REVIEW ARTICLE

Fungal endocarditis: what do we know in 2019?

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ABSTRACT
Fungal endocarditis (FE) is an infrequent but a lethal condition. *Candida* and *Aspergillus* species are the 2 most commonly implicated pathogenic fungi. Clinical presentation is most often that of a fever of unknown origin, which is hard to differentiate from bacterial endocarditis. The diagnosis of FE is extremely challenging and now shifting towards molecular diagnostic techniques. Rapid and aggressive treatment with a combination of antifungal therapy and surgical debridement is imperative to improve outcomes.

Introduction Fungal endocarditis (FE) is an uncommon yet emerging entity accounting for 2% to 4% of all cases of infective endocarditis.[1,2] It has an exceptionally high mortality rate of 30% to 50%, which can be attributed to its association with immunocompromised states, delayed diagnoses owing to negative blood cultures, and frequent failure of antifungal therapy alone, in the absence of surgery. Additionally, a high recurrence rate makes it a therapeutic challenge to this day.[3-5] Finally, the diagnosis of FE is equally challenging and requires a high degree of clinical suspicion.[6]

Etiology and risk factors *Candida* and *Aspergillus* are the 2 prime etiologic agents of FE. *Candida* species account for ~50% of all cases of FE. *Candida albicans* is implicated in half of these cases, while other species of Candida, such as *C. parapsilosis*, *C. krusei*, *C. glabrata*, and *C. tropicalis* account for the remaining cases. *Aspergillus* species (*A. fumigatus*, *A. flavus*, *A. niger*, and *A. terreus*) account for 25% cases of FE, and a wide variety of other infrequent fungi such as *Histoplasma* sp., *Cryptococcus neoformans*, *Trichophyton* sp., *Microsporum* sp., *Fusarium* sp., *Paecilomyces* sp., *Pseudallescheria boydii*, *Rhodotorula mucilaginosa*, and *Cunninghamella* sp. are implicated in the remaining 25% of cases, as listed in TABLE 1. *Aspergillus* is noted more commonly with advancing age, while the incidence of *Candida* FE is higher in the neonate and younger populations.[1,7-10]

Fungal endocarditis seldom occurs in healthy individuals and is most commonly associated with immunocompromised states, intravenous drug use, prosthetic valves and intravascular devices or previous cardiac surgery, prolonged use of broad-spectrum antibiotics, indwelling central venous catheters, long-term parenteral nutrition, and neonatal period. Native valve FE can occur in organ transplant recipients who are on immunosuppressive agents, patients with myelodysplastic syndrome, and patients on long-term glucocorticoids and cytotoxic drugs.[11,12] Multiple risk factors in a single patient are more likely to cause FE, and bacterial coinfections can be a refractory condition.[9,12] In neonates, the right atrium is most commonly affected, while mitral or aortic valve is affected more often in adults.[7,12,13]

Clinical presentations Fungal endocarditis usually presents as subacute endocarditis, and its early recognition is very challenging as it lacks the classic signs and symptoms of bacterial endocarditis.[2] The most common presentation of FE is fever of unknown origin, which is usually prolonged (>2 weeks) and is often associated with chills, sweating, and fatigue. A new-onset murmur or change in the quality of a previously recognized murmur is another common finding in patients with suspected FE.[12] Fungal endocarditis should also be considered in patients with uncontrolled fever of unknown origin with peripheral embolization in the extremities, brain,

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TABLE 1 Etiology of fungal endocarditis

Candida species (50%)	*Aspergillus* species (25%)	Others (25%)
C.albicans (25%)	*A.fumigatus*	*Histoplasma* sp.
C.parapsilosis	*A.flavus*	*Cryptococcus neoformans*
C.krusei	*A.niger*	*Trichophyton* sp.
C.glabrata	*A.terreus*	*Microsporum* sp.
C.tropicalis		*Fusarium* sp.
		Paecilomyces sp.
		Pseudallescheria boydii
		Rhodotorula mucilaginosa
		Cunninghamella sp.

lungs, kidneys, and gastrointestinal tract. Septic pulmonary embolism usually presents with fever, dyspnea, pleuritic chest pain, cough, and hemoptysis. Embolism to the gastrointestinal tract may present as an acute abdomen secondary to acute mesenteric ischemia. With valvular destruction, a patient with FE may present with heart failure. The clinical signs may range from weight loss, clubbing, petechial rash, splenomegaly, hypotension, septic shock, to death. It is unusual to see peripheral findings unique to a particular fungal infection, such as cutaneous macronodules, which is peculiar to candidiasis.[14] Patients with multichambered FE have been shown to present with sudden onset of angina with elevated troponin levels.[10]

Diagnosis Fungal endocarditis poses a significant diagnostic challenge, with the burden of diagnosis largely lying with the clinicians. Blood cultures are negative in over 50% of cases, despite vegetations seen on echocardiography, making it difficult to meet the Duke criteria.[2,15] Laboratory techniques such as lysis centrifugation can improve the yield from blood cultures.[3,12] Newer and quicker nonculture tests have been developed for the diagnosis of fungemia, such as mannan antigen and antibody tests for candidemia, with a sensitivity and specificity of 83% and 86%, respectively.[16] Likewise, 1,3-β-D-glucan has a sensitivity and specificity of 69.9% and 87.1%, respectively.[2] Detection of galactomannan along with 1,3-β-D-glucan can help diagnose FE caused by *Aspergillus* sp.[17]

Histopathologic examination is useful in culture-negative cases, which often helps determine the diagnosis based on the examination of the explanted valve, peripheral emboli, or systemic ulcers.[8] The molecular method such as polymerase chain reaction (PCR) to detect fungal nuclear material like DNA in blood or in explanted valves is 3-fold more sensitive than Gram staining and culture.[18] The PCR has been shown to be positive in all tissue samples and in 10 out of 11 blood samples.[3] Real-time PCR enables the calculation of the fungal load by quantifying gene copies. In an exhaustive review, Faraji et al[19] have outlined the various targets of real-time PCR, such as fungal 28S rDNA, fungal 18S rDNA, and mycoplasma tuf gene. Newer ready-to-use kits have been developed to detect fungal species such as *C. albicans* and *C. parapsilosis*.[20] More recently, next-generation sequencing for the direct detection of pathogens from the resected valves has been used with a reported sensitivity of 97.6% as compared with 46.2% for blood culture and 17.1% for valve culture.[21] Next-generation sequencing technology has a short turnaround time of 48 hours and can identify all types of microorganisms, including fungi and viruses simultaneously apart from detecting antimicrobial resistance gene in the identified species. This can not only aid the diagnosis of FE but also guide the postoperative antibiotic therapy and prevent recurrences.[21]

Echocardiography is an indispensable tool in the diagnostic evaluation of FE. The lesions are characteristically large, left-sided, and occasionally nonvalvular. Bilateral lesions are more common in immunocompromised patients. Echocardiography can also detect abscesses of the valve ring. Transesophageal echocardiography is more sensitive and specific for the diagnosis of endocarditis than transthoracic echocardiography.[22]

Treatment A multimodality treatment is required for the successful management of FE. An early and aggressive surgical treatment is recommended (class I indication, level of evidence B) in almost all patients with FE, in view of the extremely high mortality (due to fatal embolic attacks) and morbidity (valvular destruction and chordae rupture causing acute mitral insufficiency) among those who receive medical treatment alone, as summarized in TABLE 2. The current guidelines of the European Society of Cardiology, European Society of Clinical Microbiology and Infectious Diseases, and Infectious Diseases Society of America recommend liposomal amphotericin B (lipid formulation) with or without flucytosine or a high-dose echinocandin (caspofungin, micafungin, or anidulafungin) for FE caused by *Candida* sp. and voriconazole with or without echinocandin or amphotericin B for FE due to *Aspergillus* sp., each of which is combined with early valve replacement surgery of the infected prosthetic or native valve, along with careful and thorough debridement of all infected tissues.[18,23-25]

In the largest meta-analysis of prosthetic valve endocarditis, including 32 studies, Mihos et al[26] found that the prevalence of prosthetic valve FE was 6% to 8% and that the majority (up to 56%) of cases required valve explantation, debridement, and reimplantation of the prosthetic valve. Aortic root replacement, using the Bentall or Cabrol approach, is usually needed for infections of the aortic valve because of the high incidence of

TABLE 2 Current recommendations for the management of fungal endocarditis[23,24]

No.	Recommendation	Class	Level
1	Early valve surgery for left-sided NVE caused by fungi	I	B
2	Early valve surgery for PVE caused by fungi	I	B
3	After completion of initial parenteral therapy, lifelong suppressive therapy with an oral azole is reasonable.	IIa	B

Abbreviations: NVE, native valve endocarditis; PVE, prosthetic valve endocarditis

perivalvular abscesses.[27] Combined antifungal therapy appears to be superior to monotherapy owing to a synergistic effect. Intravenous antifungal therapy is generally continued for about 6 to 8 weeks (not less than 4 weeks).[1,28] Once the patient has stabilized and follow-up blood cultures are negative, chronic suppressive therapy with oral fluconazole, for those with susceptible organisms, is appropriate (class IIa indication; level of evidence B). In those with infected prosthetic material, fluconazole may need to be lifelong. For those who are not susceptible to fluconazole, oral voriconazole or posaconazole can be considered.[18,25] If fungi continue to be isolated from blood cultures obtained after 1 week of treatment, they should also be tested for susceptibility, as resistance may emerge during therapy. For *Aspergillus* endocarditis, voriconazole is used both for induction and for long-term suppression.[1] Fungal endocarditis caused by *Histoplasma* sp. is managed with liposomal amphotericin B followed by oral itraconazole for at least 12 months.[29]

In FE associated with pacemakers and implantable cardioverter-defibrillators, the infected pacemakers and cardiac defibrillators should be removed, and intravenous antifungal therapy should be initiated. For ventricular assist devices that cannot be removed, the antifungal regimen should be started, and chronic suppressive therapy with fluconazole (if susceptible) should be continued as long as the device is in place.[18] In high-risk patients presenting with prolonged fever, empiric antifungal therapies are necessary. Thus, FE mandates an aggressive treatment strategy, even when the patients still have fever and a negative blood culture. With the advent of new and effective antifungal agents, surgery may be safer than before.[30] Finally, in neonates, medical therapy alone is as successful as combined therapy, although each case should be considered on its own merit. Indications for a surgical intervention include the risk of disseminated infected emboli, increased mobility of the vegetation or its progressive enlargement while on treatment, as well as hemodynamic instability, congestive heart failure, valve dehiscence, and perivalvular abscess.[31]

Outcomes Several studies have shown an association between early surgical intervention and a lower mortality rate in patients with FE in general or in specific subgroups of patients such as those with heart failure or paravalvular complications. A subgroup analysis has also indicated lower in-hospital and 1-year mortality rates with early surgery.[25] Immunocompromised patients tend to have a far worse outcome, with an increased rate of recurrence and embolization.[32]

In the largest prospective study, including 70 cases of FE due to *Candida* sp., Arnold et al[4] reported that the all-cause in-hospital and 1-year mortality rates of the overall cohort were 36% and 59%, respectively. Congestive heart failure, persistently positive blood cultures, older age, and intracardiac abscess were found to be predictors of both in-hospital and 1-year mortality. More recently, in 2018, in a separate binational study of a population of 41 patients with FE due to *Candida* sp., Rivoisy et al[33] showed a 6-month cumulative mortality rate of 37% among patients with prosthetic valve endocarditis and that of 57% among patients with native valve endocarditis.

Fungal endocarditis due to *Aspergillus* sp. is more commonly associated with embolic phenomena, and the most frequently involved organs are the brain, kidneys, spleen, and lungs. Myocardial infarction due to *Aspergillus* embolism often complicates the differential diagnosis of common myocardial infarction. The use of recombinant tissue plasminogen activator in this context is based on the composition of FE vegetation, which consists not only of the colonizing fungus but also of platelets and fibrin.[34] After surgical debridement and antifungal therapy with liposomal amphotericin B or voriconazole, the 12-month survival rate was reported to be 82%.[3] In a review including 53 case reports of FE due to *Aspergillus* sp., Kalokhe et al[35] showed that only 4% of cases were treated successfully with antifungal therapy alone, while even with surgical therapy, the survival rate was 32%. This poor outcome can be in part attributed to the immunocompromised state of the patients and increased incidence of embolization. Hence, an empirical use of antifungal therapy should be initiated in immunosuppressed patients with persistent fever, when antibiotics are rendered ineffective.[12]

Conclusions Despite novel molecular diagnostic tools and several advancements in antifungal therapy, FE continues to be associated with a poor prognosis. The critical care physician will continue to see a rise in the number of cases of FE in the near future, because of an aging population, a growing number of immunocompromised patients, and an increasing frequency of implantation of intravascular devices.[1,2,12] A high index of suspicion needs to be exercised in these high-risk patients when presenting with prolonged fever. Early diagnosis and a prompt surgical intervention coupled with optimal antifungal therapy are still our only option to reduce the exceedingly high mortality and morbidity associated with FE.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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