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Review

Current updates on fungal endocarditis

Neema NEGI[a], *Aijaz AHMAD*[b,c,*]

[a]*Department of Molecular Biology, Umea University, Umea, Sweden*
[b]*Clinical Microbiology and Infectious Diseases, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[c]*Infection Control, Charlotte Maxeke Johannesburg Academic Hospital, National Health Laboratory Service, South Africa*

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ABSTRACT

Fungal endocarditis (FE) is a rare disease but in recent years its incidence as well as mortality is increasing particularly in developing nations. *Candida* and *Aspergillus* species occupy the prominent position as etiological agents of this invasive disease. Intravenous devices such as pacemakers, central line related thrombosis and prolonged use of antibiotics are major risk factors for FE. The epidemiology of endocarditis cases is also evolving over time with exceptionally rare species causing more invasive disease. Research over the last decade has also delineated the underlying pathogenic mechanism of FE. Improved understanding of these mechanisms will help to combat the increasing problem of antimicrobial drug resistance. The diagnosis of FE is dependent on the sensitivity and specificity of the method as fungi generally do not grow well in blood cultures. More advanced techniques including molecular and immunological assays now play a central role in accurate identification of causative fungal pathogens especially in culture negative scenario. In developing nations such as India, blood culture reports are generally negative due to prior antibiotic therapy. Echocardiography has emerged as the potential imaging technique for identifying invasive endocarditis including small masses of vegetation or abscess. Successful treatment often requires both the surgical interventions and prolonged antifungal therapy. In the present review, we briefly highlight the mechanisms of pathogenesis of this rare emerging disease along with the risk factors involved, the diagnostic criteria and the treatment strategy.

1. Introduction

William Osler in 1885 defined Infective Endocarditis (IE) as an inflammatory process that damages endothelial surfaces of heart especially endocardium including valves and adjacent structures (Ashley and Niebauer, 2004). It is now considered as a "modern disease" and is more prevalent in developing nations than western world due to advancement in the field medical practice and surgical interventions. In general population, IE is more frequently observed on the left side of the heart

* *Corresponding author*. Clinical Microbiology and Infectious Diseases, School of Pathology of NHLS and University of the Witwatersrand, Faculty of Health Sciences, Johannesburg, South Africa. Fax: +27 86 295 3697.
E-mail address: Aijaz.Ahmad@wits.ac.za (A. Ahmad).
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involving mitral or aortic valves while right side IE is more common among drug users affecting tricuspid valves (Frontera and Gradon, 2000). Infective endocarditis occurs when disease causing organisms such as bacteria or fungi travel from the bloodstream and inhabit the inner lining of heart. Though endocarditis caused by bacteria e.g., *Streptococci* and *Staphylococci* is more common, there are many other etiological agents such as fungi that are known to cause inflammation. Fungal endocarditis is generally caused by different species of *Candida* and *Aspergillus*, however other fungal species are also reported to cause this disease. In this modern era, increasing open heart surgeries generally end up in mycotic endocarditis which usually get established during valve replacements (Chaudhari, 1970; Cooper *et al.*, 1961). Though the administration of broad spectrum antibiotics before and after surgery generally prevents bacterial infection to a great extent but unfortunately it paves the way for fungal infection. Additionally other resources including long exposure of viscera to theatre air, tracheostomy, indwelling catheters used in such operative procedures also promotes the growth of fungi (Kinare *et al.*, 1978). As fungal kingdom shares most recent common ancestory with animal kingdom, they share similar cellular machinery, which makes them difficult to treat in infected individuals in comparison to bacterial infections (Heitman, 2011). There is a drastic change in the trend of fungal endocarditis cases reported each year. Fungal endocarditis have initially been reported in few cases of young adults with rheumatic heart disease, however with the advent of HIV and other immunocompromised conditions it has been shifted to a broader population affecting older people, intravenous drug users, immunocompromised patients and patients with intracardiac devices (Que and Moreillon, 2011). Furthermore, 1–3 % cases of prosthetic valvular heart disease patients accounts for one third of endocarditis cases after valvular heart surgery (Keys, 2000). Other important risk factors that predispose patients to fungal endocarditis are congenital heart defects (small ventricular septal defect, bicuspid aortic valve), cardiac interventions (pacemaker, prosthetic valve) and degenerative valve disease (mitral valve prolapsed, bicuspid aortic valve). The main aim of this review article is to provide a detailed overview of fungal endocarditis, its prevalence, risk factors involved, its pathogenesis and current updates on the treatment strategies of fungal endocarditis cases.

2. Epidemiology of fungal endocarditis (FE)

Historically, fungal endocarditis is a rare disease but over the years its incidence is increasing especially in high risk individuals. It is estimated that around 1.2 %–2.6 % of all endocarditis cases are caused by fungi and the incidence rate is even higher in patients who undergo valve replacement surgeries (Mylonakis and Calderwood, 2001). Despite rare, the mortality rates of fungal endocarditis is notably higher which accounts from 45 to 50 % (Badiee *et al.*, 2014). Studies have reported that approximately 15 % of endocarditis cases post-surgical interventions could be caused by fungi. Men were found to be more prone to acquiring fungal endocarditis than women (2:1) (Ellis *et al.*, 2001). The first case of FE was reported in early 1964 in patients with mitral valve replacement but since then many such cases have come to attention of infectious disease clinicians (Newman and Cordell, 1964). It has been documented that fungi are responsible for 9.6 % of the early cases of prosthetic valve endocarditis and accounts for 4.3 % of late cases (Gordon and Keys, 1995; Watanakunakorn, 1979). Fungal endocarditis caused by *Candida* species are healthcare-associated, while endocarditis caused by *Aspergillus* species occurs mostly after cardiac surgery (Gould *et al.*, 2012). Fungal endocarditis is a life threatening disease and has been associated with a high morbidity and mortality (Badiee, 2012). The mortality rate for FE is estimated to be 1 in 100,000 per year and is significantly higher in intravenous drug users. Among injecting drug users, the incidence is as high as 150–2000/100,000 person years. Though FE is rare in pediatric population, the incidence rate is increasing over the years as more newborns are kept in intensive care units or undergo cardiac surgical procedures or receiving hyperalimentation (CHA). It has been estimated that fungi contributes 0–12 % of FE cases in pediatric population worldwide and incidence rate is approximately 1.5–4 cases per 10 million children. Compared to adults, the mortality rate is high (70–90 %) in children because of poor diagnosis, lack of effective antifungal antibiotics and other underlying conditions (Ferrieri *et al.*, 2002).

3. Etiological agents

Despite the huge diversity of fungal–animal interactions, only animal pathogenic fungi have been studied extensively (Casadevall, 2007). Among several fungal species, *Candida* is the most important etiological agents of FE both in adults and pediatric population and accounts for two thirds of all reported cases. Majority of these infections are caused by *Candida* (60–70 %) and *Aspergillus* species (20–25 %) (Pierrotti and Baddour, 2002; Kossoff *et al.*, 1998) (Table 1). Other fungal species that also contributes to this disease include filamentous *Aspergillus* species (especially in immunocompromised patients and post-operative patients), *Curvularia geniculata*, *Hormodendrum dermatitidis*, *Mucorceae*, *Scopulariopsis* species, *Trichosporon* species and *Blastoschizomyces capitatus*, *Pseudallesheria boydii* (prosthetic valve endocarditis), *Trichosporon asahii* fungemia and non-albicans species of *Candida* – *Candida glabrata*, *Candida tropicalis* (Rubinstein and Lang, 1995; Ellis *et al.*, 2001; Challa *et al.*, 2004; Badiee, 2012). In few sporadic cases of FE other fungal pathogens such as *Histoplasma capsulatum*, *Candida parapsilosis*, *Pneumocystis jiroveci*, and *Candida stellatoidea* play a major role in establishing disease pathogenesis. Other fungal pathogens, such as *Blastomyces dermatitidis*, *Cryptococcus neoformans* and *Coccidioides immitis* are generally the causative agents of pericarditis but are rarely also involved in causing endocarditis (Alhaji and Sadikot, 2011). Filamentous fungi are responsible for causing disseminated fungal infections particularly in immune suppressed patients like HIV infected individuals (Tacke *et al.*, 2013). Pasqualotto and Denning (2006) in their review of 124 patients with post-operative *Aspergillus* endocarditis reported that *A. fumigatus* was the predominant pathogen in 58.7 % cases followed by *A. terreus* (12.5 %), *A. niger*, and *A. flavus* (11.2 %). The source of infection could be both internal and external. The outbreaks of these exceptional fungal cases have been reported

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