**Clostridium difficile-associated diarrhoea: effects of PPIs and H₂ receptor antagonists on clinical response and recurrence**

There is some limited evidence from previous studies that using acid-suppressing medications may be a risk factor for Clostridium difficile infection. A post-hoc observational analysis of data from 2 randomised controlled trials found that the clinical response of hospitalised patients with C. difficile-associated diarrhoea to either fidaxomicin or vancomycin for 10 days was not affected by concurrent use of proton pump inhibitors (PPIs) or H₂ receptor antagonists (H₂RAs). The use of PPIs or H₂RAs during the antibiotic treatment phase had no effect on C. difficile-associated diarrhoea recurrence rates.

Public Health England has guidance on the management and treatment of C. difficile infection.

**Overview and current advice**

_Clostridium difficile_ infection is associated with considerable morbidity and risk of mortality. Anyone who has this infection should be reviewed regularly, preferably by a multidisciplinary team, to ensure that they receive optimised care, particularly where they have multiple co-morbidities. Public Health England updated guidance on the management and treatment of _Clostridium difficile_ infection states that the treatment of _C. difficile_ infection varies depending on the severity of the infection. Oral metronidazole is recommended for mild and moderate infection, and oral vancomycin for severe infection. The guidance states that fidaxomicin should be considered for patients with severe _C. difficile_ infection who are considered at high risk of recurrence or who are not responding to oral vancomycin.

The Public Health England guidance states that there is increasing evidence that acid-suppressing medications, in particular PPIs, may be a risk factor for _C. difficile_ infection, although it remains possible that these associations are confounded by other risk factors for the infection. A recent case-control study has suggested that the reported associations between use of acid-suppressing medications and _C. difficile_ infection may not be valid because of the use of sub-optimal control groups. However, given that acid-suppressing drugs, especially PPIs, are used on a widespread basis and frequently not reviewed to determine if long-standing prescriptions are still justifiable, the guidance recommends that consideration should be given to stopping or reviewing the need for PPIs in people with or at high risk of _C. difficile_ infection.
New evidence

A post-hoc observational analysis of data from 2 randomised controlled trials (RCTs) comparing fidaxomicin with vancomycin in patients with *C. difficile*-associated diarrhoea considered whether PPIs or H2RAs affect the clinical response to these antibiotics or rates of infection recurrence (Weiss et al., 2015). See the Evidence summary: new medicine on *Clostridium difficile* infection: fidaxomicin for more details on the original RCTs.

The analysis included 701 hospitalised patients who had *C. difficile*-associated diarrhoea confirmed by clinical observation and a positive *C. difficile* toxin assay. Patients had been randomised to fidaxomicin 200 mg twice daily (n=341) or vancomycin 125 mg four times a day (n=360) for 10 days, and those included in the analysis had received at least 1 dose of study drug. Of the 701 patients included, 482 (69%) had used PPIs or H2RAs at some time during pre-treatment, treatment (days 1 to 10) or follow-up (days 11 to 40), based on medication records at each clinical study site. PPI use was more common than H2RA use (54% compared with 8% during the treatment phase).

The clinical response of patients to either fidaxomicin or vancomycin did not appear to be affected by concurrent use of PPIs or H2RAs. Clinical response (defined as the resolution of diarrhoea during treatment and for 2 days after treatment stopped) was achieved in 344/423 (81%) of patients who used PPIs or H2RAs during the treatment phase and 231/278 (83%) of patients who did not. Hypoalbuminaemia, raised serum creatinine and leucocytosis were independent predictors of poor clinical response among patients who used PPIs or H2RAs.

The use of PPIs or H2RAs during the treatment phase also had no effect on recurrence rates. Recurrence was defined as the reappearance of *C. difficile*-associated diarrhoea during follow up, *C. difficile* toxin assay, and the need for additional therapy. This occurred in 75/344 (22%) of patients who received PPIs or H2RAs during the treatment phase and 44/231 (19%) of those who did not.

The use of PPIs or H2RAs during the follow-up phase was associated with a higher rate of recurrence in a univariate analysis (76/315 [24%] compared with 43/260 [17%] for no use during the follow-up phase, p=0.025). However, this association was not detected on multivariate analysis when adjusted for confounding variables, such as age, raised serum creatinine, hypoalbuminaemia and leucocytosis.

The data used in this analysis were from RCTs, but these trials were not set up to examine the effects of acid-suppressing drugs on the treatment of *C. difficile*-associated diarrhoea. The findings from this post-hoc analysis are, therefore, subject to bias and confounding factors which could affect the validity of the results. No information on the use of PPIs or H2RAs before the onset of *C. difficile*-associated diarrhoea were available, and this analysis cannot help answer the question as to whether the use of acid-suppressing drugs increases the risk of acquiring the disease. In addition, the analysis does not address the use of acid-suppressing medications specifically in people with recurrent *C. difficile* infection. Some cases of recurrent infection would have been included in the analysis because the original RCTs could include people with 1 previous episode of *C. difficile* infection. However, the number of people with recurrent infection was low and the analysis provides no information on the effects of PPIs or H2RAs specifically in this cohort of patients.
There are two major findings from this analysis. Firstly, there does not appear to be an adverse effect of PPI or H₂RA use on response to treatment of *C. difficile*-associated diarrhoea nor on the likelihood of recurrence when adjusted for important confounding variables. Secondly, this study adds further weight to the proposed association between hypoalbuminaemia, raised serum creatinine or leucocytosis with poor prognosis. These 3 variables were statistically significantly and independently associated with reduced response to treatment. Hypoalbuminaemia and leucocytosis have been incorporated into a *C. difficile*-associated diarrhoea severity scoring system proposed by Zar et al., 2007 and Public Health England guidance on the management and treatment of *Clostridium difficile* infection recommends using any of the following to indicate severe *C. difficile* infection:

- white cell count >15×10⁹/L
- acutely rising blood creatinine (for example >50% increase above baseline)
- temperature >38.5°C
- evidence of severe colitis (abdominal signs, radiology).

From a clinical perspective it would be interesting to know if there was any difference between PPIs and H₂RAs in the risk of recurrence of *C. difficile*-associated diarrhoea. This is a particularly important question that should be further explored in RCTs because, in clinical practice, it is common for PPIs to be replaced by H₂RAs in patients with *C. difficile*-associated diarrhoea who continue to require some acid suppression (such as ventilator-associated pneumonia prophylaxis in intensive care patients). Separate data for PPIs and H₂RAs are given in this analysis. However, only 8% of patients received H₂RAs and the authors combined data from patients who had used PPIs with data from those who had used H₂RAs when reporting their primary outcome. In an earlier observational study, looking only at primary infection Howell et al., 2010 placed H₂RAs on a spectrum of risk of acquiring primary *C. difficile* infection higher than no acid suppressant but lower than PPIs.

Public Heath England guidance currently recommends that consideration should be given to stopping or reviewing the need for PPIs in people with or at high risk of *C. difficile* infection. The authors of this analysis conclude that, whilst not intending to encourage the indiscriminate use of PPIs or H₂RAs in patients with *C. difficile*-associated diarrhoea, their findings support that acid-suppression therapy could be maintained during the treatment of *C. difficile*-associated diarrhoea if it is particularly indicated. This would seem to be a sensible approach.

### Study sponsorship

This study was funded by Cubist Pharmaceuticals (a subsidiary of Merck), who market fidaxomicin in the USA.

### References


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