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## Proton Pump Inhibitors and Corticosteroids as Synergistic Risk Factors for Candida Esophagitis

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### Authors' contributions

*This work was carried out in collaboration between all authors. Author NS designed the study, wrote the protocol, and wrote the first draft of the manuscript with help of authors OS and PP. Authors OS, PP and NS managed the literature searches and data collection. Author VAD assisted in designing the protocol and analyzed the data. Authors NS, YC, VAD and WB made the final revisions in the manuscripts. All authors read and approved the final manuscript.*

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### ABSTRACT

**Introduction:** Inhaled & systemic steroids are one of the well-documented risks factors for Candida esophagitis. However, the role of gastric acid suppression remains controversial.

**Methods:** We conducted a retrospective case-control study of 420 patients consisting of 84 cases of Candida esophagitis and 336 matched controls. Our cohort was gathered from subjects evaluated from 2001 to 2012. The diagnosis of Candida esophagitis was based on endoscopic and/or histological criteria.

**Results:** On univariate analysis, proton pump inhibitors were associated with higher risk (OR = 2.14; 95 % CI: 1.30 to 3.54); steroid use also increased the risk (OR = 3.55; 95% CI: 2.10 to 6.00). Furthermore, concurrent use of proton pump inhibitors & steroids substantially raised this risk (OR

= 13.8; 95% CI 5.07 to 37.5), suggesting a synergistic effect. When adjusted for covariates (cancer, chemotherapy/radiation, antibiotic use, hypothyroidism, anemia, chronic liver disease & diabetes), anemia decreased the odds ratio for proton pump inhibitors to 1.67 (95% CI 1.02 to 2.75) and steroids to 1.69 (95% CI to 1.03 to 2.87). Hypothyroidism also substantially reduced the observed risk associated with steroid use. However, neither anemia nor hypothyroidism reduced the odds ratio for combined use of steroids and proton pump inhibitors.

**Conclusions:** Our data suggests that patients who have been treated with steroids or proton pump inhibitors are at an increased risk for developing Candida esophagitis. Our data also suggests that steroids and proton pump inhibitors act synergistically to greatly increase the likelihood of Candida esophagitis.

**Keywords:** *Candida esophagitis; esophageal moniliasis; Candida albicans; proton pump inhibitor; gastric acid inhibitor.*

## 1. INTRODUCTION

Esophageal candidiasis is known to occur in immuno-compromised patients, but has been less commonly reported in immuno-competent hosts. Esophageal candidiasis appears to occur when colonization of the esophagus is followed by subsequent invasion of the epithelial layer [1]. Colonization of the esophagus by *Candida* species is found in 20% of healthy adults [2-5]. A review by Ellepola et al. reported colonization with *Candida* species in 24-66% of patients using inhaled steroids [6]. It is one of the most common causes of infectious esophagitis [7-9]. Amongst *Candida* species, *Candida albicans* (*C. albicans*) is the most common & virulent causative organism, however, other species including *C. tropicalis*, *C. krusei* & *C. stellatoidea* have also been implicated [10].

There are multiple physiologic defense mechanisms that normally inhibit colonization. Such mechanisms include salivation, mechanical clearance of esophageal luminal contents, a mucosal barrier, an intact pH gradient including gastric acidity, and normal bacterial and fungal flora. Proton pump inhibitors (PPIs) alter the gastric pH. In the study by Karmeli et al. [11] the gastric pH in patients treated with omeprazole was found to be greater than 4.5, which may predispose to floral migration and colonization of the stomach by oral bacteria and yeasts. Additionally, PPIs also decrease salivary secretion and subsequent clearance of esophageal luminal contents.

Candida esophagitis (CE) has been associated with several risk factors, the most common being immunocompromised states such as acquired immunodeficiency syndrome (AIDS) [12-14]. Medical disorders such as diabetes mellitus, functional and mechanical esophageal obstruction, carcinomas, advanced age,

alcoholism and use of certain medications, including corticosteroids, gastric acid suppressive therapies and antibiotics have also been linked to higher rates of CE [1-5,11,15-23].

In recent years, the use of PPIs has increased because of a number of contributing factors. Easy availability as an over the counter medication, generic formulation, low cost, increased incidence of dyspepsia, and gastroesophageal reflux disease (GERD), as well as the use of non-steroidal anti-inflammatory agents. PPIs are considered to be relatively safe and thus very commonly prescribed to treat conditions like gastritis, dyspepsia, GERD, duodenal ulcers, esophagitis and utilized in stress ulcer prophylaxis in hospitalized patients.

Recent studies have suggested an association of PPIs with CE [1,11,15,23]. This class of drugs produces hypochlorhydria, which alters the physiologic gastric and esophageal environment and skews the balance of normal flora. This altered environment predisposes to commensal colonization by oral bacteria and yeast. Histamine Type-2 antagonists (H2 blockers), and prior vagotomy may have similar implications [21,24]. Oropharyngeal candidiasis is a well-documented side effect of inhaled steroids [4-6,22]. However limited data exists regarding the development of esophageal candidiasis in association with PPI use. The main aim of our study is to explore the association between the use of PPIs, corticosteroids and the risk of CE.

## 2. MATERIALS AND METHODS

### 2.1 Subjects

We retrospectively identified 84 patients who were diagnosed with CE after undergoing upper endoscopy at our facilities between January 2001 and January 2012. The diagnosis of CE was

made on the basis of endoscopy. These patients were further matched with 336 patients who underwent upper endoscopy but had no CE (controls) based upon age and gender. We excluded all known Human immunodeficiency Virus (HIV) infected patients from our study.

## 2.2 Protocol

The study was conducted at two academic Medical Centers in the north eastern United States. The protocol was approved by the Institutional Review Board of the Saint Joseph's Regional Medical Center in Paterson, New Jersey and Trinitas Regional Medical Center in Elizabeth New Jersey. The data gathered included patient demographics (age and sex), Human Immunodeficiency Virus (HIV) status, recent use of PPIs, H2 blockers, antibiotics, inhaled or systemic corticosteroids, history of diabetes mellitus, chronic liver disease, carcinoma, hypothyroidism, chemotherapy, radiation therapy, hypertension and anemia.

## 2.3 Statistical Methods

Descriptive statistics for interval data (age) were evaluated for fit-to normality by the D'Agostino-Pearson omnibus normality test and found to not fit a normal distribution. Thus, age is expressed as median and interquartile range (IQR) and ages for cases and controls were compared by a nonparametric test (Mann-Whitney). Categorical data were described as counts and percents and were evaluated for group-wise differences by Fisher's exact test for all univariate comparisons. As the study was conducted retrospectively, the effect size measurement used was the odds ratio (OR) and 95% CI. Multivariable analysis of exposures and outcomes were made using a

binary logistic regression (BLR) mode, I which included as covariates any baseline characteristic deemed to be a potential confounder using  $p \leq 0.25$  as the criterion for inclusion. This approach was used to estimate adjusted OR and 95% CI, as well as significant interaction between covariates and primary exposures. Rejection of the null hypothesis was based on a two-sided  $p$ -value  $\leq 0.05$  or exclusion of unity from the 95% 95% CI of the OR. Calculations were made using Prism® v. 5.04 (GraphPad Corp. San Diego, CA) and SPSS v. 21 (IBM Corp. Armonk, NY).

## 3. RESULTS AND DISCUSSION

### 3.1 Characteristics of Cases and Controls

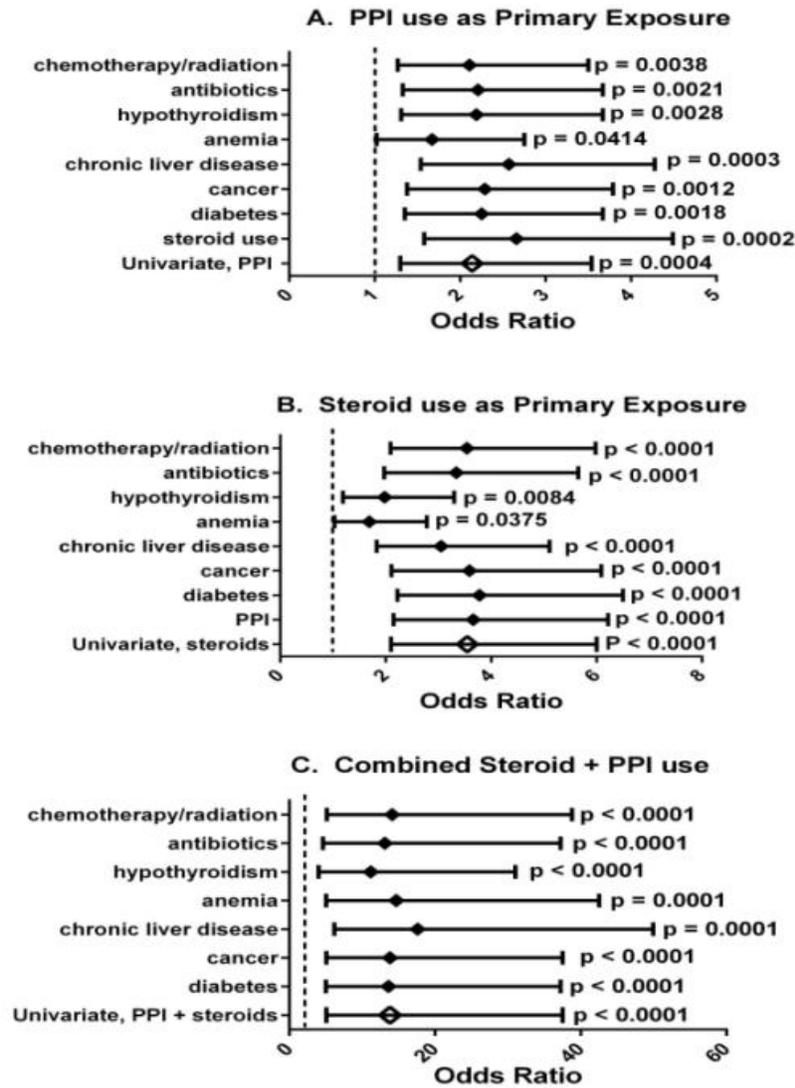
The baseline characteristics of cases and controls are given in Table 1. Few patients who were included in the study used H2 blockers, were recently post-operative or had evidence of rheumatologic disease. Thus, these characteristics could not be expected to demonstrate significant differences. Hypertensive subjects represented 55.9% of cases and 50.5% of controls; this difference was neither statistically significant nor within our criterion for inclusion in the BLR model. All other characteristics were, therefore, considered as potential confounders and included in the model.

### 3.2 PPIs and Corticosteroids as Risk Factors

The OR and 95% CI for the univariate analysis and adjusted OR are shown in Fig. 1. Upon performing univariate analysis, PPIs were associated with a higher risk of CE (OR = 2.14; 95% CI: 1.30 to 3.54); steroid use also

**Table 1. Baseline characteristics of patients in our study**

Particulars	Cases (n=84)	Controls (n= 336)	P value
Age in years : Median (IQR)	67.5 (56.0 - 78.0)	67.0 (56.0-77.0)	0.817
Gender: Male/Female	42/42	168/168	1.000
Proton Pump Inhibitors	34 (40.5%)	81 (24.1%)	0.004
H2 Blockers	2 (2.3%)	3 (0.89%)	0.574
Corticosteroid therapy	34 (40.5%)	54 (16.0%)	0.0001
Diabetes Type 1 and 2	32 (38%)	100 (29.7%)	0.18
Carcinoma	5 (5.9%)	44 (13.0%)	0.102
Antibiotics	11 (13.1%)	27 (8.03%)	0.217
Chronic liver disease	6 (7.14%)	115 (34.2%)	0.0001
Hypertension	47 (55.9%)	170 (50.5%)	0.449
Anemia	35 (41.6%)	101 (30.05%)	0.003
Rheumatologic diseases	6 (7.14%)	9 (2.6%)	0.6343
Surgery	2 (2.3%)	6 (1.7%)	0.929
Chemotherapy/radiation	6 (7.14%)	19 (5.6%)	0.066
Hypothyroidism	9 (10.7%)	20 (5.9%)	0.01



**Fig. 1. Forest plots of OR and 95% CI for PPI use as primary exposure (Fig. 1A, top panel), steroid use as primary exposure (Fig. 1B, middle panel) and combined use of PPI and steroids vs. use of neither (Fig. 1C, bottom panel)**

*Univariate OR is at bottom of each forest plot, indicated by the open diamond. Closed diamonds are used to indicate OR adjusted for each of the potential confounders*

increased the risk of CE (OR = 3.55; 95% CI: 2.10 to 6.00). In the cases of PPIs, only anemia substantially decreased the risk of CE (adjusted OR: 1.67 [95% CI 1.02 to 2.75]); nevertheless, this comorbidity did not eliminate, completely, the odds of developing CE in subjects being treated with PPI. Similarly, anemia [adjusted OR: 1.69 (95% CI to 1.03 to 2.87)] as well as hypothyroidism were covariates decreasing the risk of CE. In both cases, there was a substantial decrease in the OR but, as is the case of PPI, these comorbidities did not completely obviate the risk of CE. Furthermore, concurrent use of

PPIs & steroids substantially raised this risk (OR = 13.8; 95% CI 5.07 to 37.5), suggesting a synergistic effect. When adjusted for covariates (cancer, chemotherapy/radiation, antibiotic use, hypothyroidism, anemia, chronic liver disease & diabetes), anemia was found to decrease the odds ratio for PPI to 1.67 (95% CI 1.02 to 2.75) and for steroids to 1.69 (95% CI to 1.03 to 2.87). Hypothyroidism also substantially reduced the observed risk associated with steroid use. However, neither anemia nor hypothyroidism reduced the odds ratio for combined use of steroids and PPI. This OR was not affected to

any extent by the presence of cancer, diabetes, antibiotic use or chemotherapy or radiation therapy. There was a slight, but insignificant increase in the OR adjusted for anemia and a similarly insignificant decrease in the OR adjusted for hypothyroidism. Chronic liver disease increased the odds of CE by 38%; however, despite this apparently large effect on the OR for combined use of PPI and steroids, the interaction term was not statistically significant, most likely due to the extremely large confidence interval.

In this retrospective case control study involving eighty-four non-HIV/AIDS patients with CE, we found that previously recognized risk factors like steroid therapy, diabetes (type I and II), carcinoma, chemotherapy/radiation, hypothyroidism, antibiotics and chronic liver disease did correlate with the development of esophageal candidiasis. However, the most prominent finding was the synergistic risk of PPIs and steroid use with the prevalence of CE.

There is scant published evidence reporting the relationship between esophageal candidiasis and PPIs [1,11,15,23]. The relationship of inhaled and/or intravenous steroid and esophageal candidiasis is better documented in the literature [4,5,6,22]. Fidan et al. [4] reported a 42.9% frequency of esophageal candidiasis in a 21-person cohort compared to a 0.2% rate in their control group. Kanda et al. [22] (n=49) reported a 37% prevalence of esophageal candidiasis in patients using inhaled fluticasone propionate compared to 0.3% of controls. To our knowledge this is the only case control study so far, analyzing the association of PPIs and steroids use with CE. Our study has certain limitations. It is a retrospective study and it does not specify duration of exposure to PPIs. Finally, it does not stratify for active comorbidities, which may increase the risk of CE. Moreover, as is the case with any case-control study, controls with active exposure to risk factors preclude a true association with risk. The observation that anemia and hypothyroidism both have the effect of decreasing the adjusted OR for PPI and steroids. One should consider the possibility that these are merely secondary effects of therapeutic approaches to these comorbidities rather than effects directly attributable to the specific comorbidity. We did not examine that prospect and suggest that a larger, prospective cohort study, stratifying covariates by duration/intensity as well as additional exposures

attendant to these covariates, might provide additional insight into this issue.

#### **4. CONCLUSION**

Our data suggests that patients who have been treated with steroids or proton pump inhibitors are at an increased risk for developing Candida esophagitis. Our data also suggests that steroids and proton pump inhibitors act synergistically to greatly increase the likelihood of Candida esophagitis. So on the basis of this finding we recommend that PPIs be used judiciously, only in clinical conditions where they are indicated and have been proven efficacious. Also physicians should re-evaluate patients at each clinical encounter for the possibility of PPI and/or corticosteroid therapy discontinuation.

#### **CONSENT**

It is not applicable (This is a retrospective study).

#### **ETHICAL APPROVAL**

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

#### **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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