

Q&amp;A 244.3

## Clostridium difficile infection – is use of proton pump inhibitors a risk factor?

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### Summary

- ◆ *Clostridium difficile* infection (CDI) is associated with considerable morbidity and risk of mortality.
- ◆ Risk factors for CDI include antibiotic use, hospitalisation, advanced age, underlying morbidity and inflammatory bowel disease.
- ◆ Three systematic reviews/meta-analyses using data from observational case-control and cohort studies conclude that whilst a causal link has not been established, the weight of evidence suggests an association between use of proton pump inhibitors (PPIs) and CDI.
- ◆ Public Health England guidelines recommend that consideration be given to stopping or reviewing the need for PPIs in patients with or at high risk of CDI.

### Background

*Clostridium difficile* infection (CDI) is associated with considerable morbidity and risk of mortality [1]. Consequences of infection range from mild self-limiting diarrhoea to pseudomembranous colitis, toxic megacolon, perforation of the colon, sepsis and death. *C. difficile* can be part of the normal gastrointestinal flora; rates of colonisation vary from around 3% in healthy adults, to 20% in elderly patients on chronic care wards [2]. Infection occurs when other harmless bacteria in the gut are disrupted (for example, by taking antibiotics) or when the immune system is compromised allowing numbers of *C. difficile* bacteria to increase to high levels [3]. *C. difficile* diarrhoea is caused by cytotoxins produced by certain strains of *C. difficile* that damage the lining of the colon. *C. difficile* ribotype 027 produces more toxins than most other types. It causes a greater proportion of severe disease and appears to have a higher mortality [2].

Due to increasing incidence of CDIs in England and Wales enhanced mandatory surveillance of all cases in patients aged two years and over was introduced in 2007. Following local and national initiatives, the number of CDIs decreased substantially but in 2014/15 there was the first annual increase in infection rates. Evidence is also emerging that the epidemiology of CDI is changing with an increased proportion of infections among the younger population and most infections classified as community-acquired [4].

A number of risk factors for CDI have been identified including antibiotic use, hospitalisation, advanced age, underlying morbidity and inflammatory bowel disease [2]. Public Health England guidance highlights the increasing evidence that acid-suppressing medicines, in particular proton pump inhibitors (PPIs), may be a risk factor for CDI, although it is possible that these associations are confounded by other risk factors [5]. The mechanism by which these agents might increase risk of CDI 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 CDI rates [6,7].

This *Medicines* Q&A summarises the results of three systematic reviews/meta-analyses that have investigated whether there is an association between use of PPIs and incidence of CDI.

### Answer

#### Evidence

The largest systematic review and meta-analysis included 47 published reports including 37 case-control and 14 cohort studies (published 1990 to 2012) that examined the association between PPI use and incidence of CDI [8]. Pooled analysis showed a weak association between PPI use and CDI (odds ratio [OR] 1.65 [95% confidence interval {CI} 1.47 to 1.85]) compared with no use of PPIs. There was

significant heterogeneity ( $I^2 = 89.9\%$ ) due to type of study, location and study methods. The authors rated the available evidence as very low quality due to the observational nature of the studies, inconsistency of results and evidence of publication bias. Although calculating number needed to harm (NNH) assumes a cause-effect relationship between PPI and CDI, they calculated the NNH for hospitalised patients receiving antibiotics to be 50 at two weeks after admission to hospital, and the NNH for the general population to be 3,925 at one year. The authors conclude that the general population is not at significant risk of CDI from PPI use, but recommend judicious and evidence-based use of PPIs in patients at high risk for CDI, namely hospitalised patients receiving antibiotics.

Two earlier meta-analyses also evaluated the association between PPI exposure and CDI. Kwok et al (2012) included 42 controlled observational studies published up to 2011 (30 case-control and 12 cohort, involving 313,000 patients) [9]. Pooled analysis of 39 studies showed a significant association between PPI use and incident CDI (compared with a control group of non-users) (OR 1.74 [95% CI 1.47 to 2.05];  $p < 0.001$ ;  $I^2 = 85\%$ ). The same significant association was seen when the analysis was limited to studies that adjusted for confounders (1.93 [95% CI 1.61 to 2.31];  $p < 0.001$ ;  $I^2 = 86\%$ ). Pooled analysis of three studies evaluating PPI use in patients with recurrent CDI also showed a significant association: (2.51 [95% CI 1.16 to 5.44];  $p = 0.005$ ). Findings were no longer significant when the analysis was limited to the two studies reporting adjusted data. The authors conclude that there was a probable association between PPI use and incident or recurrent CDI. The authors calculated NNHs for hospitalised patients on antibiotics, hospitalised patients with no antibiotics and community patients to be 28, 202 and 899, respectively.

Janarthanan et al (2012) included 23 studies of moderate quality published between 1990 to 2010 (17 case-control and six cohort, involving 288,620 patients) that reported *C. difficile*-associated diarrhoea (CDAD) risk in patients exposed to a PPI for three months prior to acute-onset diarrhoea with laboratory confirmation of CDI [10]. PPI use was associated with a significant increase in risk of CDAD (relative risk 1.69 [95% CI 1.40 to 1.97];  $p < 0.001$ ;  $I^2 = 91.93\%$ ). The authors conclude that there is sufficient evidence to suggest that use of PPIs increases incidence of CDAD among users.

The weight of evidence from these systematic reviews/meta-analyses supports a positive association between use of PPIs and CDI, but limitations of evidence suggest findings may be overstated. However, risk of CDI in the general population taking PPIs is low; risk is greater in hospitalised patients taking antibiotics.

These meta-analyses have the following limitations:

- All included studies are observational and are therefore subject to confounding and bias which meta-analysis techniques cannot address.
- Evaluation of association between CDI and PPI therapy was not the primary objective of most studies.
- Data quality of included studies is variable with regard to selected populations and dose and duration of PPI use.
- Significant heterogeneity between studies was reported in all analyses [8,9,10]. Pooling odds ratios in these circumstances is contentious and the summary statistics must be viewed with caution.
- There may be unmeasured risk factors and confounding by indication and comorbid conditions.

Most of the studies included in these meta-analyses involved people with hospital-associated CDI. Epidemiology of CDI has changed considerably over the time they were conducted, with a large decrease in ribotype 027 prevalence and smaller decreases in ribotypes 001 and 106, with increases in some other ribotypes and a wider variety overall [11]. In addition, 2014/15 UK data shows a greater proportion of infections occurred among young people with the majority of infections classified as community-acquired [4]. Information on risk factors for community-associated infection is less clear [3].

### National guidelines

- Public Health England guidelines for managing and treating CDI recommend that consideration be given to stopping or reviewing the need for PPIs in patients with or at high risk of CDI [5].

- NICE guidance on gastro-oesophageal reflux disease and dyspepsia advises that people who need long-term management should be offered an annual review, and where appropriate, encouraged to try stepping down or stopping treatment [12].

Given the extent of PPI prescribing [13], the number of potentially avoidable CDI cases could be significant. The challenge presented by CDI, the evidence of an association with PPI use, and current concerns about overuse of PPIs, provide good reasons to critically review PPI prescribing.

## Limitations

Available data are inadequate to establish a causal relationship between PPIs and CDI.

## References

1. National Institute for Health and Care Excellence. *Clostridium difficile*-associated diarrhoea: effects of PPIs and H<sub>2</sub> receptor antagonists on clinical response and recurrence. (July 2015) (Medicines Evidence Commentary). Available at: [www.medicinesresources.nhs.uk/GetDocument.aspx?pagelid=799008](http://www.medicinesresources.nhs.uk/GetDocument.aspx?pagelid=799008)
2. NICE Clinical Knowledge Summaries. Diarrhoea – antibiotic associated. June 2013. Available at: [cks.nice.org.uk/diarrhoea-antibiotic-associated](http://cks.nice.org.uk/diarrhoea-antibiotic-associated)
3. National Institute for Health and Care Excellence. *Clostridium difficile* infection: risk with broad-spectrum antibiotics. (March 2015) (Evidence Summary: medicines and prescribing briefing [ESMPB1]). Available at: [www.nice.org.uk/advice/esmpb1/chapter/Full-evidence-summary-medicines-and-prescribing-briefing](http://www.nice.org.uk/advice/esmpb1/chapter/Full-evidence-summary-medicines-and-prescribing-briefing)
4. Public Health England. Annual Epidemiological Commentary: mandatory MRSA, MSSA and *E. coli* bacteraemia and *C. difficile* infection data, 2014/15. 9 July 2015. Available at: [www.gov.uk/government/statistics/mrsa-mssa-and-e-coli-bacteraemia-and-c-difficile-infection-annual-epidemiological-commentary](http://www.gov.uk/government/statistics/mrsa-mssa-and-e-coli-bacteraemia-and-c-difficile-infection-annual-epidemiological-commentary)
5. Public Health England. Updated guidance on the management and treatment of *Clostridium difficile* infection. May 2013. Available at: [www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/321891/Clostridium\\_difficile\\_management\\_and\\_treatment.pdf](http://www.gov.uk/government/uploads/system/uploads/attachment_data/file/321891/Clostridium_difficile_management_and_treatment.pdf)
6. Leonard J, Marshall JK, and Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol* 2007; 102: 2047-2056.
7. Cunningham R and Dial S. Is over-use of proton pump inhibitors fuelling the current epidemic of *Clostridium difficile*-associated diarrhoea? *J Hosp Infect* 2008; 70: 1-6.
8. Tleyjeh IM, Bin Abdulhak AA, Riaz M, et al. Association between proton pump inhibitor therapy and *Clostridium difficile* infection: A contemporary systematic review and meta-analysis. *PLoS ONE* 2012; 7(12): e50836.
9. Kwok CS, Arthur AK, Anibueze CI, et al. Risk of *Clostridium difficile* infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol* 2012; 107:1011–1019.
10. Janarthanan S, Ditah I, Adler DG and Ehrinpreis MN. *Clostridium difficile*-associated diarrhoea and proton pump inhibitor therapy: a meta-analysis. *Am J Gastroenterol* 2012; 107(7): 1001-10.
11. Public Health England. *Clostridium difficile* ribotyping network (CDRN) for England and Northern Ireland. 2011-13 report.
12. National Institute for Health and Care Excellence. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. (September 2014) (CG184). Available at: [www.nice.org.uk/guidance/cg184/resources/gastrooesophageal-reflux-disease-and-dyspepsia-in-adults-investigation-and-management-35109812699845](http://www.nice.org.uk/guidance/cg184/resources/gastrooesophageal-reflux-disease-and-dyspepsia-in-adults-investigation-and-management-35109812699845)
13. Forgacs I and Loganayagam A. Overprescribing proton pump inhibitors is expensive and not evidence based. *BMJ* 2008; 336: 2-3.

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### Search strategy

- ◆ MIDatabank [clostridium difficile].
- ◆ Embase via NICE Evidence. 1980-date [Clostridium difficile or Clostridium difficile infection (exp, major) + Antiulcer agent or proton pump inhibitor (exp, major)].
- ◆ Medline via NICE Evidence. 1980-date [Clostridium infections (MeSH, major) + Anti-ulcer agents (MeSH, major)].
- ◆ Public Health England, [www.gov.uk/government/organisations/public-health-england](http://www.gov.uk/government/organisations/public-health-england) [clostridium].
- ◆ Cochrane Library of Systematic Reviews