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A Review of Esophagitis Due to *Candida* Species in Human Immunodeficiency Virus (HIV) Infected Patients

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Abstract

The present study aimed to provide an overview of epidemiology, pathogenicity, clinical diagnosis, and treatment of *Candida* esophagitis in human immunodeficiency virus (HIV)-infected patients. The review process involved studying all the existing literature published on this *Candida* infection. Esophageal candidiasis (EC) is the most common manifestation of mucosal candidiasis and patients with HIV are predominantly at the risk of this opportunistic infection. The prevalence of EC indicated diverse ranges among HIV patients in different geographic areas due to antiretroviral therapy (ART). The main factors for EC were gastric ulcers, $CD4^+$cell count <200 cells/mL, and HIV viral load >400 cells/mL in the ART era. However, a low $CD4^+$ cell count (<200 cells/mL) was significantly associated with EC in the pre-ART era. The interactions between the *Candida* virulence factor and host immune defense lead to the host responses against this fungal pathogen. During the *Candida albicans* invasion, secretion of candidalysin which is encoded by the hyphal gene *ECE1* has a potential role in epithelial cell damage and secretion of stimulated cytokine. Early trials of the empirical antifungal therapy are recommended before an endoscopic examination. Esophageal biopsy should be considered in patients with a failure of empiric antifungal treatment as it may allow the possibility of drug-resistant *Candida* and other opportunistic pathogens. The first-line induction treatment of *Candida* esophagitis is based on oral fluconazole. The shift from *C. albicans* to non-*albicans Candida* (NAC) may be correlated with the development of fluconazole resistance and relapse or therapeutic failure in this infection. An increase in the intrinsic and acquired resistance has raised the significance of the optimal antifungal therapy for the critically ill patient. *Candida* esophagitis requires a systematic suspicion for early diagnosis and appropriate management of HIV infected patients in order to prevent delayed treatment related to undesirable morbidity or even mortality scores.

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Background

Despite various efforts to prevent and detect the HIV infection, it is still a major public health issue which leads to high morbidity and mortality related to opportunistic infections.[1] Mucosal candidiasis is a major debilitating opportunistic infection in immunocompromised individuals.[2] Esophageal candidiasis (EC) is the most prevalent manifestation of this infection which patients with HIV are predominantly exposed at its risk.[3] *Candida* esophagitis as an opportunistic fungal infection can result in the total significant morbidity related to retrosternal pain, odynophagia, and dysphagia leading to weight loss which is a major contributor to reducing general health in most patients with AIDS. In spite of prolonged antifungal treatment relapses due to the emerging resistant *Candida* species are frequent.[4,5] Understanding the clinical features, as well as diagnostic and therapeutic approaches, are essential to facilitate early diagnosis and treatment strategies of EC in this group of patients. Therefore, this study sought to present an overview regarding various aspects of *Candida* esophagitis in HIV infected patients.

Epidemiology

The incidence of EC demonstrated various ranges among HIV patients in different geographic areas because of antiretroviral therapy (ART).[6] The prevalence of EC had a decrease of about 25%–50% after one or two years of ART. Few studies investigated EC occurrence and risk factors

in the last decades.[7,8] In the ART era, the main factors related to the *Candida* esophagitis were recognized as gastric ulcers, $CD4^+$ cell count <200 cells/mL, and HIV viral load >400 cells/mL.[9] However, a low $CD4^+$ cell count (<200 cells/mL) is found to be significantly correlated with EC in the pre-ART era.[10-12] In a low-income country with limited health care, the annual frequency of oral thrush and esophageal fungal infections is described to be about 10 million and 2 million cases, respectively.[13] Actually, a decrease was observed in the incidence of EC from 42.8 to 16.7% during 1991-2008.[14] In addition, in the United State, the emergence of ART which resulted in EC prevalence, decreased from 13.6% to 9.0% during 2002–2003 and 2012–2014, respectively.[6] However, Takahashi et al indicated that EC incidence rate was nearly 2% (1219/78 624) in non-HIV infected patients which was negligible compared to those of the HIV infected patients (9.8%).[6] During 2008–2010, EC was the second most common leading of opportunistic infection after *Pneumocystis jiroveci* pneumonia among the HIV population.[15] There is a significant difference in the male to female ratio (2:1) among HIV infected patients diagnosed with EC in several investigations.[16-18] The reasons for such gender differences are poorly understood, but it is supposed that sexual behaviors and habits and even job play putative roles in this respect. Further, patients within the age range of 20–45 years were the most affected group in the reported studies.[16,17] *Candida albicans* is the most common species that was isolated from HIV infected individuals; however, the prevalence of mucosal candidiasis caused by NAC species has increased significantly[19-21]; in the 1980s and 1990s, accounting for 3.4% and 16.8% of oral isolates from HIV infected patients, respectively, were NAC species.[22,23] The most common NAC species were *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and C. *dubliniensis*.[23] The analysis of epidemiological data from some countries is recommended to establish appropriate measures for EC infection control in HIV positive individuals and prompt diagnosis to improve antifungal therapeutic stewardship.

Pathogenicity

Candida species is a normal flora of the gastrointestinal that can cause esophagitis in patients infected with HIV during the life. In addition, these patients commonly expose to *Candida* species in food and other sources as exogenous factors which increase the prevalence of gastrointestinal tract infection in this population.[24] The interactions between *Candida* virulence factor and host immune defense leads to host responses against this fungal pathogen. The *C. albicans* develops several strategies including adhesions, phenotypic switching, dimorphism, and secretion of hydrolytic enzymes to evade the immune system and facilitate its invasion.[24] Due to the lack of data on host and effective yeast factors in the pathogenesis of EC, the impact of each virulence factor on the incidence of EC remains unknown. Apparently, adhesions and the secreted aspartyl proteinase (Saps) are considered more important virulence factors in the pathogenesis of oropharyngeal among those HIV positive patients.[6,24] Swidergal and Filler reported a strong correlation between candidalysin and pathogenesis of oropharyngeal candidiasis. During the *C. albicans* invasion, secretion of candidalysin which is encoded by the hyphal gene *ECE1* has a potential role in damaging the epithelial cell and secreting the stimulated cytokine.[26]

Host Defense

The defense system against mucosal fungal infection is dependent on the role of $CD4^+$ T cells. Thus, these infections exclusively occur during cellular immunity defect. The HIV induces immunosuppression and facilitates the development of *Candida* species in mucosal surface.[23] *Candida* esophagitis is an AIDS-defining diagnosis and tends to occur at lower $CD4^+$ T cell counts (<100 cells/mL). However, 25% of the EC patients have $CD4^+$ cell counts > 400 cells/mL.[6] The protective mechanism of mucosal $CD4^+$ T cells against EC is still incompletely understood. Several studies confirmed an effect of decreased E-cadherin levels on episodes of acute oropharyngeal candidiasis.[23,27,28] Further, Cytokines, especially interferon gamma released from the macrophages may induce an increase in chemokine synthesis from intestinal epithelial cells. The CD8 responses could be important in controlling the infection in this group of patients.[23] However, CD8 or macrophage responses in HIV patients may lead to an unusual cytokine release and intestinal damage. More importantly, the decreased capacity to support HIV-1 infection was reported into M1 polarization of human macrophages induced by tumor necrosis factor-α (TNF-α) and IFN-γ.[29] Accordingly, studies focusing on the balance between various cytokines and their tissue receptors against mucosal infection in HIV individuals are needed.

Clinical Diagnosis

Esophagitis due to infection with *Candida* is associated with different clinical manifestations ranging from dysphagia, odynophagia, and oral candidiasis to hemorrhage, stenosis, and esophagotracheal fistula.[30-32] However, some patients (30%-43%) may not have any symptoms of esophageal involvement.[33] Endoscopic features are well-defined as yellow-white plaques, ulceration, luminal narrowing, and necrosis which are essential in diagnosing this infection. Furthermore, its diagnosis requires performing biopsy, which would yield high costs and numerous invasions in the high-risk population.[34] Therefore, oropharyngeal candidiasis and characteristic symptoms of esophagitis as the clinical criteria are probably acceptable for empiric antifungal therapy in these patients without being confirmed by endoscopy.[35] Esophageal biopsy should be highlighted

in patients with empiric antifungal treatment failure as it may allow the possibility of drug-resistant *Candida* species and other opportunistic pathogens.

Treatment and Antifungal Drug Resistance

Choosing the antifungal agents should be guided by the extension of EC infection, potential adverse effects, and the efficiency of prior treatments. A systemic therapy administration has always been an important benefit in *Candida* esophagitis.[12] Moreover, early trials of empirical antifungal therapy is recommended before an endoscopic examination. The first-line induction treatment of *Candida* esophagitis is based on daily receiving of oral fluconazole at a dose of 200–400 mg (3–6 mg/kg) for 14-21 days. Intravenous fluconazole or echinocandins is reserved for patients who cannot tolerate oral treatment. The antifungal dosing for treating *Candida* esophagitis in HIV infected patients are summarized in Table 1.[36] It was found that ART significantly reduced the prevalence of EC in HIV infected patients and are strongly recommended for decreasing the recurrent infection.[23] Recurrent or refractory *Candida* esophagitis was reported in a considerable number of patients as a result of long-term fluconazole therapy in this population due to the low $CD4^+$ T cell counts and persistent exposure to clinical azoles.[37-39] The shift from *C. albicans* to the NAC may be correlated with the development of fluconazole-resistance and relapse or therapeutic failure.[19,20] Additionally, increasing the intrinsic and acquired resistance, the optimal antifungal therapy for the critically ill patient became essential. However, Pfaller et al found that patients with recurrent episodes of EC responded to an increased dose of fluconazole and thus the relapse risk decreased.[38] The recommended alternative treatment strategy for fluconazole-refractory disease included azole and echinocandin regimens (Table 1). Itraconazole and posaconazole were used as effective alternatives for fluconazole-refractory oropharyngeal or EC, in 64%-80% and 75% of the patients respectively.[36] In a randomized study by Andes et al, daily administration of micafungin (300 mg vs. 150 mg) to both groups of *Candida* esophagitis patients with less than daily administration in high dose group revealed a higher response (85% vs. 79%) and lower relapse rate (6% vs. 12%) in the group receiving a high dose of micafungin compared to the other group. The efficacy and safety of high dose echinocandin regimens on fungal infection were confirmed in several studies.[40-43] Using terbinafine, flucytosine, echinocandins, and GM-CSF (the Granulocyte-macrophage colony-stimulating factor) in combination with fluconazole was suggested as a potential therapeutic option for managing refractory mucosal candidiasis in patients with HIV.[23,44] As a result, it is recommended to use combination therapy as an alternative antifungal strategy and effective approach to avoid further emergence of drug resistance to *Candida* esophagitis among the HIV population.

Conclusion

Candida esophagitis is as an opportunistic fungal infection with a high morbidity rate. Accordingly, to prevent delayed treatment which leads to undesirable morbidity or even mortality scores, *Candida* esophagitis needs a systematic suspicion among HIV infected patients so that to be quickly diagnosed and appropriately managed.

Authors' Contributions

The authors alone are responsible for the content and writing of the paper.

Ethical Approval

Not applicable.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

Table 1. The Antifungal Dosing in Treatment of *Candida* Esophagitis in HIV Infected Patients

Antifungal Agent	Administration	Total Daily Dose	Comment
Fluconazole	Orally	200–400 mg (3–6 mg/kg)	Strong recommendation, strong evidence, should always be offered
Alternatives for Fluconazole Refractory Disease and Patients Who Unable to Tolerate Oral Fluconazole			
Fluconazole	Intravenous	400 mg (6 mg/kg)	
Itraconazole	Oral solution	200 mg	Strong recommendation and evidence
Voriconazole	Intravenous/ orally	200 mg (3 mg/kg) twice daily	
Posaconazole	Suspension	400 mg twice daily	Weak recommendation and poor evidence
	Orally	300 mg	
Micafungin	Intravenous	150 mg	
Caspofungin	Intravenous	70 mg loading dose and 50 mg daily	Strong recommendation and evidence
Anidulafungin	Intravenous	200 mg	
AmB deoxycholate	Intravenous	0.3–0.7 mg/kg	Strong recommendation, moderate evidence

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