Since publication of their article, the authors report no further potential conflict of interest.

3. Cadle RM, Mansouri MD, Logan N, Kudva DR, Mushcr DM.

**Fidaxomicin for Clostridium difficile Infection**

**TO THE EDITOR:** In their randomized study comparing fidaxomicin with vancomycin for *Clostridium difficile* infection, Louie et al. (Feb. 3 issue) found that substantially fewer patients in the fidaxomicin group had recurrences of *C. difficile* infection within 4 weeks after the conclusion of treatment. We recently reported on an observational study involving U.S. veterans in which the recurrence of *C. difficile* infection within 90 days was significantly reduced in patients who did not receive proton-pump inhibitors (PPIs) as compared with those who received PPIs concurrent with treatment for *C. difficile* infection, independent of the treatment regimen for *C. difficile* infection. Other observational studies have shown associations of PPI use with an increased risk of recurrent *C. difficile* infection and use of gastric acid suppressants with an increased risk of recurrent pseudomembranous colitis. In the trial reported on by Louie et al., we expect that randomization effectively equalized the distribution of PPI users between treatment groups, but it would be of interest and potential clinical importance to know whether there were any between-group differences in PPI use and whether the investigators found any potential effect modification between PPI use and either antibiotic treatment regimen for *C. difficile* infection on the rate of recurrent *C. difficile* infection.

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3. Cadle RM, Mansouri MD, Logan N, Kudva DR, Mushcr DM.

**TO THE EDITOR:** Louie et al. report that the benefit of fidaxomicin for reducing the recurrence of *C. difficile* infection was primarily limited to *C. difficile* infection that was not caused by North American Pulsed Field type 1 (NAPI), restriction-endonuclease analysis (REA) type BI, or polymerase-chain-reaction ribotype 027 (referred to collectively as the NAP1/BI/027 strain). Given the favorable pharmacokinetic and pharmacodynamic profile of fidaxomicin in the gut, this difference in efficacy is surprising and unexplained. The clinical applicability of this finding is uncertain as well, since, in most instances, the infecting strain is not known at the time of diagnosis and treatment of *C. difficile* infection. The authors do not report serum antibody levels to *C. difficile* toxin A and whether or not there was an interaction effect between serum antibody levels and the efficacy of fidaxomicin. A subgroup analysis would be interesting because patients with lower serum antibody levels to *C. difficile* toxin A have a higher risk of recurrence of *C. difficile* infection.

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No potential conflict of interest relevant to this letter was reported.


**THE AUTHORS REPLY:** Linsky et al. ask about the influence of exposure to acid-suppressive agents...
on the recurrence of *C. difficile* infection in patients in our clinical trial of fidaxomicin as compared with vancomycin. Very similar results of a second trial, involving 535 patients, were presented at the European Congress of Clinical Microbiology and Infectious Diseases 2010. In these two phase 3 trials, involving a total of 1105 patients, the use of PPIs and H2-receptor antagonists was both common and similar across both groups. In the combined trials, from days 1 to 40, in the fidaxomicin group, 44.9% of the patients were receiving PPIs and 7.8% of the patients were receiving H2-receptor antagonists; in the vancomycin group, 39.8% of the patients were receiving PPIs and 8.1% of the patients were receiving H2-receptor antagonists. We did not observe a difference in the rate of recurrence of *C. difficile* infection among patients with or without exposure to PPIs and H2-receptor antagonists. In the fidaxomicin group, the rate of recurrence was 15.8% with exposure versus 13.0% without exposure (P=0.38), and in the vancomycin group, the rate was 27.0% with exposure versus 24.8% without exposure (P=0.42). Adjusting for age, markers of severity of illness, and exposure to PPIs and H2-receptor antagonists, our data showed that only the treatment group was a significant predictor of recurrence.

With respect to the NAP1/BI/027 strain, it is notable that the trend observed in the first study — treatment groups having similar recurrence rates within this subgroup — was not repeated in the second study by Crook et al.1 In the second study, there was a trend toward a lower recurrence rate among subjects with the BI strain who received fidaxomicin than among those who received vancomycin (22.2% vs. 38.3% within the modified intention-to-treat population, P=0.08); this result was more in line with the population as a whole. The underlying demographic characteristics that might explain the differences between these trials are being evaluated. The observations may simply be an issue of small numbers of patients, since the studies were not powered around subgroup analyses (and subjects with BI strains made up only one third of the subjects with typeable strains). As Safdar and Craig point out, the strain is typically not known at the initiation of therapy. Nevertheless, in our trials, patients with BI strains who received fidaxomicin did not have a worse outcome than those who received vancomycin; furthermore, those with non-BI strains, who made up the majority of the population, did significantly better in terms of recurrence and global cure. These trials did not measure serum antibody concentration, and we agree with Safdar and Craig that this variable should be considered in future studies.

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### Gout

**TO THE EDITOR:** We take issue with Neogi’s recommendation (Feb. 3 issue) that a patient who was having exacerbations of gout despite the use of allopurinol should continue to take hydrochlorothiazide. Hydrochlorothiazide is a weak antihypertensive agent that lowers blood pressure at 24 hours by only 6.5/4.5 mm Hg, which in head-to-head comparisons was inferior to all other drug classes. There is no evidence that the typical daily dose of 12.5 to 25 mg of hydrochlorothiazide reduces the rate of heart attack, stroke, or death. However, as Neogi indicates, the use of hydrochlorothiazide may contribute to an increased urate level (by as much as 20%). Since the drug also increases insulin resistance and visceral fat accumulation, it is not an attractive choice for the patient who is described in the vignette. In contrast, most other classes of antihypertensive drugs reduce morbidity and mortality and are neutral with regard to uric acid. Generically available losartan is known to decrease uric acid by about 20%. Thus, a simple switch from hydrochlorothiazide to another antihypertensive drug might improve blood-pressure con-