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Fungal Infection in the Oral Cavity: A Review

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ABSTRACT

Fungal infection in the oral cavity is a completely microbes-oriented disease most probably caused due to biofilm formation on the floor of the mouth and its surrounding. Most of the studies revealed that *Candida* and *Aspergillus* spp. are frequently isolated fungus. Smoking, alcohol consumption, high intake of carbohydrate diet, loss of salivary function and immunosuppression are colonizing factors and predisposing factors for fungal infection in the oral cavity and may lead to the chronic stage at its severity. Oral candidiasis is an opportunistic infection of the oral cavity and the incidence depends on the age of the patient and certain predisposing factors. There are three varieties of oral candidiasis such as acute candidiasis, chronic candidiasis and angular cheilitis. CD4 T lymphocyte and CD8 T lymphocyte provides primary as well as secondary immunity towards oral fungal infection. Denture wearers, HIV patients, children and elders are mostly infected by an oral fungal infection. This systematic review tends to focus on etiological factor, salivary action, and immunity behind fungal infection in the oral cavity with management and treatment of oral fungal infection.

Key Words: Oral cavity, Fungal infection, Fungal biofilm, *Candida* spp, Antifungal agent

INTRODUCTION

Fungal infection in oral cavity emerges due to both chemical as well as biological reasons and stands before us as a worldwide problem varies according to age groups but seems to be very common among old ages particularly in those who do not take care of their mouth. Fungal infection arises in the oral cavity due to the colonizing character of microbes, especially by food debris. The biofilm formation through pathogenic organisms alternately converted into white fungal patches¹. Initially, the biofilm formed in the oral cavity promotes contamination and attracts fungal infection. Systemic oral fungal infection is seen approximately 50% to 60% of cases that depend upon dentures in old age^{2,3}. Persons having diabetes mellitus, high carbohydrate on their diet and smoking like habits could disturb the normal microflora of the oral cavity and that can initiate fungal infection^{4,5}. Patients suffering from fungal infection in oral cavity increases eventually due to many reasons and arise the number of difficulties particularly for immunocompromised patients such as those receiving chemotherapy during cancer treatment and fighting with human immunodeficiency virus (HIV)². Those hav-

ing poor immunologic response this fungal contamination remains a significant problem throughout their life⁶. Fungal infection frequently occurs those have an immunosuppressive illness or going through organ transplant surgery⁷. The oral fungal infection seems to be very opportunistic in HIV patients that are more than 90% people showing developmental oral fungal infection⁸

METHODS FOR LITERATURE SEARCH

For searching the published articles, we conducted an electronic search of the Google Scholar, Scopus, Medline, Scopus and PubMed databases. The search term in the database included oral cavity, fungal infections, *Candida* infection and oral thrush. The abstracts of the published articles are identified by this search method and other articles identified manually from the citations. This review article reviews the oral cavity fungal infection. This review article sets out a framework on which more prospective trials can be formulated and support as a spur for further research in this commonly observed clinical entity where not many studies are done.

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Etiological factors

Factors that are responsible for oral fungal infection mainly arise due to our unconsciousness about oral health care. Acid formation in the oral cavity occurs due to both smoking and alcohol consumption and high intake of sugar and carbohydrate in the food. The high rate of drinking alcohol can disrupt the oral microflora and can persist acetaldehyde formation that leads to adherence of oral fungal colonisation^{9,10}. Some of the other challenging predisposing factors that induce oral fungal infection are hormonal disorders, epithelial changes, physiological disorders, poor oral hygiene, endocrine disorders, immunologic disorders, poorly fitting dentures and empirical drug therapy¹¹. The most common colonising isolated fungi from the oral cavity is *Candida albicans*(Fig.1)^{5,12,13}, derived from Latin word candid means white.

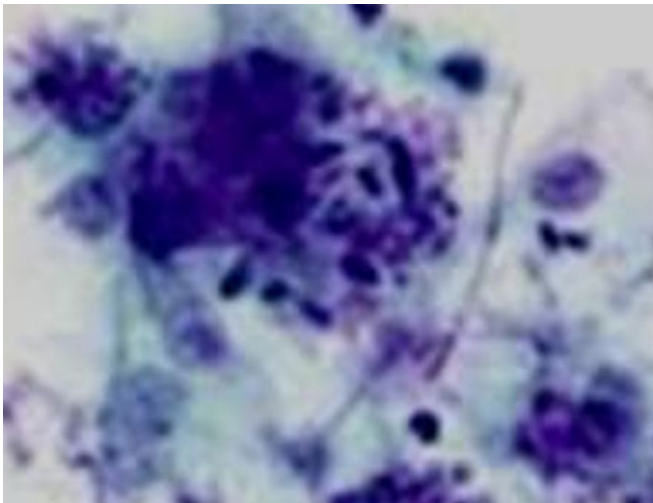


Figure 1: Candida pseudohyphae with inflammatory cells- aspiration cytology from oral thrush.

It is a spore-forming fungus that remains harmless until there are no disturbances occurred in host microflora balance of oral cavity¹⁴. With the addition to *candida spp*, *Aspergillus spp*, *Fusarium spp.*, and *Acremonium spp.* are some of the isolated contaminated factors causing fungal infection in the oral cavity. Somehow infections also caused by non-*Candida* and non-*Cryptococcus* isolates and infections caused by *Trichosporon spp.*, *Malassezia spp.*, and *Rhodotorula spp.* are mainly notable but in many cases, it is observed that *Candida* and *Cryptococcus* are factors that initiate fungal colonisation specifically candida spp. When the oral cavity comes in contact with several microbes especially spore containing fungal pathogens forms a biofilm on the upper part of epithelial cell and create the environment for the survival of them¹⁵. Except for *C. albicans*, *C. glabrata*, *C. lusitaniae* and *C. guilliermondii*. *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. krusei*, are some non-albicans found in oral cavity causing colonisation but less life threatening than *C.albicans*^{6,8}.

Etiology of fungus

According to mycological study fungi are found in both form; unicellular and multicellular depending on their stage of life style. They cannot make their own food as they are heterotrophs hence they obtain their nutrients from other source using their pseudohyphae, along with network formation of hyphae called mycelium. When nutritional, environmental as well as immunological variation occurs, a saprophytic fungus associated with oral cavity reproduces and giving rise to more compact colonies of new fungus forming a row of elongated cells found in white patches and lesions.

Role of saliva in fungal infection

The oral cavity is a wide field for the variety of microorganisms and acts as a host to survive on it. It needs a natural microflora for normal development and physiology¹⁶. The oral cavity is lined by mucosal epithelial cells and continuously filled with saliva secreted by various salivary glands and activate the mechanism of many beneficial microbes. Any disturbances occur in the secretion or function of saliva, epithelial cell damage can lead to making physiological differences in the oral cavity. Some certain microbes can affect or change the normal microflora. *C. Albicans* is a mutualistic fungus which can form fungal colonisation in the oral cavity causing oropharyngeal candidacies. In other words, we can say that saliva has a defence mechanism which stands as a barrier against the fungal attack^{17,10}. Because of the flushing action of saliva, microbial infection in the oral cavity can be diluted and appears to show minimum emergence but fungi have that capacity to multiply under these types of adverse circumstances and reflects infection¹⁸. It brings nutrients, peptides, and partially dissolved carbohydrates and delivers to oral biofilm. Addition to this it helps in lubrication for digestion, temperature regulation, including host defence by saliva flow¹⁹. Immunoglobulin action of saliva can identify protective function against fungal pathogen concerning innate immunity and contribute to first-line oral defence²⁰.

The immune system of the oral cavity

The innate immunity of our body always tends to ready for fighting any adverse condition during necessity but in case of oral fungal infection mouth act as an entry point of the outer harmful components. In the oral cavity whenever there becomes an interaction between host immunity and the foreign pathogen that leads to either mutualism and confirms salivary defend mechanism against that pathogen or break the epithelial barrier¹⁰. In the epithelial cells, there is a polysaccharide receptor named Toll-like receptor (TLR4) expresses the immune recognition against pathogenic microbes and by the action of macrophages and dendritic cell it prevents the colonisation of fungal flora like *C.albicans*^{21,22}. The cell-mediated immune system and humoral immunity play a crucial role in protecting oral

mucosa from fungal colonisation⁸. Also with the epithelial barrier, primary immunity is provided by type 1 CD4 T lymphocyte that is activated by the help of interleukin (IL)-4, IL-6, and IL-12, secondary immunity provided by CD8T lymphocyte through several immunological mechanisms⁶ using T cell receptor (TCR) on their cell surface where MHC I or MHC II helps to display fungal pathogen²³. Activated T-cells produces lymphokines that regulate the functions of macrophages and other leukocytes like interferon-gamma (IFN- γ), which is the only lymphokine that helps to enhance the microbicidal action of macrophages. T lymphocyte also activates TNF (tumour necrosis factor) synthesis by them. In the presence of suboptimal levels of IFN- γ , fungus killing by neutrophils is developed by tumor necrosis factor- α (TNF- α)^{24,25}. Whenever the CD₄ T lymphocyte count fallen down (approximately 200 cells/mm³) recurrence rate of the disease could be possible²⁶. Reduction of antibodies such as IgA, IgM and IgG defects in lymphocyte transformation and stimulate most severe types of oral fungal infection²⁷. There is a confusing relationship between inflammation and immunity that what comes first, whether the change in the integrity of the biofilm or the host immune response¹⁹.

Clinical presentation of oral fungal infection

The primary stage of oral fungal infection is initiated by the primary colonisers found in the surface of the oral cavity; later on, that is proliferated into superficial colonisation with a large number of migratory fungal colonisers forming a multi-layered biofilm. According to the differential environmental mechanism of the oral cavity such as temperature, atmospheric conditions, pH, salinity, redox potential, and liquid activity from saliva can alter the microbial composition and trigger the shelter to fungal biofilm¹⁹. Artificial equipment like dentures can restrict the arrival of oxygen and flow of saliva to the appropriate tissue area; that's why low PH and scarcity of oxygen level promote the storage of dense fungal film on the floor of the oral cavity. The microbial film deposited on the surface of the oral cavity nothing but infected scales of epithelial cells with fungal hyphae looks like curd deposits with superficial patches⁸. Oral fungal infection often remains asymptomatic mostly at the initial stage, but periodically symptoms have seen like irritation in the mouth, burning during eating, difficult to talk and alteration in sense of tasting. *Candida albicans* remain all-time common isolated microorganism in oral fungal infection. Oral candidiasis classified into primary and secondary oral candidiasis. Primary candidiasis affects oral and perioral tissue only but during secondary candidiasis, superficial candida association may lead to keratinised lesions^{28,29}. Deep fungal infection in the oral cavity with high efficiency may alter to the ulcerative lesion (Fig.2)³⁰.



Fig.2: Ulcerative fungal infections at the soft palate

Diagnostic method

Oral fungal infection can be clinically diagnosed by biopsy and there is another way that is microbiological diagnosis through oral sample culture on laboratory^{8,31}. Like another disease, a fungal infection in the oral cavity can also be diagnosed clinically and pathologically. About 90% region of the oral cavity can get infected including the tongue, lip surface and complete floor of mouth with curd-like white patches. Mostly in older adults when excessive deposition of plaque occurred on the oral cavity then mixed white and red lesions are seen with heavily keratinised surface³². The clinical diagnosis followed by biopsy can reveal hyphae or pseudohyphae of identified fungi. The cytological study can reveal microscopic evaluation and another way that is sample culture reveals the actual and exact process of diagnosis of fungal era²⁸. Diagnosis of oral fungal infection can be carried out by morphologically, biochemically, immunologically and genetically. Identification, as well as isolation of fungal infection in oral cavity, have several approaches of diagnostic method like direct microscopy of smear, staining and microbiological culture. New advanced optical devices allow the direct microscopic examination to clinicians. Cytological identification is made possible through direct microscopy by simply transformation of the sample in a glass slide collected from the infected site. Potassium hydroxide, gram stain and periodic acid-Schiff (PAS) are three diagnostic agents help to clear background, making fungi clearly visible and easily identified^{29,33,34}. In the case of the failing procedure to cytological smear identification, Sabouraud's dextrose agar (SDA) is recommended as media for fungal culture. After an incubation period of 24-28 hours at approximately 37°C, fungal colonies appeared on the plate containing SDA⁵. There is another staining diagnostic process named Gridley's or Grocott's methenamine silver (GMS) stains are ideal for confirming fungal elements in tissues, deeply dying from those stains. In further techniques, with the availability of chronic or periodic acid, the hydroxyl groups of complex polysaccharides of the yeast cell wall are oxidized to alde-

hydes³⁵. The genetical diagnostic method involves enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction PCR in which the strain persistence has been investigated by DNA fingerprinting during chronic or repeated infection and clear all hesitation to follow antifungal therapy, microevolution in infecting populations, and the cause of oral fungal infection^{31,36}.

Management and treatment

Disease and host immunity are interlinked with some agents that help to keep balance on the physiology of the human body that are vitamins and nutritional supplement. Therefore, deficiency states of iron, folic acid, vitamins B₁₂, vitamin C and vitamin A; able to weaken our immune system. As saliva has defended mechanism, salivary gland function and salivary hydration testing should be performed. Dentures should be avoided, if not, should clean those things properly soaking with white vinegar. Nutritional factors should be implemented on the treatment of fungal infection with the prohibition of carbohydrate-rich diet⁵. Smoking, alcohol and tobacco consumption should be avoided as *C.albicans* come in the very active form with cigarette smoke getting it as a nutritional factor and cigarette smoke contain aromatic hydrocarbon that can convert the enzyme system of candida species to carcinogen³⁷. Some study reveals that fluconazole and amphotericin B remain sensitive toward most of the fungal isolates in antifungal susceptibility test and very few were resistant to them⁶.

An oral fungal infection could be managed by following the required guidelines like:

1. Diagnosis by accurate medical and dental records, clinical demonstration verified with morphological, biochemical, immunological and genetical laboratory tests.
2. Predisposing factors that are responsible for the initiation of oral fungal infection should be rectified wherever required.
3. Maintaining good oral cavity hygiene and oral prostheses like dentures.
4. Adoption of antifungal therapy based on the intensity of the infection and susceptibility of the fungal species.
5. For proper maintenance of oral cavity natural remedies like grapefruit seed extract; garlic; tea tree oil, clove oil can be used as pre-treatment for better oral health.
6. Cleaning of mouth with water or mouthwash after every meal and use of an inhaler that contains corticosteroids.³⁸

CONCLUSION

Oral fungal infection reveals many microbes including *Candida* and *Aspergillus spp.* mostly. Misbalance in host

immunity and saliva function plays a crucial role in the induction of fungal suspension on the oral cavity. Immunogenic misbalance of host allows microbes to be settled. Long term deposition of fungal biofilm may lead to chronic ulceration and could be life-threatening. Self-awareness about oral hygiene and regular cleansing can control the deposition of food debris and restrict the risk of oral fungal infection. Avoiding smoking, alcohol, tobacco and by adding healthy nutritional factor in the diet could enhance the innate immunity for a better host response towards an oral fungal infection. Now treatment with empirical therapy is at high risk because many antifungals become resistant to isolated microbes. Medication should be proper following antifungal susceptibility test. Clinicians have to treat timely using proper diagnostic techniques and medication.

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