Clinical Infectious Diseases

MAJOR ARTICLE

Prosthetic Valve *Candida* spp. Endocarditis: New Insights Into Long-term Prognosis—The ESCAPE Study

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Background. Prosthetic valve endocarditis caused by *Candida* spp. (PVE-C) is rare and devastating, with international guidelines based on expert recommendations supporting the combination of surgery and subsequent azole treatment.

Methods. We retrospectively analyzed PVE-C cases collected in Spain and France between 2001 and 2015, with a focus on management and outcome.

Results. Forty-six cases were followed up for a median of 9 months. Twenty-two patients (48%) had a history of endocarditis, 30 cases (65%) were nosocomial or healthcare related, and 9 (20%) patients were intravenous drug users. "Induction" therapy consisted mainly of liposomal amphotericin B (L-amB)–based (n = 21) or echinocandin-based therapy (n = 13). Overall, 19 patients (41%) were operated on. Patients <66 years old and without cardiac failure were more likely to undergo cardiac surgery (adjusted odds ratios [aORs], 6.80 [95% confidence interval [CI], 1.59–29.13] and 10.92 [1.15–104.06], respectively). Surgery was not associated with better survival rates at 6 months. Patients who received L-amB alone had a better 6-month survival rate than those who received an echinocandin alone (aOR, 13.52; 95% CI, 1.03–838.10). "Maintenance" fluconazole therapy, prescribed in 21 patients for a median duration of 13 months (range, 2–84 months), led to minor adverse effects.

Conclusion. L-amB induction treatment improves survival in patients with PVE-C. Medical treatment followed by long-term maintenance fluconazole may be the best treatment option for frail patients.

Keywords. Candida; endocarditis; prosthetic valve.

Prosthetic valve endocarditis caused by *Candida* spp. (PVE-C) is a rare but devastating disease [1, 2]. Indeed, mortality rates have reached 57%–62.5 % in published case series [1, 3]. According to both Infectious Disease Society of America and European Society of Clinical Microbiology and Infectious Diseases guidelines, PVE-C should be treated by antifungals associated with early surgery; if surgery is not possible, azole therapy should be administered to prevent recurrences [4, 5]. Moreover, the 2016 update by the Infectious Disease Society of America stipulates that chronic suppressive antifungal therapy with fluconazole (400–800 mg/d) is recommended to prevent recurrence, without any restriction to the patients not operated on [5]. However, these recommendations are based on expert opinions or small case series [5, 6], and no data demonstrate a convincing clinical benefit of early surgery for all patients [7–9]. In the subgroup of patients in whom comorbid conditions prevent surgery, a lifelong azole "maintenance" therapy is often preferred and has been associated, in some reports and a meta-analysis, with patients' survival [10–14].

In the present study, we report data on patients with PVE-C from cases collected in Spain and France over the last decade, focusing on the long-term outcomes of the disease according to its management; these findings provide new insights into current treatment recommendations.

METHODS

Patients and Data Collection

We conducted a binational study including all consecutive patients with PVE-C diagnosed from January 2001 to December 2015 in 41centers from France (n = 16) and Spain (n = 25). Data were prospectively recorded through the French nationwide MYCENDO study on fungal endocarditis (2005–2007), the surveillance program by the French National Center

Received 20 July 2017; editorial decision 4 October 2017; accepted 24 October 2017; published online October 25, 2017.

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Clinical Infectious Diseases® 2018;66(6):825–32

DOI: 10.1093/cid/cix913

for Invasive Mycoses and Antifungals (Institut Pasteur, Paris), the French prospective cohort of the Association pour l'Etude et la Prévention de l'Endocardite Infectieuse (AEPEI), and the prospective cohort of the Spanish multicentric collaborative group named as Grupo de Apoyo al Manejo de las Endocarditis en España (GAMES).

Both AEPEI and GAMES cohorts are prospective registries performed by multidisciplinary groups dedicated to the improvement of infective endocarditis management. All consecutive episodes of infective endocarditis are prospectively recorded at their institutions and then sent to the national coordinating centers (Hospital General Gregorio Maranon, Madrid, Spain, Institut Pasteur and AEPEI, Paris).

The following data were collected: history of heart disease, underlying comorbid conditions (cardiac, renal, respiratory insufficiencies, human immunodeficiency virus infection, ongoing solid cancer or hematological cancer, diabetes mellitus), predisposing host conditions (central venous access, neutropenia within 1 month before PVE-C, antibiotics within 3 months before PVE-C, intravenous drug abuse), and characteristics of PVE-C (time to diagnosis, clinical symptoms, echocardiographic abnormalities, embolic complications, results of microbiological investigations, medical and surgical management, outcome). This study was approved by the Comité de Protection des Personnes, Hôpital Bicêtre, Paris (No. PP 14-012).

Definitions

Infective endocarditis was defined according to the modified Duke criteria [15]. The date of PVE-C was defined as the day of the first echocardiogram suggestive of endocarditis, or the first day of positive blood cultures when no cardiac abnormalities suggestive of endocarditis were evidenced [7]. The median time to diagnosis was the number of days between the first clinical symptoms of PVE-C and diagnosis.

Healthcare-associated infections were defined as previously published [16]. Death was considered related to PVE-C if there were persistent signs of endocarditis at the time of death, that is, positive blood cultures for *Candida* species, new vascular complications, and/or persistence of another major criteria defining infective endocarditis [15], or if the patient died of cardiac failure, embolic complications of endocarditis, adverse effects of antifungal treatment, or complications of the surgical procedure.

The portal of entry was determined on the basis of compatible clinical, biological, microbiological and/or radiographic features and the isolation of the same *Candida* species from this presumed source of infection, except for the skin, which was considered the portal of entry in intravenous drug users when no alternative source of infection was found after careful clinical examination. If the clinical data were ambiguous, the portal of entry was categorized as "undetermined" [7].

The "induction" treatment was defined as the antifungal treatment prescribed to cure the endocarditis episode, versus the maintenance therapy, which was the long-term antifungal treatment aimed at preventing relapses, according to the notations of individual physicians in the medical charts. A relapse was defined as a new episode of endocarditis due to the same *Candida* species, in patients having completed induction treatment and with negativation of blood cultures during the initial episode.

For the subgroup analysis on antifungal therapy, patients were assigned to treatment groups based on the antifungal drug they received for most of the first 30 days of therapy [9]. Patients receiving an echinocandin or liposomal amphotericin B (L-amB) for >15 days among the first 30 days were analyzed in the echinocandin-based or L-amB–based therapy group, respectively. A combination therapy with 5-fluorocytosine (5FC) was defined by the adjunction of 5FC for ≥2 weeks within the first 30 days of treatment.

Mycological Methods

All *Candida* isolates were identified to the species level. Fluconazole, voriconazole, flucytosine, echinocandins, and amphotericin B in vitro susceptibility testing results were obtained in each individual center, according to the method used at the time of the study.

Statistical Analysis

Groups were compared using the Mann-Whitney test for continuous variables and Pearson χ^2 test or Fisher exact test for categorical variables, when appropriate. Multivariate analyses were performed using exact logistic regression. All factors significantly associated with the outcome at $P < .25$ in the univariate analysis were included in the multivariate model. Variables were then removed from the model one by one, starting with the variable with the highest P value until all variables left in the model had P values <.05. Quantitative variables were introduced in the multivariate model as dichotomous variables using the median as the cutoff point. Confidence intervals (CIs), at the 95% level, were reported for each adjusted odds ratio (aOR). All tests were 2 tailed, and significance was set at <0.05. Data were analyzed using Stata IC software, version 13 (StataCorp).

RESULTS

Burden Estimate

During the 2005–2015 study period, 46 cases were reported, 28 from France and 18 from Spain; 36 of 46 (78%) were definite, and 10 of 46 (22%) were possible.

Patient Characteristics and Clinical Presentation

Demographic and clinical characteristics of the 46 patients are shown in Table 1. In 22 patients (48%) with a history of previous endocarditis, the median time between the 2 episodes was 338 days (interquartile range [IQR], 81–1167 days). The prior

Table 1. Characteristics, Management, and Outcome in 46 Patients With Prosthetic Valve Endocarditis Caused by *Candida* spp.

Variable	Patients, No. (%)[a]
Age, median (IQR), y	66 (48–74)
Male sex	36 (78)
Nosocomial or healthcare associated	30 (65)
Host predisposing conditions	
Antibiotics (>10 d) within 3 mo before PVE-C	29 (63)
β-Lactam antibiotics	24 (83)
Central venous access	16 (35)
Intravenous drug user	9 (20)
Chronic cardiac insufficiency	8 (17)
Chronic respiratory insufficiency	6 (13)
Chronic renal insufficiency	8 (17)
Diabetes mellitus	5 (11)
Solid or hematological cancer	4 (9)
HIV infection	2 (4)
Neutropenia within last month	1 (2)
None	13 (28)
≥2 comorbid conditions	25 (54)
Predisposing cardiac disease	
Interval between prior cardiac surgery and PVE-C, median (IQR), mo	8.9 (4–27.2)
Prosthetic location	
Aortic	33 (72)
Mitral	18 (39)
Tricuspid	6 (13)
Pulmonary	5 (11)
Multiple prosthetic valves	10 (22)
Previous infective endocarditis	22 (48)
Previous native valve endocarditis	18 (39)
Previous *Candida* endocarditis	5 (11)
Presence of pacemaker	1 (2)
Suspected portal entry	
Venous catheter	12 (26)
Surgical site infection	11 (24)
Skin lesions	7 (15)
Urinary and respiratory tract colonization	1 (2)
Undetermined	14 (30)
Time to diagnosis, median (IQR), d	11 (4–18)
Clinical findings	
Fever (≥38°C) at presentation	24 (52)
Cardiac failure	12 (26)
Septic shock	5 (11)
Embolic complications	21 (46)
Skin lesions	6 (13)
Biological findings	
Blood culture positive for *Candida* sp.	46 (100)
Positive blood cultures, median (IQR), No.	2 (1–5)
C-reactive protein, median (IQR) mg/L	68 (29–126.5)
Leukocyte count, median (IQR), cells/mm^3	8950 (5700–12 640)
Echocardiographic abnormalities	
Vegetations	30 (65)
Size of vegetation, median (IQR), mm	14 (11–20)
Annular abscess	11 (24)
Valvular stenosis	6 (13)
Valvular regurgitation	7 (15)
≥1 native valve concomitantly involved	5 (11)
No abnormality	7 (15)
First-line antifungal therapy	46 (100)
Liposomal amphotericin B	28 (61)
Caspofungin	23 (41)
Fluconazole	21 (46)
Amphotericin B deoxycholate	5 (11)
Anidulafungin	3 (7)
Initial antifungal combination	31 (67)
Duration of "induction" antifungal treatment, median (IQR), d	40 (24–69)
Valve surgery	
At time of incident episode	17 (37)
For a relapse	4 (9)
Outcome	
Relapses	9 (19.5)
Death	26 (56)
Cause of death	
Uncontrolled sepsis	7 (15)
Cardiac failure	7 (15)
Neurological embolic complications	4 (9)
Early complication of cardiac surgery	3 (7)
Liver failure	1 (2)
Digestive hemorrhage	1 (2)
Not reported	3 (7)

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; PVE-C, prosthetic valve endocarditis caused by *Candida* spp.

[a]Data represent No. (%) of patients unless otherwise specified.

episode of endocarditis was due to *Candida* in 5 cases, all occurring on a native valve and due to the same *Candida* species; the median time between these 2 infections was 426 days (IQR, 312–518 days). All 9 intravenous drug users had a history of previous infective endocarditis.

Twenty-one patients (46%) presented with ≥1 embolic complication, mainly cerebral (n = 10 patients) and splenic (n = 7 patients); 11 of them had >1 embolic complication. Pulmonary embolism was found in 4 of 11 patients (36%) with right-sided endocarditis.

Cardiac Involvement

All patients underwent echocardiography, both transthoracic and transesophageal echocardiography in 23 of 46 patients, transthoracic echocardiography alone in 10, and transesophageal echocardiography alone 13. The prosthetic valve was a bioprosthesis in 60% of cases. The median interval between initial cardiac surgery and PVE-C was 8.9 months (IQR, 4–27.2 months), but in 6 patients PVE-C developed within 30 days after valve surgery. Among 11 patients in whom the right side of the heart was involved, 8 had isolated right-sided endocarditis, including 4 active intravenous drug users. Detailed echocardiographic abnormalities are presented in Table 1.

Mycological Data

Blood cultures were positive for all patients. *Candida parapsilosis* and *Candida albicans* predominated (in 19 [41%] and 16

[35%] of 46 patients, respectively). *Candida tropicalis*, *Candida glabrata,* and *Candida guilliermondii* were isolated in 5, 4, and 2 cases, each. Cardiac samples from 15 operated-on patients were analyzed: cultures were positive in 9 of 15 (60%), to the same *Candida* species as isolated from blood cultures.

All yeasts were susceptible to conventional antifungal agents. The median minimum inhibitory concentrations (mg/L) of the main antifungals for *C. albicans* isolates were as follows: amphotericin B, 0.06 (range, 0.03–0.12); flucytosine, ≤0.12 (≤0.12–0.5); fluconazole, 0.25 (0.25–0.5); voriconazole, ≤0.01 (≤0.01 to ≤0.01); and caspofungin, 0.03 (0.03–0.06). For *C. parapsilosis* isolates, the corresponding values were 0.06 (range, 0.06–0.12), ≤0.12 (≤0.12 to ≤0.12), 0.5 (0.25–2), ≤0.01 (≤0.01–0.06), and 0.25 (0.25–1) for amphotericin B, flucytosine, fluconazole, voriconazole, and caspofungin, respectively.

Prosthetic Valve Endocarditis Caused by *Candida* spp. Management

The management and outcomes in the 46 patients is summarized in Table 1 and Figure 1. Thirty-one patients (67%) received a combined antifungal therapy as first-line strategy, which consisted of L-amB plus 5FC in 17 of 31 (55%). Ten patients presented renal insufficiency during L-amB induction therapy, leading to discontinuation in 3 patients.

Overall, 19 of 46 patients (41%) underwent 22 surgical procedures, as initial treatment in 17 patients and for a relapse in 5. The indications for surgery included valvular dysfunction (n = 8), uncontrolled *Candida* infection (n = 8), embolic complication (n = 2), and vegetations ≥20 mm (n = 5); they were unknown in 2, and some patients had >1 indication for surgery. Among 27 of 46 patients who did not undergo surgery at any time, there was a clear contraindication in 15; 3 patients refused surgery, and 9 were not operated on because their endocarditis was not considered severe by the physicians in charge.

Comparison of the characteristics of the 19 patients operated on and the 27 not operated on, by univariate analysis, is shown in Table 2. By multivariate analysis, having cardiac surgery was independently associated with age <66 years (aOR, 6.80; 95% CI, 1.59–29.13) and absence of cardiac failure (10.92; 1.15–104.06).

Relapses According to Prosthetic Valve Endocarditis Caused by *Candida* spp. Management

Overall, 31 patients were alive at the end of the induction treatment (ie, a median of 40 days after diagnosis [IQR, 24–69 days]) and thus potential candidates for a maintenance treatment (Figure 1). Among the 21 of 31 (68%) who received a maintenance treatment, 4 of 21 (19%) experienced relapse, compared with 5 of 10 (50%) among the 10 of 31 patients (32%) who did not receive maintenance treatment. Thus, relapse rates were 25% in patients who received both surgery and maintenance therapy, 50% in those received surgery but no maintenance therapy, 15% in those treated medically only with maintenance therapy, and 50% in those treated medically only without maintenance therapy.

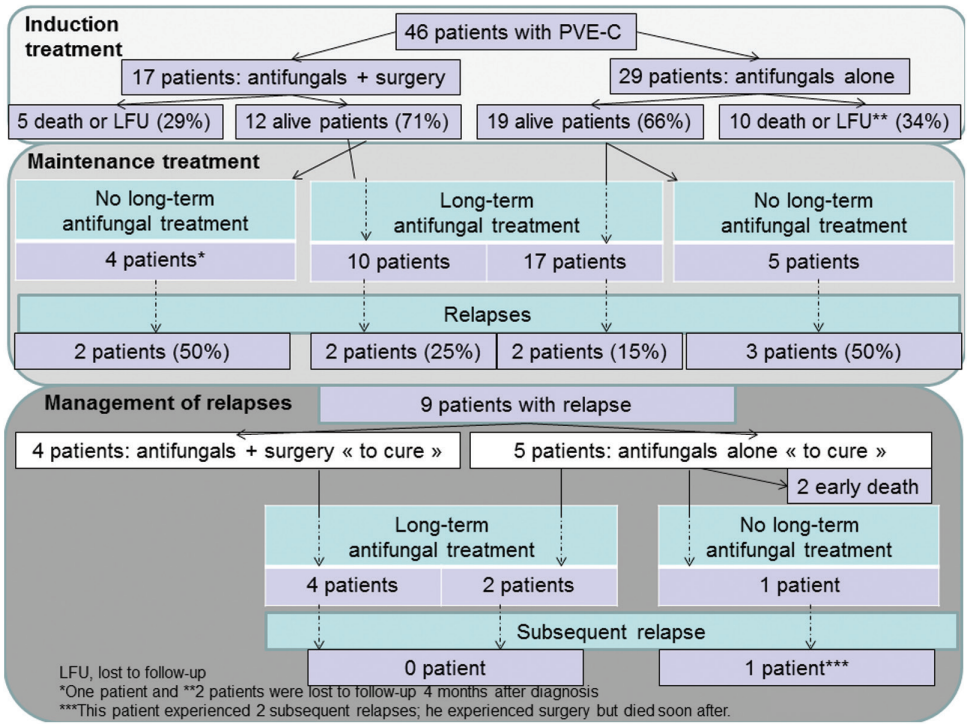

Figure 1. Outcome, focusing on relapses, of 46 patients with prosthetic valve endocarditis caused by *Candida* spp. (PVE-C) according to the management strategy. One patient in the group receiving antifungal treatment plus surgery was lost to follow-up (LFU), as were 2 in the group receiving antifungals alone. One patient experienced 2 subsequent relapses; he underwent surgery but died soon thereafter.

Table 2. Univariate Analysis of the Characteristics and Outcome in Patients With Prosthetic Valve Endocarditis Caused by *Candida* spp. by Surgical Status

Characteristic or Outcome	Patients, No. (%)[a]		
	Operated On (n = 19)	Not Operated On (n = 27)	*P* Value
Patient characteristics			
Age, median (IQR), y	52 (42–66)	73 (61–77)	.01
Ccomorbid conditions	8 (42)	19 (70)	NS
Intravenous drug abuser	5 (26)	4 (15)	NS
Chronic cardiac insufficiency	0 (0)	8 (30)	.01
Chronic respiratory insufficiency	2 (11)	4 (15)	NS
Chronic renal insufficiency	1 (5)	7 (26)	NS
HIV infection	1 (5)	1 (4)	NS
Solid or hematological cancer	1 (5)	3 (12)	NS
Neutropenia within last month	0 (0)	1 (4)	NS
History of previous endocarditis	13 (68)	9 (33)	.02
Clinical presentation			
Cardiac failure	1 (5)	11 (41)	.01
Embolic complications	11 (58)	11 (46)	NS
Septic shock	1 (5)	4 (15)	NS
Presence of vegetations at echocardiography	15 (79)	15 (56)	NS
Vegetation size, median (IQR), mm	20 (14–23)	13 (7–14)	.03
Definite endocarditis	17 (89)	19 (70)	NS
Management and outcome			
Initial antifungal combination	12 (63)	19 (70)	NS
Duration of "induction" treatment, median (IQR), d	40 (23–71)	40 (11–71)	NS
Alive at 2 mo	15 (79)	17 (68)[b]	NS
Alive at end of follow-up[c]	9 (50)	8 (32)	NS

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; NS, not significant.

[a]Data represent No. (%) of patients unless otherwise specified.

[b]Two patients were lost to follow-up (n=25).

[c]For this outcome, 3 patients were lost to follow-up (n = 18 for patients operated on; n = 25 for patients not operated on).

Nine patients experienced ≥1 relapse: 6 the induction treatment for the relapse followed by maintenance treatment, and none of them experienced a subsequent relapse. The latter patient, who was not prescribed subsequent maintenance antifungals, experienced 2 additional relapses and died soon afterward (Figure 1). The median fluconazole daily dosage for the maintenance therapy was 200 mg (IQR, 200–400 mg) among relapsing patients, versus 400 mg (237.5–400 mg) among nonrelapsing patients ($P = .32$).

Overall Mortality Rate and Risk Factors for Death

The median follow-up duration was 9 months (IQR, 1–21 months). The in-hospital mortality rate was 30% (14 of 46 patients). At 6 months, 16 patients (34%) were dead. Overall, 26 patients (56%) died during the entire follow-up, with 18 deaths (69%) related to PVE-C. PVE-C was less likely to be the cause of death among the 10 patients who died ≥6 months after the initial episode (4 of 10; 40%), than among the 14 who died earlier (14 of 16; 87%) ($P = .02$). No correlation was found between positive valve cultures and the risk of relapse or death. No difference in term of risk for death or relapse was observed between patients with possible (n = 10) or proven (n = 36) endocarditis.

We compared the characteristics of the 27 surviving patients not lost to follow-up at 6 months with those of the 16 patients who were dead at 6 months (Table 3). By univariate analysis, surviving patients were younger, were more likely to have received a L-amB–based treatment, alone or with 5FC, had received induction treatment for a longer duration, were more likely to have received long-term fluconazole treatment, and were more frequently intravenous drug addicts. When we considered only patients who survived ≥40 days, which corresponds to the appropriate timing for introducing maintenance therapy, neither a long duration (>40 days) of induction therapy nor receiving maintenance therapy was associated with a better 6-month survival rate. By multivariate analysis, patients who received L-amB–based therapy alone had a higher 6-month survival rate than those who received echinocandin-based treatment alone (aOR, 13.52; 95% CI, 1.03–838.10).

Adverse Effects of Long-term Azole Treatment

Long-term azole treatment was prescribed in 24 patients, for a median duration of 13 months (IQR, 4–23 months; range, 2–84 months). It consisted of fluconazole in 21 and voriconazole in 3; 1 of the 3 who received voriconazole later received posaconazole. Adverse effects were noted in 5 patients. With fluconazole, adverse effects included alopecia, renal failure, interaction with anti–vitamin K therapy, pruritus, and asthenia; with voriconazole, bullous eruption and drug interactions with methadone were reported. Adverse events led to discontinuation of voriconazole therapy in 2 patients.

DISCUSSION

Through the exhaustive analysis of 46 cases observed in a recent period, we provide original data on current characteristics, management, and outcome of PVE-C. Because PVE-C is rare, we pooled cohorts of patients from France and Spain, which enables the report of the largest series focusing on PVE-C to date. As already observed [3], PVE-C is not a very early complication of valvular surgery, because the median time between prosthesis implantation and endocarditis was 8.9 months. Nearly half of the patients had a history of prior endocarditis. Contrarily to what is observed for native valve *Candida* endocarditis caused by *Candida* spp. (NVE-C) [6, 7], a significant proportion of patients, 28% in our series, had no classic risk factor for invasive candidiasis; these data reinforce the need for careful long-term follow-up in all patients who undergo valve replacement, especially if they have previously had infective endocarditis.

Table 3. Comparison Between Patients Alive or Not Alive 6 Months After Prosthetic Valve Endocarditis Caused by *Candida* spp. Diagnosis, by Univariate Analysis

Characteristic or Outcome	Patients, No. (%)[a]		
	Dead by 6 mo (n = 16)	Alive at 6 mo (n = 27)	*P* Value
Age, median (IQR), y	73 (66–77)	53 (40–72)	.01
Host predisposing condition			
Central venous access	7 (44)	9 (33)	NS
Hemodialysis	2 (13)	3 (11)	NS
Intravenous drug addiction	0 (0)	8 (30)	.02
Antibiotics (>10 d) within 3 mo before PVE-C	11 (69)	16 (59)	NS
Comorbid condition			
Congestive heart insufficiency	5 (31)	3 (11)	NS
Chronic respiratory insufficiency	4 (25)	1 (4)	NS
Chronic renal insufficiency	4 (25)	3 (11)	NS
HIV infection	0 (0)	1 (4)	NS
Neoplasia	2 (13)	2 (7)	NS
History of previous endocarditis	5 (31)	14 (52)	NS
Type of prosthetic valve			
Bioprosthesis	9 (56)	13 (48)	NS
Mechanical	4 (25)	11 (41)	NS
Candida species			
C. parapsilosis	7 (44)	10 (37)	NS
C. albicans	5 (31)	11 (41)	NS
Other	4 (25)	6 (22)	NS
Clinical presentation at diagnosis of endocarditis			
Cardiac failure	5 (31)	6 (23)	NS
Embolic complications	8 (57)	12 (44)	NS
Early death (before 10 d)	3 (19)	0 (0)	NS
Antifungal treatment			
Echinocandin based	7 (44)	3 (11)	.02
L-amB based	1(6)	7(26)	
L-amB based plus 5FC	1 (6)	9 (33)	
L-amB based plus echinocandin based	2 (13)	1 (4)	
Other	5 (31)	7 (26)	
"Induction" treatment duration, median (IQR), d	23 (8–41)	43 (37–90)	.003
Surgery as initial treatment	4 (25)	12 (44)	NS
Time between diagnosis and surgery, median (IQR), d	19.5 (10.5–33.5)	17.5 (8.0–67.5)	NS
Long-term antifungal treatment			
Any	6(38)	18 (67)	.06
Fluconazole	4 (25)	17 (63)	.02
Voriconazole	2 (13)	1 (4)	NS
Death due to PVE-C	14 (88)	4 (15)	<.001

Abbreviations: 5FC, 5-fluorocytosine; HIV, human immunodeficiency virus; IQR, interquartile range; L-amB, liposomal amphotericin B; NS, not significant; PVE-C, prosthetic valve endocarditis caused by *Candida* spp.

[a]Data represent No. (%) of patients unless otherwise specified.

The clinical presentation was close to that reported previously for *Candida* endocarditis [17, 18], and no specificities of prosthetic cases could be evidenced here, underlying the relevance of our cohort and strengthening our results. Considering the outcome in PVE-C, compared with NVE-C, several points should be emphasized. First, the relapse rate was much higher in patients with PVE-C (9 of 31; 29%) than in those with NVE-C described in our previous MYCENDO study (1 of 19; 5.3%) [7], as already observed by Sun et al [6] in a retrospective study comparing fungal PVE and NVE characteristics and outcome. Second, although one would expected PVE-C to be associated with a worse outcome than NVE-C, the 6-month cumulative mortality rate in patients with PVE-C was not higher (37%) than that (57%) in patients with NVE-C reported in the MYCENDO study [7]; similarly, Sun et al did not find any difference in 3 month-mortality rates between patients with fungal NVE and those with PVE [6].

Despite major advances in diagnostic methods, surgical techniques, and antifungal therapy, PVE-C remains a very severe disease, with a global mortality rate of 56% in this series. Because global mortality rate did not seem to be a good indicator in those severely ill patients with altered health status and major comorbid conditions, we focused our analysis on risk factors for the mortality rate at 6 months, which was as high as 37%. Among our patients, only 19 (41%) underwent surgery. In the majority of cases, surgery was rejected because the clinical status of patients was considered too altered; accordingly, our multivariate analysis indicated that the 2 factors independently associated with lower odds of being operated on were older age and presentation with cardiac failure. In one-third of cases, the decision not to operate was motivated by the estimated low severity of the endocarditis, which indicates that surgeons do not systematically follow current guidelines.

Importantly, 6-month mortality outcomes in patients not operated on were similar to those in patients who underwent operation. Moreover, we did not observe more relapses among patients not operated on. It should however be noted that the reasons for surgery were mostly uncontrolled infection or vascular dysfunction (ie, emergency indications), so the possible benefit of elective surgery could not be investigated here. Although North American and European guidelines recommend early surgery for all patients, data addressing this question are altogether nonconclusive [3, 19]. Our results do not support the recommendation of early surgery for all patients with PVE-C.

Considering antifungal induction therapy, L-amB–based therapy either alone or combined with 5-FC was associated with a lower 6-month mortality rate by univariate analysis; by multivariate analysis, the 6-month survival rate was better in patients who received L-amB–based monotherapy than in those receiving candin-based monotherapy; the benefit of a combination therapy with 5-FC could not be evidenced, probably because of small sample sizes. Our results differ from those in the large series of 70 *Candida* endocarditis cases reported by Arnold et al [9], in which no benefit of amphotericin B could be evidenced in a subgroup of 25 patients receiving either an amphotericin B or a candin-based regimen, possibly owing to

a lack of statistical power. Longer duration of induction treatment was also associated with a better outcome, but this may reflect the fact that patients who died early received antifungal treatment for a shorter time.

Receiving long-term antifungal treatment with fluconazole was associated with a lower risk of death at 6 months by univariate analysis but did not constitute a protective factor against death in the multivariate analysis, probably owing to the small number of cases. However, careful analysis of the relapse risk by management strategy clearly suggests a benefit of maintenance azole treatment, especially given that tolerance was good in most patients, as in previous reports [14]. A benefit of maintenance treatment was also observed for patients who underwent operation, a fact already suggested by others [3]. It should be noted that the median fluconazole daily dosage of the maintenance therapy was lower (ie, 200 mg) among relapsing patients than among nonrelapsing patients (ie, 400 mg). Although this result obtained in a small population did not reach statistical significance, it suggests that the higher dosage be preferred as long-term therapy for susceptible *Candida* spp. PVE.

In conclusion, given that prospective studies on PVE-C are unlikely to be undertaken because of the rarity of the disease, our results provide important new insights on the optimal management of this condition. It should be based on L-amB induction treatment followed by fluconazole long-term maintenance therapy. Surgery does not seem to be mandatory for frail patients or those with uncomplicated endocarditis. Thus patients who are not good surgical candidates based on age and/or underlying heart failure can do fairly well with L-amB–based induction therapy followed by long-term azole maintenance therapy.

Notes

Acknowledgments. We thank Victoire de Lastours for reviewing the English text.

Financial support. This work was supported by the Programa Multidisciplinar para la Gestión de Antifúngicos y la Reducción de Candidiasis Invasora (PROMULGA) II Project, Instituto de Salud Carlos III, partially financed by the European Regional Development Fund (grant PI13/01148). A. V. is supported by a Rio Hortega contract from the Instituto de Salud Carlos III, also partially financed by the European Regional Development Fund (grant CM15/00181).

Potential conflicts of interest. All authors: No reported 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.

References

1. Falcone M, Barzaghi N, Carosi G, et al. *Candida* infective endocarditis: report of 15 cases from a prospective multicenter study. Medicine **2009**; 88:160–8.
2. Muñoz P, Kestler M, De Alarcon A, et al; Spanish Collaboration on Endocarditis-Grupo de Apoyo al Manejo de la Endocarditis Infecciosa en España (GAMES). Current epidemiology and outcome of infective endocarditis: a multicenter, prospective, cohort study. Medicine **2015**; 94:e1816.
3. Boland JM, Chung HH, Robberts FJL, et al. Fungal prosthetic valve endocarditis: mayo clinic experience with a clinicopathological analysis. Mycoses **2011**; 54:354–60.
4. Cornely OA, Bassetti M, Calandra T, et al. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect **2012**; 18(suppl 7):19–37.
5. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis **2016**; 62:e1–50.
6. Sun X, Zhang J, Wang G, et al. Comparison of characteristics and short-term outcome from fungal infective endocarditis in prosthetic valve endocarditis versus native valve endocarditis. Am J Cardiol **2013**; 112:111–6.
7. Lefort A, Chartier L, Sendid B, et al. Diagnosis, management and outcome of *Candida* endocarditis. Clin Microbiol Infect **2012**; 18:E99–109.
8. Tattevin P, Revest M, Lefort A, et al. Fungal endocarditis: current challenges. Int J Antimicrob Agents **2014**; 44:290–4.
9. Arnold CJ, Johnson M, Bayer AS, et al. *Candida* infective endocarditis: an observational cohort study with a focus on therapy. Antimicrob Agents Chemother **2015**; 59:2365–73.
10. Wallner M, Steyer G, Krause R, et al. Fungal endocarditis of a bioprosthetic aortic valve: pharmacological treatment of a *Candida parapsilosis* endocarditis. Herz **2013**; 38:431–4.
11. Lye DCB, Hughes A, O'Brien D, et al. *Candida glabrata* prosthetic valve endocarditis treated successfully with fluconazole plus caspofungin without surgery: a case report and literature review. Eur J Clin Microbiol Infect Dis **2005**; 24:753–5.
12. Noguchi M, Takai H, Eishi K, et al. Prosthetic valve endocarditis due to *Candida albicans* treated successfully with medical treatment alone. Jpn J Thorac Cardiovasc Surg **2004**; 52:318–21.
13. Aaron L, Therby A, Viard J P, et al. Successful medical treatment of *Candida albicans* in mechanical prosthetic valve endocarditis. Scand J Infect Dis **2003**; 35:351–2.
14. Smego RA, Ahmad H. The role of fluconazole in the treatment of *Candida* endocarditis: a meta-analysis. Medicine **2011**; 90:237–49.
15. 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.
16. Benito N, Miró JM, de Lazzari E, et al. Health care-associated native valve endocarditis: importance of non-nosocomial acquisition. Ann Intern Med **2009**; 150:586–94.
17. Ellis ME, Al-Abdely H, Sandridge A, et al. Fungal endocarditis: evidence in the world literature, 1965–1995. Clin Infect Dis **2001**; 32:50–62.
18. Pierrotti LC, Baddour LM. Fungal endocarditis, 1995–2000. Chest **2002**; 122:302–10.
19. Steinbach WJ, Perfect JR, Cabell CH, et al. A meta-analysis of medical versus surgical therapy for *Candida endocarditis*. J Infect **2005**; 51:230–47.

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