INTRODUCTION

In recent years, the number of immunocompromised individuals dramatically increased due to various factors including increasing incidence of diabetes, prolonged average life expectancies, the widespread use of broad-spectrum antibiotics and immunosuppressive agents, invasive surgical procedures such as solid organ or bone marrow transplantation and the advent of the human immunodeficiency virus (HIV). In connection to this, the incidence of opportunistic infections -oral candidosis being the most clinical relevant for dental health professionals- has increased.

This review provides a comprehensive overview of the etiology, clinical presentations, diagnosis, and management strategies of oral candidosis commonly encountered in dental practice.

1. AETIOLOGY and PATHOGENESIS

Candidosis is the most common fungal infection of the oral cavity and is caused by an overgrowth of commensal Candida species. Candida albicans (C. albicans) is the most commonly isolated species in both health and disease. Less common species include C. glabrata, C. tropicalis, C. guilliermondii, C. krusei, C. parapsilosis, and C. kefyr, and more recently, C. dubliniensis (1-5).

Colonization by Candida in the oral cavity does not necessarily equate to infection; a significant proportion of healthy individuals continuously harbor strains of C. albicans (1,4). Reported symptom-free oral carriage rate varies between 25-75%, depending on the population sampled and the sensitivity of the sampling technique (2-7). In oral cavity, C. albicans is most commonly isolated from the dorsum of the tongue followed by the palate and...
Candida species are harmless commensal members of the normal oral microbial flora just as they are in the skin, gastrointestinal tract and vagina (7-9). Whether the organism remains as a commensal, or proliferates and causes disease, is usually determined by virulence factors of the pathogen and predisposing factors of the host (1,4,5,8-12).

The transition from commensalism to disease may be associated with the virulence characteristics of Candida such as adherence, germ tube formation, dimorphism, phenotypic switching, toxins, and hydrolytic enzymes (13-15). However, it is widely accepted that predisposing host factors are of paramount importance in the development of the candidal infection (Table 1). The most relevant of these host factors are discussed below.

### Predisposing Host Factors

#### Endocrine disorders

Diabetes mellitus (DM) may increase susceptibility to development of candidal infections owing to immune system aberrations such as impaired opsonization and decreased chemotactic activity of neutrophils and monocytes (16).

Candida-associated lesions including denture stomatitis, median rhomboid glossitis, and angular cheilitis have been reported to be more prevalent in patients with DM (17). The individuals with DM are more prone to candidal infections, particularly when host resistance is modified due to local factors such as smoking and denture wearing (17,18).

Patients with poorly controlled DM may exhibit reduced salivary flow rates, reduced salivary pH, increased salivary glucose levels -factors known to facilitate oral candidal growth and colonization (18-21). While some studies have demonstrated an increased prevalence of Candida in the oral cavity of diabetic subjects (17-19,22), comparable studies present contradictory findings with reduced rates of candidal carriage in diabetic patients compared with healthy controls (23,24).

#### Nutritional factors

Several nutritional deficiencies may result in a diminished host defense and loss of epithelial integrity, which may facilitate subsequent fungal invasion and infection (10).

Iron deficiency anemia has been proposed as an important factor in the aetiology of oral candidosis (9,25). Decreased lymphocyte response to Candida antigens in some iron-deficient subjects was associated with an increased frequency of C. albicans in the oral cavity, suggesting that iron deficiency may predispose to oral candidosis by depressing cell-mediated immunity (9,26). Deficiencies of vitamin B12 and folic acid may also predispose to oral candidosis (27).

#### Blood dyscrasias and malignancies

Solid organ or haematological malignancies and their treatment with cytotoxic chemotherapy or radiotherapy are associated with impairment of host defense mechanisms, and increase the risk for development of oral candidosis. Reduced salivary function, epithelial alterations, and mucositis may result from chemotherapy or radiotherapy, and produce an oral environment favorable to fungal penetration and infection (10,28).

#### Immune defects, immunosuppression

Oral candidosis is a common manifestation in a variety of immunodeficiencies. Both humoral and cell-mediated...
immune systems participate in the prevention and elimination of candidosis (28,29). Reduced or defective immune function increases susceptibility to such infections. In HIV infection, the immunodeficiency affecting T-helper lymphocytes makes the infected patients more predisposed to secondary infections, notably opportunistic candidal infections (28,30).

Candidosis is also a common manifestation of a variety of other immunodeficiencies, including severe combined immunodeficiency syndrome, DiGeorge syndrome, hereditary myeloperoxidase deficiency and Chediak-Higashi syndrome (30).

Xerostomia
Saliva is important in maintaining the normal oral microflora. It dilutes pathogenic antigens and mechanically cleanses the mucosa. Salivary antibodies and numerous non-specific antimicrobial factors are important in decreasing fungal adherence and colonization. The flow of saliva may be compromised by aging, radiotherapy of the head and neck, medications and Sjögren’s syndrome leading to an increased risk of oral candidosis (2,4,10,31).

Medications
Use of broad-spectrum antibiotics may predispose patients to oral candidal infections by eliminating the normal symbiosis between bacterial and yeast flora (4,10,16). Use of glucocorticoids (systemic or topical) increases the risk of oral candidosis by suppressing the cell-mediated immunity (4,10,32).

Immunomodulatory and cytotoxic drugs administered in the treatment of an extensive range of immune-mediated, inflammatory and neoplastic disorders, and to prevent rejection following blood and solid organ transplants lower resistance to fungal overgrowth by inducing neutropenia and suppressing cell-mediated immunity (28).

A large number of prescribed drugs elicit xerostomic side effects. Those most commonly implicated include antidepressants, antipsychotics, anticholinergics, diuretics, antihypertensives and antiadrenergics (33). The reduction in salivary cleansing action and antifungal salivary constituents (lactoferrin, lysozyme, histatins and immunoglobulins) may provide a favorable environment for fungal overgrowth.

High-carbohydrate diet
High-carbohydrate intake has been assumed to predispose to oral candidosis. This is supported by in vitro studies showing that the growth of Candida in saliva is enhanced by glucose despite the presence of a nutrient-competing bacterial salivary flora (34). Furthermore, the adhesive properties of C. albicans to oral epithelial cells and to acrylic surfaces are augmented by dietary carbohydrates (9). In studies investigating the effects of dietary sugars on candidal adhesion and biofilm formation, glucose was shown to be the most effective followed by galactose and sucrose (35,36).

Dentures
Dentures may produce a local environment with relatively acidic and anaerobic conditions by decreasing the flow of oxygen and saliva to the underlying tissue (4,8-10,37,38). In such an environment, extracellular hydrolytic enzymes of C. albicans may be active (39-41).

Overnight denture wearing contributes to increased irritation from denture and enhanced growth of Candida in a moist, occluded environment (12). Mechanical trauma from a poorly fitting denture may reduce tissue resistance and increase the permeability of the epithelium to soluble Candida antigens and toxins thereby promoting infection (9,10,27,37).

Smoking
Smoking, either alone or in combination with other factors, appears to be an important predisposing factor for oral candidosis (6,23,42,43). However, the exact mechanism of action has not yet been established (44). One possible explanation could be that smoking may lead to localized epithelial alterations that facilitate candidal colonization (45). An alternative hypothesis is that cigarette smoke may contain nutritional factors for C. albicans. Aromatic hydrocarbons contained in cigarette smoke may be converted to carcinogen end products by Candida species (46). These partly explain why smokers may be more prone to candidal infections.

2. CLINICAL MANIFESTATIONS
Oral candidosis may present in a variety of clinical forms. The most commonly used classification of oral candidosis is the one proposed by Lehner in 1967 (47).
However, in this review, it was preferred to use the revised classification proposed by Axéll et al. (48) as it is clinically more appropriate (Table 2).

### 2.1. PRIMARY ORAL CANDIDOSIS

#### Acute and Chronic Forms

1. **Pseudomembranous candidosis**
   
   This form of the disease is the most common in immunocompromised individuals such as infants, the elderly, those on corticosteroid or long term broad-spectrum antibiotic therapy, those with severe underlying conditions such as poorly controlled diabetes mellitus, leukemia, and HIV infection/AIDS.

   It is characterized by whitish creamy plaques resembling milk curds on the tongue, palate and buccal mucosa (Fig. 1) (2-5,8,10-12,49). The lesions can be wiped away leaving behind an erythematous mucosal surface which may bleed slightly. The plaques consist of necrotic material, desquamated epithelial cells, fibrin, yeast cells and hyphae, food debris, and bacteria.

2. **Erythematous candidosis**
   
   This variant, previously known as “antibiotic sore mouth”, is mainly associated with the chronic use of broad-spectrum antibiotics. Broad-spectrum antibiotics lower the oral bacterial population and facilitate subsequent overgrowth of Candida by alleviating competitive pressures.

   Clinically, erythematous candidosis is characterized by localized erythematous areas commonly on the dorsum of the tongue and palate, and less commonly on the buccal mucosa (2-4,8,10-12,49). Erythematous candidosis is the only form of oral candidosis that is consistently painful.

   This variant is sometimes referred to as “atrophic candidosis”. The value of using the term “atrophy” to describe a red area is not comprehensive enough. Because redness may be caused not only by reduced epithelial thickness (atrophy) but also by increased vascularity. Therefore the use of the term “erythematous” which means red/reddened should be preferred (49).

3. **Hyperplastic candidosis**
   
   Chronic hyperplastic candidosis, occasionally referred to as “candidal leukoplakia”, appears as well-demarcated,
slightly elevated, adherent homogeneous or nodular white plaques that cannot be wiped away (2-5,8,10-12). The most common location is the commissural region of the buccal mucosa, and less frequently the dorsum of the tongue.

Almost all patients with hyperplastic candidosis are smokers. Recognition of such lesions is important, as the condition has been associated with varying degrees of dysplasia and malignancy (8).

Candida-associated Lesions

1. Denture stomatitis (Denture-associated erythematous candidosis)

Denture stomatitis is a chronic inflammation of denture-bearing mucosa (Fig. 2a & b). Classically, the lesion presents as erythema restricted only to the denture supporting area (2,3,12). The condition is usually asymptomatic. However, patients may complain of slight soreness or burning sensation. Denture stomatitis is commonly associated with angular cheilitis and median rhomboid glossitis (11,42,50).

2. Median rhomboid glossitis

Median rhomboid glossitis is characterized by an erythematous, elliptical or rhomboid-like area representing atrophy of the filiform papillae located on the midline of the dorsum of the tongue just anterior to the circumvallate papillae (42,49). Although median rhomboid glossitis was accepted as a developmental anomaly for a long time, recent evidence indicates that it may be an acquired chronic oral candidosis (42).

3. Angular cheilitis

Clinically, angular cheilitis appears as erythematous, fissured lesions affecting the corners of the mouth (2,3,5,10,12). Facial skin folds and wrinkling along the labial commissures and nasolabial folds, especially in older individuals, may cause saliva accumulation and a moist environment that predisposes to angular cheilitis. This is seen commonly in denture-wearing patients with reduced vertical occlusal dimension. While nutritional factors, such as iron or vitamin B12 deficiency, have all been implicated in the development of these lesions, it is now accepted that most are caused by Candida species and/or Staphylococci and Streptococci (4,51).

Keratinized Primary Lesions Superinfected with Candida

Candida is usually present in non-homogeneous leukoplakias, and it is believed that the organisms are secondary invaders (52). In patients with oral lichen planus, the lesions are frequently infected by Candida (52,53). The underlying cause of secondary candidal infection of these lesions may be structural changes of the epithelial surface or alterations in the cell-mediated immune response against C. albicans (9,53).

2.2. SECONDARY ORAL CANDIDOSIS

Chronic Mucocutaneous Candidosis

Chronic mucocutaneous candidosis (CMC) is characterized by persistent or recurrent superficial
candidosis of the skin, nails, and mucosal membranes (5,51). CMC is associated with a defect in cell-mediated immunity that may either be limited to Candida antigens or be part of a more general immune abnormality (51). CMC is associated with a variety of primary immunodeficiencies, such as severe combined immunodeficiency syndrome, Nezelof syndrome (thymic alymphoplasia), DiGeorge syndrome (congenital thymic aplasia), hyperimmunoglobulin E syndrome, myeloperoxidase deficiency, and endocrinopathies, especially Addison’s disease and hypoparathyroidism (54).

3. DIAGNOSIS

In most cases, the diagnosis of oral candidosis is based on clinical signs and symptoms in conjunction with a thorough medical and dental history (4,8,28). When the clinical diagnosis is unclear, additional tests, such as exfoliative cytology, culture, or tissue biopsy, may be useful (3,8,55,56). Each additional test has specific advantages and disadvantages, and the decision about the test to be done depends on the nature of the lesion to be investigated (28).

Exfoliative cytology involves scraping the suspected lesion with a sterile metal spatula or wooden tongue blade, and smearing the sample onto a glass slide. The specimen is then air dried and fixed in alcohol (8,56). Identification of the fungal pseudohyphae within exfoliative cytologic preparations, often provided by periodic acid-Schiff (PAS) staining, is the optimal standard for the diagnosis of oral candidosis (38,56). Because Candida is a member of the endogenous flora in a high percentage of individuals, the presence of blastospores (budding yeasts) without hyphae in the absence of clinical signs and symptoms indicates the commensal status (10).

To obtain cells for culture, a sterile cotton swab is scraped over the suspected area and cultured on specific media to verify the presence of a fungal infection. Sabouraud’s dextrose agar (SDA) is usually recommended, often in combination with a second differential medium (e.g., commercial chromogenic agars) (55). Aerobic culturing on SDA at 37°C for 24-48 hours results in the formation of convex, cream colonies (3,7,55).

Biopsy is particularly useful for the diagnosis of chronic hyperplastic candidosis (56). If the lesion is clinically suggestive of chronic hyperplastic candidosis but does not respond to antifungal therapy, a biopsy should be performed to rule out the possibility of C. albicans superimposed on epithelial dysplasia, squamous cell carcinoma, leukoplakia, or lichen planus (3).

4. MANAGEMENT

Successful management of patients with oral candidosis requires identification, and where possible correction, of the underlying predisposing factors. Without this recognition, subsequent treatment using antifungal therapy may only result in the temporary relief of the infection, with inevitable relapses. Therefore, acquiring a thorough medical and dental history is an essential component of the management process (4,10,30,51,56).

Any nutritional deficiency states (iron, folate and vitamin B12), diabetes mellitus, and any immunodeficiencies should be excluded (28,51,56). Any pharmacologic agents that may contribute should be identified, and if practical, substituted for an alternative drug. Use of corticosteroid inhalers for asthma should be coupled with rinsing the mouth with water after each use (51). Instructions should be provided on appropriate oral hygiene practices.

If the correction of the underlying predisposing factor(s) is not possible, such as an underlying disease as HIV infection or immunosuppressive therapy following organ or bone marrow transplant, antifungal therapy is necessary. Antifungal drug choice is determined by several factors, including the patient’s medical history, oral symptoms, severity of infection and predicted compliance with application method (10,28). Classification of antifungal agents is based on the target of activity, and in the treatment of oral candidosis the two classes most commonly used are the polyene and azole antifungal agents.

The treatment of mild, localized oral candidosis usually consists of topical antifungal therapy. Nystatin has been the traditional drug of choice. Nystatin oral suspension (100000IU/ml) is used as a mouthrinse four times a day for approximately 2 minutes, then swallowed (10,28). Patients should avoid eating or drinking for 20 minutes after using Nystatin oral suspension. Intraoral appliances should be removed during the treatment as the medication works topically and must be in contact with the tissue (4,38,57). Oral suspension of Nystatin contains abundant sucrose, so patients with natural teeth should be advised to brush
thoroughly before each use of the agent. In order to assess the effectiveness of therapy, a follow-up appointment is usually scheduled 3 to 7 days after the beginning of antifungal treatment (10). Treatment duration varies between 7-14 days, with therapy continued at least for 2-3 days after the last clinical signs and symptoms have disappeared. Some authors have recommended that the use of antifungal agents should be continued for at least twice the time required for the resolution of clinical signs and symptoms in order to ensure that Candida levels are back at the normal level (10,12). On the other hand, Nystatin is proposed to be ineffective for candidal lesions in cancer patients (56). Also, because of its high sucrose content, it is contraindicated in the treatment of oral candidosis in patients with diabetes mellitus (4). In these cases, oral suspension of Fluconazole (5mg/ml) can be considered as another topical treatment option.

A wide variety of mouthwashes, including chlorhexidine gluconate, trichlosan and essential oils, exhibits antifungal activity (51). Studies have shown that 0.2% chlorhexidine gluconate mouth rinses present clinical benefit in the treatment of oral candidosis. However, there are reports of reduced efficacy of Nystatin when used in combination with chlorhexidine gluconate, and therefore it is often advised to delay Nystatin treatment for 30 min after the use of chlorhexidine mouthwash (4,38,51).

Failure to respond clinically to the topical therapy might be the initial sign of underlying immunosuppression arising from undiagnosed systemic diseases. In this case, the use of systemic antifungal agents may be warranted. Once-daily regimen of Fluconazole may be an excellent systemic therapeutic choice with few side effects and drug interactions (10,51). The effects of Fluconazole in the oral cavity are enhanced as it is secreted in saliva at levels equivalent to those achieved in the plasma (4,51). In the course of the systemic treatment, topical antifungal therapy may be continued as it reduces the dose and duration of the systemic treatment required (4).

In patients with denture stomatitis, in addition to the use of antifungal agents and strict oral and denture hygiene measures, the fit of the dentures should be evaluated and corrected (9,38,56,58). Recommendations would include the regular use of antimicrobial denture cleansers with antifungal properties such as the mouthwashes mentioned above, together with the removal of dentures at night (51,58). Other chemical cleaners such as alkaline peroxides, alkaline hypochlorites, acidic solutions, ethylenediaminetetraacetic acid (EDTA) may also be employed.

In summary, dental practitioners should be prepared to play a central role in the diagnosis and management of oral candidal infections. The diagnosis of oral candidosis is generally based on clinical signs and symptoms, and can be supported by additional tests such as exfoliative cytology, culture and biopsy. Management should be based on the patient’s medical history, clinical presentation and symptoms. In case of failure to respond to topical antifungal therapy, systemic antifungal therapy should be considered; and the patient should be evaluated for the presence of undiagnosed predisposing systemic diseases. Patient’s response and compliance to antifungal therapy should be monitored by follow-up appointments in order to maximize therapeutic effectiveness.

REFERENCES


