

LETTERS TO THE EDITOR

Increased *Clostridium difficile* Recurrences following Combined Proton Pump Inhibitor–Metronidazole Therapy

To the Editor—The report by Hebert et al¹ provided strong support for increased risks of recurrent *Clostridium difficile* infections (CDI) in patients receiving either proton pump inhibitor (PPI) medications or primary metronidazole therapy. The authors did not, however, analyze *C. difficile* recurrence rates when both medications were administered concurrently. Recent studies support the possibility of inhibition of the effectiveness of metronidazole therapy by concurrent PPI administration. Al-Nassir et al² randomized 52 patients with CDI to initially receive either vancomycin or metronidazole with a protocol-driven change to the alternative medication if initial therapy was unsatisfactory. Of 34 patients initially receiving metronidazole, 9 of the 10 who required change to vancomycin were PPI consumers, compared with only 10 of the 24 not requiring antibiotic alteration ($P < .02$). Of 18 patients initially receiving vancomycin, 11 were PPI consumers, with only 1 requiring antibiotic alteration ($P < .01$).

Musher et al³ reported 35 CDI patients for whom initial metronidazole therapy had failed; 27 of the 35 were PPI consumers. Twenty-six responded to nitazoxanide, suggesting less PPI interference with nitazoxanide therapy than with the prior metronidazole therapy.

Analysis by the authors of *C. difficile* recurrence rates among their patients who were concurrently receiving PPI and metronidazole therapy would assist practitioners in deciding whether or not these medications should be used in combination and whether or not vancomycin might be a preferred therapy for CDI in patients for whom concurrent PPI therapy should not be discontinued.

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This work was performed within my private practice of internal medicine.

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Reply to Daniell

To the Editor—We appreciate Dr Daniell's¹ interesting comment on our article regarding electronic prediction of *Clostridium difficile* relapse.²

Dr Daniell cites two recent articles that suggest that the effect of proton pump inhibitors (PPI) on *C. difficile* primary treatment failure may be dependent on choice of initial treatment (metronidazole vs vancomycin or nitazoxanide). Our study was not designed to evaluate PPIs' effect on treatment failure, for two reasons:

1. Our focus was not on treatment failures. In fact, we avoided including patients with primary treatment failure by excluding any patient who received vancomycin or metronidazole in the follow-up period (after a normal course of treatment should have finished).
2. The variables that refer to metronidazole treatment and vancomycin treatment are not mutually exclusive. A patient could receive one, both, or neither of these medications. In fact, 190 (23%) patients in our study received both medications at some point during the treatment period.

What our study was designed to address is Dr Daniell's question of whether relapse is more common among those who received a PPI and metronidazole, compared to those who received only metronidazole or those who received a PPI and vancomycin. Specifically, we found the following:

1. Of those subjects who received a PPI and metronidazole alone, the relapse rate was 31.5% (40/127), compared to 22.3% (78/349) of those patients who received metronidazole alone and no PPI. The unadjusted odds ratio (OR)

- was 1.60 (95% confidence interval [CI], 1.02–2.51), $P = .04$.
- Of those subjects who received a PPI and vancomycin alone, the relapse rate was 28.0% (7/25), compared to 10.3% (8/78) in those who received vancomycin alone and no PPI. The unadjusted OR was 3.40 (95% CI, 1.09–10.63), $P = .05$.
 - Of those who received any treatment (metronidazole or vancomycin or both) and a PPI, the relapse rate was 33.8% (68/201), compared to 21.7% (123/568) for those who did not receive a PPI. The unadjusted OR was 1.85 (95% CI, 1.30–2.64), $P < .01$.
 - Of those patients who received both metronidazole and vancomycin as well as a PPI, the relapse rate was 42.9% (21/49), compared to 26.2% (37/141) for those who received both agents but not a PPI. The unadjusted OR was 2.11 (95% CI, 1.07–4.16), $P = .03$.

Our data suggest that PPI use is associated with a significantly increased risk of relapse, in unadjusted analyses, for both those who were treated with metronidazole and those who were treated with vancomycin. However, this analysis has several limitations. Our conclusions are based on unadjusted numbers, so unaccounted-for confounders may affect the results. Nevertheless, in our logistic regression model PPI use remained an independent predictor of relapse when adjusted for other factors, including age, metronidazole treatment, antibiotic exposure, and length of stay. In addition, the number of patients in our study who received vancomycin alone was small. In the subgroup of patients who received both metronidazole and vancomycin, there was an extremely high relapse rate in those who were given a PPI versus those who were not. It is possible that those patients had treatment failure with metronidazole; however, our data collection technique did not allow for that level of granularity.

In summary, our retrospective cohort study suggests that the use of a PPI is a predictor of readmission independent of choice of treatment. However, our study was not designed to address whether the concurrent use of PPI and metronidazole might lead to primary treatment failures. Dr Daniell presents an interesting insight that certainly deserves more study.

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Identification of *Clostridium difficile* Ribotype 027 for the First Time in Mainland China

To the Editor—Although several studies have shown that the incidence of infection with *Clostridium difficile* is increasing in Asia as a consequence of widespread use of broad-spectrum antibiotics,¹ very little is known about the epidemiology of *C. difficile*–associated diarrhea in developing countries. The hypervirulent epidemic strain of *C. difficile*, named ribotype 027, has also rarely been detected in Asia, especially in China.^{2,3}

In a retrospective study, we performed epidemiologic screening of patients with *C. difficile* infection (CDI) and investigated the characteristics and epidemiology of *C. difficile*–associated diarrhea in a large teaching hospital in South China. Fresh stool samples were collected from patients with suspected CDI over a 2-year period (December 2009–May 2012). Of the 3,660 stool samples, 572 (15.6%) were positive for *C. difficile* toxin by direct polymerase chain reaction (PCR).^{4,5} Logistic regression analysis showed that previous antibiotic use ($P = .04$) and CDI experience ($P < .01$) were significant risk factors for toxin-positive diarrhea. *C. difficile* ribotype 027 was not found, although 7 cases of specimens detected binary toxin successfully.

We also studied the relationship between CDI and inflammatory bowel disease. Stool specimens from 406 patients with inflammatory bowel disease, including 241 patients with Crohn's disease and 165 with ulcerative colitis, were collected from January 2010 to April 2013 in Nanfang Hospital. Thirty-four patients with Crohn's disease and 34 patients with ulcerative colitis were positive for *C. difficile*, with positive rates of 14.1% and 20.6%, respectively. Three stool samples were