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## ORAL CANDIDIASIS IN HIV INFECTED PATIENTS

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### ABSTRACT

Oral candidiasis is a general opportunistic infection of the oral cavity caused by an over growth of Candida genus, the most common being Candida albicans. The prevalence varies depending on certain predisposing factors and age. There are three extensive groupings consisting of acute candidiasis, chronic candidiasis, angular cheilitis. Risk factors comprise impaired salivary gland function, drugs, dentures, high carbohydrate diet, and extremes of life, smoking, diabetes mellitus, Cushing's syndrome and immunosuppressive conditions. Fluconazole oral suspension as a systemic therapy was used to treat oral candidiasis in HIV-infected patients and provided a longer disease-free interval before relapse

**Keywords:** Candidiasis, Candida albicans, HIV infected.

### INTRODUCTION

Oropharyngeal candidiasis is a common manifestation in immunocompromised patients, including individuals undergoing immunosuppressive therapy for cancer or organ transplantation and those exposed to broad-spectrum antibacterial therapy [1,2,3]. Most notably, oropharyngeal candidiasis is a major problem in individuals affected with the human immunodeficiency virus [4,5,6]. Candida albicans the species most commonly isolated from patients with these infections. Colonization of the mouth by Candida species has a long recorded history. Hippocrates, as early as 37 BCE, reported oral lesions that were probably caused by Candida [7]. Although C. albicans survives poorly on dry surfaces [7], it can remain viable for some time on moist objects. Candida often colonizes the human epidermis, especially moist webs of skin between fingers or toes, but the gastro-intestinal tract is considered to be the major reservoir [7]. The existence of such reservoirs ensures regular seeding of the oral cavity. Oropharyngeal candidiasis is an important disease of

immunocompromised individuals such as organ transplant recipients, cancer patients [8], and individuals with AIDS [9]. Oral candidiasis is one of the earliest indicators of the progression from HIV sero-positive status to AIDS. Esophageal lesions in AIDS patients can be extensive, requiring systemic Fluconazole therapy [10], and these lesions can be a source of infection for other forms of oral candidiasis that are often seen in AIDS patients [11]. The high frequency of oral Candida carriage [12] No single factor appears to be responsible for the pathogenicity of C. albicans. It has been proposed that a combination of different factors contributes at each stage of infection [13,14,15,16] Candida cells adhere to several host cell types, including epithelia [17], endothelia [18], and phagocytic cells [19] C. albicans expresses adhesions that recognize extracellular matrix proteins, including laminin, collagen, fibrinogen, fibronectin, and entactin [20,21]

Several studies have shown that patients with acquired immunodeficiency syndrome (AIDS) have

one predominant strain of *C. albicans*,” but others have found multiple strains.

The incidence of *C. albicans* isolated from the oral cavity has been reported to be 45% in neonates,[22] 45%–65% of healthy children,[23] 30%–45% of healthy adults,[24,25] 50%–65% of people who wear removable dentures,[26] 65%–88% in those residing in acute and long term care facilities,[26,27,28] 90% of patients with acute leukemia undergoing chemo- therapy,[29] and 95% of patients with HIV.[30] *C. albicans* is a normal commensal of the mouth and generally causes no problems in healthy people .

### **Pathogenesis**

*Candida albicans* is the most common and most invasive fungal organism present in the oral cavity and causes both systemic and superficial infections. *C. albicans* is more adherent to human buccal epithelial cells than are other *Candida* species; a relationship has been suggested between the adherence of *C. albicans* and its ability to colonize and cause disease[31]. The pathogenic significance of the yeast vs. the filamentous form of the organisms not clear[33]. The blastospore form appears to be necessary for colonization and subsequent disease to occur[31]. The filamentous form of *C. albicans* develops under suboptimal conditions invitro; however, the stimuli for its formation invivo are not known. The yeast form of most dimorphic fungi is considered the pathogenic but an association between the presence of the filamentous forms of *C. albicans* and candidiasis has been noted[33]. The significance of the surface antigenicity of the filamentous forms in oral candidiasis requires further study[33,34]. Simonetti and Strippoli[32] have present evidence indicating greater pathogenicity of the yeast form. The yeast form of *C. albicans* may be the pathogenic form, and with clinical infection, the altered micro environment favors change to the filamentous form[32,35,36, and 37]. The pathogenic effects of *C. albicans* in candidiasis are uncertain. It has been suggested that *C. albicans* produces an endotoxin[38], and immunity to the endotoxin may

confer immunity to the disease[39,40]. However, the levels of endotoxin found invivo may not be sufficient to produce toxic effects[41]. Alternatively, the organisms may produce enzymes that allow penetration of the mucous membranes[42–44]. Pugh and Cawson[43,44] state that invasion of epithelial cells by *C. albicans* depends on hydrolytic enzyme activity and mechanical force. Some evidence suggests that toxic products of the organism do not initiate candidiasis but act as irritants, aggravating tissue lesions[45]. Immediate or delayed hypersensitivity may have a role in pathogenesis[46,47]; up to 80% of the population without evidence of infection possess cellular hypersensitivity to *C. albicans* and others[48] not cell mediated hypersensitivity to *Candida* in pathogenesis and suggest that enzymes and toxins may aggravate immune-related lesions. Several reports indicate that specific immune imbalance in response to *C. albicans* plays a role in the pathogenesis of oral candidiasis [49,50,51]. Mackie et al.[50] described eight patients with candidiasis is due to resistant *C. albicans* and reported humoral antibody formation with poor cell-mediated immunologic activity. Similar findings were noted in patients with acute pseudomembranous esophageal candidiasis[52]. Inpatients with candidiasis, excess humoral antibodies may inhibit a cell-mediated response. General abnormalities of host immunity have not been described; however, specific deficiencies of the cell-mediated response to *Candida* antigen have been reported[52,51]. The specific abnormality of cell-mediated immunity may be reversible following successful treatment of acute candidiasis[49]. Deficient serum or salivary IgA, abnormal complement function, and auto antibodies to various tissues are described. Antibody for *Candida* (antimannan) is present in serum, and levels increase in chronic disease[40]. However, the significance of cell-mediated immune deficiencies in localized oral candidiasis is uncertain

### HIV-Related Oral Candidiasis

Candida infections, with oral thrush and esophagitis as frequent clinical manifestations, are the most widespread opportunistic infections encountered in AIDS [53, 54, 55]. Ever since the first clinical definition of AIDS (1981), the CDC/WHO have recognized candidiasis of the mouth, esophagus, trachea, bronchi, and lungs as "major" opportunistic infections and important indicator diseases. Subsequently, in 1986 the Walter Reed Army Institute of Research [56] adopted a staging classification of HIV infection, applicable to adults only, based on HIV-antibodies and virus isolation, chronic lymphadenopathy, T-helper cells/mm<sup>3</sup>, delayed hypersensitivity, appearance of thrush, and other opportunistic infections [57]. Also, it has been shown in prospective studies of HIV-infected patients that the occurrence of an otherwise unexpected mycosis (typically oral candidiasis) in an HIV-infected individual can be predictive of the subsequent development of full blown AIDS [53, 58]. Retrospective studies have shown that at least 58 to 81% of all AIDS patients contract a fungal infection at some time, and 10 to 20% die as a direct consequence [54]. Clearly, Candida infections appear to be the most common fungal infection, occurring in at least 75% of HIV-infected patients [59] have shown that 92% of patients with a diagnosis of AIDS had oral candidiasis, compared with only 24% of HIV infected patients who had not developed AIDS.

### Diagnosis

Diagnosis of candidiasis depends upon the presence of the organism in a direct smear, the culture of significant numbers of organisms indirectly, the effectiveness of antimycotic medication [11]. Culturing of Candida from whole, unstimulated saliva may be the most accurate method of distinguishing the carrier from the non carrier state [60,61]. Quantitative culture, unstimulated saliva or imprint culture technique may aid in diagnosis of patients with oral candidiasis [60,62,63]. Oral candidiasis has been

grouped into the following descriptive categories [64,65,66]: (1) acute pseudomembranous candidiasis (thrush); (2) acute atrophic candidiasis; (3) chronic atrophic candidiasis (denture stomatitis, angular cheilitis); and (4) chronic hyperplastic candidiasis (candidal leukoplakia), which takes two forms—chronic, localized, mucocutaneous candidiasis (monilial granuloma) and endocrine candidiasis syndrome (endocrine moniliasis syndrome). It is important for all physicians looking after older patients to be aware of the risk factors, diagnosis, and management of oral candidiasis. In a recent study 30% of doctors said they would prescribe in for oral candidiasis on the request of nursing staff without examination of the oral. [63] This is unfortunate as other pathology may be missed, the diagnosis may be incorrect, and failure to address risk factors may lead to recurrence of the candidiasis. The diagnosis of oral candidiasis can serve as a diagnostic marker of HIV infection and also as a signal of disease progression in patients known to be HIV seropositive, as evidenced by the relationship of this infection to decreasing CD4 lymphocyte counts [67]

### Treatment

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. [68] Itraconazole has a wider spectrum of activity than Fluconazole and is therefore valuable in salvage treatment of the immunocompromised patients with Fluconazole resistant candidiasis. Increasing resistance to antifungals has become increasingly common since the introduction of Fluconazole especially in patients with advanced HIV disease, and recurrent and long term treatment [69, 70]

**Nystatin:** Nystatin, if swallowed, may lead occasionally to gastrointestinal side effects such as Nausea, vomiting, and diarrhea [71]

**Clotrimazol:** Clotrimazole are the most potent topical agent in this class of antifungals but is used as a topical agent only because of its gastrointestinal and neurological toxicity [72]

**Miconazole:** Miconazole is used mainly for topical treatment of candidiasis. It is available for parenteral use against systemic mycoses, but the injection contain polyethoxylate castor oil, which may provoke allergic reactions [73].

**Ketoconazole:** Ketoconazole was the first of the imidazole agents shown to be capable of achieving therapeutic Blood levels when given orally. This led to the drug being used in the treatment of CMC and Candidiasis in immunocompromised patients, but adverse effects, including nausea, rashes, pruritus, and hepatotoxicity, have restricted its use [74]

**Fluconazole:** Fluconazole is a recently introduced biazole antifungal that acts by inhibiting fungal ergosterol production essential in cell wall formation[75]

**Itraconazole:** This is an orally active bis-triazole, similar to Fluconazole, which inhibits ergosterol biosynthesis in the fungal cell. It has a long half-life and fewer side effects than ketoconazole but is expensive [76] and is eliminated hepatically.

### Prognosis

The prognosis is good for oral candidiasis with appropriate and effective treatment[77] Relapse when it occurs is more often than not due to poor observance with therapy, failure to remove and clean dentures properly, or inability to resolve the underlying/predisposing factors to the infection. Prophylaxis with anti fungal agents reduces the incidence of oral candidiasis in patients with cancer undergoing and fluconazole are more effective than topical polyenes.[78] Prophylaxis on either a daily or weekly basis with anti fungal reduces the incidence of oral candidiasis in patients with HIV with their ductions being most marked in those with low CD 4 counts and recurrent oral candidiasis.[79,80,81,82] .The use of a chlorhexidinerinse only in bone marrow transplant

patients as prophylaxis was found to be very effective [83]

### CONCLUSION

A wide range of therapeutic approaches exists to treat patients with HIV infection or AIDS and even oropharyngeal or esophageal candidiasis. Although the more traditional anti fungal agents such as the topical polyenes and imidazole maybe satisfactory for the treatment of relatively mild and transient episodes of oropharyngeal candidiasis (e.g., thrush),the clinical utility of these agents ultimately can become promised by the numerous encumbrances imposed by a demanding dosing schedule and the need for extended contact with the oroesophageal mucosa. Although ketoconazole has a long history of use for the treatment of oropharyngeal and esophageal candidiasis, concerns about potentially serious side effects have favored the use of alternative antifungal agents instead. Moreover, oral solutions are better tolerated, with fewer drug-drug interactions and more convenient dosing schedules and are easier to administor than tablets or capsules to patients with severe oral lesions, restricted oral intake, or inability to swallow. Also that the development of these new oral solution formulations other turning point in the ongoing quest for optimal treatment strategies for oropharyngeal and esophageal candidiasis in immunocompromised patients

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