**Clostridium difficile infection – are acid suppressant medicines a risk factor?**

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

*Before using this Q&A, read the disclaimer at [www.ukmi.nhs.uk/activities/medicinesQAs/default.asp](http://www.ukmi.nhs.uk/activities/medicinesQAs/default.asp)*

Date updated: February 2012

**Summary**

- *C. difficile* is a leading cause of iatrogenic outbreaks of diarrhoea. There are national and local initiatives to reduce the incidence of *C. difficile*-associated disease (CDAD).
- Risk factors for CDAD include antibiotic use and hospitalisation. Patients most at risk are the elderly, particularly if they have underlying disease or immunosuppression.
- The use of proton pump inhibitors (PPIs) and histamine H₂ receptor antagonists (H₂RAs), which suppress gastric acid secretion, has also been suggested as a risk factor for developing CDAD.
- Five systematic reviews/meta-analyses (three only available as abstracts) have explored this association using data from a number of observational case-control and cohort studies. These studies have a number of limitations and a causal link has not been established. However, the weight of evidence suggests an association exists and it is probably stronger for PPIs than for H₂RAs.
- The US Food & Drug Administration (FDA) recommends that CDAD be considered as a diagnosis for patients on PPIs with persistent diarrhoea.
- On the basis of a positive association, and other well established reasons, it is recommended that PPIs should only be used where there is a clear indication.

**Background**

*Clostridium difficile* infection is a leading cause of iatrogenic outbreaks of diarrhoea. The consequences of infection range from minor gastrointestinal disturbance to fatal bowel inflammation. The infection is caused by an overgrowth of *C. difficile* in the colon. *C. difficile* can be part of the normal gastrointestinal flora; rates of colonisation vary from around 3% in asymptomatic healthy adults, to 20% in hospitalised patients and elderly patients in long term care facilities [1]. It is transmitted via spores that are present in faeces and can survive for long periods in the environment. Local and national initiatives have been introduced to control the infection.

A number of risk factors for *C. difficile*-associated disease (CDAD) have been identified of which antibiotic use (see Medicines Q&A 242) and hospital stay are most strongly associated; others include increasing age, severe underlying disease, non-surgical gastrointestinal procedures, presence of a nasogastric tube and increased duration of hospital stay [2,3]. The risk increases if more than one of these factors is present.

Another proposed risk factor for CDAD is use of medicines that suppress gastric acid secretion, including proton pump inhibitors (PPIs) and histamine-H₂ receptor antagonists (H₂RAs) [3,4]. The mechanism by which these agents might increase the risk of CDAD is unclear. It is biologically plausible that by raising gastric pH, they increase the burden of some ingested pathogens, but, as *C. difficile* spores have been shown to be acid-resistant *in vitro*, an increase in gastric pH would not be expected to influence *C. difficile* infection rates [5,6]. However, it has been postulated that *in vivo*, gastric acid may act synergistically with salivary nitrates to produce a sporicidal effect, and that vegetative *C. difficile*, from germinated spores, may be a ‘transient’ vector for infection and would be killed at normal gastric pH [6].

This Medicines Q&A summarises the results of five systematic reviews/meta-analyses that have investigated whether there is an association between use of acid suppressant medicines and incidence of CDAD.

**Answer**

The weight of evidence from systematic reviews/meta-analyses supports a positive association between acid suppressant medicines and CDAD. However, a causal link has not been proven. There is

From the NHS Evidence website [www.evidence.nhs.uk](http://www.evidence.nhs.uk)
a biologically plausible explanation and some evidence of a dose response relationship with the association being stronger for PPIs than H2RAs. Data suggest that PPI therapy may double risk of CDAD.

The first systematic review was published in 2007 by Leonard et al, and evaluated the association between PPI and H2RA use and CDAD [5]. The figures cited in the review for the number of included studies, the number of patients and the odds ratios (OR) for risk of CDAD vary between the abstract, the text and the summary meta-analysis plots and this raises some doubts about the accuracy of the review. In essence, it appears that the review included 20 studies (19 papers) comprising 17 case-control and three cohort studies. All but one of the studies investigated hospital inpatients. The exception was a study using data from the UK General Practice Research Database. The 20 studies included 18,468 patients and pooled data indicate a statistically significant association between any acid suppressant medicine and CDAD with an OR of 1.95 [95% CI 1.48 to 2.58].

Of 12 studies (11 papers) that evaluated the association between PPI use and CDAD, ten studies found a positive association (in only six was the finding statistically significant), one a negative association and the findings of one study was neutral. Across the 12 studies, the odds ratio for the association with PPI use was 2.05 [1.47 to 2.85]. Of 14 studies that evaluated H2RA therapy, eight reported a positive association between H2RA use and CDAD, with only three having statistically significant results. The overall odds ratio for the association was 1.47 [1.06 to 2.05]. On the basis of this data the authors suggest there is a moderate association between acid suppressant medicines and risk of CDAD. The data also suggest that the association is stronger for PPIs, which are the more potent acid suppressants, than for H2RAs.

A more recent meta-analysis, published in 2012 by Deshpande et al, focused on the association between PPIs and CDAD [7]. Thirty studies (25 case-control and five cohort) involving 202,965 subjects met the inclusion criteria. All but three studies were in hospitalised patients. The majority of studies (24) reported a statistically significant association between PPIs and CDAD. The overall odds ratio for the association was 2.15 [1.81 to 2.55], similar to that calculated by Leonard et al. When case-control and cohort studies were analysed separately, the risk of CDAD with PPI therapy remained (OR 2.22 [1.82 to 2.70] and OR 1.78 [1.41 to 2.25], respectively). The association also remained in a number of sensitivity analyses based on extent of concomitant antibiotic use, and when studies of recurrent CDAD were excluded.

Three further meta-analyses of the association between PPIs and CDAD have been published only in abstract form [8-10]. They included nine, 16 and 22 studies, and reported an OR of 2.74, a risk estimate of 1.65 and an odds ratio of 2.04, respectively, for the association. Overall, therefore, the analyses have similar outcomes (not surprisingly as they will have included many of the same studies) and suggest that patients on PPI therapy have about twice the risk of developing CDAD as non-users.

All systematic reviews/meta-analyses are based on data from observational studies as there are no relevant randomised controlled trials. Some of the observational studies were small and a number were conducted retrospectively. The limitations of such studies include confounding and bias which may not be addressed using meta-analysis techniques.

Significant heterogeneity between the studies was reported in four of the analyses [5,7,8,10]. Pooling odds ratios in these circumstance is contentious and the summary statistics must be viewed with caution. Nevertheless, in a 2012 Drug Safety Communication, the US Food & Drug Administration (FDA) states that the weight of evidence suggests a positive association between use of PPIs and CDAD and recommended that a diagnosis of CDAD be considered for patients taking PPIs who develop diarrhoea that does not improve [11].

Only one of the above analyses investigated the association between CDAD and H2RA use, and none explored the influence of dose and duration of acid suppressant medicines. Two of these issues were addressed in a cohort study that prospectively collected data on 101,796 discharges from a tertiary medical centre over a five-year period [12]. Prescribed acid suppression medicines were categorised according to ‘intensity’. After adjustment for co-morbid conditions, age, antibiotics and propensity score based on likelihood of receiving acid suppression therapy, the risk of CDAD increased as the level of acid suppression increased, from an OR of 1 (no acid suppression reference) to 1.53 [1.12 to 2.1] for H2RA use, to 1.74 [1.39 to 2.18] for daily PPI therapy, and to 2.26 [1.79 to 3.11] for more frequent PPI

Medicines Q&A 244.1 October 2008
Clostridium difficile infection – are acid suppressant medicines a risk factor?
From the NHS Evidence website www.evidence.nhs.uk
use. The authors calculate that one additional case of CDAD may be expected for every 533 patients who receive a daily PPI.

Acid suppression therapy may also increase the risk of CDAD complications and mortality [13]. A retrospective review of 485 cases of CDAD in patients aged 1-99 years found independent associations between complications (megacolon, surgery, intensive care stay and death) and acid suppression (OR 2.4 [1.2 to 4.7]) and with admission for CDAD (OR 4.14), older age (≥80 years OR 3.14) and corticosteroid use (OR 2.09). Acid suppression (OR 4.74 [1.57 to 14.37]) and age ≥80 years (OR 5.51) were associated with an increased odds of death.

National recommendations for preventing and managing C. difficile infection advise that PPIs should only be used when there is a clear clinical indication [14]. Although restricting antimicrobial prescribing and improving hygiene are two key strategies in preventing CDAD, restricting PPI use may also be valuable. Given the extent of PPI prescribing, the number of potentially avoidable CDAD cases could be significant. The challenge presented by C. difficile infection, the evidence of an association with PPI use, and current concerns about overuse of PPIs [15], provide good reasons to critically review PPI prescribing.

Limitations
Available data are inadequate to establish a causal relationship between acid suppressant medicines and C. difficile infection.

References
Clostridium difficile infection – are acid suppressant medicines a risk factor?

From the NHS Evidence website www.evidence.nhs.uk

Quality Assurance

Prepared by Oct 2008 Karoline Brennan Checked by Christine Proudlove
Updated by Feb 2012 Christine Proudlove Checked by Joanne McEntee

North West Medicines Information Centre: nwmedinfo@nhs.net

Search strategy

♦ MIDatabank [clostridium difficile].
♦ Embase 1980-date [Clostridium difficile or Clostridium difficile infection (exp, major) + Antiulcer agent or proton pump inhibitor or histamine H2 receptor antagonist (exp, major).
♦ Medline 1950-2008 [Clostridium infection (MeSH, major) + Anti-ulcer agents (MeSH, exp, major).
♦ Department of Health www.dh.gov.uk [clostridium].
♦ National electronic Library for Medicines [clostridium].
♦ Cochrane Library of Systematic Reviews