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Acid Suppression and the Risk of *Clostridium difficile* Infection

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“One of the first duties of the physician is to educate the masses not to take medicine.”

–Sir William Osler.

Clostridium difficile is a spore-forming gram-positive anaerobic bacillus that infects the gastrointestinal tract causing a spectrum of disease from asymptomatic colonization to life-threatening toxic megacolon. Morbidity is caused by toxin-mediated disruption of cytoskeletal elements leading to inflammation and cell death. Toxins A and B are the primary toxins produced; only one toxin is required to produce disease and organisms not producing these toxins are considered nonpathogenic. A third, binary toxin, has recently been described although its role in pathogenesis remains unclear (1).

The acquisition of *C. difficile* involves ingestion of the organism in spore or vegetative form, both of which are shed in the feces of those infected at a ratio of about 10:1, respectively (2). The vegetative form may survive on a moist surface for up to 6 hours (2). Whereas the vegetative organism is killed by the acidic gastric environment, the spore form survives (3, 4). Having evaded the major passive defense of gastric acid, spores can germinate in the small intestine presumably triggered by the presence of bile salts (5). A suitable colonic environment allows infection (CDI), often leading to *C. difficile*-associated disease (CDAD).

CHANGING EPIDEMIOLOGY

The last two decades have seen an increase in the incidence of CDAD in the United States and abroad (6–11), and *C. difficile* has replaced methicillin-resistant *Staphylococcus aureus* as the most common cause of healthcare-associated infection (12). Adult data have shown a concomitant increase in severity based on mortality and hospitalization rates (13–15). Additionally, an increase in community acquired CDI (CA-CDI) has been observed (16, 17).

Pediatric data have shown a similar increase in incidence but not severity (18). A population-based cohort study of CDI in children demonstrated a 12.5 fold increase in

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incidence over the study period from 2.6 (1991–1997) to 32.6 per 100,000 (2004–2009), adjusted for age and sex (19). Although the incidence of infection may be accurate, the degree of change may be falsely inflated by detection bias with transition to more sensitive PCR based assays during this period. The majority of these cases (75%) were community-acquired indicating hospital-based studies underestimate the true burden of disease.

The emergence of a hypervirulent strain has contributed to the shifting epidemiologic landscape, but it has not replaced other strains (20, 21). Naggie et al analyzed 77 stool samples positive for toxigenic *C. difficile* isolates (22), and found that only 13 (17%) produced patterns identical to the newly emerged, hypervirulent ribotype 027; in total 19 ribotypes were identified. In fact, the prevalence of hypervirulent CDIs may be decreasing (23, 24). Thus, the increase in CDIs cannot simply be attributed to an epidemic strain, but rather the sum of an evolving pathogen and a general increase in host susceptibility and/or risk.

The changes in infection rates and disease behavior have prompted examination of host risk factors for CDI in hopes that risk modification may reduce the burden of disease. Known risk factors include age, sex, antibiotic use, hospitalization or healthcare exposure, gastrointestinal operations, chemotherapy, enteral feeding, and chronic illness. Recently, controversy has surrounded the consideration of acid suppression as a risk for CDI, particularly in the setting of over-the-counter availability and increasing use (25, 26). Though the mechanism by which this may occur has not been proven, the increased risk appears biologically plausible.

ACID SUPPRESSION

Gastric acid suppression is used for conditions such as dyspepsia, gastroesophageal reflux disease, stress ulcer prophylaxis, laryngopharyngeal reflux, duodenal ulceration and *H. pylori* infection. It is accomplished through direct inhibition of the proton pump of gastric parietal cells or indirectly through inhibition by blockage of histamine, the former being more effective at increasing gastric pH. Typical acid secretion creates a gastric pH of about 1.4 (27). The generally accepted goal of therapy for these conditions, due to observed healing and reduced reflux symptoms, is a gastric pH at or above 4 (28). Commonly used PPIs achieve this goal (29, 30). However, pH above 4 has been shown to increase bacterial survival, specifically for the spores of *Clostridium perfringens*, in a mouse model (31). Additionally, *in vitro* studies have shown PPIs inhibit neutrophil bacteriocidal activity, chemotaxis, and phagocytosis (32–34). Although acid suppression is beneficial for a number of medical conditions, it may place the user at increased risk of enteric infection (35).

ACID SUPPRESSION AND CDI

Hypochlorhydria was implicated in the transmission of *C. difficile* as early as 1982 and therapeutic acid suppression was first identified as a risk factor for CDI by Brown, et. al. in 1990 (3, 36). In 2007, Leonard, Marshall, and Moayyedi systematically reviewed 12 papers evaluating 2,948 patients with CDI for previous use of acid suppression (25). They found an increased risk with acid suppression (OR 1.94, 95% CI 1.37 – 2.75). After separating therapeutic categories, they observed the association was greater for PPI use (OR 1.96, 95% CI 1.28 – 3.00) than for histamine type 2 receptor antagonist (H2RA) use (1.40, 95% CI 0.85 – 2.29). Subsequent studies focus on PPI use.

Two meta-analyses have evaluated the association between PPI therapy and risk of CDI in adults. Janarthanan et al performed a systematic literature search of MEDLINE and PubMed databases from 1990 through December 2010 (37). They analyzed studies together and grouped by study design and used a random-effects model to account for heterogeneity

among studies. Twenty-three studies, including 288,620 hospitalized patients evaluated PPI use for at least the 3 months prior to development of CDAD, found an overall risk ratio of 1.69 (95% CI, 1.395 – 1.974). When separately analyzed by study type, the risk remained significant. Deshpande et al systematically reviewed the literature between 1990 and 2010 (38). Interestingly, they did not identify one prospective study evaluating PPI use and risk of CDI. They were unsuccessful in obtaining meaningful results from antibiotic use analysis, but they did find an overall increase in risk of CDI with PPI use (OR 2.15 95% CI, 1.81–2.55). Subgroup analysis revealed no publication bias. Both studies reported significant heterogeneity.

A recent meta-analysis evaluated incident and recurrent CDI in PPI users as well as the relative impact of concurrent antibiotic use (39). The authors systematically analyzed 42 observational studies (N=313,000 patients), and found an association between PPI use and risk of CDI (OR 1.74, 95% CI 1.47 – 2.85) or risk of recurrent CDI (OR 2.51, 95% CI 1.16 – 5.44). When antibiotics and PPIs were used together, the risk of developing CDI rose above the effect of PPI alone (OR 1.96, 95% CI 1.03 – 3.70). An added risk of 19% was attributed to the interaction between the two drug types, independent of the effect of either drug in isolation. When compared with PPIs, H2RAs carried a lower risk (OR 0.71, 95% CI 0.53 – 0.97).

Few studies have been conducted to specifically evaluate PPI use as a risk factor for CA-CDI. Kuntz et al demonstrated the importance of investigating this relationship (40). They found CA-CDI occurring in populations not traditionally thought to be at risk. Twenty-seven percent of subjects with CA-CDI had no antimicrobial exposure 180 days before diagnosis. Exposure to gastric acid suppression was found in 18% of CA-CDI compared with 5% of controls (OR 2.30, 95% CA-CDI) adjusting for antimicrobial use, comorbidity, hospitalizations, age by category (<18 years of age was the reference group), and sex. Eighty-four percent of patients exposed to acid suppression who developed CA-CDI had also received one or more antimicrobial agents.

Heterogeneity in individual study results observed on meta-analysis may indicate a false association, thus it is important to understand the source. Kwok, et. al. used subgroup analysis and the random effects model to evaluate heterogeneity (39). They found a similar association of PPI with risk of CDI in all study methods and a consistent direction of effect indicating a true association. A false association may also be observed with publication bias. Janarthanan, et. al. recognized this potential and demonstrated through trim-and-fill sensitivity analysis that the association was not an artifact of unpublished negative studies (37). Finally, exposure to acid suppression may be under-reported due to its availability as an over-the-counter product. This may lead to an overstatement of risk.

Variables not easily analyzed must also be considered as sources of study heterogeneity. *C. difficile* strain variation may result in regional differences in organism susceptibility to acid or PPI. Furthermore, PPI formulation, brand, and dosing schedule are not generally reported, and these may produce different average intra-gastric pH values and differing effects on leukocyte function (35). Finally, few studies report dose or frequency though risk may be dose dependent or follow a dose-response curve. Howell, et. al. performed a pharmacoepidemiologic prospective cohort study of 101,796 discharges to evaluate for dose-response (41). After adjusting for age, antibiotic exposure, and propensity score-based likelihood of receiving acid-suppression therapy, they demonstrated increasing acid suppression resulted in an increased risk of CDI. H2RA therapy resulted in an odds ratio of 1.52 (95% CI, 1.12 – 2.10). Daily and BID PPI dosing lead to odds ratios of 1.74 (95% CI, 1.39–2.18) and 2.36 (95% CI, 1.79 – 3.11), respectively. The observation of a dose-response supports the role of PPIs as a risk factor in the development of CDI.

PEDIATRIC STUDIES

One study has been published that specifically and sufficiently evaluates an association between acid suppression and CDI in hospitalized children (42). This observational, case-control study was performed retrospectively on children admitted to the Department of Pediatrics, University of Naples “Federico II” between June 2005 and July 2009. Of 910 children admitted for abdominal pain and diarrhea who underwent testing for CDI, 68 were found to be positive. Controls were selected at random from the remaining 842 patients with a negative stool *C. difficile* toxin assay. The use of PPIs was significantly higher in those testing positive for *C. difficile* toxin (OR 4.52, 95% CI, 1.4–14.4). A trend toward statistical significance was also found in those using H2RAs but power was not sufficient to statistically confirm association. Notably, antibiotic exposure was not different between groups. On multivariate analysis, IBD and PPI use were associated with CDI.

USE, OVERUSE, AND UNNECESSARY USE OF PPI

Use of acid suppression therapy, particularly PPIs, is increasing. Lu, et. al. surveyed the Swedish Prescribed Drug Register and found sales of PPIs (in daily defined doses/1,000 inhabitants/day) increased by over 50% from 2000 to 2008 (26). Evidence-based guidelines for appropriate use in diverse clinical situations are available (43–47). Overuse occurs when dosing exceeds that which is needed to adequately treat for an appropriate indication. Unnecessary use occurs when acid suppression therapy is prescribed without an appropriate indication.

Unnecessary use and overuse have been well-documented in adults. A study evaluating prescription patterns via pharmacy audit data reviewed ambulatory use in 168,727 adult patients taking PPIs or H2RAs for longer than 90 days (48). This found an appropriate upper GI diagnosis in only 61% of patients. Heidelbaugh et al studied 946 veterans using PPI therapy and found 36% had no documented appropriate indication (49). Furthermore, the total cost of inappropriate PPI use was \$1,566,252. In patients receiving more than daily PPI dosing for an appropriate indication (GERD), step-down to daily dosing or medication discontinuation has been accomplished in some patients without significant relapse of symptoms (50, 51). Inpatient overuse and unnecessary use has also been described (52).

RECOMMENDATIONS

It is biologically plausible that an increase in pH with a decrease in barrier function of the gastric environment could put one at risk for CDI, and, on February 8, 2012, the FDA released a drug safety communication indicating that PPIs may be associated with an increased risk of CDAD (53). Adult studies confirm that patients undergoing pharmacologic acid suppression are at increased risk of developing CDI; PPI use is associated with an approximately 2 fold increase in risk over non-use, and significantly more risk than H2RA use. Antibiotics appear to act synergistically with PPIs. To date, one study specifically evaluating pediatric risk of CDI with PPI use has shown an increased risk. Further studies in children, particularly in populations at increased risk (IBD, intestinal failure, immunodeficiency) are needed (54). The importance of this grows with the increased incidence of CDI and use of PPIs. Discontinuing acid suppression in patients who need it is not advocated, however, the authors recommend consideration (and documentation) of the expected course of acid suppression when initiating therapy. We also recommend periodic holidays or dosing step-downs to assess continued need in patients who may tolerate such assessment with the understanding that temporary rebound hyperchlorhidria may occur on PPI withdrawal.

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