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Perspective

Proton Pump Inhibitors and *C. difficile* Infection: A Perspective

Arjun Gupta and Sahil Khanna*

Division of Gastroenterology and Hepatology, Mayo Clinic, USA

***Corresponding author**

Sahil Khanna, Division of Gastroenterology and Hepatology, 200 1st Street SW, Rochester, MN. 55905, USA, Tel: 507-284-2468; Fax: 507-284-0538; Email: khanna. sahil@mayo. edu

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In the last two decades, epidemiological data from United States national administrative databases and population-based studies have shown a two to six-fold increase in the incidence of *Clostridium difficile* infection (CDI), especially in the elderly [1-3]. This increase has been observed in diverse settings with *C. difficile* replacing methicillin resistant *Staphylococcus aureus* (MRSA) as the most common nosocomial infection in parts of the U. S, [4] and being increasingly recognized as a cause of diarrhea in the community [5].

Proton pump inhibitors (PPIs) are among the commonest prescribed medications in the United States, for indications including gastro-esophageal reflux, dyspepsia and peptic ulcer disease. They may be used without proper clinical indication due to over-the-counter availability [6]. There has been a massive increase in the use of proton pump inhibitors in the last 2 decades mirroring increased CDI rates, and the association may be ecological.

The primary pathway for PPIs causing CDI is postulated to be an increase in gastric pH allowing *C. difficile* survival. The role of gastric acid suppression in CDI remains controversial, although decreased gastric acid may increase susceptibility to other enteric and non-enteric infections [7,8]. There is conflicting evidence as to whether stomach acid is sporicidal for *C. difficile* [9,10]. The vegetative form of *C. difficile* does not survive gastric acid. Increased gastric pH may also allow survival of vegetative forms developing from newly germinated spores, leading to CDI. Alteration of colonic microbiota (usually by way of antibiotic exposure) is considered the primary pathway for CDI. The colonic microbiome is recognized as an essential component of host immune responses against pathogenic bacteria [11]. PPIs alter the gut microbiota by promoting bacterial colonization of the upper gastrointestinal tract, and by altering the distal colonic flora [12,13]. These alterations as well as the action of PPIs on neutrophils and epithelial cells may increase risk of CDI [14].

Initial studies demonstrating increased rates of PPI use in CDI patients compared to controls concluded that PPIs may be a risk factor for CDI [15,16]. In 2012, the U. S. Food and Drug Administration issued a warning that PPI use may be associated with CDI [17]. Data have suggested that circumventing the potential protective effect of stomach acid, for example, through the use of post-pyloric enteral feeding or the use of PPIs or histamine-2 receptor antagonists (H2RAs), may lead to a 2- to 3-fold increased risk of acquisition of CDI [18]. Two recent meta-analyses using different methodologies concluded that PPI use is associated with a small but statistically significant risk of developing CDI [19,20]. However these studies had significant unexplained heterogeneity in their risk estimates, and had residual confounding. Other rigorous meta-analyses found a statistically significant adjusted pooled odds ratio of PPI use and CDI; however quality of evidence was low with evidence of publication bias [21,22].

It is therefore debatable whether a true cause-effect relationship exists between PPI use and CDI, and it appears that confounding explains this statistical association. There may be higher PPI use in the elderly, those with a higher comorbidity burden or those in the intensive care unit on multiple antibiotics, all of which are independent risk factors for CDI. In two separate studies, the risk of developing CDI in patients taking PPI was not statistically significant in multivariable analyses adjusting for comorbid conditions even though univariate analysis showed significant association [23,24]. These findings indicate that confounding may explain the relationship between PPI use and CDI and a true causal relationship may be absent.

Therefore, the exact role of PPIs in causing CDI may not be straightforward and interactions with variables such as age, antibiotic exposure, comorbidities and other unknown confounders are likely present. In one study, there was a trend towards higher PPI use in antibiotic naïve community acquired-CDI (CA-CDI) patients compared to antibiotic exposed CA-CDI patients [15]. A retrospective review demonstrated a clinically relevant interaction between antibiotic and PPI use in hospitalized patients with CDI, with patients receiving a single antibiotic more than five times more likely to be exposed to PPI's when compared to patients receiving five or more antibiotics [25]. Hospital acquired CDI (HA-CDI) and CA-CDI may differ in their relationship to PPI use owing to differences in circulating *Clostridial* strains and the differential antibiotic exposure in the two settings [26].

Along with an increasing incidence, studies in the last decade have also demonstrated increasing rates of CDI related complications such as severe CDI, severe-complicated CDI, recurrent infection, and increasing colectomy and mortality rates [1,27]. PPI use has been described to be associated with an increased risk for recurrent CDI in studies without controlling for

important confounders [28-30]. However several other studies have countered these findings and shown that after appropriate adjustments for comorbidities, age and other co-variates, the association between PPI and adverse CDI-related outcomes do not exist [31,32]. A population- based study in Olmsted County, Minnesota showed that patients taking acid suppression medication (PPIs and/or H2RAs) were more likely to have severe (34. 2% vs. 23. 6%; P=0. 03) and severe-complicated CDI (4. 4% vs. 2. 6%; P=0. 006) than patients not undergoing acid suppression on univariate analysis [31]. However no such association was found after adjusting for age and comorbid conditions [31]. There was no relationship between PPI use and recurrent infection or treatment failure in this study.

In conclusion, with the current available data, it is not possible to state a definite cause effect relationship between PPI use and CDI incidence, and the statistical association seen is likely confounded. Prospective studies are needed to elucidate the exact relationship between PPI use and CDI incidence and outcomes. In the interim, steps should be taken to limit unnecessary PPI use in both the inpatient and outpatient settings in the absence of a defined indication. Almost 50-60% patients in studies evaluating *C. difficile* were reported to take PPIs for an unclear indication [30,33]. Decreasing unnecessary PPI use may help reduce CDI, alongside reducing health care costs and other PPI adverse effects. However, in patients with a clear indication for PPI use, these medications should not be discontinued for concern of developing CDI.

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