Oral candidiasis: An opportunistic infection: A review

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Abstract
The present review deals with oral candidiasis which is an opportunistic infection mainly caused by fungus Candida albicans. Candida infection is caused due to change in the host defense system where both immunological and non-immunological factors play essential roles making the condition favorable for proliferation of Candida. Oral candidiasis can be divided into acute, chronic and Candida-associated lesions. The diagnosis of the candidal infection in the oral cavity can be determined by microscopic examination or biopsy in case of chronic hyperplastic candidiasis. The main line of treatment is by giving antifungal ointments that can be topically applied and in some cases systemic medication can also be administered.

Keywords: Candidiasis, opportunistic, Candida albicans, proliferation, hyperplastic candidiasis

1. Introduction
Oral candidiasis is an opportunistic infection of the oral cavity. It is common and under diagnosed among the elderly, particularly in those who wear dentures and in many cases is avoidable with a good mouth care regimen. It can also be a mark of systemic disease, such as diabetes mellitus and is a common problem among the immune-compromised patients. Oral candidiasis is caused by an overgrowth or infection of the oral cavity by a yeast-like fungus, Candida. More than 20 species of Candida, Candida albicans are the most common and important causative agent of oral candidiasis. C. albicans a dimorphic fungal organism that typically is present in the oral cavity in a non-pathogenic state in about one half of healthy individuals. Normally present as a yeast, the organism under favorable conditions, has the ability to transform into a pathogenic (disease causing) hyphae form. Some other Candida species are C. tropicalis, C. glabrata, C. pseudotropicalis, C. guilliermondii, C. krusei, C. lusitaniae, C. parapsilosis, and C. stellatoidea. The conditions that contribute in the development of the infection include broad-spectrum antibiotic therapy, xerostomia, immune dysfunction, or the presence of removable prosthesis or denture.

Advances in medical management as antineoplastic chemotherapy, organ transplantation, hemodialysis, parenteral nutrition, and central venous catheters also contribute to fungal invasion and colonization. The incidence of candidiasis in the oral cavity with predominant C. albicans isolation has been reported to be 45% in neonates, 45-65% in children, 30-45% of healthy adults, 50-65% in cases of long-term denture wearers, 65-88% in those residing in acute and long-term facilities, 60-88% in patients with acute leukemia undergoing chemotherapy, and 95% of patients with HIV infection. Systemic candidiasis carries a mortality rate of 71-79%. It is important for all the clinicians treating the older patients to be aware of the risk factors, diagnosis, and treatment of oral candidiasis. In a recent study, it was found that 30% of clinicians agreed that, even without examining the oral cavity, they would prescribe nystatin for oral candidiasis on the request of assistant staff. Such negligence can result in an inaccurate diagnosis, missed pathologies, and failure to address the risk factors which may lead to recurrence of candidiasis.

2. Predisposing factors
Candida infections arise due to alteration in host defense system where both immunological and non-immunological factors play crucial roles making the conditions favorable for proliferation of Candida.
Table 1: Factors responsible for oral candidiasis [16]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Poor oral hygiene</td>
<td>Promotes organism adherence and colonization</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>Absence of antimicrobial and flushing effect of saliva</td>
</tr>
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<td>Recent antibiotics treatment</td>
<td>Inhibits competitive oral bacteria</td>
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<td>Dental appliance</td>
<td>Isolated mucosa from saliva and functional cleansing serve as organism reservoir</td>
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<tr>
<td>Early infancy</td>
<td>Immune competence has not completely developed</td>
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<tr>
<td>Genetic immune deficiency</td>
<td>Specific humoral or cellular immune defects</td>
</tr>
<tr>
<td>AIDS</td>
<td>Deficient cellular immune response</td>
</tr>
<tr>
<td>Corticosteroids therapy</td>
<td>Inhibition of immune function</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>Depletion of circulation leukocytes caused by chemotherapy, aplastic anemia and similar hemopoietic disorders</td>
</tr>
<tr>
<td>Anemia, malnutrition, malabsorption</td>
<td>Epithelial thinning and altered maturation, poor tissue oxygenation</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Recurring hyperglycemia and mild ketoacidosis</td>
</tr>
<tr>
<td>Advanced systemic disease</td>
<td>Metabolic toxicity or limited blood perfusion of tissue</td>
</tr>
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3. Classification [17]

Acute candidiasis
1. Pseudomembranous candidiasis (oral thrush)
2. Erythematous (atrophic) candidiasis

Chronic candidiasis
1. Erythematous (atrophic) candidiasis
2. Hyperplastic candidiasis (Candida leukoplakia)

Candida-associated lesions in oral cavity
1. Angular cheilitis
2. Denture related stomatitis
3. Median rhomboid glossitis
4. Linear gingival erythema (?)

3.1 Acute candidiasis
3.1.1 Pseudomembranous candidiasis
This form of candidiasis classically presents as acute infection, though the term chronic pseudomembranous candidiasis has been used to denote chronic recurrence cases. It is commonly seen in extremes of age, immune-compromised patients especially in AIDS, diabetics, patient’s on corticosteroids, prolonged broad-spectrum antibiotic therapy, hematological, and other malignancies.[18]. They commonly occur as adherent white plaques resembling curdled milk or cottage cheese on the surface of the labial and buccal mucosa, hard and soft palates, tongue, periodontal tissues, and oropharynx. The membrane can be scraped off with a swab to expose the underlying erythematous mucosa. It is often easily diagnosed and is one of the commonest forms of oropharyngeal candidiasis accounting for almost a third [19]. The symptoms of the acute form are rather mild and the patients may complain only of slight tingling sensation or foul taste, whereas, the chronic forms may involve the esophageal mucosa leading to dysphagia and chest pains. Few lesions mimicking pseudomembranous candidiasis could be white coated tongue, thermal and chemical burns, lichenoid reactions, leukoplakia, secondary syphilis and diphtheria [20].

3.1.2 Erythematous (atrophic) candidiasis
Atrophic or erythematous candidiasis is relatively rare and manifests as both acute and chronic forms [21]. Previously known as ‘antibiotic sore mouth,’” due to its association with prolonged use of broad-spectrum antibiotics [22]. This form is also associated with pseudomembranous candidiasis. When the white plaque of pseudomembranous candidiasis is scrapped, often red atrophic and painful mucosa remains. Furthermore, the erythematous stomatitis and depapillation of tongue arises because of the suppression of the normal bacterial flora. The symptoms patient often describes includes vague pain or a burning sensation.

3.2 Chronic candidiasis
3.2.1 Erythematous (atrophic) candidiasis
The chronic form is usually seen in HIV patients involving the dorsum of the tongue and the palate and occasionally the buccal mucosa. Patients who wear dentures continuously day and night are most commonly affected by the infection. This form of atrophic candidiasis is also termed as ‘Denture sore mouth’. The disease is characterized by formation of asymptomatic erythema and inflammation of entire denture bearing mucosa of the palate. (See denture-related stomatitis)

3.2.2 Hyperplastic candidiasis
Hyperplastic candidiasis is the least common of the triad of major clinical variants, with 5% of the cases. CHC can manifest in nodular form or as whitish plaques that cannot be attributed to any other disorder, do not detach upon rasping, and are typically located on the cheek mucosa and tongue, and especially bilaterally at both lip retro-commissures.[25, 24]. In this form of the infection the Candida hyphae are not only found at epithelial surface level but also invade deeper levels where epithelial dysplasia can be observed, with the associated risk of malignancy [23]. Hyperplastic candidiasis may persists for years without any symptom.

3.3 Candida-associated lesions
3.3.1 Angular cheilitis
Angular cheilitis is an inflammation of one, or more commonly both of the corners of the mouth. Initially, the corners of the mouth develop a gray-white thickening and adjacent erythema (redness). Later, the usual appearance is a roughly triangular area of erythema, edema (swelling) and maceration at either corner of the mouth [26]. Angular cheilitis can occur spontaneously but more often develops in those who wear oral dentures and appliances, those who are required to wear masks as part of their occupation, and in some small children, particularly those who slobber and use pacifiers [27]. Typically the lesions give symptoms of soreness, pain, pruritus (itching) or burning or a raw feeling in the later stage [26]. Angular cheilitis often represents an opportunistic infection of fungi and/or bacteria, with multiple local and systemic predisposing factors involved in the initiation and persistence of the lesion [28].

3.3.2 Denture related stomatitis
Denture-related stomatitis refers to an inflammatory state of the denture bearing mucosa, characterized by chronic erythema and edema of part or all the mucosa beneath maxillary dentures [29]. It is also the most commonly encountered mucosal lesion with removable prostheses, and affects one in every three complete denture wearers [30].
frequency of its development is 25–67%, frequently seen among female patients, and prevalence increases with age [31]. Denture stomatitis is also known as denture sore mouth, inflammatory papillary hyperplasia, denture-induced stomatitis, and chronic atrophic candidiasis.

Although, etiology of denture stomatitis is considered multifactorial, denture plaque, trauma, *candida albicans*, allergy, adverse systemic conditions, surface texture and permeability of the denture base and lining materials are regarded as some of the major factors associated with the condition. In majority of the cases, elimination of denture faults, control of denture plaque and discontinuing the wearing of denture are sufficient [32].

### 3.3.3 Median Rhomboid Glossitis

Median rhomboid glossitis is a diamond shaped, elevated, inflammatory lesion of the tongue, covered by smooth red mucosa. It is situated anterior to the circumvallate papillae, at about the junction of the anterior two-third and posterior one-third of the tongue [33]. It predominantly affects males [34] while few studies showed female preponderance [35, 36]. The most common clinical presentation of the disease is an erythematous or white-erythematous area on the dorsal median surface of the tongue, immediately prior to Region V of the circumvallate papillae (terminal gingiva). The erythematous region of the mucosa can be flat or raised. It is normally well circumscribed, with a rhomboid shape, and smooth. A nodular component is occasionally found, or the organ can be lobulated. The texture may be similar to the subjacent or firm part of the tongue, and its surface is relatively soft [37].

Sometimes, soft palate erythema may be seen where the lesion of median rhomboid glossitis touch the palate. This erythematous area is termed as ‘kissing lesion’. Generally, median rhomboid glossitis is asymptomatic. However, in few cases pain and ulceration has been reported.

### 3.3.4 Linear gingival erythema

Linear gingival erythema (LGE), which was formally referred as HIV-gingivitis, is the most common form of HIV-associated periodontal disease in HIV-infected population. It is considered resistant to conventional plaque-removal therapies, being considered, nowadays, a lesion of fungal etiology. It is characterized by a fired, linear band 2 to 3 mm wide on the marginal gingival accompanied by petechiae-like or diffuse red lesions on the attached gingival and oral mucosa, and may be accompanied by bleeding. The prevalence of this lesion varies widely in different studies, ranging from 0 to 48% probably because in many of them, LGE was misdiagnosed as gingivitis [38].

### 4. Diagnosis

The diagnosis of oral candidiasis is essentially clinical and is based on the recognition of the lesions by the professional, which can be confirmed by the microscopic identification of *Candida* [39]. The techniques available for the isolation of *Candida* in the oral cavity include direct examination or cytological smear, culture of microorganisms and biopsy which is indicated for cases of hyperplastic candidiasis because this type could present dysplasias [40].

#### 4.1 Microscopic examination

A classical microscopical procedure typically involves removing a representative sample from the infected site (exfoliative cytology) which is transferred to a microscopic slide and treated with potassium hydroxide (KOH), Gram stain, or periodic acid-Schiff (PAS) stain [41]. Microscopic examination can be made with fresh samples, using 10% potassium hydroxide (KOH), which dissolves the epithelial cells and leaves *Candida* intact, or 15-30% sodium hydroxide (NaOH) [42]. Moreover, Candida species stain poorly by hematoxylin and eosin. In this case, staining with periodic acid Schiff (PAS) or Gridley’s or Gomori’s methenamine silver (GMS) can be done. Fungi in these stains take up pinkish-red. The presence of blastospores and characteristic pseudohyphae or hyphae in the superficial epithelium tissues identifies the fungus as a species of *Candida* [43].

### 4.2 Culture media

The most frequently used primary isolation medium for *Candida* is SDA [44] which, although permitting growth of *Candida*, suppresses the growth of many species of oral bacteria due to its low pH. Incorporation of antibiotics into SDA will further increase its selectivity [45]. Typically SDA is incubated aerobically at 37 °C for 24-48 hrs. *Candida* develops as cream, smooth, puffy convex colonies on SDA and differentiation between species is rarely possible [46].

In recent years, other differential media have been developed that allow identification of certain *Candida* species based on colony appearance and color following primary culture. The advantage of such media is that the presence of multiple *Candida* species in a single infection can be determined which can be important in selecting subsequent treatment options [47]. Examples of these include Pagano-Levin agar or commercially available chromogenic agars, namely, CHRO Magar Candida, Albicans ID, Fluorople, or Candichrom albicans [48].

### 4.3 Biopsy

In case of chronic hyperplastic candidosis, a biopsy of the lesion is necessary for subsequent detection of invading *Candida* by histological staining using either the PAS or Gomori’s methenamine silver stains. Demonstration of fungal elements within tissues is done as they are dyed deeply by these stains. The presence of blastospores and hyphae or pseudo hyphae may enable the histopathologist to identify the fungus as a species of *Candida* and, given the presence of other histopathological features, make a diagnosis of chronic hyperplastic candidosis [48].

### 5. Treatment

The treatment of oral candidiasis is based on four fundamentals [49]: making an early and accurate diagnosis of the infection; Correcting the predisposing factors or underlying diseases; Evaluating the type of *Candida* infection; Appropriate use of antifungal drugs, evaluating the efficacy / toxicity ratio in each case. When choosing between some treatments it will take into account the type of Candida, its clinical pathology and if it is enough with a topical treatment or requires a more complex systemic type [50], always evaluating the ratio efficacy and toxicity [51]. Mostly the infection is simply and effectively treated with topical application of antifungal ointments. However in chronic mucocutaneous candidiasis with immunosuppression, topical agents may not be effective. In such instances systemic administration of medication is required [52]. The anti-fungal agents that can be administered is given in the table 2.

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6. Conclusion
Oral candidiasis is a condition which arises due to some predisposing factors like altered local resistance to infection, compromised immune system function and generalized patient debilitation. Candida albicans that cause the disease is usually present in the oral cavity in an inactive form. In most of the cases the disease is often unnoticed and only proper oral examination by the dentist can diagnose it. Furthermore, it should be noted that every white lesion in the oral cavity is not due to the candidal infection. Although, after the proper laboratory investigations the disease can be confirmed. Diagnosis of oral candidiasis can be done by microscopic examination and/or biopsy. The disease can be easily controlled by administering topical or systemic antifungal agents. Prognosis of oral candidiasis is good.

7. References
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