# *C. difficile* Infection, PPI Link Strengthened

BY MARY ANN MOON

FROM THE ARCHIVES OF INTERNAL MEDICINE

Use of proton pump inhibitors appears to increase the risk of recurrent *Clostridium difficile* infection and may even have a causal effect, according to two cohort studies.

In the first study, PPI use during treatment for an incident *C. difficile* infection was associated with a 42% higher risk of recurrent *C. difficile* infection. The second study demonstrated a dose-response effect between increasing levels of acid suppression among inpatients taking PPIs and increasing risk for nosocomial *C. difficile* infection.

Neither study was designed to definitively establish causality; an adequately sized randomized controlled trial would be both prohibitively expensive and possibly unethical. But both of these studies add to the growing body of evidence linking PPIs with *C. difficile* infection, and their findings should prompt clinicians to take several reasonable, important steps to limit patients' exposure to PPI therapy, both groups of investigators noted.

In the first study, Dr. Amy Linsky of Boston Medical Center and her associates examined pharmacy and administrative databases for eight Veterans Affairs medical centers in New England. They identified 1,166 patients who began treatment for an index case of *C. difficile* during a 4-year period.

**VITALS**

**Major Finding:** Proton pump inhibitor use during treatment for incident *C. difficile* infection was associated with a 42% higher risk of *C. difficile* recurrence.

**Data Source:** 1,136 patients in the pharmacy and administrative databases of eight Veterans Affairs medical centers in New England.

**Disclosures:** Support was provided by the VA Cooperative Studies Program and the VA Boston Healthcare System. No financial conflicts of interest were reported.

This included 527 patients (45%) who used an oral PPI at some time during the 14 days following diagnosis and 639 (55%) who did not use any PPIs during that interval. Omeprazole was the PPI used by 97% of patients who were given PPI therapy.

The primary end point was recurrent *C. difficile* infection during the 90 days following the incident diagnosis. This occurred in 25% of the PPI-exposed group, compared with 19% of the nonexposed group, a significant difference.

After the data were adjusted to account for patient age, initial antibiotic treatment, additional antibiotic treatment, duration of hospitalization, and differences in baseline comorbidities and medications, the hazard ratio for PPI exposure remained elevated at 1.42. This represents a 42% increase in risk for recurrent *C. difficile* infection for patients taking PPIs, Dr. Linsky and her colleagues said (Arch. Intern. Med. 2010;170:772-8).

In the second study, Dr. Michael D. Howell of Beth Israel Deaconess Medical Center, Boston, and his associates performed a secondary analysis of data prospectively collected on 101,796 discharges from their center in 2004-2008. Nosocomial *C. difficile* infection had developed in 665 (0.7%) of these cases.

In unadjusted analysis, the risk of acquiring the infection rose from 0.3% with no exposure to PPIs to 0.9% with daily use of PPIs to 1.4% with more frequent than daily use of PPIs.

This dose-response effect persisted after the data were adjusted to account for patient age, comorbid conditions, and receipt of antibiotics. The odds ratios were 1 (reference) for no exposure to PPIs, 1.74 for daily exposure, and 2.36 for more frequent exposure to PPIs. This represents more than a 70% increase in the risk of developing nosocomial *C. difficile* if a patient is taking a daily PPI, and more than a doubling of the odds if a patient is taking the drugs more frequently, Dr. Howell and his colleagues said (Arch. Intern. Med. 2010;170:784-90).

The findings suggest that "we should expect at least 1 additional case of nosocomial *C. difficile* infection for every 533 patients who receive a daily PPI, after controlling for other risk factors," Dr. Howell and associates noted.

"Although this seems like a relatively large number-needed-to-harm, the magnitude of exposure is large. We found that 60% of patients received acid-suppressive therapy, similar to others' estimates," the researchers added.

Given the widespread use of PPIs and the millions of hospital discharges every year, "the number of potentially attributable nosocomial *C. difficile* cases in the United States numbers in the tens of thousands per year," they noted.

This figure is particularly alarming because research has shown that PPIs are not strictly indicated for more than two-thirds of inpatients who receive them, added Dr. Howell and his colleagues, who reported no conflicts of interest.

To limit unnecessary exposure to PPIs, physicians should ensure that every hospitalized patient is given the least-intense acid-suppressive therapy that is appropriate for his or her condition. "In particular, unless and until there is clear evidence that low-risk, noncritically ill patients receive benefit from stress ulcer prophylaxis, we should strive to minimize exposure to acid-suppressive medications in this group," they said.

Hospitals should reexamine standing protocols that include stress ulcer prophylaxis, and also should ensure that such medications are discontinued at discharge, they added. ■

# Bacterial Overgrowth Found in 50% of Those Using PPIs

BY JENNIE SMITH

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Fifty percent of the people taking proton pump inhibitors to treat gastroesophageal reflux disease develop small intestinal bacterial overgrowth, compared with a quarter of the patients with irritable bowel syndrome who are not taking PPIs, according to a study conducted by Dr. Lucio Lombardo and his colleagues.

In the study, 450 consecutive patients underwent glucose hydrogen breath tests, which measure the metabolic activity of enteric bacteria (Clin. Gastroenterol. Hepatol. 2010 [doi:10.1016/j.cgh.2009.12.022]).

**VITALS**

**Major Finding:** Evidence of small intestinal bacterial overgrowth was found in 50% of patients on proton pump inhibitors, 24.5% of patients with irritable bowel syndrome, and only 6% of controls.

**Data Source:** Two hundred gastroesophageal reflux disease patients who were taking PPIs, 200 IBS patients not taking PPIs, and 50 healthy controls.

**Disclosures:** The study was not funded by outside grants, and neither Dr. Lombardo nor his colleagues reported any competing interests.

Two hundred of the patients had been diagnosed with gastroesophageal reflux disease and had been taking one of several PPIs for a median of 36 months, although some had taken the medication for as little as 2 months.

The investigators recruited an additional 200 study subjects who had been diagnosed with irritable bowel syndrome (IBS) and were not taking PPIs. Dr. Lombardo and his colleagues noted that the symptoms of IBS—including bloating, diarrhea, and constipation—frequently overlap with the symptoms of small intestinal bacterial overgrowth (SIBO). They also recruited 50 healthy controls who did not have symptoms of either IBS or SIBO and had not taken a PPI for at least 3 years.

Patients with other gastric diseases, who had recent gastric surgery, who were taking antibiotics, or had other potentially confounding factors were excluded.

Evidence of SIBO was found in 50% of the patients on PPIs, 24.5% of patients with IBS, and only 6% of healthy controls, wrote Dr. Lombardo, of the gastroenterology department of Mauriziano U.I. Hospital, Turin, and his colleagues.

Moreover, the researchers found a correlation between the duration of PPI treatment and the detection of SIBO, with more than 70% of the PPI group testing positive for SIBO after 13 months of PPI use—more than triple the proportion of positives among those taking PPIs for a year or less.

Although several studies have used breath-based tests to assess the prevalence of SIBO in patients with IBS, few have been designed to assess the independent influence of PPIs, the investigators wrote. This, they said, is as an "important oversight," as PPI use is widespread in patients with IBS.

The authors cited a recent study reporting that IBS patients not taking PPIs and GERD patients on PPIs have roughly equal rates of SIBO, as assessed by lactulose breath tests. However, the researchers wrote that no mention was made in that study of the duration of PPI treatment, while their own study showed that PPI treatment increased the incidence of SIBO drastically after the first year.

Dr. Lombardo and his colleagues speculated that PPI-related SIBO might be frequently underdiagnosed or misdiagnosed as IBS because of the overlap of common symptoms.

Patients in the investigation with SIBO were treated with the antibiotic rifaximin 400 mg three times daily for 14 days. Eradication of SIBO, as confirmed by a glucose hydrogen breath test, occurred in 87% of the PPI group and 91% in the IBS group.

In the PPI arm of the study, eradication was more successful among subjects who had taken PPIs for less than a year, which suggested "a more profound or qualitatively different alteration in enteric microflora after a year of treatment," according to the investigators.

In both the PPI and IBS groups, symptom severity was reduced by more than 90% in subjects whose SIBO eradication had been confirmed by breath testing and to a lesser but measurable degree in those subjects whose SIBO had not been eradicated after the same course of rifaximin.

The investigators did not seek to learn whether SIBO returned after eradication in patients who continued PPI therapy but cited another study suggesting that such an outcome was likely.

The authors noted a few limitations of the study, which included a lack of distinction between specific PPIs taken by the patients, the observational open-label study design, and that fact that *Helicobacter pylori* was not investigated as an independent contributor (although all 450 patients were tested, with 68% found to be negative). ■