

# Candida in Oral and Maxillo-facial Pathology: Clinical Findings and Risk Factors

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## ABSTRACT

**Background:** *Candida*, and especially *Candida albicans*, colonizes the oral mucosa and becomes invasive when the immune system weakens. Therefore, frequently, oral and maxillo-facial pathology can be associated with *Candida*. **Objective:** The qualitative and quantitative assessment of *Candida* colonization of the oral cavity in patients with oro-maxillo-facial conditions; to establish an association between the different contributing factors and colonization. **Material and methods:** Samples were collected from 70 patients hospitalized in the Clinic of Oral and Maxillo-Facial Surgery, by rinsing the mouth with sterile saline; historical data were also collected. The samples were analyzed at the Microbiology Laboratory of the University of Medicine and Pharmacy of Tîrgu Mureş, using Sabouraud agar medium. For each isolate, the antifungigram for Fluconazole and Voriconazole was performed following the CLSI standards. **Results:** From the 70 samples 45.7% were positive for 11 different yeast species. Regarding predisposing factors, most importantly, smoking was significantly associated with *Candida* colonization (OR = 2.34; 95% CI = 1.42–3.84; p <0.05). Other factors, such as radiotherapy, oral hygiene or antibiotics, are related, but not statistically significant in our study. *Candida albicans* was the predominant species (38.8%). The testing of *Candida albicans* and non-albicans to Fluconazole showed an increased resistance (52.4%) in both cases, while the resistance to Voriconazole was 50% and 12.5%, respectively. **Conclusions:** Colonization of the oral cavity with *Candida* is present in about half of the patients with OMF conditions, and this is probably not only due to classical predisposing factors, but also due to chronic oral pathology and to several risk factors like smoking or radiotherapy.

**Keywords:** *Candida*, colonization, factors, oral

## INTRODUCTION

Oral candidiasis is a frequent medical condition that occurs in patients undergoing antibiotic or immunosuppressive treatment, chemo- or radiotherapy, due to the weakened immune system.<sup>1</sup>

Although there are a series of studies or articles that provide information regarding the manifesting disease, there are rather few data about the colonization

of the oral mucosa and/or skin with fungi and its arising risks.<sup>2</sup> Indeed, the literature incriminates *Candida albicans* as the most frequently isolated yeast in lesions, but the attention must also be focused on the other yeasts species (e.g. *C. krusei*, *C. glabrata*, *C. tropicalis*), which gain more ground and rapidly develop resistance to the usual antifungal drugs; on one hand, this is mostly due to the lack of targeted therapy, but also because these yeasts encounter a susceptible host, weakened by the previous bacterial or fungal infections or several non-infectious conditions.<sup>3</sup>

Yeast infections that affect the human organism are caused especially by *Candida* spp. Oral candidiasis in particular is caused mostly by *Candida albicans*, *Candida glabrata* or *Candida tropicalis*.<sup>3</sup>

Although *Candida albicans* is a commensal yeast present in 10–60% of the population, when encountering favorable conditions, it colonizes in a large number the oral mucosa and skin and becomes pathogenic, causing acute, chronic or even associated mucous-cutaneous infections.<sup>4</sup>

Local and general factors of the host organism will initiate and sustain *Candida* adhesion and multiplication. The risk factors involved in the appearance of oral candidiasis are divided into three categories: 1) related to the host organism: endocrinopathies (diabetes mellitus, hypoparathyroidism, Addison disease) or associated disorders (hematological conditions, use of immunosuppressive drugs, cancer); 2) iatrogenic factors (antibiotics that can act in three different ways: direct stimulation of pathogenic yeast growth, inhibition of the antimicrobial flora of the organism, and breaking the balance between mucous-cutaneous and intestinal biogenesis); 3) factors related to the living environment (lack of oral hygiene, alcohol consumption, smoking).<sup>5</sup>

The acute forms of oral candidiasis are pseudomembranous and atrophic. The first is characterized by white-yellow deposits comparable with “curd”. These can be easily removed by wiping the oral mucosa with a sterile swab, leaving a congested, erythematous mucosa behind. The second acute manifestation of candidiasis is represented by the atrophic form, dominated by erythematous lesions.<sup>5</sup>

Chronic candidiasis is represented by angular cheilitis that affects oral commissures, atrophic candidiasis, or rhombic median glossitis. Hyperplastic candidiasis is also framed in this category. The particularity of this form of yeast infection is that once entered in the oral mucosa, it cannot be swabbed off. The most common areas affected are the retrocommissurae, hard palate and the posterior one third of the dorsal mucosa of the tongue.<sup>4</sup>

In case of a severely compromised organism, a relatively rare form of chronic generalized candidiasis develops, the mucous-cutaneous candidiasis.<sup>4</sup>

Even in the absence of the described lesions, the asymptomatic carriage represents an increased risk of complications, in case the immune system of the host weakens. Studies showed that the clinical changes appear only in chronic carriers of *Candida albicans*.<sup>2</sup>

Furthermore, for immune-depressed patients, for example after radiotherapy or in systemic diseases such as HIV infection, due to the high risk of complications given by the high percentage of oral *Candida albicans* colonization, it is necessary to apply a prophylaxis method.<sup>6</sup>

Common for all types of oral candidiasis are the subjective manifestations, represented by stomatopyrosis, unpleasant taste and increased sensibility when consuming spiced or sour food or soda.<sup>3</sup>

When talking about the treatment of oral candidiasis and the prevention of further relapses, it is necessary to apply a prolonged treatment that consists in local and systemic therapy, but also in a series of measures that are designed to prevent or eliminate the risk factors of oral colonization.<sup>7</sup>

First of all, a hygienic-dietary regime is recommended; avoiding products that present high amounts of carbohydrates, maintaining a rigorous oral hygiene or rinsing the oral cavity with antiseptic solutions are the most important measures. For patients with dentures, it is recommended to design them with a transparent acrylic or metal base. Patients should wash the dentures with antiseptic solutions, NaCO<sub>3</sub>, or apply Nystatin powder on their surface.<sup>8</sup>

Due to the fact that most accounts of candidiasis are uncomplicated, local treatment should be effective by applying iodine solution or crystal violet solution on the lesion. Also, propolis acts synergistically with antifungal agents. Nistatin, Miconazole, Econazole, Izoconazole suspensions can be applied locally. Reducing or abandoning smoking can play an important role in *Candida* prevention.<sup>7</sup>

Systemic, cutaneous, mucous-cutaneous, digestive and genital tract candidiasis have to be treated by administering antifungal drugs. There are five drug classes: polyenes (Amphotericin B), which destroy the fungal cells; fluoropyrimidines (Fluoruridine), which block protein synthesis; allylamines (Naftifine), which act by inducing defects of the fungal membrane; echinocandins (Anidulafungin), which inhibit cell wall synthesis; and azoles (Fluconazole, Voriconazole), which affect cell structure integrity.<sup>7</sup>

In mycosis therapy, major importance is attributed to the identification of *Candida* strains that have determined or will determine illness and to the prevention of antifungal drug resistance by targeted therapy (antifungigram).<sup>9</sup>

The purpose of the study was to identify the risk factors that determine increased colonization of the oral mucosa

by *Candida* spp., because in certain conditions that induce immune suppression, these patients are more likely to develop yeast infections.

## MATERIAL AND METHOD

This prospective study was conducted on a group of 70 patients admitted to the Oral and Maxillo-Facial (OMF) Clinic in Tîrgu Mureş. The patients presented various OMF conditions, acute infections (abscess, cellulitis, superinfected jaw cysts, salivary lithiasis, and related conditions), major salivary gland tumors, tongue and mouth floor tumors, or were undergoing chemo- and radiotherapy for OMF tumors. The study was performed between February and March 2014 and was approved by the Ethics Committee of the institution where the study was conducted (decision no. 134/23.10.2013).

Each patient included in the study filled out a questionnaire that included authentication of the patient, presenting reasons, history of the actual condition, family medical history, and possible risk factors: personal medical history, personal dental history, followed treatments, previous hospitalizations, diagnosis and treatment of the current condition, vicious habits (alcohol consumption, smoking), oral hygiene status. The patients were asked to sign an agreement, in order to use and publish the data.

Each patient was asked to vigorously rinse the oral cavity with 10 ml sterile saline. The obtained oral lavage fluid was collected in sterile containers; the patient's data were noted on the container.

The samples of oral lavage fluid were transported in less than 1 hour to the Microbiology laboratory of the University of Medicine and Pharmacy Tîrgu Mureş, where they were processed. Materials used for processing consisted in Sabouraud agar medium (Oxoid, UK), chromogenic medium (Brilliance Candida Agar, Oxoid, UK), specific diagnostic tests to identify every candida strain (ID32C, Biomerieux), Mueller-Hinton agar supplemented with 2% glucose, Fluconazole and Voriconazole antifungal discs.

From the centrifuged, but also unprocessed mouth rinsing fluid, 10 µl were inoculated on Sabouraud medium, and the agar plates were incubated 24–48 hours at 37°C. For preliminary identification, the yeast colonies developed on Sabouraud agar were isolated on chromogenic medium, where each species of *Candida* develops a different color: *Candida albicans* – blue-green-gray; *Candida krusei* – flat purple with white contour; *Candida glabrata* – white; *Candida tropicalis* – dark blue; other species produce light purple to dark purple colors. The *non-albicans* species were further identified using ID32C tests.

For the validity of the results, the cultures were correlated with direct microscopic examination of the harvested product, using wet mounts, following the presence of yeasts, parasites, bacteria, lymphocytes, leucocytes, red blood cells and desquamated epithelial cells. In parallel, Gram staining was used.

Also for every *Candida* isolate, the antifungal susceptibility testing was performed using Fluconazole and Voriconazole disks, following CLSI guidelines. Mueller-Hinton agar medium supplemented with 2% glucose (as growth stimulation) and 0.5 µg/ml of Methylene Blue (to accentuate the inhibition zone) was inoculated with 200 µl of 0.5 McFarland yeast suspension, which was evenly spread with the help of a sterile cotton swab on the surface of the plate in 3 directions. After drying, disks of 1 µg Fluconazole as well as 25 µg Voriconazole were placed. After 20–24 hours of incubation at 35°C, the diameters of the inhibition zones were measured and interpreted according to the CLSI standards M27-A2 appendix C.

The data was statistically interpreted to determine the relation between *Candida* colonization and certain factors that affect the organism. All calculations were performed in the Graphpad InStat 3 program (GraphPad, San Diego, CA, USA) and spreadsheet software, with a significance threshold of  $p < 0.05$ .

## RESULTS

The study showed that from 70 patients with OMF pathology, 44.29% were diagnosed with infectious diseases, 8.57% with oral tumors (malignant tongue, floor of the mouth, jaws, benign-inflammatory hyperplasia etc.). Major salivary gland conditions (benign and malign parotid and submandibular glands tumors) were found in 11.43%, while exo-oral tumors (skin, cervical tumors) were present in 12.85% of the patients. A small percentage (2.86%) presented other pathology. Twenty percent of the patients received radiation treatment.

From the total number of patients included in the study, 66% were males, and of these, 54% presented *Candida* colonization. In term of female patients (24%), seven of them were yeast carriers.

To check if the yeast oral colonization is related to age, three age groups were defined. Results showed that 53.8% of patients within the age group of 40–60 years presented *Candida* colonization. In younger (under 40 years) and in elderly (over 60 years) patients, the yeast carriage rate was 35.3% and 44.4%, respectively.

We identified 11 different *Candida* species and one non-identifiable. From the 32 patients who presented oral

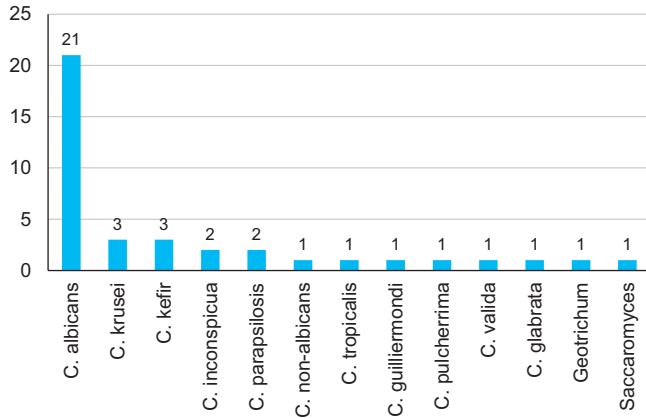


FIGURE 1. Identified *Candida* species

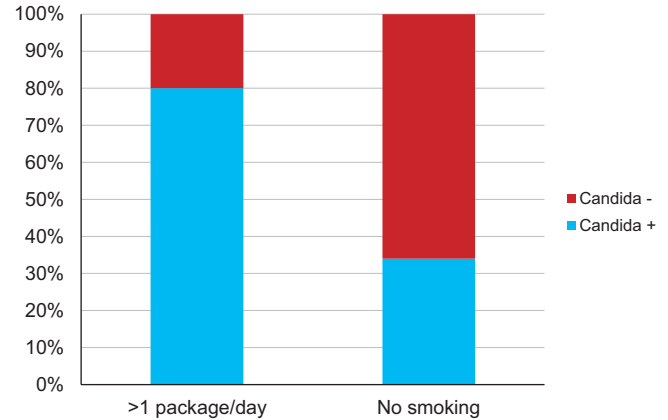


FIGURE 2. Smoking as a risk factor

*Candida* colonization, 21 isolates of *Candida albicans* were identified (Figure 1).

We studied several risk factors that are described in the literature to be correlated with high *Candida* colonization rates. The most important in our study was smoking, where we found statistically significant differences ( $p < 0.05$ ). Thus, from 15 patients (21.4%) who smoked more than one pack of cigarettes a day, 80% presented yeast oral colonization. From those who smoked less than one pack of cigarettes a day, 42.5% were *Candida* positive and from the patients who did not smoke ( $n = 41$ ), 34.1% were *Candida* positive (Figure 2).

Another studied risk factor was alcohol intake. From the 35 patients (50%) who declared that they consume alcohol on special occasions, 48.6% presented oral *Candida* colonization. Also, from the two patients who consumed alcohol on a daily basis, one was positive for *Candida* spp.; from the 33 patients (47%) who declared they do not drink alcohol at all, 42.4% were *Candida* carriers (Table 1).

From the 14 patients (20%) undergoing radiotherapy, 10 (71.43%) presented *Candida* spp. colonization. Also, from the six patients diagnosed with oral tumors, five (83.33%) presented oral *Candida* colonization.

Regarding oral hygiene, approximately 55% of those who never brushed their teeth and those who brushed once a

day, presented oral *Candida* colonization; from those who brushed twice and three times a day, 40% and 30% presented *Candida* colonization, respectively (Figure 3).

Regarding the influence of antibiotic use on the yeast oral colonization, from 49 patients (70%) treated with antibiotics, 50% presented *Candida* colonization; from the rest of the patients who did not follow antibiotic treatment, 45% presented *Candida* colonization.

The antifungigram showed that more than half of the identified *Candida albicans* species were resistant to Fluconazole and Voriconazole (52.38%) and that *non-albicans* species were more sensitive to Voriconazole (12.5% presented resistance) than to Voriconazole (50% resistance) (Figure 4).

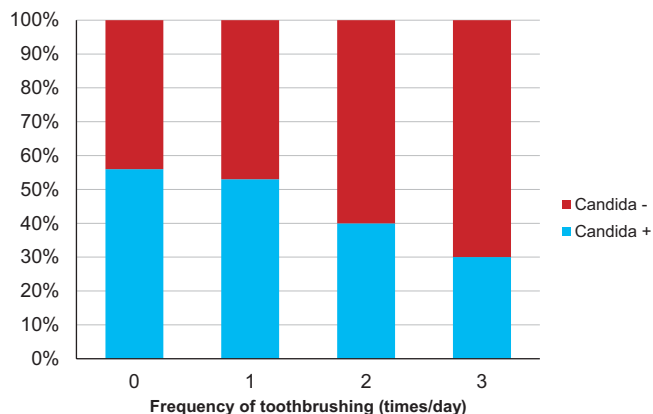
## DISCUSSIONS

Our results show that approximately half of the patients presented colonization with *Candida* species. Although 11 different species were identified, most of them were *Candida albicans*; this finding is in concordance with the literature. An article from 2006 concludes that both healthy patients and those with underlying conditions like diabetes mellitus present colonization with *Candida albicans*.<sup>10</sup> In this study, most of the patients (two thirds) were males.

TABLE 1. Alcohol intake vs. oral *Candida* colonization

Alcohol intake	No. of patients	CA	CNA	CA + CNA	Negative samples for <i>Candida</i> spp.	Positive samples for <i>Candida</i> spp. (%)
Occasionally	35	11	4	2	18	48.6%
Daily	2	0	0	1	1	50.0%
No alcohol	33	7	7	0	19	42.4%

CA – *Candida albicans*; CNA – *Candida non-albicans*



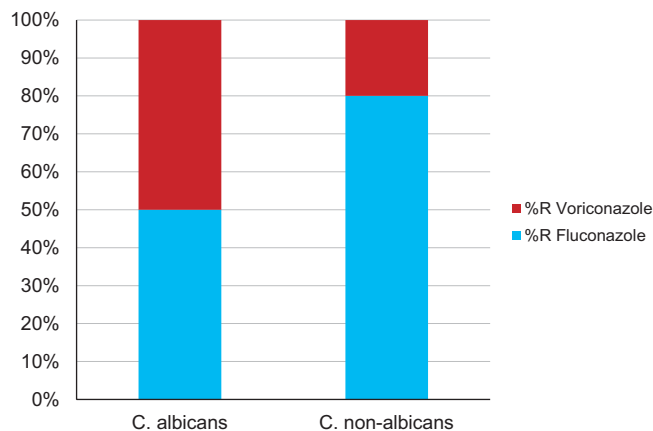
**FIGURE 3.** Oral hygiene as a risk factor

The prevalence of *Candida* colonization was two times higher in men than in women, although this was statistically not significant.<sup>11</sup> Other studies showed that the majority of *Candida* carriers were women, because of the metabolic and endocrine changes that appear after menopause. These changes reduce the immune response to bacteria and fungi, offering a susceptible ground for *Candida* colonization.<sup>12</sup> In the same context, another study conducted by Fawad Javed *et al.* on 58 patients diagnosed with diabetes, most patients with fungal colonization were women.<sup>13</sup> Given these information, additional studies are needed to confirm or infirm the relation between gender and yeast colonization.

The present study does not highlight a link between age and *Candida* colonization. On the contrary, some articles acknowledge that elderly who wear dentures present higher fungal carriage, for example the study of Kleinegger *et al.*<sup>14</sup>

Most of the patients admitted to the OMF clinic received antibiotics, radiotherapy or other treatments. Even though the literature contains studies that demonstrate a tight link between *Candida* oral colonization and the use of antibiotics, this study could not tabulate antibiotic treatment as a risk factor for *Candida* carriage. A study of Samonis *et al.* sustains the fact that broad-spectrum antibiotics that act on anaerobes determine a higher *Candida* colonization of the gastrointestinal tract in comparison to antibiotics that have a reduced activity on anaerobes, which determine a low and inconsistent colonization.<sup>15</sup> Another study demonstrates that macrolides determine a moderate colonization of the gastrointestinal tract.<sup>16</sup> Analyzing these findings, the conclusion could be that only certain classes of antibiotics determine *Candida* oral colonization and only if they are used for longer periods.

We did not find alcohol to be a significant risk factor for *Candida* oral colonization, even if consumed on a daily ba-



**FIGURE 4.** Resistance to antifungal medication

sis. This result may be explained by the fact that alcohol enhances the effect of smoking or other favorable factors and does not cause yeast infections on its own.<sup>17</sup> A similar result is sustained by Epstein *et al.*, who show that *Candida* colonization is present in patients who consume both alcohol and cigarettes.<sup>18</sup>

Oral hygiene influences to some extent *Candida* multiplication and oral colonization. We have found an increased carriage of *Candida* in patients who brushed their teeth less often, although not statistically significant. Some studies agree with this result and incriminate the lack of flossing as a risk factor for oral *Candida* colonization.<sup>19</sup> Opposed to these findings, the study of Jørgensen *et al.* conducted on 233 elderly patients concluded that there is a higher rate of *Candida* colonization in persons with poor oral hygiene.<sup>20</sup> In addition, Grimoud *et al.* showed that after improving oral hygiene, *Candida* colonization decreased significantly, from 41.9% to 24.9%.<sup>21</sup>

Even though the literature incriminates diabetes as a risk factor for high *Candida* carriage in the oral cavity, this study did not show a higher prevalence of *Candida* colonization in this type of patients.<sup>10</sup> This result can be explained by the low number of patients with this condition in our study, but also by the fact that the patients admitted to the clinic were already using antifungal medication as prophylaxis. From this point of view, an additional study with a higher number of patients with diabetes mellitus should be carried out.

Hypertension, one of the frequent underlining conditions identified, did not influence *Candida* carriage. The literature does not provide data regarding hypertension and oral *Candida* colonization.

The reduced number of patients undergoing radiotherapy included in this study did not allow having significant results, but revealed that most of them presented

oral *Candida* spp. colonization. A study conducted on 22 patients undergoing radiotherapy in the head and neck area showed that *Candida* oral colonization was present in every patient, suggesting the need for prophylactic treatment in these cases.<sup>6</sup> In his research, Karbach explained that due to radiotherapy, the salivary glands are affected, leading to a reduced quantity of saliva, thus favoring high colonization with *Candida albicans*, but also with other *Candida* species.<sup>22</sup>

A major role in oral *Candida* colonization belongs to active smoking. The results showed that over two thirds of the active smokers were *Candida* positive. The contribution of this factor in oral *Candida* carriage is sustained by recent studies that confirm that the presence of *Candida* can be correlated with smoking. Furthermore, smoking tobacco influences oral hygiene by increasing the quantity of oral plaque and tartar, fact sustained by the literature.<sup>23</sup> Conversely, another study conducted on a group of 100 patients showed that there is no link between smoking and the occurrence of *Candida*.<sup>24</sup>

The present study showed that more than half of the *Candida albicans* species identified presented resistance to Fluconazole. Also, half of the *non-albicans* species developed resistance to Fluconazole, but kept their susceptibility to Voriconazole. These findings are similar with the one of Mandras *et al.*, who described that the resistance of *Candida albicans* in an Italian population is most often a restrictive phenomenon, but if it is present, Voriconazole is a good substitute.<sup>25</sup> A possible explanation for the low susceptibility of *Candida* spp. to Fluconazole could be the association of substances that lower the yeast's susceptibility to this antifungal, for example Sodium diclofenac.<sup>26</sup>

Finally, yet importantly, this research shows that centrifugation of the oral lavage fluid delivers exact data, and that there is no need for comparative tests between native product and sediment. Optical microscopy does not offer conclusive data, and this is why the yeast culture is mandatory.

## CONCLUSIONS

Our study revealed oral colonization with *Candida* in a considerable number of subjects, the *albicans* species presenting the highest incidence. From the generally described risk factors, we found only smoking having a great impact on oral *Candida* colonization, but radiotherapy may also stimulate oral *Candida* colonization. Gender, age, alcohol consumption or oral hygiene did not influence the colonization rate in our group, and antibiotics influenced only in certain conditions oral *Candida* colonization. The antifungal susceptibility of both *Candida albicans* and *non-*

*albicans* against Fluconazole is low, but Voriconazole is still a viable solution.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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