Candida Infective Endocarditis During the Infectious Diseases and Substance Use Disorder Syndemic: A Six-Year Case Series

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Treatment for *Candida* infective endocarditis (IE) has not been extensively studied in the setting of rising injection drug use. There were 12 cases of *Candida* IE at the Maine Medical Center between 2013 and 2018. The patient characteristics, treatment regimens, and outcomes were retrospectively analyzed.

Keywords. amphotericin B; *Candida*; echinocandins; endocarditis; injection drug use (IDU).

Fungal infective endocarditis (IE) accounts for approximately 2% of IE cases and is associated with hospital mortality rates up to 33%–47% [1–3]. Risk factors include prosthetic valve implantation, cardiac implantation devices, and injection drug use (IDU) [4–6]. The epidemiological profile for IE has evolved over time, including an increase in IDU and prosthetic valve and cardiac device implantations [7–9]. The Infectious Diseases Society of America Candidiasis and American Heart Association Endocarditis guidelines recommend treatment of *Candida* endocarditis with either amphotericin B with or without flucytosine, or high-dose echinocandin therapy, followed by an oral azole for lifelong suppression [4, 5]. This recommendation is based on limited data consisting of observational studies and case reports demonstrating no difference in efficacy between treatment options [1, 10]. In addition, people who inject drugs (PWID) are underrepresented in these studies, and rising IDU rates make this an increasingly prevalent risk factor for *Candida* IE. In the setting of a surge of fungal IE cases at our facility, we sought to characterize *Candida* IE at a large academic teaching hospital heavily impacted by increasing IDU [11].

METHODS

A retrospective review was performed to identify patients with *Candida* IE at the Maine Medical Center, which is a 637-bed, academic, tertiary care facility located in Portland, Maine. Patients with blood cultures positive for *Candida* spp from January 2013 through December 2018 were evaluated for provider-diagnosed *Candida* IE. Patient and endocarditis characteristics, microbiology, treatment regimens, and outcomes were collected.

Injection drug use was defined as any history of self-reported or suspected IDU as documented in the provider note. Initial treatment was defined as the first antifungal therapy started within 24 hours after the first positive blood culture. Any combination regimen was defined as at least 2 antifungals used concomitantly for more than 3 days of the first 30 days of therapy. Time to clearance of fungemia was defined as the number of days between the first positive and negative blood culture. Time to surgery was defined as the number of days between the first positive blood culture and surgery.

RESULTS

Of 77 patients with candidemia, 12 patients (16%) were diagnosed with *Candida* IE. Baseline characteristics are shown in Table 1. Eight patients (67%) reported any history of IDU. Six patients (50%) reported IDU within 6 months of diagnosis, and 2 patients (17%) self-reported sobriety for 1 and 12 years. Self-reported drugs used included heroin, methamphetamines, cocaine, buprenorphine/naloxone, benzodiazepines, and oxycodone.

Cardiac and microbiology characteristics, treatment regimens, and outcomes are shown in Table 2. Cardiac imaging confirmed vegetation in all patients, 2 patients via transthoracic echocardiogram and 10 patients via transesophageal echocardiogram. Fifty percent of patients (n = 6) had prosthetic valve IE. Infective endocarditis was classified as left-sided in 10 patients (83%), with 3 and 7 patients having an affected mitral and aortic valve, respectively. Right-sided IE was diagnosed in 3 patients (25%). One patient had multivalvular IE, with both aortic and pulmonic valve vegetations. A vegetation larger than 1 centimeter was documented in 6 patients (50%). Six patients had a history of prior IE, 4 (67%) of which reported any history of IDU. Five patients had bacterial IE and 1 patient had fungal IE.

Candida parapsilosis was the most commonly implicated organism (n = 8, 67%), followed by *Candida glabrata* (n = 3, 25%) and *Candida albicans* (n = 1, 8%). Of the 8 patients reporting

Table 1. Baseline Characteristics of Twelve Patients With *Candida* Endocarditis With and Without History of Injection Drug Use[a]

Characteristics	Overall (n = 12)	Non-IDU Group (n = 4)	IDU Group (n = 8)
Age, years, median (range)	43 (30–76)	59 (37–76)	41 (30–51)
Male gender	9 (75)	2 (50)	7 (87.5)
Race, white	12 (100)	4 (100)	8 (100)
Comorbidities			
Diabetes	2 (16.7)	2 (50)	0 (0)
End-stage renal disease	1 (8.3)	1 (25)	0 (0)
Congestive heart failure	1 (8.3)	1 (25)	0 (0)
Chronic hepatitis C	6 (50)	0 (0)	6 (75)
Malignancy, active	0 (0)	0 (0)	0 (0)
HIV	0 (0)	0 (0)	0 (0)
ICU admission	11 (91.7)	4 (100)	7 (87.5)
Infectious diseases consult	12 (100)	4 (100)	8 (100)
Length of stay, days, median (range)	34 (8–97)	19 (13–26)	48.5 (8–97)

Abbreviations: ICU, intensive care unit; IDU, injection drug use; HIV, human immunodeficiency virus.

[a]Data are presented as n (%) unless otherwise indicated.

IDU, 7 were infected with *C parapsilosis* (88%) and 1 was infected with *C glabrata* (13%). The micafungin minimum inhibitory concentration (MIC) median was 1 mcg/mL (range, 0.5–2) for *C parapsilosis* compared with MIC of ≤0.008 mcg/mL and 4 mcg/mL for *C glabrata* and 0.015 mcg/mL for *C albicans*. Three patients (25%) were treated for polymicrobial endocarditis, all of whom had history of IDU.

Initial antifungal regimens included micafungin (n = 8, 67%), amphotericin B (n = 3, 25%), and amphotericin B and flucytosine (n = 1, 8%). Throughout the treatment course, 7 patients (58%) received treatment with any combination regimen, and 8 patients (67%) received suppressive therapy with fluconazole on discharge. Median time spent on initial regimen was 10 days (range, 3–40). Median duration of intravenous antibiotics was 21 days (range, 8–98). Seven patients (58%) underwent cardiac surgery, with a median time to surgery of 8 days (range, 3–54). Fluconazole was not prescribed to 4 patients (33%) due to death, discharge to hospice, leaving hospital early, and an adverse reaction to fluconazole. The fluconazole reaction was due to QTc prolongation (670 ms) with concurrent amiodarone. Of note, this patient did have cardiac surgery and had documented plans for rechallenge with fluconazole once amiodarone was discontinued.

The median time to clearance of fungemia was 8 days (range, 0–31). In patients with prolonged clearance of fungemia greater than 72 hours, *C parapsilosis* was the implicating pathogen, and 5 of these 8 patients (62.5%) received micafungin as initial therapy. Of these 5 cases, 4 patients were switched to amphotericin B and flucytosine due to persistent fungemia.

In-hospital and 90-day mortality were 8% (n = 1) and 16% (n = 2), respectively. All remaining patients touched base with the healthcare system at least 1 year after admission. Five patients (50%) were readmitted within 90 days. Reasons for readmission included congestive heart failure (n = 1, non-PWID),

Clostridioides difficile colitis (n = 1, non-PWID), acute kidney injury (n = 1, non-PWID), calf pain (n = 1, PWID), and leaving the hospital early (n = 2, PWID). Six PWID (75%) were treated with medication for opioid use disorder on discharge.

DISCUSSION

Candida IE is a rare but serious disease with increasing prevalence in patients with history of IDU. Previous studies report lower rates of IDU in patients with *Candida* IE (10%–30%) compared with our cohort (67%) [1, 3, 10]. The majority of our cohort was diagnosed with *Candida* IE in 2017 and 2018 and were PWID, supporting the observation of a recent rise in IDU prevalence and related comorbidities. Previous studies found that patients who survived often had a history of IDU and were younger, suggesting that these factors in our population could be contributory to the lower mortality rates in our cohort compared with other studies [1, 3, 10, 11]. Prior studies have compared pathogen acquisition, predisposing conditions, surgical intervention, and mortality in IDU vs non-IDU with IE, but data are lacking on differences in fungal organisms or specific treatments between these groups [11, 12]. The implicated pathogen in our cohort was predominantly *C parapsilosis* (67%), which is higher than previous studies (15%–33%) [1, 3, 10]. Because the majority of PWID were infected with *C parapsilosis*, there is potential benefit in further exploration of this relationship.

In our cohort, the majority of patients infected with *C parapsilosis* were treated empirically with micafungin (n = 5, 62.5%); however, 4 of these patients required a change in therapy due to persistent fungemia. Although generalized conclusions cannot be made regarding the relationship between *Candida* IE, IDU, and best empiric therapy, the data collected from these 12 patients suggest the necessity for further evaluation of the best empiric treatment regimen for

Table 2. Cardiac and Microbiology Characteristics, Treatment Regimens, and Outcomes of Twelve Patients With *Candida* Endocarditis

Patient	Year	Age (years), Gender	IDU	Site Involved	Pathogen	History of IE	Medical Treatment	Disposition	Surgery (time to surgery, days)	Time to Clearance of Fungemia (days)
1	2014	66 F	No	Native AV	*C glabrata*	No	MICA 150 mg q24h × 19d + FLU × 11d	SNF on FLU	No	3
2	2015	52 M	No	Prosthetic AV	*C glabrata*	Yes	LAMB 4 mg/kg q24h + 5FC 1500 mg q24h × 7d	Died day 7	No	No (unknown)[a]
3	2015	37 M	No	Prosthetic PV	*C parapsilosis*	Yes	LAMB 3 mg/kg q24h × 9d; FLU × 8d	Home on FLU	Yes (3)	5[b]
4	2016	41 M	Yes	Native bicuspid AV	*C parapsilosis*	No	MICA 100 mg q24h × 1d; MICA 150 mg q24h × 2d; AMB-d 60 mg q24h × 31d + 5FC 2000 mg q6h × 11d; LAMB 2.7 mg/kg q24h × 18d; FLU PO 400 mg × 1d	Homeless shelter on FLU	Yes (9)	10[b]
5	2017	76 F	No	Prosthetic AV[c]	*C albicans*	No	MICA 150 mg q24h × 19d	SNF on FLU	No	0.5
6	2017	51 M	Yes	Prosthetic MV	*C parapsilosis*[d]	Yes	LAMB 4.6 mg/kg q24h × 13d; LAMB 5.5 mg/kg q24h × 17d + FLU × 6d	Hospice	No	20
7	2017	45 M	Yes	Native AV and PV	*C parapsilosis*	Yes	LAMB 5 mg/kg q24h × 39d; FLU × 2d; MICA 150 mg q24h × 13d	Home on FLU	Yes (6)	7[b]
8	2018	36 M	Yes	Native AV	*C parapsilosis*	No	MICA 150 mg q24h × 10d; LAMB 5.3 mg/kg q24h × 6d; LAMB 5.3 mg/kg q24h + 5FC 500 mg q6h × 9d; LAMB 5.3 mg/kg q24h + 5FC 500 mg q6h + MICA 150 mg q24h × 20d; LAMB 5.3 mg/kg q24h + MICA 150 mg q24h × 54d	Home on FLU	Yes (54)	31
9	2018	36 M	Yes	Native MV	*C parapsilosis*	No	MICA 150 mg q24h × 7d; LAMB 5 mg/kg q24h × 15d, LAMB 3.5 mg/kg q24h × 11d + 5FC 1500 mg q6h × 30d + FLU × 2d; FLU × 17d	Home on FLU	Yes (15)	17[b]
10	2018	50 M	Yes	Native bicuspid AV	*C parapsilosis*	No	MICA 150 mg q24h × 6d; FLU 400 mg q24h × 4d; MICA 150 mg q24h × 15d	Shelter on MICA	Yes (6)	8[b]
11	2018	30 F	Yes	Prosthetic TV	*C glabrata*[e]	Yes	MICA 150 mg q24h × 8d	Left hospital early	No	2
12	2018	34 M	Yes	Prosthetic MV	*C parapsilosis*[f]	Yes	MICA 150 mg q24h × 5d; LAMB 4.2 mg/kg × 5d, LAMB 3.2 mg/kg × 29d + 5FC 2500 mg q6h × 6d; FLU 800 mg × 1d	Home on FLU	Yes (8)	8

Abbreviations: 5FC, flucytosine; AMB-d, amphotericin B deoxycholate; AV, aortic valve; d/c, discharge; F, female; FLU, fluconazole; IE, infective endocarditis; IDU, injection drug use; IVC, inferior vena cava; LAMB, liposomal amphotericin B; M, male; MICA, micafungin; MV, mitral valve; PV, pulmonic valve; SNF, skilled nursing facility; TV, tricuspid valve.

[a]Patient deceased before clearance of fungemia.

[b]Time to clearance of fungemia exceeds surgery based on delays in obtainment of final blood cultures.

[c]Patient had an intracardiac device (pacemaker, IVC filter).

[d]Patient was cotreated for methicillin-resistant *Staphylococcus aureus* bacteremia.

[e]Patient was cotreated for polymicrobial bacteremia with multiple Gram-positive and Gram-negative organisms.

[f]Patient was cotreated for *Enterobacter cloacae*.

Candida endocarditis in PWID. Due to the superior safety profile of echinocandins compared with amphotericin B, it is an appealing therapy to treat *Candida* IE that has not been adequately explored, especially in PWID. A recent study conducted by Rivoisy et al [13] reported outcomes for 46 patients with prosthetic valve *Candida* endocarditis. Most patients were infected with *C parapsilosis* (n = 19, 41%) and 9 patients (20%) reported IDU. Patients who received liposomal amphotericin B therapy alone had better 6-month survival rates than those who received echinocandins. Further exploration is needed to provide more insight into choosing empiric treatment for *Candida* IE in PWID.

All cases of polymicrobial endocarditis (n = 3) in our cohort were in PWID. Previous studies have not commented on the prevalence of polymicrobial endocarditis, which is a comorbid condition that could impact treatment outcomes. It is important that concurrent bacteremia in patients with *Candida* IE is examined further, especially in the context of IDU.

In addition, it is important to consider the increased risk of bacterial and fungal infections due to unsafe and unsterile injection practices [14]. Data regarding injection practices were unavailable in our cohort; however, existing literature indicates that the use of lemon juice or vinegar to dissolve base heroin and crack cocaine can increase risk for *Candida* infections [15]. It would be valuable to further investigate the relationship between injection practices and fungal infections such as *Candida* IE to contribute to preventive care and harm reduction awareness.

Limitations of our study include the small sample size and the retrospective design. *Candida* IE diagnosis was determined through retrospective review of positive blood cultures, resulting in potential missed diagnoses in patients that were transferred for cardiothoracic surgery and may have cleared cultures before arrival. Due to retrospective design, IDU was defined as any self-reported or provider-documented IDU history, leading to inaccurate reports and potential overestimation of active IDU. Selection bias in choosing empiric therapy cannot be ruled out due to variations in treatment preferences.

CONCLUSIONS

The higher prevalence of IDU and *C parapsilosis* in patients at a large academic facility heavily impacted by the drug epidemic contributes to the limited literature regarding treatment outcomes for *Candida* IE in PWID. Further studies are needed to investigate treatment outcomes for *Candida* IE during the drug use epidemic.

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