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MAJOR ARTICLE

Candidemia in Patients With Cardiovascular Implantable Electronic Devices: Uncertainty in Management Based on Current International Guidelines

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Background. In contrast to bloodstream infection due to a variety of bacteria in patients with cardiovascular implantable electronic devices (CIED), there are limited data regarding candidemia and risk of CIED infection.

Methods. All patients with candidemia and a CIED at Mayo Clinic Rochester between 2012 and 2019 were reviewed. Cardiovascular implantable electronic device infection was defined by (1) clinical signs of pocket site infection or (2) echocardiographic evidence of lead vegetations.

Results. A total of 23 patients with candidemia had underlying CIED; 9 (39.1%) cases were community onset. None of the patients had pocket site infection. The duration between CIED placement and candidemia was prolonged (median 3.5 years; interquartile range, 2.0–6.5). Only 7 (30.4%) patients underwent transesophageal echocardiography and 2 of 7 (28.6%) had lead masses. Only the 2 patients with lead masses underwent CIED extraction, but device cultures were negative for *Candida* species. Two (33.3%) of 6 other patients who were managed as candidemia without device infection subsequently developed relapsing candidemia. Cardiovascular implantable electronic device removal was done in both patients and device cultures grew *Candida* species. Although 17.4% of patients were ultimately confirmed to have CIED infection, CIED infection status was undefined in 52.2%. Overall, 17 (73.9%) patients died within 90 days of diagnosis of candidemia.

Conclusions. Although current international guidelines recommend CIED removal in patients with candidemia, the optimal management strategy remains undefined. This is problematic because candidemia alone is associated with increased morbidity and mortality as seen in this cohort. Moreover, inappropriate device removal or retention can both result in increased patient morbidity and mortality.

Keywords. candidemia; cardiovascular implantable electronic device; diagnosis; outcome; relapse.

Occult bloodstream infections (BSIs) in patients with cardiovascular implantable electronic device (CIED) may result in devastating outcomes [1]. These infections can be indicative of CIED infection, hematogenous seeding of a CIED from an ectopic nidus of infection, or ectopic infection without CIED infection [2]. Establishing an accurate diagnosis of CIED infection is critical because management may require complete CIED removal, which is associated with both risks of mortality and significant financial costs. The likelihood of CIED infection after BSI varies widely depending on the type of bacteria. This makes diagnosis more challenging and has received considerable attention in the current literature [3–5].

Candidemia often occurs in older patients with multiple comorbid conditions and underlying medical devices including CIED [6, 7]. However, the risk of CIED infection with candidemia is not as well defined compared with that with bacteremia [8]. This is partly because CIED infections due to *Candida* species are rare [9]. In addition, the optimal approach to managing patients with candidemia in the setting of a CIED is not well established. Therefore, we retrospectively reviewed our institutional data to further examine the clinical course of candidemia in patients with CIED.

MATERIALS AND METHODS

Study Design

We conducted a retrospective study of all consecutive, adult patients (age 18 years or older) with cardiovascular implantable electronic device who developed candidemia and were hospitalized from January 1, 2012 to December 31, 2019 at

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the Mayo Clinic, Rochester, Minnesota. Patients were excluded if (1) they had an left ventricular assist device (LVAD) or (2) declined Minnesota research authorization to use their medical records for research. Both the Mayo Clinic Cardiovascular Clinical Database and Mayo Data Explorer software were used to identify patients. Charlson comorbidity index (CCI) scores were calculated using automated extraction of diagnosis codes. All other variables including baseline demographic, clinical course, treatment, and outcomes were manually abstracted from electronic medical records. The primary objective of the study was to describe the clinical characteristics and outcome of patients with CIED who developed candidemia.

Patient Consent Statement

The study was reviewed and granted an exempt status by Mayo Clinic Institutional Review Board (IRB) (Study IRB number 20-009376). The research was conducted according to the Helsinki Declaration guidelines. An individual written informed consent for patients was waived due to the use of deidentified and retrospective data.

Definitions

Cardiovascular implantable electronic device included automatic implantable cardioverter-defibrillators (AICD), cardiac resynchronization therapy (CRT) devices, and permanent pacemakers (PPMs). Candidemia was defined as a positive blood culture with *Candida* species [6]. Community-onset candidemia was defined as a positive blood culture obtained <3 days after admission [10]. Due to its rarity, the 2010 Scientific Statement from the American Heart Association on the management of CIED infection [8] and the 2019 European Heart Rhythm Association (EHRA) International Consensus document [11] did not provide standard guidance on the diagnosis of candidal CIED infection; in our study, this was defined by either (1) clinical sign of pocket site infection or (2) presence of lead vegetation in the setting of candidemia. Time to positivity was the duration from the time of blood culture collection to the time of *Candida* growth. Duration of candidemia was the duration from the first day of positive blood culture until the first day of negative blood culture (if available). Complete CIED extraction was removal of the generator, including all leads and lead material from the generator and the cardiovascular space. Relapse of candidemia was defined as a positive blood culture with the same *Candida* species at any time frame after resolution of the initial candidemia episode.

Statistical Analysis

Descriptive statistics were used and reported as median (interquartile range [IQR]) for continuous variables and count (percentage) for categorical variables. Kaplan-Meier curve was plotted to demonstrate the 90-day survival. All analyses were performed using R statistical software (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

RESULTS

Baseline Demographics

A total of 541 patients developed candidemia during the study period and 29 (5.4%) of them had a CIED at the time of candidemia. Six patients were excluded because they also had an LVAD; thus, a total of 23 patients were included in the study. Detailed baseline demographics are listed in Table 1. The median age was 73 years (IQR, 62.5–77.0). Eleven (47.8%) patients were female and 20 (87.0%) were White. The median CCI was 4 (IQR, 2–7). Types of CIED included 12 (52.2%) PPM, 8 (34.8%) AICD, and 3 (13.0%) CRT devices. None of the patients had multiple CIEDs or a prior history of CIED infection.

Clinical Courses

The median time from CIED placement to candidemia episode was 3.5 years (IQR, 2.0–6.5). The most common *Candida* species was *Candida glabrata* (current nomenclature:

Table 1. Baseline Demographics of 23 Patients With CIED Who Developed Candidemia From 2012 to 2019

	Total of 23 Patients
Clinical variables	Count (%) or Median [IQR]
Age, years	73.0 [62.5–77.0]
Female sex	11 (47.8%)
Race	...
White	20 (87.0%)
Hispanic	2 (8.7%)
Black	1 (4.3%)
Coronary artery diseases	13 (56.5%)
History of coronary artery bypass graft	5 (21.7%)
Atrial fibrillation/flutter	8 (34.8%)
Heart failure	15 (65.2%)
Congenital heart diseases	2 (8.7%)
Prosthetic heart valve	6 (26.1%)
Other valvular heart disease	6 (26.1%)
History of cerebrovascular accident	4 (17.4%)
Peripheral vascular diseases	1 (4.3%)
Diabetes mellitus	7 (30.4%)
Chronic kidney diseases stage 3 or worse	4 (17.4%)
End-stage kidney disease requiring hemodialysis	5 (21.7%)
Morbid obesity	2 (8.7%)
Chronic pulmonary diseases	4 (17.4%)
End-stage liver diseases	3 (13.0%)
Active solid organ malignancy	6 (26.1%)
Active hematologic malignancy	3 (13.0%)
Solid organ transplantation	1 (4.3%)
Chronic total parenteral nutrition	1 (4.3%)
Prior history of CIED infection	0 (0.0%)

Abbreviations: CIED, cardiovascular implantable electronic device; IQR, interquartile range.

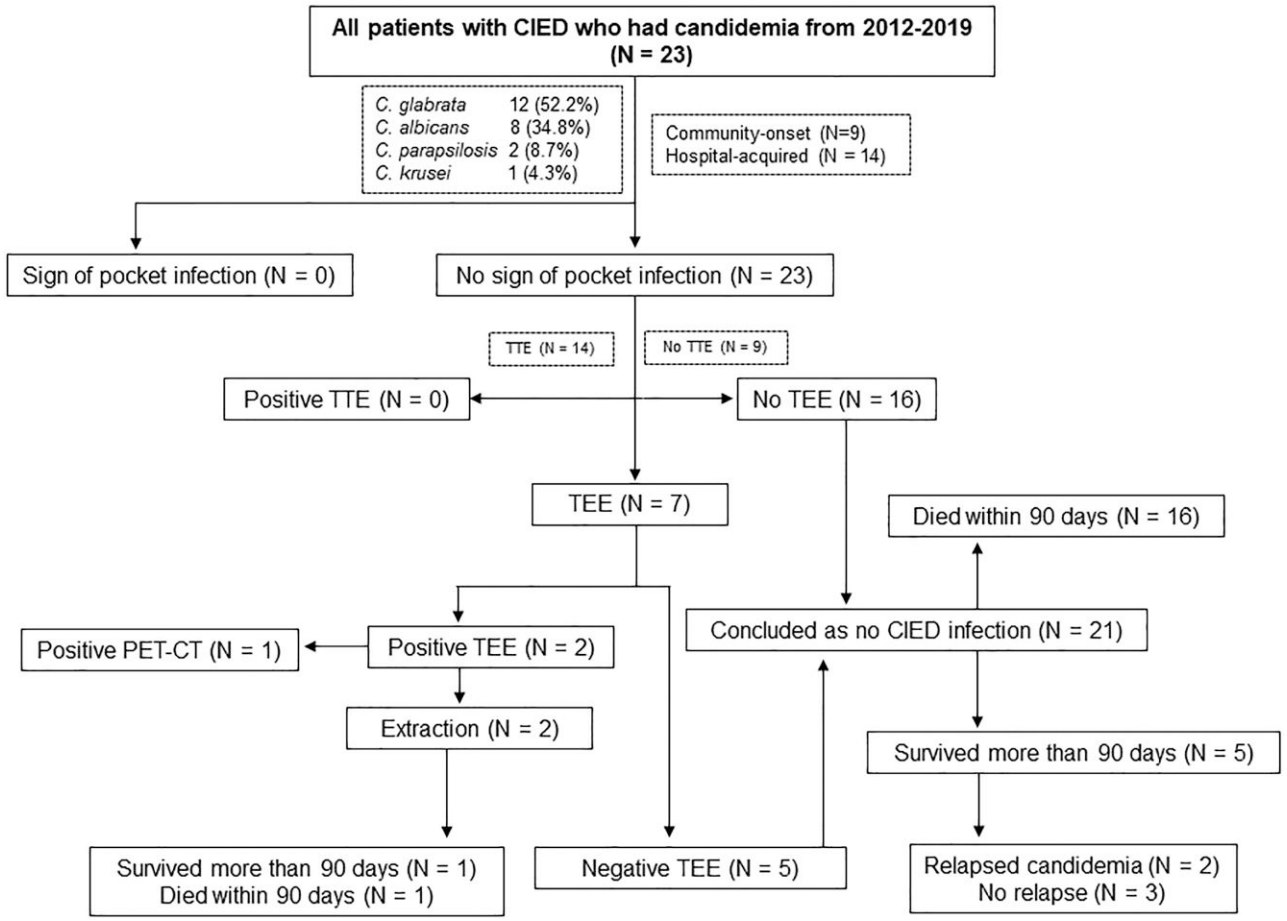

Figure 1. Clinical course of 23 patients with cardiovascular implantable electronic device (CIED) who developed candidemia from 2012 to 2019. PET-CT, positron emission tomography-computed tomography; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Nakaseomyces glabrata) (N = 12, 52.2%) followed by *Candida albicans* (N = 8, 34.8%), *Candida parapsilosis* (N = 2, 8.7%), and *Candida krusei* (current nomenclature: *Pichia kudriavzevii*) (N = 1, 4.3%). Nine (39.1%) patients had community-onset candidemia. The median time to positivity was 35 hours (IQR, 29.0–56.0) with a median duration of candidemia of 2.5 days (IQR, 2.0–5.0). None of the patients had signs of CIED pocket site infection. Fourteen (60.9%) patients had intra-abdominal infection as a source of candidemia, whereas 5 (21.7%) patients had central venous catheter-related candidemia. Urinary tract and epidural abscess were sources of candidemia in 1 (4.3%) patient each. Two (8.7%) patients had no defined source of candidemia.

Infectious diseases consultation was obtained in 20 (87.0%) patients. Fourteen (60.9%) patients underwent transthoracic echocardiography (TTE) and no vegetations were seen. Seven (30.4%) patients underwent TEE and 2 of 7 (28.6%) patients had lead masses. Of the 16 patients who did not undergo TEE, the following factors were listed as responsible and included: (1) palliative approach shortly after candidemia (N = 10), (2) death at the time of candidemia (N = 2), and (3) unknown (because the plan for TEE was not mentioned in any clinical documentation) (N = 2), (4) planning for TEE if TTE positive (N = 1) and (5) planning for TEE if candidemia is persistent (N = 1). One patient with a lead mass underwent 18F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT), which showed possible FDG uptake along the CIED lead.

Nineteen (82.6%) patients received empiric antifungal therapy at the time of candidemia: 12 caspofungin, 3 anidulafungin, 3 fluconazole, and 1 micafungin. Four patients who did not receive antifungal therapy were either transitioned to comfort care or had blood cultures reported after death. The 2 patients with lead masses underwent CIED extraction: 1 complete, and 1 partial (retained epicardial lead). No other patients underwent device extraction. Details of the clinical course of all patients are outlined in Figure 1 and Table 2.

Clinical Outcomes

Seventeen (73.9%) patients died within 90 days of the candidemia episode (Figure 2) including 1 of the 2 patients who

Table 2. Detailed Clinical Course of 23 Patients With CIED Who Developed Candidemia From 2012 to 2019

Case	Age/ Gender	CIED	Time to Candidemia From CIED Placement (Years)	Organism	Duration of Candidemia (Days)	Source	TEE[b]	Reasons for No TEE During an Index Hospitalization	Extraction
1[a]	55/M	CRT	4.0	*Candida albicans*	5	Unknown	Pos	N/A	Complete
2[a]	76/M	AICD	2.8	*C albicans*	7	CVC	Pos	N/A	Partial
3[a]	62/F	AICD	8.2	*Candida parapsilosis*	1	CVC	N/A	Planning for TEE if persistent candidemia	No[d]
4[a]	68/F	PPM	1.7	*C albicans*	1	Unknown	N/A	Unknown[c]	No[d]
5	31/F	PPM	3.4	*Candida glabrata*	N/A	IAI	N/A	Death at the time of candidemia	No
6	94/F	PPM	4.7	*C albicans*	N/A	IAI	N/A	Death at the time of candidemia	No
7	65/F	PPM	1.8	*C glabrata*	1	IAI	Neg	N/A	No
8	75/M	AICD	12.3	*Candida krusei*	N/A	IAI	N/A	Palliative approach shortly after candidemia	No
9	84/M	PPM	0.1	*C glabrata*	N/A	CVC	N/A	Palliative approach shortly after candidemia	No
10	76/M	PPM	2.5	*C albicans*	N/A	IAI	N/A	Palliative approach shortly after candidemia	No
11	75/M	PPM	0.0	*C albicans*	2	IAI	Neg	N/A	No
12	75/M	AICD	3.5	*C glabrata*	5	IAI	N/A	Palliative approach shortly after candidemia	No
13	61/M	CRT	23.0	*C glabrata*	2	CVC	N/A	Palliative approach shortly after candidemia	No
14	70/F	PPM	20.9	*C parapsilosis*	2	IAI	Neg	N/A	No
15	83/M	CRT	2.3	*C glabrata*	9	IAI	N/A	Palliative approach shortly after candidemia	No
16	51/M	AICD	1.2	*C albicans*	2	CVC	N/A	Palliative approach shortly after candidemia	No
17	78/F	PPM	9.1	*C glabrata*	8	IAI	N/A	Palliative approach shortly after candidemia	No
18	52/F	PPM	1.6	*C glabrata*	7	IAI	Neg	N/A	No
19	63/M	AICD	5.4	*C glabrata*	1	IAI	N/A	Unknown[c]	No
20	93/F	PPM	3.3	*C albicans*	2	IAI	N/A	Palliative approach shortly after candidemia	No
21	81/M	AICD	5.1	*C glabrata*	3	Urinary	N/A	Palliative approach shortly after candidemia	No
22	72/F	PPM	3.8	*C glabrata*	4	Epidural abscess	N/A	Planning for TEE if positive TTE	No
23	73/F	AICD	7.6	*C glabrata*	3	IAI	Neg	N/A	No

Abbreviations: AICD, automatic implantable cardioverter-defibrillator; CIED, cardiovascular implantable electronic device; CRT, cardiac resynchronization therapy; CVC, central venous catheter; F, female; IAI, intra-abdominal infection; M, male; N/A, not applicable; Neg, negative; Pos, positive for vegetation on the lead; PPM, permanent pacemaker; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a]Four cases of known CIED infection (see Supplementary Table 1).

[b]Only initial TEE; did not include TEE for the relapsed episode.

[c]Plan for TEE was not mentioned in any clinical documentation.

[d]CIED was not extracted at an initial episode but was extracted at the relapsing episode.

underwent device extraction. Two of six patients who survived beyond 90 days had relapse of candidemia and were subsequently diagnosed with CIED infection. Among 23 patients with CIED who developed candidemia, a total of 4 (17.4%) patients had confirmed candidal CIED infection; 7 (30.4%) patients had no clear evidence of CIED infection (negative TEE or no relapse for at least 90 days after onset of candidemia); 12 (52.2%) patients had an unknown status of CIED infection (no TEE and died within 90 days of candidemia onset). Details of clinical outcome and brief descriptions of 4 patients with CIED infection can be found in the Table 3 and Supplementary Table 1.

DISCUSSION

In contrast to our understanding of the risk of CIED infection in the setting of bacteremia due to a variety of Gram-positive and Gram-negative organisms, the risk of CIED infection in the setting of candidemia is mainly undefined. To date, only case reports and case series exist that describe CIED infection due to patients with fungemia. Indeed, the only systematic review on this topic was largely limited to case reports and case series with 48 cases from 41 different publications [12, 13]. We noted that the review included a variety of fungal infections and did not include definition of CIED infection. Based on this

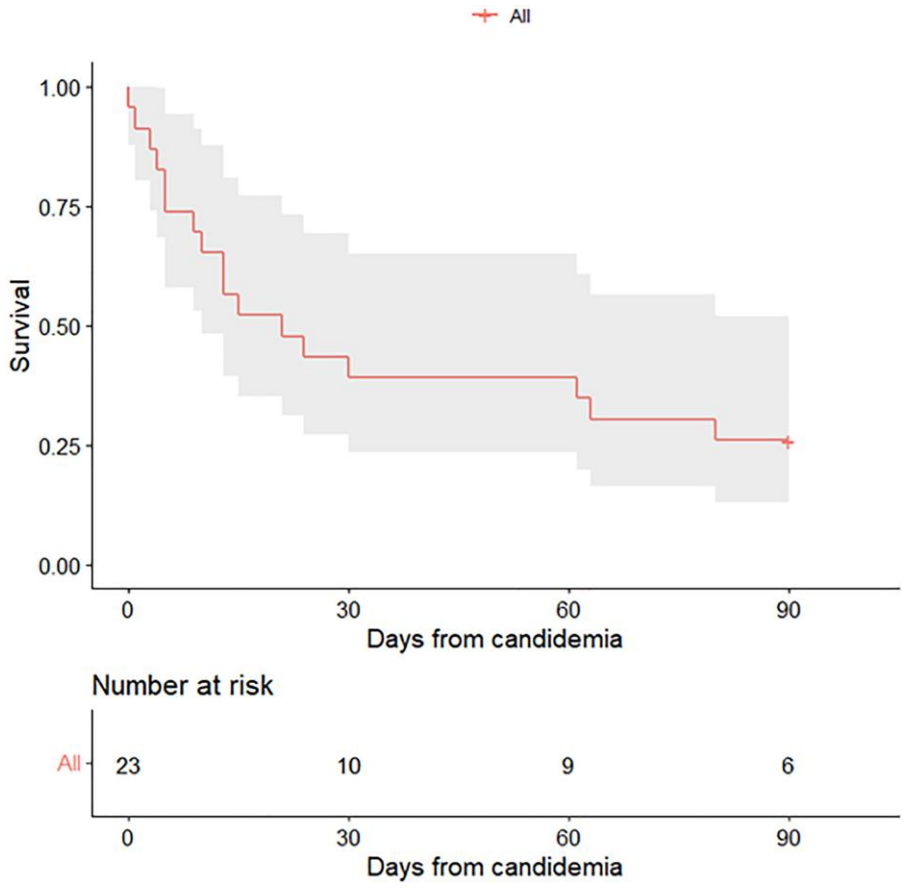

Figure 2. Kaplan-Meier curve demonstrating 90-day survival for 23 cardiovascular implantable electronic device patients with candidemia.

limited data, how can we determine optimal diagnostic and management strategies for these patients? This gets to the pivotal question of whether complete CIED removal is warranted in cases of candidemia while recognizing that both action (device removal) and inaction (no device removal) are associated with mortality risk, and, for the former, removal of an uninfected device in a device-dependent patient harbors additional infectious and noninfectious risks. To answer this critical question, we conducted a retrospective review of candidemia cases in the setting of CIED at our institution.

Several observations from our study deserve additional comments. First, BSI due to *Candida* species is characterized by high rates of morbidity and mortality, regardless of whether CIED infection is present. An active population-based surveillance from the Emerging Infections Program demonstrated that an all-cause in-hospital mortality within 7 days of candidemia was 15% and increased to 25% during the entire hospitalization. These high rates are, in part, related to the advanced age and multiple comorbid conditions that typically characterize patients with candidemia as was seen in the present cohort [6, 14]. In addition, previous studies have shown that *Candida* has the ability to form biofilm on the surface of implanted devices. The biofilm-forming ability especially in *C albicans* and *C parapsilosis* may enhance their virulence, which is associated with a worse clinical outcome in candidemia [15–17]. Second, we do not have data from large cohort studies to estimate the expected rate of CIED infection among patients with BSI due to *Candida* species. These data, in contrast, are available for staphylococci, streptococci, enterococci, and Gram-negative bacilli and can be helpful in guiding diagnostic evaluation of CIED infection [2–5, 18]. In our study, 5% of patients with candidemia had a CIED and rates of confirmed infection were 17%. Third, none of our patients presented with evidence of pocket site infection at the time of candidemia. In contrast, most patients with CIED infections due to bacteria presented with pocket site changes that required device extraction to achieve cure. Fourth, the time interval between CIED placement and the onset of candidemia was measured in years in our cohort. This suggests that the pathogenesis of CIED infection due to *Candida* species may be different from that of bacterial pathogens. In particular, the prolonged time interval from the CIED placement suggests that candidemia likely

Table 3. Clinical Outcome of 23 Patients With CIED who Developed Candidemia From 2012 to 2019

Case	Time From Candidemia to Death (Days)	Autopsy	Cause of Death Within 90 Days of Candidemia	Time From Candidemia to Relapse (Days)
1[a]	13	No	Cardiogenic and septic shock	N/A
2[a]	788	No	N/A	N/A
3[a]	N/A	N/A	N/A	68
4[a]	N/A	N/A	N/A	109
5	0	No	Cardiogenic and septic shock	N/A
6	1	No	Septic shock from bowel perforation	N/A
7	3	No	Cardiogenic shock	N/A
8	4	No	Cardiogenic and septic shock	N/A
9	5	No	Decompensated heart failure	N/A
10	5	No	Multiorgan involvement of lymphoma	N/A
11	9	Yes	Systemic candidiasis and multiorgan involvement of metastatic small cell carcinoma. No evidence of CIED or cardiac valve involvement from autopsy.	N/A
12	10	No	ARDS with respiratory failure	N/A
13	13	No	Mesenteric ischemia and cardiogenic shock	N/A
14	15	No	Cardiogenic shock	N/A
15	21	No	Septic and cardiogenic shock	N/A
16	24	No	Cardiogenic shock	N/A
17	30	No	Septic shock and cardiogenic shock	N/A
18	61	No	Multiorgan involvement of sarcoma	N/A
19	63	No	Septic shock	N/A
20	80	No	Septic and cardiogenic shock	N/A
21	177	No	N/A	N/A
22	830	No	N/A	N/A
23	N/A	N/A	N/A	N/A

Abbreviations: ARDS, acute respiratory distress syndrome; CIED, cardiovascular implantable electronic device; N/A, not applicable.

[a]Four cases of known CIED infection (see Supplementary Table 1).

occurred due to non-CIED sites of infection. Indeed, more than 80% of our patients had either intraabdominal (60.9%) or central venous catheters (21.7%) as primary sources of candidemia.

The current position on management of candidemia in the setting of CIED has not been well established. The 2019 EHRA International Consensus document recommended complete removal of CIED in cases of candidemia, which was based on expert opinion [11]. However, based on the findings of our current investigation, it is our opinion that CIED removal may not be necessary in all patients with candidemia. This is critical because uncertainty in diagnosis can result in unnecessary device removal, which could lead to fatal complications such as vasculature injury, cardiac structure perforation, cardiac tamponade, or pulmonary embolism. There were 2 patients who were initially diagnosed as candidemia only without device infection who later relapsed with candidemia. Both of them underwent CIED removal, and device cultures grew the same *Candida* species as recovered in blood cultures taken during the initial bout of candidemia. Of note, neither patient had undergone TEE or PET-CT at the time of the initial episode of candidemia. Unfortunately, both TEE and PET-CT have limitations as diagnostic tools in CIED infection. For TEE, the major concern is that masses on leads can represent noninfected clots, which are common, rather than infected "vegetations" [19]. These results could prompt unnecessary device removal. For PET-CT, sensitivity to detect infected device leads is limited (~65%) [20]. It is interesting to note that less than one third of patients underwent TEE in our cohort and only 1 (4%) patient underwent PET-CT to evaluate for CIED infection or valvular endocarditis. This is, in part, because most patients died soon after the diagnosis of candidemia.

Our study highlights the difficulties in determining which patients with candidemia have underlying CIED infection due to low prevalence of echocardiography and identifies several areas for future investigations. First, although our cohort is the largest to date to examine this question, the overall number of cases was still small, which limits our ability to identify risk factors associated with CIED infection. Second, the diagnosis of candidemia-related CIED infection remains uncertain, and the high early mortality rate limited our ability to fully assess the prevalence of this syndrome. Finally, as a retrospective study conducted at a single institution, our findings may be subject to biases that limit their generalizability.

CONCLUSIONS

In conclusion, this study highlights the conundrum regarding patients who develop candidemia with underlying CIED and how best to diagnosis and manage device infection. We have underscored the limited understanding of the association between candidemia and CIED infection due to a mortality rate and a low rate of echocardiography. The latter finding is critical as decisions are focused on whether complete device removal is warranted, which is recommended by current international guidelines. A multidisciplinary approach involving (1) infectious diseases specialist and (2) cardiologists with expertise in echocardiography and electrophysiology is pivotal.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the

posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. The contributions of each author include the following: conception and design and analysis/interpretation of data (SC, LMB, HT, MF, DWC, and DCD); drafting of the manuscript or revising it critically for important intellectual content (SC, LMB, MRS, BRP, MM, HT, MF, DWC, and DCD); and final approval of the manuscript submitted (SC, LMB, MRS, BRP, MM, HT, MF, DWC, and DCD).

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