

## ORAL CANDIDOSIS

### Definition

Oral candidosis and oral candidiasis are synonymous.

Oral candidosis is the most common oral fungal infection in man and it is caused by different *Candida* species, usually *C.albicans*.

*Candida* is a yeast, which is an obligate organism in humans and a normal constituent of the digestive and vaginal tracts.

*Candida* species are opportunistic pathogens, which may cause disease mostly when there are changes in oral ecology or when the host defenses have been compromised, hence the epithet "candidosis is the disease of the diseased".

Oral candidosis, in the form of thrush (whitish, semi-adherent membranes), has been known since ancient times (Hippocrates, 600BC), as a disease mostly affecting infants and debilitated individuals. During the last three decades, candidosis reemerged as an important disease with the introduction of broad-spectrum antibiotics, organ and bone marrow transplantation, immunosuppressive therapies, and the pandemic of human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS). Oral candidosis is the earliest and most common manifestation of HIV-infection.

### Epidemiology

*Candida* species reside in the oral cavities of a majority of healthy individuals as commensal organisms, with a colonization prevalence ranging between 30% to 40%. Oral *Candida* carriage increases, up to 75%, in immunocompromised and immunosuppressed individuals, in HIV-infected patients, in patients receiving anticancer chemotherapy and in head and neck cancer patients receiving radiotherapy.

*Candida albicans* accounts for 70% to 95% of the oral isolates, from smears taken from either healthy individuals or from lesions of clinical infection. *Candida tropicalis*, *Candida krusei*, *Candida glabrata*, *Candida parapsilosis*, *Candida guilliermondii*, *Candida famata* and *Candida dubliniensis* are less commonly isolated species. An epidemiological shift of *Candida*, with a change from single to multiple *Candida* species isolates has recently been reported in several groups of patients, with an incidence ranging from 7% to 29%.

The dorsum of the tongue is the primary oral reservoir, which may, at least partially, explain why the dorsum of the tongue is a major location of different forms of oral candidosis.

In HIV subjects, oral candidosis is the most frequent HIV-related oral lesion, affecting about half of the HIV-infected patients who do not receive antiretroviral therapy. In head and neck cancer patients treated with radiotherapy, oral candidosis will develop in at least one out of three patients.

### **Clinical presentation**

Oral candidosis may present with a variety of clinical patterns or forms. We can consider: acute forms (erythematous, pseudomembranous), chronic forms (erythematous, pseudomembranous, hyperplastic), candida-associated lesions (angular cheilitis, denture-related stomatitis, median rhomboid glossitis), and oral manifestations of systemic mucocutaneous candidosis.

Some patients may exhibit more than one clinical form of candidosis and in more than one oral site, thus presenting with multifocal candidosis. Oral candidosis is, in most cases, endogenous and most often remain superficial and localized in the oral mucosa. Regional extension and systemic or deep-seated candidosis may occur, but it is relatively uncommon.

Erythematous candidosis (*atrophic*) is the most common type. Before the era of AIDS, it was most commonly seen after the use of antibiotics. This acute painful lesion is characterized by a diffuse loss of the filiform papillae of the dorsum of the tongue, which appears red (Figure 1). Erythematous candidosis in HIV disease appears as asymptomatic red areas or patches usually located on the dorsum of the tongue and the hard palate (Figure 2). The patient may seek consultation because of dysgeusia or xerostomia.

Pseudomembranous candidosis (*thrush*) appears as semi-adherent, whitish or yellowish, soft, drop-like or confluent membranes or plaques, which resemble curdled milk (Figure 3). These pseudomembranes can be wiped off, and reveal a red underlying mucosa. Any mucosal surface may be affected. The pseudomembranes consist, mainly, of tangled masses of candidal pseudohyphae, with budding yeast cells (Figure 4), desquamated epithelial cells, and debris. Patient may complain of a burning sensation, xerostomia, dysgeusia or anorexia (loss of appetite).

Pseudomembranous candidosis is rarely painful.

Angular cheilitis (*perleche*) of candidal aetiology presents as red fissures radiating from the commissures of the mouth, sometimes covered by dry, crusting membranes (Figure 5). The scaling and fissuring may extend on the vermilion border, thus, presenting similar to exfoliative cheilitis. Angular cheilitis in general, is bilateral, and may develop alone or with other forms of candidosis.

Chronic hyperplastic candidosis is a rare form of candidosis presenting as white plaque, infiltrated by *Candida* hyphae. This lesion should heal after antifungal treatment. Oral hyperplastic candidosis may also be seen in association with immunologic or endocrine abnormalities.

Some cases of median rhomboid glossitis, denture stomatitis and linear gingival erythema may be associated with candidal infection. These cases will respond and heal after antifungal treatment.

Several other oral mucosal diseases, such as lichen planus, may be secondarily infected by *Candida* organisms, increasing the severity of the disease.

*Candida* may, also, secondarily infect cases of oral leukoplakia, increasing the risk for malignant change.

### **Aetiopathogenesis**

As the term “candidosis” implies, the cause of the disease, is the yeast *Candida*. *Candida* species may cause an “opportunistic” infection, under certain predisposing host factors. Local and systemic host factors often co-exist and act in a synergistic fashion.

Virulent yeast-related factors play a role in the development of disease, too.

#### Local host factors

- Loss of integrity of the oral mucosa.
- Thin or ulcerated epithelium, resulting from an ill-fitting denture, or after anticancer chemotherapy or head and neck radiotherapy, ect., allows for *Candida* to adhere on the epithelial cells, penetrate the mucosa, and cause infection.
- Heavy smoking, non-specific leukoplakia and other oral mucosal diseases make oral mucosa prone to the development of candidal infections.
- Xerostomia result in decreased flushing action and in reduced antifungal components of saliva, thus enhancing the development of candidosis.
- Local corticosteroids, via local immunosuppression, also promote oral candidosis.

#### Systemic host factors

- Immunodeficiency and immunosuppression are important host factors, especially in view of the increasing numbers of patients with acquired immune deficiency syndrome/AIDS and of individuals who receive corticosteroid or immunosuppressive or cytotoxic treatment (organ and bone marrow

transplant recipients, patients with malignant disease, patients with autoimmune disorders).

- Broad spectrum antibiotics may enhance the development of candidosis mainly by locally disturbing oral ecology.
- Dietary factors, such as poor nutrition, iron and vitamin deficiencies locally alter the integrity of the oral mucosa, promoting the development of candidosis.
- Endocrine disorders, such as diabetes mellitus, haematologic dyscrasias, malignant diseases, age (neonatal, elderly) also enhance candidosis.

### **Diagnosis**

A presumptive diagnosis can be made on the basis of the different clinical forms of candidosis. Thus, a good knowledge of the clinical forms of the infection is the first important step.

The definitive diagnosis of candidosis is established by the clinical signs, in conjunction with positive direct microscopic findings or culture, while positive response of the lesion to antifungal therapy, which is the principal defining criterion, is necessary to confirm the diagnosis. No definitive colony count has been established that allows for differentiation between commensalisms and disease. Therefore, a positive culture in the absence of signs and symptoms does not necessarily imply candidal disease.

The differential diagnosis, in the case of erythematous candidosis, will mainly include the geographic tongue and atrophy/erythema due to iron or B<sub>12</sub> deficiency anemias. In the case of candidosis during chemo- and/or radio- therapy, the infection has to be differentiated from chemo- and radiation-induced mucositis. Again, healing of the lesion following antifungal treatment is the principal differentiating/defining criterion. *Candida* organisms penetrate the epithelium, causing inflammation, with oedema and polymorphonuclear leukocyte aggregation (microabscess formation). Hence, exfoliative cytologic examination or smear taken by rubbing a sterile cotton swab over the lesion will reveal, upon direct microscopic observation, *Candida* hyphae, blastospores, epithelial cells, and polymorphonuclear leukocytes. Hyphae and blastospores may be demonstrated with potassium hydroxide, periodic acid Schiff or Gram's stain.

Apart from smear and cytology, several other laboratory techniques may be also used such as imprint culture, impression culture, salivary culture, oral rinse technique.

Culture of the clinical material will define the pathogenic *Candida* species. The identification of the different *Candida* species depends on a combination of morphological and physiological characteristics.

The serodiagnosis of *Candida* infection is important in systemic candidosis.

### **Treatment**

The management of patients with oral candidosis involves the identification and elimination of predisposing factors, as discussed above (see pathogenesis), and the use of antifungal medications. If the predisposing factor can not be eliminated or treated, candidosis is likely to recur.

At present, the aim of antifungal treatment is the healing of the clinical infection. The time required to achieve healing of the clinical infection is usually one to two weeks. Eradication of the yeast (mycological cure) from the oral cavity of a carrier is difficult to achieve or it may not be possible, as in AIDS patients or in head and neck cancer patients after radiotherapy. Even after total eradication of the yeast from the oral cavity, recolonization from the gastrointestinal tract or the vagina may occur.

Several antifungal agents are available for topical or systemic use, depending on the form and the extent of the infection, the *Candida* species isolated and, most importantly, the condition of the host and the underlying pathology.

Nystatin (formulated as suspension and pastille) was the first effective antifungal drug, for topical use. It is not absorbed across the gastrointestinal tract. Due to its sucrose content, it is not indicated in xerostomia-related, caries-prone individuals. Amphotericin B (as suspension and lozenge), clotrimazole (as troche), and miconazole (as gel) are also useful for topical treatment. Miconazole is also effective against staphylococcal infections, hence, miconazole oral gel is best for the treatment of angular cheilitis.

Ketoconazole (as tablets) due to its potential liver toxicity, is not introduced as initial therapy. Fluconazole and itraconazole are triazole agents, formulated as capsules and suspension, and for both topical and systemic use. Fluconazole, also available for intravenous administration, is excellently absorbed across the gastrointestinal tract. Acidic environment is not required, while liver toxicity is rare at the therapeutic doses used.

Voriconazole, for per os or intravenous administration, is an azole sustained for deep-seated cases of candidosis. Posaconazole suspension is another triazole antifungal agent, under investigation against invasive fungal infections. Caspofungin (echinocandin) is another fungostatic agent against invasive fungal infections

## **Prognosis and complication**

In most cases, oral candidosis has a good prognosis. Infection usually clears readily, after one or two weeks of antifungal treatment, especially when an early diagnosis has been achieved and the predisposing factor has been eliminated.

Recurrences may occur in patients at risk, with continuing presence of the predisposing factor.

In some patients, oesophageal candidosis may arise. Oral candidosis may be the first sign of oesophageal candidosis in AIDS patients. Candidosis may also develop and complicate head and neck radiotherapy or systemic cancer chemotherapy, causing diagnostic and therapeutic difficulties, since it is superimposed on radiation- and chemotherapy-induced mucositis. Prompt diagnosis and early treatment of oral candidosis has been found to significantly reduce the incidence of oesophageal candidosis.

In susceptible, immunocompromised and immunodeficient individuals, oral candidosis may extend regionally, while haematogenous, invasive hepatosplenic and other organ candidosis may occur as a life-threatening infection. Haematogenous candidosis is one of the most common nosocomial blood-stream infections with a high mortality rate. Prompt diagnosis and early treatment of oral candidosis has been found to significantly reduce the incidence of systemic candidosis.

Oral candidosis or increased numbers of *Candida* organisms may complicate and aggravate oral lichen planus and other autoimmune disorders of the oral mucosa. Antifungal medication is recommended, by some authors, in oral *Candida* carriers with symptomatic lichen planus, either before or concurrently with corticosteroid medication.

*Candida* organisms may penetrate the epithelium of non-specific leukoplakia and candidosis may be superimposed on leukoplakia. Increased risk for dysplastic changes of leukoplakia has been attributed to the penetration by *Candida* organisms. Antifungal therapy may modify the clinical presentation of leukoplakia from non-homogeneous to homogeneous.

An important complication that has to be taken into consideration, in cases of persistent candidosis which require prolonged antifungal treatment, is the potential development of *Candida* strains resistant to antifungals.

## **Prevention**

Identifying and correcting local or systemic predisposing factors, whenever possible, is the first step for the prevention of oral candidosis. Good oral hygiene, prosthetic rehabilitation and elimination of local irritants are essential.

However, specific groups of patients are particularly susceptible to the development of oral candidosis include:

Patients who receive topical or systemic corticosteroid or immunosuppressive treatment. These patients should be closely followed. Some authors have suggested the administration of antifungal prophylaxis, in oral *Candida* carriers, concurrently with the immunosuppressive medication, to prevent the potential development of oral candidosis.

HIV infected/AIDS patients, with CD4+ T lymphocyte counts below 200 cells/ $\mu$ L, who are not receiving a successful antiretroviral therapy. These patients are also at increased risk for oral candidosis, with potential regional extension and systemic dissemination. Antifungal prophylaxis may be needed to prevent candidosis in these patients.

Neutropenic patients or patients at risk for neutropenia, such as patients with leukaemia or other malignant haematological disease or solid cancer, who undergo chemotherapy or haematopoietic stem cell transplantation (bone marrow transplantation), are at increased risk for oral and oropharyngeal candidosis. In these patients, the oral cavity can serve as a site of colonization and infection, from which systemic candidosis may follow, causing significant morbidity and mortality. In leukaemic patients, who undergo transplantation, invasive fungal infection, mostly candidosis, may account for as many as 30% of deaths. Fluconazole prophylaxis has been found superior than oral polyenes and is recommended, being widely used to prevent candidosis in the above group of patients. Itraconazole oral solution has also been found to successfully prevent systemic fungal infections in children undergoing bone marrow transplantation and in adults with hematological malignancies.

Head and neck cancer patients who receive radiotherapy. At least one out of three of these patients are anticipated to develop oral candidosis, which will be superimposed on oral radiation-induced erythema and ulcerative/pseudomembranous mucositis. Oral candidosis, in those cases, will add to patients' discomfort during radiotherapy, while it will cause diagnostic and therapeutic problems, leading, at times, to unnecessary treatments.

The administration of antifungal prophylaxis to prevent oral candidosis during radiotherapy is under investigation. Preliminary results, with small numbers of study patients, have indicated that fluconazole prophylaxis may be of benefit.

The development of resistant *Candida* strains has to be taken into account in all antifungal prophylactic interventions.



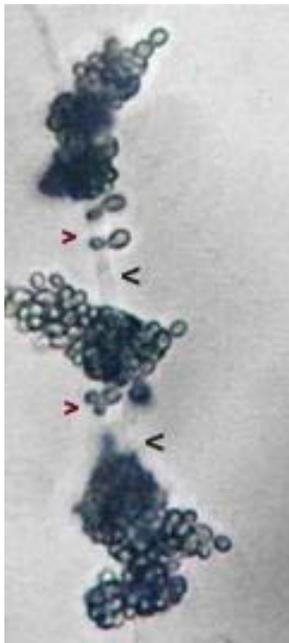
**Figure 1.** Acute, painful erythematous candidosis on the tongue of a 63 year-old female, after antibiotics.



**Figure 2.** Erythematous candidosis on the palate of a 7 year-old girl, with vertical HIV transmission. Red patches can be observed. Candidal lesions (angular cheilitis) are also seen at the commissures.



**Figure 3** Pseudomembranous candidosis on the palate of a 26 year-old male with AIDS. Whitish, semi-adherent membranes and plaques, resembling curdled milk, can be observed.



**Figure 4.** Microscopic morphology of *Candida albicans* pseudohyphae (black arrows) bearing clusters of single and budding yeast cells (red arrows) stained with lactophenol cotton blue. Microphotography with Nikon Eclipse 800. Courtesy of A. Velegaki, Mycology Reference laboratory, Medical School, University of Athens, Greece.



**Figure 5.** Angular cheilitis and erythematous candidosis on the tongue of a 69 year-old male. Patient wore dentures. Red fissures radiate from both comissures, while a red patch can be seen on the dorsum of the tongue.

### **Further reading**

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### **Links**

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