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 krusei 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 (ssp.) 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 gastrointesttal 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 (Chellamall, 1993). 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.,...
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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) (Table 1).

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 have 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-
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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 (Stein, 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 (Ehrensai 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 candidiasis 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 0-25 percent (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

<table>
<thead>
<tr>
<th>Predisposing host factor</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>Local host factors</strong></td>
<td></td>
</tr>
<tr>
<td>Denture wearing</td>
<td>(Campisi et al., 2008)</td>
</tr>
<tr>
<td>Steroid inhaler use</td>
<td>(Fukushima et al., 2005; Fukushima 2003)</td>
</tr>
<tr>
<td>Reduced salivary flow</td>
<td>(Radfar, 2003)</td>
</tr>
<tr>
<td>High sugar diet</td>
<td>(Ohman, 1988)</td>
</tr>
<tr>
<td><strong>Systemic host factors</strong></td>
<td></td>
</tr>
<tr>
<td>Extremes of age</td>
<td>(Weerasuriya and Snape, 2008) (Soysa, 2006)</td>
</tr>
<tr>
<td>Endocrine disorders (e.g diabetes)</td>
<td>(Egusa, 2008)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>(Soysa, 2008)</td>
</tr>
<tr>
<td>Receipt of broad spectrum antibiotics</td>
<td>(Samaranayake, 1986)</td>
</tr>
<tr>
<td>Nutritional deficiencies</td>
<td></td>
</tr>
<tr>
<td>Solid tumors or haematological malignancies</td>
<td>(Tortorano, 2006)</td>
</tr>
<tr>
<td>Premature birth</td>
<td>(Tortorano, 2006)</td>
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Table 2: Putative virulence factors of Candida albicans

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

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, Sewingel 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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