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REVIEW

# Risk of *Clostridium difficile* Infection With Acid Suppressing Drugs and Antibiotics: Meta-Analysis

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OBJECTIVES: **Several studies have raised concern regarding the possible association between proton-pump inhibitors (PPIs) and *Clostridium difficile* infection (CDI). We aimed to perform a systematic review of incident and recurrent CDI in PPI users, and to evaluate the relative impact of concurrent antibiotic use, or switching acid suppression to histamine-2-receptor antagonists (H2RAs).**

METHODS: **We searched MEDLINE and EMBASE from inception to December 2011 for controlled observational studies that reported on the risk of CDI with and without PPI use. We performed random effects meta-analysis and assessed statistical heterogeneity using the $I^2$ statistic.**

RESULTS: **We included 42 observational studies (30 case-control, 12 cohort) totalling 313,000 participants overall. Pooled analysis of 39 studies showed a statistically significant association between PPI use and risk of developing CDI, odds ratio (OR) 1.74 (95% confidence interval (CI) 1.47–2.85, $P<0.001$, $I^2=85\%$) compared with non-users. A pooled analysis of three studies showed a significant associated risk of recurrent CDI associated with PPIs, OR 2.51 (95% CI 1.16–5.44, $P=0.005$, $I^2=78\%$). Subgroup analysis failed to fully clarify the source of the substantial statistical heterogeneity. Adjusted indirect comparison demonstrated that use of H2RAs as an alternative carried a lower-risk OR 0.71 (95% CI 0.53–0.97) compared with PPIs. Conversely, concomitant use of PPI and antibiotics conferred a greater-risk OR 1.96 (95% CI 1.03–3.70) above that of PPIs alone. For PPI and antibiotics, the Rothman's synergy index was 1.36 and attributable proportion of risk from interaction 0.19, indicating an increased risk from interaction beyond the effects of each drug alone.**

CONCLUSIONS: **Despite the substantial statistical and clinical heterogeneity, our findings indicate a probable association between PPI use and incident and recurrent CDI. This risk is further increased by concomitant use of antibiotics and PPI, whereas H2RAs may be less harmful.**

**SUPPLEMENTARY MATERIAL** is linked to the online version of the paper at http://www.nature.com/ajg

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## INTRODUCTION

*Clostridium difficile* infection (CDI) is a major avoidable cause of morbidity and mortality in hospital patients (1,2). Studies suggest rising incidence, severity, and mortality of CDI with outbreaks in Canada, United States, and the United Kingdom (1–4). Greater awareness and increased availability of stool-toxin testing, and the guidance on active surveillance may have partly contributed to the increased incidence, but these factors alone cannot explain the dramatic rise in the rate of CDI (5).

The most prominent risk factor for CDI appears to be the use of antimicrobial therapy, with approximately 90% of cases occurring during or up to 8 weeks following antimicrobial treatment (6,7). Other risk factors include age, severe underlying disease, prolonged duration of hospitalization, and enteral tube feeding (8–10). However, there have been concerns that reduced gastric acidity may predispose to infections, with two systematic review demonstrating increased risk of enteric infections with acid-suppressive therapies (11,12). In 2007, Leonard *et al.* (11) reported an elevated risk of CDI with acid-suppression therapies, with PPIs conferring a higher risk than histamine-receptor-2 antagonists (H2RA), but this review was based on a literature search from 2005. Another more recent review by Bavishi *et al.* (12) did not provide any statistical analysis of the associated risk for PPI and H2RAs but was limited to the range of

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odds ratios (ORs) and numeric counts of studies with significant findings.

Decreased gastric acidity could lead to inadequate sterilization of ingested organisms, with subsequently elevated risk of colonization of the normally sterile upper gastrointestinal tract (13). PPIs may also contribute to the disruption of the bowel flora, resulting in bacterial colonization of the stomach and upper small intestine (14). Moreover, PPIs appear to have direct effects on leucocyte activity, which may mediate defence activities against CDI (15–17).

The relative clinical impact of different acid-suppressive agents, and the influence of concomitant antibiotic therapy on CDI has yet to be elucidated. It is unclear whether H2RAs represent a significantly safer option in reducing risk of CDI, and whether PPIs may further heighten the recognized risk of CDI in patients receiving antibiotics. Hence, we aimed to perform a systematic review and meta-analysis on the associated risk of incident and recurrent CDI with PPI use, and to evaluate the impact of concomitant antibiotic use, as well as alternative acid-suppressive agents.

## METHODS

### Eligibility criteria

We selected controlled observational studies (case-control or cohort design) that evaluated the association of PPI exposure with CDI. The specific inclusion criteria were that the studies had to report ORs/risk ratios for CDI with PPI use, or to report sufficient raw data to allow for calculation of ORs/risk ratios. We did not restrict studies by healthcare settings, methods of diagnosing CDI, or type of PPI regimen, but we aimed to look at subgroups of studies where such data was available.

### Search strategy

We searched MEDLINE and EMBASE from inception up to December 2011 (Ovid SP) with no language limitations using the search terms shown in **Supplementary Appendix S1** online. In addition, we signed up with PubMed to receive automated electronic notifications for any new articles. Bibliographies of included studies and recent review articles were checked for additional relevant studies.

### Study selection and data extraction

Two reviewers (CSK and YKL) evaluated all titles and abstracts for studies that met the inclusion criteria, and excluded any articles that clearly did not meet the selection criteria. Full reports (where available) of potentially relevant studies were retrieved and independently checked for eligibility. Data from the included studies were then extracted by one of three reviewers (CSK or CIA or AKA) who collected information on study design, drug exposure, study location, case definition, and characteristics of participants onto a pre-formatted spreadsheet. The data table was then checked (in an unblinded manner) by at least one other reviewer (SS or RC or YKL). For the outcomes data, YKL and CSK independently extracted ORs (unadjusted or adjusted) where available; otherwise raw numbers were recorded to enable calculation of unadjusted ORs. Any uncertainties or discrepancies were resolved through rechecking against the source papers, and through discussion with a third reviewer. Also, we contacted authors if there were any areas that required clarification.

### Assessment of risk of bias

In accordance with the recommendations of the Cochrane Adverse Effects Methods Group, we considered participant selection, ascertainment of PPI exposure, and definition of adverse outcomes (which in this case was CDI), and statistical adjustment for confounders (18).

We aimed to generate funnel plots to assess the possibility of publication bias, provided that there were >10 studies available in the meta-analysis, with no evidence of substantial statistical heterogeneity (19).

### Data analysis

We used RevMan 5.1.1 (Nordic Cochrane Centre) to conduct random effects meta-analysis using inverse variance method for pooled OR. We assumed similarity between the risk ratio and OR because the incidence of adverse outcomes was low (20). We evaluated both adjusted and unadjusted data from primary studies, although we preferentially used adjusted data where available.

Statistical heterogeneity was assessed using $I^2$ statistic (21), with $I^2$ values of 30–60% representing a moderate level of heterogeneity. Prespecified subgroup analysis was performed by evaluating the effect of study design, study setting, and outcome ascertainment.

We aimed to summarize the results of the meta-analysis using Forest plots. As the inverse variance method requires conversion of the 95% confidence interval (CI) to the standard error on a natural logarithmic scale and back, the Forest plots may occasionally have minor variations in the 95% CI compared with the primary study due to rounding up or down. This does not affect the actual point OR estimates which were exactly as keyed in.

The number needed to harm (NNH; and 95% CI) was estimated by using the pooled OR from the meta-analysis to the average event rate. The NNH is the number of patients who need to be treated with PPI for one additional person to have an adverse outcome.

***Secondary outcomes***. In studies that reported on the risk of CDI with PPIs, we aimed to evaluate the relative impact of: (i) concomitant use of antibiotic therapy with PPIs, and (ii) use of H2RA, as compared with PPI use alone.

We calculated the pooled OR for CDI with concomitant PPI and antibiotic therapy, and compared this against the pooled OR with PPIs alone from the same set of studies. We also generated pooled ORs from the studies that reported both H2RA or PPIs risk from multivariate adjusted analysis for each drug class as an independent variable. We carried out adjusted indirect comparisons with Bucher's method using ITC software (22,23), and evaluated the pooled ORs from PPI users against the pooled ORs from different categories of exposure (i.e., antibiotic with PPI, or H2RA alone). In order to maintain clinical similarity amongst the studies within the indirect comparison (24), each paired evaluation in the indirect comparison is based on a specific set of studies sharing similar

clinical settings and control participants. For instance, when conducting the H2RA–PPI indirect comparison, we ensured that the pooled risk estimates for H2RA against controls were derived from the exactly the same studies that yielded the pooled risk estimate for PPI against controls. This enables us to determine the relative extent to which the associated risk of CDI with PPI alone differs from that of use with concomitant antibiotic therapy, or with alternative acid-suppression agents.

In addition, we used an Excel spreadsheet published by Andersson *et al.* (25) to calculate the Rothman synergy index and the attributable proportion of risk due to interaction for concomitant PPI and antibiotic use based on the ORs obtained from the meta-analysis. The attributable proportion of risk due to interaction gives an estimate of the proportion of cases with CDI that are attributable to any interaction between the two causes (PPIs and antibiotics) beyond either factor alone. If the two drugs did not have any biological interaction to increase the risk of CDI, the synergy index would show 1.0, and the attributable proportion would be zero (25).

## RESULTS

After a review of 419 citations, we identified 42 studies (from 41 articles) covering 313,000 patients for inclusion in our analysis of the association of PPIs with CDI (3,8,26–64). The process of study retrieval and selection is shown in **Figure 1** and the main characteristics of the included studies are described in **Electronic Supplementary Table S1** online. Outcomes, interventions, and quality assessments of the included studies are shown in **Electronic Supplementary Table S2** online.

Most of the studies were focused on inpatients in single hospitals, thus potentially capturing only a limited sample. One study only included children (62), while another enrolled patients with chronic liver disease (29). Almost all the studies involved patients with diarrhea, or where stool samples were sent for laboratory analysis because of clinical suspicion of CDI. The exceptions were one study that used oral vancomycin as a proxy measure of CDI, and another involving routine screening of patients following hospital admission (for this study, we extracted data on patients with symptomatic CDI rather than asymptomatic cases).

### Validity assessment/risk of bias

A key limitation of this dataset is the lack of information on actual type of PPI, dosing regimen, and duration of use before the diagnosis of CDI. Ascertainment of PPI use was variable, and typically relied on prescribing databases and medical records (with no specific evaluation of patient adherence or actual PPI use). Although these methods may reliably capture inpatient PPI use, there was hardly any data available on dose or duration of outpatient prescriptions or over-the-counter preparations before hospital admission. Misclassification or inconsistent recording of drug exposure is a possibility within the included studies, and the lack of information precluded us from assessing dose response.

Almost all the studies used laboratory methods to ascertain CDI, typically through stool toxin immunoassays, while a few studies included culture or histopathology. Two studies relied on electronic coding, while another considered oral vancomycin prescription as a proxy measure of CDI (38,39,53).

More than half of the studies adjusted for potential confounders using multivariate models, although there was considerable diversity in the type of model and the selection of available variables for adjustment. There may be confounding variables that were not fully identified and recorded.

Owing to the lack of detailed information on PPI exposure, none of the studies were considered to be at low risk of bias.

***Risk of incident CDI with PPI use.*** Pooled analysis of 39 studies showed a significant association between PPI use and risk of developing CDI, OR 1.74, (95% CI 1.47–2.05, $P < 0.001$, $I^2 = 85\%$) as compared with non-users (3,8,26–32,34–47,49,51–64) (**Figure 2**).

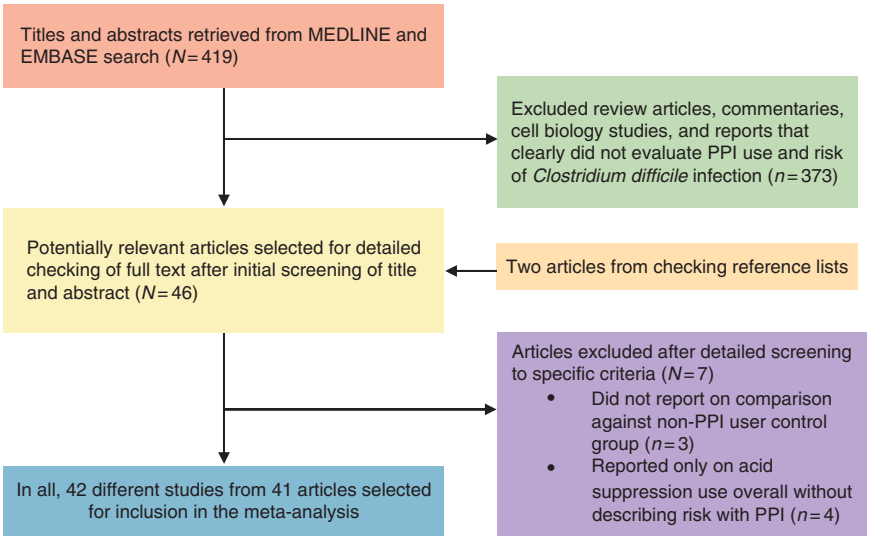


**Figure 1.** Flow diagram of the process of article selection for meta-analysis. PPI, proton-pump inhibitor.

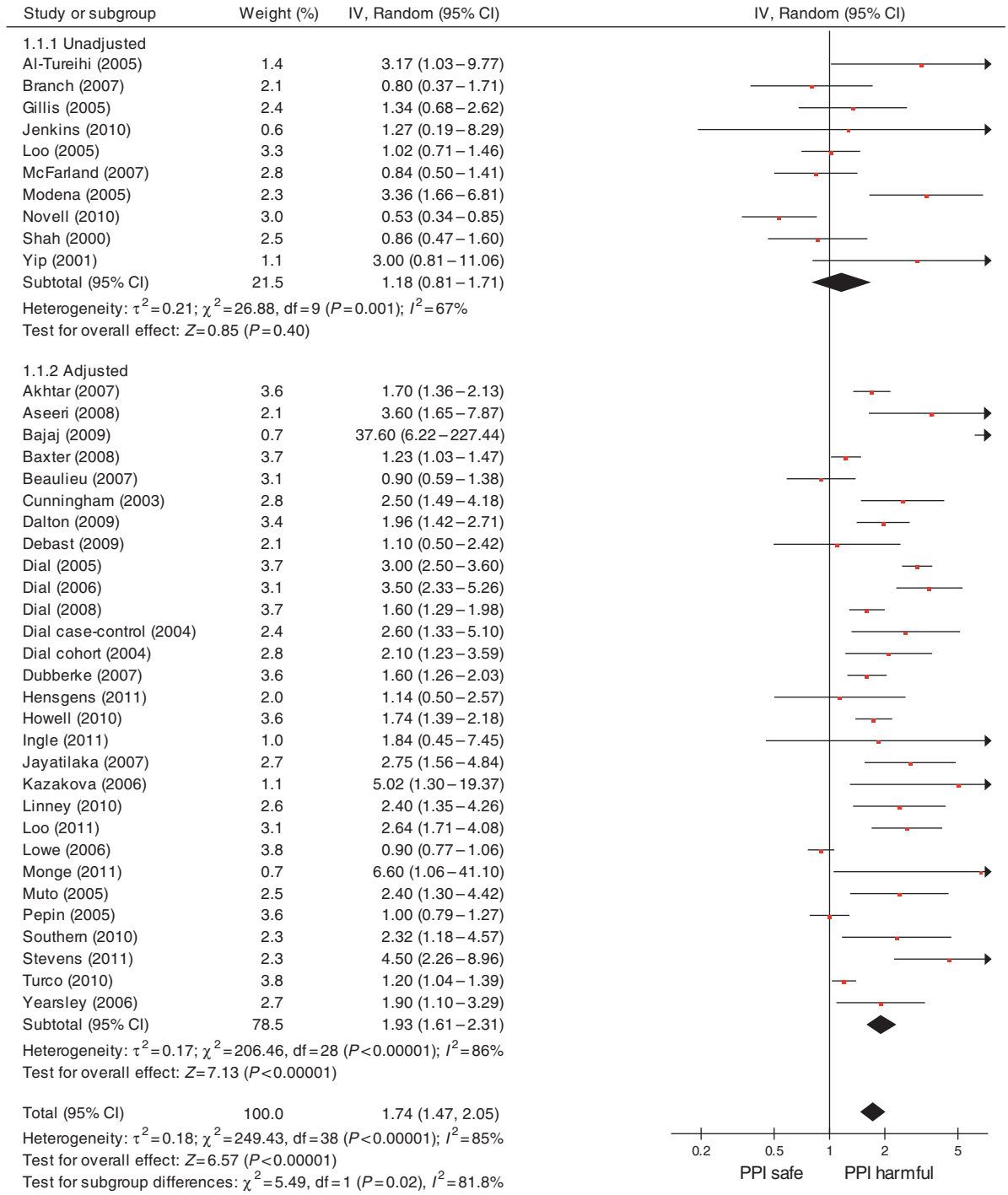


**Figure 2.** Risk of incident *Clostridium difficile* infection with proton-pump inhibitor (PPI) use.

This significant association in risk of CDI among PPI users remained consistent after limiting the meta-analysis to studies that provided adjusted data, with a pooled OR of 1.93 (95% CI 1.61–2.31, $P<0.001$, $I^2=86\%$). Although there is substantial statistical heterogeneity in the meta-analysis, examination of the direction of effect among the 39 included studies suggests that most studies shared a similar direction of effect, thus indicating that some of the heterogeneity may stem from variation in the magnitude (rather than direction) of the estimated risk.

***Risk of Clostridium difficile recurrence with PPI use.*** A pooled analysis of three studies that evaluated PPI use in patients with

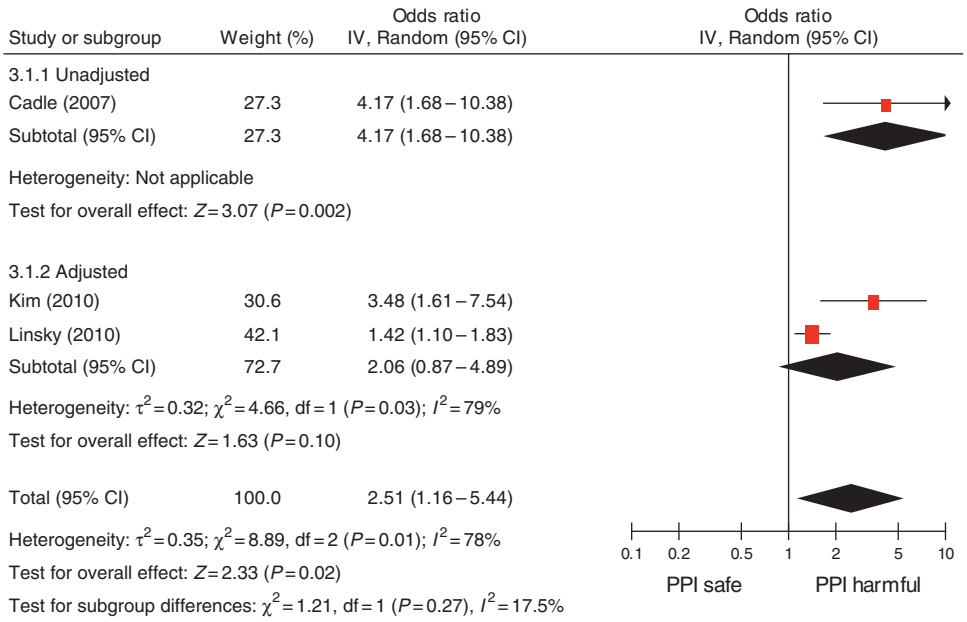


**Figure 3.** Risk of *Clostridium difficile* recurrence with proton-pump inhibitor (PPI) use.

recurrent CDI showed a significant associated risk, pooled OR 2.51 (95% CI 1.16–5.44, $P=0.02$, $I^2=78\%$) (33,48,50) (**Figure 3**). Again, while there was substantial heterogeneity in the estimate, all the risk estimates had a similar direction of effect in demonstrating a significant association.

***Risk of incident CDI with different drug exposures as compared with PPI alone***. Adjusted indirect comparison of the pooled ORs (**Table 1**) showed that concomitant PPI and antibiotic therapy increase the relative likelihood of CDI, with an OR of 1.96 (95% 1.03–3.70) when compared with PPI alone from six studies (26,32,34,36,61,63).

From the three studies that reported data on CDI risk for the three separate exposures of antibiotic alone, PPI alone, and concomitant PPI/antibiotic (26,34,63), we calculated Rothman's synergy index to be 1.36, and attributable proportion of risk from the interaction was 0.19. This indicates an added risk of 19% from the interaction between the two drugs that goes beyond the effects of each drug in isolation (see **electronic Supplementary Figure S4** online).

We analyzed the associated risk from the use of H2RA as compared with PPI from 15 studies that reported on the estimates of risk independently associated with H2RAs, and PPIs within their sample of participants (3,28,31,35–40,43,45,47,51,57,61). This showed an elevated risk of CDI with H2RA, OR 1.50 (95% CI 1.23–1.83), whereas the risk with PPI use in the same 15 studies was 2.10 (95% CI 1.66–2.66). Here, the adjusted indirect comparison (**Table 1**) demonstrated a reduction in the associated likelihood of CDI with an OR of 0.71 (95% 0.53–0.97) for use of H2RAs rather than PPIs.

***Subgroup analysis and exploration of heterogeneity***. We performed subgroup analysis on the 39 studies reporting risk of incident CDI by restricting the studies according to design (case–control or cohort), presence of laboratory verification of CDI, or to hospital setting only (**Table 2**). The significant association between PPI use and CDI was present in all the subgroup analyses, even when we restricted it to studies that provided adjusted data and had laboratory diagnostic confirmation. No single source to account for the heterogeneity was identified within this subgroup analysis as the $I^2$ values remained elevated throughout. In view of the heterogeneity, we did not perform asymmetry testing for publication bias (19).

**Table 1. Adjusted indirect comparison between different drug therapies, and assessment of interaction**

| Drug exposure | Pooled OR (95% CI) | $I^2$ (heterogeneity) |
|---|---|---|
| *Studies that reported data on PPI alone, and on H2RA alone* (n=15) (3,28,31,35–40,43,45,47,51,57,61) | | |
| PPI alone | 2.10 (1.66–2.66) | 85 |
| H2RA alone | 1.50 (1.23–1.83) | 60 |
| *Studies that reported data on PPI alone, and on PPI with antibiotics* (n=6) (26,32,34,36,61,63) | | |
| PPI alone | 1.98 (1.39–2.83) | 66 |
| PPI + antibiotic | 3.87 (2.28–6.56) | 72 |
| *Studies that reported data on antibiotic alone, PPI alone, and on PPI with antibiotics* (26,34,63) | | |
| Antibiotics alone | 1.97 (1.29–3.01) | 60 |
| PPI alone | 1.82 ((1.50–2.21) | 0 |
| PPI + antibiotic | 3.44 (2.43–4.87) | 16 |

CI, confidence interval; H2RA, histamine-2-receptor antagonist; OR, odds ratio; PPI, proton pump inhibitor.

### NNH for CDI

A recent large prospective surveillance study of the incidence of symptomatic CDI at 14 days after hospital admission demonstrated that after excluding those with known colonization on admission, the overall proportion of non-PPI users developing CDI was 1.67% (51). Given this baseline risk, we estimate a NNH of 67 (95% CI 48–101) if these patients were given PPIs, or an NNH of 121 (95% CI 74–262) if H2RAs were prescribed (**Table 3**).

The surveillance study also found that incidence of symptomatic CDI in PPI users was 5.26% at 14 days (51). If antibiotics were given to PPI users, we estimate increased risk of CDI with an NNH of 22 (95% CI 9–670). By contrast, if PPI users were switched to H2RA, one case of CDI would be prevented for every 69 (42–668) patients who were switched over.

We should also consider the lower magnitude of absolute harm with PPI use in patient with lower baseline susceptibilities (e.g., those not on antibiotics, or community patients) where the NNH ranges from 202 at 14 days (hospitalized patients with no antibiotic use) to 899 per year (community patients; **Table 3**). Conversely, PPIs carry much greater absolute harm (NNH 28) in patient with high susceptibility to CDI, such as those with antibiotic use who are admitted to hospital.

**Table 2. Subgroup analysis**

| Study characteristic | Number of studies | Pooled OR (95% CI) | Heterogeneity (%) |
|---|---|---|---|
| Case control (8,26–30, 32–34,36–42,45–50, 52–59,62,64) | 29 | 1.71 (1.40–2.10) | 87 |
| Cohort (3,31,35,36,43, 44,51,60,61,63) | 10 | 1.81 (1.36–2.41) | 77 |
| Laboratory confirmation (3,8,26–36,40–52,54–64) | 35 | 1.68 (1.43–1.96) | 75 |
| No laboratory confirmation (37–39,53) | 4 | 1.95 (1.02–3.72) | 97 |
| Inpatients only (3,8,26–36, 40–43,45,46,48–53,55–64) | 33 | 1.65 (1.40–1.94) | 80 |
| Community patients, or a mixture of community and inpatients (37–39,44,47,54) | 6 | 2.13 (1.35–3.35) | 87 |
| Adjusted data, with laboratory confirmation (3,8,26,28–31,35,36,40, 42–45,47,49,51,56,59–62) | 23 | 1.77 (1.49–2.11) | 76 |

CI, confidence interval; OR, odds ratio.

## DISCUSSION

### Principal findings

The overall pooled estimates indicate that PPI therapy is associated with a near-doubling in the likelihood of incident CDI. Additionally, we uncovered evidence of an association between PPI use and recurrence of CDI, and demonstrated evidence of interaction between PPIs and antibiotic risk that contributed to an excess risk beyond that conferred by either treatment alone. Conversely, use of H2RA appears to be associated with a lower risk of CDI when compared with PPI therapy, thus indicating that extent of acid suppression is an important mediator of CDI. Despite statistical heterogeneity and differences in the actual point estimates, the elevated risk of CDI with PPI use was consistently similar in the direction of effect in the majority of cases. Several subgroup analyses covering different study designs, healthcare settings, and methods of diagnosing CDI showed similarly elevated risks.

### Comparisons with other studies

Although our analysis is based on non-randomized studies, only one trial has a sample size comparable with the observational

**Table 3. Estimate of absolute risks and number needed to treat (NNT) for harm**

| Population | Estimated incidence | Odds ratio with change in therapy | Change in CDI cases per 1,000 patients | NNT for harm |
|---|---|---|---|---|
| Unselected hospital admissions without PPI use (51) | 16.7/1,000 at 14 days | Add PPIs: 1.93 (1.61–2.31) | +15 | 67 (48–101) |
| PPI users admitted to hospital (51) | 53/1,000 at 14 days | Switch from PPI to H2RA 0.71 (0.53–0.97) | −15 | If 69 (42–668) PPI users switched to H2RA, one case of CDI prevented |
| PPI users admitted to hospital (51) | 53/1,000 at 14 days | Add concomitant antibiotics to PPI 1.96 (1.03–3.70) | +45 | 22 (9–670) |
| *Impact of adding PPIs according to baseline risk of CDI in different settings* | | | | |
| Hospital admissions with antibiotic use (51) | 42/1,000 at 14 days | Add PPIs: 1.93 (1.61–2.31) | +36 | 28 (21–42) |
| Hospital admissions with no antibiotic use (51) | 5.4/1,000 at 14 days | Add PPIs: 1.93 (1.61–2.31) | +5 | 202 (144–307) |
| Community patients (72) | 1.2/1,000 per year | Add PPIs: 1.93 (1.61–2.31) | +1 | 899 (638–1,369) |

CDI, *Clostridium difficile* infection; H2RA, histamine-2-receptor antagonist; PPI, proton pump inhibitor.

studies. The Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) study randomized 3,873 participants to omeprazole or placebo, and found a significantly higher diarrhea rate with omeprazole (3.0%. vs. 1.8% during a median follow up of 106 days, $P=0.01$) (65). The investigators state that none of these cases of diarrhea were caused by CDI but no details were given on the extent or nature of any stool sample tests. The generalizability of trial data is limited as the participants had relatively short exposure to PPIs, and are likely to have fewer comorbidities or risk factors for CDI when compared with real-world patients (some of whom were receiving antibiotics and cancer chemotherapy) in the observational studies.

A number of other recent systematic reviews have similarly identified an elevated risk of CDI with PPIs. Deshpande *et al.* (66) analyzed a smaller number of studies ($n=30$ as compared with 42 in our dataset) and reported a similar magnitude of associated risk. However, Deshpande's meta-analysis is limited by the reliance on unadjusted risk estimates, which are subject to confounding. Another systematic review reported an elevated adjusted risk of CDI with PPIs in 17 of 27 included studies, but did not summarize the data in a Forest plot, or evaluate heterogeneity (12). There did not appear to be any explicit assessment of recurrent CDI, or any statistical evaluation of the impact of H2RAs or antibiotics in either of these two recent reviews (12,66). A previous meta-analysis dating back to 2007 with 11 included studies reported similar findings to our review, with significant links demonstrated between CDI and PPI or H2RA exposure, but again no clear source for heterogeneity was identified (11). More recently, the US Food and Drug Administration issued a warning on the risk of CDI with PPIs based on an analysis of 28 studies, but did not comment on CDI recurrence or risk with H2RAs (67).

### Strengths and limitations of our review

We used a sensitive search strategy supplemented by regular automatic updates from PubMed, thus ensuring that our systematic review is up to date, and less likely to have missing studies. In addition, we have found studies that reported both on PPI use, as well as H2RAs or antibiotics, and we were able to statistically estimate the relative impact of these other agents.

There are several limitations in this review. The quality of the studies is variable with regards to ascertainment of dose and duration of actual PPI use (including intermittent symptomatic use, or over-the-counter availability). We found only one study that reported on a potential dose–response relationship, with elevated risk of CDI in those who used PPIs more frequently (43). All the studies were observational in nature, and are thus subject to residual confounding despite statistical adjustment. There may be unmeasured risk factors in the PPI-exposed patients, and confounding by indication as well as severity of comorbid conditions is possible. Differences in the exposure duration, patient characteristics, and types of antibiotic use could have potentially contributed to the significant heterogeneity.

In the presence of substantial heterogeneity, the recommended approach for the meta-analysis is to avoid focusing on the overall estimate, but to concentrate instead on assessing consistency of effects, uncovering treatment modifiers, and judging boundary conditions (68). Our subgroup analyses had a broad range of studies suggesting a significant association between PPI use and CDI, with a consistent direction of effect in most instances. We have also attempted to account for heterogeneity using the random effects model, which incorporates study variability to generate the pooled estimate.

Overall, the GRADE of evidence could be considered to be of low strength (i.e., further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) because of the heterogeneity, imprecision, plausible role of confounders from observational designs, and lack of data on different doses or duration of treatment. This is partly offset though by the real-world nature of the evidence, which is directly applicable or generalizable to many settings, and the pragmatic reality that randomized controlled trial to determine the precise nature and extent of this risk are unlikely.

### Implications for clinical practice and research

We estimate that there an additional 15 cases of CDI for every 1,000 hospital inpatients who are given PPIs, and an extra 45 CDI cases per 1,000 hospitalized PPI users who are given antibiotics. In this regard, the need for PPI use should be critically reviewed, especially as there is evidence that 63% of PPI users who suffered CDI did not have valid indications for PPI therapy (69). The classic indications and evidence base for therapeutic applications of PPIs may also need reappraisal (70). For instance, pharmacological stress ulcer prophylaxis may be used in ICU (intensive care unit) patients, but studies have shown that early enteral nutrition may be a safer and a more effective way of reducing the risk of gastrointestinal bleeding in these patients (71). Equally, in patients who are at high risk of CDI (e.g., older age, receiving antibiotics, or chemotherapy) the clinicians and patients should weigh the benefits and harms of continuing PPI therapy against the risk of stopping PPI or switching to H2RA.

Any future randomized clinical trials involving PPI should incorporate CDI as a prespecified outcome measure with standardized toxin testing. Epidemiological studies should consider the dose, timing/duration of PPI exposure, intraclass differences for PPI and risk of CDI, and possible interactions with antibiotics. Prospective cohort studies focusing on ascertainment of symptomatic CDI in new users of PPIs should be a key part of future research, with close matching of patients (perhaps with propensity score techniques) on extent of comorbidities.

In conclusions, given the widespread use of PPIs and antibiotics, our findings have important implications for public health and infection control, and it may be prudent to withhold PPI use in patients receiving antibiotics, unless there are clear gastrointestinal indications for acid-suppression therapy. Our meta-analysis also showed that PPI therapy was associated with recurrent CDI, and discontinuation of PPIs should be strongly considered in patients diagnosed with CDI.

REVIEW

## CONFLICT OF INTEREST

**Guarantor of the article**: Yoon Kong Loke, MBBS, MD.

**Specific author contributions**: C.S.K., S.S., R.C., and Y.K.L. conceptualized the review, developed the protocol, abstracted and analyzed data, and wrote the manuscript. C.S.K., A.K.A., and C.I.A. extracted the data.

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