LETTERS TO THE EDITOR

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

To the Editor—The report by Hebert et al[1] 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 al[2] 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 al[3] 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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Reply to Daniell

To the Editor—We appreciate Dr Daniell's[1] 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)