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Review Article

ORAL CANDIDIASIS: A REVIEW IN HIV SEROPOSITIVE PATIENTS

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ABSTRACT
Candida are true 'opportunistic pathogens' and only instigate oral infection when there is an underlying predisposing condition in the host. Oropharyngeal candidiasis is a common occurrence in the course of *human immunodeficiency virus* (*HIV*) disease progression. The majority of infections are due to *Candida albicans* although other species such as *Candida glabrata, Candida tropicalis, Candida krussei* and *Candida parapsilosis* are increasingly isolated. The prevalence varies depending on certain predisposing factors. The article reviews common clinical types of candidiasis, its diagnosis current treatment modalities. The systemic azoles, ketoconazole, fluconazole and itraconazole, have been an important benefit in treatment. To date, resistance has primarily been a problem with fluconazole in Acquired Immuno Deficiency Syndrome (AIDS).

Keywords: *HIV, Candida, AIDS, Fluconazol*

INTRODUCTION
In recent decades, concerns about *HIV* and its transmission has increased (Ghasemzadeh *et al.,* 2013). Risk of many *HIV*-related diseases varies with the patient's degree of immunosuppression. CD4 counts and quantitative *HIV-1* RNA levels are most commonly used as surrogate markers of immune function (Mellors *et al.,* 1996; Cameron *et al.,* 1998). Oral manifestations are the earliest and most important indicators of *HIV* infection. Seven cardinal lesions: Oral Candidiasis (OC), Hairy leucoplakia, Kaposi sarcoma, linear gingival erythema, Necrotizing ulcerative gingivitis, Necrotizing ulcerative periodontitis and Non Hogkin Lymphoma are strongly associated with *HIV* and have been identified internationally. These lesions may be present in up to 50% of people with *HIV* infection and in up to 80% of those with a diagnosis of AIDS (Patton *et al.,* 2000). In cases where a person's *HIV* status is unknown, the lesions provide a strong indication of the presence of *HIV* infection (Lifson *et al.,* 1994). Hairy leukoplakia and Pseudomembranous candidiasis are the most common lesions seen in *HIV* infection and are used in all current classifications of *HIV* disease. The presence of either of these oral lesions indicates progression to AIDS (Greenspan, 1997).

Candida
The term *candida (C.)* originates from the Latin word candid meaning white (Zunt, 2000). The *candida* genus is comprised of over 150 species (spp.) of asporogenous 'yeast like' fungi. Members of this genus are ubiquitously distributed, persisting as saprophytes in soil and aquatic environments, as well as colonizing several animal reservoirs (Brandao *et al.,* 2010; Hsieh *et al.,* 2010; Edelmann *et al.,* 2005). *Candida* species may be recovered from up to one-third of the mouth of normal individuals and are considered inhabitants of the normal flora of oral and gasterointestinal tract (Anthony). Colonization of the mouth by *candida* spp. has a long recorded history. Hippocrates, as early as 37 BCE, reported oral lesions that were probably caused by *candida* (Odds, 1988). The commonly isolated species are *Candida albicans (C. albicans), C. glaborata, C. tropicalis* and *C. krusei* and to lesser extent *C. lusitaniae, C. idubliniensis, C. kefyr, C. guillermondii, C. parapsilosis* and *C. lipolytica* (Samaranayake, 1992). Oropharyngeal candidiasis is the commonest fungal infection amongst *HIV* infected patients worldwide (Anwar, 2012). OC is one of the earliest indicators of the progression from *HIV* sero positive status to AIDS (Chellammal, 2014). The incidence of *C. albicans* isolated from the oral cavity has been reported to be 45% in neonates (Manning *et al.,* 1985), 45%-65% of healthy children (Berdicevsky 1980), 30%-45% of healthy adults (Lucas, 1993; Arendorf and Walker, 1980), 50%-65% of people who wear removable dentures (Aldred, 1991), 65%-88% in those residing in acute and long term care facilities (Aldred *et al.,*

1991; Cumming *et al.,* 1990; Holbrook and Hjorleifsdottir, 1986), 90% of patients with acute leukemia undergoing chemo-therapy (Rodu, 1988) and 95% of patients with *HIV* (Dupont, 1992). According to Chellammal (2014), *C. albicans* is a normal commensal of the mouth and generally causes no problems in healthy people.

Oral Candidiasis

Oral candidal colonization and candidiasis have recently received increased attention by the health care providers and researchers alike, particularly following the emergence of *HIV* infection and the widespread use of broad spectrum antibiotics and immunosuppressant therapy (Samaranayake, 1992). *C. albicans* is the species largely responsible for OC which is the most common human fungal infection especially in childhood and the elderly (Darwazeh and Darwazeh, 2014). If the superficial oral candidal infection was not well managed in severe immunosuppression, the patient may become susceptible to esophageal spread of infection or to the potentially lethal systemic candidemia (Vazquez, 2010). At some point of illness all *HIV* sero-positive patients develop oral lesions (Arendorf and Holmes, 2000). In the west, the reported prevalence of oral lesions in HIV/AIDS is 56% (Schmidt-Westhausen *et al.,* 1997) whereas in India it is reported to be about 64% (Anil and Challacombe, 1997). In *HIV* infected patients candidiasis is reported to occur in over 60% and more than 80% in case of AIDS patients (Palmer *et al.,* 1996; Carthy, 1991). OC is one of the most common, treatable oral mucosal infections seen in persons with *HIV* infection or AIDS (Greenspan, 1994).

Pathogenesis

The transition from the harmless commensal existence of *candida* to a pathogenic state can occur following alteration of the oral cavity environment to one that favours the growth of *Candida*. The causes of such changes are the so-called predisposing factors for *Candida* infection (candidosis) and most often these relate to a weakening of host immune defences (Williams and Lewis, 2011) (Table1).

The transition of *Candida* from a harmless commensal to a pathogenic organism is complex and is related to subtle environmental changes that lead to expression of a range of virulence factors. A number of *candida* virulence factors have been proposed that in the event of host debilitation contribute to tissue damage and persistence of the organism within the host (Williams and Lewis, 2011) (Table 2).

It is the combined effect of both host and candidal factors that ultimately contribute to the development of oral candidosis (Marsh and Martin, 2009). The process by which *Candida* spp. colonizes and penetrates the epithelium of the digestive tube can be analyzed in four stages: initial adhesion to the epithelium; replication and colonization; formation of hyphae; and epithelial lesion and penetration (Calderone and Braun, 1991; Hostetter, 2003). Genes INT1 and PLB1 have been related to colonization (Bendel *et al.,* 2000; Leidich *et al.,* 1998).

C. albicans is the principal species associated with human oral mycoses and is the most virulent among pathogenic candida spp. (Samaranayak and MacFarlane, 1990). It has a well-known pathogenic potential and its main pathogenicity and virulence factors are: capacity to adhere to different mucosae and epithelia; dimorphism, with production of pseudohyphae helping tissue invasion; thermotolerance; and production of exoenzymes like aspartyl proteinases (SAPs) and phospholipases (PLs) (Dignani, 2003).

C. albicans possesses at least 10 different genes that encode for SAPs (Hube *et al.,* 1997). SAPs can directly induce damage to host cells, facilitate hyphal growth for invasion of tissue, increase adherence following exposure of receptor sites, and also degrade host immunoglobulins and other defence proteins. (Ramage, 2006; Gropp *et al.,* 2009; Reinholdt *et al.,* 1987; Ruchel, 1983; Ruchel, 1986).

Another group of hydrolytic enzymes produced by *Candida* species are the phospholipases (PLs) and seven distinct encoding genes have been identified in *C. albicans*. Through the hydrolysis of ester linkages of phospholipids, PLs can effectively degrade the membrane of host cells leading to cell lysis and death. By this process, both adherence of *Candida* to receptor sites and its subsequent penetration of damaged tissue can be facilitated (Tsang, 2007).

The role of extracellular lipase and esterase production by *Candida* in pathogenic processes is less well understood (Schaller, 2005). Both lipases and esterases hare the ability to hydrolyse the ester bonds in glycerides, although the latter only act on soluble substrate molecules. A total of 10 Candida lipase (LIP1-

10) genes have been identified in *C. albicans* and sequence-related genes found in *C.tropicalis, C. parapsilosis,* and *C. krusei* (Fu *et al.,* 1997). Lipases of *C. albicans* have recently been shown to exhibit cytotoxic effects on host cells (Paraje *et al.,* 2009) and LIP gene expression detected in oral candidosis (Stehr, 2004).

Haemolysins are substances that lyse red blood cells and their production by *Candida* is considered an important attribute in promoting survival within the host through and increased ability to sequester iron. Luo *et al.,* (2001) demonstrated alpha and beta haemolysis by clinical isolates of *C. albicans, C. dubliniensis, C. kefyr, C. krusei, C. zeylanoides, C. glabrata, C. tropicalis,* and *C. lusitaniae*.

Host Response to Oral Candidosis

Immunocompetent individuals rarely suffer from oral candidosis even when *Candida* is present in the oral cavity. Prevention of mucosal infection by Candida is mediated primarily by the functions of the innate immune response (Williams and Lewis, 2011). With respect to defense against systemic *C. albicans* infections, clinical observations and experimental studies suggest that polymorphonuclear leukocytes are the predominant cell type that protects against candidemia and systemic candidiasis (Ehrensaft *et al.,* 1979; Elin *et al.,* 1974; Holm and Marwin; 1967; Odds; 1988). In particular, neutrophils and macrophages are key to successful phagocytosis and killing of *Candida*. Professional phagocytes recognize *Candida* through pattern recognition receptors (PRRs), which interact with specific molecules (pathogen-associated molecular patterns; PAMPs) exposed on the surface of *Candida* (Mukhopadhyay *et al.,* 2004).

Following recognition, these cells release cytokines and chemokines to further modulate the immune response. Dendritic cells (DCs) are professional antigen presenting cells that provide a sentinel role in mucosal tissue. Interaction of DCs with *Candida* leads to DC activation and phagocytosis. Following phagocytosis, DCs migrate to the lymph nodes where the Candida antigen is processed and presented on the surface of the DC to naive CD4 T-cells (Bonifazi *et al.,* 2009; Jouault *et al.,* 2009; Gil and Gozalbo, 2009; Verdijk, 2009; Del Prete *et al.,* 2004). Interaction between DCs and T-cells cause the latter to differentiate into mature effective T-cells (Ryan 2008). The type of T-cell generated is thought to be under direction of the DC and examples of effective T-cells include T-helper 1 (Th1), T-helper 2 (Th2), T-helper 17 (Th17), and regulatory T-cells (Tregs). Previously it was generally accepted that a Th1 elicited response was a protective one, whilst Th2 responses were implicated in infection. More recently, evidence suggests that a Th17 response is predominant in protection of mucosal surfaces (Conti and Gaffen, 2010).

Oral Candidiasis in HIV Seropositive Persons

Oropharyngeal candidiasis is the most common fungal infections among *HIV* infected patients (Anwar, 2012). It usually presents as an opportunistic infection in patients with CD4 lymphocyte counts less than 200 cell / mm3 (Glick *et al.,* 1994; Anwar, 2012).

Four prevalent clinical presentations have been reported for oral manifestations of candidiasis among *HIV* infected patients. The most prevalent type is erythematous (atrophic) candidiasis (EC), followed by pseudomembranous candidiasis (PC) (thrush), angular cheilitis (AC) and hyperplastic candidiasis (HC) (Patton *et al.,* 2000; Reznik 2004).

EC usually presents with red and flat patches on the mucosal surface of palates or dorsal surface of the tongue (Freeman 2012). Patients may complain of difficulty in eating, dryness of the tongue, burning of the mouth and even spontaneous gingival bleeding (Dupont and Drouhet, 1988; Nicolatou *et al.,* 2004; Tosti *et al.,* 1999). This type is also related to lower CD4 lymphocyte count and progression to AIDS.

PC is typically characterized by a creamy white plaque that affects mostly tongue and other mucosal surface of oral cavity (Castro *et al.,* 2013). It can also affect the esophagus and if the *candida* growths unusually in the mucosal surface give a white and swelling appearance to mucosa that called thrush (McManus *et al.,* 2011). If the plaque has obliterated with scraping, a red or pinkish surface with mild bleeding will be appeared (Hegde, 2012). PC is also, correlated with lower CD4 count and progression to AIDS. Angular cheilitis presents with fissuring, erythema and ulceration of the corners of the lips. It can be associated with other conditions of candisiasis such as erythematous and pseudememranous (Sharon and Fazel, 2010).

HC is a rare variant of oral candidiasis among HIV infected patients. This condition typically is a whitish plaque that appears in mucosa of the buccal area which is not removable by scraping and may be nondifferentiable with EC (Pappas, 2012).

Diagnosis

The diagnosis is often made based on clinical examination and thorough history. In clinical practice, two tests are essential to diagnose oral candidiasis. Oral swab obtained from the lesion is usually cultured on the selective medium, for example, Sabouraud's agar, and incubated aerobically for approximately 48 hours. This is combined with oral smear test and direct microscopy following rapid staining. *Candida* species stain poorly by hematoxylin and eosin; therefore, staining with periodic acid-Schiff (PAS), Gridley stain, or Gomori methenamine silver (GMS) stain is in use (Teraia and Shimahara, 2009). It is widely accepted clinically that combining the presence of the clinical signs suggestive for oral candidiasis and positive results of swab and smear tests is confirmatory for the clinical candidal infection (Darwazeh and Darwazeh, 2014).

Treatment of Oral Candidiasis

Topical antifungal therapy is the recommended first line treatment for uncomplicated oral candidiasis and where systemic treatment is needed topical therapy should continue as this reduces the dose and duration of systemic treatment required (Epstein and Polsky, 1998).

Patients with mild to moderate EC can be treated with topical treatments such as clotrimazole and nystatin suspensions (Robinson *et al.*, 1997). It is demonstrated that clotrimazole troches are safer than nystatin oral suspension because fructose which is used in the composition of clotrimazole oral treatments is less cariogenic than sucrose which is used in the formulation of nystatin oral suspension (Kasper, 2013). Patients with moderate to severe EC should be treated with systemic agents such as fluconazole, voriconazole and itraconazole (Patel, 2012). The treatment strategy in PC is same as EC (Williams *et al.*, 2011). Angular cheilitis can be treated with topical antifungal ointment (Patton *et al.*, 2002)

In several studies fluconazole resistance has been reported to be between 5-56% in vivo. On the other hand, resistance to other azoles such as ketoconazole and itraconazole was less frequent and reported between 0-25percent (Heinic *et al.*, 1993; Barchiesi *et al.*, 1994; He *et al.*, 1994). In Patients with refractory oral candidiasis who are resistant to azoles, intravenous amphotericin B is recommended (Albougy and Naidoo, 2002).

Table 1: Host-related factors associated with oral candidosis

Predisposing host factor	Reference
Local host factors	
.Denture wearing	(Campisi *et al.*, 2008)
.Steroid inhaler use	(Fukushima *et al.*, 2005; Fukushima 2003)
Reduced salivary flow	(Radfar, 2003)
.High sugar diet	(Ohman, 1988)
Systemic host factors	
.Extremes of age	(Weerasuriya and Snape, 2008) (Soysa, 2006)
.Endocrine disorders (e.g diabetes)	(Egusa, 2008)
. Immunosuppression	(Soysa, 2008)
.Receipt of broad spectrum antibiotics	(Samaranayake, 1986)
.Nutritional deficiencies	
Solid tumors or haematological malignancies	(Tortorano, 2006)
premature birth	(Tortorano, 2006)]

Table 2: Putative virulence factors of *Candida albicans*

•	**Virulence factor**	•	**Effect**
•	**Adherence**	•	**Promotes retention in the mouth**
•	Cell surface hydrophobicity	•	Non-specific adherence
•	Expression of cell surface adhesions	•	Specific adherence
•	**Evasion of host defences**	•	**Promotes retention in the mouth**
•	Phenotypic switching	•	Antigenic modification
•	Hyphal development	•	Reduces phagocytosis
•	Secreted aspartyl proteinase production	•	Secretory IgA destruction
•	Binding of complement	•	Antigenic masking
•	**Invasion and destruction of host tissue**	•	**Enhances pathogenicity**
•	Hyphal development	•	Promotes invasion of oral epithelium
•	Hydrolytic enzyme production	•	Host cell and extracellular matrix damage

All of the *HIV* associated candidiasis should be treated with topical or systemic antifungal medications at least for 2 weeks to decrease the risk of recurrent oral candidiasis. However, an important subject to prevent oropharyngeal candidiasis is the use of combination of potent antiretroviral treatment (ART) (Bensadoun *et al.,* 2011, Scwingel *et al.,* 2012).

Several studies have been demonstrated that fluconazole can reduce the risk of oral candidiasis among patients with *HIV* infection. However, there were no significant associations between prophylactic use of antifungal medications and patients survival (Leen *et al.,* 1990; Marriott *et al.,* 1993). In additions some investigators showed that long term and frequent use of antifungal can result in refractory and even resistant infections. Accordingly, prophylactic consumption of antifungals is not recommended (Schuman *et al.,* 1997).

CONCLUSION

The most common opportunistic fungal infection in *HIV* positive patients is candidiasis, affecting the mainly mucocutaneous system. *C. albicans* remains the most common species responsible for candidiasis, disease due to newer species like *C. dubliniesis* are also increasing. A routine check for opportunistic infections including oropharyngeal candidiasis is important and should be carried out because oral lesions in HIV patients show the potency of immune system, prognosis of the disease and treatment response to ART medication (Tami-Maury *et al.,* 2013). Identifying candida to its species level is important because it helps guiding proper treatment.

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