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Proton pump inhibitor (PPI) administration and *Clostridioides difficile* infection - is this a real clinical problem? A critical review of the literature

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ABSTRACT

Background: Proton pump inhibitors (PPIs) are widely used drugs that reduce gastric acid secretion. In recent years, there has been a gradual increase in their use. The safety of prolonged PPI therapy and the potential for cumulative side effects of these drugs raise legitimate concerns. An association between PPI administration and the risk of *Clostridioides difficile* infection has been suggested. The findings regarding this phenomenon require further unequivocal verification.

Material and methods: A review of publications obtained from the PubMed database and published between 2016-2023. Based on the keywords "*proton pump inhibitor*", "*PPI*" and "*Clostridium*", 132 articles were selected. Finally, 6 meta-analyses were included in the analysis.

Results: Studies conducted in recent years have shown a statistically significant increase in the risk of *C. difficile* infection in patients taking PPIs compared to those who avoid this therapy. The aforementioned relationship was observed in both adults and pediatric patients. One study proved that the risk remained high even up to 1 year after the end of treatment. The described relationship is still a matter of debate due to the fact that patients using antacids are usually elderly, have several comorbidities and a higher risk of developing *C. difficile* infection regardless of PPI use.

Conclusions: The relationship between the use of PPIs and the risk of developing *C. difficile* infection is still controversial, which justifies the need for continued clinical trials to objectively resolve this issue. PPIs exert high efficacy in the treatment of acid-dependent diseases, but due to the many ambiguities surrounding possible side effects, caution in their administration seems warranted, especially for long-term therapy in elderly patients with polypharmacy.

Keywords: *Clostridium difficile* infections; proton pump inhibitors; gut microbiota

INTRODUCTION

Proton pump inhibitors (PPIs) are commonly used drugs that reduce gastric juice acidity. [1] Their mechanism of action involves selective and irreversible binding to the cystine groups of potassium and hydrogen ion-dependent ATP-ase, resulting in inhibition of proton pump activity, reduction of hydrogen ion secretion into the gastric lumen and decrease of basal and stimulated gastric secretion. [2] The PPIs need acid to become active and inhibit the proton pump. It is crucial to administer PPIs around mealtime since they only attach to the proton pumps that are currently producing acid. In the fasting state, only 5% of the gastric proton pumps are active, whereas 60% to 70% of them are active during a meal. To achieve the best outcome, it is recommended to take PPIs 30 to 60 minutes before a meal to ensure that the enteric-coated medication is absorbed and available in the bloodstream when the most of proton pumps are susceptible to inhibition. [3] The main indications for the use of PPIs include gastroesophageal reflux disease, treatment and prevention of recurrent peptic ulcers, *Helicobacter pylori* eradication, high gastric secretion leading to Zollinger-Ellison syndrome, histologically confirmed gastritis or prevention of peptic ulcer disease associated with the use of non-steroidal anti-inflammatory drugs. [4] Long-term PPI therapy (>8 weeks) is indicated for Barrett's esophagus, Zollinger–Ellison syndrome, severe erosive GERD (Los Angeles grade C/D), peptic stricture or a history of bleeding gastric ulcers. [5]

Over the past two decades, the PPI administration has widely increase. They are among the most commonly prescribed drugs in the world now. Their use is even even higher than estimated due to the increase in over-the-counter PPIs. For many years, PPIs have been, and continue to be, considered well-tolerated and safe drugs - especially within short treatment periods. Unfortunately, PPIs are often used for too long and quite frequently outside the proper. For this reason, the safety of long-term PPI therapy has been a growing concern in recent years. [4,6]

Among the potential consequences of taking PPIs for extended periods of time, impaired nutrient absorption, leading to deficiencies in iron, calcium, magnesium and vitamin B12, has been cited. Other presumed consequences of taking drugs that decrease gastric juice acidity include pneumonia, osteoporosis, development of gastric polyps, Alzheimer's disease, kidney failure, small intestinal bacterial overgrowth (SIBO), and more frequent gastrointestinal infections. Among them, are infections caused by *Clostridioides difficile*. [6, 7]

CLOSTRIDIOIDES DIFFICILE INFECTION

Clostridium difficile is a Gram-positive, anaerobic bacterium that produces spores and potent exotoxins. Symptomatic *C. difficile* infection (CDI) is defined as an acute gastrointestinal illness manifested by at least three loose stools in 24 hours. According to the National Institute of Public Health - NIH, the CDI incidence in Poland was 53.78 per 100 000 population in 2022. Transmission of the pathogen occurs via the fecal-oral route. Factors predisposing to the infection include antibiotic therapy in the previous 2-3 months, contact with healthcare facilities, age above 65 years, chronic illness, immunosuppression, and the aforementioned use of hydrochloric acid blockers. It is estimated that approximately 30% of CDIs are associated with contact with the healthcare community. Recurrence of infection occurs in approximately 20% of patients. The clinical picture is heterogeneous and ranges from asymptomatic carriage, through various degrees of diarrhea, to the most severe pseudomembranous colitis. [8, 9]

POTENTIAL MECHANISM FOR PPI-ASSOCIATED CDI

The mechanism by which PPIs may increase the risk of CDI is not fully explained. Long-term suppression of hydrochloric acid secretion by PPIs and an increase in intragastric pH may lead to changes in the gut microbiome, making it more susceptible to *C. difficile* overgrowth. The reduction in microbial diversity commonly observed in patients with CDI may decrease competition for nutrients in the gut, giving *C. difficile* an advantage in utilizing available amino acids. [6] *C. difficile* then begins to dominate and take possession of the colon, which may be the first stage of infection. The virulence of the pathogen is due to the production of exotoxins that damage the cytoskeleton of epithelial GI mucosa cells, leading to disruption of tight junctions, neutrophil adhesion and local inflammation. As a result a breakdown of the integrity of the intestinal barrier and as well as loss of its function occurs. [10]

In addition, low pH in the stomach prevents an evolution of *C. difficile* spore to the reproductive phase, while high pH levels in both the stomach and intestines provide an environment in which the bacterium can survive and the spores can spore and germinate into a vegetative form. [11]

MATERIAL AND METHODS

The purpose of this work is to evaluate the relationship between long-term use of proton pump inhibitors (PPIs) and the risk of developing of *Clostidioides difficile* infection (CDI).

The literature obtained from the PubMed database and published between 2016-2023. Only articles in English were eligible for further analysis. Based on the keywords "*proton pump inhibitor*", "*PPI*" and "*Clostridium*" 132 articles were selected. Finally, 6 meta-analyses, consistent with the topic of the paper, were included in the analysis.

RESULTS

TABLE 1. CHARACTERISTICS OF THE STUDIES INCLUDED

No.	Year	Author	Study design	Number of subjects	CDI risk assessment	Conclusions
1	2021	Palna Mehta et al.	Systematic review and Meta-analysis	9	OR 1.84 (95% CI 1.18-2.85)	The use of PPIs increases the risk of CDI recurrence
2	2021	Kristin M. D'Silva et al.	Systematic review and Meta-analysis	16	OR 1.69 (95% CI 1.46–1.96)	The use of PPIs increases the risk of CDI recurrence
3	2018	Tadayuki Oshima et al.	Systematic review and Meta-analysis	67	OR 2.30 (95% CI 1.89–2.80) adults OR 3.00 (95% CI 1.44–6.23) pediatric patients	The use of PPIs increases the risk of CDI in adults and pediatric patients
4	2018	F. Cao et al.	Meta-Analysis	50	RR 1.29 (95% CI 1.14–1.44) hospital-acquired CDI RR 1.17 (95% CI 0.74–1.59) community-associated CDI	The use of PPIs increases the risk of hospital-acquired and community-associated CDIs
5	2017	Anca Trifan et al.	Systematic review and Meta-Analysis	56	OR 1.99 (95% CI 1.73-2.30)	The use of PPIs increases the risk of CDI
6	2016	Vanessa Arriola et al.	Meta-Analysis	23	OR 1.81 (95% CI 1.52-2.14)	The use of PPIs increases the risk of hospital-acquired CDI

A 2021 systematic review and meta-analysis by Palna Mehta et al. examined the association between recurrent *Clostridium difficile* infection (CDI) and the use of gastric acid suppressants in hospitalized patients (Table 1). Nine studies involving a total of 5668 patients

were included, of whom 1003 (17,7%) developed recurrent CDI. Results indicated that the use of proton pump inhibitors (PPIs) was associated with an 84% increased risk of recurrent CDI compared with patients on no PPIs treatment (OR 1.84; 95% CI 1.18-2.85). This led to the conclusion that unnecessary use of PPIs should be discontinued. [12]

A similar systematic review and meta-analysis was conducted by Kristin M D'Silva et al. in 2021 (Table 1). Cohort and case-control studies were eligible for their study. Participants were adults with a history of prior CDI who were or were not receiving PPI therapy. Ultimately, 16 studies involving 57,477 patients with CDI were included, of whom 6870 (12%) were receiving PPIs. The results of the study showed a significantly higher of CDI recurrence in patients who received PPIs (OR 1.69; 95% CI 1.46-1.96) compared to those who did not. The authors concluded that stricter recommendations for the use of gastric acid inhibitors in patients with CDI are needed. [13]

In 2018, Tadayuki Oshima et al. conducted a systematic review and meta-analysis to assess the risk of primary and recurrent CDI in adults and children treated with PPIs (Table 1). Inclusion criteria included (a) observational studies (both case-control and cohort studies), (b) a population of adults and children (aged <18 years) who received PPI therapy before the onset of acute diarrhea and were compared with a control group and (c) a diagnosis of CDI based on laboratory confirmation of *C. difficile* or clinical definition. A total of 67 studies were finally included in the analysis. PPI use was found to be significantly associated with the risk of CDI (OR 2.34; 95% CI 1.94-2.82). In addition, a subgroup analysis showed a significant association between PPI use and increased incidence of CDI not only among adult patients (OR 2.30; 95% CI 1.89-2.80), but also, and even more so, among pediatric patients (OR 3.00; 95% CI 1.44-6.23). This may be explained by the stronger potential impact of PPIs on the just-developing microbiome in children compared to the more stable microbiome in adults. This led to the conclusion that the discontinuation of PPIs at any age should be considered if they are not really indicated. [14]

A meta-analysis by Cao et al. from 2018 also assessed the association between the use of gastric acid suppressants and the risk of CDI (Table 1). A pooled analysis of 50 studies (both case-control and cohort) showed a significant association between PPI use and the risk of developing CDI (OR 1.26; 95% CI 1.12-1.39) compared with non-PPI users. Furthermore, these results were particularly significant for hospital-acquired CDI with a relative risk (RR) of 1.29 (1.14-1.44) in comparison to community-associated CDI (RR 1.17, 95% CI 0.74-1.59). The results indicates that hospital patients are more likely to develop CDI. The risk of PPI use

on the development of CDI in the hospital setting was further stratified. CDI cases in intensive care units and general wards were studied. Based on the results, the relative risks (RR) of hospital-acquired CDI in intensive care units and general wards were 1.43 (0.74-2.11) and 1.29 (1.13-1.45) respectively. The authors concluded that strict guidelines on the use of PPIs could help control CDI in the future. [15]

The association between proton pump inhibitor (PPI) therapy and CDI risk was also investigated by Anca Trifan et al. in 2017 (Table 1). Of the 56 studies included, 40 were case-control and 16 were cohort studies. Most studies were single-centre. Both nosocomial and community-acquired infections were included. A total of 356,683 patients aged above 18 years were included. There were no restrictions related to PPI treatment regimen. The meta-analysis showed that the risk of *C. difficile* infection was almost twice as high (OR 1.99; CI 1.73-2.30) in PPI users than in non-users. However, the authors suggested that further high-quality, prospective studies assessing this association are needed. [16]

Vanessa Arriola et al. in their 2017 meta-analysis examined the association between PPI use and the risk of hospital-acquired *C. difficile* infection in adults (Table 1). Twenty-three studies were included in the analysis, of which 19 were case-control studies and the remaining 4 were cohort studies. No randomised controlled trials (RCT) evaluating the association between PPIs and CDI were found. In total, the studies included 186,033 cases. Of these, 10,307 cases of hospital-acquired CDI were reported. The mean age of the patients was 70 years. All studies involved hospitalised patients and three studies focused exclusively on patients in the intensive care unit (ICU). Studies with different types, doses and durations of PPI taken were included. Any exposure to the drug in the past 90 days was considered. Unfortunately, 18 of the 23 studies identified potential confounders, such as antibiotic/H2RA (histamine type-2 receptor antagonists) administration or immunosuppression. The results of the meta-analysis suggest that PPIs significantly increase the risk of hospital-acquired CDI (OR 1.81; CL 1.52-2.14). [17]

DISCUSSION

The findings on the relationship between PPI use and the risk of *C. difficile* infection remain the subject of continues debate. Current evidence supports the existence of this association. However, the studies conducted to date have some limitations. Many of them do not specify the dose and duration of PPI therapy. Undoubtedly, this is an area that requires further research. [14]

Another problem is also the insufficient adjustment for confounding in previous studies, mainly involving the use of antibiotics and the number of antibiotics received, the use of H2RAs, immunosuppression, the duration of PPI use or the number of days spent in hospital. [17]

This issue was attempted to be addressed by Malin Inghammar et al. in their nationwide cohort study published in 2021 and evaluated the effect of PPIs on the development of out-of-hospital *C. difficile* infection. This study used the SCCS (self-controlled case series analysis) method, which compared the number of exposure and non-exposure events within the same individual, only in those with an outcome event. This way, confounding factors could be controlled for and remain constant during the observation period. [18] Self-controlled case series analyses were used to estimate incidence rates (IRRs) for community-associated CDI, comparing periods with and without exposure to PPIs. The models accounted for constant confounders such as chronic disease, genetics and socioeconomic status. In addition, time-varying confounders, including hospital stays and antibiotic or corticosteroid use, were adjusted for. A total of 3,583 episodes of CDI were identified, of which 964 occurred during current PPI use, 324 episodes occurred up to 6 months after treatment cessation, and 123 episodes occurred 6-12 months after treatment cessation. PPI use was shown to be associated with a doubling of the risk of CDI in outpatients (adjusted IRR 2.03; CI 1.74-2.36). This risk decreased after cessation of treatment; nevertheless, it still remained significantly increased up to 1 year after PPI therapy cessation (for 0-6 months IRR 1.54; CI 1.31-1.80, for 6-12 months IRR 1.24; CI 1.00-1.53). [19]

Most of the literature focused on the potential PPI adverse effects includes observational studies and meta-analyses. Moreover, these meta-analyses often incorporate the same observational studies. Therefore there is a need for higher quality studies. [20] At present, there are no randomised controlled trials primarily designed to evaluate the effect of proton pump inhibitor therapy on the risk of *C. difficile* infection, which may be explained by the fact that such trials would require a large patient population. Additional problems would be posed by the recruitment of patients for a study in which a potential adverse effect was assessed. In contrast, RCTs in which *C. difficile* infection was a secondary outcome are available in the literature. Nevertheless, their results remain conflicting. In a 2018 randomised controlled trial conducted by Krag et al. reported a case of CDI as an outcome, and the relative risk (RR) was 0.76 (95% CI 0.42-1.39). These results indicates a reduced risk of *C. difficile* infection in PPI patient. [21]

The correlation between PPIs and CDI remains controversial, which is related to the fact that PPI patients tend to be older, have several comorbidities and a higher baseline risk of developing *C. difficile* infection regardless of PPI use. Moreover, there are emerging studies evaluating the impact of PPI on the course of CDI. A 2019 retrospective cohort study by Evan Stuart Bradleyv et al. sought to evaluate the impact of proton pump inhibitors used in the acute phase of *C. difficile* infection on the 180-day mortality. The study included 874 elderly patients (> 65 years) diagnosed and treated for CDI. The results revealed that the administration of PPIs when treating CDI in elderly patients was associated with a 55% reduction in the risk of 180-day all-cause mortality (aHR 0.45; CI 0.28-0.72). In addition, the risk of 180-day mortality was associated with more advanced patient age (aHR 1.45; CI 1.14-1.84) , a more severe course of infection (aHR 1.87; CI 1.22-2.88) and hospital-acquired *C. difficile* infection (aHR 3.01; CI 1.81-4.99). [22]

CONCLUSIONS

The relationship between PPI use and the risk of developing *Clostridioides difficile* infection is still controversial. Given the widespread use of PPIs, this is an issue of great clinical importance. It is therefore necessary to continue further clinical studies to objectively resolve this problem. Undoubtedly, PPIs show great efficacy in the treatment of acid-dependent diseases. However, due to the many uncertainties associated with possible side effects, caution in their administration seems warranted, especially in case of long-term therapy in elderly patients with polypharmacy. Careful PPI prescribing at the lowest effective dose and only for the duration of clear indications is strongly recommended. Proper monitoring of PPI indications as well as wide patient education regarding the disease and treatment options are crucial for their safety.

Author Contributions

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The authors declare no conflict of interest.

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