A single-center 18-year experience with oral candidiasis in Brazil: a retrospective study of 1,534 cases

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Abstract: Despite the large number of published studies about oral candidiasis and associated risk factors, reports of large single-center retrospective studies on the prevalence of oral candidiasis, risk factors, and the oral candidiasis types diagnosed more frequently in oral diagnostic reference centers are scarce. The objective of the present study was to retrospectively survey the demographic and clinical profiles of 1,534 patients diagnosed with candidiasis and treated at the Center for Diagnosis of Oral Diseases (CDOD), Pelotas Dental School, Federal University of Pelotas between 1997 and 2014. Using a retrospective, cross-sectional, epidemiological design, data on race, gender, age, systemic diseases, oral candidiasis type and location, symptoms, and harmful habits such as smoking and alcohol consumption were collected. The statistical analysis was performed using STATA version 13.1. Risk factors for chronic atrophic candidiasis (CAC) were evaluated using Poisson regression with robust variance (p ≤ 0.05). The majority of patients with oral candidiasis seen at the CDOD over the 18-year period of analysis were Caucasian women, aged 51–60 years, nonsmokers, and nondrinkers, with no systemic disease, and who wore some form of dental prostheses. CAC was the single most common clinical type of candidiasis detected, and the most frequently affected oral site was the palate. These data from a large single-center in Brazil agree with previous evidence about the clinical and demographic profiles of patients with oral candidiasis.

Keywords: Drug Resistance, Fungal; Candidiasis, Oral; Retrospective Studies.

Introduction

Oral candidiasis is the most common oral fungal infection. In the majority of cases, it manifests as a chronic condition, with varying degrees of severity. Oral candidiasis affects a large segment of the population, particularly children and older adults, and is particularly common in those who wear dental prostheses. Oral candidiasis is considered an opportunistic infection, occurring more frequently in persons with impaired immunity.[1] The impaired competitive ability of the host microbiota is a prerequisite for candidiasis, and this facilitates *Candida* growth.[2] However, the mere presence of the fungus is not indicative of an infection. This

requires tissue penetration, which usually only occurs under select circumstances, including patients with diabetes, cancer, or HIV.[3,4] Oral candidiasis is an important condition in the context of HIV/AIDS because it affects quality of life and is an indicator the progression of HIV infection.[5,6,7,8,9]

Consequently, a large amount of information has been published on oral candidiasis incidence and the associated factors. However, there is still a lack of large single-center retrospective studies conducted to evaluate oral candidiasis for identifying common risk factors for oral candidiasis and comparing with those identified in other studies.[10,11,12,13,14] Thus, the present 18-year retrospective survey was performed to capture the local epidemiology of oral candidiasis at a specialist center for oral diagnosis in Brazil (Pelotas, Rio Grande do Sul) for identifying risk factors for oral candidiasis and to characterize the demographic and clinical profiles of affected patients.

Methodology

This retrospective study was approved by the Research Ethics Committee of Federal University of Pelotas, Pelotas, Rio Grande do Sul, Brazil. Formal consent was not required.

A total of medical records of 1,594 patients diagnosed with oral candidiasis between 1997 and 2014 from the Center for Diagnosis of Oral Diseases (CDOD) at Pelotas Dental School, Federal University of Pelotas (Pelotas, Rio Grande do Sul, Brazil) were reviewed. Of these, records of 60 patients were excluded because they were incomplete. Two dental students, *i.e.*, a master's degree student and an undergraduate dental student, carried out the data collection. All 1,534 records included in the sample were assessed. The following data were collected and recorded: race, gender, age, systemic diseases, antifungal medications, clinical form of candidiasis, type and location of candidiasis, symptoms, and smoking and alcohol consumption. The clinical forms of candidiasis were classified as follows: median rhomboid glossitis, angular cheilitis, chronic atrophic candidiasis (CAC), hyperplastic candidiasis, and acute pseudomembranous and/or erythematous candidiasis.

The undergraduate students under supervision of pathologist professors at the reference center usually diagnose oral candidiasis through a macroscopic examination of removable white plaques or erythematous tissues in the mouth, and a microscopic examination of a sample of the oral mucosa with characteristic findings. Oral candidiasis diagnosis can be made on the basis of both clinical and microbiological examinations. In the present study, the diagnosis was predominantly based on a clinical examination in most of the reported cases. For example, the diagnosis of CAC in clinical practice is usually established with clinical signs in combination with an exfoliative cytological examination. However, the presumptive identification of the microorganism must be made by means of culture (specific culture) followed by biochemical/physiological and auxanographic methods. However, the use of molecular/biological methods may be the only way to genetically differentiate the *Candida* strains. Samples from only 10% patients in the present study were evaluated microscopically. Samples were collected by scrubbing sterilized swabs only on the palatal mucosa or on the palatal mucosa and tongue.

All variables (appearance of oral candidiasis, common sites of white plaques or erythematous tissues with characteristic findings in the oral cavity, dental prosthesis use characteristics (*e.g.*, type of dental prostheses, duration of use, cleaning practices, nocturnal wear) diabetes mellitus, smoking, and stomatitis) were collected during face-to-face interviews. Individuals who returned more than once answered the questionnaire only once and had their data in the dental records of the oral diagnosis center.

The oral cavity examination of each patient and the interviews were performed by undergraduate students who were supervised by three standardized oral pathologists. Quality control for the data collection was made by follow-up of the fieldwork by one of the responsible pathologists. A soft tissue examination was undertaken using a mouth mirror and gauze compresses. Data were recorded on the patient's questionnaire. The diagnosis of clinical oral candidiasis was made according to the clinical presentation established by others studies (Table 1).[15,16,17]

Table 1. Clinical characteristics of candidiasis presentations.

Clinical type	Appearance and symptoms	Common sites	Associated factors and comments
Pseudomembranous (thrush) (Fig.1D)	Creamy-white plaques; removable; Burning sensation, foul taste	Buccal mucosa, tongue, palate	Antibiotic therapy, immunosuppression
Erythematous	Red macules, burning sensation	Posterior hard palate Buccal mucosa, dorsal tongue	Antibiotic therapy, xerostomia, immunosuppression, idiopathic
Central papillary atrophy (median rhomboid glossitis) (Fig.1B)	Red, atrophic mucosal areas; asymptomatic	Midline posterior dorsal tongue	Idiopathic, immunosuppression
Chronic multifocal	Red areas, often with removable white plaques; burning sensation, asymptomatic	Posterior palate, posterior dorsal tongue, angles of mouth	Immunosuppression, idiopathic
Angular cheilitis (Fig.1C)	Red, fissure lesions; irritated, raw sensation	Angles of mouth	Idiopathic, immunosuppression, loss of vertical dimension
Denture stomatitis (chronic atrophic candidiasis, denture sore mouth) (Fig.1A)	Red, asymptomatic	Confined to palatal denture bearing mucosa	Probably not true infection; denture is often is positive on culture but mucosa is not
Hyperplastic (*Candida* leukoplakia)	White plaques that are not removable; asymptomatic	Anterior buccal mucosa	Idiopathic, immunosuppression; care must be taken not confuse this with keratotic lesions with superimposed candidiasis
Mucocutaneous	White plaques, some of which may be removable; red areas	Tongue, buccal mucosa, palate	Rare; inherited or sporadic idiopathic immune dysfunction
Endocrine-candidiasis syndromes	White plaques, most of which are not removable	Tongue, buccal mucosa, palate	Rare; endocrine disorder develops after candidiasis

Statistical analysis

Data were extracted from clinical records and tabulated in a Microsoft Office Excel 2010 spreadsheet and organized as follows: gender (male or female); age (< 50 years, 51–60 years, 61–70 years, or > 70 years); ethnicrtity (Caucasian or of other ethnicity); smoking (yes or no); alcohol intake (yes or no); presence of systemic diseases (yes or no); denture wear (yes or no); type of candidiasis (CAC or other); affected site (palate or other); and antifungal medication used (the "service protocol," nystatin cream, Daktarin gel, or other. The "service protocol" consisted of giving the patient the choice of nystatin cream, Micostatin®, or Daktarin® gel; symptoms (asymptomatic, pain, burning sensation, or other); comorbid oral lesions (yes or no); and treatment duration (< 1 year, 1–2 years, or ≥ 3 years).

Qualitative variables are expressed as absolute and relative frequencies and quantitative variables are expressed as means (standard deviations). Data were tabulated and analyzed in STATA 13.1 (Stata Corp., College Station, TX, USA). The assessment of risk factors for CAC was performed using Poisson regression with robust variance at the 5% significance level.

Results

The records of 1,534 patients with a clinical diagnosis of oral candidiasis seen between 1997 and 2014 at the CDOD were reviewed. Most of these patients were women (80.3%). The majority of the patients were aged 51–70 years and 1,308 patients were Caucasian.

Approximately 71.0% patients were self-reported nonsmokers. Only 23 patients reported alcohol intake.

Systemic diseases were absent in 61.1% patients. These included systemic hypertension, diabetes, and depression; 62.8% had systemic hypertension, 2.5% had cancer, 2% had some type of blood dyscrasia, 2.3% had HIV, 9.2% had diabetes, 10.3% had depression, 7.8% had heart problems, 0.5% had glaucoma, 0.8% had arthritis, 1.6% had thyroid problems, and one patient had Chagas disease.

Approximately 59.3% participants wore dentures (Table 2).

Table 2. Profile of 1,534 patients seen at the CDOD in Southern Brazil (Pelotas, 1997–2014).

Variable	n	%	95%CI
Sex			
Female	1,232	80.3	78.2–82.2
Male	302	19.7	17.8–21.8
Age (years)			
< 50	415	27.1	24.9–29.3
51–70	804	52,4	48,1–56.6
≥ 70	315	20.5	18.6–22.6
Ethnicity			
Caucasian	1,308	86.1	84.2–87.7
Other ethnicity	226	13.9	12.3–15.8
Smoking			
No	1,089	71.0	68.7–73.2
Yes	445	29.0	26.8–31.3
Alcohol consumption			
No	1,511	98.5	97.8–99.0
Yes	23	1.5	1.0–2.2
Systemic diseases			
Absent	937	61.1	58.6–63.5
Present	597	38.9	36.5–41.4
Denture wearer			
No	624	40.7	38.2–43.2
Yes	910	59.3	56.8–61.8

CAC was the most common type of candidiasis (Figure A), which was diagnosed in 1,500 patients (95%). The other types accounted for 34 patients: 2% with median rhomboid glossitis (Figure B), 2% with hyperplastic candidiasis, and 1% with pseudomembranous candidiasis (Figure D) (Table 3). The most commonly affected site was the palate in 90.9% of all cases.

The antifungal medication service protocol for candidiasis was prescribed to 52.2% patients. The "service protocol" consists of offering the patient the choice of nystatin cream, Micostatin®, or Daktarin® gel. Nystatin cream was specifically prescribed to 467 patients (30.4% of all topical antifungal treatments), and Daktarin® gel was given to 144 (9.4%). Other treatment types were administered to 123 patients (8%). The most prevalent treatment duration was < 1 year, which was observed in 70.3% patients (Table 3).

Most patients (61.1%) were asymptomatic; 19.4% reported a burning sensation, 11.9% reported pain, and 7.6% reported other symptoms.
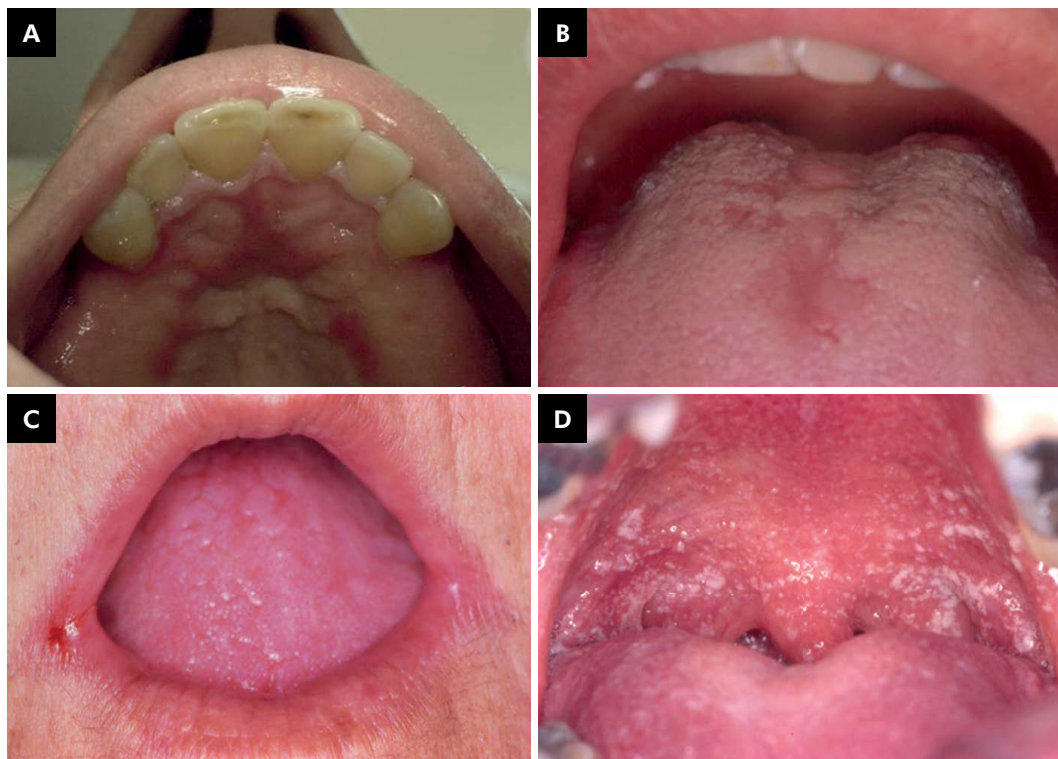

Figure 1. Clinical manifestations of oral candidiasis A Chronic atrophic candidiasis (Denture stomatitis) B Median rhomboid glossitis C Angular cheilitis D Pseudomembranous candidiasis.

A total of 71.1% patients had no oral lesions other than those caused by candidiasis, whereas 28.9% had additional oral lesions, such as fibromas, ulcers, hyperplasia, torus, and carcinoma.

The prevalence analysis of risk factors for CAC yielded the following results. Overall, 1,500 patients were diagnosed with CAC: 1,204 women (95.7% women in the sample) and 296 men (91.1% men in the sample). This difference was statistically significant.

A total of 406 patients aged < 50 years, 436 of those aged 51–60 years, 350 of those aged 61–70 years, and 308 of those aged > 70 years had CAC. These differences were significant.

Of the 1,500 patients with CAC, 1,262 were Caucasian, and 238 were of other ethnicity; 1,064 were nonsmokers, and 436 were smokers; 1,477 did

not report alcoholism, whereas 23 did; 937 had no systemic diseases, whereas 563 had some systemic disease; 610 did not wear any type of dental prosthesis, while 890 were denture wearers. These analyses yielded no statistical differences (Table 4).

Discussion

The CDOD is a reference center for the treatment of oral candidiasis, located at the Pelotas Dental School, Federal University of Pelotas, in the city of Pelotas, state of Rio Grande do Sul, Southern Brazil, which operates within the Unified Health System (Sistema Único de Saúde, SUS) framework. On average, the center sees 250 patients per month, both from within Pelotas and from neighboring municipalities (Rio Grande, Piratini, Canguçu, Morro Redondo, and others). This epidemiological study was conducted

Table 3. Prevalence of oral candidiasis in relation to the independent variables in 1,534 patients seen at CDOD in Southern Brazil (Pelotas, 1997–2014).

Variable	n	%	95%CI
Type of candidiasis			
CAC	1,5	95.0	93.6–95.8
Other	34	5.0	4.2–6.4
Site			
Palate	1,388	90.9	89.4–92.3
Other	146	9.1	7.7–10.6
Antifungal medication used			
Protocol	800	52.2	49.6–54.6
Nystatin cream	467	30.4	28.2–32.8
Daktarin	144	9.4	8.0–11.0
Other	123	8.0	6.8–9.5
Symptoms			
Asymptomatic	937	61.1	58.6–63.5
Bodily pain	183	11.9	10.4–13.7
Burning	298	19.4	17.5–21.5
Other	116	7.6	6.3–9.0
Other oral lesions present			
No	1,09	71.1	68.7–73.3
Yes	444	28.9	26.7–31.3
Treatment duration (years)			
< 1	1,003	70.3	67.8–72.7
1–2	304	17.7	15.7–19.8
≥ 3	227	12.0	10.3–13.8

CAC: chronic atrophic candidiasis.

Table 4. Risk factors for chronic atrophic candidiasis in 1,500 patients seen at CDOD in Southern Brazil (Pelotas, 1997–2014).

Variable	n	%	95%CI		p-value*
Sex					0.009
Female	1,204	95.7	94.4	96.7	
Male	296	91.1	87.3	93.8	
Age (years)					0.002
<50	406	91.1	87.9	93.5	
51–70	786	95.8	94.7	97. 2	
≥70	308	97.5	95.0	98.7	
Ethnicity					0.48
Caucasian	1,262	95.3	94.0	96.3	
Other ethnicity	238	91.4	86.7	94.5	
Smoking					0.49
No	1,064	95.0	93.6	96.2	
Yes	436	94.2	91.6	96.0	
Alcohol consumption					0.15
No	1,477	95.0	93.7	96.0	
Yes	23	82.6	61.2	93.5	
Systemic conditions					0.06
Absent	937	95.7	94.2	96.9	
Present	563	93.3	91.0	95.0	
Denture wearer					0.18
No	610	95.7	93.8	97.0	
Yes	890	94.2	92.5	95.5	

*Poisson regression analysis with robust variance for estimation of prevalence ratios (PRs).

in a region of Southern Brazil with a population of approximately 350,000, distributed across urban and rural areas.[18] Few cases (<4%) were lost to follow-up in this large single-center retrospective study and this reflects the high level of excellence of the CDOD service at Federal University of Pelotas and quality of the entries made by the team.

In the present study, women were affected four times more frequently than men, and there was no significant difference in the presence of oral candidiasis across age groups. Other studies have suggested that women are affected by oral candidiasis more often than men; however, it is known that women are more likely to seek medical attention for *Candida* symptoms and that incidence increases with age, i.e., older adults have a higher incidence of this condition, particularly due to difficulties in oral hygiene and denture use.[19,20,21,22]

Furthermore, candidiasis is often associated with local diseases (e.g., other oral lesions such as traumatic fibromas, aphthous stomatitis, and carcinoma) or systemic diseases (*e.g.*, diabetes, cardiovascular disorders, depression, or immunosuppression).[23] It is important to note that nearly half of the patients diagnosed with oral candidiasis in the present study had some kind of systemic disease. However, the relationship between the presence of systemic diseases and oral candidiasis is unclear based on the evidence in literature. Smokers are also strong "candidates," as smoking induces a variety of changes in the oral cavity.[13,24] The present study found that most individuals afflicted with oral candidiasis were nonsmokers with no systemic diseases and no comorbid oral lesions.

Candidiasis is often asymptomatic or may cause some discomfort for the patient, such as stinging, burning, and even pain[15,25]. In the present study, most people reported no symptoms.

Denture-associated angular cheilitis is found in patients with deep creases at the angle of the mouth, usually caused or aggravated by wearing full dentures with an incorrect vertical dimension, which creates points of low oxygenation at the labial commissures.[11,13,26] In our sample, <0% of patients had angular cheilitis, and it was associated with palatal lesions in most cases. Other forms of candidiasis are

less common than CAC but are not less clinically important. Pseudomembranous candidiasis can affect individuals of any age, but is particularly common in debilitated patients and those living with chronic illness. This form of candidiasis presents as white or yellowish plaques or nodules that easily rub off.[16,27]

Hyperplastic candidiasis is a generally asymptomatic condition that presents as a hard lesion with a smooth, nodular, or fissured surface, ranging in color from white to red. This lesion is usually located on the dorsum of the tongue, in front of the vallate papillae, and has a rhomboid border, which is the reason for its alternate name "rhomboid glossitis".[19,26] In the present study, in line with the findings of Kramer et al.[26] and Pedersen et al.,[24] the palate was the site most commonly affected by candidiasis, with the other affected sites being (in the decreasing order of frequency) the dorsum of the tongue, the labial commissure, or the alveolar ridge and the most common type of candidiasis was CAC.

The treatment of choice for a *Candida albicans* infection involves pharmacotherapy with antifungals, such as nystatin, administered as a suspension, applied topically onto the lesion, or in the form of a tablet or ointment. Ketoconazole is recommended particularly for chronic lesions and disseminated infections. Nystatin cream is used in cases of denture-related stomatitis, in which it is applied to the affected tissues as well as to the prosthesis; thus, providing prolonged contact and eliminating any microorganisms present at the denture base. Nystatin oral suspension, when allowed to remain in contact with an oral lesion, can be used to treat chronic and severe cases, with good clinical outcomes. Other medications, such as Daktarin® gel and Micostatin®, also provide high treatment efficacy. However, in most cases, treatment is slow and protracted, sometimes requiring months to induce remission, and potentially causing discomfort and treatment discontinuation by patients. Thrush has a high recurrence rate, which reinforces the need to provide the appropriate treatment for this disease.[19,27]

The recurrence of *Candida* is high. Recurrence was observed in 18 years of follow-up, and some cases required retreatment. This may be related to antifungal resistance or incorrect adherence of some patients to the recommended antifungal treatment.[14,20].

In the present study, we established the clinical and demographic profile of patients with a clinical diagnosis of oral candidiasis. All healthcare providers, including dentists, dental hygienists, and assistants as well as public/private institutions and non-governmental organizations, should be involved in promoting preventive measures and in educating the entire population, with a particular emphasis on individuals who wear dental prostheses. The regular publication of epidemiological data has an extremely important role to play in the implementation of preventive campaigns and in raising awareness of the etiologies of oral candidiasis.

The majority of patients in the present study were Caucasian women who denied alcohol abuse.

CAC was the single most important clinical type of candidiasis detected in patients diagnosed with oral candidiasis, and the most affected oral site was the palate. These data of a large single-center from Brazil agree with previous evidence about the clinical and demographic profile of patients with oral candidiasis.

Acknowledgements

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