# More Evidence for *C. difficile*, PPI Association

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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 showed 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 establish causality; a large randomized controlled trial would be 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 and hospitals 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.

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 took one.

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, antibiotic treatment, duration of hospitalization, and differences in baseline comorbidities and medications, there was 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," they 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," 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, Dr. Howell and his colleagues added. ■

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