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Review Article

New Insights into the involvement of the complement system in cases of fungal endocarditis

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Abstract

Fungal endocarditis, a rare but serious infection of heart valves, is widely recognized for its high mortality and complexity in diagnosis and treatment. There is a predominance of species of *Candida* and *Aspergillus* as the main etiological agents. These infections are frequently associated with risk factors such as the use of prosthetic valves, immunosuppression, prolonged use of broad-spectrum antibiotics and a history of intravenous drug abuse. Such infections are diagnosed by advanced methods, such as next-generation sequencing or cultures of surgically removed valve tissue, due challenges at isolation in blood cultures. The complement system plays a pivotal role in fungal infections, mediating pathogen recognition, opsonization, and inflammation through components such as C3 and C5. However, fungi like *Candida* and *Aspergillus* have evolved mechanisms to evade complement-mediated immunity. Here, the main features of fungal endocarditis and the differences between fungal endocarditis caused by *Candida* and *Aspergillus* infection are presented. At the end, the possible participation of the complement system in the establishment of this disease is explored, bringing new perspectives to the management of this rare but devastating condition.

Introduction

Endocarditis is an inflammation of the endocardium, usually involving the heart valves, frequently caused by bacterial or fungal infection [1,2]. Symptoms include fever, chills, night sweats, fatigue, weight loss, musculoskeletal pain, and, in advanced cases, manifestations such as heart murmurs, heart failure, or embolic events (cerebral or peripheral) that can lead to serious complications [3-5].

The incidence of endocarditis varies globally, with an incidence of approximately 3-10 cases per 100,000 people, with significant differences between developed and developing countries [6,7]. The burden of endocarditis has been increasing globally, with over 1.09 million cases reported in 2019 [8,9]. Despite advances in treatment, the disease maintains a high overall mortality rate of around 25% [10]. In high-income nations, endocarditis is increasingly associated with medical interventions, such as prosthetic valves, and predominantly affects the elderly [1,11]. In low-income countries, rheumatic disease continues to be an important risk factor, affecting younger populations [12]. For a comprehensive understanding of endocarditis trends in specific regions, further population-based studies are needed, particularly in regions like Latin America and Africa where data are limited.

Fungal Endocarditis (FE) is a rare but highly serious form of infective endocarditis, accounting for approximately 2-5% of all cases of infective endocarditis [13]. It is characterized by a high mortality rate, often exceeding 50% and reaching up to 90% in specific scenarios, even with appropriate therapy [14]. *Candida albicans* are the most frequently implicated fungal agents [15]. Filamentous fungi such as *Aspergillus* spp. are less common but have also been reported, especially in immunocompromised patients [16]. Most symptoms are indistinguishable from symptoms secondary to bacterial endocarditis, but recently two different systematic reviews revealed a lower rate of fever in patients with fungal en-

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docarditis [17,18]. Literature about immunological alterations associated with fungal endocarditis is limited, mainly due to the rarity and severity of the condition. This form of endocarditis involves complex immunological alterations that influence both the response to the pathogen and clinical outcomes.

Traditional diagnostic methods, based on the modified Duke criteria, which include clinical findings, blood cultures, and transesophageal echocardiography, remain crucial in the identification of FE. However, the limited sensitivity of these methods for fungal pathogens is a significant challenge [19,20]. Recent studies report that less than 50% of cases have positive blood cultures, especially in infections caused by *Aspergillus* and *non-albicans Candida* species, which often results in delayed diagnosis [14,16]. To overcome these limitations, advanced techniques such as Next-Generation Sequencing (NGS) and Polymerase Chain Reaction (PCR) have been introduced, allowing direct detection of fungal DNA in blood or valve tissue samples [21-24]. These methods offer greater sensitivity and specificity, especially in cases with negative blood cultures, but are not yet widely available due to their high cost and the need for specialized laboratory infrastructure. In addition, recent studies emphasize the increasing role of testing for fungal antigens, such as 1,3-β-D-glucan and galactomannan for *Aspergillus* infections, which may be useful in the detection of invasive fungal infections in general [25-27,18]. These biomarkers, when combined with advanced imaging methods such as cardiac computed tomography and fluorodeoxy-glucose positron emission tomograph, can improve diagnostic accuracy in high-risk patients [28]. The lack of specific clinical criteria and the reliance on invasive methods for definitive diagnosis remain critical barriers. Despite these advances, significant gaps still exist. The lack of standardization in molecular testing limits their large-scale clinical implementation. In addition, there is a need for multicenter studies that evaluate the diagnostic accuracy and clinical impact of new technologies in diverse populations. Future research should focus on: (a) developing more specific biomarkers for cardiac fungal infections; (b) implementing and validating affordable and rapid molecular technologies; and (c) studying strategies for early screening in high-risk patients, such as those with implanted cardiac devices or immunosuppression. These efforts can improve early diagnosis, allowing for more effective interventions and reducing mortality associated with this devastating condition.

Candida endocarditis

FE caused by Candida species is a rare condition, accounting for approximately 1% to 2% of all cases of endocarditis, but with high morbidity and mortality, which can reach up to 80% [15,29]. Among the species, *Candida albicans* is the most frequently isolated, although infections by *Candida parapsilosis*, *Nakaseomyces glabrata*, formerly known as *Candida glabrata*, and *Candida tropicalis* have increased in recent years due to factors such as indiscriminate use of antifungals and increased dependence on medical devices [19,30]. *C. auris*, in particular, presents intrinsic resistance to several antifungal therapies, worsening the prognosis, although are uncommon cases [31,14]. The ability of some *Candida* species to form biofilms on medical devices also contributes to the difficulty in clinical management [32].

Candida has a remarkable ability to adhere to cardiac endothelium, especially on prosthetic or damaged valves [33-36]. This adhesion is mediated by surface proteins that interact with host components such as fibrinogen and fibronectin [37,38]. Once attached, *Candida* is capable of forming biofilms, multicellular structures that protect the fungus from immune attack and increase resistance to antifungal agents [39,40]. The ability of *Candida* to form biofilms on heart valves represents a central aspect in the pathogenesis of fungal endocarditis [41]. Biofilms, three-dimensional structures composed of fungal cells embedded in an extracellular matrix, are essential for the colonization and persistence of the infection [40]. In the heart valves, biofilm facilitates the formation of vegetations-aggregates composed of pathogen cells, plasma proteins, and elements of the extracellular matrix-that protect the fungus from the action of the immune system and antifungal agents [42,14]. The process of biofilm formation by *Candida albicans* begins with the initial adhesion of blastoconidium cells to valve surfaces, which are often damaged or coated with plasma proteins due to mechanical trauma, such as that caused by medical devices. After adhesion, the cells transition to hyphal forms, which have greater invasive capacity and contribute to the complex architecture of the biofilm [43-45]. The extracellular matrix surrounding the cells in the biofilm contains polysaccharides, proteins and extracellular DNA, functioning as a physical barrier that prevents the penetration of antifungal agents and hinders elimination by the complement system and other innate immune responses [36]. Recent studies indicate that environmental factors, such as the type of valve surface (natural or prosthetic), influence biofilm formation. On bioprosthetic valves, for example, *Candida* finds favorable conditions for growth due to the presence of hydrophobic substrates and protein deposits that promote adhesion [46,47]. Furthermore, the ability of *C. albicans* to modify the composition of its extracellular matrix and produce proteolytic enzymes contributes to immune evasion and dissemination of systemic infection, worsening the clinical condition of patients [48]. These finds emphasize the need for innovative approaches in the management of *Candida* endocarditis, such as strategies to prevent biofilm formation on medical devices and the development of antifungal therapies targeting the extracellular matrix. A deeper understanding of the mechanisms of adhesion, biofilm formation, and immune resistance of *Candida* is essential to improve the clinical outcomes of this often fatal condition.

The treatment of Candida endocarditis is challenging and often requires a combination of broad-spectrum antifungals, such as echinocandins or liposomal amphotericin B, and surgical intervention to remove the infectious focus, especially in cases of large vegetations or significant valvular insufficiency [29,18,14]. Prolonged therapy and rigorous control of the infectious focus are crucial to improve the prognosis. Despite this, the mortality rate remains high, reinforcing the importance of preventive measures [18,14]. Currently, there is still a need for faster and more specific diagnostics, since late detection often compromises clinical management and worsens the outcome of cases. Awareness of predisposing factors and the implementation of prevention protocols are essential to mitigate the incidence of this disease.

Aspergillus endocarditis

Aspergillus is a filamentous fungus widely distributed in the environment, known to cause opportunistic infections in immunocompromised patients, particularly those with prolonged neutropenia or chronic pulmonary diseases [49]. Aspergillus endocarditis is a rare but highly lethal form of fungal endocarditis [50]. Aspergillus species, most commonly *Aspergillus fumigatus* (responsible for 60% to 90% Aspergillus endocarditis cases), can invade the endocardium due to hematogenous dissemination

from a primary infection or through direct contamination from cardiac surgery or implantable devices [51]. Aspergillus endocarditis accounts for approximately 24-28% of fungal endocarditis cases, with an increasing incidence in patients with cardiac abnormalities, cardiac surgery, solid organ or hematologic malignancies and transplantations [52,53]. Prolonged use of antibiotics, immunosuppressive and chemotherapy and cytotoxic therapies remain significant risk factors [54]. Recently, cases of Aspergillus endocarditis in patients without a history of recent heart disease but post-COVID-19 infection have been reported. Suggesting that Aspergillus endocarditis should be considered in any patient with suspected endocarditis who has a history of COVID-19 infection [55-57].

Aspergillus infection can be complex, as this fungus is capable of forming granulomas and necrotizing lesions, which may lead to septic emboli, valve damage, and heart failure [58]. The diagnosis of Aspergillus endocarditis is particularly challenging. Blood cultures are almost invariably negative, fever may be absent, and the condition is often identified through histopathological examination of resected valve tissue or emboli [50]. Noninvasive diagnostic tools, such as β-D-glucan tests, galactomannan assay, histopathological examination, with the presence of characteristic septate hyphae and PCR analysis, have proven valuable [59]. Advanced imaging techniques, including transesophageal echocardiography, are crucial for identifying large vegetations and embolic phenomena [60,61].

The *β-D-glucan* test is a component of the cell wall of several fungi, and it measures the concentration of this substance in the patient's serum. It is a useful diagnostic tool for detecting invasive fungal infections [62]. This test has a sensitivity of 80-90% for invasive *Aspergillus* infections, including fungal endocarditis. Its advantage lies on its ability to detect the infection before complete clinical manifestations occur, allowing for earlier therapeutic interventions [63]. However, it is important to note that the *β-D- glucan* test is not specific to *Aspergillus* and may yield positive results in infections caused by other fungi, such as *Candida* or Pneumocystis jirovecii. Therefore, it should be interpreted alongside other diagnostic tests and the patient's clinical evaluation [64].

Another significant test in the diagnosis of fungal endocarditis is the Galactomannan (GM) assay, which detects the presence of the galactomannan antigen, a carbohydrate found in the cell wall of *Aspergillus* [65]. This test is widely used for diagnosing *Aspergillus* infections, particularly in high-risk patients such as those who are immunocompromised [66]. The GM test has high specificity for *Aspergillus*, with sensitivity ranging from 60-90%, depending on the patient's immune status and the location of the infection. In the context of fungal endocarditis, the GM test can be crucial for detecting the infection before blood cultures turn positive, which may take a longer period [67].

The cornerstone of Aspergillus endocarditis management involves a combination of surgical and antifungal therapy. Voriconazole and liposomal amphotericin B are the primary antifungal agents. Long-term or lifelong antifungal therapy is often required to prevent recurrence [68]. Early valve replacement or debridement is essential for controlling infection and mitigating embolic risks. Surgery is typically prioritized even in high-risk patients due to the poor outcomes associated with medical therapy alone [16].

While both *Candida* and *Aspergillus* endocarditis are rare, they pose significant diagnostic and therapeutic challenges (Table 1). The contrasting features of these infections necessitate tailored diagnostic approaches and treatment regimens. A multidisciplinary strategy is critical to improve outcomes in both conditions.

Table 1: Diagnostic and therapeutic challenges.

Feature	*Candida*	*Aspergillus*
Prevalence	Most common cause of FE	Less common, but more lethal
Risk Factors	Hospital-acquired infections, prosthetics	Immunosuppression, native valves
Diagnosis	Blood cultures often positive	Blood cultures usually negative
Treatment	Echinocandins, azoles, surgery	Voriconazole, amphotericin B, surgery
Mortality	~40-50%	>50-96%

The role of the complement system in fungal endocarditis

The complement system plays a fundamental role in innate immunity, contributing to the body's defense against fungal infections [69]. It acts through three main activation pathways: classical, alternative and lectin, which converge in the formation of C3 convertase, culminating in the opsonization of pathogens, activation of phagocytic cells and formation of the Membrane Attack Complex (MAC). These mechanisms promote both the direct destruction of pathogens and the recruitment and activation of immune cells [70,71].

In the context of fungal infections, activation of the complement system is essential for the control of these pathogens. All pathogenic fungi activate the complement system, using a combination of the classical and alternative pathways [72,73]. The molecular mechanisms for activation vary between fungi, likely due to differences in the structure of the cell wall. Complement proteins, such as C3b and C5a, facilitate phagocytosis of fungi by macrophages and neutrophils [74]. However, Candida can develop evasion mechanisms, such as the expression of proteins that inhibit complement activation, contributing to the persistence of the infection and serious complications such as the formation of intracardiac vegetations [75,74].

The complement system plays an important role not only in the defense against fungal infections, but also in the regulation of cardiovascular diseases, especially those associated with inflammation and tissue remodeling [76,77]. The role of this system has already been explored in cases of heart failure, atherosclerosis and arterial hypertension [77-80]. In heart failure, chronic activation of the complement system has been associated with worsening of the clinical picture due to amplification of inflammatory processes and modification of the extracellular matrix [81-83]. Patients with idiopathic dilated and ischemic cardiomyopathies have increased complement activation. High plasma levels of C3a in patients with left ventricular ejection fraction predicted risk for cardiovascular events and mortality. The interaction between C5a-C5a receptor is involved in cardiomyocyte dysfunction and heart failure. Thus, complement activation appears to be involved in the pathophysiology of several cardiac diseases. Therefore, a possible association between fungal infection, dysfunction in the complement system and the establishment of fungal endocarditis would not be impossible.

Some studies indicate that patients with infective endocarditis, mainly caused by bacteria, exhibit high levels of activated complement fragments, such as C3a and C5a, associated with an

exacerbated inflammatory response [84,85]. However, the participation of the complement system in the immune response to fungal endocarditis is an aspect that has not yet been explored. Understanding this system may offer new perspectives for therapeutic interventions that optimize clinical outcomes and reduce the high mortality rate associated with this complex disease. Therapeutic strategies targeting the complement system should be explored. Antifungal agents, such as triazoles (e.g., voriconazole), are effective in the treatment of fungal endocarditis and can be combined with strategies to minimize excessive complement activation. This integrated approach may improve clinical outcomes in high-risk patients, particularly those undergoing cardiac surgery. C5 inhibitors, for example, show potential to modulate inflammation without completely compromising the antimicrobial activity of the system [86,87]. However, the challenge lies in balancing protection against the pathogen and preventing collateral damage caused by over-activation of complement. Therefore, understanding the interactions between the complement system and fungal pathogens in endocarditis is essential for the development of more effective therapies that are less damaging to cardiac tissue. Further studies are needed to clarify the underlying molecular mechanisms and explore targeted interventions that balance immunity and inflammation.

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