

Prevalence of Oral Candidiasis in Asthma and COPD Patients Using Inhaled Corticosteroids in the Philippine General Hospital Department of Out-patient Services

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ABSTRACT

Background and Objectives. Oral candidiasis (OC) is a well-known local side effect of inhaled corticosteroid (ICS) therapy in patients with asthma and chronic obstructive pulmonary disease (COPD). This study aimed to determine the prevalence of OC and its association with ICS-related factors in out-patient asthma and COPD patients of the Departments of Pulmonology and Pediatric Pulmonology of the Philippine General Hospital (PGH).

Methods. This is a cross-sectional study conducted from October 2019 to January 2020. Data was collected through a two-part questionnaire accomplished by doctors and patients with asthma or COPD.

Results. A total of 67 patients were included in the study. Oral candidiasis was observed in 4 (5.97%) ICS users, and the prevalence was 1.65% to 14.59% (95% CI, SE: 0.028946).

Conclusion. This study determined the prevalence of oral candidiasis in asthma and COPD patients and its association with ICS-related factors, including the dosage, medication, device, and duration of therapy. The prevalence of OC in ICS users in PGH cannot be interpreted as high or low due to the small number of respondents, but is consistent with OC prevalence found in related literature. Increased prevalence was observed in adult females with asthma under low dose ICS therapy with Fluticasone/Salmeterol DPI for more than a year. There was no statistically significant correlation among OC prevalence, age, sex, and components of ICS-therapy including dosage, medication, device, frequency, and duration of therapy. A large-scale study is recommended for more accurate assessment of OC prevalence in the population and to determine statistically significant associations among the factors. It is also recommended to quantifiably measure patient compliance, inhalation technique and instruction, and its association to OC prevalence. Findings may be used to strengthen patient education, preventive measures, and disease management to facilitate improved compliance and effective treatment outcomes.

Keywords: oral candidiasis, corticosteroids, asthma, chronic obstructive pulmonary disease, inhaled corticosteroids, asthma/COPD therapy

INTRODUCTION

Oral candidiasis (OC), also known as oral thrush, is the most common fungal infection of the oral cavity, especially in extremes of age.¹ It is a well-known local side effect associated with inhaled corticosteroid (ICS) therapy in asthma² and chronic obstructive pulmonary disease (COPD) patients.³ ICS is the first-line therapy for patients with persistent asthma, controlling asthma symptoms, and preventing exacerbations.⁴ It is also recommended to improve lung function, health status, and reduce exacerbations in moderate to severe COPD patients.⁵

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OC is caused by the overgrowth and increased virulence of commensal flora *Candida albicans* and other *Candida* species.¹ Diagnosis is usually based on clinical appearance and risk factors. Microscopic identification, and other diagnostic methods are mainly for confirmation of *Candida* invasion of oral mucosa.⁶ When corticosteroid particles are deposited in the upper airways, it predisposes individuals to develop oral candidiasis through local immunosuppression⁷ or promotion of *Candida* growth due to increased salivary glucose.⁸ It has also been found that certain aspects of ICS therapy (such as ICS medication, inhaler device type, dosage, frequency of use, duration of use, and correct inhalation technique) affect the occurrence of OC. Oral candidiasis associated with ICS exhibits as white, soft plaques with an underlying erythematous, eroded, or ulcerated surface. Common sites where oral candidiasis manifests are the buccal mucosa, oropharynx, and lateral aspects of the tongue.⁹

While oral candidiasis is one of the most common fungal infections in the mouth, it may be underreported and underdiagnosed. It is necessary to diagnose and treat OC as this may cause patient discomfort and difficulty in eating, which could lead to poor nutrition, poor adherence to ICS therapy, and poor treatment outcomes.¹⁰ There are no statistics describing the prevalence of oral candidiasis in the Philippines and in PGH. The Global Initiative for Asthma (GINA)⁴ and the Global Initiative for Chronic Obstructive Lung Disease (GOLD)⁵ guidelines followed by PGH doctors for diagnosis and management of asthma and COPD, respectively, do not include oral examination as part of their protocol. Therefore, it is uncertain that doctors are able to check for oral candidiasis and provide treatment for it as necessary. A visit to the dentist is also debatable, since more than half of the Filipinos who have seen a dentist admit to only consulting when in pain.¹¹ Oral thrush is not necessarily associated with symptoms, with only approximately one in three patients complaining of sore throat or hoarseness.¹² Therefore, the absence of symptoms may contribute to the lack of awareness of the disease and consequently to underdiagnosis and underreporting.

This study aimed to determine the prevalence of oral candidiasis in asthma and COPD patients using inhaled corticosteroids in the Philippine General Hospital Department of Out-patient Services (PGH DOPS). It also investigated the association between ICS-related factors and OC occurrence. The findings of the study provided knowledge to healthcare providers and policy-makers on the prevalence of OC in ICS users, and which aspects of ICS therapy contribute to this number. This knowledge may be used to strengthen patient education, preventive measures, and disease management. With decreased prevalence of oral candidiasis, asthma and COPD patients will have improved therapy compliance, effective treatment outcomes, and good nutrition.

This study also promotes holistic management through the inclusion of the oral cavity in medical examinations. It

raises awareness of oral candidiasis and reinforces practices that would prevent its occurrence. Additionally, the findings may serve as baseline data if adapted into a large-scale study involving other risk groups and a bigger population that would better represent the Filipino population.

METHODS

Study Design

This is a cross-sectional study done to determine the prevalence of oral candidiasis among asthma and COPD patients using inhaled corticosteroids in the Philippine General Hospital Department of Out-patient Services.

Study Setting

The study was conducted in the out-patient services of the Departments of Pulmonology and Pediatric Pulmonology of the Philippine General Hospital. The proposed period for data collection was 1 month. However, given the low turnout of respondents on the initial month, the data collection was conducted from October 2019 to January 2020. Further extension of data collection was not possible due to the onset of COVID-19 in the Philippines in February 2020.

Population and Sampling Technique

Purposive sampling through total enumeration was done to enroll participants in the study. All consenting patients who were eligible were included.

Those included in the study were pediatric and adult out-patients of PGH DOPS diagnosed with asthma or COPD, with or without any dental or oral infection during data collection, and have been using any ICS-containing inhaler device for at least a month prior to data collection. In a prescription sequence study by van Boven, et al., they found that prescriptions for OC medication was highest within the first three months of ICS initiation (SR 2.72, 95% CI 2.19-3.38), but decreased (SR 1.47, 95% CI 1.11-1.59) in the 9-12 months after initiation.¹³ Rachelefsky, et al. found that there was a 3.6-fold greater risk for developing OC in the first three months after ICS initiation.¹⁴ There is, however, no consensus on the actual onset of ICS-related OC.

The exclusion criteria included the use of systemic steroids or broad-spectrum antibiotics for the past month prior to data collection. Additionally, those with immunocompromising diseases (such as HIV, diabetes mellitus, cancer, etc.), xerostomia and conditions that may cause xerostomia (such as radiation therapy, diabetes, salivary gland diseases, etc.) were excluded. Those diagnosed with oral candidiasis prior to the start of ICS therapy and those wearing complete or partial dentures were also excluded from the study.

Data Collection Procedure

All data were gathered through a two-part questionnaire: one part accomplished by doctors, and the other by participants of the study. Consent and assent forms were given to eligible

participants prior to oral examination and administration of the questionnaire.

The diagnosis for asthma and COPD, as well as the prescribed medication and dosage, were based on the patient's chart reviewed by the doctor during patient consultation. Oral examination for candidiasis was done during said consultation and patients were classified as either with or without candidiasis. Diagnosis of OC was based on clinical appearance. Patients who exhibited white, soft plaques with an underlying erythematous, eroded, or ulcerated surface found anywhere in the buccal mucosa, oropharynx, or lateral aspects of the tongue⁹, and have been using ICS-containing inhalers were clinically diagnosed with OC. They were prescribed with oral nystatin for 1-2 weeks. Patients were scheduled for regular check-ups at the pulmonary clinic, but this was not monitored by the researchers. All these were noted in the doctors' questionnaire.

Patient demographics such as age and sex, as well as ICS use-related factors such as the type of inhaler device, frequency and duration of inhaler use, and inhalation technique instruction were determined through the patient's questionnaire. The type of inhaler device used was classified as dry-powder inhaler (DPI), metered-dose inhaler (MDI) or MDI with spacer device. It was determined whether proper inhalation technique instruction was given by the doctor and if so, was classified as given once, sometimes, and always.

Data Processing and Analysis

The data collected through questionnaires were encoded using Microsoft Excel to create a contingency table reflecting the relationship between the variables. This software was also used to compute for the prevalence of oral candidiasis in the population. Stata version 14 software was used to analyze data for descriptive statistics and the association of factors with oral candidiasis.

The proposed statistical test to determine the association of factors with oral candidiasis was logistic regression. However, due to multicollinearity, some variable categories and observations were omitted, and the multivariate model itself could not be interpreted. As a remedial measure, the chi square test for homogeneity was performed to determine the distribution of proportions across populations. This particular test was used because the variables were categorical, and it described the association between variables without excluding outlying observations.

Ethical Considerations

The study was given ethical clearance by the University of the Philippines Manila Research Ethics Board (UPMREB) and permitted by the PGH Extended Hospital Research Office (EHRO) to conduct the study and collect data.

The study involved a non-invasive visual examination of the mouth, done by doctors during consultation. An informed consent form was given to patients and guardians prior to answering the questionnaires. The form stated that

participation is entirely voluntary, and refusing to do so has no repercussion or effect on the service and treatment they receive from PGH. Patients 12 to 15 years old were given assent forms. Guardians answered the questionnaires and informed consent forms for patients below 18 years old. The form also stated the study's risk, benefits, compensation, confidentiality, access to results of study, and person to contact for queries. Accomplishment of the assent and consent forms, and questionnaire was done in an enclosed area within PGH DOPS. Patients diagnosed with oral candidiasis were educated on proper use and prescribed with nystatin. Respondent doctors were waived of informed consent documentation since adequate information about the study was given to them and answering the questionnaire implies consent, according to the provisions of the National Ethical Guidelines for Health and Health-Related Research (NEGHHR) 2017.

In compliance with the Data Privacy Act of 2012 and the provisions of NEGHHR 2017, gathered information of the patients was not to be disclosed to anyone other than the researchers and was used only for this study and future studies related to it. Identities of the participants were not revealed to the researchers and the public. The data collected was encoded by the researchers and stored in a hard drive designated solely for the study. The questionnaires, as well as the hard drive, were stored in a storage box with a lock and kept within the UP College of Dentistry building to ensure privacy. Access to these was only given to the researchers.

All data were kept throughout the duration of the study and 10 years after the final paper presentation for access for future related studies. After this period, all questionnaires will be shredded and disposed of, while the electronic data will be permanently deleted from the drive and undergo media sanitization with the help of an Information Technology specialist.

RESULTS

Table 1 shows the baseline demographic and clinical characteristics of patients included in the study. Among the 67 patients, 28 were male (41.8%) and 38 were female (56.7%). The mean age of patients was 37.69 ± 25.6 years (range: 2-77 years). There were more patients with asthma (n=56; 83.5%) than COPD (n=10; 14.9%), and more adults (n=41; 62.12%) than pediatric patients (n=25; 37.31%).

Table 2 shows the characteristics of ICS therapy in the study population. The most common type of inhaler device type used was the MDI (n=38; 56.7%), followed by the DPI (n=21; 31.3%). The two most prescribed medications were Budesonide/Formoterol (n=32; 47.8%) and Fluticasone/Salmeterol (n=29; 43.3%). Most participants were on low dose medication (n=45; 67.2%), and majority have been on treatment for more than a year (n=36; 53.7%). Inhalation technique instructions were always given for over half of the participants (n=36; 53.7%); however, the second largest proportion was advised only once (n=21; 31.3%).

Table 1. Baseline Demographic and Clinical Characteristics of Patients using ICS

Baseline Characteristics	Total (n=67)
Age (mean, SD)	37.69 ± 25.6
Adult (%)	41 (62.12)
Pediatric (%)	25 (37.31)
Not indicated (%)	1 (1.5)
Sex (%)	
Male	28 (41.8)
Female	38 (56.7)
Not indicated	1 (1.5)
Respiratory Disease (%)	
Asthma	56 (83.5)
COPD	10 (14.9)
Not indicated	1 (1.5)

Table 2. Proportion of Participants and Characteristics of ICS Therapy

Factors	Total (n=67)
Inhaler Device Type (%)	
DPI	21 (31.3)
MDI	38 (56.7)
MDI + spacer	7 (10.4)
Not indicated	1 (1.5)
ICS Medication (%)	
Budesonide/Formoterol	32 (47.8)
Fluticasone/Salmeterol	29 (43.3)
Budesonide	3 (4.5)
Not indicated	3 (4.5)
Dosage (%)	
High	3 (4.5)
Medium	14 (20.9)
Low	45 (67.2)
Not indicated	5 (7.5)
Frequency of Inhalation (%)	
Once a day	8 (11.9)
Twice a day	56 (83.6)
Thrice a day	2 (3.0)
Not indicated	1 (1.5)
Duration of ICS Use (%)	
1-3 months	8 (11.9)
3-6 months	13 (19.4)
6-12 months	9 (13.4)
>1 year	36 (53.7)
Not indicated	1 (1.5)
Inhalation Technique Instruction (%)	
Once	21 (31.3)
Sometimes	7 (10.4)
Always	36 (53.7)
Never	2 (3.0)
Not indicated	1 (1.5)

Four (5.97%) out of 67 respondents were diagnosed with OC. The prevalence was between 1.65% and 14.59% (95% CI; SE: 0.028946).

Table 3 shows that among those with OC, all were adult females with a mean age of 53.29 ± 12.28 (range: 38-77). Three patients had asthma and one had COPD. All patients were under low dose ICS therapy with Budesonide/Formoterol or Fluticasone/Salmeterol using an MDI or DPI. Three (75%) patients administered their medication twice a day, had been under ICS therapy for more than a year, and reported that proper inhalation technique was taught every consultation. However, no significant correlation was found between the occurrence of oral candidiasis and ICS use in asthma and COPD patients, as well as in the different aspects of ICS therapy (device type, ICS medication, dosage, frequency and duration of use, and inhalation technique instruction).

DISCUSSION

Prevalence is defined as the proportion of a population who have a specific characteristic in a given period of time.¹⁵ It is the number of existing cases of a disease at a specific period of time divided by the total number of people in that population.¹⁵ Prevalence estimates the probability of the population having the disease at the period of time being studied and is useful in the study of the burden of chronic diseases and implication for health services.¹⁵

In this study, the researchers observed 4 (5.97%) respondents with OC. The prevalence in the population was 1.65% to 14.59% (95% CI, SE: 0.028946). This is consistent with the findings of Buhl, et al. that oral candidiasis incidence related to ICS use ranges from <1% to 70% in multiple studies.¹⁶ The prevalence of 1.65% to 14.59% (95% CI, SE: 0.028946) cannot be interpreted as high or low due to the small number of respondents. There was also no statistically significant correlation among prevalence, age, sex, and components of ICS-therapy including dosage, medication, device, frequency, and duration of therapy.

All patients who had oral candidiasis at the time of consult were adult females with a mean age of 53.29 ± 12.28 (range: 38-77). However, this study found no significant correlation between oral candidiasis, age, and sex. Likewise, van Boven, et al. found that age and sex had no significant effect on the incidence of oral candidiasis.¹³

Oral candidiasis was prevalent in those under low dose ICS therapy, use of DPIs, Fluticasone/Salmeterol, and therapy duration of >1 year. However, no significant correlation between prevalence of oral candidiasis and these factors was observed.

The small number of respondents with OC may be attributed to the correct inhaler technique instruction given in both adult and pediatric clinics every consult. It was found that poor inhaler technique leads to oropharyngeal complications due to high percentage of aerosol deposited in the mouth.¹⁷ Repeated instruction and training are correlated

with correct inhaler use¹⁸, which optimizes therapeutic effects and reduces side effects. Of the 64 (95.52%) respondents who reportedly received inhaler technique instruction at least once, only three of them had oral candidiasis and were noted to have poor inhaler technique despite always being given instruction. All 25 (37.31%) pediatric respondents

whose technique were repeatedly reinforced did not have OC. However, the study found no significant correlation between inhalation technique instruction and occurrence of OC (p value: 0.602).

The study also showed that there is a higher prevalence of OC in those who used DPIs (14.29%), than those who used

Table 3. Comparison of Patients with and without Oral Candidiasis and their Age, Sex, Respiratory Disease, and Characteristics of ICS Therapy

	Oral Candidiasis		χ^2	p value
	With OC (n=4)	No OC (n=63)		
Age (mean, SD)	53.29 ± 12.28		2.6976	0.260
Adult (%)	4 (9.76)	37 (90.24)		
Pediatric (%)		25 (100)		
Sex (%)			3.2464	0.197
Male	-	28 (100)		
Female	4 (10.53)	34 (89.477)		
Not indicated	-	1 (100)		
Respiratory Disease (%)			0.3903	0.823
Asthma	3 (5.36)	53 (94.64)		
COPD	1 (10)	9 (90)		
Not indicated	-	1 (100)		
Inhaler Device (%)			1.0142	0.798
DPI	2 (14.29)	12 (85.71)		
MDI	2 (5.26)	36 (94.74)		
MDI + spacer	-	7 (100)		
Not indicated	-	1 (100)		
ICS Medication (%)			0.2389	0.887
Budesonide/Formoterol	2 (6.25)	30 (93.75)		
Fluticasone/Salmeterol	2 (6.9)	27 (93.1)		
Budesonide	-	3 (100)		
Not indicated	-	3 (100)		
Dosage (%)			2.0797	0.556
High	-	3 (100)		
Medium	-	14 (100)		
Low	4 (8.88)	41 (91.11)		
Not indicated	-	5 (100)		
Frequency of Inhalation (%)			0.8356	0.841
Once a day	1 (12.5)	7 (87.5)		
Twice a day	3 (5.36)	53 (94.64)		
Thrice a day	-	2 (100)		
Not indicated	-	1 (100)		
Duration of ICS Use (%)			1.5697	0.814
<3 months	-	8 (100)		
3-6 months	1 (7.69)	12 (92.3)		
6-12 months	-	9 (100)		
>1 year	3 (8.33)	33 (91.67)		
Not indicated	-	1 (100)		
Inhalation Technique Instruction (%)			2.7442	0.602
Once	-	21 (100)		
Sometimes	1 (14.29)	6 (85.71)		
Always	3 (8.33)	33 (91.67)		
Never	-	2 (100)		
Not indicated	-	1 (100)		

Results were compared using chi-square test for homogeneity (χ^2).

MDIs with or without spacers (4.65%). Previous literature has shown a decreased risk for OC following ICS initiation when using MDIs¹³, while those who used DPIs had higher frequency of oral candidiasis (16.7%) than patients who used MDIs with spacer devices (6.1%).¹⁹ All seven pediatric respondents using an MDI with a spacer device did not have OC. This is also consistent with the findings of Cheng, et al. that there is a significant decrease in the incidence of oral candidiasis when using a spacer device with an MDI.²⁰

It was found that there is a higher prevalence of OC in respondents under Fluticasone/Salmeterol medication (6.9%) than Budesonide/Formoterol (6.25%). A study by Dekhuijzen, et al. found that significantly fewer patients prescribed with Budesonide/Formoterol had oral thrush compared to Fluticasone propionate/Salmeterol.³ Additionally, 45 (67.2%) of the respondents were given low dose ICS, which may have contributed to the small frequency of OC. High daily doses have been reported to be correlated with a higher incidence of oral thrush.^{3,21}

There was also an increase in OC prevalence among respondents who had been under ICS therapy for more than a year (8.33%) than for only 3-6 months (7.69%). In contrast, a prescription sequence study by van Boven, et al. found a significant increase in the number of patients receiving medication for oral candidiasis in the first year after therapy initiation.¹³ This contradiction may be due to differing methodologies used in the studies.

Study Limitations

This study was limited to asthma and COPD patients of PGH DOPS using ICS. No sample randomization was done; all eligible respondents were included in the study. Due to the small number of respondents, the exact value of prevalence of OC in the population was not identified. It also did not reflect all characteristics and experiences of the population; therefore, no correlation between the factors and OC was found statistically significant.

The study also did not measure the respondents' inhalation technique due to lack of existing parameters. It was only described by the doctors as "poor" according to their clinical standards. Likewise, patient compliance was not measured, seeing as a number of self-reported frequency of inhalation did not coincide with the doctors' prescription.

Data collection was initially proposed to be 1 month. However, given the low turn-out of respondents on the initial month, data collection was conducted from October 2019 to January 2020. Further extension of data collection was not possible due to the onset of COVID-19 in the Philippines in February 2020.

CONCLUSION

This study determined the prevalence of oral candidiasis in asthma and COPD patients and its association with ICS-related factors, including the dosage, medication, device, and

duration of therapy. The prevalence of OC in ICS users in PGH of 1.65% to 14.59% (95% CI, SE: 0.028946) cannot be interpreted as high or low due to the small number of respondents, but is consistent with OC prevalence found in related literature. Increased prevalence of OC was observed in adult females with asthma under low dose ICS therapy with Fluticasone/Salmeterol DPI for more than a year. No statistically significant correlation was found between the prevalence of OC and age, sex, ICS medication, device, dose, frequency, duration, and inhalation technique.

It is recommended to enroll more respondents in future studies for a more accurate value of prevalence of OC in the population, and to determine statistically significant associations among the factors. Since poor inhalation technique was speculated to have promoted OC in some respondents, this should be measured with clinical parameters. Patient compliance and oral hygiene may also be measured to determine their association with OC. Findings may be used to strengthen patient education, preventive measures, and disease management to facilitate improved compliance and effective treatment outcomes.

It is also recommended that clinicians who are taking care of patients on chronic ICS should examine the oral cavity during regular follow ups, instruct and remind patients on correct inhaler use, and reinforce oral hygiene practices to prevent occurrence of OC.

Acknowledgments

The authors would like to thank the Philippine General Hospital Department of Pulmonology, the Philippine General Hospital Department of Pediatric Pulmonology, Dr. Norman Maghuyop, Dr. Arianne Evangelista, Dr. Justine April Jacinto, the University of the Philippines College of Dentistry, the UPCD Department of Community Dentistry, Dr. Jessica Rebuena Santos, Dr. Arlene Cecilia Alfaro, Ms. Frances Mae Rivera, Dr. Samuel Nicolai Baltazar, Dr. Rosalie Buban and Edwin Buban, and Augusto, Josie, Jamie and Augusto Jr. Arevalo.

Statement of Authorship

JCA contributed in the conceptualization of work, drafting and revising, final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; ERDB contributed in the conceptualization of work, acquisition and analysis of data, and drafting and revising.

Author Disclosure

Both authors declared no conflicts of interest.

Funding Source

None.

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