ORIGINAL ARTICLE

Spectrum of Oral Candidiasis in HIV/AIDS: Treatment and Response to Various Antifungal Agents in a Tertiary Hospital in Abuja

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ABSTRACT

Background: Oral candidiasis is one of the commonest opportunistic infections seen in people with Human Immunodeficiency Virus/Acquired Immune deficiency Syndrome (HIV/AIDS) infection. Although oral candidiasis can occur at any stage of HIV infection, it is more predominant in patients with declining CD_4^+ count. Majority of the candida isolates are *Candida albicans* and they are sensitive to topical/systemic antifungal agents such as fluconazole, itraconazole and oral nystatin.

Objective: This study seeks to identify the candida species implicated in oral candidiasis among HIV/AIDS patients and the response rate to various antifungal agents used in our facility.

Methodology: This is a prospective study of all HIV/AIDS infected patients admitted into our facility over a period of nine months (December 2016- August 2017) and were clinically diagnosed with oral candidiasis. A proforma was designed to capture their bio-data, symptoms such as burning sensations in the mouth, odynophagia, dysphagia and clinical types of oral candidiasis. Their CD_4^+ count, liver function test, full blood count, candida species isolation and their treatment response were noted and documented.

Results: Of the 312 HIV/AIDS infected patients admitted, 82(26.3%) had clinically diagnosed oral candidiasis. *Candida albicans* accounted for 79.3%, and *Candida dubliniensis* accounted for 7.3%. The mean CD_4^+ count was 94.4cells/µl and 55.0% of those who had oral candidiasis responded to Itraconazole within seven days of therapy.

Conclusion: The most common specie isolated among HIV infected patients admitted at the University of Abuja Teaching Hospital was *Candida albicans* and its response to itraconazole was good even at a low CD_4^+ count.

Keywords: *Immunosuppression, Candidasis, CD4⁺count, Fluconazole, Itraconazole, Nyastin*

INTRODUCTION

Oral candidiasis is one of the most common manifestations of opportunist infections in HIV/AIDS and it is one of the parameters used in the World Health Organization (WHO) clinical staging of HIV infection.[1,2] The HIV pandemic has led to a rising incidence of oral candidiasis worldwide.

Various species of candida have been implicated in the etiology of oral candidiasis, of which *Candida albicans* accounts for about 50% of all oral candidiasis.[3,4] Other candida organisms isolated include: *Candida glabrata*, *Candida parapsillosis*, *Candida krusei*, *Candida dubliniensis*, *Candida tropicalis* and *Candida famata.*[4]

Generally, about 50% of the population has candida as a normal commensal.[5] However, in a situation of compromised immunity such as salivary gland hypo function, HIV infection, diabetes mellitus, the use of corticosteroids and prolong antibiotic usage; candida organism can evade the host immunity and become pathogenic.[5] This is noticed in HIV infection with a progressive decrease in $CD4^+$cells count less than 350 cells/µl.[6]

There are various clinical descriptive types of oral candidiasis. These include: Pseudomembranous, erythematous [atrophic], angular cheilitis, and hyperplastic.[1] The pseudomembranous type appears as creamy, white, curd-like plaques on the buccal mucosa, tongue and other oral surfaces. The plaques can be wiped away, typically leaving a red or bleeding underlying surface. The erythematous or atrophic type present as a red, flat, subtle lesion on the dorsal surface of the tongue or on the hard or soft palates. It may present as a "kissing" lesion if a lesion is present on the tongue. The palate should be examined for a matching lesion and vice versa.[4]

Angular cheilitis present as erythema or fissuring of the corners of the mouth. It can occur with or without erythematous [atrophic] or pseudomembranous type and would persist for a while if left untreated.

Hyperplastic type is sometimes termed "plaque-like candidiasis or 'nodular candidiasis".[3,4] It appears as persistent white plaque that does not rub off. The lesion may be rough or nodular in texture.[4] Hyperplastic candidiasis is usually uncommon, accounting for about 5% of oral candidiasis cases and is usually chronic and found in adults. The most common site of involvement is the commissural regions of the buccal mucosa, on both sides of the mouth.[4,5]

Oral candidiasis can be associated with pharyngeal involvement which can cause dysphagia. The presence of dysphagia in oral candidiasis can worsen the clinical state of HIV patients by compromising their feeding habit thereby leading to nutritional deficiencies and anaemia.[4,5] Early treatment would improve morbidity and overall wellbeing. Its treatment ranges from topical to systemic antifungal agents such as the polylenes and the triazoles. The azoles group comprises ketoconazole, fluconazole and itraconazole which have been documented to clear the disease rapidly.[5,6]

Oral nystatin suspension is used in the treatment of uncomplicated cases with good response.[5] The hepatoxicity adverse effect of azoles is well documented and is often associated with high dosage and longer duration of therapy. Also, azoles are expensive and have a potential for drug to drug interactions. It is therefore of interest to know the minimum effective dose for clearance of oral candidiasis, the cheapest and the one with least side effect in our HIV patients. This study seeks to identify the candida species implicated in oral candidiasis among HIV/AIDS patients and the rate of response to various antifungal agents used in our facility.

METHODOLOGY

Study Design

This was a prospective cross-sectional study carried out in the male and female medical wards of the University of Abuja Teaching Hospital. Our study population was made up of patients who had HIV/AIDS with clinically diagnosed oral candidiasis and admitted into the hospital between December 2016 and August 2017.

Patients who met the inclusion criteria were randomly assigned to different treatment protocols. The study protocol was reviewed and approved by the University of Abuja Health Research Ethics Committee and was prepared in accordance with the 'Declaration of Helsinki', Good Clinical Practice (GCP) and within the laws and regulations of Nigeria.

Inclusion Criteria: All HIV patients admitted into the medical wards for various medical conditions, who presented with symptoms and signs of oral candidiasis and gave written consent.

Exclusion Criteria: HIV patients with oral candidiasis who had abnormal liver function test parameters (values above the normal range), those on anti-tuberculosis medications and those who had been on antifungal agents in the last three months, inability to take oral medications, as well as those that did not consent to the study.

Randomization, Masking and Treatment Procedures

After obtaining written consent, subjects were randomized and assigned in a 1:1:1:1 ratio to either of the four treatment groups. As patients were recruited, they were assigned to a treatment protocol consecutively until the required number was reached. Investigators were masked to the assignment of subjects before, but not after randomization.

The subjects were assigned to four treatment groups of antifungal regimen as follows:

Group A: Tabs fluconazole 200mg once daily

Group B: Tabs fluconazole 200mg twice daily

Group C: Tabs Itraconazole 100mg once daily

Group D: Oral nystatin suspension 100,000 IU four times daily

During the treatment, clinical efficacy was evaluated weekly until day 21. Patient was judged to be clinically cured once the lesions disappear and patient no longer complain of dysphagia, burning sensation in the mouth or odynophagia; whereas those whose pre-treatment signs and symptoms persisted after exposure to drug treatment were considered as clinical failure.

A questionnaire containing patients' bio-data, symptoms such as dysphagia, odynophagia, burning sensation, altered taste sensation, previous exposure to antifungal agents, concurrent illness, and clinical type of oral candidiasis was administered to those that fulfilled the study criteria. Routine investigations such as liver function tests, full blood count and CD_4^+count were done and documented. The $CD4^+$ count was done using the Partec Cyflow counter (Made in Germany 2014; Serial No: 1411146722, now Sysmex).

Five (5) ml of whole-blood was collected in an EDTA vacutainer bottle and gently mixed to avoid lysing of cells. Samples were prepared in a Rohren test tube by adding 20 µl of CD4 PE mAb with 20 µl of well mixed

EDTA whole blood collected within 6 hours. The mixed specimen was incubated in the dark for about 15mins at room temperature. Additional 800 µl of CD4 buffer was added and mixed and the result read in a Partec Cyflow counter.

A sample was collected from the oral mucosa using spatula and a cotton swab into a universal bottle and sent to the microbiology laboratory for analysis. A potassium hydroxide solution was added to the specimen (KOH) and viewed under the microscope for hyphae. Fungal culture was done using Sabouraud Dextrose Agar (SDA) plates as a culture medium and identification of *Candida albicans* was determined using the germ tube test. Various specie isolates were noted and documented.

The subjects response to therapy were judged clinically by assessing appearance of lesions weekly and the disappearance of symptoms like dysphagia,burning sensation in the mouth or odynophagia.

Outcome Measures for Assessment of Efficacy and Safety

The patients were evaluated for clinical characteristics, compliance with the treatment and presence of side effects. The primary analyses were to compare the number of patients with clinical cure and time to clinical cure among the different arms of treatment. Cure was defined as complete resolution of signs and symptoms of oral candidiasis.

Ethical issues

Ethical Approval was obtained from University of Abuja Ethical Committee. Written informed consent was obtained from each consented participant. They were assured of confidentiality of information provided and were free to opt out of the study without any undue consequences.

Data Analysis

Data generated was keyed into SPSS 20.0 version and analyzed. Frequency and percentage of occurrence of various clinical types of oral candidiasis and different specie isolates were calculated. The General Linear Model (GLM) univariate analysis was used to analyse the effect of different treatment arms, $CD4^+$ count on rate of clearance of oral candidiasis. *P*-value <0.05 was considered statistically significant.

RESULTS

A total of 312 patients who had HIV/AIDS were admitted within the 9 months period of this study and 91 (29.2%) were diagnosed with oral candidiasis. Five patients diagnosed of oral candidiasis were excluded from the study because of liver function test abnormality (that is their serum alanine transaminase and serum aspartate transaminase were three fold increased suggesting abnormal liver function). Another four were also excluded because they died within 24 hours of being recruited into the study. Thus, 82(26.3%) formed our study population. Thirty nine 39 (47.6%) of them were males and (52.4%) were females giving a ratio of male to female of 1:1.1. The mean age was 37.1 ±9.2 years and the mean CD4+ count was 94.4 ±86.2 cells/µl.

Distribution of clinical presentation of the study population was documented in Table 1. Of the 82 patients with oral candidiasis, 35 (42.7%) had burning sensation, 20 (24.4%) odynophagia, 15 (18.3%) dysphagia and 12 (14.6%) were asymptomatic.

The various clinical types of oral candidiasis and the distribution of the treatment arms among the types, species and the patients'

gender were presented in Table 2. Out of the 82 participants there were 53 (64.6%) pseudomembranous, 15(18.3%); angular cheilitis;11(13.4%) erythematous (atrophic) and 3 (3.7%) erythematous /angular cheilitis. Of the 82 participants, species isolated were *Candida albicans* 65 (79.3%), *Candida krusei* 4(4.9%), *Candida tropicalis* 1 (1.2%), *Candida albicans/tropicalis* 1(1.2%), *Candida albicans/krusei* 5(6.1%) and *Candida dubliniensis* 6 (7.3%).

Clinical Response

The overall clinical response to treatment at day 7 is shown in Table 3. In the itraconazole 100mg daily arm, 11 of 21 patients (55.0%) were clinically cured, compared with 5/21 in fluconazole 200mg b.d and oral nystatin arm as well as no cure with fluconazole 200mg daily arm. Oral nystatin took the longest time to treat the candidiasis with most of the patients in this arm achieving clinical cure by day 21, while in fluconazole arm maximum efficacy was observed by day 14. However, it can be observed that all the drugs exhibited resistance ranging from 10-18.2%. Those that had non clearance had very low $CD4^+$ cell counts below 55 cells/µl (Table 3).

Treatment and $CD4^+$ count both individually and collectively had significant effects on days of clearance of oral candidiasis ($P<0.0001$) as shown in Table 4.

Table 1. Distribution of clinical presentation

Variable	N (%)
Clinical Presentation	
Asymptomatic	12 (14.6)
Burning sensation	35 (42.7)
Odynophagia	20 (24.4)
Dysphagia	15 (18.3)

Table 2. Treatment arms and clinical types of oral candidiasis

Treatment Group	A N (%)	B N (%)	C N (%)	D N (%)	Total N (%)
Oral Candidiasis Clinical Type					
Pseudomembranous	14 (26.4)	15 (28.3)	12 (22.6)	12 (22.6)	53 (100.0)
Angular Cheilitis	5 (33.3)	1 (6.7)	4 (26.7)	5 (33.3)	15 (100.0)
Erythematous (Atrophic)	3 (27.3)	1 (9.1)	4 (36.4)	3 (27.3)	11 (100.0)
Angular Cheilitis& Erythematous	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	3 (100.0)
Oral Candidiasis Clinical Specie					
Candidiasis albicans	16 (24.6)	19 (29.2)	16 (24.6)	14 (21.5)	65 (100.0)
Candidiasis krusei	0 (0.0)	0 (0.0)	2 (50.0)	2 (50.0)	4 (100.0)
Candidiasis tropicalis	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Candidiasis albicans/tropicalis	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Candidiasis albicans/krusei	4 (80.0)	1 (20.0)	0 (0.0)	0 (0.0)	5 (100.0)
Candidiasis dubliniensis	0 (0.0)	0 (0.0)	2 (33.3)	4 (66.7)	6 (100.0)
Sex					
Male	8 (20.5)	11 (28.2)	8 (20.5)	12 (30.8)	39 (100.0)
Female	14 (32.6)	9 (20.9)	12 (27.9)	8 (18.6)	43 (100.0)
Total	22 (100.0)	20 (100.0)	20 (100.0)	20 (100.0)	82 (100.0)

Group A: Tabs fluconazole 200mg once daily; Group B: Tabs fluconazole 200mg twice daily; Group C: Tabs Itraconazole 100mg once daily; Group D: Oral nystatin suspension 100,000 IU four times daily

Table 3. Clinical response to different treatment arms

Treatment Group	A N (%)	B N (%)	C N (%)	D N (%)	Total N (%)	$CD4^+$ Count Mean (SE)
Clinical cure:						
≤ 7 days	0 (0.0)	5 (25.0)	11 (55.0)	5 (25.0)	21 (25.6)	67.0 (58.6)
8-14days	10 (45.5)	13 (65.0)	6 (30.0)	5 (25.0)	34 (41.5)	126.4 (107.0)
15-21days	8 (36.4)	0 (0.0)	0 (0.0)	8 (40.0)	16 (19.5)	90.3 (66.9)
Clinical failure	4 (18.2)	2 (10.0)	3 (15.0)	2 (10.0)	11 (13.4)	53.5 (44.0)
Total	22 (100.0)	20 (100.0)	20 (100.0)	20 (100.0)	82 (100.0)	94.4 (86.2)

SE- standard error of mean
Group A: Tabs fluconazole 200mg once daily; Group B: Tabs fluconazole 200mg twice daily; Group C: Tabs Itraconazole 100mg once daily; Group D: Oral nystatin suspension 100,000iu four times daily

Table 4. Effects of anti-fungal treatment and CD 4 count on days of clearance of oral candidiasis

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	71.443[a]	46	1.553	81.538	<0.0001
Intercept	187.405	1	187.405	9838.783	<0.0001
Treatment	3.447	3	1.149	60.325	<0.0001
CD 4 count	57.371	40	1.434	75.300	<0.0001
Treatment & CD 4 count	3.130	3	1.043	54.783	<0.0001
Error	0.667	35	.019		
Total	301.000	82			
Corrected Total	72.110	81			

R Squared = .991 (Adjusted R Squared = .979); Dependent Variable: Days of clearance

Table 4 presents the effects of anti-fungal treatment protocols and CD 4+ count on days of clearance using General Linear Model (GLM) univariate analysis. The result shows a statistically significant effect of treatment protocol and CD4+ count on days of clearance (p<0.0001). Also, treatment and CD4+ count when combined together have significant effect on days of clearance of oral candidiasis (p<0.0001).

DISCUSSION

Oral candidiasis can be clinically debilitating. Typically, it affects majority of people living with HIV/AIDS infection who are yet to commence antiretroviral therapy or those on a failing regimen.[5,6,7,8] It indicates the presence of declining immunity and progression of HIV induced disease.[8,9] Our findings showed that 26.2% of HIV patients who were admitted in our facility had oral candidiasis and 15 (18.3%) had oesophageal candidiasis with difficulty in swallowing their medications, thereby worsening morbidity. A previous study revealed that 90% of persons with advanced untreated HIV infection developed oropharyngeal candidiasis, with 60% having at least one

episode per year with frequent recurrences.[10,11,12,13,14] Our figures are low because some of the patients were already on antiretroviral therapy.

Recently, *Candida dubliniensis,* a specie that is phenotypically similar to *C. albicans* have been suggested to be responsible to up to 15% of candida infection that was previously ascribed to *C. Albicans*.[15,16] *Candida albicans* accounted for 79.3% of the oral candidiasis isolates in our findings while 7.3%, 4.9%, 1.2%, 1.2% and 6.1% were due to C. *dubliniensis,* C. *krusei,* C. *tropicalis,* C. *albicans/tropicalis and* C. *albicans/krusei,* respectively. There are no clear differences between the strain species isolated in HIV infection when compared with other immunosuppressive state. However, studies have shown that C. *dubliniensis* are more commonly identified in HIV-infected persons but it is indistinguishable from C.*albicans* in its clinical presentation.[15,16] These corroborate our findings where over 85% of the candida isolates were either C. *albicans or* C. *dubliniensis*.

Furthermore, the level of immunosuppression plays important role in the development of oral candidiasis.[17,18,19] Other host factors in defence of candida infections include: patients' blood group secretor status (presence or absence of specific Lewis antigens), salivary flow rates, condition of the epithelial constituents of the saliva, presence of normal bacterial flora and local immunity.[12,19] Other findings have shown impairment in a number of anti-candida host defence mechanism in people living with HIV infection.[12,18]

Also, high viral load of HIV infection have been associated with increased rate of mucocutaneous candidiasis.[20] A declining $CD4^+$count is highly suggestive of compromised immunity.[20,23,24] This tends to correlate with increased rate of opportunistic infection of which oral candidiasis is one of them. The mean $CD4^+$count of our patients in this study was 94.4cells/µl. This indicates that most of the patients presented either late (advanced disease state) or due to antiretroviral drug resistance for those who had already commenced antiretroviral therapy.

Many patients with oral candidiasis present asymptomatic. However, in some, they may have burning and painful sensation, altered taste sensation and difficult or painful swallowing of either liquid or solid. We found 12 (14.6%) patients asymptomatic, 35 (42.7%) had burning sensation with altered taste, 20 (24.4%) had odynophagia and 15 (18.3%) had dysphagia respectively. Previous studies have shown that about 40% of HIV patients have dysphagia and odynophagia which is similar to our findings.[1,2]

Notably, the commonest clinical type of oral candidiasis seen in this study was pseudomembranous candidiasis (64.6%) just as observed in other studies.[5,12]

Oral candidiasis can be treated either topically or systemically.[11,22] Treatment should last a minimum of seven (7) days. Numerous studies suggest fluconazole at 100mg once daily as being effective in the management of oral candidiasis when taken for two weeks.[22] Others have suggested that its effect as a prophylaxis is unclear.[22] Also, itraconazole at 100mg (capsule) may be used for the treatment of oral candidiasis for 14 days.[10,11,25] But our findings show that Itraconazole at 100mg daily was the most effective agent in clearing oral candidiasis in less than seven days when compared with either fluconazole at 200mg daily or twice

daily or oral nystatin at 100, 000 iu four times a day. There were minimal or no observable side effects within this period of medications among cohorts.

However, 11 (13.4%) of the patients treated for about 14 days and above did not respond to treatment and *Candida albicans* isolates were responsible. These may be due to resistance to the anti-fungal drugs or extreme immune suppression as seen in the declining $CD4^+$ counts (53.5 cells/µl).

CONCLUSION

Candida albicans was found to be the commonest specie isolate. Patients' response to itraconazole at 100mg daily was better than other anti-fungal agents even though resistance was experienced in all the anti-fungal agents due to *Candida albicans* and possibly due to low $CD4^+$ counts.

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