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Review

Recent advances in delivery of antifungal agents for therapeutic management of candidiasis

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ABSTRACT

Candidiasis is a fungal infection caused by yeasts that belong to the genus *Candida*. There are over twenty species of *Candida* yeasts that can cause infection in humans, the most common of which is *Candida albicans*. *Candida* yeasts normally reside in the intestinal tract and can be found on mucous membranes and skin without causing infection; however, overgrowth of these organisms can cause symptoms to develop. Presence of other diseases that compromises the patient's immunity makes it more difficult to treat. Candidiasis is majorly divided into superficial infections (oral or vaginal) and systemic infections, also known as invasive candidiasis. The conventional therapeutic modalities used to treat candidiasis are associated with several side effects that limits the dose and dosing frequency. Development of novel drug delivery systems for reduction in dose and alleviation of side effects is an important strategy to improve the clinical efficacy and patient acceptability. This review gives a bird's eye view of the classification and current therapeutic regime of candidiasis. It presents the varied types of drug delivery systems that have been exploited for delivery of antifungal agents with measurable benefits. It also touches upon echinocandins a relatively new class of drugs that are amenable for translation into novel dosage forms with application against biofilm producing and fluconazole resistant strains contributing to a better therapeutic management of candidiasis.

1. Introduction

The past two decades have witnessed an increase in the incidence of fungal infections, especially in case of immunocompromised or hospitalized patients. The potential cause are disruption of mucosal and/or cutaneous barrier, metabolic dysfunction and age [1–3]. Additionally, broad-spectrum antibiotics, cytotoxic chemotherapies and transplantation also increases the risk of opportunistic fungal infections [2–5]. *Candida* has been found to be the most important cause of opportunistic mycoses worldwide. The prevention and treatment of candidiasis becomes a challenge, due to comorbidities like AIDS that lower the immune resistance of an individual.

Candida albicans is responsible for two major types of infections that include superficial (oral or vaginal) and systemic infections [5]. *C. albicans* and other *Candida* species to a lesser extent are present in the oral cavity of up to 75% of the human population. However, the immunocompromised patients are often at a higher risk of suffering from 'oral candidiasis', which is associated with its secondary form like denture stomatitis [6]. These infections affect the oropharynx and/or esophagus leading to dysfunction in the adaptive immune system [7]. Vulvovaginal candidiasis (VVC) is a type of superficial infection affecting approximately 75% of women at least once in their lifetime while 40–50% experience at least one additional episode of infection and a small percentage of women (5–8%) experiences at least four recurrent VVC per year. Invasive candidiasis, a group of infectious syndromes, responsible for bloodstream infection is the leading cause of morbidity and mortality in infants [8].

The virulence of *Candida albicans*, is related to its ability of morphological transitions between yeast and hyphal form, biofilm formation, gene expression; that is responsible for adhesion and invasion on the cell surface, phenotypic switching, secretion of hydrolytic enzymes, adaptability to environmental pH change, stress response and metabolic flexibility [9]. *Candida albicans* is a polymorphic fungi and can either grow as ovoid-shaped budding yeast at low pH (< 6) or as parallel walled true hyphae at high pH (> 7). Both forms are important for its pathogenicity [10,11]. Another important factor determining the virulence is the ability to form biofilm on the abiotic or biotic surfaces like catheter, dentures and mucosal surface. Mature biofilm possesses a complex architecture comprising of expression of drug efflux pumps and metabolic plasticity responsible for resistance to antimicrobial

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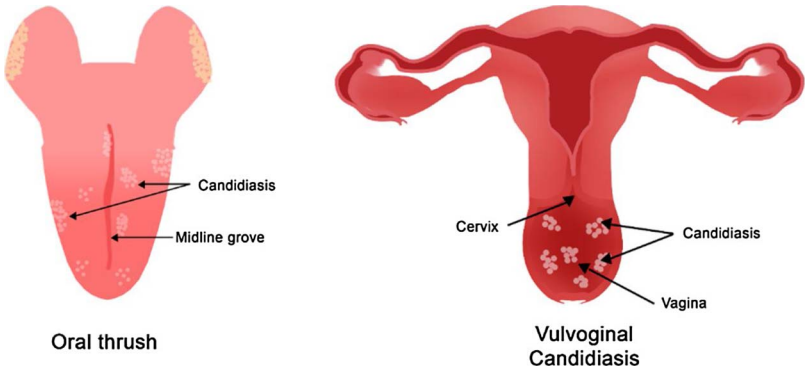

Fig. 1. Oral thrush and vulvovaginal candidiasis.

agents [12,13].

The authors have made an attempt to provide an overview of various classes of candidiasis including their pathophysiology, limitations of conventional antifungal dosage forms and novel approaches for the development of more efficient drug delivery systems that will help to alleviate the drug related side effects. This review describes the recent advances in the delivery of antifungal agents to improve their therapeutic profile. The use of novel drug delivery systems to overcome the deficiencies of conventional drug delivery systems and enhancement in the overall efficacy of these drugs has been thoroughly evaluated and discussed.

2. Pathophysiology of candidiasis

The knowledge of local epidemiology plays an important role in planning the appropriate treatment for systemic *Candida* infections, since type and severity of candidiasis is closely related to *Candida* species present at the site of infection [14–17]. A pictorial representation of oral thrush and vulvovaginal candidiasis in shown in Fig. 1. Based on the site of infection, candidiasis can be classified into three types:

2.1. Oral candidiasis

Oral pharyngeal candidiasis (OPC) is the most common opportunistic infection found commonly in the human immunodeficiency virus (HIV) infected patients (up to 90%) due to decrease in the immunity. HIV- infected patients in advanced stages are much more prone to oral candidiasis than the early HIV-infected stages [18]. The occurrence of OPC is associated with a fall in $CD4^+$ T-cells (below < 200 cells/mm^3). A study performed by Campo I et al. indicated a direct correlation of OPC with age and smoking habits in HIV-infected patients. Smoking produces a degree of xerostomia (dryness in the mouth), which when combined with a reduction in salivary IgA, facilitates invasion by *Candida* species [19–21]. It is generally associated with four primary oral forms viz. pseudomembranous candidiasis (oral thrush), acute erythematous oral candidiasis, chronic erythematous oral candidiasis and chronic hyperplastic candidiasis. The characteristic features of these forms are described in Table 1. These primary forms of candidiasis are also associated with lesions referred to as secondary forms of candidiasis viz. angular chelitis [22], median rhomboid glossitis [23] and *Candida*-associated denture stomatitis [24–26].

2.2. Vulvovaginal candidiasis (VVC)

VVC affects about three-quarters of women with at least one episode of VVC during their reproductive age and approximately half of the women population from two or more episodes. The causative agent is predominantly *Candida albicans* followed by *Candida glabrata* [35,36]. VVC is divided into two cases as shown in Fig. 2 viz. uncomplicated cases characterized by sporadic episodes of mild infections caused by *Candida albicans* and complicated cases characterized by severe infection caused by other species of *Candida* during pregnancy or associated medical conditions like immunosuppression or diabetes [35–41].

2.3. Invasive candidiasis

Invasive candidiasis includes various types of severe invasive disorders like candidemia, disseminated candidiasis, endocarditis, meningitis and endophthalmitis [42]. Candidemia is the fourth most common bloodstream infection that affects more than 250,000 individuals worldwide every year and is responsible for more than 50,000 deaths [43]. Recently, other species of *Candida* like *Candida glabrata*, *Candida parapsilosis* have also emerged as causative agents alongside *Candida albicans* [44]. A large variation seen in the virulence of different *Candida* species like *Candida parapsilosis* and *Candida krusei* are less virulent than *Candida albicans, Candida tropicalis* and *Candida glabrata* and is characterized by a low mortality rate amongst *Candida parapsilosis* infected population [45].

The pathogenesis of invasive candidiasis includes increased fungal burden due to inconsistent use of broad-spectrum antibiotics, recent surgery and trauma, use of intravascular devices and immune dysfunction [44,46]. *Candida* adheres to vaginal, gastrointestinal and oral epithelial cells, platelet fibrin clots, acrylic and plastic materials, lymphocytes and forms biofilm with unique phenotypic and genotypic characteristics that is resistant to currently used antifungal agents [47,48]. The risk factors in adults include prolonged time for treatment, renal failure, hemodialysis, use of broad-spectrum antibiotics, immunosuppressive drugs, chemotherapy and *Candida* multiplication at different sites. Additionally, children and neonates are predisposed to premature birth and congenital defects [41].

3. Therapeutic management of candidiasis

Oral candidiasis is treated by managing the identifiable predisposing factors like adequate cleaning of dentures in patients with chronic erythematous candidiasis using 1% sodium hypochlorite preparations or chlorhexidine solution (0.2% w/v). However, use of chlorhexidine may cause discoloration of teeth and tongue [49,50]. Another method to maintain good oral hygiene is the use of automated toothbrush with the ability to remove plaques at inaccessible sites due to fluid shear force generated [51]. In cases like AIDS and leukemia, the compromised immune system and predisposing factors makes it difficult to eradicate the fungal infection and hence antifungal therapy is required. Antifungal agents are classified into polyenes (heterocyclic amphipathic compounds), azoles, fluorinated pyrimidine analogue 5-flucytosine and echinocandins. Azoles and polyenes are commonly used in the treatment of candidiasis and their mechanistic pathway is depicted in Fig. 3 [52,53,54].

Polyenes are frequently used in the treatment of oral erythematous candidiasis. Amphotericin B is administered as an oral suspension for refractory oral candidiasis, frequently observed in the HIV-infected and