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# PROTON PUMP INHIBITOR THERAPY AS A RISK FACTOR FOR CLOSTRIDIUM DIFFICLE ASSOCIATED DIARRHEA AMONG HOSPITALIZED PATIENTS

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**Abstract:**

***Background:*** *Inhibition of gastric acid removes a defense against ingested bacteria and spores, increasing the risk of some forms of gastroenteritis. A possible link between acid suppression therapy and Clostridium difficile- associated diarrhea (CDAD) has long been debated, however, despite the high incidence of CDAD among patients being administered Proton Pump Inhibitors (PPI) therapy for gastric acid suppression, conclusive evidence regarding a link between CDAD and PPI therapy remains unavailable.*

***Objective:*** *This research hopes to investigate whether gastric acid suppression by PPI therapy is a risk factor for CDAD among hospitalized patients.*

***Methodology:*** *This retrospective analysis comprised of a total data set of 377 in-patients (derived from the hospital records via non-probability consecutive sampling) who developed CDAD (ascertained by positive laboratory reports of assay results for C. difficile toxin and clinical correlation of diarrhea) during the course of their hospital stay. The patient records were also reviewed and all patients being administered PPI therapy were identified. Variables such as admission date, antibiotic exposure, gender, age groups, patient location (medical or surgical unit), and room type at time of admission were also noted. The data obtained was analyzed using MS. Excel 2017 and SPSS v. 21.0.*

***Results:*** *Among the 377 subjects with a CDAD, 206 were males and 171 were females. The mean age of the sample was 31 years and the mean hospital stay recorded (at the time of diagnosis of CDAD) was 13 days. Regarding patient location, 301 patients hailed from the medical wards (general medicine – 273 and oncology – 28) and 76 from the surgical ward. 212 (56.2%) of the subjects were administered PPI therapy during the hospital stay.*

***Conclusion:****An elevated risk of developing CDAD among hospitalized patients that underwent acid suppression via PPI therapy, was found in our study.*

**Keywords:** *Proton Pump Inhibitors, Clostridium Difficile, Diarrhea and Acid Suppression.*

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## INTRODUCTION:

Clostridium difficile (C. difficile) is a Gram-positive anaerobic spore-forming bacterium. The toxin produced from this pathogen is known to cause illnesses ranging in severity from mild diarrhea to fulminant colitis and death. **[1]** C. difficile is the most common cause of hospital-acquired diarrhea in developed countries. **[2]** The incidence and morbidity of Clostridium difficile–associated diarrhea (CDAD) are on the rise **[3]** in fact, CDAD rates have doubled from 1996 to 2003 **[4]** and a further rise is expected in to have taken place in the years that followed. The incidence and severity of this condition is getting so worryingly high that CDAD has become a global concern with widespread implications in health care.

Much research has been done to unearth the cause of the rise in incidence and severity and as a result of which, in addition to the broad-spectrum antimicrobial therapy which has long been deemed the most prominent causative factor for CDAD, **[5]** other potential risk factors have been identified such as: advanced age, hospitalization (particularly in intensive care units), immunosuppression, renal insufficiency, hypoalbuminemia, lengthy hospital stay, the use of nasogastric tubes, invasive gastrointestinal procedures, chemotherapy, the presence of comorbidities, environment-related factors, and the emergence of a hyper-virulent strain of the bacterium. **[6]** However, there might be some other risk factors for the CDAD epidemic in the recent years despite tighter control on the use of antibiotics and stricter control policies on hospital-related infections. **[7]**

An association between the use of proton pump inhibitors (PPIs) and the development of CDAD has been suggested and numerous studies have examined it, reporting conflicting results. **[8, 9]** A potential mechanism for this phenomenon is inhibition of gastric acidity resulting in the loss of a defense mechanism against ingested spores and bacteria. Having higher gastric pH than normal facilitates the survival of C. difficile spores and their toxins while in the vegetative state by affecting leukocyte function. **[10]** Moreover, recent data suggest that PPI prescribing has increased over the last few years, and PPIs are now among the most widely prescribed class of medications around the world. **[11]** The use of proton pump inhibitors (PPIs) in the hospital has recently increased (because of the availability of intravenous (IV) formulations, competitive marketing, and expanded indications) due to such an extent that nearly all in-patients are administered PPI's without evaluating the necessity, only to prevent stress ulcers. **[12]**

To date, the literature is controversial and inconclusive in terms of the association between PPI therapy and CDAD, especially in hospitalized patients. To better understand this matter, we designed this research at a tertiary care hospital to examine the use of PPIs and their potential role as a risk factor for increasing the risk of CDAD.

## METHODOLOGY:

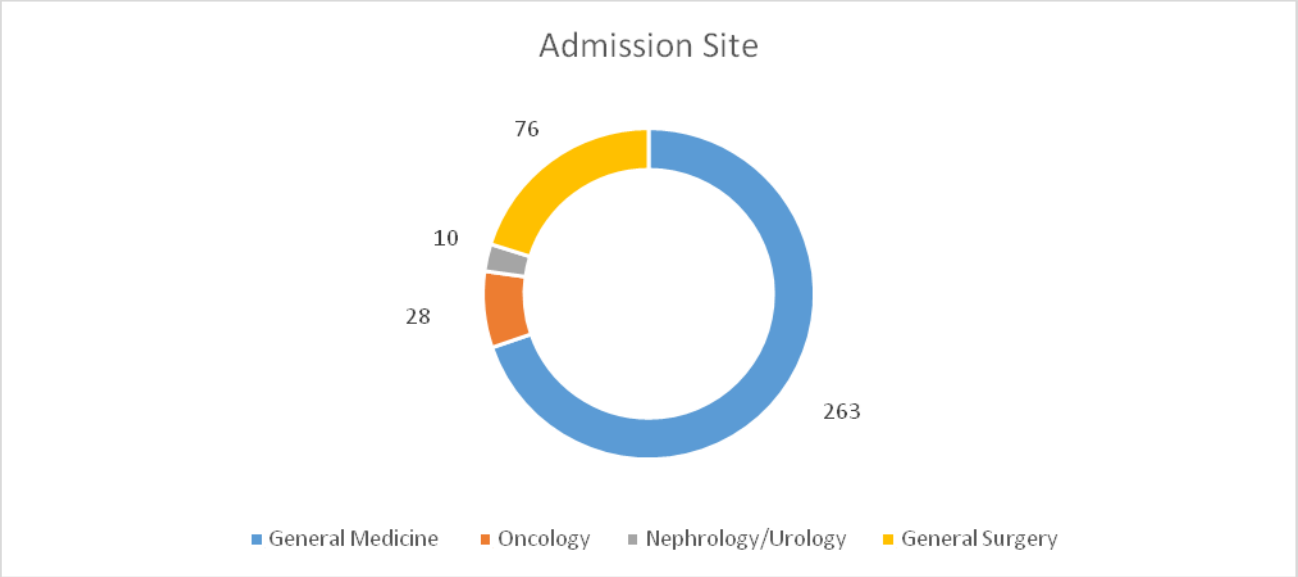
This retrospective analysis, comprised of a total data set of 377 in-patients (derived from the hospital records via non-probability consecutive sampling) who developed CDAD (ascertained by positive laboratory reports of assay results for C. difficile toxin and clinical correlation of diarrhea) during the course of their hospital stay. The patient records were also reviewed and all patients being administered PPI therapy were identified.

Exposure to PPI therapy for gastric acid suppression was considered only if the exposure occurred before admission based on the admission medication history and was continued during the hospital stay and before CDAD development or if the exposure occurred at least 3 days before development of CDAD as an in-patient.

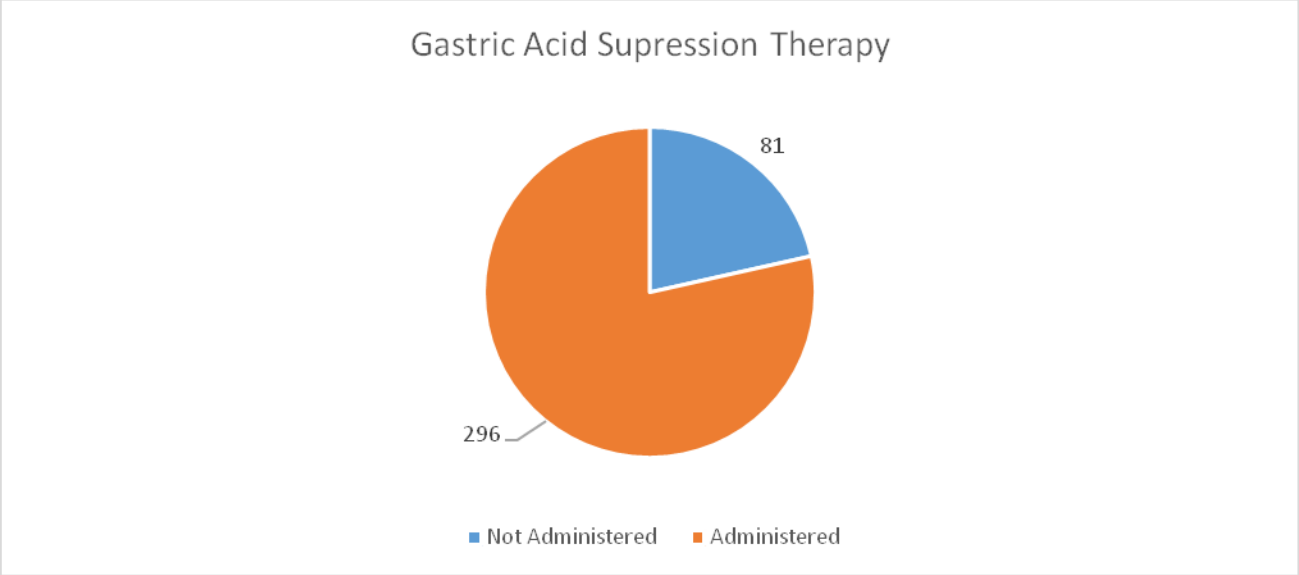
Variables such as admission date, antibiotic exposure, gender, age groups, patient location (medical or surgical unit), and room type at time of admission were also noted. The data obtained was analyzed using MS. Excel 2017 and SPSS v. 21.0.

## RESULTS:

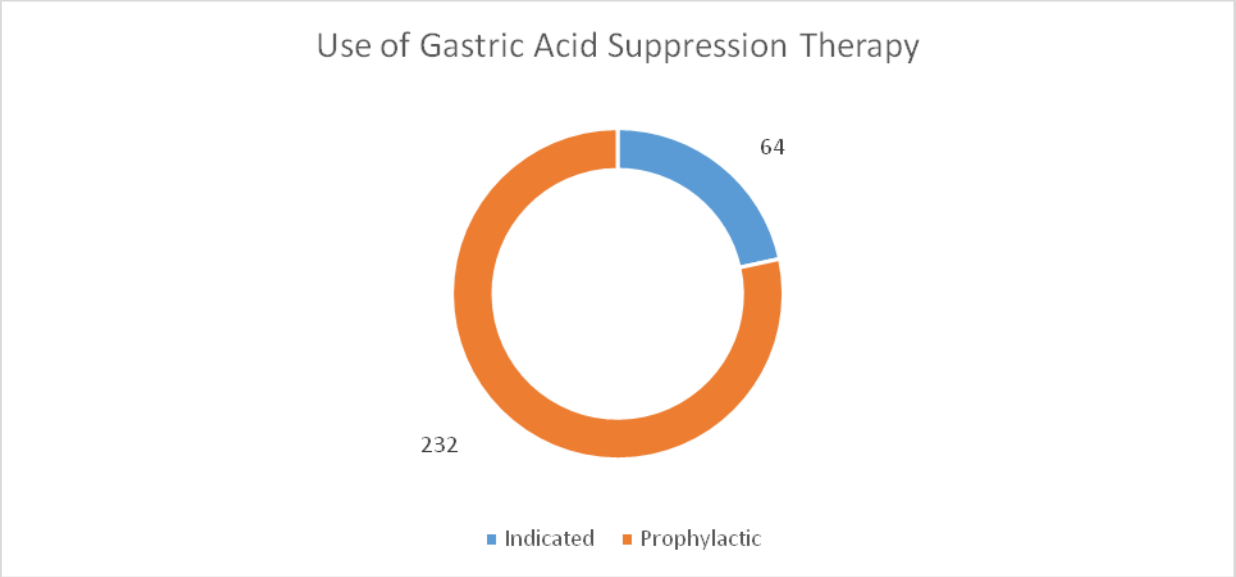
Among the 377 subjects with a CDAD, 206 were males and 171 were females. The mean age of the sample was 31 years and the mean hospital stay recorded (at the time of diagnosis of CDAD) was 13 days. Regarding patient location, 301 patients hailed from the medical wards (general medicine – 263, oncology – 28 and nephrology – 10) and 76 from the surgical ward.



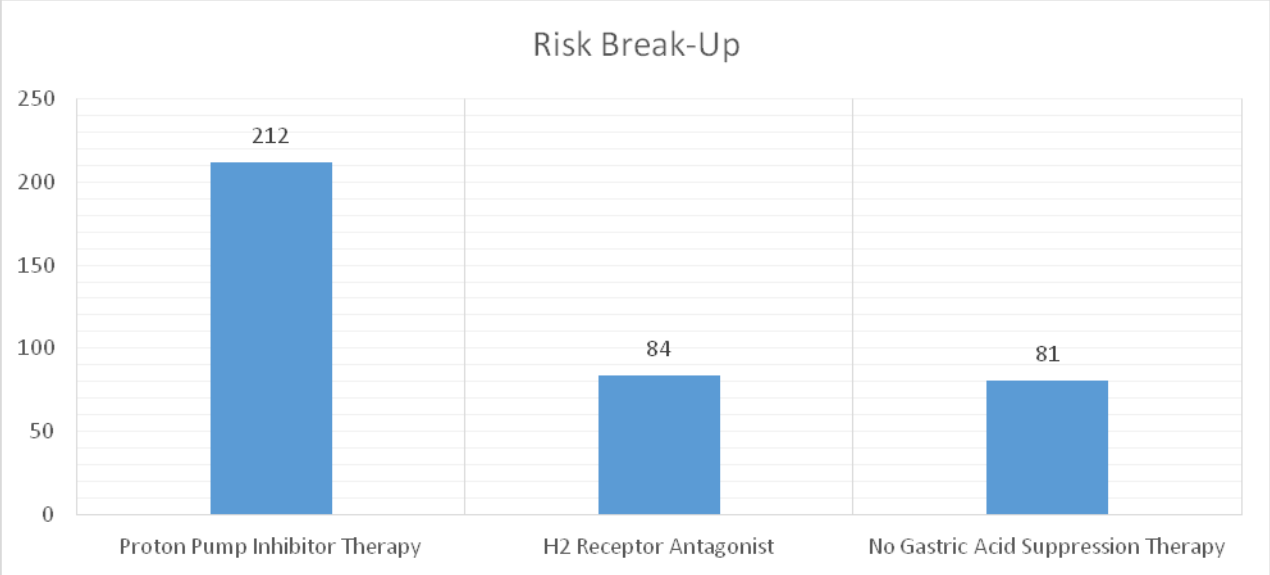

212 (56.2%) of the subjects were administered PPI therapy during the hospital stay. 84 patients were administered H2 receptor antagonists. The remaining 81 received no form of gastric acid suppression therapy.




However, in-depth analysis of patient records revealed that strong indication for gastric acid suppression drug administration was only present in 64 patients, while the rest were probably administered gastric acid suppression therapy prophylactically.




A retrospective view reveals that our sample (patients contracting C. difficile) comprised mostly of people that used PPI therapy, followed by those that received other forms of gastric acid suppression and finally those whose gastric acid secretions were not suppressed.




**DISCUSSION:**

In studies evaluating PPIs as a risk factor for CDAD, results have been mixed. **[8–14]** This relationship has been somewhat ambiguous, and the exact mechanism of action is only speculative. However, the results of our study suggest that inhibition of gastric acid secretion using PPI therapy is significantly associated with an increased risk of CDAD among hospitalized patients, especially those concurrently receiving antibiotic therapy, the elderly, the immuno-compromised and those receiving chemotherapy.

Ingestion of C. difficile can result in either excretion, asymptomatic colonization of the gut, or disease with diarrhea, colitis or pseudomembranous colitis. **[13]** The normal stomach acidity is an important host defence against ingested pathogens and provides protection against enteric infections. **[14]** We hypothesized that the decreased gastric acidity induced by the use of proton pump inhibitors increases the susceptibility of hospital patients to colonization and subsequent infection with C. difficile. Significant bacterial overgrowth and even colonization with fecal type bacteria **[15]** has been demonstrated in the upper gastrointestinal tract of

patients receiving acid suppressive therapy, **[16]** with higher counts in patients taking proton pump inhibitors, **[17]** presumably because these agents are more effective than H2 blockers at blocking gastric acid secretion.

Decreased gastric acidity has been associated with renal failure **[18]** and older age, **[19]** and it may be a factor contributing to the association of C. difficile diarrhea with renal failure and older age observed in our study, and in previous reports. **[18, 19]** Use of proton pump inhibitors has been associated with elevated gastrin levels, **[20]** which have been shown to have trophic effects on the colonic mucosa. **[21]** We have postulated that decreased gastric acidity results in inadequate sterilization of ingested organisms, but other mechanisms are possible. Proton pump inhibitors may also contribute to the disruption of the bowel flora by allowing bacterial colonization of the stomach and upper small intestine; **[22]** however, it is unclear what effect this might have on colonic flora. Use of proton pump inhibitors may then contribute significantly to outbreaks of C. difficile diarrhea by resulting in increased numbers of susceptible hosts as well as possibly increasing the numbers of carriers in the population.

Some researcher however, have questioned the biological plausibility of a link between CDAD and acid suppression because C. difficile spores are resistant to acid digestion. **[23]** In an animal model, it has been shown that most ingested spores evolved into the vegetative state within one hour of ingestion. **[24]** It is conceivable that this transformation might be more likely to occur within the stomach in older patients with achlorhydria (due to atrophic gastritis or acid suppression), and/or delayed gastric emptying. **[25]** An increased risk of CDAD with acid- suppression therapy could thus arise from undigested vegetative cells being allowed to pass into the distal gastrointestinal tract.

A recent large community- based study has noted an increased risk of pneumonia in patients receiving acid suppression therapy, with an incident rate of 2.5 per 100 person per year for current PPI users. In addition to that, patients on PPI therapy have a higher prevalence of colonization of gastric juice with oropharyngeal flora than control patients, with evidence that the prevalence of these bacteria increases with both duration of therapy and rising intra-gastric pH levels. **[26]** Thus, it is safe to state that the effects of excessive use of PPI are more far reaching than previously anticipated and that there is now sufficient evidence to recommend suspension or cessation of PPI therapy in hospitalized patients requiring antibiotics unless there is a clear- cut indication for maintaining potent acid suppression (for example, active peptic ulcer disease).

## CONCLUSION:

An elevated risk of developing CDAD among hospitalized patients that underwent acid suppression via PPI therapy, was found in our study. Thus a judicious use of PPI therapy, especially among patients exposed to multiple risk factors for CDAD is advised and our data suggest that initiatives to curtail inappropriate use of proton pump inhibitors should be considered.

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