Review Article

Oral Candidiasis - A Review

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ABSTRACT

Candidiasis, a common opportunistic and important fungal infection of the oral cavity is caused by Candida species. There are some local risk factors mainly acidic saliva, dry mouth, use of prosthetic dentures at night, tobacco, carbohydrate rich-diets and patients receiving radiotherapy and chemotherapy in maxillofacial regions that make the oral cavity more prone to Candida infection. Oral hygiene maintenance and early diagnosis of the infection is very important. Management involves proper history taking, clinical examination, and appropriate antifungal treatment with a few requiring samples to be taken for laboratory analysis.

Key words: Candidiasis, Candida Species, Risk Factors, Radiotherapy and Chemotherapy.

INTRODUCTION

Oral candidiasis is also known as oral candidosis, oral thrush, oropharyngeal candidiasis, moniliasis, candidal stomatitis, muguet. It is an opportunistic infection affecting the oral mucosa. These lesions are very common and caused by the yeast Candida albicans. Candida albicans are the normal components of oral microflora and around 30% to 50% people carry this organism. The rate of carriage increases with advancing the age of the patient. Candida albicans are recovered from 60% of dentate patient’s mouth over the age of 60 years. [1]

There are seven Candida species of major medical importance. By far the most important of these is C. albicans which is isolated most frequently (over 80%) and believed to more virulent in humans. [2] The other Candida spp. encountered in human infections are:

a. Candida tropicalis
b. Candida glabrata
c. Candida parapsilosis
d. Candida stellatoidea
e. Candida krusei and
f. Candida kyfer. [3]

Candida albicans is a dimorphic fungus that causes severe opportunistic infections in humans. [4] There is an interesting feature of Candida albicans that is its ability to grow in two different ways, reproduction by budding, forming an ellipsoid bud, and in hyphal form, which can periodically fragment and give rise to new mycelia, or yeast-like forms. [5] Yeast is
innocuous and hyphal forms are associated with invasion of host tissue.

There are three general factors which helps the Candida albicans infection to develop in the patient’s body. They are:

a. Immune status of the patients
b. Oral mucosal environment
c. Strain of Candida albicans

The main factors which are responsible for increasing the susceptibility of oral candidiasis are:

a. Immunosuppression
b. Nutritional deficiencies
c. Endocrinopathies
d. Malignancies
e. Epithelial alteration
f. Dental prosthesis
g. High carbohydrate diet
h. Infancy and old age
i. Poor oral hygiene
j. Heavy smoking. [6]

Classification
Oral candidiasis is classified as: [7]

1. Primary oral candidosis
   a. Acute form
      i. Pseudomembranous
      ii. Erythematous
   b. Chronic form
      i. Erythematous
      ii. Pseudomembranous
      iii. Plaque like
      iv. Nodular
   c. Candida associated lesions
      i. Denture stomatitis
      ii. Angular chealosis
      iii. Median rhomboid glossitis

2. Secondary oral candidosis
   i. Familial mucocutaneous candidiasis
   ii. Diffuse chronic mucocutaneous candidiasis
   iii. Familial mucocutaneous candidiasis
   iv. Chronic granulomatous disease
   v. Candidosis endocrinopathy syndrome
   vi. Acquired immune deficiency syndrome (AIDS).

Predisposing factors of oral candidiasis:
Pathogenic agents: Candidiasis is caused by candida and this is a fungus and it was first isolated in 1844 from the sputum of a tuberculous patient. [8] Several studies have demonstrated that infection with candida is associated with certain pathogenic variables. Adhesion of candida to epithelial cell walls, an important step in initiation of infection, is promoted by certain fungal cell wall components such as mannose, C3d receptors, mannoprotein, and saccharins. [9]

Other factors implicated are:
   a. Germ tube formation
   b. Presence of mycelia
   c. Persistence within epithelial cells
   d. Endotoxins
   e. Induction of tumour necrosis factor and
   f. Proteinases. [10]

Phenotypic switching which is the ability of certain strains of Candida albicans to change between different morphologic phenotypes has also been implicated. [11]

They are non-photosynthetic, eukaryotic organisms with a cell wall that lies external to the plasma membrane. There is a nuclear pore complex within the nuclear membrane. The plasma membrane contains large quantities of sterols, usually ergosterol. The macroscopic and microscopic cultural characteristics of the different candida species are similar except some exceptional features. They can metabolise glucose in both aerobic and anaerobic conditions. Temperature influences their growth with higher temperatures such as 37°C that are present in their potential host, promoting the growth of pseudohyphae. They have been obtained from animals and environmental sources. They can be found in gastrointestinal tract, the vagina, and skin being the most common sites and Candida albicans being the commonest species isolated from these sites. They require fixed carbon for their growth from the
environmental sources. Filamentous growth and apical extension are seen with hyphae and mycelium, and single cell division is associated with yeasts.\textsuperscript{[12]}

\textbf{Local predisposing factors:} Impaired salivary gland function can be predisposing factors to oral candidiasis.\textsuperscript{[13]} Antimicrobial proteins in the saliva such as lactoferrin, sialoperoxidase, lysozyme, histidine-rich polypeptides, and specific anticandida antibodies, interact with the oral mucosa and prevent overgrowth of candida. Therefore the conditions which causes decrease salivary flow such as Sjögren’s syndrome, radiotherapy of the head and neck, or drugs can lead to an increased risk of oral candidiasis.

Prosthetic dentures predispose to infection with candida in as many as 65% of elderly people wearing full upper dentures.\textsuperscript{[14]} Wearing of dentures produces a microenvironment conducive to the growth of candida with low oxygen, low pH, and an anaerobic environment. This may be due to enhanced adherence of Candida species to acrylic, reduced saliva flow under the surfaces of the denture fittings, improperly fitted dentures, or poor oral hygiene.

Inhaled steroids have been shown to increase the risk of oral candidiasis because steroids possibly suppress cellular immunity and phagocytotic activities. The local mucosal immunity reverts to normal on discontinuation of the inhaled steroids.\textsuperscript{[15]} Other factors are oral cancer/leukoplakia, lichen planus and a high carbohydrate diet. Growth of candida in saliva is enhanced by the presence of glucose and its adherence to oral epithelial cells is enhanced by a high carbohydrate diet.\textsuperscript{[16]}

\textbf{Systemic factors:} There are so many systemic factors which predispose to candida infections. Extremes of life predispose to infection because of reduced immunity.\textsuperscript{[17]}

Some drugs such as broad spectrum antibiotics alter the local oral flora creating a suitable environment for candida to proliferate. The normal oral flora is restored once the antibiotics are discontinued but in some cases it requires treatment. Immunosuppressive drugs such as the antineoplastic agents have been shown in several studies to predispose to oral candidiasis by altering the oral flora, disrupting the mucosal surface and altering the character of the saliva.\textsuperscript{[18]} And other immunosuppressive agents like steroids predispose to candida infections.

Other factors which predispose the candida infections are:
\begin{itemize}
  \item a. Smoking
  \item b. Diabetes
  \item c. Cushing’s syndrome
  \item d. Immunosuppressive conditions such as HIV infection
  \item e. Malignancies such as leukaemia and
  \item f. Nutritional deficiencies— vitamin B deficiencies.
\end{itemize}

A study showed that 15%–60% of people with malignancies will develop oral candidiasis while they are immunosuppressed.\textsuperscript{[19]} In those with HIV infection rates of between 7% to 48% have been quoted and more than 90% has been reported in those with advanced disease. Relapse rates are between 30% and 50% on completion of antifungal treatment in severe immunosuppression.\textsuperscript{[20]}

\textbf{Laboratory Tests:} Laboratory investigations can be used for the confirmation of the clinical diagnosis of candidiasis, however, they are rarely done unless the lesion does not resolve following appropriate treatment. If lab investigations are required, a potassium hydroxide stained cytologic preparation that demonstrates the fungal pseudohyphae penetrating the epithelial cells can be used for confirmation. Confirmation by biopsy and a periodic acid Schiff stain (PAS) is also possible, as the stain will turn
the spores and pseudohyphae bright magenta, making them easily visible by light microscope. Fungal cultures are not typically used to confirm the diagnosis of oral candidiasis, as candida albicans is a normal component of the oral flora. \[21\]

If oral lesions fail to improve following appropriate therapy a definitive diagnosis is indicated utilizing the above laboratory investigations, and the possibility of a resistant strain of candida should be explored. \[22\] Prior antifungal drug treatment in either prophylactic or suppressive doses of fluconazole (50-100 mg/day) has contributed to the development of fluconazole-resistant candida albicans.

**Diagnosis:** Oral candidiasis is mainly diagnosed on the basis of clinical sign and symptoms. Sometimes laboratory investigations are also required for the confirmation of the clinical diagnosis.

**Treatment:** When the topical therapy does not show good result then start with systemic therapy because failure of drug response is the initial sign of underlying systemic disease. Follow-up after 3 to 7 days is important to check the effect of drugs. Always continue the treatment for 2 weeks after resolution of the lesions.

**Main Goals of treatment are:** \[23\]
- a. To identify & eliminate possible contributory factors
- b. To prevent systemic dissemination
- c. To eliminate any associated discomfort
- d. To reduce load of candida

**Primary line of treatment:** Nystatin is the drug of choice as a primary line of treatment and for the mild and localized candidiasis this primary line of treatment is used other drugs includes Clotrimazole which is available as Lozenges and Amphotercin B as oral suspension. \[24\]

1. **Nystatin:** It is available as cream & oral suspensions. It is to be applied four times a day and allowed to act approximately for two minutes in the oral cavity and then it is to be swallowed. Nystatin shows no significant drug interaction or side effects. It acts by binding to the cell membrane of the fungi and alters the cell permeability leading to the leakage of intracellular components followed by cell death.

2. **Amphotercin B:** Amphotercin B is available as Lozenge (Fungilin 10mg) and oral suspension (100mg/ml) which is to be applied 3 to 4 times daily. It inhibits the adhesion of Candida to epithelial cells. It is a nephrotoxic drug.

3. **Clotrimazole:** Clotrimazole reduces the fungal growth because this drug inhibits the synthesis of ergosterol which is a part of cell membrane of fungi. It is not indicated for systemic infection. This drug is available as Creams and Lozenge (10mg).

The main side effects are:
- 1. Unpleasant mouth sensation
- 2. Increases liver enzyme levels
- 3. Nausea and
- 4. Vomiting

**Second line of treatment:** The second lines of treatment are used for severe, localized, immunosuppressed patients and patients who respond poorly to primary line of treatment. Drugs mainly used in second line of treatment are: \[24\]

1. **Ketoconazole**
2. **Fluconazole**
3. **Itraconazole**

**Ketoconazole:** It is absorbed from the gastro intestinal tract (GIT) and metabolized in the liver and blocks ergosterol synthesis in fungal cell membrane.

**Dosage:** The dose is 200 - 400mg tablets once or twice daily for 2 week.

**Side effects:**
- a. Nausea,
- b. Vomiting,
c. Liver damage and
d. Interacts with anticoagulants.

**Fluconazole:** It is used in oropharyngial candidosis. This drug inhibits fungal cytochrome P450 sterol C-14 alpha demethylation.

**Dosage:** 50 – 100mg capsule once a day for 2-3 weeks.

**Side effects:**
- Nausea,
- Vomiting and
- Headache.

It interacts with anticoagulants and this drug is contraindicated in pregnancy, liver & renal disease

**Itraconazole:** It is one of the broad spectrum antifungal drugs.

**Dosage:** 100 mg capsule once a day for 2 weeks.

**Side effects:**
- Nausea
- Neuropathy and
- Rashes.

It is contraindicated in pregnancy & liver disease.

**CONCLUSION**

The prognosis of oral candidiasis is good when the proper treatment is given and predisposing factors associated with this infection are eliminated. When the systemic predisposing factors are associated with the candidiasis, there are more chances of recurrence of the disease. In most of the cases oral candidiasis is a cause of secondary superficial infection which can easily be resolved with antifungal therapy and proper oral hygiene maintenance.

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**REFERENCES**


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