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The presentation of oral candidiasis in cases who attended the Wits Oral Health Centre over a 5-year period: a retrospective study.

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The presentation of oral candidiasis in cases who attended the Wits Oral Health Centre over a 5-year period: A retrospective study.

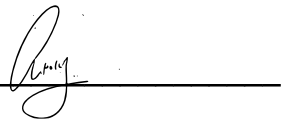
Dr Mishka Antooley

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Dentistry.

JULY 2022

DECLARATION

I Mishka Antooley declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Science in Dentistry at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



(Signature of candidate)

27 day of July 2022

DEDICATION

To my husband and daughter; Shaheen and Zeynep, thank you so much for your love, support and understanding.

To my parents; Noor and Jurene, your immeasurable moral support through this journey are greatly appreciated.

ABSTRACT

INTRODUCTION

Oral candidiasis, remains one of the most prevalent opportunistic fungal infections throughout the world and this high incidence is attributed to the multiplicity of predisposing factors that facilitate the metamorphosis of oral commensal candida to fungal infection. This explains why there has been such an emphasis on oral candidiasis and its associated risk factors. There are few published retrospective studies that asses the prevalence of oral candidiasis, the types diagnosed more frequently as well as the risk factors and treatment prescribed.

PURPOSE

The purpose of this study was to identify the presentation of oral candidiasis according to the diagnostic criteria by Samaranayake over a 5-year period. From this cohort the sites affected will be highlighted, the potential risk factors will be identified, and the treatment options will be commented on.

METHODOLOGY

This was a retrospective observational study making use of quantitative variables as contained in patient files and histological reports dating from 01 January 2015 up to 31 December 2019. Descriptive statistics of mean, median, interquartile range were used to summarize age; and percentage as well as frequency was used to summarize categorical variables. Chi-squared and Fischer's exact test were used to determine the association between the diagnosis and gender, risk factors and site. Mann Whitney U test was used to determine the significant difference between the type of oral candidiasis and age. Binary logistic regression was used to determine the predictor of the type of oral candidiasis. Level of significance was set at p-value less than 0.05.

RESULTS

The cohort consisted of 122 patients of which 59% were females. There was no significant association between gender and the type of oral candidiasis ($p>0.05$). There was no significant difference in the age of the participants that presented with any of the type of oral candidiasis ($p>0.05$). Pseudomembranous candidiasis was the most prevalent type accounting for 52% of the cases and the major risk factor identified was HIV (28%). The tongue (64%) was the most affected site. The treatment most commonly prescribed was a combination of chlorhexidine gluconate 0.2% mouth rinse and miconazole oral gel 2% (59.2%). Denture stomatitis showed a significant association with the use of dental prosthesis ($p=0.000$), chemotherapy and or radiotherapy ($p=0.048$). Furthermore the use of dental prosthesis significantly increased the odds of presenting with denture stomatitis by 99 (11.65 - 841.27) times and chemotherapy and or radiotherapy by 10.8 (1.37-85.10) times. Pseudomembranous candidiasis was significantly associated with the buccal mucosa ($p=0.010$) and the odds of pseudomembranous presenting in the buccal mucosa is significantly increased by 3.187 (1.282-7.927) times, p-value=0.013. Erythematous candidiasis showed significant association with the tongue ($p=0.015$) and the odds of erythematous presenting on the tongue are significantly increased by 4.713 (1.313-16.911) times, p-value=0.017. There was a significant association between oral candidiasis in the buccal mucosa site and HIV ($p=0.031$). Further analysis using binary logistic regression showed that the odds of presenting with oral candidiasis in the buccal mucosa is increased by 2.786 times in patients that are HIV positive compared to patients that are HIV negative. There was a significant association between oral candidiasis in the palatal site and the use of dental prosthesis ($p=0.002$). Further analysis using binary logistic regression showed that the odds of presenting with an oral candidiasis in the palate is increased by 4.981 times in patients with dental prosthesis compared to patients without dental prosthesis.

CONCLUSION

As the results indicate that specific risk factors play an integral role in the development of oral candidiasis and therefore the presentation of oral candidates in given population may differ depending on both local and systemic factors that the patients may be affected by. In South Africa specifically HIV is prevalent and therefore it is expected that pseudomembranous and erythematous candidiasis would predominate within the period of the study. It is interesting to see that although more women presented for the treatment of oral candidiasis, there was no significant association between gender and the type of oral candidiasis.

ACKNOWLEDGEMENTS

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NOMENCLATURE

HIV - Human immunodeficiency syndrome

AIDS - Acquired immunodeficiency syndrome

Chapter 1

1.1 INTRODUCTION

Oral candidiasis, remains one of the most prevalent opportunistic infections throughout the world (Akpan and Morgan, 2002, Farah et al., 2010, Singh et al., 2014, Berberi et al., 2015). The fungal species, *Candida* is a constituent of one's physiological commensal oral flora, however, it is when this species undergoes morphological change that it becomes pathological to cause widespread symptomatic tissue destruction (Patil et al., 2015b, Fourie et al., 2016a). The principle *Candida* species implicated in oral candidiasis remains *Candida albicans* (McCullough and Savage, 2005).

1.2 LITERATURE REVIEW

Candida Albicans

Candida albicans is a dimorphic organism, proliferating in either yeast or hyphal form and is capable of transitioning between the two (Molero et al., 1998, Whiteway and Bachewich, 2007). Under various environmental and genetic conditions fungal blastospores form germ tubes which eventually elongate to form pseudohyphae and hyphae (Molero et al., 1998, Whiteway and Bachewich, 2007). There is a view that the morphological hyphal structure enables this microorganism to be more adherent and contributes to its virulence (Jackson et al., 2014).

Histopathology

Histopathologically, *Candida* organisms may be detected in cytological preparations under the microscope or in tissue sections derived from an incisional biopsy (Neville, 2002). Tissue biopsy is beneficial in cases of hyperplastic candidiasis (Neville, 2002). The candidal yeast and hyphae may be identified using the Periodic Acid-Schiff (PAS) staining

method, where the hyphae take on a characteristic bright magenta color (Neville, 2002). The histopathological findings may vary according to the clinical variant submitted for histology. However, characteristics that are commonly found across all variants of oral candidiasis may include, thickening of the parakeratin layer on the surface of the lesion, the appearance of a chronic inflammatory cell infiltrate below the infected epithelium, clusters of neutrophils in the parakeratin and superficial spinous layer in close proximity to the organisms and characteristic candidal hyphae which are often identified in the parakeratin layer and less frequently in the healthy epithelium (Neville, 2002).

Clinical forms of Oral Candidiasis

Oral candidiasis may present in different clinical forms with clinical classification variations. For the purpose of this study Samaranayake's (Samaranayake, 1991) has been used.

Table 1. Samaranayake's Classification

Primary oral candidiasis
Acute forms
Pseudomembranous
Erythematous
Chronic forms
Hyperplastic
Nodular
Plaque-like
Erythematous
Candida-associated lesions
Denture stomatitis
Angular cheilitis
Median rhomboid glossitis

Linear gingival erythema
Secondary oral candidiasis
Oral manifestations of systemic mucocutaneous candidiasis as a result of diseases such as athymic aplasia and candidiasis endocrinopathy syndrome

A description of the clinical forms:

Pseudomembranous candidiasis

Pseudomembranous candidiasis presents clinically as friable, white plaques on the oral mucosa that when wiped off, leaves an erythematous base (McCullough and Savage, 2005, Patil et al., 2015b, Fourie et al., 2016a). This variant is often observed in new born babies, the elderly, as well as persons with compromised immunity (Samaranayake et al., 2009b). These plaques contain blastospores, fungal hyphae, bacteria, fibrin, inflammatory cells and desquamated epithelial cells (Samaranayake et al., 2009b). Patients may experience tenderness, a burning sensation and difficulty in swallowing (Samaranayake et al., 2009b, Fourie et al., 2016a).

Erythematous candidiasis

Erythematous candidiasis presents clinically as widespread erythema that commonly affects the tongue (with areas of depapillation), the buccal mucosa and the palate (McCullough and Savage, 2005, Samaranayake et al., 2009b, Patil et al., 2015b, Fourie et al., 2016a). Lesions may be asymptomatic or accompanied by a burning sensation (Samaranayake et al., 2009b).

Hyperplastic candidiasis

Hyperplastic candidiasis manifests as a white patch that cannot be rubbed off and can affect any oral mucosal site, however often presents on the buccal mucosa, closer to the

commissures of the mouth (McCullough and Savage, 2005, Samaranayake et al., 2009b, Patil et al., 2015b, Fourie et al., 2016a). Lesions may vary in size from small translucent white areas to larger opaque plaques (Samaranayake et al., 2009b).

Angular cheilitis

Angular cheilitis presents as erythematous fissures radiating from the commissures of the mouth (McCullough and Savage, 2005, Samaranayake et al., 2009b, Patil et al., 2015b, Fourie et al., 2016a). It is usually painful and may be associated with denture stomatitis, decreased immunity or certain vitamin deficiencies. This clinical entity is associated with a fungal and bacterial etiology. (Samaranayake et al., 2009b, Fourie et al., 2016a).

Denture stomatitis

Denture stomatitis commonly affects the denture bearing area of the palate covered by the prosthesis (Jackson et al., 2014). The oral mucosal lesions may be classified by Newton (1962) into three subtypes namely: Type 1: pinpoint hyperemia or localized simple inflammation, Type 2: Diffuse erythema affecting either part of or the entire denture bearing mucosa, and Type 3: A papillary or granular type often affecting the central part of the hard palate or the alveolar ridge (Samaranayake et al., 2009b). Although this condition is usually asymptomatic, it may in certain cases be coupled with discomfort of the mucosa which is in contact with the prosthesis (Samaranayake et al., 2009b).

Median rhomboid glossitis

Median rhomboid glossitis manifests as an erythematous symmetrical localized area on the dorsum of the tongue, that comprises of atrophic filiform papillae (Samaranayake et al., 2009b) .

Linear gingival erythema

Linear gingival erythema manifests as a distinct erythematous band along the gingival margin which may be identified by its distinct erythematous band with little or no plaque buildup and patients may experience gingival bleeding or discomfort (McCullough and Savage, 2005, Samaranayake et al., 2009b, Patil et al., 2015b, Fourie et al., 2016a) .

Chronic mucocutaneous candidiasis syndromes

Chronic mucocutaneous candidiasis syndromes are stubborn forms of candidiasis, where lesions have a poor prognosis and are resistant to topical anti-fungal treatment (Samaranayake et al., 2009b) .

Management

The management of oral candidiasis includes correcting predisposing factors, maintaining good oral hygiene and selecting an appropriate topical or systemic anti-fungal medication (Samaranayake et al., 2009b, Patil et al., 2015b, Fourie et al., 2016a).

Manifestation of oral candidiasis due to an underlying systemic condition

Oral candidiasis may manifest in a variety of systemic conditions such as diabetes mellitus, endocrine disorders, certain malignancies and diseases that contribute to a weakened immune system (Samaranayake et al., 2009b, Fourie et al., 2016a, Rodrigues et al., 2019). It remains the most common oral manifestation of HIV and forms a part of oral lesions most strongly associated with the virus (Blignaut et al., 2002, Aškinytė et al., 2015, Mukherjee et al., 2017). Factors that predispose individuals to oral candidiasis include, smoking, xerostomia, malignancies, being immunocompromised and those that make use of a dental prosthesis (Samaranayake et al., 2009b, Patil et al., 2015b, Fourie et al., 2016a).

The Literature

Several studies conducted in South Africa, extensively investigated the relationship between HIV/AIDS and oral candidiasis (Blignaut et al., 2002, Bajomo et al., 2013, Berberi et al., 2015, Owotade et al., 2016). It is said that there is an increased likelihood that persons living with HIV will present with oral candidiasis at some stage (Schwartz et al., 2019, Tufa and Denning, 2019). A cross-sectional prospective study was conducted at Charlotte Maxeke Johannesburg Academic Hospital, which included 175 participants all attending the HIV clinic (Bajomo et al., 2013). It was reported that amongst the HIV positive cohort, females were most commonly affected and the condition frequently sited was pseudomembranous candidiasis (Bajomo et al., 2013, Reinhardt et al., 2018).

Motivation: Justifying the need for this study

To the best of our knowledge, this proposed study is unique in that it will be first to investigate and report on the clinical presentations of oral candidiasis to be conducted at the Wits Oral Health Centre at Charlotte Maxeke Johannesburg Academic Hospital. The information gathered from this study may direct subsequent prospective studies, focusing on characteristics of the condition, treatment patterns, resource utilization, costs, and clinical outcomes associated with the disease.

1.3 AIM

To identify the presentation of oral candidiasis according to the diagnostic criteria by Samaranayake (1991) that presented to the Wits Oral Health Centre, over a 5-year period, from 2015-2019.

1.4 OBJECTIVES

1. To identify the **presentation** of oral candidiasis according to the diagnostic criteria of Samaranayake (1991) in the specified cohort.
2. To determine the **sites** affected by oral candidiasis.
3. To highlight potential **risk factors** that may have an association with oral candidiasis.
4. To identify various **treatment** modalities associated with oral candidiasis in this cohort.

CHAPTER 2

2.1 ETHICAL CLEARANCE

The title was approved by Faculty (Appendix - B). Ethical clearance was obtained from the Human Research Ethics Committee, University of The Witwatersrand (Appendix - C). Permission to access data for research was obtained from the Head of School, Wits Oral Health Centre (Appendix - D). All patients were assigned a number and their information kept anonymous.

2.2 METHODOLOGY

2.2.1 STUDY DESIGN

This was a retrospective observational study making use of quantitative variables as contained in patient files and histological reports.

All histologically confirmed cases of oral candidiasis was extracted from the National Heath Laboratory Services Academic Affairs, Research and Management System for data analysis.

Files dating from 01 January 2015 up to 31 December 2019 was assessed and applicable information noted on a standard data collection sheet.

2.2.2 INCLUSION AND EXCLUSION CRITERIA

Only cases with an existing confirmatory laboratory diagnosis was accepted.

Only patients attending the Wits Oral Health Centre was accepted.

Only cases that fell within the diagnostic criteria by Samaranayake (1991) was assessed.

2.2.3 STUDY SAMPLING

2.2.3.1 SAMPLE SIZE

Selecting the correct sample size is important to ensure an adequate number of patients to draw conclusive evidence from the various clinical forms of oral candidiasis that presented at the Wits Oral Health Centre. All patients' records with supporting laboratory diagnosis that met the inclusion criteria was included in the study.

2.2.3.2 STUDY INSTRUMENTATION

The data was retrieved from existing laboratory reports and patient records from the Wits Oral Health Centre.

2.2.4 DATA EXTRACTION SHEET

The information was transferred from the file using a standard data extraction sheet, formulated by the researcher (Appendix - A).

The data form included patient demographics; the age and gender. The clinical aspect of the disease namely the diagnosis, how the diagnosis was made, the intra oral site of the lesion, risk factors involved and the treatment prescribed.

Samaranayake's proposed classification of oral candidiasis was used as a standard guide (Samaranayake, 1991).

2.2.5 STATISTICAL ANALYSIS

Objectives	Variables	Data analysis
To identify the presentation of oral candidiasis in the specified cohort.	Presentation of candidiasis – Categorical variable	Frequencies and percentages will be used to summarize the forms of candidiasis.
To determine the sites affected by oral candidiasis.	Sites affected by oral candidiasis – Categorical variable	Frequencies and percentages will be used to summarize the sites affected by oral candidiasis
To highlight potential risk factors that may have an association with oral candidiasis.	Identify risk factor – Categorical variable	Frequencies and percentages will be used to summarize risk factors. Association between the risk factors of oral candidiasis and the site will be performed using Chi-Squared test or Fischer's exact test as appropriate. Association between the risk the clinical forms of oral candidiasis and the site will be performed using Chi-Squared test or Fischer's exact test as appropriate.
To identify various treatment modalities associated with oral candidiasis in this cohort.	Identify various treatment modalities – Categorical variables	Frequencies and percentages will be used to summarize the various treatment modalities.

Descriptive statistics of mean, median, interquartile range were used to summarize age; and percentage as well as frequency was used to summarize categorical variables. Chi-squared and Fischer's exact test were used to determine the association between the diagnosis and gender, risk factors and site. Mann Whitney U test was used to determine the significant difference between the type of oral candidiasis and age. Binary logistic regression was used to determine the predictor of the type of oral candidiasis. Level of significance was set at p-value less than 0.05.

CHAPTER 3

3.1 RESULTS

There were 139 cases of oral candidiasis laboratory reports provided by the NHLS AARMS of which 17 cases were diagnosed as superimposed candidiasis which was excluded based on Samaranayake's classification of oral candidiasis 1991, furthermore there were zero cases of secondary oral candidiasis recorded.

3.1.1 DEMOGRAPHIC INFORMATION

Demographic characteristics considered in this study included age and gender. The mean age of the participants in the study was 49.12 years (SD ± 16.75 years). The median age was 49 (Interquartile range ± 36.5-64.25) and the range was 12 - 83 years (Table 2). Approximately 59% of the participants were female, and 41% were males (Figure 1)

Table 2: Demographic characteristics of the patients (N=122)

Age in years	
Mean (SD)	49.12(16.75)
Median (Interquartile range)	49 (36.5-64.25)
Minimum - Maximum	12 - 83
Gender, n (%)	
Female	72 (59)
Male	50 (41)

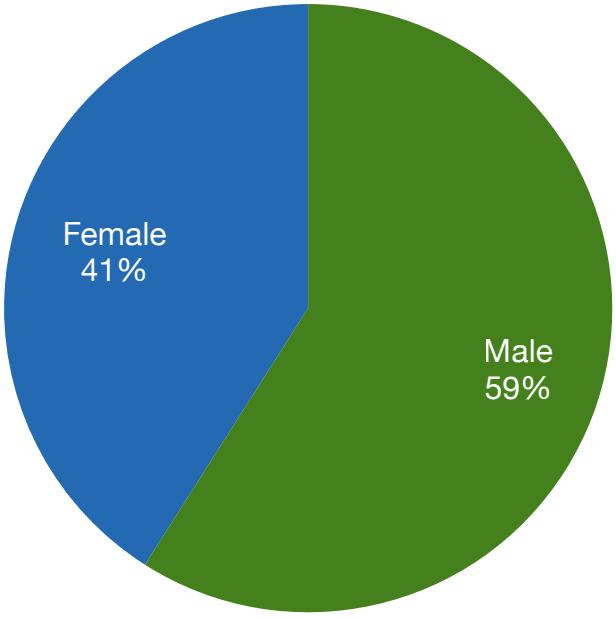

Figure 1: Gender of the participants (n=122)

3.1.2 RISK FACTORS

Risk factors were reported in 60.7% (n=74) of the participants, of which HIV was the most prevalent with 28%. The use a dental prosthesis was the second most prevalent risk factor with 18%, followed by smoking (16%), the use of a steroid inhaler (9%), diabetes (4%) and the least reported was participants who received chemotherapy and or radiotherapy (3%) (Figure 2).

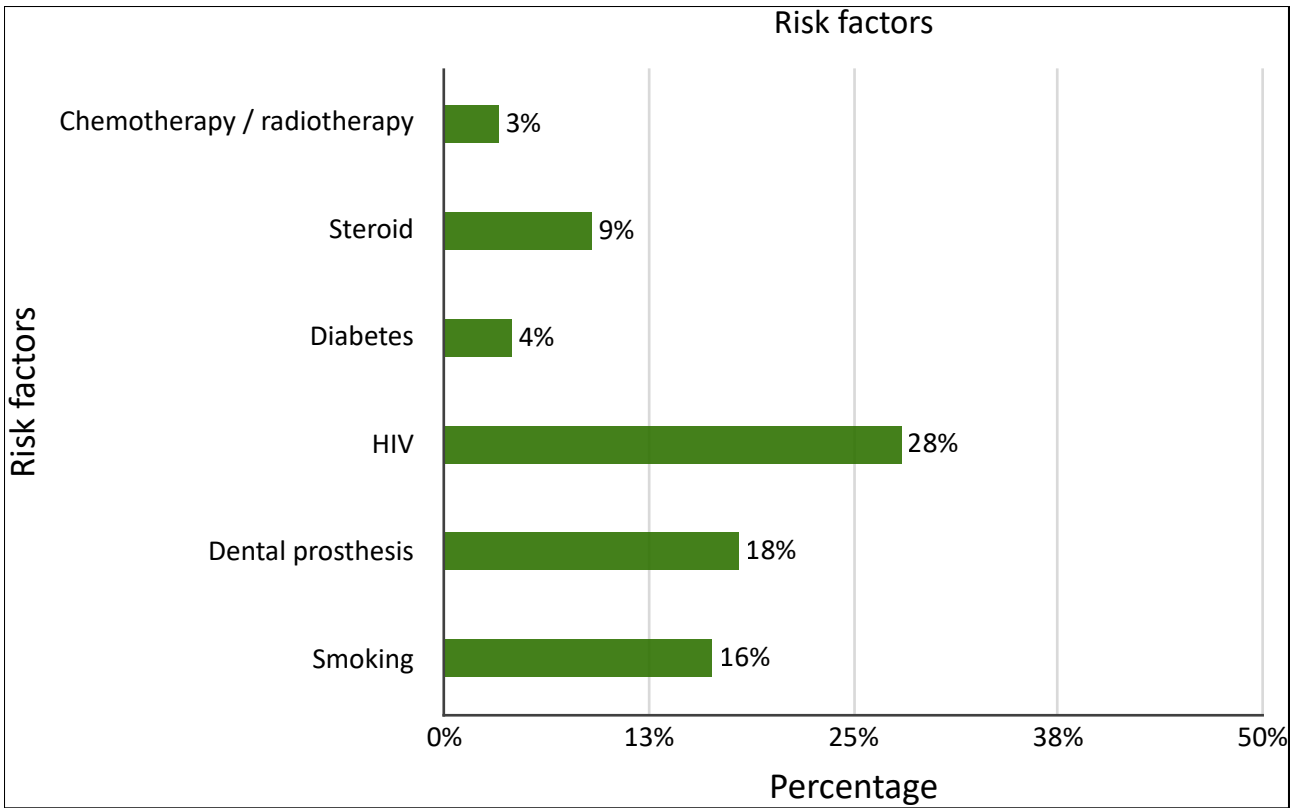

Figure 2: Risk factors (n=122)

3.1.3 SYMPTOMS

Symptoms were reported in 15.6% (n=19) of the cases of which pain (11%) was the most reported symptom followed by burning (3%), dry mouth (3%), difficulty eating (3%) and bleeding (2%). Of all the cases, 2% was reported as asymptomatic.

Table 3: Symptoms (n=122)

Symptoms	n	%
Pain	11	9
Burning	3	2.5
Asymptomatic	2	1.6
Dry mouth	3	2.5
Bleeding	2	1.6
Difficulty eating	3	2.5

3.1.4 THE PRESENTATION OF ORAL CANDIDIASIS

There were no cases of secondary candidiasis recorded and of the 122 cases pseudomembranous candidiasis (51.6%) was the most prevalent followed by erythematous candidiasis (18.9%). Chronic hyperplastic candidiasis was present in 10.7% of the participants of which one case indicated the presence of mild to moderate dysplasia. Denture stomatitis was reported in 9.8% of cases, angular cheilitis in 4.1% and median rhomboid glossitis in 1.6%. 11.5% of the cases were not specified (Table 4). Certain cases presented with more than one type of oral candidiasis, this include pseudomembranous candidiasis and denture stomatitis reported in two cases, pseudomembranous candidiasis and erythematous candidiasis reported in two cases, pseudomembranous candidiasis and angular cheilitis reported in two cases and erythematous candidiasis and denture stomatitis reported in four cases (Table 5).

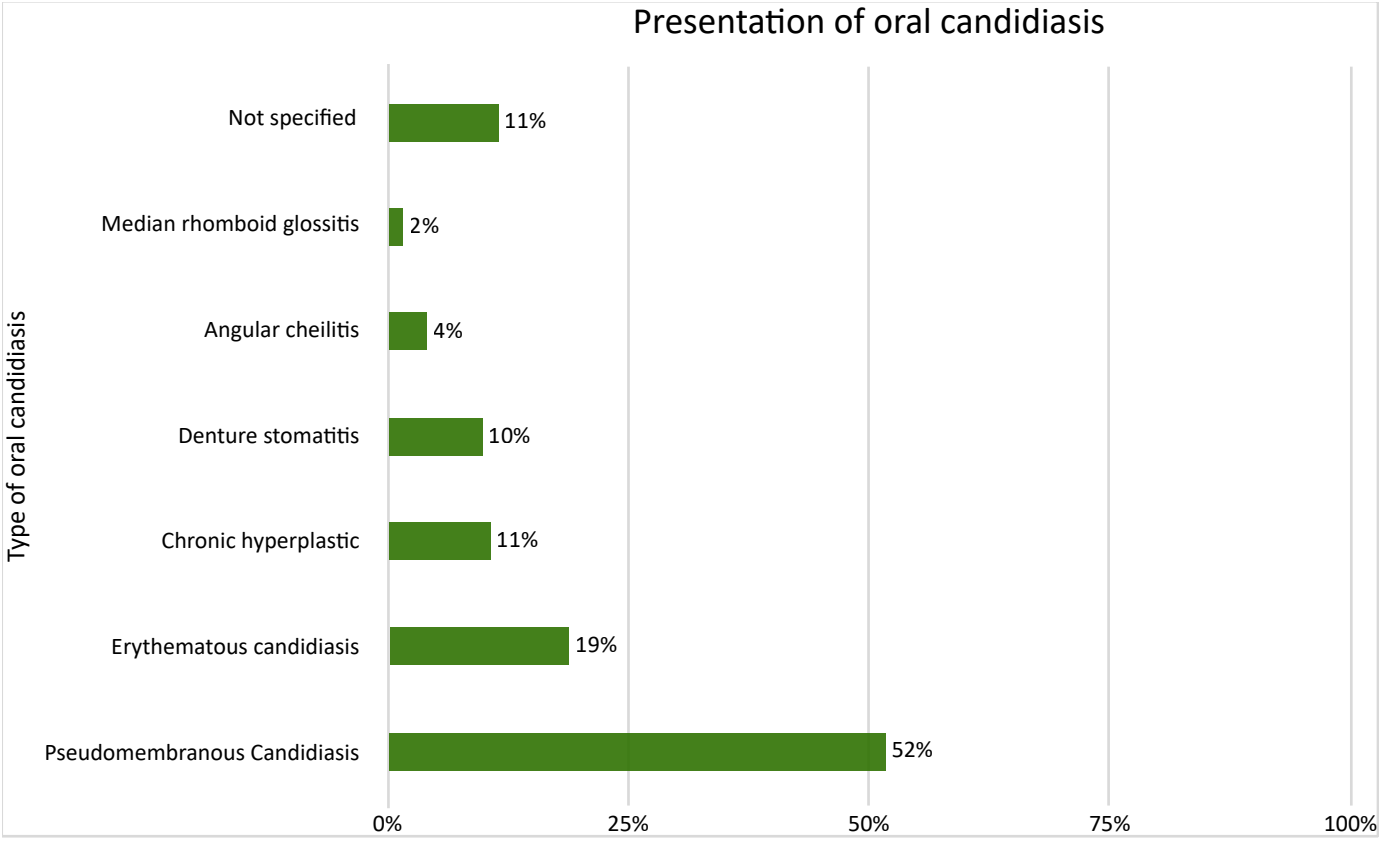

Figure 3: Frequency of type of oral candidiasis (n=122)

Table 4: Type of oral candidiasis (n=122)

	n	%
Pseudomembranous candidiasis	63	51.6%
Erythematous candidiasis	23	18.9%
Chronic hyperplastic	13	10.7%
Denture stomatitis	12	9.8%
Angular cheilitis	5	4.1%
Median rhomboid glossitis	2	1.6%
Not specified	14	11.5%

*note there are two types of oral candidiasis reported in 10 patients

Table 5: Cases of oral candidiasis with more than one type

	n
Pseudomembranous candidiasis and denture stomatitis	2
Pseudomembranous candidiasis and erythematous candidiasis	2
Pseudomembranous candidiasis and angular cheilitis	2
Erythematous candidiasis and denture stomatitis	4

3.1.5 ASSOCIATION BETWEEN DIAGNOSIS AND DEMOGRAPHICS

There was no significant association between gender and the type of oral candidiasis ($p>0.05$) as shown in Table 6. There was no significant difference in the age of the participants that presented with any of the type of oral candidiasis ($p>0.05$). The p-value of the Fisher's exact test (gender) and Mann-Whitney test (age) is presented in Table 6.

Table 6: Association between diagnosis and demographics

	Demographics	
Type of OC	**Age**	**Gender**
Pseudomembranous candidiasis	0.706	0.582
Erythematous candidiasis	0.115	1.000
Chronic hyperplastic	0.997	0.378
Denture stomatitis	0.395	1.000
Angular cheilitis	0.755	0.078
Median rhomboid glossitis	0.518	1.000
Not specified	0.300	0.083
Fischer's exact test – Gender Mann Whitney U test – Age		

3.1.6 ASSOCIATION BETWEEN DIAGNOSIS AND RISK FACTORS

Denture stomatitis showed a significant association with the use of dental prosthesis ($p=0.000$) and with chemotherapy/radiotherapy ($p=0.048$) as shown in Table 7.

Table 7: Association between diagnosis and risk factors

Diagnosis	HIV	Smoking	Diabetes	Dental Prosthesis	Steroids	Chemotherapy / Radiotherapy
Pseudomembranous candidiasis	0.687	0.810	0.058	0.639	0.532	1.000
Erythematous candidiasis	0.608	0.531	0.582	1.000	0.433	0.571
Chronic hyperplastic	0.754	1.000	1.000	0.459	1.000	1.000
Denture stomatitis	0.176	0.688	1.000	0.000*	1.000	0.048*
Angular cheilitis	0.618	0.590	1.000	0.584	1.000	1.000
Median rhomboid glossitis	1.000	1.000	1.000	1.000	1.000	1.000
Not specified	1.000	0.700	1.000	0.461	0.360	1.000

*p-value less than 0.05

Further analysis using univariate binary logistic regression to determine the predictor of denture stomatitis is outlined in Table 8. The use of dental prosthesis significantly increased the odds of presenting with denture stomatitis by 99 (11.65 - 841.27) times in reference to the patients that did not use dental prosthesis. In addition, chemotherapy/ radiotherapy significantly increased the odds of presenting with denture stomatitis by 10.8 (1.37-85.10) times compared to the patients that did not undergo chemotherapy/ radiotherapy.

Table 8: Risk factor predictor of denture stomatitis

Risk factor	Univariate Binary Logistic Regression	
Dental prosthesis	Exp (Lower - Upper) 95%CI	p-value
Yes	99(11.65 - 841.27)	0.000*
No	Reference	
Chemotherapy		
Yes	10.8(1.37-85.10)	0.024*
No	Reference	

*p-value less than 0.05

3.1.7 SITE OF ORAL CANDIDIASIS

The site that was commonly affected included the tongue (64%), specifically the dorsal aspect of the tongue (83%), (Figure 4 and 5). Other sites of the tongue include the ventral aspect (7%), lateral aspect (7%), whilst 3% of the sites on the tongue were not specified (Figure 5). The palate was the second most reported site with 33% followed by the buccal mucosa (24%), commissures of the mouth (4%), the labial mucosa (3%), gingiva (2%) and floor of the mouth (2%). 4% of the cases included other sites namely; maxillary alveolar ridge, maxillary alveolar mucosa, lingual mucosa, retromolar pad area and the vestibule (Figure 4).

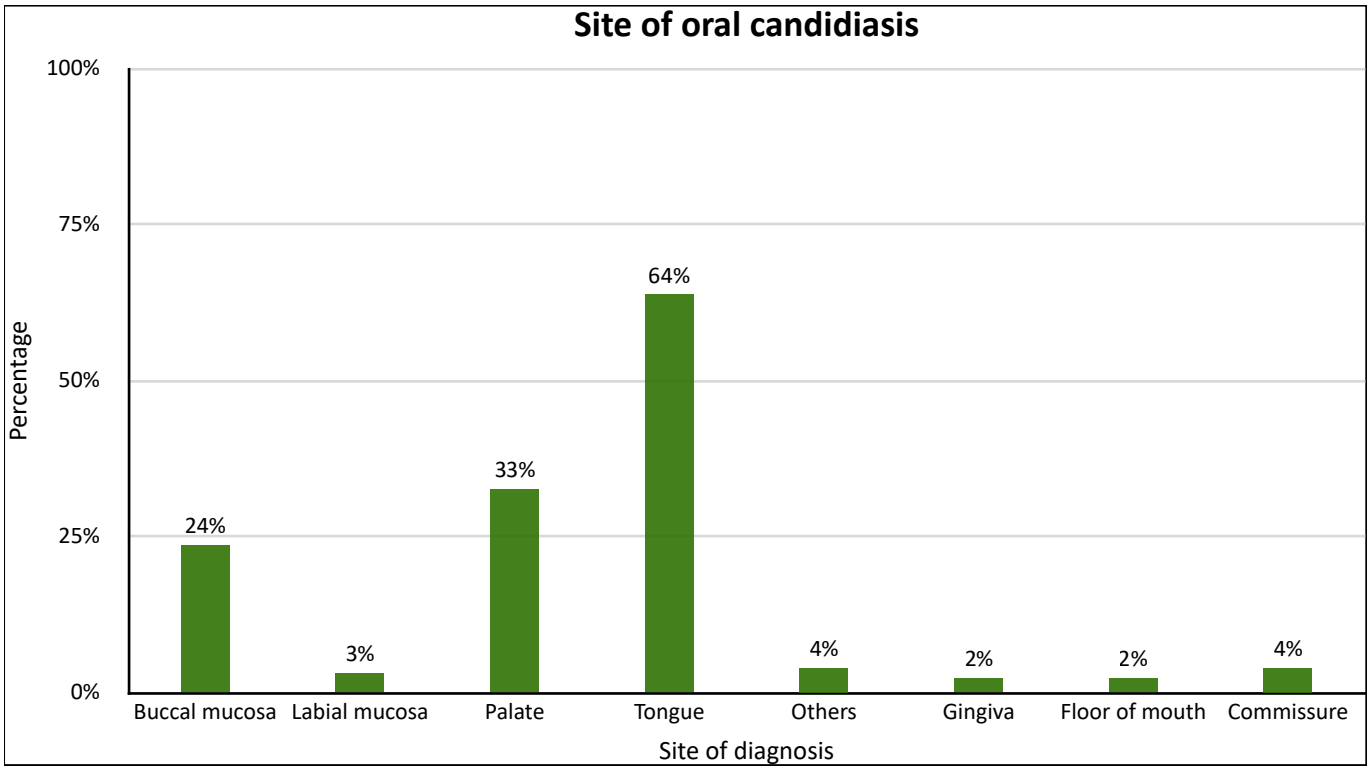

Figure 4: Intra oral site affected by candidiasis (n=122)

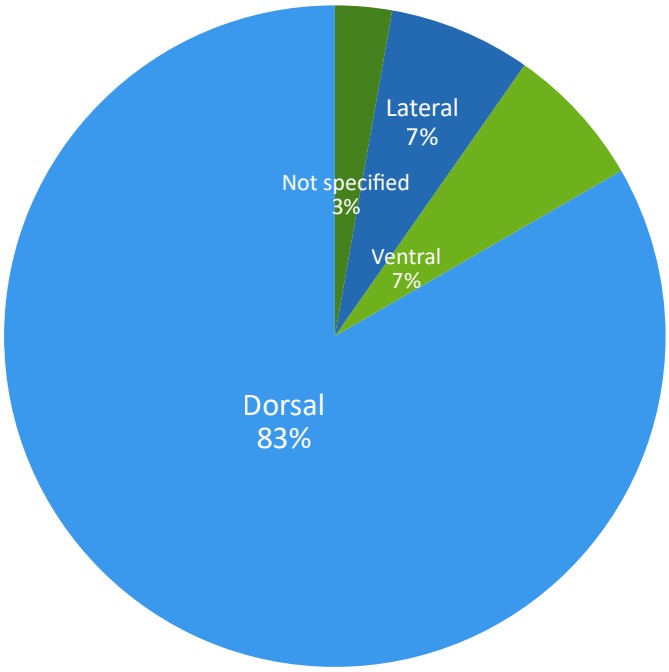

Figure 5: The surfaces of the tongue affected by oral candidiasis (n=72)

3.1.8 ASSOCIATION BETWEEN THE TYPE OF ORAL CANDIDIASIS AND SITE

Further analysis using univariate binary logistic regression was used to determine the dimension of the association in all the diagnoses that showed significant association using Fischer's exact test with the site of diagnosis ($p<0.05$) (Table 9).

Pseudomembranous candidiasis

Using Fischer's exact test, pseudomembranous candidiasis was significantly associated with the buccal mucosa ($p=0.010$). Further analysis using univariate binary logistic regression to determine the dimension of the relationship showed that the odds of pseudomembranous candidiasis presenting in the buccal mucosa is significantly increased by 3.187 (1.282-7.927) times, p-value=0.013, compared to the absence of pseudomembranous in the buccal mucosa.

Table 9: Relationship between type of oral candidiasis and site

	Pseudomembranous	Erythematous	Chronic hyperplastic	Denture stomatitis	Angular cheilitis	Median Rhomboid Glossitis	Not specified
Buccal mucosa	0.010*	0.432	0.037*	0.067	0.59	1	0.317
Labial mucosa	1	0.582	0.362	1	1	1	0.39
Palate	1	0.811	0.22	0.000*	0.657	0.102	0.034
Tongue	0.707	0.015*	0.373	0.348	0.535	0.056	0.569
Others	0.366	0.582	0.436	1	1	1	1
Gingiva	0.61	0.469	0.289	1	1	1	1
Floor of mouth	0.245	1	1	1	1	1	1
Commissures	0.672	0.582	1	1	1	0.000*	1

Erythematous candidiasis

Erythematous candidiasis showed significant association with the tongue (p=0.015). Further analysis using univariate binary logistic regression to determine the dimension of the relationship showed that the odds of erythematous candidiasis presenting on the tongue are significantly increased by 4.713 (1.313-16.911) times, p-value=0.017, compared to the absence of erythematous on the tongue.

Denture stomatitis

Denture stomatitis showed a significant association with the palate (p=0.00). Univariate binary logistic regression showed that the palatal site was not a predictor of denture stomatitis (B=0.00 and p-value=0.996).

Chronic Hyperplastic

Chronic Hyperplastic showed a significant association with buccal mucosa (p=0.037). Univariate binary logistic regression showed that buccal mucosa site was not a predictor of chronic hyperplastic (B=0, p=0.998).

Median rhomboid glossitis

Median rhomboid glossitis showed significant association with the commissure of the mouth (p=0.000). Univariate binary logistic regression showed that commissure of the mouth was not a predictor of median rhomboid glossitis (B=0, p=0.999).

3.1.9 ASSOCIATION BETWEEN ORAL CANDIDIASIS AND RISK FACTORS

There was a significant association between the prevalence of oral candidiasis and the palate (p=0.034) (Table 10). Further analysis using univariate binary logistic regression showed that patients are 7.348 (0.926 – 58.318) times more likely to be diagnosed with oral candidiasis in the palate, but it is not significant, p=0.059 (Table 11). Oral candidiasis showed no significant risk factor with gender, age and risk factors (p-value>0.05).

Table 10: Association between oral candidiasis and risk factors

Demographics	p-value
Gender	0.083
Age	0.300
Risk factors	
Smoking	0.700
Dental prosthesis	0.461
HIV	1
Diabetes	1

Steroids use / asthma	0.360
Chemotherapy	1
Site	
Buccal mucosa	0.317
Labial mucosa	0.390
Palate	0.034*
Tongue	0.768
Gingiva	1
Floor of mouth	1
Commissure	1
Others	1
Mann Whitney U – Age Fischer's exact test – gender, smoking, dental prosthesis, HIV, diabetes, chemotherapy, buccal mucosa, labial mucosa and palate. Chi-Squared test – Steroids use	

Table 11: Predictor of oral candidiasis

Risk factor	**Univariate Binary Logistic Regression**	
Palate	Exp (Lower - Upper) 95%CI	p-value
Yes	7.348 (0.926 – 58.318)	0.059
No	Reference	

3.1.10 ASSOCIATION BETWEEN THE SITE OF ORAL CANDIDIASIS AND RISK FACTORS

Table 12: Association between site and risk factors

Site	Risk factors					
	Smoking	**Dental Prosthesis**	**HIV**	**Diabetes**	**Chemotherapy / radiotherapy**	**Steroid use**
Buccal mucosa	0.566	0.277	0.031*	0.592	1	1
Labial mucosa	0.516	0.554	1	1	1	1
Palate	0.800	0.002*	0.83	1	0.103	0.749
Tongue	1	0.148	0.209	0.653	1	0.324
Others	1	0.637	0.811	1	1	1
Gingiva	1	1	0.559	1	1	1
Floor of mouth	1	1	0.187	1	1	1
Commissure of the mouth	0.590	0.584	0.618	1	1	1

HIV

There was a significant association between oral candidiasis in the buccal mucosa site and HIV (p=0.031). Further analysis using binary logistic regression showed that the odds of presenting with an oral candidiasis in the buccal mucosa is increased by 2.786 times in patients that are HIV positive compared to patients that are HIV negative.

Table 13: HIV as a predictor of oral candidiasis in the buccal mucosa

Risk factor	**Univariate Binary Logistic Regression**	
HIV	Exp (Lower - Upper) 95%CI	p-value
Yes	2.786 (1.157 – 6.706)	0.022
No	Reference	

Dental prosthesis

There was a significant association between oral candidiasis in the palatal site and dental prosthesis (p=0.002). Further analysis using binary logistic regression showed that the odds of presenting with an oral candidiasis in the palate is increased by 4.981 times in patients with dental prosthesis compared to patients without dental prosthesis.

Table 14: Dental prosthesis as a predictor of oral candidiasis in the buccal mucosa

Risk factor	**Univariate Binary Logistic Regression**	
Dental prosthesis	Exp (Lower - Upper) 95%CI	p-value
Yes	4.981(1.875-13.229)	0.001
No	Reference	

3.1.11 DIAGNOSTIC CHOICE OF TECHNIQUE

As seen in figure 6, 97% of the cases were diagnosed by cytological smear and 3% with tissue biopsy.

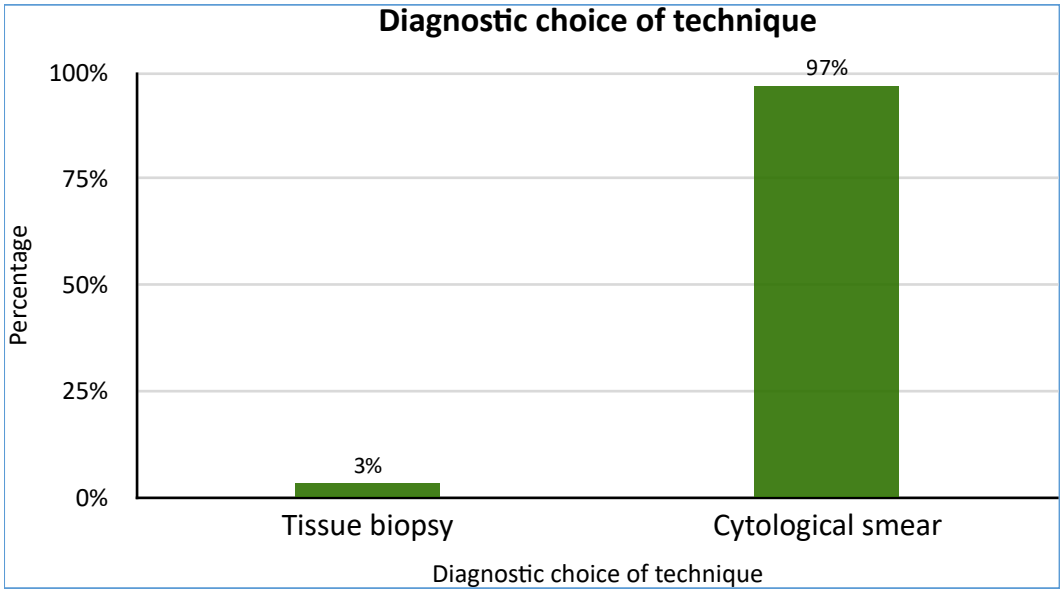

Figure 6: Diagnostic technique choice

3.1.12 PHARMACOLOGICAL TREATMENT

Treatment was recorded in 49 cases. As seen in table 15, some treatment included the prescription of a single drug and some included the prescription of multiple drugs. The combination that was most commonly prescribed was chlorhexidine gluconate 0.2% mouth rinse and miconazole (Daktarin) oral gel 2% (59.2%). The second most commonly prescribed drug included miconazole (Daktarin) oral gel 2% (14.3%), followed by nystatin suspension (6.1%). The drugs that were least prescribed included a combination of fluconazole tablets and nystatin suspension (4.1%), chlorhexidine gluconate 0,2% mouth rinse, miconazole gel 2% and nystatin suspension (4.1%), chlorhexidine gluconate 0,2% mouth rinse and nystatin suspension (2%), miconazole gel 2% and nystatin suspension (2%), fluconazole 150 mg tablets and chlorhexidine gluconate 0.2% mouth rinse (2%). Single drugs that were least prescribed included chlorhexidine gluconate 0,2% mouth rinse (2%), fluconazole 150 mg tablets (2%) and miconazole 400 mg tablets (2%).

Table 15: Pharmacological treatment

Treatment (n= 49)	n	%
Chlorhexidine gluconate 0,2% mouth rinse	1	2,0%
Chlorhexidine gluconate 0,2% mouth rinse and nystatin suspension	1	2,0%
Miconazole oral gel 2% and nystatin suspension	1	2,0%
Fluconazole 150 mg tablets	1	2,0%
Fluconazole tablets 150 mg tablets and Chlorhexidine gluconate 0,2% mouth rinse	1	2,0%
Miconazole 400 mg tablets	1	2,0%
Fluconazole tablets and nystatin suspension	2	4,1%
Chlorhexidine gluconate 0,2% mouth rinse, miconazole gel 2% and nystatin Suspension	2	4,1%
Nystatin suspension	3	6,1%
Miconazole oral gel 2%	7	14,3%
Chlorhexidine gluconate 0,2% mouth rinse and Miconazole oral gel 2%	29	59,2%

Chapter 4

4.1 DISCUSSION

Oral candidiasis, remains one of the most prevalent opportunistic fungal infections throughout the world (Akpan and Morgan, 2002, Farah et al., 2010, Singh et al., 2014, Berberi et al., 2015). The main reason for the high incidence of oral candidiasis is due to the multiplicity of predisposing factors that facilitate the change of oral commensal candida to fungal infection (Samaranayake et al., 2009a).

This retrospective study included 122 participants that attended the Wits oral health centre over a 5-year period (2015-2019). Laboratory reports were received from the National Heath Laboratory Services Academic Affairs, Research and Management System and was meticulously assessed together with clinical data from the patients' records. In this study the various forms of oral candidiasis, the risk factors and site, in addition to the treatment were noted.

There were 17 cases of superimposed candidiasis, however this was excluded from the study based on Samaranayake's 1991 classification of oral candidiasis (Samaranayake, 1991). This was not an uncommon finding as it is known that *Candida* is a commensal that may co-exist with other pathological entities (Rossie and Guggenheimer, 1997, Dangi et al., 2010). There were no cases of secondary oral candidiasis reported and this may be due to the fact that this group of candida infection may be diagnosed and treated by other medical professionals based on its mucocutaneous nature (Patil et al., 2015a).

In this study the cohort consisted of predominantly women (59%), however there was no significant association between the gender and the type of oral candidiasis ($p>0.05$). The

mean age was 49.12 years (SD ± 16.75 years), whilst the median age was 49 (Interquartile range ± 36.5-64.25) years. The minimum and maximum age was 12 and 83 years. There was no significant difference in the age of the patients that presented with any of the type of oral candidiasis ($p>0.05$) and these findings were consistent with a study reported in Brazil (Reinhardt et al., 2018). There are studies that have suggested that women are more commonly affected by oral candidiasis as opposed to men; however it is known that women are more likely to seek medical attention for *Candida* infection and the incidence increases with age (Reinhardt et al., 2018). In contrast, men are less likely to seek medical attention and this has been noted by the theory of health and help seeking behaviors (Galdas, 2009, Cornally and McCarthy, 2011).

Pain was reported in 9% of the patients and was also the most reported symptom. Other symptoms reported include a burning sensation (3%), xerostomia (3%), difficulty eating (3%), bleeding (2%) and 2% of the participants reported being asymptomatic. It is interesting to note that pain was the most reported symptom in contrast to the literature where oral candidiasis is often associated with a burning sensation (Samaranayake et al., 2009a, Williams and Lewis, 2011). There is a possibility that burning may have been translated into pain, as a burning sensation is in fact a type of pain (Świeboda et al., 2013).

Pseudomembranous candidiasis accounted for majority of the cases (52.5%) followed by erythematous candidiasis (20.8%). These findings are understandable given the context that there is still a high incidence of HIV in South Africa and the association between oral candidiasis and HIV is known (Zhang et al., 2009, Bodhade et al., 2011, Patil et al., 2015a, Mushi et al., 2017). It has been said that there is an increased likelihood that a person infected with HIV will present with oral candidiasis at least once in their disease life span

(Samaranayake et al., 2009a, Mushi et al., 2017). Pseudomembranous candidiasis was the most prevalent form of oral candidiasis amongst HIV-infected populations in sub-Saharan Africa, with 66.6% in South Africa (Mushi et al., 2017). Another study conducted at Johannesburg hospital outpatient HIV clinic reported just over half of the participants presented with pseudomembranous candidiasis (Bajomo et al., 2013). Chronic hyperplastic candidiasis was the least common of the triad of major clinical variants, being present in only 10.7% of the participants of which one case involved mild to moderate dysplasia. This too is consistent with the literature (Patil et al., 2015a). Of the *Candida*-associated lesions, denture stomatitis was the most prevalent, reported in 9.8% of cases, followed by angular cheilitis in 4.1% and median rhomboid glossitis in 1.6%. A further 11.5% of the cases were not specified.

HIV was the most prevalent risk factor reported in this study (28%). This may explain the prevalence of pseudomembranous and erythematous candidiasis. The use of dental prosthesis (18%) was the second most prevalent risk factor, followed by smoking (16%), the use of a steroid inhaler (9%), diabetes (4%) and the least reported was chemotherapy and or radiotherapy (3%). The factors listed above are known risk factors that contribute to the pathogenicity of oral candidiasis (Williams and Lewis, 2011, Sardi et al., 2013, Patil et al., 2015a, Fourie et al., 2016b).

A retrospective cross-sectional study conducted in Brazil at Pelotas dental School, assessed 1594 patients diagnosed with oral candidiasis (Reinhardt et al., 2018). A significant portion of the patients reported with chronic atrophic candidiasis (95%) of which approximately 59.3% of the candidates wore dentures with the most common site affected being the palate (90.9%)(Reinhardt et al., 2018). This study reinforces the observation made in this study of a dental prosthesis being a risk factor in oral candidiasis.

The site that was commonly affected included the tongue (64%), specifically the dorsal aspect of the tongue (83%). The tongue acts as a primary reservoir for oral *Candida* carriage and the dorsal surface of the tongue specifically is the initiating point of infection for majority of the clinical forms of oral candidiasis (Vila et al., 2020). The palate was the second most reported site with 33% followed by the buccal mucosa (24%), commissures of the mouth (4%), the labial mucosa (3%), gingiva (2%) and floor of the mouth (2%). Other sites namely; the maxillary alveolar ridge, maxillary alveolar mucosa, lingual mucosa, retromolar pad area and the vestibule accounted for 4% of the cases. It is also evident that oral candidiasis may affect any mucosal surfaces and there may be preferred sites however there is no mucosal surface that may be spared.

There was no documentation of non-pharmacological management of oral candidiasis in the patient records, with 40.2% of the cases pharmacologically treated. The pharmacological treatment combination refers to two or more drugs prescribed to the patient upon diagnosis. The treatment combination most commonly prescribed was chlorhexidine gluconate 0.2% mouth rinse and miconazole oral gel 2% (59.2), followed by miconazole oral gel 2% (14.3%) alone and nystatin suspension (6.1%). There are studies that suggest that chlorhexidine gluconate 0.2% mouth rinse may be used as an adjunctive treatment when treating oral candidiasis (Ellepola and Samaranayake, 2001, Fourie et al., 2016b) however it is not common practice according to the literature and it is advised to use first line treatment such as nystatin oral suspension as well as amphotericin B (Samaranayake et al., 2009a, Garcia-Cuesta et al., 2014). Azoles should be considered as a second line of treatment due to these drugs gradually losing their potency as a result of the emergence of drug resistant strains (Samaranayake et al., 2009a, Patil et al., 2015a). Chlorhexidine and nystatin pharmacological combination was prescribed in one case and in two cases nystatin suspension, chlorhexidine gluconate 0.2% and miconazole

was prescribed in one sitting. Studies that assess the effectiveness of using multiple anti-fungal drugs in combination are few. However there is a study that was conducted in 1989 that proved the anti-fungal ineffectiveness of chlorhexidine-nystatin drug combination (Barkvoll and Attramadal, 1989). In a clinical review it was stated that topical anti-fungal medication should be the first line of treatment, followed by systemic anti-fungal medication, which should be reserved for recalcitrant cases. Furthermore, it also suggests that any topical anti-fungal agent (polyene derivative and azole) should be equally effective for first line treatment, if correctly used (Fourie et al., 2016b).

Clinicians should review the manner in which they treat oral candidiasis and should formulate an evidence based approach in treating these lesions especially given the fact that oral candidiasis is a complex disease that is multifactorial and may be recalcitrant to treatment as a result of drug resistance. There are few acceptable treatments, many of which various *Candida* species have already indicated some form of resistance. It is imperative to take the risk factor into account as this will determine the success of one's treatment.

A few interesting associations were identified in the study many of which have already been mentioned throughout the literature.

Denture stomatitis showed a significant association with patients who were receiving chemotherapy and or radiotherapy ($p=0.048$) and further analysis using univariate binary logistic regression indicated that chemotherapy and or radiotherapy significantly increased the odds of presenting with denture stomatitis by 10.8 (1.37-85.10) times. This information is consistent with the literature as receiving chemotherapy and or radiotherapy is a risk factor for developing oral candidiasis, it is now evident from the data that these patients

are at a significant risk for developing denture stomatitis specifically (Samaranayake et al., 2009a, Fourie et al., 2016b).

In addition, denture stomatitis showed a significant association with the use of dental prosthesis (p=0.000) and further analysis using univariate binary logistic regression indicated that the use of dental prosthesis significantly increased the odds of presenting with denture stomatitis by 99 (11.65 - 841.27) times. There was a significant association between oral candidiasis in the palate and the use of a dental prosthesis (p=0.002). Further analysis using binary logistic regression showed that the odds of presenting with an oral candidiasis in the palate is increased by 4.981 times in patients with dental prosthesis compared to patients without dental prosthesis. Although, denture stomatitis showed a significant association with the palate (p=0.00), it was not a significant predictor of denture stomatitis. These findings are consistent with the literature as denture stomatitis is significantly associated with the use of a dental prosthesis and the use of a dental prosthesis increases ones risk of developing denture stomatitis (Shulman et al., 2005, Gendreau and Loewy, 2011, Kossioni, 2011, Reinhardt et al., 2018). The prevalence of denture stomatitis in denture wearers is high (Shulman et al., 2005, Gendreau and Loewy, 2011, Kossioni, 2011, Reinhardt et al., 2018), In addition to wearing a dental prosthesis there are other predisposing factors that contribute to the development of denture stomatitis such as continuous use thereof (Gendreau and Loewy, 2011, Kossioni, 2011). Furthermore it is known that denture stomatitis invariably affects the palatal mucosa. It has been said that *Candida*-associated denture stomatitis occurs in up to 65% of denture wearers (Webb et al., 1998).

There was a significant association between oral candidiasis in the buccal mucosa and HIV (p=0.031). Further analysis using binary logistic regression showed that the odds of presenting with oral candidiasis in the buccal mucosa is increased by 2.786 times in

patients that are HIV positive, compared to patients that are HIV negative. Although HIV has not shown a specific association with a single entity of oral candidiasis one can deduce that this may be due to the fact that HIV is a risk for all types of oral candidiasis as it strongly associates with many oral candida infections.

In this study the association between the diagnosis and oral site was also assessed. Pseudomembranous candidiasis was significantly associated with the buccal mucosa (p=0.010). Further analysis using univariate binary logistic regression indicated that the odds of pseudomembranous presenting in the buccal mucosa is significantly increased by 3.187 (1.282-7.927) times, p-value=0.013. This information is consistent with the literature (Patil et al., 2015a)

Erythematous candidiasis showed significant association with the tongue (p=0.015). Further analysis using univariate binary logistic regression indicated that the odds of erythematous presenting in the tongue are significantly increased by 4.713 (1.313-16.911) times, p-value=0.017. This information is consistent with the literature as erythematous candidiasis commonly affects the tongue amongst other surfaces in the oral cavity (Patil et al., 2015a).

Chronic hyperplastic candidiasis showed a significant association with buccal mucosa (p=0.037) but buccal mucosa was not a significant predictor of chronic hyperplastic candidiasis. Chronic hyperplastic candidiasis may affect any oral mucosal site however the retro-commissural and buccal mucosa are frequently affect sites (Sitheeque and Samaranayake, 2003, Patil et al., 2015a, Fourie et al., 2016b)

CHAPTER 5

5.1 CONCLUSION

There are many studies that focus on specific risk factors and oral candidiasis as well as anti-fungal resistance, however there are few studies that assess oral candidiasis in its entirety. This study has shown that HIV still has a significant impact on the development of oral candida lesions. It would be interesting to observe any changes that might have occurred since the outbreak of the SARS-CoV-2 virus as there are already emerging articles that has shown an association between COVID-19 and oral candidiasis (Amorim dos Santos et al., 2021, Elamrousy et al., 2021, Katz, 2021). Furthermore the study highlighted various pharmacological treatment combinations, some of which the efficacy is still to be proven.

5.2 STUDY STRENGTHS AND LIMITATIONS

Patient records are not easily attainable and are in certain instances poorly documented. The information from this study may provide a good basis for other studies related to oral candidiasis.

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APPENDICES

Appendix- A

Data extraction sheet

Patient number				
Age				
Gender	Male			
	Female			
Diagnosis				
Pseudomembranous				
Erythematous				
Chronic Hyperperplastic				
Candida Associated lesions	Denture Stomatitis			
	Angular Cheilitis			
	Median rhomboid glossitis			
	Linear gingival erythema			
Secondary Oral Candidiasis	Oral manifestations of Systemic mucocutaneous. Candidosis (due to diseases such as thymic aplasia and candidosis endocrinopathy syndrome)			
Diagnostic technique	Biopsy			
	Cytological smear			
Intra-oral site affected				
Tongue	Yes	Dorsal	Ventral	Lateral
Palate	Yes			
Buccal Mucosa	Yes			

Floor of the mouth	Yes			
Commissure	Yes			
other:	Specify			
Symptomatic	Yes	Pain	Burning	Other
Asymptomatic	Yes			
Presence of other oral lesions	If Yes specify: _____	No		
Treatment Prescribed				
Topical Antifungal Medication	Specify			
Systemic Antifungal Medication	Specify			
Risk Factors Involved				
Smoking	Yes	No		
Dental prosthesis	Yes	No		
HIV reactive:	Yes	No		
Diabetes	Yes	No		
Steroid inhaler	Yes	No		
Other				

Appendix-B

Title approval by faculty

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

11 February 2021
Person No: 2212619
PAG

Dr M Antooley
Postnet Suite 35
Private Bag X2818
Makhado
0920
South Africa

Dear Dr Mishka Antooley

Master of Science in Dentistry: Approval of Title

We have pleasure in advising that your proposal entitled *The presentation of oral candidiasis in cases who attended the Wits Oral Health Centre over a 5 year period: A retrospective study.* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix-C

Ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr M Antooley

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210201

NAME: (Principal Investigator)	Dr M Antooley
DEPARTMENT:	School of Oral Health Sciences Department of Oral Medicine and Periodontology Dental School University
PROJECT TITLE:	*The presentation of oral candidiasis in cases who attended the Wits Oral Health Centre over a 5 year period: a retrospective study*
DATE CONSIDERED:	2021/02/26
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs S Hassam, T Mafojane and G Mohangi
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/05/05

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **February** and therefore reports and re-certification will be due in the month of **February** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

05/05/2021
Date

Appendix-D

Permission from the head of school of Wits Oral health Centre to access data for research

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

School of Oral Health Sciences
DEPARTMENT OF ORAL MEDICINE AND PERIODONTOLOGY

7 York Road, Parktown, 2193. Tel: 011 488 4865 cell: 082 8505 215
Email: tumane.mafojane@wits.ac.za

10/03/2021

RE: Permission from the head of the Wits Oral Health Centre to access data for research.

Motivation / Reason for request:

The topic is relevant to the department of Oral Medicine and Periodontology as the research study is investigating: The presentation of oral candidiasis in cases who attended the Wits Oral Health Centre over a 5 year period: A retrospective study

Student Surname and Full name(s)	Antooley Mishka
Student number	2212619
Degree	Master of Science in Dentistry (MSc)
Div / Dept / School	School of Oral Health Sciences
Title	The presentation of oral candidiasis in cases who attended the Wits Oral Health Centre over a 5 year period: A retrospective study
Protocol number	M210201

(Supervisor 1) : Dr S Hassam Essa
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Signature:

(Supervisor 3): Dr G U Mohangi
Telephone No: 0837771771
Email: vicky.mohangi@gmail.com

RECOMMENDATION BY HEAD OF DIVISION / ~~DEPARTMENT~~ / SCHOOL:

PROF MS NEMUTANDANI (Full name and surname) (Sign) 16/03/2021 (Date)

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APPENDIX - E

Plagiarism report

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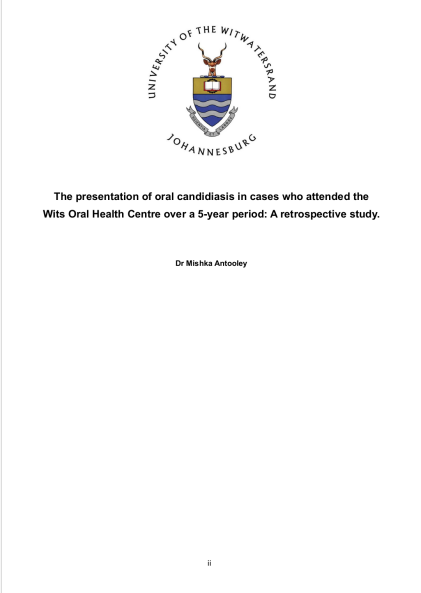

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

The presentation of oral candidiasis in cases who attended the Wits Oral Health Centre over a 5-year period: A retrospective study.

Dr Mishka Antooley

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