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Proton Pump Inhibitors Associated with Increased Risk of Clostridium difficile Diarrhea

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Background
Evidence-based risk factors associated with Clostridium difficile infectious diarrhea have been identified through systematic review of the literature. Factors identified include increasing age, increased severity of underlying diseases, non-surgical gastrointestinal procedures, presence of a nasogastric tube, stays in intensive care units, increasing duration of hospital stay, increased duration of antibiotic treatment, and multiple antibiotic administration.1

C. difficile is associated with significant morbidity, mortality, increased length of hospital stay, and increased cost. Its incidence doubled between 2000 and 2002.2 Two recent studies have identified the use of proton pump inhibitors as an associated risk factor for C. difficile diarrhea.3,4 Commonly prescribed proton pump inhibitors include esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), and rabeprazole (Aciphex).

In the current investigation both cohort and case-controlled studies were undertaken to assess acid-suppressive therapy as a risk factor for C. difficile infection.4

Citation

Results
C. difficile diarrhea developed in 6.8% of the cohort patients. Of the patients who received antibiotics and a proton pump inhibitor 9.3% developed C. difficile diarrhea. Whereas those who received antibiotics but no proton pump inhibitor experienced a 4.4% incidence (RR 2.1, 95% CI 1.4 to 3.4). The relative risk of C. difficile was higher in patients receiving proton pump inhibitors compared with H2-blocker recipients (OR 2.1, 95% CI 1.2 to 3.5 vs. OR 1.1, 95% CI 0.4 to 3.4).

In the case-control study, 94 patients developed C. difficile diarrhea. The case and control subjects were similar in age, number and type of antibiotic, and comorbidity factors. Case subjects were more likely to be female, have renal disease, MRSA colonization, and had past admissions. It was also noted that one patient receiving a proton pump inhibitor but no antibiotics, developed C. difficile diarrhea. Of the cases, 64% were receiving proton pump inhibitors
as compared with 36% of the controls (unadjusted OR 3.1, 95% CI 1.7 to 5.6).

**Author Conclusions**

Inpatients receiving proton pump inhibitors were at greater risk for *C. difficile* diarrhea.

**Commentary**

*Clostridium difficile* is an anaerobic gram-positive rod accounting for approximately 15% to 25% of all causes of antibiotic-associated diarrhea. Some of the clinical signs of infection include watery diarrhea, fever, abdominal pain and tenderness, and nausea. It may also cause pseudomembranous colitis.5

It is most frequently transmitted by the hands of health care workers who have had contact with contaminated feces or environmental surfaces.5

Symptomatic patients should be tested for *C. difficile* if they are or have recently been hospitalized and have taken antibiotics or are receiving antibiotics at home or in a nursing care facility. Stool culture and toxin assays are recommended diagnostic tests for *C. difficile*.5

When *C. difficile* is confirmed, first-line antibiotic treatment with oral metronidazole should be prescribed. The recommended dose is 250 mg four times daily or 500 mg twice daily for ten to 14 days.5 Intravenous metronidazole may be effective in those unable to take the drug orally.7 Oral vancomycin (125 mg four times daily for ten to 14 days) should be reserved for those who have failed first-line treatment, are intolerant to metronidazole, or have metronidazole contraindications. Intravenous vancomycin is not excreted into the colon and therefore should not be used for *C. difficile*.5

Patients who have *C. difficile* colonization test positive but are asymptomatic. These colonized cases should not be treated with antibiotics since there is decreased risk for active disease.5

Prevention and control of *C. difficile* requires contact precautions for all symptomatic cases including frequent handwashing, use of gloves, use of gowns if soiling is possible, and private room placement. Appropriate medical device and environmental cleaning with EPA-approved disinfectants is essential.5

Judicious use of antibiotics is a key preventative measure. The antibiotics most often associated with *C. difficile* diarrhea are clindamycin, broad-spectrum penicillins, cephalosporins, and in several case reports, quinolones.8,9

Methotrexate or paclitaxel chemotherapy can also present risks.8

Several case reports have identified *C. difficile* colitis associated with “triple” regimen therapy to eradicate *Helicobacter pylori*. The regimens consisted of clarithromycin, metronidazole, and omeprazole or clarithromycin, amoxicillin, and lansoprazole.10-12

Proton pump inhibitors are prescribed for a variety of indications including duodenal and gastric ulcer, esophagitis, gastroesophageal reflux disease, peptic ulcer disease, Zollinger-Ellison Syndrome, heartburn, prophylaxis of upper gastrointestinal bleeding associated with non-steroidal anti-inflammatory agent use, and acute upper gastrointestinal bleeding. The overuse of acid-suppressing drugs has been described in hospitalized patients.13 Inappropriate use especially as prophylaxis of stress ulcers in low-risk patients is common.13

The normal pH of the stomach is a host defense and barrier to ingested pathogens.14 Bacterial overgrowth and colonization with fecal bacteria have been identified in studies with acid-inhibitory therapy.14,15 Acid-suppressing drugs are associated with bacterial overgrowth in the stomach and influenza viruses in the gastric mucosa.14,16 Studies have also shown that bacterial overgrowth depends on the intensity of inhibition of gastric acid secretion and corresponding increase in pH. Proton pump inhibitors have greater inhibition of gastric acid secretion compared with H₂ receptor antagonists.15,17

Careful consideration should be taken when proton pump inhibitors are prescribed for inpatients when concomitant antibiotics are used. Prophylactic use of proton pump inhibitors should be examined for appropriateness given the findings of this study. Accepted indications for proton pump inhibitors include treatment of active gastroesophageal reflux disease (GERD), acute upper gastrointestinal bleeding, active peptic ulcer disease, and Zollinger-Ellison Syndrome.18,19

Preliminary evidence suggests that development of *C. difficile* infection is a potential consequence when proton pump inhibitors are combined with antibiotic therapy in hospitalized patients.
Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the LEVEL OF EVIDENCE for the statements we publish.

<table>
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<th>Level</th>
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| A     | High-quality randomized controlled trial (RCT)  
       | High-quality meta-analysis (quantitative systematic review) |
| B     | Nonrandomized clinical trial  
       | Nonquantitative systematic review  
       | Lower quality RCT  
       | Clinical cohort study  
       | Case-control study  
       | Historical control  
       | Epidemiologic study |
| C     | Consensus  
       | Expert opinion |
| D     | Anecdotal evidence  
       | In vitro or animal study |


References