

Treatment of Oral Thrush and Oral Ulcer

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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.
- 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”.
- 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.

Oral Candidiasis



Healthy Mouth



Candidiasis

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.
- An example of local immunosuppression is inhaled corticosteroids, often prescribed in the preventive treatment of asthma and chronic obstructive pulmonary disease.
- *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.
- Similar to the oral cavity, *C. albicans* asymptotically 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

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.

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
<ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• 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)

Chronic oral ulcers

- It is generally accepted that if the ulcer lasts for more than 2 weeks, it can be considered a chronic ulcer.
- 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. 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).
- The underlying mechanism of drug-induced oral ulceration is often unclear.

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- **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 . 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.**
 - **Pemphigus vulgaris and mucous membrane pemphigoid may result in chronic oral ulcers. 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.**
 - **Bacterial infections such as syphilis, tuberculosis, and actinomycosis may also cause oral ulcers. Aspergillus fumigatus may cause long-standing ulcers of the gingiva or oral mucosa, as may Histoplasma capsulatum. Systemic mycoses may cause oral ulcers, typically in immunosuppressed hosts.**

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- **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.**

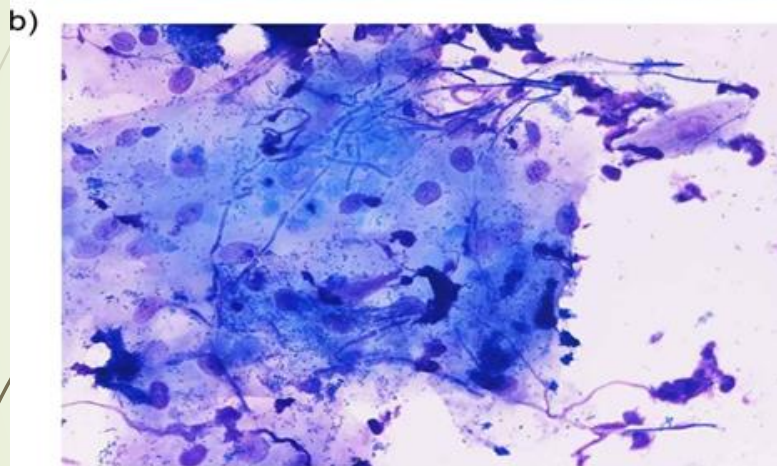




Figure 1. Chronic oral ulcers associated with Candida (COUC) in the left border of the tongue. a: Tongue ulcer of a 3-month duration with complaint of tongue pain while eating. b: Fungal pseudohyphae revealed in the ulcer margin by quick cytological staining [10]. c: The ulcer disappeared after 2 weeks of anti-fungal treatment.

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. 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.**
- ▶ **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. The use of miconazole in the mouth is limited since it induces vomiting and diarrhea. However, it is prescribed to manage angular cheilitis and denture stomatitis. Nystatin is a widely used topical antifungal for treating oral candidiasis, available as pastille, mouth wash, and oral suspension. 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.**

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- ▶ **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.**
 - ▶ **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.**
 - ▶ **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.**

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- 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.

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.

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. Each sampling method has individual advantages and disadvantages, and the choice of technique is governed by the nature of the lesion to be investigated.**

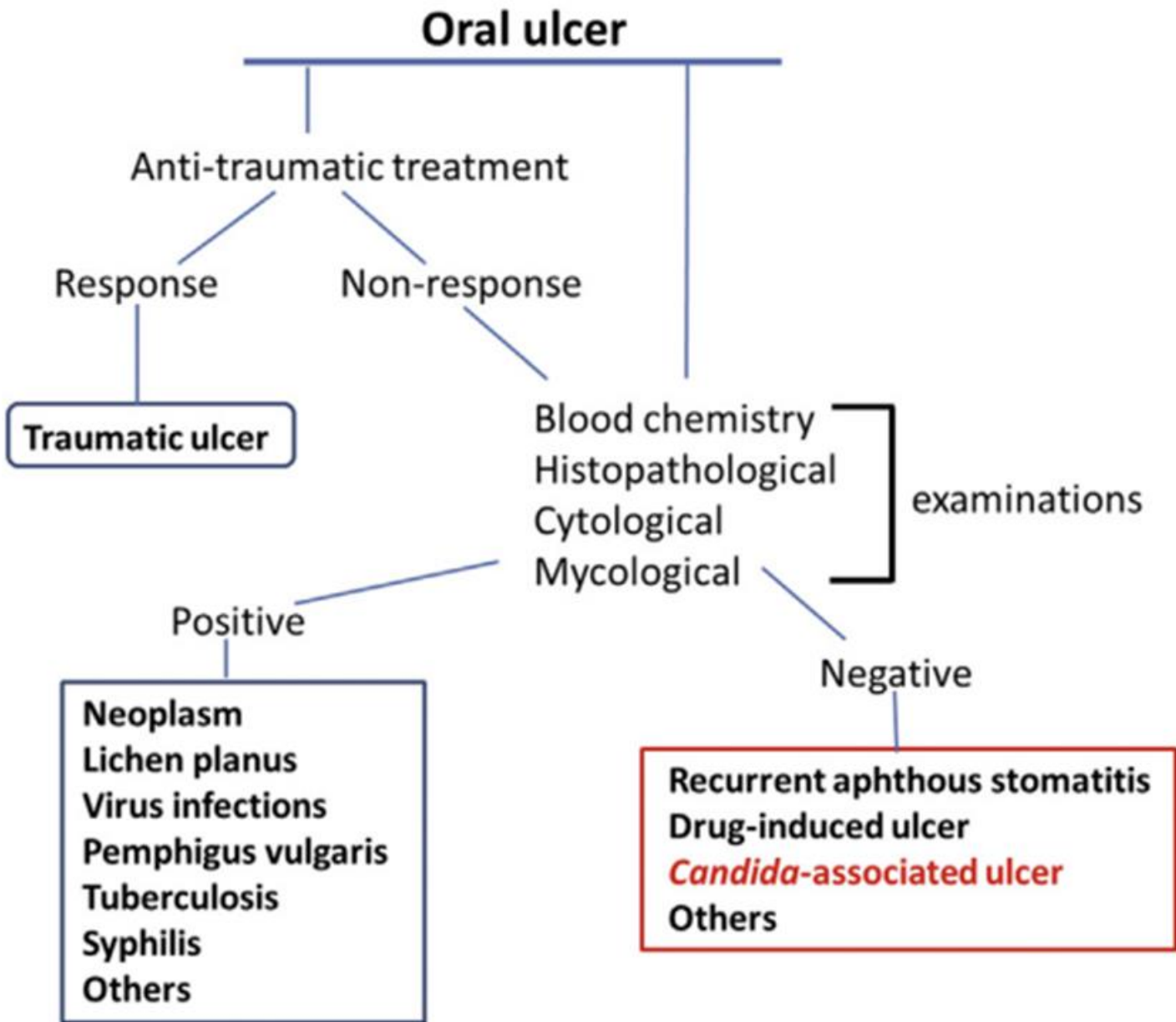


Figure 2. Diagnostic sequence of an oral ulcer.



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