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Post-Cardiac Surgery Fungal Endocarditis

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1. Introduction

Infective endocarditis (IE) is a threatening disease associated with a high risk of morbidity and mortality. The most etiologic agents are the bacteria followed by fungi. Fungal Endocarditis (FE) is an uncommon occurrence and the most severe form of IE, however, its rate has increased in recent decades. The first report of FE after a mitral valve replacement was in 1964 (1) but there have been many cases reported in recent years indicating the importance of such infections (2-4). Fungal endocarditis accounts for 1.3% to 6% of all IE cases (5-8). Ranges between 1.7 to 3.8 per 100,000 person-years have been reported in different studies for mean annual incidence (5, 9). Increase in the number of cases of fungemia and FE has been seen during the last 2 decades (10, 11). Men are more at risk of infections than women (7, 12, 13), and younger persons (third to fourth decades of life) are in more risk factor. The incidence of FE varies based on the criteria and methods of diagnosis (5) and population under survey; in liver transplants (14) the incidence of FE after transplantation was 1.7%. The mortality rate was 72% (15) but is still high (about 50%) despite the treatments (7). In an international multicenter prospective cohort study that included 33 cases of *Candida* endocarditis treated between 2000 and 2005, the mortality rate was 30 % (16), and in post-surgical invasive aspergillosis (17) and *Aspergillus* endocarditis the rate was too high (100%) even with combined medical and surgical therapy (2).

Fungi are important causes of prosthetic valve endocarditis, responsible for 1%–10% of these infections (18). Also, there are reports that fungi are responsible for 9.6% of the early cases of prosthetic valve endocarditis (60 days after the insertion of prosthesis) and for 4.3% of late cases (>60 days after the insertion of prosthesis) (19, 20). The incidence of FE in culture-documented cases has been reported to range from 12% to 20% (21) or to 37.5% (22).

Many fungal species cause FE, of which the most important are *Candida albicans* 60%-67% and filamentous *Aspergillus* spp. 20–30% (ratio rate 2/1) (7, 15, 23), In addition, non-*albicans* species of *Candida*, *Torulopsis glabrata, Candida tropicalis*, and other filamentus fungi like *Aspergillus* spp., *Curvularia genuculata, Hormondendrum dermatitidis, Mucoracae*, *Scopulariopsis* spp., *Trichosporon spp. and Blastoschizomyces capitatus* have been reported in the literature (10, 15, 22, 24, 25). In some studies, the most common etiologic agent was different, as in Rubinstein E et al. *Candida parapsilosis* accounts for half of the culture-documented patients, whereas *C. albicans* and *Candida stellatoidea* account for 12%-15% only (21). *Pneumocystis jiroveci* caused fungal infection in 9% to 11% of all heart transplant recipients in the past, with a mortality rate of 11% to 38% (26) but with use of prophylaxis, the rate of this infection has decreased.

The source of infection can be internal or external, the former usually with *Candida* spp. This organism is the normal flora of the patient's body and causes contamination during the surgery, and is recognized as the catheter-related blood stream infection (27). However, conidia of the external agents could contaminate the tissues during the surgery or post operative contamination by environmental isolates present in high counts (17).
Time of presenting of infection is different and maybe during the first 2 weeks in hospital period to months after heart surgery at home, and in some cases 12 years later (15). Diagnosis should be prompt because the time interval between the first symptom and hospital admission in some cases is long and may be one year (15). Early diagnosis could be helpful for the patients' survival. The onset of symptoms is usually about 2 weeks or less from the initiating bacteremia.
Anatomical cardiac condition diseases (cardiac abnormality), intravenous drug abusers and open heart cardiac surgery are the top risk factors for the infections. There are many risk factors for progressive FE, including the use of multiple immunosuppressive drugs such as azathioprine, corticosteroids, cyclosporine A, and cyclophosphamide (12, 13, 15). Malignancy, exposure to multiple broad-spectrum antibiotics, prolonged use of intravenous catheters (28), use of high glucose concentrations intravenous catheters especially in premature neonates (29), rheumatic heart disease (22), previous bacterial endocarditis, prior surgery, prolonged intravenous hyper alimentation, pacemaker implantation, and reconstructive cardiovascular surgery are other risk factors (15,30-32). In some cases no predisposing factor has been identified (7, 33)
The mechanism of endocarditis includes high turbulent blood flow due to cardiac abnormality or other risk factors (e.g., particulate material in the repeated injections of drugs in IV drug abusers) which disrupt the surface of endocardia and endothelium. The response of the body is repairing the damaged tissue with platelet-fibrin meshwork which is sticky and proper site for infection. After temporary bacteremia, it sticks to this meshwork and proliferation of organism causes the infection that invades the cardiac valves.
Infective endocarditis is classified into definite, probable, and possible according to Pelletier and Petersdorf (34). Other classifications include definite, probable, possible and rejected by von Reyn (35) and definitive, possible and rejected by Duke criteria (36) (Table 1). Briefly, proven FE is defined as the isolation of fungi from the normally sterile sites, the blood or heart biopsy or vegetation, by culture and/or the evidence of fungal invasion of tissue by histopathological methods. Probable FE is defined as when the culture is negative for the infective agents, and clinical conditions of the respective patients are not recovered despite the administration of standard antibacterial therapy. Role of echocardiography, definition of rejected IE and major and minor clinical criteria were added to the previous definition in 1994 (37). According to Duke criteria, the diagnosis of definitive IE requires the presence of either two major criteria, one major and three minor criteria, or five minor criteria.

2. Clinical manifestations

The clinical manifestations of acute or sub-acute IE are related to the underlying pathophysiology of embolization, bacteremia/ candidemia, immunologic response, and valvulitis (30). Common clinical features are changing heart murmur, fever, and major peripheral emboli (common in fungal endocarditis) (10, 33). Some cases presented with the systemic symptoms associated with bacteremia include fever, tachycardia, septic shock; and the general symptoms and signs of cardiac involvement including chest pain, arrhythmias,

Pelletier and Petersdorf criteria (34)	
Definite IE	-Histologic evidence of vegetation on tissue from surgery or autopsy
Probable IE	- Positive blood cultures with known underlying valvular heart disease and evidence of emboli to viscera or skin - OR fever >38ºC with negative blood cultures in individuals, embolic phenomena and new regurgitant valvular heart murmurs
Possible IE	- Positive blood cultures with known underlying heart disease - Embolic phenomena; or negative blood cultures with fever, known underlying valvular heart disease, and embolic episodes.
Property	- Many patients with clinical features of infective endocarditis did not meet the above criteria due to lack of sensitivity.
von Reyn criteria (35)	
Definite	- Histologic evidence from surgery or autopsy - Positive bacteriology evidence of valvular vegetation or peripheral embolus (staining or culture).
Probable	-Persistently positive blood cultures plus one of the following: New regurgitant murmur and predisposing heart disease, vascular phenomena, negative or intermittently positive blood cultures, plus three of the following: new regurgitant murmur, fever, vascular phenomena - petechiae, Roth spots, Osler's nodes, Janeway lesions, splinter hemorrhages, aseptic meningitis, conjunctival hemorrhages, glomerulonephritis, or central nervous system, pulmonary, coronary or peripheral emboli.
possible	-Persistently positive blood cultures plus one of the following: predisposing heart disease - definite valvular or congenital heart disease, or a cardiac prosthesis (excluding permanent pacemakers) , vascular phenomena -Negative or intermittently positive blood cultures with all three of the following: fever, predisposing heart disease, vascular phenomena. -Only for viridans streptococcal endocarditis: fever with at least two positive blood cultures without an extra cardiac source
Rejected	-Endocarditis unlikely, alternative diagnosis generally apparent or endocarditis likely, empiric antibiotic therapy warranted - Culture negative diagnosed clinically as endocarditis, but excluded by postmortem
property	- Lacked prospective validation, but improved the specificity of the classification system, a large proportion of cases being classified as probable or possible (most patients do not require valve surgery).

Duke criteria (36)	
Major clinical criteria	- Persistently positive blood cultures for organisms, new or partial dehiscence of a prosthetic valve or an abscess in the tissues surrounding a heart valve, presented of vegetation or other typical findings of endocarditis in echocardiography; new regurgitate murmur, serological or culture evidence of infection with Coxiella burnetii.
Minor clinical criteria	- Positive blood cultures that do not meet the strict definitions of a major criterion, fever, predisposing valvular condition[a] -OR intravenous drug abuse, elevated erythrocyte sedimentation rate and C-reactive protein hematuria and splenomegaly.
Definitive	- Pathological criterion: vegetation or intracardiac abscess, confirmed by histology showing active endocarditis, positive Gram stain results or cultures of specimens obtained from surgery or autopsy - Clinical criteria: 2 major criteria OR 1 major and 3 minor criteria OR 5 minor criteria
Possible IE	- 1 major criterion and 1 minor criterion OR 3 minor criteria
Rejected IE	- Firm alternate diagnosis for manifestations of endocarditis - Resolution of manifestations of endocarditis, or no pathologic evidence of infective endocarditis at surgery or autopsy after antibiotic therapy for four days or less - Does not meet criteria for possible infective endocarditis, as above

[a] Prosthetic heart valve or a valve lesion that leads to significant regurgitation or turbulence of blood flow; Vascular phenomenon like emboli to the brain or organs, hemorrhages in the mucous membranes around the eyes; Immunologic phenomenon include lesions such as Roth's spots or "Osler's nodes and glomerulonephritis.

Table 1. Definition of three criteria for the diagnosis of infective endocarditis

edema, dyspnea, murmur on examination, cardiac failure, and persistent sepsis would also present. Other symptoms include abdominal pain, malaise, weight loss, night sweats, arthritis, finger clubbing, cough, hemoptysis, sudden death, coagulopathy, jaundice, nausea, hypotension, and renal failure. *Candida spp*. is the most etiologic agent of FE; therefore, patients can present endophthalmitis, meningitis, osteomyelitis and other complications of candidemia. The more specific cutaneous or mucocutaneous lesions of IE include Osler's nodes, Roth spots (rare), and Janeway lesions are more specific signs but less common and not diagnostic . Petechiae and splinter hemorrhages (nonblanching, linear reddish-brown lesions found under the nail bed) are not specific but are common skin manifestations. They may be present on the extremities of skin, or on mucous membranes. Other organs may be involved due to embolic events such as splenic or renal infarcts, or immune reactions like arthritis and glomerulonephritis, or spread by the blood passing to other organs like soft tissues, vertebral osteomyelitis, and the brain causing meningitis and/or encephalitis.

3. Diagnosis of fungal endocarditis

The diagnosis of IE is based upon high index of suspicion, careful history and physical examination, echocardiographic or histopathological findings, laboratory results, and chest

radiography. Gold standard tests for the detection of documented infections are the isolation of fungi from the blood, heart biopsy or vegetation by culture and the presence of tissue invasion by histopathology. Isolation of fungi from blood samples is difficult due to non-growth of fungal etiologic agents in blood culture. The rate of culture positive of *Candida* spp. in the blood is about 50% of the documented cases and positive blood culture for *Aspergillus* is rare (38-40). Fungi are cleared rapidly, due to large size, in the blood by the host's reticuloendothelial system; therefore, the blood culture results are negative in many suspicious patients. The use of lysis-centrifugation system (41), or Bactec blood culture (42), may help the isolation of fungal agents but none is recommend as a standard method. Heart tissue is the best sample for the isolation of fungal agents. As resistance to the antifungal agents has been reported in many studies (43-45), in case of positive culture, sensitivity test of the isolated fungi to antifungal agents can contribute to the best management of infections.

Another definitive microbiologic diagnosis depends upon the evidence of fungal tissue invasion with histopathologic investigation. The samples (tissue valve or emboli) are stained with specific stains like Gomori methenamine silver or Periodic acid-Schiff. With histopathology examination, morphological differentiation between *Aspergillus* spp. and other fungi is not completely available.

Given the frequent negative blood cultures, and difficulty in obtaining the material from the surgical sites in the operating rooms, echocardiography, either transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE), are used as the diagnosis tools with the sensitivity of about 77% (15) for the evaluation of FE and the presence of vegetation, based on the major diagnostic Duke criterion. Echocardiography can also detect intra cardiac abscess, new or progressive valvular regurgitation, the size and location of vegetation. The size of vegetation may be small, medium, or large and anatomic site of the vegetation may be aortic valve, on tricuspid, mitral or endocardium, or on the previous aortic valvular surgery.

Transesophageal echocardiography should be considered as the standard diagnostic procedure for IE (46). This method is able to evaluate the prosthetic valves, intracardiac complications, inadequate TTE, fungemia or bacteremia, and has superior sensitivity (47), compared to TTE, but significantly more invasive and expensive than it. Transthoracic echocardiography is the first line procedure for the detection of FE especially in native valve and prosthetic valve vegetations, and local extension of infection. The sensitivity of TTE in infants and younger children is about 80 percent (48, 49), therefore, the negative result of it cannot definitively rule out FE and examination should be repeated in respective patients. If there is a high clinical suspicion for FE and the TTE is negative, we should turn to TEE. Once treatment is completed, repeated evaluation may be necessary to establish a new baseline of valvular and myocardial functions for the patient. Unfortunately, both TTE and TEE may yield false negative results if the vegetations are small, or large size of the vegetation suspected as a mural thrombus, vegetation is attached to the mural endocardium and if embolization of the vegetation has occurred.

Chest radiography and echocardiography are not useful in the diagnosis of IE; x-ray may present the septic pulmonary emboli (Minor Duke's Criteria) and echocardiography may show evidence of some complications.

Over the last several decades, non-culture laboratory methods have been directed at the development for the diagnosis of systemic fungal infections such as FE. Serological diagnostic methods can serve as the non-invasive methods for detecting the circulating

fungal antigens, fungal metabolites, or antibody in the blood (50, 51). The major limitation of these methods is unavailability to detect some fungi like *Mucor* spp.

Galactomannan (GM) is a more promising circulating fungal antigen used to detect fungal infections especially invasive aspergillosis, but it is an exoantigen released from the tip of mycelium of many fungi spp. during growth (52), therefore, cross-reactivity has been described with other fungi (53-55). False negative reactivity without any known reason (56) and false positive reactivity with use of some drugs and foods have been reported (57-61). Sensitivity range of GM test, for the diagnosis of documented invasive aspergillosis cases was reported to be between 50.0% (62) and 90.6% (63). There are limited studies using this method for the diagnosis of FE. In one study, GM test to establish the diagnosis of invasive aspergillosis was only positive (≥1 ng/mL) in 2/7 patients with endocarditis and mediastinitis(17) and four out of nine cases in another study (33). To diagnose systemic candidiasis, enolase (64), phospholipase and proteinase enzymes (65), *Candida* mannan antigen (66, 67), and β-D-glucan (68-71) have been detected in some studies. However, there are a few reports on the use of such antigens in patients with FE.

Antibody assays can be helpful for some species of fungi which are not the normal flora but there are problems with both specificity and sensitivity when *Candida spp.* is responsible for infections, since it is a part of the body normal flora. Immunosuppressed hosts may be unable to produce strong antibodies; therefore, the sensitivity of the assay in this high-risk population is decreased.

The current focus of non-culture methods is on the development of a polymerase chain reaction (PCR) assay for the detection of fungal infections (72, 73). Panfungal PCR with universal primers (74), nested PCR (75, 76) and real-time PCR (77, 78) can serve as sensitive and quantitative methods to detect fungal DNA in the human blood specimens (74, 79). The sensitivity and specificity of nested PCR for invasive aspergillosis in the blood are 92.8% and 94%, respectively (55). Although these methods have not been standardized and are not widely used, limited studies indicate a good sensitivity for FE diagnosis and close to blood cultures (33, 80). Using the molecular methods with reduced PCR steps like real time- PCR, the result can be released within 6 hours (81). Due to the inhibitory factors in human blood samples, PCR may yield false negative (82) and for the abundant conidia of fungi in the environment, false positive may also be seen, which is rare and limited. The significance of PCR tests is their ability to detect fungal infections in early stages (83).

Other nonspecific laboratory outcomes include: a normochromic normocytic anemia, elevated erythrocyte sedimentation rate and C-reactive protein indicative of inflammation, elevated rheumatoid factor titers (minor Duke criteria), hematuria and proteinuria (minor Duke criteria).

Totally, in patients suspicious to FE, microscopy examination and culture of tissue materials obtained from heart surgery, with antifungal susceptibility test on the isolated fungi are the best methods for the diagnosis and management of FE. In patients with suspected FE in early stage of infection, use of nonaggressive method (i.e., serologic or molecular) is recommended. Combination of serological and microbiological tests is more useful if we are to avoid over-treatment.

4. Treatment

The high mortality rate, difficulty in sterilizing large fungal vegetation or abscesses, and the risk of embolization associated with medical therapy alone (84) are the reasons for the

recommendation of combined surgical and medical treatment in patients with FE for better prognosis (7, 8, 85). It is also the suggestion of the 2009 Infectious Diseases Society of America guidelines for the treatment of native and prosthetic valve *Candida* endocarditis (86). However, there are some reports of *Candida* endocarditis in which medical treatment alone proved successful (85, 87-89) with either caspofungin alone or in combination with flucytosine or fluconazole (87-90). The higher dose of antifungal agents than normal dose is recommended for treatment (86). In critically ill patients for whom surgical resection cannot be done, antifungal therapy is recommended for months and even life-long. In combination therapy a minimum of 6 weeks medication after surgery is advocated (91), but the treatment should be continued till signs and symptoms of the infection disappear and radiographic abnormalities are stabilized, and life-long prophylactic therapy is recommended. Relapses are common either with medical or combined therapy (37, 92, 93) and may appear early or late; mean 25 months (92). Due to high relapse rates, patients should receive life-long therapy (92, 93) and careful follow-up is also essential for successful therapy.

Treatment of FE in immunocompromised patients needs to take into account the underlying disease of patients and the intervention of antifungal agents with the patient's condition. For example, use of amphotericin B deoxycholate, in patients with renal insufficiency or those who are on multiple nephrotoxic drugs is not suggested and for fewer adverse effects, lipid formulations of amphotericin B are recommended (94). Many studies have reported the resistance of some fungi to this antifungal agent (44, 45, 95), therefore, to limit the use of amphotericin B, current treatment options including azole due to its broad antifungal activity, and echinocandins as a new class of antifungal drugs, are recommended (96).

In transplant recipients and HIV patients, use of triazoles which have interaction with human P450 cytochromes (97), can block the metabolism of certain anti-HIV drugs and also some drugs such as cyclosporine, statins, and benzodiazepines (98). Therefore, close monitoring of drug levels needs to be calibrated with the dose of immunosuppressive drugs (99, 100). Physicians should prescribe triazole agents in consultation with a pharmacist because inhibitory activities among triazoles are different and fluconazole is of less active inhibition of P450 than other azole agents such as itraconazole, voriconazole, and posaconazole. In patients receiving these antifungals, monitoring of drug levels in respective sera is suggested (96).

Echinocandins; caspofungin, micafungin, and anidulafungin; are new antifungal agents which damage the fungal cell walls by inhibiting the b-(1, 3)-glucan synthesis. Drug–drug interactions between echinocandins such as caspofungin are observed with tacrolimus and cyclosporine, certain anti-HIV drugs and rifampin (96). Use of caspofungin in patients with impaired liver function and those receiving cyclosporine should be carefully considered, because of the common side effects of this agent including increased liver enzymes, pruritus, facial swelling, headache and nausea. They have fungicidal activity against *Candida* biofilm (101) and most isolates of *Candida* species including *C. glabrata in* vitro and in vivo with benign toxicity profile (102).

If the patients are not responsive to their initial mono-antifungal therapy regimen, the use of the combination antifungal regimen is recommended that include an echinocandins with voriconazole or liposomal amphotericin B. Combination therapy by amphotericin B and a triazole is not suggested in the literature (103). The function of combination

antifungal therapy is controversial due to probable increase in side effects and toxicity level (104, 105).

5. Prevention

Fungal endocarditis may be caused by endogenous or exogenous fungi. The prevention of FE could be through adopting two strategies; one is general and useful for all infections like hand-washing, personal hygiene, and indwelling central venous catheters care, and the other is especially for fungal infections. Practical ways to achieve this goal is use of non-drug or drug prevention (prophylaxis). Avoiding opportunistic endogenous agents like *Candida* spp. which colonize in the human body sites is difficult. The best strategy for the management of *Candida* endocarditis is the evaluation of colonization pre-surgery to determine the susceptibility pattern of the isolated organisms, which may cause infection after surgery and enhance the success of management of systemic or endocarditis candidiasis. Care of central venous catheters is important for reducing candidemia and *Candida* endocarditis; and the removal of all existing central venous catheters for the reduction of morbidity and mortality (106-108) is helpful. However, in patients with obligate central venous access, new sites should be obtained (109, 110).

Fungal spores are abundant in the environment, and unfiltered air, dust, and contaminated materials are full of fungal conidia (111, 112). In many cases, fungal infections may occur during the surgery, via contaminated air, surgical site or equipment with conidia. To prevent the contamination, use of high-efficiency particulate air filters for air sterility (113), and sterile equipment in the operation room are recommended.

Antifungal prophylaxis could be used to avoid the development of fungal infections in high risk patients (114), based on the susceptibility patterns of the etiologic agents in each region. Empiric therapy (antifungal treatment of febrile patients at risk for infections) was first introduced to prevent invasive fungal infections in the 1980s in patients with undiagnosed fevers, particularly invasive candidiasis (115). To prevent the relapse in patients with history of fungal infections who have received complete antifungal therapy, clinicians can turn to secondary prophylaxis.

6. Conclusion

Fungal endocarditis is one of the most serious manifestations of invasive fungal infections. The first line of prevention is decreasing fungal conidia transition during surgery in operating rooms by using high-efficiency particulate air filters and sterile equipment. Early diagnosis and immediate appropriate antifungal therapy are critical for the survival of the respective patients. For high quality care of the patients, echocardiography with non-cultural methods such as GM assay and PCR which can detect infection in early stages should be performed. In patients with suspected FE and positive test results, it is recommended that they receive antifungal agents pre-operation and also the clinical management be continued once the documented diagnosis is made based on the sample obtained in the operation room. As high relapses are common, treatment should be followed by careful review of the clinical, mycological (serum GM level and DNA load) and echocardiography sign and symptoms of the infections.

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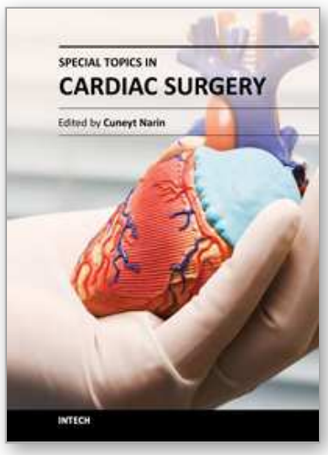

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This book considers mainly the current perioperative care, as well as progresses in new cardiac surgery technologies. Perioperative strategies and new technologies in the field of cardiac surgery will continue to contribute to improvements in postoperative outcomes and enable the cardiac surgical society to optimize surgical procedures. This book should prove to be a useful reference for trainees, senior surgeons and nurses in cardiac surgery, as well as anesthesiologists, perfusionists, and all the related health care workers who are involved in taking care of patients with heart disease which require surgical therapy. I hope these internationally cumulative and diligent efforts will provide patients undergoing cardiac surgery with meticulous perioperative care methods.

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