



Oral candidiasis: relation to systemic diseases and medications

Xiaozhu Chu¹

¹University of Pittsburgh, School of Dental Medicine

Abstract

Background: Oral candidiasis is by far the most common oral fungal infection in humans. It is caused by the fungal organism *Candida albicans*. When the host is debilitated by other diseases and conditions, *C. albicans*, which is usually a part of the normal oral flora, can turn pathogenic and invade the host tissue to cause the infection. The purpose of this paper is to investigate the role of systemic diseases and medications in the development of oral candidiasis. **Methods:** A total of 12 cases with code indicating oral candidiasis were collected from the University of Pittsburgh School of Dental Medicine Dental Registry and DNA Repository. The systemic diseases and medications were descriptively analyzed. **Results:** 50% of the subjects had more than two systemic diseases. The most prevalent diseases were mental illnesses (50%), cardiovascular diseases (41.7%), and respiratory system diseases (33.3%). 50% of subjects were on polypharmacy therapies and 75% of subjects were taking medications that may contribute to oral candidiasis. Among the medications, antidepressants and inhalational corticosteroids may have strong potentials to cause oral candidiasis. **Conclusion:** Oral candidiasis is associated with having systemic diseases and intake of medication, especially with those medications can cause xerostomia. As the number of systemic diseases and medications increases, the risk of developing oral candidiasis may increase too.

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Email: xic81@pitt.edu

Introduction

Candidiasis is by far the most common oral fungal infection in humans and has a variety of clinical manifestations. It is the infection caused by the yeast-like fungal organism *Candida albicans*. As many other pathogenic fungi, *C. albicans* can exist in two forms—the yeast form and the hyphal form. The hyphal form is believed to be able to invade the host tissue and cause the infection. [1] *C. albicans* is considered as part of the normal oral flora and the prevalence of oral *Candida* carriage in the healthy population has been estimated to range from 23% to 68%. [2] Candidiasis used to be considered as only an opportunistic infection but it has been recognized that people who are otherwise healthy can develop oral candidiasis too. However, as a

result of complex host and organism interaction, a large percentage of patients with candidal infection are still individuals who are debilitated by another diseases and conditions. Many risk factors can modify an individual's susceptibility to oral candidiasis, including compromised autoimmunity, tobacco consumption, hyposalivation, denture wearing, systemic disease, and medication.

Compromised autoimmunity

T-cell immunity has a critical role in host defense against candidal infection. Chronic mucocutaneous candidiasis (including oral candidiasis) is an infectious phenotype in patients with inherited or acquired T-cell deficiency. Studies have shown that Th17 cell, as well as other cell expressing retinoic acid-related orphan receptor

γ T (ROR γ T), produce interleukin (IL)-17, which has an essential role in defending against candidal infections in humans. Four genetic etiologies, AR IL-17 receptor A, IL-17 receptor C and ACT1 deficiencies, and AD IL-17F deficiency, are identified as underlying risk factors for chronic mucocutaneous candidiasis. Each of these gene defects has a direct negative effect on IL-17 signaling. Patients with these gene defects may have severely reduced frequencies of circulating IL-17-producing T cells. Or they may produce neutralizing autoantibodies against IL-17. As a result, the ability of neutrophil cells to kill *C. albicans* is impaired and chronic mucocutaneous candidiasis may develop. [3]

Tobacco consumption



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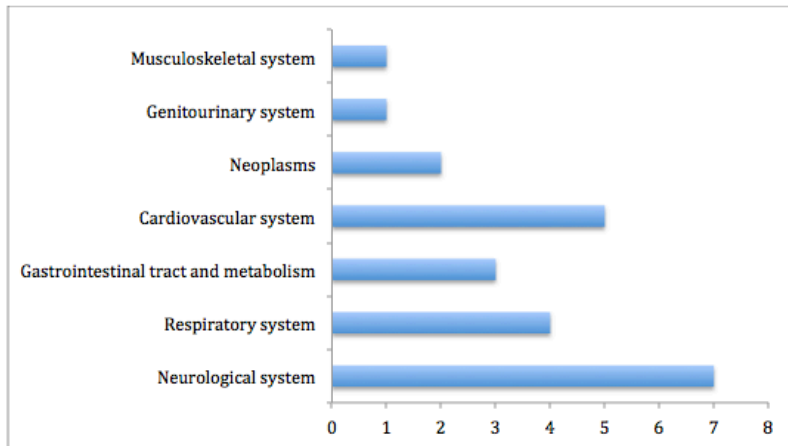


Figure 1. Distribution of systemic diseases/medical conditions at the organ level. The x-axis shows the cumulative numbers of individuals.

Tobacco smoking has been considered as one of the many factors that can predispose individuals to oral candidiasis. Literatures revealed that the rate of oral candidal carriage in tobacco smokers is significantly higher than in non-smokers. Besides *C. albicans*, the oral carriage of other species such as *C. glabrata*, *C. dubliniensis* and *C. tropicalis* are also associated with smoking. The observation is even more striking in HIV-infected individuals. It has been reported that HIV-positive smokers are 50 times more likely to be oral candidal infection positive compared to HIV-infected non-smokers. It has not been cleared yet that why tobacco consumption can increase candidal carriage. However, there are studies suggesting that smoking may lead to localized epithelial alterations, which facilitate candidal colonization. Another hypothesis is that cigarette smoke may contain nutritional factors for *C. albicans*. [4]

Hyposalivation

Adequate salivation is essential for oral health, since it provides support for the microbial population of the mouth, while at the same time containing antimicrobial products that control these microbial populations. Histatin 5 (Hst 5) is an important salivary antimicrobial protein. It has been shown that Hst 5 has potent and selective antifungal activity. After coupling with the carrier molecule spermidine, Hst 5 significantly enhances the killing of *C. albicans*. [5] Reduced salivary secretion, as occurred in patients with Sjögren's syndrome, can result in a significant increase in oral candidal carriage. The prevalence of oral candidal carriage among Sjögren's syndrome patients is estimated to range from 68% to 100%, compared to the range from 23% to 68% in normal population [2].

Denture wearing

Denture stomatitis is considered to be a form of erythematous candidiasis and it's a common inflammatory lesion of the oral mucosa covered by denture. Epidemiological studies show a prevalence of denture stomatitis among denture wearers from 15% to over 70%. Etiological factors include poor denture hygiene, continual and nighttime wearing of removable dentures, accumulation of denture plaque, and bacterial and yeast contamination of denture surface. All together, these factors may increase the ability of *C. albicans* to colonize both denture and oral mucosal surfaces, exerting its pathogenic effort. [6]

Systemic diseases Many systemic diseases have been associated with oral candidiasis. The primary cause is attributed to the decreased salivary secretion, leading to the reduced concentration of immunoglobulin in the saliva and less efficient humoral-mediated host defense against *C. albicans*.

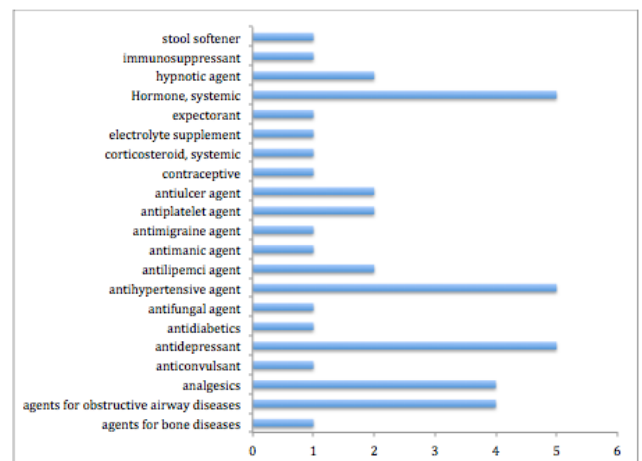


Figure 2] Distribution of prescribed medications. The x-axis shows the cumulative number of individuals taking the certain medication.

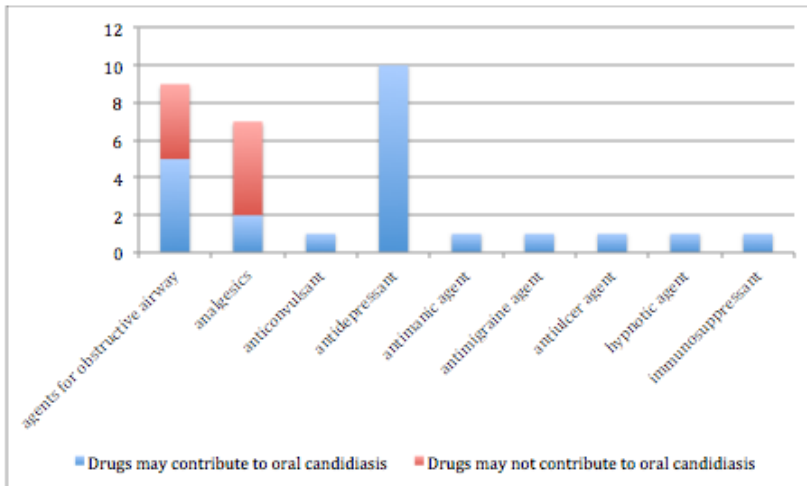


Figure 3 Profiles for medication categories based on their potential contributions to the development of oral candidiasis. Y-axis is number of individuals taking the drugs.

For patients with diabetes mellitus, besides the reduced salivary flow, the high level of blood glucose also plays a significant role. It is associated with reduced salivary pH and facilitates oral candidal overgrowth and colonization. [7] As an opportunistic infection, oral candidiasis is also associated with a wide spectrum of systemic diseases that suppress the host autoimmunity [8].

Medication

Several drugs may cause the development of oral candidiasis by many mechanisms. The pharmacological action of the broad-spectrum group of antibiotics may break the balance within the normal oral flora, resulting in the overgrowth of *C. albicans*. Drugs such as corticosteroids may suppress either the nonspecific inflammatory response or the T-cell-mediated immunity, which can in turn predispose individuals to oral candidiasis. Drugs that have xerogenic effects can cause

oral candidiasis by directly reducing the salivary flow. [8]

It appears that the association between oral candidiasis and systemic diseases, intake of medications has been well established. The purpose of this study is to analyze the 12 cases collected from the University of Pittsburgh School of Dental Medicine Dental Registry and DNA Repository, and further investigate which systemic diseases and medications may be potent and contribute to the development of oral candidiasis.

Methods

By the time of the study started, 5,869 subjects from the University of Pittsburgh School of Dental Medicine Dental Registry and DNA Repository were available for analysis. Since the September of 2006, the registry invited all patients who seek treatment at the University of Pittsburgh School of Dental Medicine to participate and give written consent to authorize their clinical information to be

used for academic research purpose. 12 cases with codes indicating oral candidiasis were collected from the 5,869 subjects. Compared to the estimated prevalence of oral candidal carriage, which ranges from 23% to 68% in the normal population [2], the number 12 in 5,869 subjects (0.2%) seems to be unreasonably small. This can be a result of the inconsistent report of the oral lesions by clinical faculty members and student dentists. For the 12 cases with oral candidiasis, the data on current (i.e. time of examination) systemic diseases/medical conditions, daily intake of prescribed or OTC medications were obtained from the registry. The total number of systemic diseases and medical conditions were counted. All medications were categorized by using the internationally approved Anatomical Therapeutic Chemical (ATC) classification system. And their impacts on oral hygiene and dental treatment were obtained from the website Lexicomp Online for Dentistry (<http://www.wolterskluwer.com/online-for-dentistry/>). All data then were descriptively analyzed.

Results

Characteristics of the 12 study samples are presented in Table 1. Among the 12 cases, only one participant (8.3%) did not report any systemic disease or medical condition. For the other 11 cases, the number of systemic diseases/medical conditions reported by the participants varied from 1 to 8 (33.3% reporting more than four diseases). The highest scores by

number of diseased individuals were found for neurological system disease (58.3%, N = 7) including depression, epilepsy, and bipolar disorder, cardiovascular system diseases (41.7%, N = 5) including mainly hypertension, irregular heartbeat, and heart failure, and respiratory system disease (33.3%, N = 4) including asthma (Figure 1). Less frequent diagnosis included gastrointestinal tract and metabolic diseases (liver diseases and diabetes, 25%, N = 3), neoplasms (neuroblastoma and unspecified throat cancer, 16.7%, N = 2), genitourinary system diseases (kidney disease, 8.3%, N = 1), and musculoskeletal system diseases (prosthetic joint, 8.3%, N =1).

All the study subjects had intake of prescribed or OTC (over the counter) medications. The number of medications taken on daily basis varied from 1 to 14. Among the 12 cases, three individuals took only one medication (25%), three took 2-4 medications (minor polypharmacy, 25%), and six took more than 4 medications (major polypharmacy, 50%). The distribution of prescribed medication (Figure 2) shows that antihypertensive agents, antidepressant,

systemic hormones, analgesics, and agents for obstructive airway diseases predominated. This medication pattern reflected the disease burden among the study subjects.

Since intake of medication is an important risk factor to the development of oral candidiasis, all the medications taken by study subjects were analyzed by their impacts on oral cavity environment and dental treatment. Based on the information obtained from the website Lexicomp Online for Dentistry, all medications that can cause xerostomia, change in salivation, candidal infection were labeled as “may contribute to oral candidiasis”. The 63 medications were fitted into 22 categories based on the Anatomical Therapeutic Chemical (ATC) classification system. Among the predominated categories, antidepressant contained 10 medications, all of which may contribute to the development of oral candidiasis. It had been followed by agents for obstructive airway diseases and analgesics, which had 5 out of 9 (55.5%) and 2 out of 7 (28.6%) medications, respectively, fell into the category “may contribute to

oral candidiasis”. The other categories, which contained medications that may contribute to oral candidiasis, included anticonvulsant, antimanic, antiulcer, hypnotic and immunosuppressant agents. (Figure 3) Among all 12 subjects, 9 (75%) were taking medications that fitting into the “ may contribute to oral candidiasis” category.

Discussion and Conclusion

In my study, 50% of the study samples were having three or more than three systemic diseases, which is in agreement with previous observations suggesting that having multiple systemic diseases and medical conditions is associated with oral candidiasis. The most frequent diseases involving in this study were mental diseases including depression and bipolar disorder, and obstructive airway diseases including asthma, chronic obstructive pulmonary disease, and an unspecified lung disease. Those are not diseases that directly cause change in salivary secretion and salivary glands or those suppress the host autoimmunity. Their primary association with the development of oral candidiasis is more attributed to the medications that were taken by subjects to treat the systemic diseases. However, it may not be true for one subject who was diagnosed as insulin-dependent diabetes. On the morning the dental examination was performed, the subject reported that her blood glucose level was 235mg/dl. Compared with the preferable goal of a good diabetic management, which is close to the 70 to 120mg/dl

Table 1 Characteristics of the study sample.

Participants	
N = 12	
Systemic Disease/Medical Conditions	
Healthy	8.3% (N=1)
1 disease	25.0% (N=3)
2 diseases	16.7% (N=2)
3 diseases	16.7% (N=2)
4+ diseases	33.3% (N=4)
Medications	
1 medication	25.0% (N= 3)
Minor PP (2-4 medications)	25.0% (N= 3)
Major PP (≥5 medications)	50.0% (N= 6)

PP, polypharmacy.

range, it's safe to assume the diabetes was not well controlled. Besides all other drugs she took, the level of blood glucose may play an important role in the development of her oral candidiasis. It has been reported that highest rate of *C. albicans* colonization occurs in diabetic patients with poor glycemic control. In addition, subjective oral dryness is a frequent complaint among diabetic patients. [7]

The five most commonly reported medications included systemic hormones, antidepressants, antihypertensive agents, agents for obstructive airway diseases, and analgesics. Among the five categories, the association between antidepressants and oral candidiasis has been well established. All salivary secretion is mediated by neurotransmitters and relies on stimulations from the autonomic nervous system. Stimulation of the cholinergic system leads to secretion of "watery" saliva thus anticholinergic drugs reduce the secretion. Many antidepressants have an anticholinergic effect that blocks the peripheral cholinergic innervation, resulting in hyposalivation and xerostomia. [9] Among other agents used to manage obstructive airway diseases, corticosteroids are widely used as oral inhalers due to its anti-inflammatory and immunosuppressive properties. However, the repeated use of corticosteroids oral inhalers also suppress an individual's resistance to candidal infection by suppressing either the nonspecific inflammatory response or the T-cell-mediated immunity, which predispose the oral

inhaler users to oral candidiasis. [10] In this study, 75% of the study subjects was on polypharmacy therapies and took medications that had xerogenic or immunosuppressive properties, including 10 antidepressants and 2 inhalational corticosteroids. The finding is in line with previous studies indicating that intake of medications is an important risk factor for the development of oral candidiasis.

When treating patients with systemic diseases and taking multiple medications, the dental professionals must be able to recognize the early signs and symptoms of oral candidiasis and adjust the treatment plans to meet the special needs of those patients and prevent the development of oral candidiasis.

In conclusion, based on the descriptive analysis of 12 cases with oral candidiasis, the findings support the concept that the development of oral candidiasis is associated with having multiple systemic diseases and intake of medications.

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