out of 2,636 patients with PVE.

In our study, we found that the risk of one-year mortality is relatively low in patients who did not have any indication for surgery during the antibiotic therapy of IE (16%). Small studies have already shown that patients with hemodynamically stable PVE could be treated with antibiotics alone [12]. We therefore provide original long-term follow-up data with a large number of patients and close monitoring of relapses to support these findings and confirm the importance of a careful selection of patients for surgery by endocarditis team.

Our studies have limitations. First, although comparable to previous studies, this study is limited by the small sample size. Second, there was no control group who underwent surgery. Third, we do not have the causes of death in our cohort. Third, streptococci were particularly frequent in our cohort and the number of drug users was particularly low: these two characteristics may limit the generalizability of the findings in other countries and continents. Last, to define relapse, the literature is inconsistent about the time between the first and second episodes with the same micro-organism with definitions ranging from 3 to 12 months [4,7,9]. We chose a maximal delay of one year after the initial endocarditis to avoid

underestimating relapse rate. Furthermore, we did not use molecular methods to distinguish relapse from reinfection with a different strain of the same species.

This study adds some knowledge to our current understanding of non-operated PVE: the late mortality in IE was not the result of relapses. The mortality rate was low in PVE with absence of surgical indication and was lower than expected in patients with indication. We can therefore conclude that (i), very selected PVE could be treated safely with antibiotics alone, (ii) follow-up should focus on co-morbidities management and reinfection prevention, (iii) the risk of relapse in case of enterococcal IE should be considered for therapeutic decisions.

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Conflict of Interest

All authors: No Potential conflicts of interest. All authors have submitted the ICMJE form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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TABLE

Table 1. Main characteristics of the 129 patients with non-operated prosthetic valve endocarditis with a focus on patients with relapse, reinfection and death^a.

	All patients n=129	Relapse n=7/129 (5.4%)	Reinfection n=7/129 (5.4%)	Death n=31/129 (24.0%)
Demographics				
Age, y	77 [69-84] ^b	81 [77.5-84.5] ^b	83 [65-85] ^b	78 [72.5-81.5] ^b
Male sex	102 (79.1)	7 (100)	7 (100)	23 (74.2)
Comorbidities				
Charlson index	6 [4-8] ^b	7 [5-8] ^b	5 [4.5-6.5] ^b	7 [5-8] ^b
Injection drug use	3 (2.3)	0	1 (14.3)	0
Healthcare associated	22 (17.1)	1 (14.3)	0	7 (22.6)
Duke classification				
Definite IE	109 (84.5)	6 (85.7)	4 (57.1)	27 (87.1)
Type of prosthesis				
Mechanical	26 (20.2)	2 (28.6)	1 (14.3)	7 (22.6)
Bioprothetic ^c	84 (65.1)	3 (42.9)	5 (71.4)	20 (64.5)
TAVR	19 (14.7)	2 (28.6)	1 (14.3)	4 (12.9)
Valve localization				
Aortic	116 (89.9)	5 (71.4)	6 (85.7)	27 (87.1)
Mitral	29 (22.5)	3 (42.9)	1 (14.3)	9 (29.0)
Multivalvular ^d	19 (14.7)	1 (14.3)	0	7 (22.6)
Echocardiography finding				
Vegetation	75 (58.1)	3 (42.9)	3 (42.9)	16 (51.6)
Intracardiac abscess	29 (22.5)	0	1 (14.3)	13 (41.9)
Regurgitation	56 (43.4)	4 (57.1)	3 (42.9)	15 (48.4)
Dehiscence	33 (25.6)	3 (42.9)	2 (28.6)	10 (32.3)
Embolic Events				
Patients with at least one event	66 (51.1)	4 (57.1)	1 (14.3)	16 (51.6)
Patients with CNS events	33 (25.6)	1 (14.3)	0	8 (25.8)
Microorganism				
Staphylococci	30 (23.3)	1 (14.3)	0	9 (29.0)
MSSA	16 (12.4)	0	0	4 (12.9)
MRSA	3 (2.3)	1 (14.3)	0	0
CoNS	11 (8.5)	0	0	5 (16.1)
Streptococci	56 (43.4)	1 (14.3)	2 (28.6)	13 (41.9)
<i>S. gallolyticus</i>	21	1 (14.3)	1 (14.3)	7 (22.6)
Viridans streptococci	24	0	0	5 (16.1)
Other streptococci ^e	11	0	1 (14.3)	1 (3.2)
Enterococci ^f	23 (17.8)	4 (57.1)	3 (42.9)	6 (19.4)
Other ^g	9 (7.0)	1 (14.3)	0	1 (3.2)
Culture negative	11 (7.8)	0	2 (28.6)	2 (6.5)
No surgery despite indication	56 (43.4)	4 (57.1)	3 (42.9)	19 (33.9)
Follow-up				

1-year mortality	31 (24.0)	3 (42.9)	1 (14.3)	-
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Data are reported as No. (%) of patients unless otherwise indicated. Patients who relapsed and died are present in the two columns.

Abbreviations: PVE, Prosthetic valve endocarditis; IE, infective endocarditis; IQR, interquartile range; TAVR, transcatheter aortic valve replacement.

^aDeath after completion of antibiotics.

^bMedian (IQR).

^cExcept TAVR

^dAt least 2 locations.

^eDetails: *S. Agalactiae*: 6 cases (one patient died); *S. Dysgalatiae* 5 cases (one patient had a reinfection).

^fNo vancomycin-resistant enterococci

^gOther microorganisms: *S. maltophilia* (The patient relapsed and died), *E. coli*, *P. aeruginosa*, *S. marcessens*, *C. koseri*, *K. pneumoniae* *Aggregatibacter aphrophilus*, *H. parainfluenzae*, *Corynebacteria sp.*

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