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Candida Infective Endocarditis: an Observational Cohort Study with a Focus on Therapy

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***Candida* infective endocarditis is a rare disease with a high mortality rate. Our understanding of this infection is derived from case series, case reports, and small prospective cohorts. The purpose of this study was to evaluate the clinical features and use of different antifungal treatment regimens for *Candida* infective endocarditis. This prospective cohort study was based on 70 cases of *Candida* infective endocarditis from the International Collaboration on Endocarditis (ICE)-Prospective Cohort Study and ICE-Plus databases collected between 2000 and 2010. The majority of infections were acquired nosocomially (67%). Congestive heart failure (24%), prosthetic heart valve (46%), and previous infective endocarditis (26%) were common comorbidities. Overall mortality was high, with 36% mortality in the hospital and 59% at 1 year. On univariate analysis, older age, heart failure at baseline, persistent candidemia, nosocomial acquisition, heart failure as a complication, and intracardiac abscess were associated with higher mortality. Mortality was not affected by use of surgical therapy or choice of antifungal agent. A subgroup analysis was performed on 33 patients for whom specific antifungal therapy information was available. In this subgroup, 11 patients received amphotericin B-based therapy and 14 received echinocandin-based therapy. Despite a higher percentage of older patients and nosocomial infection in the echinocandin group, mortality rates were similar between the two groups. In conclusion, *Candida* infective endocarditis is associated with a high mortality rate that was not impacted by choice of antifungal therapy or by adjunctive surgical intervention. Additionally, echinocandin therapy was as effective as amphotericin B-based therapy in the small subgroup analysis.**

Candida infective endocarditis (CIE) accounts for only 1 to 2% of all cases of infective endocarditis (IE) (1). This infection is important because it is associated with an exceptionally high mortality rate ranging from 30 to 80% (1–5). In addition, rates of fungemia have increased significantly in recent years, resulting in a growing number of patients at risk for this disease (2, 6).

Due to its rarity, our understanding of the clinical features, treatment, and mortality of CIE has been derived predominantly from retrospective reviews of case series, case reports, and several small prospective series (1, 2, 7). The standard-of-care treatment for CIE has historically been an amphotericin B-based regimen coupled with adjunctive surgical therapy. However, the options for treating invasive *Candida* infections changed with the development of the echinocandins. Echinocandins have fungicidal activity and exert their effect by inhibiting beta-glucan synthesis and disrupting the fungal cell wall. In 2003, caspofungin, the first echinocandin, was approved as therapy for invasive candidiasis, and since that time there has been a small but growing body of literature regarding echinocandin use in CIE (1, 2, 8–13). This has resulted in the addition of echinocandins to both the most recent Infectious Diseases Society of America (IDSA) and European Society for Microbiology and Clinical Infectious Diseases (ESCMID) guidelines for treatment of CIE, which now recommend either an amphotericin B-based regimen or an echinocandin-based regimen, both of these in combination with adjunctive surgical therapy if possible (14, 15). Nevertheless, these guidelines are based largely on case reports, case series, and clinical experience. To date, the largest prospective series have included 30 and 33 patients, respectively (1, 2). Additionally, there are no studies to date comparing amphotericin B- to echinocandin-based therapy for candidal infective endocarditis.

In this study, we used two large, contemporary, multinational, prospective cohorts of patients to better investigate the clinical features, treatment, and predictors of mortality in patients with CIE. Additionally, we compared amphotericin B- to echinocandin-based therapy in a subset of the cohort.

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MATERIALS AND METHODS

Study design. Data for this observational cohort study were derived from the International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) and ICE-Plus databases. ICE-PCS and ICE-Plus have each been previously described, including a detailed description of the ICE organization and methodologies for data collection and cataloging (3, 16, 17). Briefly, the ICE-PCS database contains prospective data on 4,794 patients with definite IE from 64 sites in 28 countries occurring between June 2000 and September 2006. The ICE-Plus database contains prospective data on 1,112 patients with definite IE from 29 sites in 16 countries occurring between September 2008 and December 2010. Data for each of these databases were gathered prospectively via a case report form (CRF) developed by ICE collaborators according to standard definitions (3, 18). Additionally, for this study, a supplemental CRF was sent to enrolling sites from which cases of CIE were identified. This supplemental CRF was designed to obtain detailed information regarding antifungal therapy and additional risk factors for CIE, as well as 42-day follow-up information. The ICE databases are maintained at the Duke Clinical Research Institute (DCRI), which serves as the coordinating center for the ICE studies, with institutional review board approvals from the Duke University School of Medicine and the participating ICE-PCS and ICE-Plus sites.

Study population. Patients were included in this study if they met both of the following criteria: (i) diagnosis of definite IE by the modified Duke criteria (19) and (ii) fungal IE caused by a *Candida* species only. Only patients for whom supplemental CRF information was obtained were included in the subgroup analysis specifically examining the association between antifungal therapy and outcomes.

Definitions. Infective endocarditis was defined according to the modified Duke criteria (19). A predisposing valvular condition was defined as having a native valve known to be affected at baseline by regurgitation or stenosis. Liver disease included a composite of mild, moderate, and severe disease as defined by a Child's Pugh score of ≥5. Renal disease was defined as a composite of acute kidney injury (AKI), chronic kidney disease (CKD) at all stages, and end-stage renal disease (ESRD), including patients on hemodialysis (HD). Endocavitary device included the presence of either a pacemaker, an internal cardiac defibrillator (ICD), a left ventricular assist device (LVAD), or a right ventricular assist device (RVAD). The presence of any prosthetic material was defined to include patients who had any of the following: prosthetic valve, endocavitary device, intravenous graft material, prosthetic joint, orthopedic rod, and bone plates or screws.

Hospital-acquired IE was defined as IE developing in a patient hospitalized for more than 48 h prior to the onset of signs/symptoms consistent with IE. Health care-associated IE was defined as IE diagnosed within 48 h of admission in an outpatient with extensive health care contact as reflected by any of the following criteria: (i) receipt of intravenous therapy, wound care, or specialized nursing care at home within the 30 days prior to the onset of infection; (ii) attendance at a hospital or hemodialysis clinic or receipt of intravenous chemotherapy within the 30 days before the onset of infection; (iii) hospitalization in an acute care hospital for 2 or more days in the 90 days before the onset of infection; or (iv) residence in a nursing home or long-term care facility (20). Community-acquired IE was defined as IE diagnosed at the time of admission (or within 48 h of admission) in a patient not fulfilling the criteria for health care-associated IE.

Paravalvular complication was defined as the presence of any of the following in a patient with native valve IE: paravalvular abscess, paravalvular fistula, or valvular perforation. Prosthetic valve complication was defined as the presence of any of these same complications in a patient with prosthetic valve IE. Persistently positive blood culture was defined as having positive blood cultures >72 h following initiation of antifungal therapy.

For the subgroup analysis on antifungal therapy, patients were assigned to treatment groups based on the antifungal drug that they received for the majority of the first 30 days of therapy. These groups were termed majority regimen backbone groups. Patients receiving an echinocandin-based regimen for >15 days of the first 30 days of treatment were classified as being in the echinocandin backbone therapy group, and those receiving an amphotericin B-based regimen for >15 days of the first 30 days of treatment were placed in the amphotericin B backbone therapy group. An amphotericin B-based regimen was defined as a regimen that included any of the following: amphotericin B deoxycholate, amphotericin B colloidal dispersion (ABCD), amphotericin B lipid complex (ABLC), or amphotericin B liposomal formulation (LAmB). An echinocandin-based regimen was defined as a regimen that contained caspofungin, micafungin, or anidulafungin. A treatment regimen was defined as a majority combination therapy regimen if the patient received at least two antifungal drugs concomitantly for >15 days of the first 30 days of therapy. A treatment regimen was defined as receiving any combination therapy if the patient received >1 day of two antifungal drugs concomitantly at any point during therapy. Suppressive antifungal therapy was defined as transition of antifungal therapy to azole-based therapy following initial treatment period for patients treated with either amphotericin B- or echinocandin-based therapy. For patients treated from onset of infection with azole-based therapy, suppressive therapy was defined as a duration of azole therapy of >120 days.

Outcomes. Clinical characteristics, complications (both clinical and echocardiographic), and mortality were compared between those receiving amphotericin B-based therapy and those receiving echinocandin-based therapy. These same variables were compared between the following groups: (i) those receiving adjunctive surgical therapy versus those receiving medical therapy alone and (ii) those infected with *Candida albicans* versus those infected with *Candida parapsilosis*. Additionally, univariate analysis was performed to look for predictors of in-hospital and 1-year mortality in the overall cohort.

Statistical analysis. All statistical analyses were performed using JMP Pro (version 11.0). Patients' demographics and clinical variables were described as means and standard deviations for continuous data and proportions for categorical data. The χ^2 or Fisher exact test was used to compare categorical variables between groups, as appropriate. The Student *t* test or 1-way analysis of variance (ANOVA) was used to test significant differences of continuous variables between groups, as appropriate. A two-tailed *P* value of 0.05 or less was considered significant.

RESULTS

A total of 70 cases of definite *Candida* infective endocarditis (CIE) were identified, 52 cases from ICE-PCS and 18 cases from ICE-Plus. Forty-three patients (61%) were men. The mean age was 54.3 years. The majority of patients were over the age of 50 (63%), and nearly half were over the age of 60 (Table 1). Forty-six percent of patients had a prosthetic cardiac valve, and 20% had an endocavitary device. The most common other comorbidities were congestive heart failure (CHF), diabetes mellitus (DM), and renal disease. Twenty-six percent of patients had a history of a previous episode of infective endocarditis (IE) (Table 1).

Over half of the infections were hospital acquired, and only 27% were community acquired (Table 1). Among the 19 patients with community-acquired disease, 7 (37%) engaged in intravenous drug abuse (IVDA). Of the remaining 12 patients with community-acquired disease, 7 had prosthetic valves (2 with a concomitant endocavitary device), 2 had endocavitary devices alone, and 3 had only one of the following nonoverlapping comorbidities: HIV, renal disease, or liver disease.

The most common clinical complication was systemic embolization (34%), followed by CHF (31%) and intracardiac abscess (24%) (Table 1). Echocardiographic evidence of complications was present in 19% of those with native valves and 34% of those with prosthetic valves (Table 1). Sixty-one patients (87%) had

TABLE 1 Characteristics of overall *Candida* infective endocarditis cohort and comparison by species

Characteristic[a]	No. (%)			
	Overall cohort ($n = 70$)	*C. albicans* ($n = 31$)	*C. parapsilosis* ($n = 19$)	P^b
Age (mean ± SD, 54.3 ± 17.2 yr), ≥50 yr	44 (63)	16 (52)	14 (74)	0.12
Gender, male	43 (61)	18 (58)	7 (37)	0.72
Comorbidities				
Prosthetic valve	32 (46)	15 (48)	11 (58)	0.51
Predisposing valve condition	18 (26)	7 (23)	5 (26)	0.76
Previous IE	18 (26)	9 (30)	7 (37)	0.62
Renal disease	18 (26)	7 (23)	4 (21)	1.00
CHF	17 (24)	7 (23)	3 (16)	0.72
Diabetes mellitus	15 (21)	5 (16)	8 (42)	**0.04**
Endocavitary device	14 (20)	5 (16)	5 (26)	0.38
Hemodialysis	10 (14)	3 (10)	4 (21)	0.40
Cancer	9 (13)	7 (23)	1 (5)	0.13
IVDA	8 (11)	4 (13)	2 (11)	1.00
Congenital heart disease	8 (11)	6 (20)	0	0.07
Liver disease	6 (9)	4 (13)	1 (5)	0.64
HIV	2 (3)	1 (3)	0	1.00
Clinical complications				
Embolization	24 (34)	13 (42)	5 (26)	0.26
CHF	22 (31)	11 (35)	6 (32)	0.78
Intracardiac abscess	17 (24)	9 (29)	5 (26)	0.84
Persistently positive cultures	12 (17)	7 (23)	2 (11)	0.45
Stroke	8 (11)	2 (6)	4 (21)	0.18
Mycotic aneurysm	2 (3)	0	1 (5)	0.38
Echocardiographic complications				
Regurgitation	37 (54)	18 (60)	8 (42)	0.22
Vegetation	59 (84)	28 (93)	14 (74)	0.09
Paravalvular complication	13 (19)	7 (23)	2 (11)	0.45
Paravalvular perforation	2 (3)	0	0	1.00
Paravalvular abscess	11 (16)	7 (23)	2 (11)	0.45
Paravalvular fistula	2 (3)	2 (7)	0	0.51
PV complication	11 (34)	7 (47)	2 (18)	0.22
PV dehiscence	5 (15)	3 (20)	1 (9)	0.61
PV paravalvular regurgitation	10 (31)	7 (47)	1 (9)	0.08
Acquisition				
Community	19 (27)	4 (14)	8 (44)	**0.04**
Hospital acquired	37 (53)	22 (76)	6 (33)	**<0.01**
Health care associated	10 (14)	3 (10)	4 (22)	0.40
Unknown	4 (6)	2 (6)	1 (5)	1.00
Surgery	32 (46)	14 (45)	12 (63)	0.22
Mortality				
In hospital	25 (36)	14 (45)	5 (26)	0.18
1 yr	40 (59)	19 (66)	11 (61)	0.76

[a] Abbreviations: IVDA, intravenous drug abuse; CHF, congestive heart failure; IE, infective endocarditis; PV, prosthetic valve.
[b] *P* value for comparison of *C. albicans* to *C. parapsilosis*. Boldface indicates statistically significant values.

evidence of at least one clinical or echocardiographic complication.

The most common organisms isolated were *C. albicans* ($n = 31$) and *C. parapsilosis* ($n = 19$), comprising over 70% of the cases (Table 2). One patient was infected with both *C. albicans* and *C. parapsilosis* and was excluded from the analysis comparing infections with these two organisms. Those infected with *C. parapsilosis* were more likely to be diabetic (42% versus 16%, $P = 0.04$) and were more likely to have community-acquired infection (44% versus 14%, $P = 0.04$) than were those with *C. albicans*. The majority of other patient characteristics and outcomes were similar between these two organisms (Table 1).

Thirty-two patients (46%) were treated with adjunctive surgical therapy. Patients receiving surgery were younger than those receiving medical therapy alone (Table 3). Those with intracardiac abscess were more likely to receive adjunctive surgical therapy

TABLE 2 Microbiology of the overall cohort

Organism	No. (%) in overall cohort ($n = 70$)
C. albicans	31 (44)
C. parapsilosis	19 (27)
C. tropicalis	7 (10)
C. glabrata	4 (6)
C. krusei	1 (1)
C. albicans plus *C. parapsilosis*	1 (1)
NOS[a]	7 (10)

[a] NOS, not otherwise specified.

(38% versus 13%, $P = 0.02$). All other characteristics evaluated were similar between those receiving adjunctive surgical therapy and those receiving medical therapy alone. There was no difference in in-hospital or 1-year mortality (Table 3).

The all-cause mortality of the overall CIE cohort was 36% in hospital and 59% at 1 year. This did not differ by therapy or by species. On univariate analysis, CHF at baseline was found to be a predictor of both in-hospital and 1-year mortality (Table 4). Other predictors of in-hospital mortality included older age and persistently positive blood cultures, while other predictors of 1-year mortality were nosocomial acquisition of infection, CHF as a complication, and intracardiac abscess (Table 4).

Detailed data regarding antifungal therapy were obtained for 33 patients using the supplemental CRF. The majority of patients received either an amphotericin B-based regimen ($n = 11$) or an echinocandin-based regimen ($n = 14$) (Table 5). Of the remaining patients, 6 received primarily azole-based therapy and 2 received a combination of amphotericin B and an echinocandin. The two patients receiving both amphotericin B and an echinocandin as their primary backbone regimen were excluded from the analysis when comparing the two therapies. Overall, 45% of patients received combination antifungal therapy at some point during treatment. The most common concomitantly prescribed antifungal was flucytosine, followed by fluconazole.

Treatment regimens were highly varied, with many patients undergoing sequential changes in therapy. The most common reason for a change in therapy was renal failure, followed by transition to suppressive therapy. Overall, 21/33 (64%) patients received amphotericin B at some point during their treatment course. Twelve of these patients (57%) developed acute kidney injury necessitating a change in therapy: amphotericin B therapy was discontinued altogether in 8 patients (38%) and changed to a lipid-based preparation of amphotericin B in the remaining 4 patients. Discontinuation of therapy due to adverse events was not observed in any patients receiving echinocandin-based therapy.

There was a higher percentage of older patients in the echinocandin group than in the amphotericin B group (Table 5). The majority of infections in the amphotericin B group were community acquired (82%), compared to less than half of the infections in the echinocandin group (42%) ($P = 0.05$). The rates of utilization of combination antifungal therapy, suppressive antifungal therapy, and adjunctive surgery did not differ between the two groups. Mortalities measured at all 3 time points (in hospital, 42 days, and 1 year) did not differ between the two groups (Table 5).

TABLE 3 Characteristics of those receiving adjunctive surgical treatment versus medical therapy alone for overall cohort

Parameter[a]	No. (%)		
	Adjunctive surgery ($n = 32$)	Medical therapy alone ($n = 38$)	P^b
Age			
Mean ± SD, yr	47.9 ± 17.0	59.7 ± 15.3	**<0.01**
≥50 yr	16 (50)	28 (74)	**0.04**
Organism			
C. albicans	14 (44)	17 (45)	0.85
C. parapsilosis	12 (38)	7 (19)	0.08
Other	6 (19)	13 (35)	0.13
Community acquired	10 (36)	9 (24)	0.29
Risk factors			
Prosthetic valve	15 (47)	17 (45)	0.86
Predisposing valve condition	7 (22)	11 (29)	0.50
Congenital heart disease	5 (16)	3 (8)	0.45
Endocavitary device	7 (22)	7 (18)	0.72
Previous IE	9 (28)	9 (24)	0.72
CHF	6 (19)	11 (29)	0.32
Renal disease	5 (16)	13 (34)	0.08
Liver disease	3 (9)	3 (8)	1.00
Diabetes mellitus	8 (25)	7 (18)	0.50
Cancer	3 (9)	6 (16)	0.49
IVDA	5 (16)	3 (8)	0.46
Echocardiographic complications			
Regurgitation	20 (65)	17 (46)	0.13
Paravalvular complication	6 (19)	7 (19)	0.99
Prosthetic valve complication	7 (47)	4 (24)	0.27
Clinical complications			
Stroke	4 (13)	4 (11)	1.00
Embolization	13 (41)	11 (29)	0.31
CHF	9 (28)	13 (34)	0.58
Intracardiac abscess	12 (38)	5 (13)	**0.02**
Mycotic aneurysm	1 (3)	1 (3)	1.00
Persistently positive cultures	7 (22)	5 (14)	0.53
Mortality			
In hospital	12 (38)	13 (34)	0.77
1 yr	19 (66)	21 (62)	0.76

[a] Abbreviations: IE, infective endocarditis; CHF, congestive heart failure; IVDA, intravenous drug abuse.
[b] Boldface indicates statistically significant values.

DISCUSSION

Candida IE (CIE) is a rare, but often deadly, disease. To date, our understanding of its clinical features and treatment practices has been based largely on case series and reports. Prospective studies have been small, with the two largest to date including 30 and 33 patients, respectively (1, 2). An earlier study by Baddley et al. included 33 patients from 2000 to 2005 and was the first examination of CIE cases from the ICE database (2). Our current study has an additional 37 patients from 2005 to 2010, making it the largest prospective study to date on this serious infection. It is also the first to compare relatively newer antifungal therapy (echinocandins) to historically standard therapy (amphotericin B).

Similar to prior studies, we found a high proportion of health care-associated infections (1, 2). Data previously reported from the ICE cohort showed a 51.5% incidence of health care-associated infection (2). In our current analysis, this has risen to 67%,

TABLE 4 Predictors of in-hospital and 1-year mortality on univariate analysis for overall *Candida* infective endocarditis cohort[a]

Parameter	In-hospital mortality, no. positive/total no. (%)	RR (95% CI)	1-yr mortality, no. positive/total no. (%)	RR (95% CI)
Organism				
C. albicans	5/19 (26)	1 (ref)	11/18 (61)	1 (ref)
C. parapsilosis	14/31 (45)	1.72 (0.74–4)	19/29 (66)	1.07 (0.68–1.69)
Age (yr)				
≤50	5/26 (19)	1 (ref)	12/22 (55)	1 (ref)
≥50	20/44 (45)	**2.36 (1.01–5.54)**	28/41 (68)	1.25 (0.81–1.93)
Comorbidities				
Native valve	14/38 (37)	1 (ref)	21/32 (66)	1 (ref)
Prosthetic valve	11/32 (34)	0.93 (0.49–1.76)	19/31 (61)	0.93 (0.64–1.36)
Nondiabetic	19/55 (35)	1 (ref)	31/48 (65)	1 (ref)
Diabetes mellitus	6/15 (40)	1.16 (0.56–2.38)	9/15 (60)	0.93 (0.58–1.48)
No CHF at baseline	14/53 (26)	1 (ref)	24/47 (51)	1 (ref)
CHF at baseline	11/17 (65)	**2.45 (1.38–4.33)**	16/16 (100)	**1.96 (1.48–2.59)**
First episode of IE	19/51 (37)	1 (ref)	28/44 (64)	1 (ref)
History of previous IE	6/18 (33)	0.89 (0.43–1.88)	11/18 (61)	0.96 (0.62–1.48)
Clinical complications				
No stroke	24/62 (39)	1 (ref)	36/55 (65)	1 (ref)
Stroke	1/8 (13)	0.32 (0.05–2.07)	4/8 (50)	0.76 (0.37–1.57)
No systemic embolization	17/46 (37)	1 (ref)	28/41 (68)	1 (ref)
Systemic embolization	8/24 (33)	0.90 (0.46–1.78)	12/22 (55)	0.80 (0.52–1.23)
No CHF as complication	14/48 (29)	1 (ref)	20/43 (47)	1 (ref)
CHF as complication	11/22 (50)	1.71 (0.93–3.15)	20/20 (100)	**2.15 (1.56–2.96)**
No intracardiac abscess	17/53 (32)	1 (ref)	27/48 (56)	1 (ref)
Intracardiac abscess	8/17 (47)	1.47 (0.77–2.78)	13/15 (87)	**1.54 (1.12–2.12)**
Bloodstream clearance ≤72 h	14/56 (25)	1 (ref)	29/50 (58)	1 (ref)
Persistently positive blood cultures	9/19 (75)	**3 (1.72–5.25)**	9/11 (82)	1.41 (0.98–2.03)
Echocardiographic complications				
No paravalvular complication	20/56 (36)	1 (ref)	31/51 (61)	1 (ref)
Paravalvular complication	4/13 (31)	0.86 (0.35–2.09)	8/11 (73)	1.20 (0.78–1.83)
No prosthetic valve complication	6/21 (29)	1 (ref)	12/21 (57)	1 (ref)
Prosthetic valve complication	5/11 (45)	1.60 (0.62–4.06)	7/10 (70)	1.22 (0.71–2.12)
Mode of acquisition				
Community acquired	3/19 (16)	1 (ref)	6/16 (38)	1 (ref)
Hospital/health care associated	21/47 (45)	2.83 (0.96–8.38)	32/44 (73)	**1.93 (1.01–3.74)**
Therapy				
Medical therapy alone	13/38 (34)	1 (ref)	21/34 (62)	1 (ref)
Adjunctive surgical therapy	12/32 (38)	1.10 (0.58–2.05)	19/29 (66)	1.06 (0.73–1.54)

[a] Abbreviations: CHF, congestive heart failure; IE, infective endocarditis; RR, risk ratio; CI, confidence interval; ref, reference. Boldface indicates statistically significant values.

which is consistent with data indicating *Candida* as an emerging pathogen for nosocomial bloodstream infections (21). In conjunction with the high proportion of health care-associated infection was the overall advanced age of the CIE population, with nearly half of the patients being over the age of 60. Elderly patients with multiple comorbidities are more likely to have contact with the health care system and thus are more likely to acquire this predominantly nosocomial infection. With respect to community-acquired infection, intravenous drug abuse (IVDA) is classically associated with CIE; nevertheless, fewer than half of community-acquired CIE cases were associated with IVDA. Among those with non-IVDA community-acquired infection, most patients had a prosthetic valve or endocavitary device as risk factors. Community-acquired infection outside IVDA, prosthetic valve, or an endocavitary device was exceedingly rare, occurring in only 3 patients (4%).

The mortality rate for CIE was exceptionally high in our cohort. The in-hospital mortality rate was over one-third, and the 1-year mortality rate approached two-thirds, similar to what has been reported in the literature (1, 2, 7). Despite advances in antifungal therapy and surgical technique, the mortality rate has remained this high throughout studies over time. Furthermore, in our study mortality did not appear to be impacted by either use of adjunctive surgical therapy or choice of antifungal therapy. This is likely reflective of the overall poor health of elderly hospitalized patients with multiple comorbidities who are predisposed to acquiring this infection. Indeed, baseline characteristics such as older age, preexisting heart failure, and nosocomial acquisition

TABLE 5 Antifungal therapy for *Candida* infective endocarditis subgroup analysis

Parameter[a]	No. (%) for group:			P^b
	Overall treatment subgroup ($n = 33$)	Amphotericin B group ($n = 11$)	Echinocandin group ($n = 14$)	
Organism				
C. albicans	13 (39)	3 (27)	3 (21)	1.00
C. parapsilosis	12 (36)	5 (45)	7 (50)	0.82
Other	8 (24)	2 (18)	4 (29)	0.66
Age (yr)				
Mean (95% CI)	61.0 (55.5–66.4)	52.4 (43.4–61.3)	62.5 (52.6–72.4)	0.12
≥50	26 (79)	8 (73)	10 (71)	1.00
≥60	19 (58)	3 (27)	10 (71)	**0.05**
≥70	14 (42)	1 (9)	7 (50)	**0.04**
Community acquired	10 (31)	9 (82)	6 (42)	**0.05**
Risk factors				
Prosthetic valve	13 (39)	3 (27)	7 (50)	0.41
Predisposing valve condition	8 (24)	4 (36)	3 (21)	0.66
Congenital heart disease	1 (3)	0	1 (7)	1.00
Endocavitary device	8 (24)	1 (9)	5 (36)	0.18
Previous IE	8 (24)	4 (36)	2 (14)	0.35
CHF	12 (36)	4 (36)	6 (43)	1.00
Intravenous catheter	16 (52)	5 (50)	4 (29)	0.40
Any prosthetic material	20 (61)	5 (45)	10 (71)	0.24
Renal disease	12 (36)	5 (45)	5 (36)	0.70
Liver disease	5 (16)	3 (33)	1 (7)	0.26
Diabetes mellitus	10 (30)	2 (18)	5 (36)	0.41
Cancer	5 (15)	0	2 (14)	0.49
IVDA	2 (6)	2 (18)	0	0.18
ICU in last 14 days	11 (33)	3 (27)	3 (21)	1.00
Surgery in last 30 days	11 (33)	3 (27)	3 (21)	1.00
TPN	7 (21)	2 (18)	2 (14)	1.00
Echocardiographic complications				
Regurgitation	17 (52)	6 (55)	6 (43)	0.56
Paravalvular complication	8 (24)	2 (18)	3 (21)	1.00
Prosthetic valve complication	4 (31)	1 (33)	0	0.30
Clinical complications				
Stroke	4 (13)	1 (10)	3 (21)	0.61
Embolization	11 (33)	3 (27)	4 (29)	1.00
CHF	13 (39)	3 (27)	7 (50)	0.41
Intracardiac abscess	11 (33)	5 (45)	3 (21)	0.39
Mycotic aneurysm	1 (3)	1 (10)	0	0.42
Persistently positive cultures	2 (6)	0	1 (7)	1.00
Therapy				
Majority regimen combination antifungal therapy	13 (39)	5 (45)	5 (36)	0.62
Any combination antifungal therapy	15 (45)	6 (55)	6 (43)	0.56
Suppressive antifungal therapy received	14 (42)	5 (45)	6 (43)	0.90
Adjunctive surgical therapy	13 (39)	6 (55)	5 (36)	0.35
Mortality				
In hospital	13 (39)	5 (45)	4 (29)	0.43
42 days	14 (42)	5 (45)	5 (36)	0.62
1 yr	21 (66)	7 (64)	9 (69)	1.00

[a] Abbreviations: IE, infective endocarditis; CHF, congestive heart failure; IVDA, intravenous drug abuse; ICU, intensive care unit; TPN, total parenteral nutrition.
[b] *P* value for comparison of amphotericin B-based therapy to echinocandin-based therapy. Boldface indicates statistically significant values.

were all associated with higher mortality on univariate analysis. Higher mortality was also associated with clinical developments such as refractory candidemia and new CHF, features which may help identify candidates for early, aggressive interventions.

Adjunctive surgical therapy has long been considered to be the gold standard in treating CIE. The current IDSA and ESCMID guidelines recommend surgical therapy if possible (14, 15); however, this is based largely on case series and reports as well as expert

opinion. A large meta-analysis published in 2005 reported a trend toward improved survival with surgical therapy, although this did not meet statistical significance (odds ratio [OR], 0.56; confidence interval [CI], 0.16 to 1.99) (7). Interestingly, in that analysis survival among those receiving combination antifungal therapies appeared similar to that of those receiving adjunctive surgical therapy. One conclusion suggested by the authors was that newer antifungal therapies potentially lent hope to those who could not undergo surgical therapy. In our study, mortality did not differ between those undergoing surgical therapy and those receiving medical therapy alone. The two groups appeared similar overall with respect to distribution of comorbidities. Additionally, the surgical group was comprised of younger patients, which should bias the results toward a better outcome with surgical therapy over medical therapy. Acknowledging the small numbers included in each study, similar to the study by Steinbach et al. (7), our study calls into question the dogma of recommending surgical therapy for all patients with CIE, based solely on the organism.

Amphotericin B-based therapy has long been considered the standard therapy for CIE, based largely on experience and case series. The echinocandins are in comparison relatively new agents, having been approved for candidemia only within the past decade. Like amphotericin B, the echinocandins are fungicidal, and similar to the lipid formulations of amphotericin B, they have good activity against candidal biofilms (12, 22, 23). Although the two therapies have been compared for treatment of invasive candidiasis, no studies have compared them for treatment of infective endocarditis (24).

Our study is the first to attempt to compare the amphotericin B- and echinocandin-based therapies for CIE. Despite the limited number of patients in the subgroup analysis comparing therapies, there are still some important findings. There was no difference in mortality between patients receiving the two therapies. The echinocandin group had several factors that should have biased toward a worse outcome, including a statistically significant higher percentage of older patients as well as a higher percentage of nosocomial infection, both of which were shown to be associated with higher mortality on univariate analysis. Additionally, although not statistically significant, there were a higher percentage of patients with prosthetic valves in the echinocandin group. Despite these differences, the mortalities did not differ between the two groups. Coupling this with the substantially lower rate of adverse events, specifically renal failure, associated with echinocandin therapy, echinocandin-based therapy appears to be an attractive option for this disease. Given the observational nature of this study and small sample size, no definitive recommendations can be made; however, our study provides additional supporting evidence for the use of echinocandins in CIE (14).

Our study, like all studies to date on CIE, is limited by small sample size. While the overall cohort represents the largest prospective cohort to date, the subgroup for antifungal therapy was small at only 33 patients. This may have limited our ability to demonstrate statistically significant differences between the therapy groups. Additionally, we were limited to analyzing antifungal therapy in only those patients whose enrolling sites completed the supplemental CRF, which could result in selection bias. Although the majority of the data were collected prospectively, the data on antifungal therapy were obtained retrospectively. Since this is an observational study, definitive conclusions about antifungal treatment regimen cannot be drawn; however, a randomized treatment trial for CIE would be logistically impossible to perform.

In conclusion, CIE is a rare but potentially devastating infection that affects older individuals with health care exposure. Although our study is small, it lends support to a growing body of evidence for the use of echinocandin-based therapy in the treatment of CIE based on a lower rate of renal dysfunction and similar mortality. Furthermore, similar to a previous study, our study calls into question the necessity of surgical therapy as a rule in all patients with CIE. Although the rarity of this disease makes it challenging to investigate, future studies are needed to validate these findings.

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