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REVIEW ARTICLE

Implications of Oral *Candida* Carriage in Clinical Practice - A Review

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ABSTRACT

Oral candidiasis is a fungal infection that affects the oral cavity. *Candida* species are commensal organisms that reside in the oral cavity, gastrointestinal tract and genitourinary tract of humans without causing harm under normal circumstances. However, disruptions in the host's immune defence mechanisms or alterations in the local microbiota can lead to the overgrowth of these fungi resulting in infection. Oral candidiasis is one of the common manifestations seen in immunocompromised individuals specially in HIV and cancer patients undergoing treatment. Emergence of antifungal drug resistance is of serious concern owing to the associated morbidity and patient outcomes. This review article provides an in-depth knowledge of oral Candidiasis, risk factors, diagnostic approaches, management strategies and patient outcomes. Understanding oral Candidiasis is essential for both clinicians and researchers to prevent and manage *Candida*-associated oral infections.

Keywords: Candida; Oral cavity; Candidiasis; HIV; Chemotherapy; Radiotherapy

INTRODUCTION

Candidiasis is a common fungal infection that affects people of all ages, especially those with compromised immune systems or underlying medical conditions like malignancies, post chemotherapy and radiotherapy compromises the cell mediated immunity predisposing the person to fungal infections. *Candida* species, predominantly *Candida albicans*, is the common commensal organisms that live in the oral cavity. *Candida albicans* is a highly adaptable commensal organism that is well suited to its human host; yet changes in the host microenvironment may promote the transition from commensalism to pathogen[1]. Oral Candidiasis, characterized by the presence of *Candida* species in the absence of clinical symptoms, serves as a reservoir for the growth of *Candida*. Clinically, oral candidiasis manifests as white, curd-like lesions on the mucosal surfaces of the mouth, which may be accompanied by redness, soreness, and difficulty swallowing. Although not life-threatening, oral candidiasis can significantly impact the quality of life and may serve as an indicator of underlying systemic conditions. In severe cases, especially in immunocompromised patients, the infection can disseminate, leading to more serious complications. Though the most frequent variety of oral candidiasis is acute pseudomembranous candidiasis or oral thrush, it's vital to note that there are other types as well, and that white and erythematous can be typical of a *Candida* infection. Both chronic hyperplastic candidiasis and acute pseudomembranous candidiasis are examples of white lesions. Red lesions are chronic erythematous candidiasis, angular cheilitis, median rhomboid glossitis, and linear gingival erythema. There are other rare oral types of candidiasis which include cheilocandidiasis, chronic mucocutaneous candidiasis and chronic multifocal candidiasis[2].

Since tumours are radio responsive and surgery is not advised due to anatomical barriers, radiotherapy is used as

a primary mode of treatment for carcinomas at the base of tongue. Radiation therapy results in ulcers, dysphagia, dysgeusia and oral mucositis. Both structural and functional changes in the salivary glands take place during radiotherapy if salivary glands are involved. It alters saliva in both qualitative and quantitative ways, making it to become thick and ropy as its amount decreases causing xerostomia. It has been shown that radiation induced oral ulcerations and xerostomia promote the growth of *Candida*[3]. This review aims to describe the importance of oral *Candida* carriage and its implications in clinical practice.

Risk factors for oral Candida carriers

Many factors predispose to carriage of oral *Candida* which includes immunosuppression, long term antibiotic treatment, corticosteroid therapy, diabetes, dry mouth, use of denture, and poor oral hygiene[4].Patients with weakened immune systems, such as those with HIV/AIDS and those who are receiving chemotherapy, are particularly susceptible to *Candida* colonization and subsequent infection. The immunosuppressive nature of these treatments, coupled with the frequent use of corticosteroids and antibiotics, creates an environment conducive to fungal overgrowth[5].Acute pseudomembranous candidiasis caused by fungal overgrowth can arise in patients with chronic renal failure, immunocompromised conditions and long-term usage of antidepressant and antihistamines[6]. There are multiple risk factors linked to the onset or progression of OSCC [oral squamous cell carcinoma]. The primary risk factors identified in this regard are oral potential malignant illnesses, immunological disorders, dyskeratosis congenital, Fanconi anaemia, usage of betel nut and areca nut and HPV. In addition, lifestyle factors such as smoking and alcohol consumption, Epstein-Barr Virus, Plumer-Vinson syndrome, diet low in fruits, carotenoids, dental hygiene, and green vegetables are also associated with increased carriage rates of oral *Candida*[7].

Mechanisms of oral Candida carriage

The oral cavity provides an ideal environment for *Candida* colonization, characterized by factors such as humidity, pH, temperature, and presence of epithelial surfaces for adherence. Adherence to oral mucosal surfaces, evasion of host immune responses, and interplay with oral microflora are key mechanisms contributing to *Candida* infection[8]. Recent research has shown that *Candida albicans* can also induce inflammation, produce carcinogenic byproducts and mimic molecules in order to further aid in the development of cancer[9]. In addition, the formation of biofilms on oral surfaces facilitates *Candida* persistence and resistance to antifungal therapy, presenting challenges in managing oral *Candida* carriage. In individuals with compromised immune systems, such as HIV patients, cancer patients and diabetics, *Candida albicans* exabits enhanced virulence characterized by increased adherence ability, higher production of virulence factors like secreted aspartyl protease, hydrolytic enzymes and phospholipases and also enhanced hyphae formation. These factors contribute to a lower infectious dose threshold, enabling *Candida* to cause oral candidiasis even at a lower count. Notably, *Candida* virulence in asymptomatic HIV-positive patients varies independently of CD4 counts. Elevated *Candida* counts in these vulnerable individuals can collectively lead to increased tissue damage, highlighting the need for vigilant monitoring and management[10].

Epidemiology and prevelence

The prevalence of *Candida* in the oral cavity varies among different populations, influenced by factors such as age, immune status, systemic diseases, use of medication, and practices of oral hygiene. Oral candidiasis ranges from about 30% in healthy individuals to more than 90% in immunocompromised patients[11]. In addition, the emergence of drug-resistant *Candida* strains and healthcare-associated infections has raised concerns about the management of carriage of oral *Candida* in the clinical settings.

Large number of studies have shown that *C. albicans* infection increases the host susceptibility to cancer such as oral, gastric, and colorectal cancer. Anti-cancer therapy can also affect *C. albicans* colonization. *C. albicans* may promote the development of cancer by damaging the mucosal epithelium, stimulating the production of carcinogens which can trigger chronic inflammation including Th17 cell-mediated immune response[12].

Numerous studies detected high quantities of *C. albicans* and various other species of *Candida* were found in cancer patients. Significantly more number of *Candida* were isolated from patients who underwent radiotherapy and chemotherapy when compared to healthy individuals[13]. Prakash et al., identified non-albicans *Candida* species [28.19%] predominate over *Candida albicans* [15.95%] out of 188 patient specimens[14]. Approximately 65% of cancer patients who underwent radiotherapy were tested positive for oral *Candida* in Odisha, India. *Candida albicans* and non-albicans species were detected from oral swab[15]. A study investigated how oral prosthetic treatment impacts oral candidiasis by analysing salivary flow rate, *Candida albicans* count and intraoral symptoms. The findings highlighted the significant role of stimulated saliva in alleviating oral candidiasis symptoms[16]. Some studies showed higher levels of *Candida albicans* in patients undergoing chemotherapy than non-albicans *Candida*[17]. Rebolledo et al., predominantly isolated non-albicans *Candida* species such as *C. glabrata, C. tropicalis*[18].In a prospective study conducted by Jham et al., among 21 Brazilian population, 42.9% showed colonization with only *Candida albicans* before taking radiotherapy treatment. *Candida* colonization was found to

be greater [60%] in infected patients when compared to non-infected individuals [30%][9]. The rate of oral candidiasis was increased from 9.1% to 15.2% among 66 patients undergoing radiotherapy treatment for head and neck cancer at the Mario Penna Institute, Brazil[19].

Oyetola et al., revealed from their study that around 96.5% of Chronic Kidney Disease patients had candidiasis. Among the oral lesions observed include candidiasis, periodontitis, halitosis, and abnormal lip pigmentation[20]. A cross-sectional study involving 66 patients was carried out. These patients were divided into two groups: group A, consisting of 33 RT [renal transplant] patients, and group B, consisting of 33 CRF [chronic renal failure] patients. They collected information on oral hygiene, blood leucocyte clinical laboratory results, therapy type and duration and diagnosis of oral candidiasis. Risk factors connected to *Candida* were looked upon. Of the 66 patients, 12 from the RT group and 9 from the CRF group had microbiologic evidence of oral candidiasis. There was no difference in the oral candidiasis frequency between study groups among patients with renal impairment [RT and CRF], which was reported to be 31.82 percent. Among patients with RT and CRF, *Candida albicans* was the most frequently isolated species[21]. Despite the fact that a number of studies have linked hyposalivation to an increased incidence of oral *Candida* colonization and oral candidiasis, no previous systematic review has looked more closely at this relationship[22].

Nine studies were included for the synthesis of qualitative and quantitative data out of the 429 papers that were found through database searches. Xerostomic patients and controls were subdivided into two groups for the analysis: oral candidiasis and *Candida* growth. According to the subgroup analysis for *Candida* growth, xerostomic patients had a 95% higher chance of oral *Candida* growth than controls. Similarly, the subgroup analysis for oral *Candida* indicates that xerostomic patients had a higher risk of manifestation of oral candidiasis. The second instance had the same oral symptoms and was diagnosed with acute pseudomembranous candidiasis in relation to tricyclic antidepressants [10 mg of amitriptyline] and antihistamines [10 mg of levocitrizine][6].

Emerging pathogen Candida auris

A novel *Candida* species *Candida auris* was first reported in Japan in 2009. This species often be misidentified in biochemical typing. Numerous investigations have compared the precision of phenotypic diagnostics with genetic methods in the identification of *Candida auris*. It is yet unclear if this organism will disappear as fast as it appeared or if it will continue to be a source of worry for people around the world. The likelihood of latter scenario appears unlikely based on the growing number of cases found in several countries[23].

Candida auris commonly transmits from person to person either direct or indirect contact[24]. Invasive infections caused by *C. auris* have a high fatality rate. This species is considered as multidrug resistant. Moreover, It is difficult to detect and control *C. auris* because yeast identification done by laboratory, often misidentify this species[25]. Due to similarities with other phenotypically related *Candida* species and the lack of commercially available diagnostic procedures, the prevalence of *Candida auris* infection is unknown and most likely underreported[26]. Except Antarctica, it has spread to every continent since its discovery in 2009 in Japan. In order to identify 15,271 *Candida* isolates that were collected between 2004 to 2015 from 152 international medical centres such as Asia, Europe, Latin America and North America, a study queried the global SENTRY Antifungal Surveillance Program. The study showed that prior to 2009, there were no *Candida auris* isolates identified and the prevalence of *C. auris* was less before 2009[27]. Misidentified samples were recovered from South Korea in 1996, 2004 and 2006. In the year 2008 *C. auris* was detected through surveillance study[28].

Diagnostic approach

Various tests are used to detect and quantify *Candida* carriage by collecting oral swab and saliva. Culture based and molecular techniques can be done for identification of speciation followed by antifungal susceptibility testing. Although molecular techniques have improved sensitivity and specificity, culture-based methods remain the gold standard[29]. Comparing PCR-RFLP [Polymerase chain reaction- restriction fragment length polymorphism] to HiChrome Candida differential agar, it was discovered that the sensitivity of the latter was 100%. Even though HiChrome media may be the method of choice in a lab setting with minimal resources, the PCR-RFLP method is more reliable for detecting *Candida* species. Therefore, it is highly recommended to use a molecular approach like PCR for the identification of *Candida* species, as it has a higher discriminatory power and gives quick results[30]. Additionally, advances in imaging techniques, such as confocal laser scanning microscopy allow visualization of *Candida* biofilms and their association with host tissues, helps in the accuracy of diagnosis and management of oral candidiasis.

Clinical impact

Persistent carriage of *Candida* in oral cavity can lead to frequent or chronic oral infections, which can affect the quality of life and overall health of an individual. Early diagnosis and management of oral *Candida* colonization is essential to prevent the progression from mild to invasive candidiasis, which can have serious manifestations such as bloodstream infections and disseminated candidiasis.

Studies suggest that some antifungal drugs can effectively prevent oral thrush caused by cancer treatment[31]. The prevalence of oral candidiasis was less in HAART-treated HIV positive patients than in untreated. Nucleoside based HAART therapy has reduced the colonization of oral *Candida*[32].While HAART has significantly improved the overall health and longevity of people living with HIV, those with suboptimal adherence to HAART, or those who experience HAART failure, remain susceptible to opportunistic infections like oral candidiasis.

Management strategies

Effective management of oral *Candida* carriage involves both preventive and therapeutic approaches. Strategies include oral hygiene measures, antifungal therapy, treatment of underlying conditions, and addressing predisposing factors. Amphotericin B was the first antifungal agent for the treatment of systemic infection[33,34]. Up to 80% of the patients' use of Amphoteric B has been limited due to nephrotoxicity[35]. This can affect the immune system and can stimulate the host defences against fungal infection. So specific breakpoint of Amphotericin B has not been studied[36]. Therefore, the correlation of in vitro and in vivo susceptibility pattern of patients was not predictable[37]. Oral fluconazole, clotrimazole and nystatin is highly recommended for the treatment of moderate to severe oral candidiasis[38].

A study by Badiee et al., showed lowest MIC pattern to amphotericin B, voriconazole and caspofungin whereas *Candida* species were resistant to fluconazole and itraconazole due of their high MIC. Another study revealed voriconazole showed maximum sensitivity of 86% and ketoconazole showed 56%. *Candida krusei* showed resistance to fluconazole[39]. Large isolates of *Candida* species showed susceptibility to nystatin followed by fluconazole and amphotericin B[40]. Other study analysed most of the *Candida* isolates were sensitive to amphotericin B, also less quantities of isolates were resistant to anidulafungin, fluconazole, and itraconazole[41]. Most isolates of *Candida* species were sensitive to fluconazole and less resistance was detected to echinocandins[42]. Among azole class, the study showed lowest susceptibility of 29.32% to miconazole, 40.23% were intermediate and 30.45% were resistant out of 440 tested *Candida* isolates[43].

Antifungal agents, such as azoles, polyenes, and echinocandins, are commonly employed for topical or systemic treatment. Agents such as xylitol has the ability to inhibit microbial metabolism in the oral cavity. Therefore, it is incorporated in chewing gums and tablets and also in health care products such as dentifrice and oral rinses. Even though it has a limited effect on *Candida*, it can be beneficial in preventing of mixed biofilm infection[44]. People who are using corticosteroids containing inhaler can minimise the risk of developing oral thrush by washing out the mouth with water or mouthwash after use of an inhaler[45]. Also, patient education regarding the importance of oral hygiene practices and regular dental visits is crucial in preventing *Candida*-associated oral infections.

Our goal

Further research is needed to elucidate the complex interactions between *Candida* species, host factors, and oral microbiota. In addition, the development of new diagnostic methods and targeted therapeutic interventions has the potential to improve the management of *Candida*-associated oral infections. Also, a multidisciplinary approach involving dentists, microbiologists, and disease specialists are essential for the comprehensive management of oral *Candida* carriage and associated complications.

CONCLUSION

Oral *Candida* carriage represents a key stage in the pathogenesis of candidiasis, with implications for oral and systemic health. Effective prevention and management of *Candida* –related oral infections require a comprehensive understanding of epidemiology, mechanisms, risk factors and diagnostics. Continued research efforts are needed to uncover the complexities of carriage of oral *Candida* and advance treatment paradigms to improve the patient outcomes.

Conflict of Interest

No conflicts of interest declared.

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