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Outcomes in patients with fungal endocarditis: A multicenter observational cohort study

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ABSTRACT

Objective: To compare the clinical and epidemiological features, treatments, and outcomes of patients with isolated right-sided and left-sided fungal endocarditis and to determine the risk factors for in-hospital mortality in patients with *Candida sp* endocarditis.
Methods: A retrospective review of all consecutive cases of fungal endocarditis from five hospitals was performed. Clinical features were compared between patients with isolated right-sided and left-sided endocarditis. In the subgroup of fungal endocarditis due to *Candida* species, binary logistic regression analysis was performed to determine variables related to in-hospital mortality.
Results: Seventy-eight patients with fungal endocarditis were studied. Their median age was 50 years; 55% were male and 19 patients (24%) had isolated right-sided endocarditis. Overall, cardiac surgery was performed in 46 patients (59%), and in-hospital mortality was 54%. Compared to patients with left-side fungal endocarditis, patients with isolated right-sided endocarditis had lower mortality (32% vs. 61%; $p = 0.025$) and were less often submitted to cardiac surgery (37% vs. 66%; $p = 0.024$). The most frequent etiology was *Candida spp* (85%). In this subgroup, acute heart failure (odds ratio 5.0; $p = 0.027$) and exclusive medical treatment (odds ratio 11.1; $p = 0.004$) were independent predictors of in-hospital death, whereas isolated right-sided endocarditis was related to a lower risk of mortality (odds ratio 0.13; $p = 0.023$).
Conclusions: Patients with isolated right-sided fungal endocarditis have particular clinical and epidemiological features. They were submitted to cardiac surgery less often and had better survival than patients with left-sided fungal endocarditis. Isolated right-sided endocarditis was also a marker of a less harmful illness in the subgroup of *Candida sp* endocarditis.

Introduction

Fungal endocarditis accounts for 2% of overall infective endocarditis episodes and remains an infection associated with extremely high mortality rates, ranging between 30% and 80% (Badiee et al., 2014; Arnold et al., 2015; Tattevin et al., 2014). The number of cases of fungal endocarditis will probably increase in the near future because of the increasing age of the world population, the growing number of immunocompromised patients, and the more frequent implantation of intravascular devices, all known risk factors for fungemia.

Isolated right-sided endocarditis is an uncommon disease often related to intracardiac devices or a history of intravenous drug use.

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Previous reports have shown that although between 5% and 16% of infectious endocarditis episodes are located in the right side of the heart, only 3% occur in patients without intracardiac devices or a history of intravenous drug use. Additionally, its clinical presentation, treatment, and outcome differ from the corresponding aspects of left-sided endocarditis (Akinosoglou et al., 2012; Ortiz et al., 2014; Revilla et al., 2008; Kamaledeen et al., 2012). It has been suggested that, overall, patients with isolated right-sided bacterial endocarditis have a more favorable prognosis and that many patients can be cured with medical treatment alone. However, the clinical profile, treatment, and outcome of patients with isolated right-sided endocarditis caused by fungi are not completely understood. In a retrospective review of patients with Candida endocarditis, the authors demonstrated that patients with left-sided Candida endocarditis may have higher mortality than those with right-sided endocarditis (Steinbach et al., 2005).

The aim of this study was to compare the clinical and epidemiological features, treatments, and outcomes of patients with isolated right-sided and left-sided fungal endocarditis. The secondary end-point was to determine the risk factors for in-hospital mortality in the subgroup of patients with *Candida sp* endocarditis.

Methods

Study population

This was a collaborative retrospective study of 78 consecutive adult patients with fungal endocarditis seen across a wide time span in five hospitals in Brazil: two cardiology referral hospitals (Heart Institute (InCor), University of São Paulo Medical School (between 1980 and 2015) and Instituto Nacional de Cardiologia (INC), Rio de Janeiro (between 2006 and 2015)), two general university hospitals (Clinics Hospital, University of São Paulo Medical School (between 2008 and 2014) and Hospital Universitário Clementino Fraga Filho (HUCFF) of Rio de Janeiro Federal University (between 1990 and 2014)), and one oncology hospital (Instituto do Câncer do Estado de São Paulo (ICESP), between 2007 and 2014). Patients were identified by local routine infection control team surveillance. The local ethics committees approved the study.

Definitions

A diagnosis of fungal endocarditis was made in patients who fulfilled the definite or possible criteria for endocarditis, according to the modified Duke criteria (Li et al., 2000). In all cases, fungi were identified in cultures (blood, heart valves, and/or emboli). As part of routine clinical practice, all blood samples were incubated for 5 days (BacT/Alert, Organon Teknika Corp., Durham, NC, USA).

Isolated right-sided endocarditis was defined as the presence of vegetations located in the tricuspid or pulmonary valves or superior vena cava or right atrium, without any involvement of the aortic or mitral valves, in patients without a cardiac implantable electronic device.

Recurrence was defined as a new fungal endocarditis episode diagnosed more than 6 months after the end of treatment of a prior episode for native valves or more than 1 year for prosthetic ones (Mansur et al., 2001).

Healthcare-associated fungal endocarditis was defined according to the Centers for Disease Control and Prevention (CDC) healthcare-associated infection definition (WWW.CDC.GOV/HAI, 2016).

Previous chronic heart failure (CHF) was considered when this diagnosis was present, according to current guidelines (Habib et al., 2015; Baddour et al., 2015), before the acute episode of fungal endocarditis.

Perivalvular complications were defined by echocardiographic or surgical findings of periannular abscess, cardiac fistula, or valve perforation.

Clinical outcomes

The primary outcome was in-hospital mortality.

Follow-up

Patients were followed-up until November 2015. To evaluate recurrence-free survival, patients were contacted by phone, and/or the last outpatient consultation was obtained from the medical chart.

Statistical analysis

Categorical variables are presented as numbers and percentages; these were compared using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables are presented as the median and interquartile range (IQR); these were compared using the Mann–Whitney test. Patients with isolated right-sided and left-sided endocarditis were compared.

In the analysis of risk factors for in-hospital mortality, only patients with endocarditis due to *Candida spp* were included to

Table 1
Baseline characteristics and outcomes of patients with fungal endocarditis.

	All patients ($n = 78$)	Left-sided ($n = 59$)	Isolated right-sided ($n = 19$)	p-Value
Male sex, *n* (%)	43/78 (55)	36/59 (61)	7/19 (37)	0.065
Age (years), median (IQR)	50 (36–61)	50 (37–63)	48 (34–60)	0.657
Diabetes mellitus, *n* (%)	16/77 (21)	10/59 (17)	6/18 (33)	0.134
Chronic heart failure, *n* (%)	25/77 (32)	23/59 (39)	2/18 (11)	0.027
Renal failure on dialysis, *n* (%)	22/78 (28)	11/59 (19)	11/19 (58)	0.002
Cancer, *n* (%)	10/78 (13)	7/59 (12)	3/19 (16)	0.656
Prosthetic heart valve, *n* (%)	44/78 (56)	42/59 (71)	2/19 (10)	<0.001
Healthcare-related infection, *n* (%)	74/78 (95)	59/59 (100)	17/19 (89)	–
Fever, *n* (%)	68/74 (92)	50/55 (91)	18/19 (95)	0.598
Vegetation length ≥10 mm	25/33 (76)	13/21 (62)	12/12 (100)	–
Complications				
Acute heart failure, *n* (%)	32/78 (41)	28/59 (47)	4/19 (21)	0.060
Emboli, *n* (%)	35/77 (46)	25/59 (42)	10/18 (56)	0.325
Perforation/abscess/fistula, *n* (%)	9/78 (12)	9/59 (15)	0/19	–
Valve surgery, *n* (%)	46/78 (59)	39/59 (66)	7/19 (37)	0.024
Death, *n* (%)	42/78 (54)	36/59 (61)	6/19 (32)	0.025

IQR, interquartile range.

avoid bias related to the particularities inherent to other rare fungi (Pierrotti and Baddour, 2002). Binary logistic regression analysis was performed to determine variables related to mortality, and variables with a *p*-value less than 0.1 on univariate analysis were selected for the logistic regression multivariate model. *p*-Values of <0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics v. 22.0 (IBM Corp., Armonk, NY, USA).

Results

Seventy-eight episodes of fungal endocarditis were included, of which 75 (96%) were definite according to the modified Duke criteria. Regarding the type of hospital, 44 (56%) patients were from cardiology hospitals, 25 (32%) were from general hospitals, and nine (12%) were from the oncology hospital. With regard to the presence of risk factors for fungemia, 56 (73%) patients had previous use of antibiotics (in the last 30 days), 43 (55%) patients had central intravenous lines, and 21 (27%) patients had been submitted to cardiac or non-cardiac surgery less than 60 days prior to symptom onset.

Aortic valve endocarditis occurred in 34 (44%) episodes, mitral valve endocarditis in 32 (41%), there was multivalve involvement in seven (9%), and isolated right-sided endocarditis in 19 (24%). Among patients with isolated right-sided endocarditis, 13 had valve involvement (12 tricuspid and one pulmonary) and six had right atrium and superior vena cava vegetations. Only one patient had both right- and left-sided endocarditis. The median vegetation size as estimated by echocardiography was 15 mm (range 5–40 mm). Baseline characteristics and complications during the hospital stay for all patients and a comparison between patients with isolated right-sided and left-sided endocarditis are shown in Table 1.

The most frequent etiology was *Candida spp* (*n* = 66; 85%). Other fungi were *Aspergillus sp* (*n* = 3; 4%) and *Trichosporon spp* (*n* = 2; 3%), and there was one episode each of the following: *Fusarium sp*, *Histoplasma sp*, *Wangiella dermatitidis*, *Rhodotorula graminis*, *Pichia anomala*, *Cryptococcus neoformans*, and a non-identified yeast.

The fungi were identified in blood cultures in 77 (98%) cases. Surgically excised cardiac valves were cultured in 45 cases, of which 22 (49%) were positive. Cultures of emboli were also positive in four cases: spleen (*n* = 1), vertebrae (*n* = 1), and femoral arteries (*n* = 2).

The antifungal monotherapy was amphotericin B in 36 (46%) patients, fluconazole in six (8%), and an echinocandin in 11 (14%) patients. Dual antifungal therapy was given in 17 (22%) patients. The median time from first medical evaluation to the beginning of antifungal therapy was 8 days. The median duration of antifungal therapy was 31 days. Eight (10%) patients did not receive antifungal therapy because they died before the culture results were available to the attending physician. Valve replacement surgery was performed in 58% of cases, and the median time between the onset of antifungal therapy and surgery was 9 days.

Clinical outcomes

During the hospital stay, 42 (54%) patients died (Table 1). Patients with isolated right-sided endocarditis had lower mortality than patients with left-sided endocarditis (32% vs. 61%, $p = 0.025$).

Long-term follow-up

Thirty-six patients were discharged, of whom 22 (61%) were followed up for a mean of 3.7 years (from 9 days to 15 years). Definite recurrence was diagnosed in six (27%) patients. Among 13 patients with isolated right-sided endocarditis who were discharged, 12 had follow-up data available; there were no recurrences during follow-up in six patients who had received exclusive medical treatment (Table 2) and four recurrences among six patients who had received surgical treatment.

Candida sp *endocarditis*

There were 66 cases of Candida endocarditis. In 61 patients, *Candida* species were identified, and non-albicans species predominated (36/61; 59%). Five cases were due to *Candida albicans*, 20 cases were due to *Candida parapsilosis*, 13 cases were due to *Candida tropicalis*, and the remaining cases were due to *Candida psilosis*, *Candida glabrata*, and *Candida lusitaniae*. In five cases, the *Candid*a species was not determined. The overall in-hospital mortality was 50% (IQR 36–61%). There was no difference in mortality for patients included before or after the year 2000 (48% vs. 52%, $p = 0.729$). Univariate and multivariate analysis results are shown in Table 3. Acute heart failure and exclusive medical treatment were independent predictors of in-hospital death, and only isolated right-sided endocarditis was related to a lower risk of death.

Table 2
Clinical features and follow-up data of patients with isolated right-sided endocarditis who had received exclusive medical treatment.

Sex	Age, years	Valve prosthesis	Site	Fungus	Vegetation width dimension (mm)	Embolism	Follow-up (days)	Degree of valve dysfunction	Antifungal agent	Therapy duration (days)	Suppressive treatment	Recurrence
F	60	No	Right (TV)	*C. parapsilosis*	15	No	899	Mild	Fluconazole	54	No	No
F	60	No	Right (sup. cava vein thrombus)	*C. parapsilosis*	Not available	No	921	None	Echinocandin	31	No	No
M	57	No	Right (TV)	*Candida sp*	13	No	7363	None	Amphotericin B + fluconazole	61	No	No
M	33	No	Right (TV and sup. cava vein)	*C. parapsilosis*	4	Yes	9 (died)	None	Amphotericin B + micafungin	60	Yes	No
F	34	No	Right atrium	*C. parapsilosis*	31	No	600	None	Amphotericin B + fluconazole	53	No	No
M	47	No	Right atrium and sup. cava vein	*C. tropicalis*	30	Yes	90	None	Echinocandin	48	Yes	No

F, female; M, male; TV, tricuspid valve.

Table 3
Univariate and multivariate analysis of risk factors for in-hospital mortality in 66 patients with *Candida sp* endocarditis.

Variable	All patients, *n* (%)	Patients who died, *n* (%)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Male	34 (51)	18 (52)	1.12 (0.48–3.35)	0.624		
Age ≥60 years	17 (26)	14 (82)	7.36 (1.87–29.08)	0.002	3.9 (0.79–18.9)	0.096
Diabetes	14 (21)	7 (50)	1.00 (0.31–3.25)	0.999		
Chronic dialysis	20 (30)	9 (45)	0.75 (0.26–2.15)	0.592		
Cancer	10 (15)	6 (60)	1.61 (0.41–6.33)	0.492		
Chronic heart failure	20 (30)	13 (65)	2.41 (0.82–7.17)	0.11		
Prosthetic heart valve	35 (53)	20 (57)	1.85 (0.69–4.91)	0.218		
Non-albicans Candida[a]	36 (56)	18 (44)	0.53 (0.18–1.50)	0.205		
Right-sided endocarditis	17 (26)	4 (23)	0.21 (0.06–0.75)	0.011	0.13 (0.02–0.75)	0.023
Local complications[b]	7 (11)	5 (71.4)	2.77 (0.50–15.42)	0.230		
Embolic event	30 (45)	14 (46.7)	0.83 (0.31–2.19)	0.702		
Acute heart failure	26 (40)	19 (73.1)	5.04 (1.71–14.89)	0.003	5.06 (1.20–21.3)	0.027
Severe valvular regurgitation	11 (17)	6 (54.5)	1.27 (0.32–4.94)	0.730		
Exclusive medical treatment	28 (42)	19 (67.9)	3.62 (1.29–10.1)	0.013	11.1 (2.17–55.5)	0.004

OR, odds ratio; CI, confidence interval.
[a] *n* = 61; *Candida* species were not determined in five cases.
[b] Abscess, fistula perforation.

Discussion

In this collaborative multicenter observational study of fungal endocarditis, two major findings were identified. First, patients with isolated right-sided fungal endocarditis have particular clinical characteristics that may deserve specific treatment approaches, including exclusive medical treatment in selected cases. Second, considering all patients with *Candida spp* endocarditis, only acute heart failure and medical treatment were independent predictors of in-hospital mortality, whereas isolated right-sided endocarditis was related to a lower risk of mortality.

Overall, in this cohort, the great majority of fungal endocarditis episodes represented healthcare-associated infections (94%), caused most frequently by *Candida spp* (mainly non-albicans *Candida* species), with high rates of mortality (54%) and recurrence (27%). These findings are in line with previously published observational studies on fungal endocarditis (Arnold et al., 2015; Steinbach et al., 2005; Ortiz et al., 2014; Antinori et al., 2014; Nguyen et al., 1996; Baddley et al., 2008).

This is the first study to evaluate the clinical characteristics and outcomes of isolated right-sided endocarditis caused by fungi. Isolated right-sided endocarditis occurred in 24% of patients with fungal endocarditis, which was higher than expected. Antinori et al. reviewed 968 episodes of fungal endocarditis published from 2001 to 2011 and reported tricuspid involvement in 0.9% to 17% of cases (mean 5%) (Antinori et al., 2014). In a previous meta-analysis, Steinbach et al. reviewed 163 cases of Candida endocarditis and compared three types of treatment: exclusive medical therapy with one antifungal agent, exclusive medical therapy with a combination of antifungal agents, and surgical plus medical antifungal therapy. As they observed an important association between patients treated prior to 1980 and mortality, the authors only reported in detail on the 92 patients included after this date. Of these, 20 (22%) had right-sided endocarditis (Steinbach et al., 2005).

We observed that patients with isolated right-sided endocarditis more often had renal failure on dialysis at baseline and less often had a history of chronic heart failure and valve prosthesis. They also had fewer complications (acute heart failure or perivalvular complications) when compared to patients with left-sided endocarditis. Additionally, despite being referred to valve surgery less often, patients with isolated right-sided fungal endocarditis had lower mortality than patients with left-sided endocarditis. This finding is in line with previous studies comparing isolated right-sided and left-sided endocarditis caused by bacteria (Ortiz et al., 2014; Revilla et al., 2008; Kamaledeen et al., 2012). However, in the study on Candida endocarditis by Steinbach et al., treatment success was not different between patients with right-sided and left-sided endocarditis (70% vs. 68%, respectively). These conflicting results could be explained by the different definitions of right-sided endocarditis used: they excluded patients without valve vegetations, i.e., vegetations in the atrium or vena cava, and they did not mention if these patients also had involvement of the left side of the heart[8]. Similar to their study, the most frequent vegetation location in the present study was the tricuspid valve (63%), but 32% of our patients had vegetations in the right atrium/superior vena cava.

Fungal endocarditis has always been considered per se a mandatory indication for cardiac surgery and valve replacement because of the poor prognosis and high mortality rates in patients with exclusive medical treatment (Habib et al., 2015; Baddour et al., 2015). In our cohort, only 37% of patients with isolated right-sided fungal endocarditis were submitted to cardiac surgery. Steinbach et al., in a meta-analysis, suggested that some patients with Candida endocarditis who receive proper contemporary antifungal treatment may be treated without cardiac surgery (Steinbach et al., 2005). Previous studies on bacterial infectious endocarditis have also shown that surgical treatment in right-sided endocarditis patients is very particular. For example, surgeons usually perform a vegetectomy and valve repair of the tricuspid valve, avoiding a prosthesis in this location, or they simply remove the vegetation, in the cases of right atrium vegetations[4]. In the present study, the six patients submitted to exclusive medical treatment only for fungal endocarditis, who were followed up after discharge without recurrence, shared similar clinical characteristics: they all had native valve endocarditis, *Candida spp* infections, and isolated right-sided endocarditis. Previous studies on fungal endocarditis did not evaluate isolated right-sided endocarditis as a singular disease but only as a part of all fungal endocarditis. This could represent a bias of those studies, because the present study showed that isolated right-sided fungal endocarditis has particular clinical features and outcomes and may deserve a specific approach.

The secondary analysis of *Candida spp* endocarditis showed an overall mortality of 50%, which is similar to reports in the literature (44% to 80%) (Arnold et al., 2015; Baddley et al., 2008; Ellis et al., 2001). This study found that acute heart failure and exclusive medical treatment were independent predictors of in-hospital mortality. It was also confirmed in this subgroup that isolated right-sided endocarditis was related to a lower risk of mortality.

This study has some limitations that should be considered. First, the number of patients with only right-sided endocarditis was small, but this is a limitation inherent in the study of rare diseases. Second, definite conclusions on recurrence rates cannot be drawn due to loss of follow-up in nearly 45% of patients. Third, susceptibility patterns of *Candida sp* were not analyzed. Finally, due to the long period of inclusion, changes in treatment over time could have interfered in the prognostic analysis.

Overall, patients with fungal endocarditis have a poor prognosis. It appears consistent in all studies, including the present study, that the presence of left-sided fungal endocarditis, acute heart failure, and exclusive medical treatment are independent risk factors for mortality. This study suggests, for the first time, that patients with isolated right-sided endocarditis comprise a particular group with a singular disease. Moreover, selected patients with isolated right-sided fungal endocarditis due to *C. albicans* (those without valve dysfunction, prosthesis, or complications) may be cured with exclusive medical treatment. Further studies are needed to test this hypothesis.

In conclusion, patients with isolated right-sided fungal endocarditis have particular clinical and epidemiological features, are submitted to cardiac surgery less often, and have better survival than patients with left-sided endocarditis. In patients with Candida endocarditis, acute heart failure and exclusive medical treatment were found to be independent predictors of in-hospital death, whereas isolated right-sided endocarditis was a marker of a less harmful illness.

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Ethical approval

This study was approved by the local ethics committee, which waived the need for informed consent.

Conflict of interest

All authors declare no conflict of interest related to this study.

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