Republic of Iraq

Ministry of Higher Education & Scientific Research

Al-Iraqia University

College Of Dentistry

Treatment of Oral Thrush and Oral Ulcer

A Project Submitted

To the department of Dentistry, Al-Iraqia University in partial fulfillment of the requirements for the Degree of Bachelor in Dental Surgery (BDS).

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بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

قُلْ هَلْ يَسْتَوِي الَّذِينَ يَعْلَمُونَ وَالَّذِينَ لَا يَعْلَمُونَ

صدق الله العظيم

DEDICATION

بسم الله الرحمن الرحيم والحمد لله رب العالمين والصلاة والسلام على آخر الأنبياء والمرسلين رسول الله محمَّد وعلى آله وصحبه ومن تبعهم بإحسان إلى يوم الدين أجمعين، أمَّا بعد: فإني أحمدُ الله جلَّ وعلا على ما آتاني فضله، فقد هيأ لي كل الظروف ويسر لي إنجاز هذا العمل بفضله العظيم وكرمه العميم، فله الحمد أولاً وآخرًا على كل شيء سبحانه وتعالى

.. إلى من بلغ الرسالة وأدى الأمانة .. ونصح الأمة .. إلى نبي الرحمة ونور العالمين

.. سيدنا محمد صلى الله عليه وسلم إلى من كلله الله بالهيبة والوقار

إلى من علمني العطاء بدون انتظار .. إلى من أحمل أسمه بكل افتخار .. أرجو من الله أن يمد في عمرك لترى ثماراً قد حان قطافها بعد طول انتظار وستبقى كلماتك نجوم أهتدي بها اليوم وفي الغد وإلى الأبد ..والدي العزيز

إلى ملاكي في الحياة .. إلى معنى الحب وإلى معنى الحنان والتفاني .. إلى بسمة الحياة وسر الوجود إلى من كان دعائها سر نجاحي وحنانها بلسم جراحي إلى أغلى الحبايب أمي الحبيبة

إلى أخي ورفيق دربي وهذه الحياة بدونك لاشيء معك أكون أنا وبدونك أكون مثل أي شيء .. في نهاية مشواري أريد أن أشكر على مواقفك النبيلة إلى من تطلعت لنجاحي بنظرات الأمل أخي.

AKNOWLEDGEMENT

First and foremost, We would like to express Our utmost gratitude to **Allah** for giving Us the strength, endurance and patience to achieve this project.

I consider it an honor to work with my supervisor **Dr. Sumayah Al-Mahmood,** her guidance is greatly beneficial for us in all the time of research and writing of this project.

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INTRODUCTION

Oral candidiasis (OC), commonly referred to as “thrush” encompasses infections of the tongue and other oral mucosal sites and is characterized by fungal overgrowth and invasion of superficial tissues [1–3]. The colloquial term “thrush” refers to the resemblance of the white flecks present in some forms of candidiasis with the breast of the bird of the same name. The etymology of oral thrush dates back to the time of Hippocrates (around 400 Before Christ (BC)) who, in his book “Of the Epidemics,” described OC as “mouths affected with aphthous ulcerations” [4]. The early descriptions of the disease predated the concept of “contagion” and, therefore, as recently as the early 1900s, it was thought that the disease was of host origin.

Approximately 200 years were required before the etiological agent of thrush was correctly identified as a fungal pathogen. In 1771, Rosen von Rosenstein defined an invasive form of thrush; however, in 1839, Langenbeck was credited with first documenting a fungus associated with thrush in a patient with typhoid fever [5,6]. In 1846, Berg presented observations that thrush was caused by a fungus, which was classified in 1847 by the French mycologist, Charles Philippe Robin as Oidium albicans, the first use of albicans which means “to whiten” [6,7]. In 1923, Berkhout reclassified the fungus under the current genus Candida, a name derived from the Latin word toga candida, referring to the white toga (robe) worn by Roman senators of the ancient Roman republic, a probable reference to the whitish colonies on agar or white lesions [6–8]. However, it was not until 1954 that the binomial Candida albicans was formally endorsed. In the 1980s, there was a clear surge of interest in oral candidal infections largely due to the increased incidence of OC because of the escalation in the acquired immune deficiency syndrome (AIDS) epidemic, and, to date, OC remains the most common oral opportunistic infection in human

immunodeficiency virus (HIV)-positive individuals and in individuals with weakened immune systems [9–13]. In fact, the opportunistic nature of the infection was first highlighted by Hippocrates, who referred to this malady as “a disease of the diseased” [14].

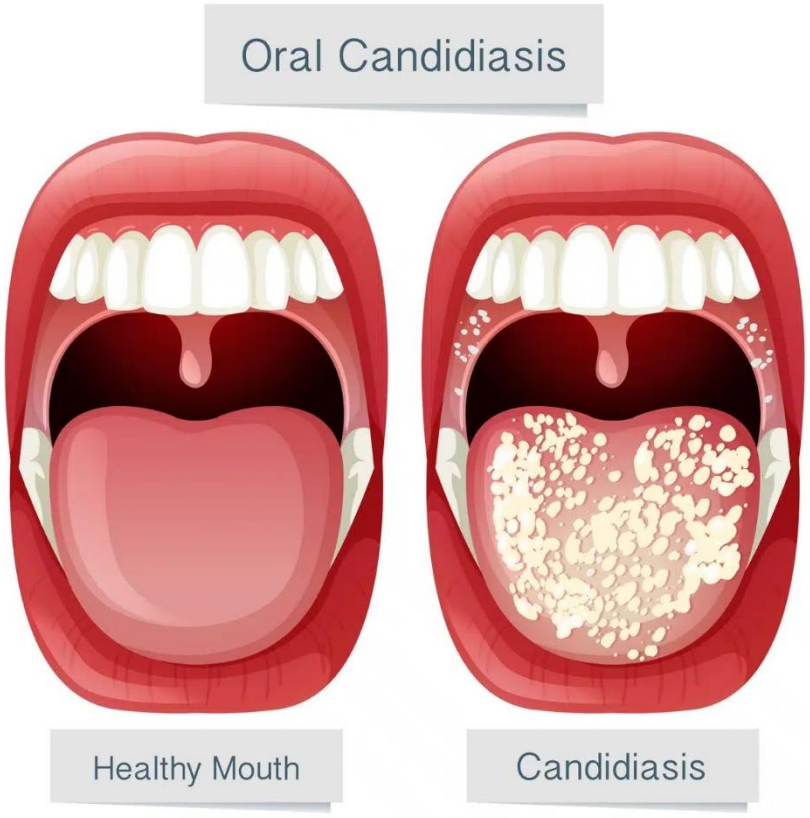


Fig. 1 Oral Candidiasis.

1. Oral Thrush

Oral candidiasis is an infection of the oral cavity by *Candida albicans*, first described in 1838 by pediatrician Francois Veilleux. The condition is generally obtained secondary to immune suppression, which can be local or systemic, including extremes of age (newborns and elderly), immunocompromising diseases such as HIV/AIDS, and chronic systemic steroid and antibiotic use.[1][2] An example of local immunosuppression is inhaled corticosteroids, often prescribed in the preventive treatment of asthma and chronic obstructive pulmonary disease.

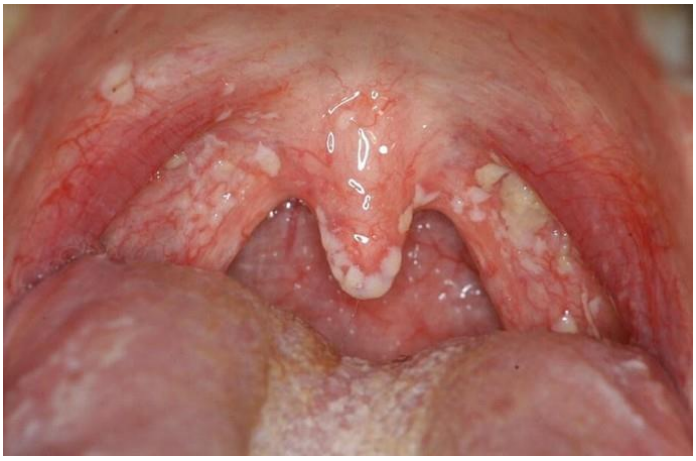


Fig. 2 Oral Thrush.

1.1. Candida albicans:

An Opportunistic Pathogen C. albicans is by far the main causative agent of OC accounting for up to 95% of cases. Although considered a pathogen, C. albicans is a ubiquitous commensal organism that commonly colonizes the oral mucosa and is readily isolated from the oral cavities of healthy individuals. In fact, up to 80% of the general population are asymptomatic carriers, and simple carriage does not predictably lead to infection [15–19]. Similar to the oral cavity, C. albicans asymptomatically colonizes the gastrointestinal tract and reproductive tract of healthy individuals where its proliferation at these various sites is controlled by the

host immune system, and other members of the microbiota [20,21]. Uniquely, C. albicans is a highly versatile commensal organism that is well adapted to its human host, and any changes in the host microenvironment that favor its proliferation provide this pathogen with the opportunity to invade virtually any site. This can manifest with superficial mucosal infections to invasive disseminated disease with involvement of multiple organs [10,14,15,22–26]. Notwithstanding, however, is the impressive repertoire of virulence factors that C. albicans possesses, enabling it to rapidly transition to a pathogen, the most notable of which are listed in Table 1 [27,28].

First and foremost, in order for Candida to cause infection, it has to be retained within the mouth. However, removal of loosely attached Candida cells from mucosal surfaces via the effects of salivary flow and swallowing is an important factor in host defense against Candida overgrowth [14]. Therefore, the ability to circumvent these removal mechanisms can be regarded as a key virulence attribute. Although, during its commensal yeast state, C. albicans reversibly adheres to oral epithelial cells through electrostatic interactions, attachment to oral epithelial surfaces is mediated by cell-wall receptors such as the agglutinin-like sequence (ALS) family of glycoproteins [15,16,29–32]. Most notable among the members of the family is the hyphal-specific adhesin Als3p, which was also shown to act as a receptor for bacterial adherence to C. albicans hyphae [33,34]. Similarly, the hyphal wall protein (Hwp1) is another major adhesin, and deletion of either ALS3 or HWP1 genes was shown to result in attenuated virulence [35,36].

Once attached to host surfaces, C. albicans can switch morphology to the invasive filamentous form which facilitates epithelial penetration [14]. In fact, core to C. albicans pathogenesis is its ability to undergo morphologic switching between yeast and hyphal forms. Yeast-to-hypha transition is triggered in response to a

variety of host environmental stimuli that activate multiple regulatory signaling pathways, eventually leading to the expression of master activators of hyphal formation [13]. The distinct morphological states of C. albicans dictate phases of colonization, growth, and dissemination, where the yeast form is associated with both initial attachment and dissemination, while the hyphal form enables C. albicans to invade host tissue [23,27]. In fact, hypha formation is associated with the expression of hypha-associated virulence factors that aid in adhesion to and invasion into host cells. One important property of hyphal cells is their ability of directional growth in response to contact with a surface (thigmotropism), allowing the fungus to specifically invade intercellular junctions [27]. In addition to active penetration which is a fungal-driven process, another complementary mechanism utilized by C. albicans for host cell invasion is endocytosis, a passive fungal-induced but host cell-driven process whereby lytic enzymes and invasins expressed on hyphae bind to and degrade E-cadherin and other inter-epithelial cell junctional proteins, enabling the organism to penetrate between epithelial cells [27].

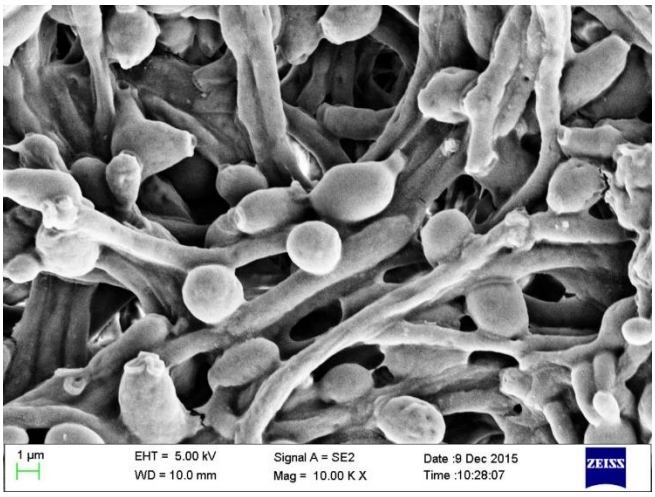


Fig.3 Candida albicans under electronic microscope

Aside from the physical effect of filamentous growth, destruction of host tissue by C. albicans is augmented by extracellular hydrolytic enzymes released by the fungus into the local environment. Most notable of the extracellularly secreted

enzymes frequently implicated in the virulence of C. albicans are secreted aspartyl proteinases (SAPs) and secreted phospholipases (PL), which are involved in host tissue invasion and nutrient acquisition [23]. Importantly, in addition to digesting and destroying cell membranes, SAPs also allow C. albicans to evade host defenses by degrading molecules of the host immune system, including antibodies and antimicrobial peptides [14]. Interestingly, recently it was discovered that hyphae-induced epithelial damage was mainly mediated through the secretion of a cytolytic peptide toxin called candidalysin, encoded by the hyphal-specific gene ECE1. The importance of this newly identified virulence factor was clearly established when C. albicans mutants were found to be incapable of inducing tissue damage, and were highly attenuated in a mouse model of oropharyngeal candidiasis.

The major biological feature of C. albicans with significant clinical implications resides in its ability to form biofilms. In fact, the majority of C. albicans infections are associated with formation of biofilms on a variety of surfaces, and the transition of C. albicans from budding yeast to a filamentous hyphal is central to its ability to form pathogenic biofilms. Biofilms are structured communities of surface-associated microbial populations embedded in an extracellular matrix which are described to have a multifaceted role. The C. albicans biofilm matrix is largely composed of the polysaccharides β-1,3-glucan, β-1,6-glucan, and mannans which form the mannan–glucan complex (MGCx). In the oral cavity, hyphae formation and adherence to oral epithelial cells and other abiotic surfaces such as dentures promotes the development of monomicrobial and polymicrobial biofilms. Once a biofilm is established, the expression of Candida virulence factors increases, and susceptibility to antimicrobials and phagocytosis decreases drastically [23].

Importantly, in addition to Candida pathogenic factors and interactions with the host immune system, it is now acknowledged that the bacterial component of the

oral microbiome plays an important role in the development and exacerbation of OC [14].

1.2. Clinical Manifestations of Oral Candidiasis

As the primary reservoir for oral Candida carriage, the tongue dorsum is the initiating point of infection for the majority of the clinical forms of oral candidiasis (OC). This includes oropharyngeal candidiasis (OPC) (Figure 1A), characterized by invasion of the epithelial cell lining of the oropharynx, which often occurs as an extension of OC. There are multiple clinical presentations and several classification systems for OC; however, the most simplistic classification encompasses oral manifestations that can generally be classified into three main broad categories, namely, (1) acute manifestations, (2) chronic manifestations, and (3) chronic mucocutaneous candidiasis syndromes. It is important to note that several clinical forms can occur in the oral cavity and in multiple oral sites at one time [67]. Additionally, although other non-albicans Candida species can cause OC, the oral manifestations are identical, irrespective of the causative species.

1.2.1. Acute Manifestations of Oral Candidiasis

1.2.1.1. Acute Pseudomembranous Candidiasis

Acute pseudomembranous candidiasis, often referred to as "thrush" usually presents as multifocal curdy yellow-white plaques throughout the oral mucosa (Figure IA,B). A diagnostic feature of this infection is that these plaques, consisting of desquamated epithelial and immune cells together with yeast and hyphae, can be removed by gentle scraping, leaving behind an underlying red erosive base (1,3,14). The diagnosis of pseudomembranous candidiasis is essentially a clinical diagnosis

based on the presence of distinctive clinical features. Alternatively, a swab from the white patches can be sent for microscopic identification of Candida or for culture to identity the Candida species present.

Although the pseudomembranous candidiasis form is common in neonates and the vast majority of cases are due to the use of inhaled steroids, there is a direct relationship with immunodeficiency. In fact, pseudomembranous candidiasis is considered the main opportunistic infection in patients with AIDS and cancer, and in patients receiving immunosuppressive therapies. In the case of AIDS, chronic and recurrent infection is frequent, which can subsequently progress to esophageal candidiasis leading to difficulties in swallowing and nutrition.

1.2.1.2. Acute Erythematous Candidiasis

Acute erythematous candidiasis is historically referred to as “antibiotic sore mouth” as it frequently occurs as a consequence of the reduction in levels of the bacterial oral microflora following broad-spectrum antibiotics which facilitates overgrowth of Candida. Cessation of antibiotic therapy restores the normal homeostatic balance of the microbial community, which subsequently resolves the infection without the need for therapeutic intervention [14]. This form of OC presents as painful reddened lesions throughout the oral cavity; lesions can either arise de novo or subsequent to shedding of the pseudomembrane from of acute pseudomembranous candidiasis [3,14].

1.2.2. Chronic Manifestations of Oral Candidiasis

1.2.2.1. Chronic Erythematous Atrophic Candidiasis

Chronic erythematous atrophic candidiasis presents similarly to the acute form and usually occurs as an extension of it. This form is also often encountered in HIV+ individuals. The most prevalent form of chronic erythematous/atrophic candidiasis is Candida-associated denture stomatitis (DS), which most commonly presents as erythema of the denture-bearing palatal mucosa (Figure 1C). DS is seen in up to 75% of denture wearers and, often, there are no clinical symptoms [23]. Inadequate denture hygiene, ill-fitting dentures, or continuous wearing of dentures (especially nocturnal use) are the main host predisposing factors to DS [74,75]. Under these conditions, coupled with the limited flow of saliva at this location, the stagnant area beneath the denture provides an ideal environment for the growth of Candida. Frictional irritation by ill-fitting dentures can damage the mucosal barrier, allowing infiltration of colonizing Candida into the tissue causing infection [15,23]. Additionally, the abiotic acrylic material acts as a chronic reservoir allowing continuous seeding of Candida onto the palatal tissue; this in turn elicits a robust local inflammatory response that clinically manifests as tissue erythema and hyperplasia [14,23]. Given the propensity of Candida to adhere to and colonize the denture, this condition is considered a classic Candida biofilm-associated infection. In fact, C. albicans is recovered more frequently from the denture surface than from the associated palatal mucosa and, therefore, clinical management is primarily focused on eradication of the biofilm formed on the denture to prevent re-colonization and relapse.

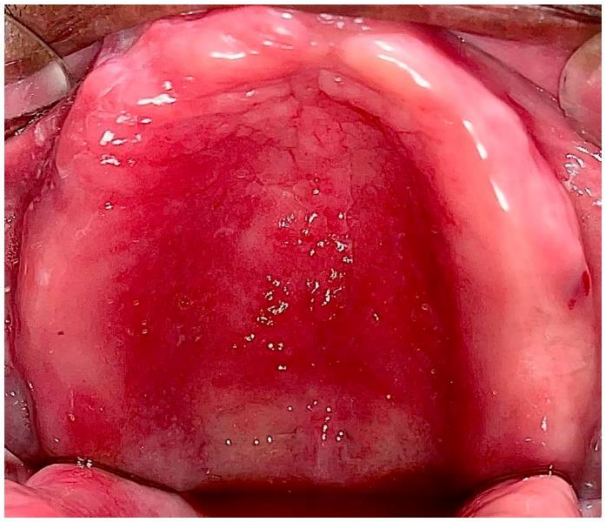


Figure 4. Chronic Erythematous Atrophic Candidiasis

1.2.2.2. Angular Cheilitis

Angular cheilitis, as the term implies, affects the angles or commissures of the mouth and presents with erythema, maceration, fissuring, crusting, or a combination thereof (Figure 1D). The presentation may be unilateral but is more often bilateral. Angular cheilitis is commonly associated with DS or another pre-existing primary form of OC where the elevated numbers of Candida in the oral cavity result in direct spread and auto-inoculation of the angles of the mouth [3,14]. Furthermore, it is not uncommon for these lesions to be co-infected with Staphylococcus aureus and, therefore, the exact role that Candida itself plays in the infection is difficult to ascertain. One important predisposing factor is the reduced vertical occlusal dimension in elderly edentulous patients, predisposing individuals to exuberant redundant folds and maceration. Importantly, angular cheilitis can be secondary to hematinic deficiencies warranting further investigation with blood tests.

1.2.2.3. Cheilocandidiasis

Cheilocandidiasis is a recently recognized form of chronic candidiasis that features crusting and ulcerations of the lips. Candida thrives in moist environments and, therefore, cheilocandidiasis occurs as a consequence of continuous applications of petrolatum-based products, chronic lip-licking, or thumb-sucking. These and other factors that promote moist environments can cause pre-existing angular cheilitis to extend into the perioral skin.

1.2.2.4. Chronic Hyperplastic Candidiasis

Chronic hyperplastic candidiasis, also referred to as candidal leukoplakia, usually arises on the anterior buccal mucosa proximal to the anterior commissures (retrocommissural area), but may also occur on the lateral tongue which is the second most common site of occurrence. Patients present with well-demarcated leukoplakias or raised fissured white plaques that cannot be removed by gentle scraping. The highest prevalence of this rare form of OC is in middle-aged male smokers. An important consideration of chronic hyperplastic candidiasis is its association with an increased risk of malignant transformation (up to 10%) to oral squamous cell carcinoma, although the exact mechanism is currently unknown.

1.2.2.5. Median Rhomboid Glossitis

Median rhomboid glossitis, also referred to as atrophic glossitis or central papillary atrophy, presents as a central elliptical or rhomboid area of atrophy and erythema of the midline posterior tongue dorsum, anterior to the circumvallate papillae [3,78]. This lesion was historically attributed to a developmental origin; however, this is unlikely as pediatric cases are seldom encountered. This condition is often associated with frequent use of steroid inhalers or tobacco smoking [14].

1.2.2.6. Chronic Mucocutaneous Candidiasis Syndromes

Chronic mucocutaneous candidiasis syndromes represent a group of several very rare heterogeneous immunologic disorders characterized by underlying immune deficiencies. Clinically, affected patients suffer from chronic and sometimes life-long persistent or recurrent mucocutaneous candidiasis involving the skin, nails, and genital mucosa; however, greater than 90% of patients present with oral involvement [80,81]. It is thought that the severity of the clinical manifestation correlates with the severity of the underlying immune defect. Many types of chronic mucocutaneous candidiasis syndromes exist that include the sporadic form, forms secondary to immunosuppressive therapies, diabetes, T-cell deficiency or HIV infection, inherited familial genetic forms, and autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) [80,81]. These patients are often refractory to standard antifungal therapies and have an increased susceptibility to developing oral squamous cell carcinoma [70,81].

1.3 Risk Factors

Oral thrush is usually the result of another medical condition or a side effect of medical treatment. It is one of the most common side effects of cancer treatment. Chemotherapy can damage the mucous membranes and weaken the immune system, allowing the fungus to spread more easily. Radiotherapy in the head and neck region also increases the risk of oral thrush. The more intensive the treatment is, the more likely oral thrush is to develop.

Dentures, diabetes and certain medications (e.g. broad-spectrum antibiotics used for several weeks at a time) can also promote the

development of oral thrush. Infections are generally more likely to occur if the body and immune system are weakened. This can happen as a result of HIV/AIDS, for instance. Oral thrush can also affect older people who require nursing care and are generally very weak overall, eat and drink very little or are fed through a tube.

Table 2. Predisposing factors to oral candidiasis.

Local Factors	Systemic Factors
• Salivary dysfunction (quantitative and qualitative reductions in saliva and diminished salivary antimicrobial factors) • Poor denture hygiene and prolonged wear • Ill-fitting dentures (mucosal trauma) • Topical corticosteroid therapy (steroid rinses or topical gels for management of oral mucosal disease, steroid inhalers) • Smoking	• Age-related immunosenescence (infants and elderly) • Broad-spectrum antibiotics (alteration in local oral flora) • Immunosuppressive therapy (systemic corticosteroids, biologic immunomodulating agents, immunosuppressive therapies) • Chemoradiation (head-and-neck cancer) • Immunocompromising conditions (thymic aplasia, hyper-immunoglobulin E (IgE)/Job's syndrome, chronic mucocutaneous candidiasis syndromes, Sjogren's syndrome, graft-versu-host disease, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), leukemia) • Nutritional deficiencies (iron, zinc, magnesium, selenium, folic acid, vitamins A, B6, B12, and C) • Endocrine dysfunction (diabetes, Addison's disease, hypothyroidism)

1.4 Treatment / Management

Treatment focuses on *Candida* species. It should be targeted to the extent of the patient's involvement and degree of immunosuppression. Topical antifungal therapy is the first-line therapy for uncomplicated cases of oral candidiasis and should continue simultaneously when systemic treatment is indicated.[4] Systemic antifungal therapy is usually reserved for patients who are refractory to topical treatment, those who are intolerant to topical therapy, and those at increased risk of developing systemic infections.[4]

Topical antifungal therapy and oral hygiene measures are usually sufficient to resolve mild oral candidiasis. Topical antifungal drugs available include nystatin, miconazole, clotrimazole, and ketoconazole.[4] The use of miconazole in the mouth is limited since it induces vomiting and diarrhea.[4] However, it is prescribed to manage angular cheilitis and denture stomatitis.[12] Nystatin is a widely used topical antifungal for treating oral candidiasis, available as pastille, mouth wash, and oral suspension.[4] Patients are indicated to rinse their mouth with topical nystatin four times daily for two weeks. Its adverse effects most commonly include nausea, vomiting, and diarrhea.[4]

Nystatin (oral rinse) and clotrimazole (troches) are high in sucrose. Therefore, triazoles - fluconazole or itraconazole – prescribed once daily can be an alternative [14] in oral candidiasis associated with diabetes mellitus or if there is a high risk of dental caries.[4]

Topical treatment is recommended for patients with a mild presentation or first presentation of the disease. One option is clotrimazole troches 10 mg orally five times daily (dissolved over 20 minutes). Another is nystatin oral suspension (100000 units/mL) 5 mL orally four times daily (swished for several minutes then

swallowed).[15][16] In the appropriate circumstances, miconazole oral gel may also be an option.[17]

For moderate to severe disease, fluconazole 200 mg orally once, then 100 mg orally once daily for 7 to 14 days, is recommended. Data regarding the safety of fluconazole during breastfeeding is reassuring.[18]

For refractory disease, options are itraconazole oral solution 200 mg once daily without food for 28 days, posaconazole suspension 400 mg orally twice daily for three days, then 400 mg orally daily for a total of 28 days, and voriconazole 200 mg orally two times daily for 28 days.

Additionally, single-dose oral fluconazole 150 mg has shown to be effective in patients with advanced cancer, thus helping reduce pill burden.[19]

Oral azoles are teratogenic and should not be used to treat mucosal candidiasis during the first trimester. Clotrimazole troches, nystatin swish and swallow topical therapies, and miconazole buccal tablets are also treatment options.

Dosing for these regimens should be adjusted according to weight for pediatric patients.

In addition to treatment, patients should receive counseling on decreasing immunosuppressing conditions such as uncontrolled diabetes mellitus, smoking, and malnutrition.

1.4.1 Management of Dentures

Denture hygiene is particularly important in treating denture stomatitis; however, it must be indicated in managing all forms of oral candidiasis to eradicate the *Candida* colonization from dentures, which acts as a reservoir.[12]

- Patients must clean and disinfect their dentures daily and remove them for at least six hours every night.[4]
- Dentures should be soaked in chlorhexidine and allowed to dry, as air also kills *Candida* adhered to dentures.[4] Hypochlorite can be used instead of chlorhexidine in dentures with no metallic components.[12]
- Dentures must be taken out every time an antifungal rinse is used and, in established cases of chronic atrophic candidiasis, soaked in chlorhexidine before placing them back in the mouth.[4]
- In denture stomatitis cases, patients should be recommended to apply topical miconazole to the dentures' internal surface and place them back in the mouth.[12]
- Mixing an antifungal agent with a denture liner is recommended for denture wearers that cannot hold antifungal rinse in their mouth for long enough.[4]
- Nystatin and chlorhexidine digluconate combination inactivates both; hence, it is contraindicated.[4]

1.4.2 Specific Considerations

Acute Pseudomembranous Candidiasis in Infants

The management of acute pseudomembranous candidiasis in breastfed infants includes topical antifungals for the infant and the mother's nipples, even if the mother does not show signs of involvement. A systemic antifungal, typically fluconazole, is prescribed to the mother in addition to topical treatment if the nipples show symptoms of thrush.[20] Nystatin oral suspension is applied to the infant's oral

lesion [21] and miconazole 2% cream to the mother's nipples. It is worth noting that miconazole 2% cream is an off-label indication to treat oral candidiasis in breastfeeding women.

Acute Erythematous Candidiasis

Most cases of acute erythematous candidiasis are secondary to antibiotic therapy; stopping the antibiotic treatment usually resolves the candidiasis without intervention.[12] Alternatively, if symptoms are more severe systemic fluconazole 50 mg once daily for one week can be indicated.[12]

Angular Cheilitis

The treatment of angular cheilitis includes antifungal and steroid creams.[4] Miconazole cream is recommended, and treatment should continue for ten more days after the complete resolution of lesions. Miconazole cream can be indicated alone or in its combined formulation with hydrocortisone.[12] Concomitant oral lesions must be simultaneously treated.[4] Dietary deficiencies must also be resolved.[4]

Staphylococci aureus reservoir is in the nostrils;[4] therefore, applying mupirocin cream to the anterior nares aids in eliminating this niche.

Chronic Hyperplastic Candidiasis

The treatment of chronic hyperplastic candidiasis includes fluconazole 50 mg daily for seven to fourteen days, depending on the extent of the lesion, and smoking cessation.[12] Patients must be aware of malignant transformation risk.[12]

In suspected cases of chronic hyperplastic candidiasis, prescribing systemic antifungal treatment for seven days before taking a biopsy has been shown to help identify true dysplasia rather than dysplasia caused by the presence of *Candida*.[12]

Linear Gingival Erythema

Debridement, chlorhexidine mouthwash, and ensuring patients receive appropriate antiretroviral treatment are included in the management of linear gingival erythema in addition to antifungal therapy.

2. Chronic oral ulcers

It is generally accepted that if the ulcer lasts for more than 2 weeks, it can be considered a chronic ulcer [4]. Acute ulcers with abrupt onset and short duration such as traumatic ulcers, recurrent aphthous stomatitis, Behcet's disease, viral infections, allergic reactions, and others are excluded from this category.

Numerous systemic drugs have been implicated as causative agents of oral ulceration [11]. Drugs reported to induce oral ulcers include beta-blockers (labetalol), immunosuppressants (mycophenolate), anticholinergic bronchodilators (tiotropium), platelet aggregation inhibitors (clopidogrel), vasodilators (nicorandil), bisphosphonates (alendronate), protease inhibitors, antibiotics, nonsteroidal anti-inflammatory drugs, antiretrovirals, antirheumatics, and antihypertensives (enalapril, captopril) [1,4,11—17]. The underlying mechanism of drug-induced oral ulceration is often unclear [1].

Oral lichen planus is by far the most common dermatological disorder to cause oral ulcers [5]. The etiology of this disease has been related to a cytotoxic T cell-mediated attack on basal keratinocytes [18,19]. However, the precise trigger for this immunological reaction is unknown. There is no evidence that clinical features of idiopathic oral lichen planus are any different from those of drug-induced diseases [20].

Pemphigus vulgaris and mucous membrane pemphigoid may result in chronic oral ulcers [4]. Pemphigus vulgaris is an immune-mediated chronic vesiculobullous mucocutaneous disease that almost invariably has oral features. Over half of the patients with pemphigus vulgaris have initial lesions in the oral mucosa [4].

Bacterial infections such as syphilis, tuberculosis, and actinomycosis may also cause oral ulcers [1,2,4,5]. Aspergillus fumigatum may cause long-standing ulcers

of the gingiva [21] or oral mucosa, as may Histoplasma capsulatum [22]. Systemic mycoses may cause oral ulcers, typically in immunosuppressed hosts [4,5].

Eosinophilic ulcer of the oral mucosa is an uncommon self-limited oral condition that mostly appears on the tongue [23]. Its etiology is uncertain; however, the possibility that trauma may play a role in its development has often been postulated. It can remain for weeks or months and heals spontaneously [4]. Therefore, once malignancy is excluded by biopsy, the better approach is to wait and see. In many instances, no treatment is necessary [23].

2.1. Candida-associated lesions of the mouth

Traditionally, classifications of oral candidiasis include acute pseudomembranous candidiasis (thrush), acute atrophic candidiasis, chronic hyperplastic candidiasis, and chronic atrophic candidiasis [24,25]. It is now generally accepted that oral candidiasis can be divided into two broad categories: primary oral candidiasis and secondary oral candidiasis (Table 1) [26,27]. Candidal infections confined to oral and perioral tissues are considered primary oral candidiasis, and disorders where oral candidiasis is a manifestation of generalized systematic candida infection are categorized as secondary [27,29]. The primary oral candidasis are subdivided into three major variants: pseudomembranous, erythematous, and hyperplastic. In addition to these well-defined candidal lesions, a group of diseases have been termed ‘‘Candida-associated lesions’’ because their etiology is multifactorial and may or may not include candidal infection or infestation [27]. These include Candida-associated denture stomatitis, angular cheilitis, median rhomboid glossitis, and linear gingival erythema [27,28]. However, in 2009 we reported chronic oral ulcers associated with Candida among frequent

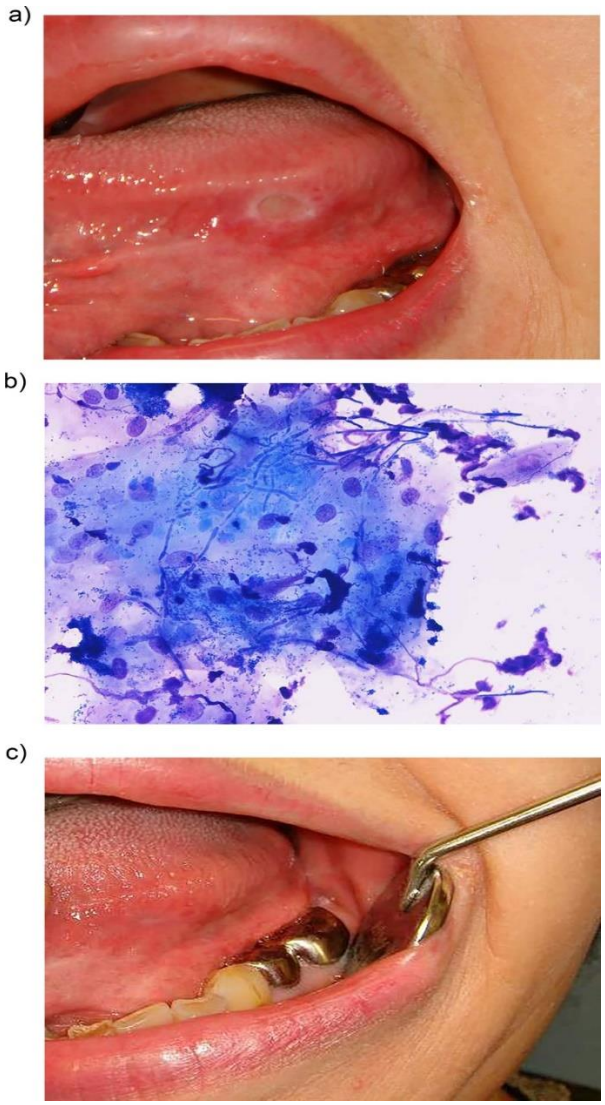
outpatients [10], and we have clinically encountered many additional identical cases since then. Therefore, we propose that this lesion should be included as a ‘‘Candida-associated lesion.’’ The details of chronic oral ulcers associated with Candida are described in the following section.

2.2. Chronic oral ulcers associated with Candida (COUC)

We previously reported chronic oral ulcers associated with Candida [10]. The summary of the study is as follows. In patients with an HIV infection, fungal diseases may cause ulceration in the oral cavity; however, there have been few studies of oral ulcerative lesions associated with Candida in patients without an HIV infection. Six patients with chronic oral ulcers of unknown origin were included in the study; these patients were referred to our department after topical steroid therapy of the lesion was ineffective. Cases of traumatic ulcers and recurrent apthous stomatitis were excluded. Blood, histopathological, culture, and direct cytological examinations were performed. Histopathological examination revealed no specific findings other than inflammatory cellular infiltration with positive hematoxylin—eosin staining in all cases. Candida spp. were isolated in four cases with a culture test, and fungal pseudohyphae were detected in four cases by direct examination. All cases were treated successfully with anti-fungal agents.

Although many oral ulcers have similar clinical appearances, their etiologies can range from reactive to neoplastic to oral manifestations of dermatological diseases. Diseases that induce erosive and ulcerative oral lesions should be considered in the differential diagnosis of chronic ulcers, including chronic ulcerative stomatitis, erosive lichen planus, pemphigus vulgaris, cicatricial pemphigoid, linear IgA bullous dermatosis, bullous lupus erythematosus, and

desquamative gingivitis [30]. To diagnose COUC, we excluded these erosive and ulcerative lesions by histopathological and blood examinations. Neoplasm and viral infection were excluded on the basis of the clinical features and findings of histopathological and blood examinations. COUC presented with distinct clinical features and a usually single, nonindurated ulcer that showed no response to topical steroid and/or anti-traumatic therapy, persistent or chronic (Figs. 5, 6). Hence, COUC is different from recurrent apthous stomatitis, which recurs at intervals of a few days to up to 2—3 months and is usually treated with topical steroids. The clinical features of oral ulcers in our study can be summarized as follows: (i) the lesion had a sharply demarcated margin without induration, (ii) it was single and static despite the long disease duration, (iii) all the lesions had been clinically diagnosed as recurrent apthous stomatitis or traumatic ulcer, and (iv) histopathological examination with hematoxylin-eosin staining of biopsy specimens showed no specific findings.



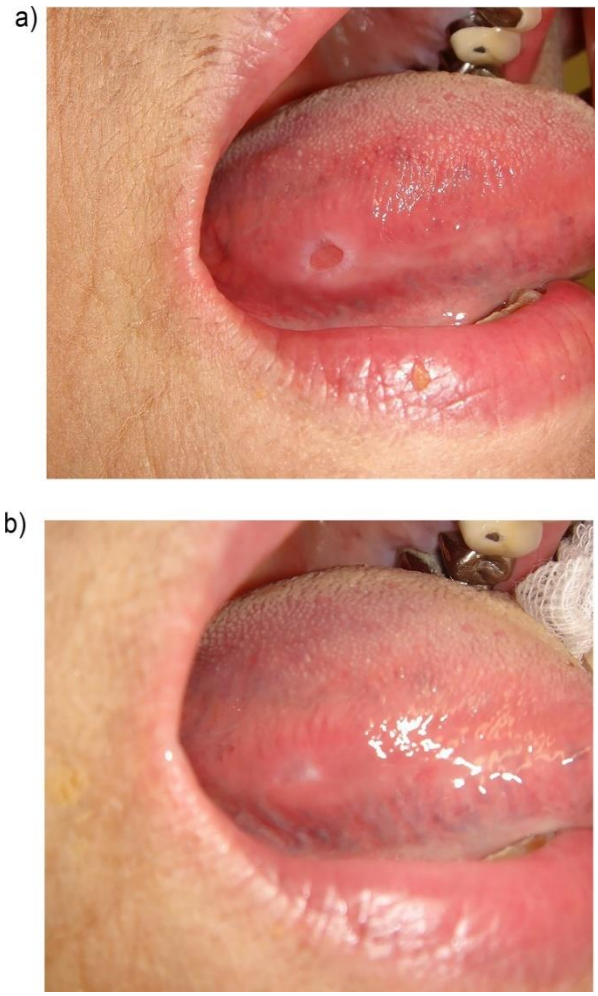


Figure 5. Chronic oral ulcers associated with Candida (COUC) in the left border of the tongue. a: Tongue ulcer of a 3-month duration with complaint of tongue pain while eating. b: Fungal pseudohyphae revealed in the ulcer margin by quick cytological staining [10]. c: The ulcer disappeared after 2 weeks of anti-fungal treatment.

Figure 6. Chronic oral ulcers associated with Candida (COUC) on the right border of the tongue. a: Tongue ulcer of a 2-month duration with complaint of tongue pain while eating. b: The ulcer disappeared after 2 weeks of anti-fungal treatment. However, results of cytological and mycological examinations were negative for candidiasis.

However, there have been few studies of oral ulcerative lesions associated with Candida other than studies of patients with an HIV infection [6,8]. It has been reported that the most common mycoses in the oral cavity are candidasis, which typically cause non-ulcerous lesions [4], or Candida species, usually Candida albicans, which is the most common fungal infection of the mouth but rarely causes oral ulcers [5]. These are opposite opinions to our proposal. The cause of this difference may be the difficulty of detection of Candida in COUC. Approximately one third false-negative results were obtained when testing oral candidasis such as COUC and oral atrophic candidiasis, despite performing mycological, cytological, and histopathological examinations [10,31]. However, favorable outcomes from anti-fungal treatment suggested that Candida was involved as an etiological agent in these lesions because the ulcers resolved dramatically with only anti-fungal treatment. Furthermore, we encountered COUC among our frequent outpatients without an HIV infection. The clinical features of this lesion and outcomes of anti-fungal treatment suggest that it should be included as a ‘‘Candida-associated lesion.’’

2.3. Candida infection of the primary mucosal lesion (secondary candidiasis)

Occasionally, we encounter Candida infection such as oral lichen planus after topical steroid treatment of the primary oral mucosal lesion. These secondary candidasis have been reported in some patients with oral lichen planus being treated with steroids [32,33]. Generally, Candida species have been identified in oral lichen planus lesions with or without topical steroid treatment. Culture studies have demonstrated Candida infection in 37%—50% of cases of oral lichen planus [34—

36]. However, biopsy studies of lichen planus showed a lower frequency of Candida infection than culture studies. Holmstrup and Dabelsteen [37] reported that only one biopsy specimen had Candida invasion in the 43 biopsies of oral lichen planus lesions. Concurrent with the aforementioned findings, it is very difficult to identify Candida with a biopsy and/or direct examination of Candidaassociated lesions.

In the classification of oral candidiasis, secondary candidiasis is usually accepted as an oral manifestation of systemic mucocutaneous candidiasis [27] or systemic candidiasis with secondary involvement of the oral cavity [28]. However, here, secondary candidiasis indicates Candida infection of the primary oral mucosal lesion with or without topical steroids.

3. Conclusions

Generally, the diagnosis of oral candidiasis is based on clinical features and symptoms in conjunction with a thorough medical history. Provisional diagnoses are often confirmed through further histopathological and mycological examinations. A number of methods for the detection of Candida have been developed. Such methods include a swab, imprint culture, collection of whole saliva, oral rinse sample, and incisional biopsy [38]. Each sampling method has individual advantages and disadvantages, and the choice of technique is governed by the nature of the lesion to be investigated [39].

In pseudomembranous candidiasis, the presence of Candida hyphae can be confirmed with periodic acid-Schiff (PAS) staining of a cytology smear of the pseudomembrane, allowing a quick and accurate diagnosis. However, in other oral candidal lesions, cytological smears usually fail to show any hyphal elements [39,40]. We fully agree with this idea, because our previously reported cases highlighted the low detectable rate of Candida pseudohyphae by direct examinations and culture tests [10,31].

Therefore, it is recommended that Candida involvement be considered in diagnosis of a certain chronic oral ulcer, that remains of unknown origin even if some examinations have been performed (Fig. 5). In drug-induced oral ulcers, histopathological examination usually reveals non-specific ulcer formation with marked infiltration of inflammatory cells [41]. Therefore, careful medical review of a patient's medications is very important in such cases.

When drug-induced oral ulcerations are suspected after careful clinical observation and review of medications, the prescribing doctor should be contacted to discuss the possibility of an alternative medication or a dose reduction [41]. When

oral ulcers show typical clinical findings, differential diagnosis may be easy. However, the exact diagnosis is difficult in most cases. Although the most important principle for dealing with mucosal lesions in the mouth is constant observation for malignancy, clinicians should also consider Candida association in chronic and static lesions, even among frequent outpatients. Further COUC cases are required for further investigation.

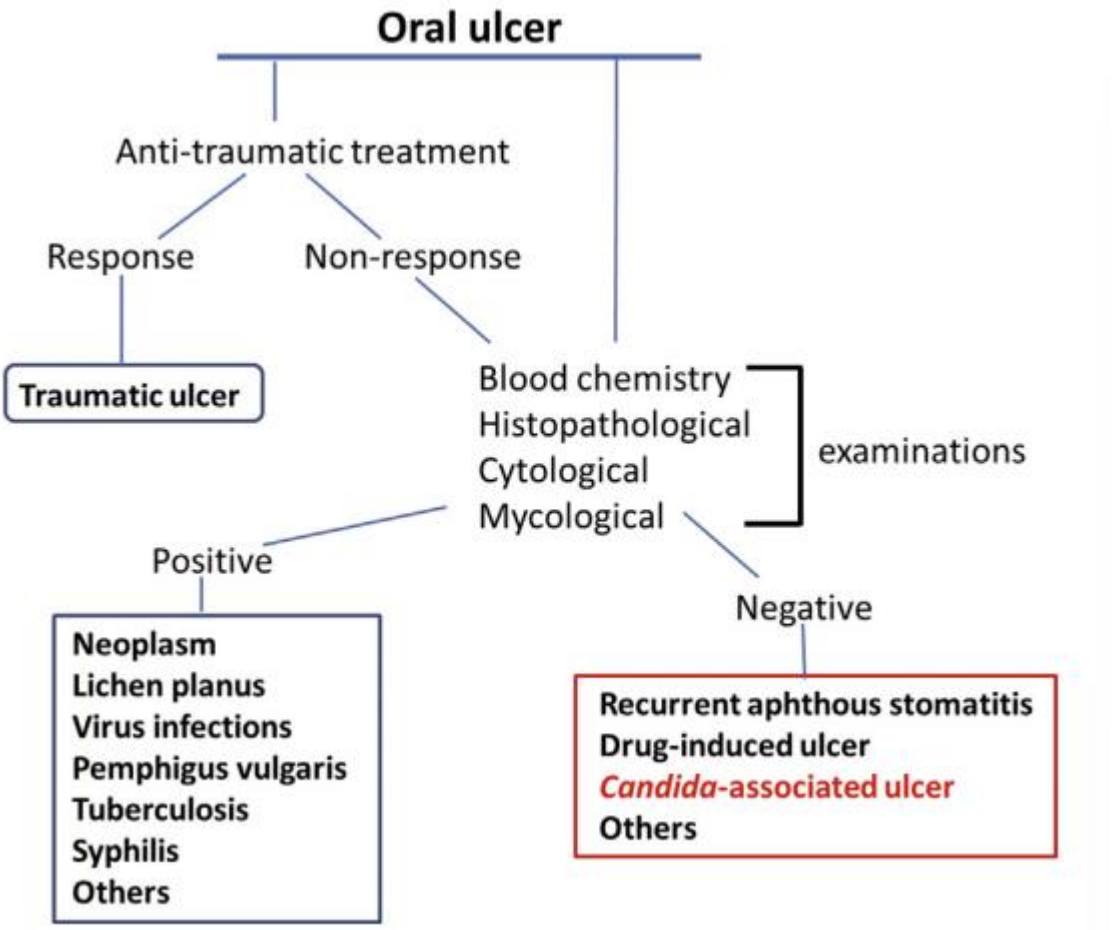


Figure 7. Diagnostic sequence of an oral ulcer.

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