

## Candida endocarditis: Update on management considerations

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### Abstract

The rise in incidence rates of invasive candidiasis warrants an increase in attention and efforts toward preventing and treating this virulent infection. Cardiac involvement is one of the most feared sequelae and has a poor prognosis. Despite the introduction of several novel antifungal agents over the past quarter century, complications and mortality rates due to Candida endocarditis have remained high. Although fungal endocarditis has a mechanism similar to bacterial endocarditis, no specific diagnostic criteria or algorithm exists to help guide its management. Furthermore, recent data has questioned the current guidelines recommending a combined approach of antifungal agents with surgical valve or indwelling prostheses removal. With the emergence of multidrug-resistant *Candida auris*, a focus on improved prophylactic measures and management strategies is necessary.

**Key Words:** Candida; Candida endocarditis; Fungal endocarditis; Invasive fungal infection

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**Core Tip:** The incidence of Candida infective endocarditis has observed a noticeable rise. Despite the progress in medical understanding, Candida endocarditis (CE) continues to be linked with a notable increase in in-hospital mortality. This comprehensive review aims to elucidate the existing diagnostic modalities for identifying CE while emphasizing their inherent limitations. Furthermore, we clarify the prevailing standard treatment protocols, encompassing medical and surgical interventions. Additionally, we highlight the role of screening techniques in identifying high-risk patients and explore the discussion of prophylactic measures tailored to specific patient phenotypes.

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## INTRODUCTION

Although our understanding of endocarditis has evolved since its first description by William Osler in the late 19<sup>th</sup> century, it remains a disease of high morbidity and mortality[1,2]. Candida endocarditis (CE) which accounts for only 1%-2% of all endocarditis cases, is associated with a mortality rate as high as 80%[3-6]. Given that CE is particularly rare, formal studies comparing various management approaches and subsequent outcomes are limited. Current guidelines recommend a treatment regimen of antifungal agents combined with surgical interventions, whether valves or indwelling prostheses removal[7,8]. However, individuals suffering from CE often have multiple comorbidities and are at high risk for reinfection, making conducting invasive interventions challenging.

Furthermore, the uptrend in fungemia incidence rates in recent years has led to an increased number of patients at risk for CE[9]. Nonetheless, CE studies have relatively small sample sizes, which make them insufficiently powered to get robust research evidence into use. Therefore, this review explores the current diagnostic techniques and treatment considerations when evaluating and managing patients with CE.

## BACKGROUND AND EPIDEMIOLOGY

Per definition, community-onset candidemia occurs within 48 h of hospitalization, with most cases identified on the day of admission, whereas nosocomial candidiasis occurs after 48 h of hospitalization[10]. The incidence of invasive candidiasis in the community and nosocomial infections has increased. There has been a noticeable increase in the incidence of community-acquired cases since the 1970s due to the intravenous drug (IVD) use epidemic, the use of impure brown heroin, and poor harm reduction practices, which have been associated with *Candida albicans* (CA)[11]. With the implementation of harm reduction strategies in the 1990s, the causative organisms have shifted to non-albicans Candida (NAC) species. The increased likelihood of the latter among IVD users has led again to the recognition of IVD use as an important risk factor for candidemia[12].

Different factors were found to increase the incidence of nosocomial candidemia, including increased antibiotics use, prolonged fluconazole prophylaxis in immunocompromised patients, use of total parenteral nutrition, and use of long-term catheters and medical devices[13-16]. Additional risk factors include malignancies of the gastrointestinal tract, genitourinary tracts, and the breast associated with CA infection and hematologic malignancy associated with NAC infection. Lastly, immunosuppressive therapies, including chronic steroid therapy, have been found to increase the incidence of CE and mortality risk[17].

Different Candida species can lead to advanced clinical infections, yet the most common agent leading to CE remains CA despite distinct patient characteristics and underlying risk factors[18]. Moreover, *Candida parapsilosis* was linked to infected medical devices such as prosthetic valves and transmitted through direct contact[19-21]. *Candida dubliniensis* and *Candida glabrata* are predominantly found among human immunodeficiency virus/acquired immunodeficiency syndrome patients with oral thrush and patients who are immunosuppressed on broad-spectrum antibiotics, respectively [18,22]. Although CA is primarily sensitive to antifungals, there is an emergence of intrinsic resistance of various Candida species to antifungals. Thus, it is essential to conduct antifungal susceptibility to ensure appropriate coverage[23]. *Candida auris* has recently emerged as a pathogen of significant concern worldwide, especially among chronically hospitalized patients. It is intrinsically resistant to multiple currently available antifungal therapies with a high mortality rate, often due to delayed diagnosis and initiation of antifungal therapy[24].

Despite the availability of effective antifungal therapy in most cases, mortality rates related to candidemia remain elevated, ranging from 30%-80%[25]. The latter is likely attributed to patients predisposing factors such as immunocompromised status and malignancies, recent surgery, and prior infective endocarditis (IE). Early diagnosis and administration of appropriate antifungal therapies *via* a multidisciplinary approach may have improved mortality rates over the years[4,23,27-28].

## DIAGNOSTIC EVALUATION

Healthcare providers should be vigilant of an underlying CE when managing high-risk febrile patients with predisposing factors such as IVD users, prolonged antibiotic therapy, indwelling central venous catheter, prosthetic heart valve, history of endocarditis, parenteral nutrition, neutropenia, and diabetes mellitus[29]. Although the clinical presentation of CE can sometimes be indistinguishable from those of bacterial endocarditis, the loss of visual acuity, presence of cutaneous nodules, and cerebral embolization should raise concerns for a Candida infection[30,31]. Nevertheless, it remains a challenge to establish the diagnosis and differentiate CE from bacterial endocarditis.

In 1994, Durack *et al*[32] proposed the Duke Criteria, which are used to classify each case as definite, possible, or probable, and has been validated in several subsequent studies. Additionally, further trials emphasized Duke Criteria's high diagnostic sensitivity and specificity[33-35]. Furthermore, in 2000, Li *et al*[36] introduced the modified Duke Criteria, which have become the standard of care. Nevertheless, these criteria were developed to evaluate patients with suspected left-sided native valve IE, as its sensitivity is low in patients with cardiac device infection, prosthetic valves, and right-sided IE[37]. Duke Criteria were primarily implemented in the workup of bacterial endocarditis; however, to date, there are no specific diagnostic criteria for fungal endocarditis.

### Fungal culture

Isolation of the causative organism is critical in establishing the microbiologic diagnosis and selecting appropriate therapeutic agents. However, Candida traditionally does not grow well in standard bacterial blood culture media, if at all, requiring a longer time for the organism to grow. The sensitivity of detection of Candida in blood cultures is limited to 50%-75% [38,39]. In one case series from France, 14% of 620 IE cases had negative blood cultures, while another study showed that 31% had negative cultures[40]. Hence, this will delay the diagnosis and treatment, which could lead to drastic outcomes. Therefore, modifications to the original Duke Criteria have been suggested to include additional risk factors, such as CRP/ESR elevation, hematuria, central non-feeding venous lines, and peripheral lines, as part of the criteria. These, in turn, led to increased diagnostic sensitivity[42]. However, when the modified Duke Criteria was tested in blood culture-negative IE, it performed poorly, possibly due to the lack of serological criteria[43].

### Immunoassay studies-1, 3-β-D-glucan

In light of earlier addressed issues related to fungal isolation and culture difficulties, which remain the gold standard of diagnostic testing, non-culture-based tests have been developed, and some have found clinical applications. 1, 3-β-D-glucan is a polysaccharide ubiquitous in the fungal cell wall. Its detection in the serum with a cutoff of 60 pg/mL has a sensitivity and specificity of 69.9% and 87.1%, respectively, in a patient with candidemia[31]. It carries several advantages, including improved sensitivity on serial testing, strong specificity, positive likelihood ratio, and most importantly, antifungal agents do not affect 1, 3 β-D-glucan serum levels[44,45]. In a patient with *Candida glabrata* IE, β-D-glucan was found to be a helpful tool in assessing treatment response, whereby after treatment, the assay became negative[46]. Hence, this could be used as a screening tool for CE and to monitor clinical response to therapy.

### Mannan antigen and anti-mannan antibody

Mannan is an essential constituent of the Candida cell wall. Both mannan and anti-mannan antibodies have been found in the serum of patients with candidiasis. A meta-analysis by Mikulska *et al*[47] showed that combined testing using immunosorbent assays for detecting mannan antigen and anti-mannan antibodies have a sensitivity of 83% and specificity of 86% in patients with invasive candidiasis. However, its usefulness is limited due to rapid clearance from the bloodstream. Furthermore, immunosuppressed patients may not develop adequate antibody response against the mannan antigen, thus resulting in false negative tests[48].

### Polymerase chain reaction

The development of molecular diagnostic techniques has improved the ability to identify the causative pathogen and decreased the required time for microorganism identification from days to hours. Rice *et al*[49] found polymerase chain reaction (PCR) to have a threefold increase in sensitivity in detecting causative agents in the setting of IE compared to traditional bacterial Gram-stain and culture. Multiple cases of successful diagnosis of culture-negative fungal endocarditis utilizing this technique have been reported[50,51]. Multiplex PCR systems, such as BioFire®, are now employed routinely in clinical settings and have been shown to offer a rapid and accurate diagnosis of selected Candida species in fungemic patients. Recent advancements have also led to the development of a novel immuno-based microfluidic device that can rapidly detect CA in under 2 h with a capture efficiency of 77.4% ± 4.4% [52]. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry is a technique that analyzes large biomolecules, such as DNA, protein, and sugar, as unique molecular fingerprints to allow rapid and accurate identification of microorganisms to decrease wait time for establishing correct diagnosis and initiation of appropriate therapy[53,54].

### Limitations

These non-culture-based tests have several disadvantages, which have limited their widespread use. The yield of these tests is time-sensitive, and results might be altered with antifungal administration, which increases the possibility of false negative results. The accuracy of the test and its ability to make an identification depend on the quality of the database from which the test references, which is ever-expanding and improving. Thus, careful interpretation of test results is essential since sometimes the test may detect multiple or unusual organisms, which implies a critical determination of their clinical relevance. The availability of the test remains limited, and the turn-around time is significant, making them

not a first-line diagnostic tool. Finally, these tests are costly, further limiting their widespread use[55,56].

## IMAGING MODALITIES

The use of echocardiography in the diagnosis of endocarditis is well established. Transthoracic echocardiogram (TTE) has a sensitivity of approximately 70% in the diagnosis of native-valve endocarditis (NVE) and about 50% for prosthetic-valve endocarditis (PVE). The sensitivity for each will improve to more than 90% when a transesophageal echocardiogram (TEE) is used, suggesting the superiority of TEE. For fungal endocarditis, echocardiography has shown an overall sensitivity of 77%[6]. Indeed, for patients with candidemia, TTE was shown to detect vegetation in 2.9% of patients compared to 11.5% of patients with TEE[57]. Moreover, TTE had a sensitivity of 88.9% with NVE and 76.5% with PVE in the diagnosis of CE compared to TEE, which had an improved sensitivity of 92% with NVE but a worse sensitivity of 61.1% in the case of PVE, which could be related to the small sample of patients with PVE that underwent TEE[4,6].

Other imaging techniques have been developed that have shown promising applications in diagnosing endocarditis [38]. Positron emission tomography with 2-deoxy-2-(fluorine-18) fluoro-D-glucose integrated with computed tomography (18F-FDG-PET/CT), which identifies increased uptake of labeled glucose by cells in inflamed tissue, has improved sensitivity and specificity of the modified Duke criteria to 82% and 96%, respectively, even better if the NVE cases were excluded, up to 96% and 94% if only PVE and cardiac-device-related IE are considered. Limitations of this technique include potential myocardial and respiratory artifacts that need to be gated out, difficulty distinguishing between inflammatory from infectious lesions, and limited ability to detect small vegetations along the device leads[58]. 18F-FDG-PET/CT was reported to help diagnose CE and improve accuracy. Hence, it is promising in situations where TTE/TEE might not be diagnostic[59].

Single photon emission tomography with technetium 99m-hexamethyl propylene amine oxime (HMPAO)-labeled autologous leukocytes (<sup>99m</sup>Tc-HMPAO-labeled SPECT/CT), on the other hand, takes advantage of the natural homing and recruitment of leukocytes to the site of inflammation/ infection to identify potential areas of abnormality. This technique does require additional time to prepare and complete compared to <sup>18</sup>F-FDG-PET/CT. It takes time to obtain, isolate, and prepare autologous leukocytes from the host, and the images are acquired in multiple phases. Other imaging limitations include affection by metallic artifacts, non-specific bowel activity due to hepatic HMPAO excretion, and its limited ability to detect small vegetations[60]. These techniques are technically challenging and require well-trained radiologists who are familiar with the technique. Therefore, they are not widely available and are usually implemented when other evaluation techniques, such as echocardiograms, are inconclusive. The yield of either study may be affected by antibiotic exposure; thus, finding the optimal time to utilize this imaging modality to achieve the maximal result in the course of patient evaluation remains an important question[61,62]. Nevertheless, these techniques have demonstrated very promising results in the diagnosis of PVE and cardiac device-related IE, with one study showing a sensitivity of 80%, specificity of 91%, negative predictive value of 80%, and positive predictive value of 91% using <sup>18</sup>F-FDG PET/CT and 60%, 100%, 100%, and 85% for <sup>99m</sup>Tc-HMPAO-SPECT/CT, that the use of nuclear imaging study when appropriate has been included as a consideration in European IE guidelines[61-63].

## MANAGEMENT

### Medical management

Current Infectious Diseases Society of America (IDSA) guidelines recommend treating native or prosthetic valve CE with either a lipid formulation of amphotericin with or without flucytosine or a high dose echinocandin for initial therapy, with step-down therapy to fluconazole for patients who have susceptible isolates, that have demonstrated clinical improvement, and have cleared Candida from their bloodstream. Step-down therapy to oral voriconazole can be used for susceptible isolates that are not susceptible to fluconazole. Valve replacement is recommended if there is no contraindication, followed by continued antifungal treatment for six weeks after surgery. Finally, long-term therapy with fluconazole is recommended for patients who cannot undergo valve replacement[8]. Despite this seemingly straightforward algorithm, this infection has seen little or no improvement in patient outcomes. While this may indicate an inherent defect in our approach to treatment, one must further analyze this sophisticated pathogen and the hosts most likely to become infected.

As Candida is known to form biofilms that result in decreased cell membrane ergosterol content through reduced expression of ergosterol biosynthetic genes while upregulating the expression of genes involved in amino acid and nucleotide metabolism and efflux pumps[64,65], a combination antifungal regimen would theoretically be more effective in the treatment of fungal infection. However, using an *in vitro* model, Pai *et al*[66] compared the activities of flucytosine, micafungin, and voriconazole as either single agents or in combination against several Candida species and found no difference in the reduction of fungal burden between triple *vs* single agent antifungal therapy. Conversely, a 2011 meta-analysis of 64 cases of CE who received fluconazole alone, concurrently, or in sequence with other antifungals without surgical intervention suggested that multiple-agent therapy is preferable. In this study, Smego and Ahmad[67] reported that combination regimens, including fluconazole cured or improved 86% and 68% of patients with native and prosthetic valve infections, respectively. Furthermore, fluconazole administered alone was associated with a 42% rate of relapse or death. At the same time, the best outcomes were found in patients maintained on chronic suppressive fluconazole therapy following an initial amphotericin or echinocandin regimen for a minimum of six months. Although antifungal



agents tend to have significant side effects and drug-drug interaction profiles, prolonged fluconazole use is relatively benign. In a retrospective study of individuals receiving chronic fluconazole for suppression of artificial implant infection, Penk and Pittrow[68] found no significant adverse events. Of note, this study's maximum duration of treatment was 4.5 years, and the maximum daily dose was 750 mg.

A study compared amphotericin B and echinocandin-based therapy directly. While there was a higher percentage of older patients in the echinocandin group and the majority of infections in the amphotericin B group were community-acquired, the rates of utilization of combination antifungal therapy, suppressive antifungal therapy and adjunctive surgery were statistically equivalent. Mortality rates measured in-hospital, at 42 d and 1 year, did not differ between the two groups. Based on this study, the echinocandin group could be a better choice of initial therapy given similar clinical outcomes and a better side effect profile than amphotericin[69].

Combination antifungal therapy of amphotericin B and flucytosine was shown to have similar clinical outcomes compared to an antifungal followed by adjunctive surgical intervention[70]. Different antifungal combinations have been tried, including azoles plus echinocandins, 5-FC-combination therapies, and polyenes plus azoles[71]. Amphotericin B and flucytosine have been found to work synergistically, albeit with nephrotoxic side effects[67]. Furthermore, the combination of amphotericin B and fluconazole demonstrated antagonism[69]. IDSA guidelines recommend echinocandins with or without fluconazole as first-line therapy, which was found to be non-inferior to amphotericin B in managing endocarditis[8,69]. Additional challenges are encountered with NAC species, such as *Candida lusitanae* and *Candida krusei*, which are intrinsically resistant to polyenes and fluconazole, respectively[72,73].

Significant differences in clinical outcomes have been observed between right and left-sided disease in bacterial and fungal infections[74-6]. In a 2018 retrospective study, Siciliano *et al*[77] found that patients with isolated right-sided CE had a 32% mortality rate *vs* 61% for left-sided disease. Furthermore, individuals with right-sided disease have lower rates of acute heart failure and perivalvular complications. While right-sided CE still portends a poor prognosis, isolated valve involvement should be a characteristic considered when discussing outcomes and treatment options.

### **Surgical management**

Literature on the surgical approach in CE is limited to small prospective studies with conflicting evidence and weak recommendations. For instance, 15 case reports from patients with CE showed that a combination of surgical and medical, when carried out early on admission, had lower mortality than single therapy[27]. A meta-analysis of 879 cases of CE found that patients who underwent adjunctive surgery had lower mortality. However, higher mortality was seen in surgical repairs before 1980, fungal monotherapy, and left-sided endocarditis. Although, this did not meet statistical significance[70]. In contrast, an observational cohort study in 2015 failed to show mortality benefits between those undergoing surgical therapy and those receiving medical treatment alone[69]. The European Society of Clinical Microbiology and Infectious Diseases recommends earlier surgery in the setting of prosthetic valves as opposed to infection involving native valves[38]. The need for surgical intervention may differ among cases caused by different *Candida* species. A recent retrospective study showed that surgery was performed earlier in cases of CE caused by *Candida parapsilosis* compared to CA endocarditis[78]. Rivoisy *et al*[79] demonstrated that in patients with prosthetic valve CE, early surgery was not associated with better survival at six months compared to medical management alone with liposomal amphotericin B induction and long-term suppression with fluconazole.

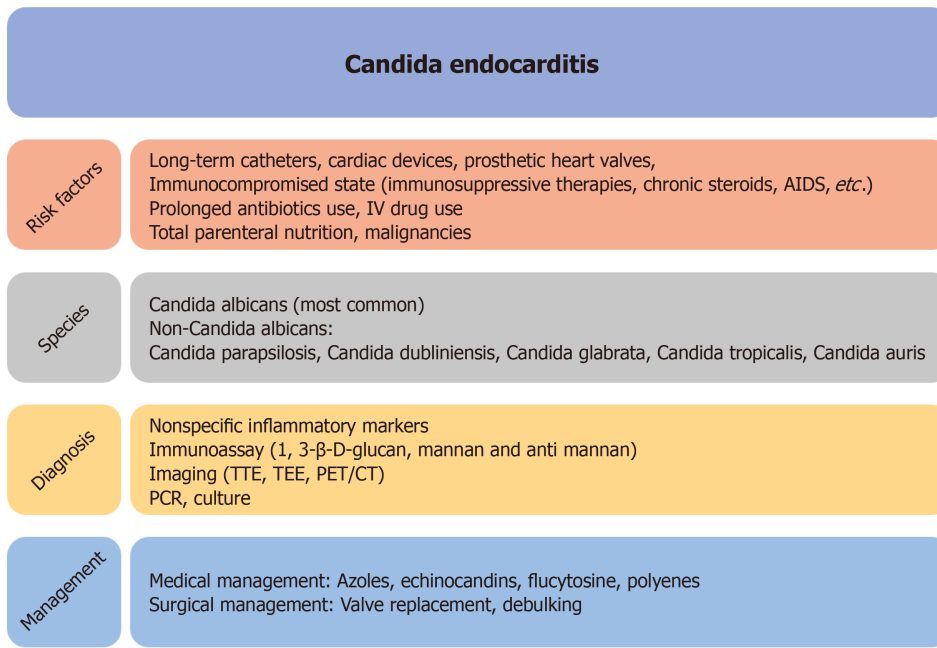
A newer approach with minimally invasive surgical intervention with angioVac has been used in right-sided IE with vegetation debulking. A meta-analysis of AngioVac-assisted vegetation debulking demonstrated procedural and clinical success of 89.2% and 79.1%, respectively. Also, greater than 50% vegetation removal was achieved in 90% and bacteremia clearance of 82.5% with procedure-related complications of 10.1%. However, documentation of this approach for left-sided endocarditis is not yet available[80]. It has been proposed that debulking in CE can lead to the resolution of fungemia similar to bacteremia in bacterial endocarditis[81].

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## **PROPHYLACTIC MEASURES**

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Prophylactic measures have been given to selected patients at high risk of complications from candidemia. Several studies have explored high-risk populations, and many were found to have similar underlying genetic alterations leading to candidemia. Some generic modifications include Toll-like receptor signaling influence and certain single nucleotide polymorphisms[82-84]. A meta-analysis by Shorr *et al*[85] showed that prophylactic fluconazole reduced the risk of infection but failed to show improved mortality. The latter was also demonstrated in another randomized controlled trial between 1995-2000 in 26 intensive care units (ICU), where patients with central line catheters were randomized to fluconazole 800 mg *vs* placebo. It also failed to improve primary composite outcomes, including fever resolution, absence of invasive fungal infection, and discontinuation of prophylaxis due to toxicity and the need for additional systemic antifungal medication[86]. On the other hand, prophylaxis might increase the risk of resistance to antifungal drugs, which was described in the SNETRY Antifungal surveillance program that underlined both intrinsic and acquired resistance to fluconazole based on differences in species distribution among the geographic areas, variation in antifungal usage and infection control practice. Other disadvantages include cost and side effects[87]. IDSA guidelines report that prophylaxis with fluconazole (12 mg/kg) loading dose and then 6 mg/kg daily gained weak recommendation when administered to high-risk ICU patients[8]. This points to the need for a new screening modality to identify patients at high risk for severe candidemia and its complications.



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**Figure 1 Central Illustration.** AIDS: Acquired immunodeficiency syndrome; TEE: Transesophageal echocardiogram; TTE: Transthoracic echocardiography; PCR: Polymerase chain reaction; PET/CT: Positron emission tomography/computed tomography.

## CONCLUSION

Despite advances in cardiac surgery and antifungal therapy, overall mortality and morbidity due to CE have not improved significantly. Given the increasing incidence of candidemia and the emergence of multi-drug resistant Candida species, there is an urgent need for further development of fungal-specific diagnostic criteria, including novel diagnostic tests, and management guidelines, both therapeutic and surgical. While the modified Duke criteria have been applied to diagnose fungal endocarditis, one of the major criteria requires positive blood cultures, which can be a source of delay in diagnosing CE. As there are limited data regarding some of the newer diagnostic techniques, criteria specific for fungal endocarditis utilizing fungal antigens and PCR technology would lead to earlier diagnosis and treatment (Figure 1).

New techniques, such as minimally invasive suction thrombectomy, can remove and debulk vegetations[88,89] without the risk and complications associated with conventional surgery and may provide alternative solutions. Current and future innovations in diagnostic tests and medical and surgical management of CE will permit earlier recognition of infection, reduce rates of potential complications, and improve long-term outcomes. The most successful strategy will likely require increased attention to the prophylactic reduction of indwelling foreign devices, antibiotic stewardship, and dedicating resources to the IVD use epidemic.

## FOOTNOTES

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