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CME

Systematic Review of the Risk of Enteric Infection in Patients Taking Acid Suppression

Jennifer Leonard, M.D., F.R.C.P.C., John K. Marshall, M.D., M.Sc., F.R.C.P.C., and Paul Moayyedi, B.Sc., M.B. Ch.B., Ph.D., M.P.H., F.R.C.P.(London), F.R.C.P.C.
Department of Medicine, Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada

CONTEXT: Proton pump inhibitors (PPIs) and H_2 receptor antagonists (H_2RAs) have become the mainstay of therapy in acid-related upper gastrointestinal disorders. There have been concerns raised about the possible association of PPIs with enteric infections.

OBJECTIVE: We conducted a systematic review to evaluate any association between acid suppression and enteric infection. We also assessed differences between types of enteric infections and the type of acid suppression.

DATA SOURCES: Electronic searches of MEDLINE (1966–2005), EMBASE (1988–2005), and CINAHL (1982–2005) were undertaken using a combination of subject headings and text words related to PPI therapy, H_2RAs, and enteric infections.

STUDY SELECTION: All observational studies were eligible, including cross-sectional, case control, and cohort studies that evaluated risk of enteric infection associated with antisecretory therapy. Eligibility assessment was made by two independent researchers.

DATA EXTRACTION: Information on study design, patient population, type of acid suppression, type of infection, and outcomes was collected. The odds ratio (OR) of taking acid suppression therapy in cases and controls was calculated and results were synthesized using a random effects model (DerSimonian and Laird, Stats direct version 2.4.4).

DATA SYNTHESIS: A total of 12 papers evaluating 2,948 patients with *Clostridium difficile* were included in the review. There was an increased risk of taking antisecretory therapy in those infected with *C. difficile* (pooled OR 1.94, 95% CI 1.37–2.75). There was significant heterogeneity between the studies ($P = 0.0006$) that was not explained by planned subgroup analysis. The association was greater for PPI use (OR 1.96, 95% CI 1.28–3.00) compared with H_2RA use (OR 1.40, 95% CI 0.85–2.29). A total of six studies evaluated *Salmonella*, *Campylobacter*, and other enteric infections in 11,280 patients. There was an increased risk of taking acid suppression in those with enteric infections (OR 2.55, 95% CI 1.53–4.26). There was significant heterogeneity between the studies ($P < 0.0001$) that was not explained by subgroup analysis. The association was greater for PPI use (OR 3.33, 95% CI 1.84–6.02) compared with H_2RA use (OR 2.03, 95% CI 1.05–3.92).

CONCLUSION: There is an association between acid suppression and an increased risk of enteric infection. Further prospective studies on patients taking long-term acid suppression are needed to establish whether this association is causal.

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INTRODUCTION

Proton pump inhibitors (PPIs) and H_2 receptor antagonists (H_2RAs) have become the mainstay of therapy in acid-related upper gastrointestinal disorders including gastroesophageal reflux disease and peptic ulcer disease (1). Acid suppression is one of the commonest prescriptions to be issued in Canada and PPI use over the past few years has dramatically increased (2). H_2RAs are available over the counter and in certain countries PPIs have also been made available without prescription. PPIs and H_2RAs are thought to be well tolerated. There are known side effects including diarrhea and headache. Concerns over the more serious side effects such as community-acquired pneumonia have also been raised but their biologic plausibility is uncertain (3). Recently there have been concerns raised about the possible association of acid suppressive therapy with enteric infections. Gastric acid is

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important in eliminating ingested bacteria from the digestive tract. Thus it is biologically plausible that raising the pH of the stomach with acid suppressive therapy may result in an increased load of pathogenic microbes. A recent study has suggested an association with *Clostridium difficile* and PPI therapy in hospitalized patients (4). Another study, however, showed little increased risk of bacterial gastroenteritis among users of acid-suppressing drugs (5). We therefore conducted a systematic review to establish whether there is any association between acid suppression and enteric infection. *C. difficile* is a spore forming organism that is relatively acid stable compared with other enteric infections (6). We therefore hypothesized that any association between antisecretory therapy and enteric infections would be less marked for *C. difficile* than other infections. We also hypothesized that the association would be more marked for PPI compared with H_2RA therapy as the former is a more potent acid suppressor.

METHODS

Search Strategy

Studies were identified from searches of MEDLINE (1966–2005), EMBASE (1988–2005), and CINAHL (1982–2005) electronic databases. The original intention was to identify papers that evaluated enteric infections and combine this search with papers that assessed acid suppressive therapy. This search strategy proved to be too narrow as many papers on risk factors for enteric infections did not mention acid suppressive therapy in the abstract but this information was present in the full paper. We therefore identified papers on infective diarrhea and combined this with papers that evaluated appropriate methodology for assessing risk factors. For example, for MEDLINE, papers on enteric infections were identified using the MeSH headings and free text terms gastroenteritis, *Salmonella* food poisoning, *Salmonella enteritidis*, *Salmonella typhimurium*, *Salmonella* infections, *Escherichia coli*, *Shigella dysenteriae*, *C. difficile*, *Campylobacter*, *Campylobacter jejuni* together with free text terms enteric adj5 infection and infect$ adj5 diarrhea all combined using the set operator "OR." These were combined using the set operator "AND" with papers that used appropriate epidemiological methodology using MeSH headings and the free text terms case–control studies, cohort studies, cross-sectional studies together with the free text term observational. A recursive search of the bibliography of identified papers was conducted. General medical and major gastroenterology journals were routinely scanned over the previous year to ensure that the most recent studies were included. Papers were considered regardless of language and publication status. Abstracts were only included when further details were available from the authors.

Study Selection

The studies identified by the above search were evaluated and those that were potentially relevant were collated onto a singe database. Each potentially relevant study was evaluated by two independent investigators (JL and PM) according to the predefined eligibility criteria. Any discrepancies were decided by consensus involving a third researcher (JM). The criteria for inclusion consisted of: observational studies (cross-sectional, case control, and cohort), adult populations who received any PPI or H_2RA and were compared with a control group who received no acid suppression, an outcome of enteric infection with either microbial isolation of the pathogen (*Salmonella*, *Campylobacter*, *E. coli*, *C. difficile*, *Shigella*) or a clinical definition (acute increase in stool frequency by greater than three stools per day that is self-limiting lasting less than 2 wk).

Data Extraction

A single investigator extracted data onto specially developed electronic forms. This was checked in a blinded fashion by a second investigator. The following characteristics of each study were included: details of participants including demographic characteristics, number of subjects, description of type of study, details of type of drug used, and type of enteric infection.

Data Synthesis

C. difficile and other enteric infections were analyzed separately. All outcomes included in this review were binary. The association between acid suppression and enteric infection was expressed in terms of odds ratios (ORs) together with their 95% confidence intervals for all studies. The ORs were combined using a random effects (DerSimonian and Laird) model as significant heterogeneity ($P < 0.1$) was detected in all analyses (7). Funnel plots were produced for the principal outcome for each comparison, and Egger's test of funnel plot asymmetry was used to investigate whether publication bias or other small study effects may have adversely affected the results (8). Reasons for heterogeneity were explored by subgroup analysis. Factors that were defined prospectively included type of acid suppression (PPI *vs* H_2RA), definition of infective diarrhea (organism identified on stool culture *vs* clinical definition), study design (case control *vs* cohort), and country of origin.

RESULTS

A total of 2,478 citations were reviewed and 52 papers were identified as potentially relevant. From these, 27 papers (4, 5, 9–33) met our eligibility criteria, two did not have extractable data (12, 20). We extracted data on the remaining 25 and included them in our analysis. The reasons for ineligibility are outlined in Figure 1. The 25 papers analyzed included 29,748 patients. Twenty-three studies were case control and three were cohort; Dial *et al.* (2004) included both a case control and cohort study design within a single paper (4). Most were inpatient populations with only seven examined outpatients or the general population (5, 16–19, 25, 27). The papers are summarized in Table 1.

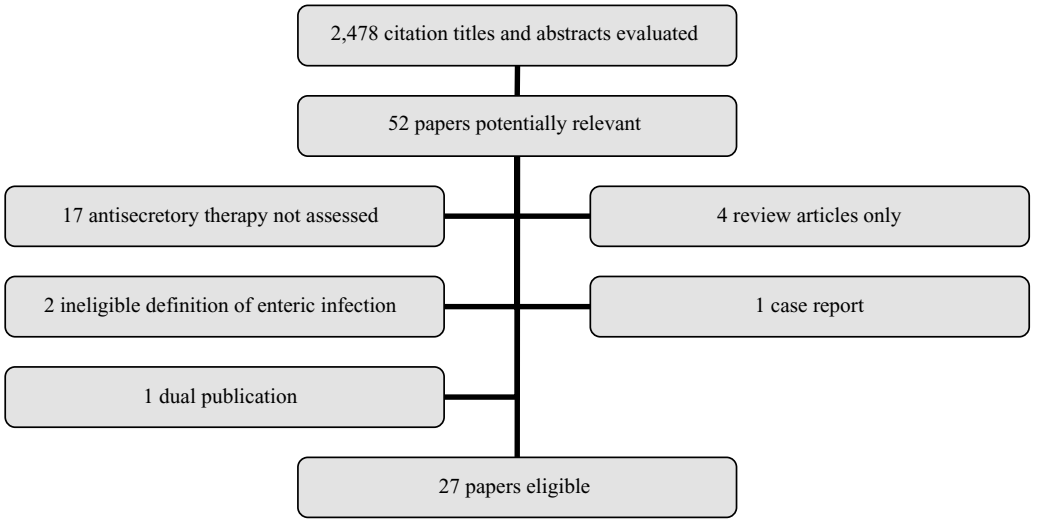

Figure 1. Overview of papers evaluated for systematic review.

C. difficile

A total of 19 papers evaluating 18,468 patients evaluated any acid suppression (4, 9–11, 13–15, 21–24, 26–33). There was a statistically significant association between acid suppression and *C. difficile* infection with an OR of 1.95 (95% CI 1.48–2.58). There was significant heterogeneity between the studies (χ^2 87.4, df 19, $P < 0.0001$). When evaluating only those with H_2RA therapy there were 13 papers (4, 9–11, 15, 21–24, 27–30) evaluating 17,314 patients. The OR was 1.48 (95% CI 1.06–2.06) with statistically significant heterogeneity between the studies ($\chi^2 = 40.8$, df = 13, $P < 0.0001$) (Fig. 2). A total of 11 papers (4, 10, 11, 15, 24, 27–32) evaluated PPI therapy only in 126,999 patients. The OR was 2.05 (95% CI 1.47–2.85) with significant heterogeneity between the studies (χ^2 50.9, df 11, $P < 0.0001$) (Fig. 3).

Other Enteric Infections

A total of six papers evaluating 11,280 patients were included (5, 16–19, 25). Again there was a statistically significant association between acid suppression and other enteric infections with the OR 2.55 (95% CI 1.53–4.26) with significant heterogeneity between the studies (χ^2 37.5, df 6, $P < 0.0001$). When evaluating only those with H_2RA therapy there were five papers (5, 16, 17, 19, 25) evaluating 7,682 patients. The OR was 2.03 (95% CI 1.05–3.92) with significant heterogeneity between the studies (χ^2 19.0, df 4, $P = 0.0008$) (Fig. 4). A total of four papers (5, 16, 19, 25) evaluated PPI therapy only in 10,430 patients. The OR was 3.33 (95% CI 1.84–6.02) with statistically significant heterogeneity between the studies (χ^2 15.2, df 4, $P = 0.004$) (Fig. 5).

The observed heterogeneity in these analyses could not be explained by any of the predefined factors outlined above. There was no statistically significant funnel plot asymmetry in any of the analyses of PPI or H_2RA as a risk factor for either *C. difficile* or other enteric infections. The OR for the association between acid suppression and *C. difficile* was lower than for other enteric infections although this was of marginal statistical significance (Cochrane Q 2.84, df 1, $P = 0.09$). The OR for the association between risk of enteric infection and PPI therapy was higher than for H_2RA but again this was of marginal statistical significance (Cochrane Q 3.14, df 1, $P = 0.08$).

DISCUSSION

There has been concern surrounding the potential causal link between potent acid suppression and enteric infections (32). The risk of *Salmonella* infection has been shown to be increased postgastric surgery (12). The literature on the impact of antisecretory therapy on risk of enteric infections however has been conflicting. This systematic review suggests that there is a modest association between risk of enteric infections and use of acid suppression. There was a trend for the association to be stronger for *Salmonella*, *Campylobacter*, or *Shigella* compared with *C. difficile* although this was not statistically significant. Statistical tests of homogeneity have low power when only two groups are being compared so this does not exclude a difference between *C. difficile* and other enteric infections, which is biologically plausible. The pathogenicity of *C. difficile* is related to the ability of its spores to resist acid degradation in the stomach allowing for colonization in the intestine (34). Therapy that reduces gastric acidity might, therefore, be expected to have less effect on risk of *C. difficile* infection than other enteric pathogens that are more sensitive to an acid environment. These data suggest further evaluation of whether different enteric infections have different strengths of association with acid suppression is warranted. There was a trend for the strength of association with enteric infections to be greater with PPI than H_2RA therapy but again this did not reach statistical significance. Further evaluation of the type of acid suppression, dose of drug, and duration of treatment would help clarify whether there is a dose response to the association between acid suppression and risk of enteric infection.

Table 1. Summary of Included Trials

Reference	Study Description	Cohort	Cases	Controls
Al-Tureihi *et al*. (31)	United States. Case control, hospital based.		25 inpatients, initially identified by receiving either metronidazole or vancomycin, *C. difficile* cytotoxin A/B immunoassay positive, chart documented diagnosis.	28 inpatients treated with antibiotic other than metronidazole or vancomycin matched to age.
Aziz *et al*. (14)	United Kingdom. Case control, hospital based.		35 inpatients with at least one stool positive for *C. difficile* toxin.	67 inpatients, for each case 2 consecutive admissions following case matched to age, elective or emergent admission.
Banatvala *et al*. (18)	United Kingdom. Case control, population based, telephone interview.		143 patients with isolate of *Salmonella* in North Thames region.	2 sets: 143 patients matched to age, sex, and area of residence. 854 randomly selected people from greater London area.
Brown *et al*. (22)	United States. Case control, hospital based.		37 inpatients, every 10th name from all *C. difficile* toxin-positive patients selected, diarrhea not present before admission, culture >48 h after admission.	37 adult inpatients matched for date of admission that did not have a stool culture requested during their admission.
Cunningham *et al*. (11)	United Kingdom. Case control, hospital based.		170 inpatients positive for *C. difficile* toxin.	Inpatients matched to sex, age within 5 yr, month of admission, admitting consultant, diagnostic code.
Dial *et al*. (4)	Canada. Both cohort and case control, hospital based.	1,187 inpatients who received antibiotics identified from pharmacy database compared with those who also received PPI or H_2 blocker, cases defined as positive for *C. difficile* toxin.	94 inpatients with a history of diarrhea and positive for *C. difficile* toxin.	94 inpatients matched to ward, age within 5 yr, and class of antibiotic.
Dial *et al*. (27)	United Kingdom. Case control, population based, United Kingdom General Practice Research database.		1,233 patients, *C. difficile* toxin assay positive or diagnosis recorded by physician, no admission to hospital in prior year.	12,330 patients, 10 for each case matched to general practice, age within 2 yr, and no clinical or pathological diagnosis of *C. difficile*.
Doorduyn *et al*. (25)	Netherlands. Case control, population based, questionnaires mailed to participants.		245 *S. enteritidis*, 232 *S. typhimurium* (DT104 and non-DT104), laboratory confirmed from examination of fecal samples.	3,409 from population registries by frequency matching for age, degree of urbanization, and season.
Gerding *et al*. (9)	United States. Case control, hospital based.		109 inpatients with diarrhea plus a positive *C. difficile* stool culture, *C. difficile* cytotoxin in stool, or endoscopic evidence of pseudomembranous colitis.	108 inpatients without diarrhea matched to hospital ward, time of admission within 2 wk, operative procedure or medical diagnosis

(*Continued*.)

Table 1. Continued

Reference	Study Description	Cohort	Cases	Controls
Gillis *et al*. (24)	Canada. Case control, hospital based.		75 inpatients with diarrheal illness, *C. difficile* toxin positive stool, during or within 1 month of admission.	75 inpatients matched to age within 5 yr, sex, and use of high-risk antibiotics.
Jensen *et al*. (21)	United States. Case control, hospital based.		22 inpatients with *C. difficile* cytotoxin B positive.	125 inpatients with stool analysis negative for *C. difficile* cytotoxin B.
Kyne *et al*. (32)	United States. Cohort, hospital based.	252 adults on 2 general medical wards, received antibiotics, expected length of stay >2 days, cases defined as diarrhea with a positive stool *C. difficile* cytotoxin test.		
Loo *et al*. (28)	Canada. Case control, hospital based.		237 inpatients, computer-generated random sample of 15% of patients with *C. difficile*-associated diarrhea from 12 hospitals.	237 inpatients matched to age within 5 yr, Charlson index, date of admission within 1 month, ward, length of time admission compared with length of time to diagnosis in case.
Modena *et al*. (29)	United States. Case control, hospital based.		50 inpatients with diarrhea, *C. difficile* cytotoxin A or B positive, no prior positive test.	200 inpatients, received antibiotics at least 5 days, did not develop *C. difficile*-associated diarrhea.
Muto *et al*. (30)	United States. Case control, hospital based.		203 inpatients with signs and symptoms of *C. difficile* disease, *C. difficile* toxin assay positive at least 72 h after admission.	203 inpatients, *C. difficile* toxin assay negative matched to date of admission, type of service, length of stay
Nath *et al*. (13)	Canada. Case control, hospital based.		80 adult inpatients, hospitalized more than 3 days, having >5 episodes of diarrhea in 24 h for 3 or more days, stool positive for *C. difficile* toxin A and B.	290 adult inpatients matched for hospital ward with no history of *C. difficile*, 80 were matched to age, admitting diagnosis, and unit of admission.
Neal and Slack (19)	United Kingdom. Case control, population based.		531 patients >age 18 with diarrheal illness, *Campylobacter* isolated from fecal specimen.	512 people, 2 identified by each case, matched to age and sex.
Neal *et al*. (17)	United Kingdom. Case control, population based.		188 patients >age 45 yr with *Salmonella* infection confirmed by fecal culture	376 patients, 2 following each case matched to age within 5 yr and sex
Neal *et al*. (16)	United Kingdom. Case control, population based.		211 patients over age 45 with fecal culture confirmed *Campylobacter* infection.	422 patients, consecutive 2 following case matched for sex and age within 2 yr.
Nelson *et al*. (26)	United States. Case control, hospital based.		33 inpatients, history of diarrhea or incontinence starting after admission, stool *C. difficile* cytotoxin positive	2 sets: 32 inpatients matched to ward

(*Continued*.)

Table 1. Continued

Reference	Study Description	Cohort	Cases	Controls
				32 inpatients with diarrhea or incontinence occurring after admission but *C. difficile* cytotoxin negative
Rodriguez and Ruigomez (5)	United Kingdom. Case control, population based.		374 outpatients in the General Practice Resource Database with a diagnosis of confirmed bacterial gastroenteritis.	2,000 patients randomly selected from the General Practice Resource Database that did not have a diagnosis of gastroenteritis
Shah *et al*. (10)	United Kingdom. Case control, hospital based		126 inpatients above age 65 yr who developed a diarrheal illness after admission with *C. difficile* toxin confirmed in stool.	126 inpatients above age 65 yr who developed a diarrheal illness after admission with *C. difficile* toxin negative stool.
Simor *et al*. (33)	Canada. Cohort, hospital based.	504 inpatients at a long-term care facility, fecal specimens obtained if diarrhea or received antimicrobial agents, cases defined as positive *C. difficile* culture and toxin assay.		
Watanakunakorn *et al*. (23)	United States. Case control, hospital based.		91 inpatients >age 17 with stool *C. difficile* cytotoxin assay positive >3 days after admission, identified from laboratory logbooks.	91 inpatients with stool *C. difficile* cytotoxin assay negative, listed following cases in laboratory logbooks.
Yip *et al*. (15)	Canada. Case control, hospital based.		27 inpatients positive for *C. difficile* toxin A with acute onset loose stools persisting for at least 2 days and the onset of symptoms at least 3 days after admission.	2 sets: 27 inpatients matched to age, gender, date of admission, ward. 27 inpatients matched to duration of hospital stay, day of admission.

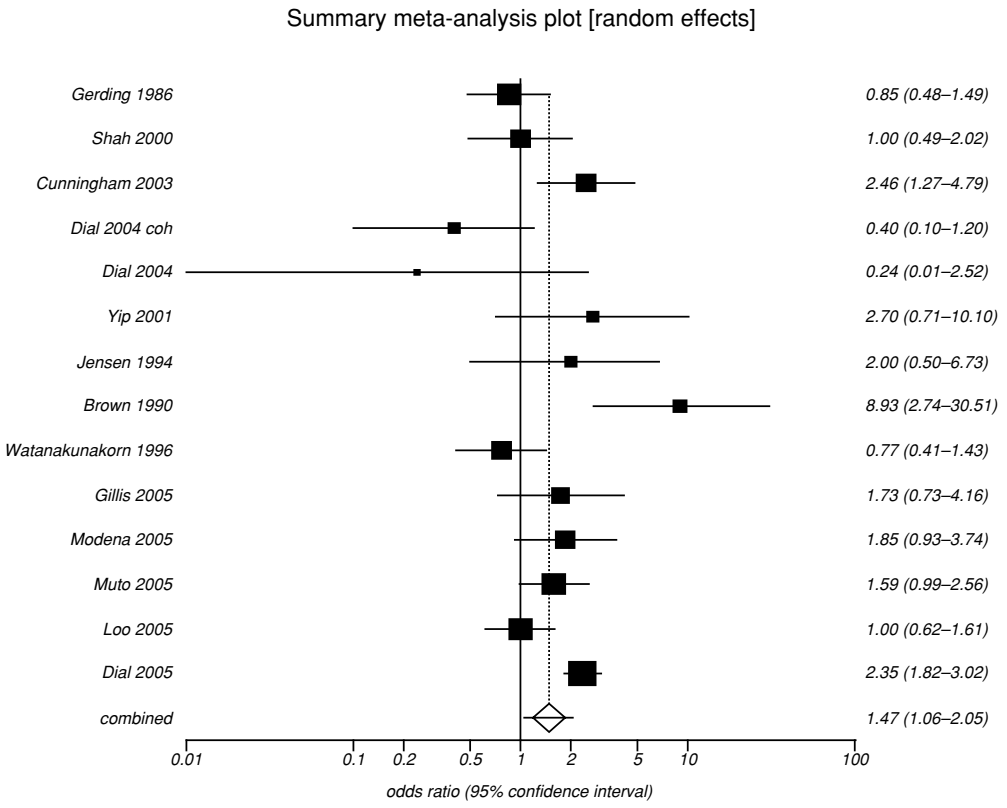

Figure 2. Studies of risk association of *C. difficile* with H_2RA therapy.

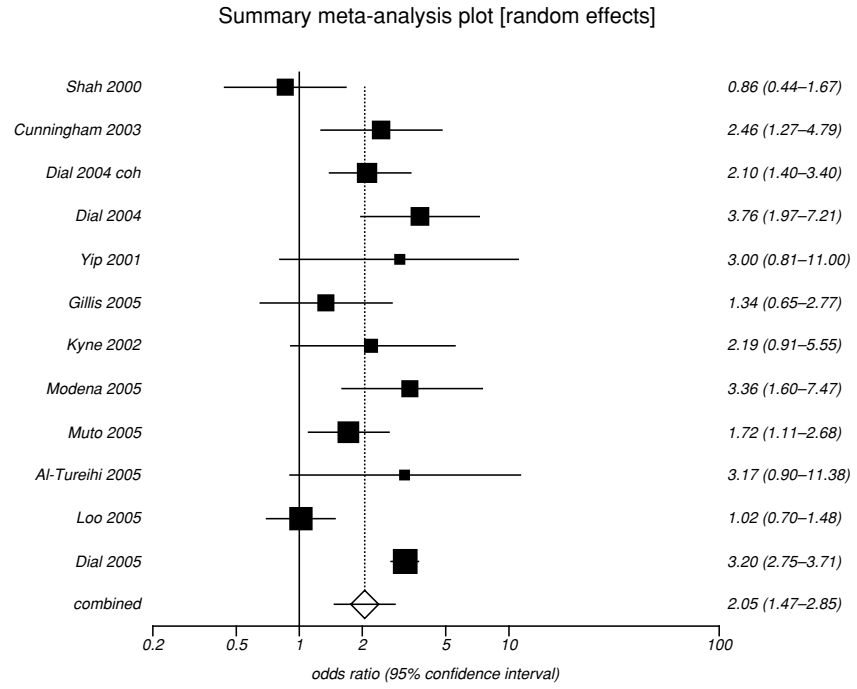

Figure 3. Studies of risk association of *C. difficile* with PPI therapy.

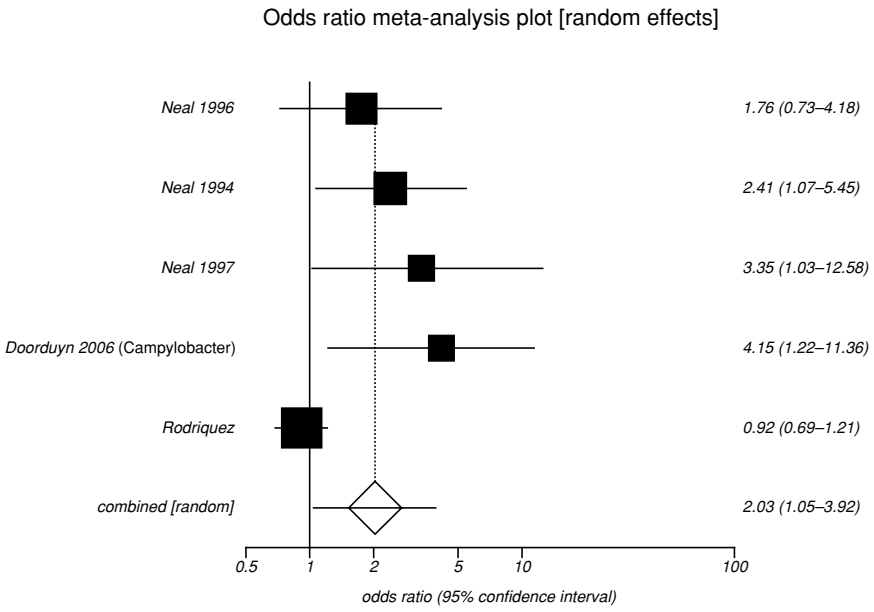

Figure 4. Studies of risk association of other enteric infections with H_2RA therapy.

Because of the limitations of the study designs included in this review, it is not possible to draw conclusions regarding the causality between acid suppression and enteric infections. Case–control and cohort studies are observational and thus enable us only to show a positive association between the two variables. It is possible that the association could be because of bias or confounding factors although often observational studies and randomized controlled trials give similar results (35). Furthermore there is biological plausibility to the association and there is some evidence that this exhibits a dose–response relationship. PPI therapy results in more potent acid inhibition thereby increasing the intragastric pH to a greater degree when compared with H_2RA therapy and the association was stronger for PPI therapy. Unfortunately not enough

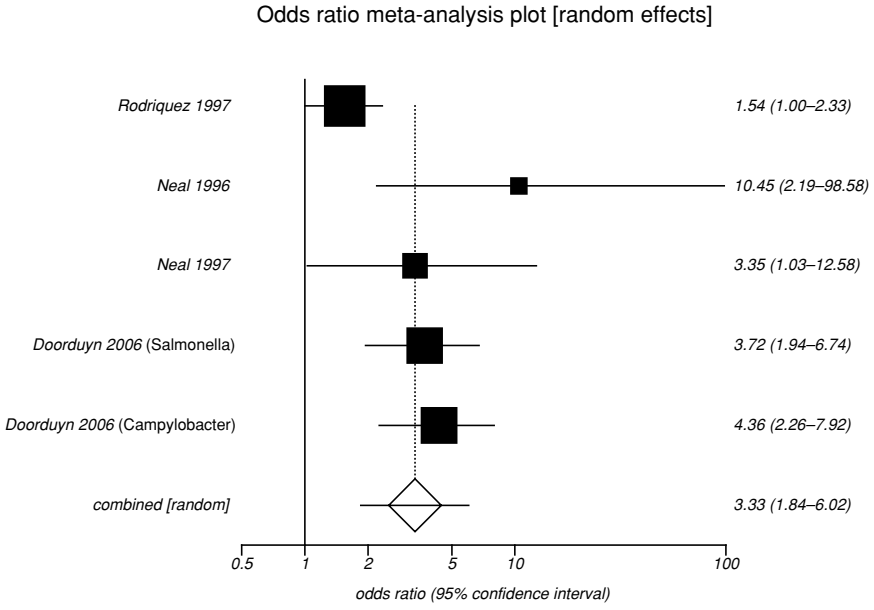

Figure 5. Studies of risk association of other enteric infections with PPI therapy.

data were provided within the papers to evaluate whether a dose–response effect was present within the PPI-treated patients.

There is considerable heterogeneity between studies that is not explained by the study methodology or variations in subjects being studied. For example, two well-conducted case–control studies from the same geographical area and at least in part in the same hospitals reported either no association between antisecretory therapy and *C. difficile* (28) or a strong positive association (4). Two studies evaluating the association of H_2RA prescription and enteric infections both using the UK General Practice Database also reported conflicting conclusions although one study specifically addressed *C. difficile* (5) while the other evaluated other enteric infections (27). These differences might be explained by the strain of bacteria, dosage of acid suppression, duration of therapy, and concomitant illness or medication. Unfortunately this information was often not reported in a manner that allowed subgroup analysis in the papers included in the systematic review.

The pooling of ORs when data are heterogeneous is contentious. One of the reasons for this is that random effects models place an increased reliance on smaller studies compared with fixed effects models (36). Studies with a small sample size are often of poorer quality so greater weight is being placed on inferior data (36). This is particularly true of randomized controlled trials although the relationship between quality and sample size is less clear with observational data as recruiting subjects is generally easier for epidemiological studies and more emphasis is placed on design issues that can control for bias and adjust for potential confounding factors (37). This is the case with this review with no clear relation between sample size and study quality and the random and fixed effects models give similar conclusions (data not shown). We therefore pooled the ORs of individual studies so that an overall impression of the data could be obtained although the summary statistic should be interpreted with caution. There is a need for large prospectively designed studies evaluating the risk of enteric infections in subjects on long-term acid suppression carefully addressing possible confounding factors. Future studies should particularly address the impact the duration of therapy and dose of acid suppression has on the risk of enteric infection.

Antisecretory therapy is an important therapeutic option in patients with upper gastrointestinal symptoms and in particular PPI use has increased dramatically over the last decade. Prescription of antisecretory therapy is encouraged by dyspepsia guidelines that recommend empirical acid suppression for some of these patients (38). Upper gastrointestinal symptoms are very prevalent (39) and are associated with a significant reduction in quality of life that is improved by PPI therapy (40). Furthermore studies have suggested that PPIs improve the outcome of patients with bleeding peptic ulcer disease (41) and may reduce the risk of peptic ulcer bleeding in high-risk groups (42). Despite the undoubted benefits of antisecretory drugs, this systematic review highlights the need to consider risks and benefits before initiating both PPI and H_2RA therapy. This is particularly true for those at high risk of developing enteric infections (*e.g.*, those traveling to high-risk countries), those at risk of developing *C. difficile* (*e.g.*, hospitalized patients on antibiotics), and those at particular risk of deleterious effects of enteric infections (*e.g.*, frail and elderly).

Reprint requests and correspondence: Paul Moayyedi, Division of Gastroenterology, McMaster University Medical Centre, 1200 Main Street West, HSC Rm 4W8E, Hamilton, 0N, L8N 325, Canada.

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CONFLICT OF INTEREST

Guarantor of the article: Paul Moayyedi acts as the guarantor for the paper.

Specific author contributions: Jennifer Leonard planned the study, identified relevant papers, assessed eligibility, data extracted, and wrote the manuscript. John Marshall planned the study, acted as referee for discrepant decisions, helped in the analysis of the data, and contributed to writing the paper. Paul Moayyedi planned the study, helped identify relevant papers, assessed eligibility, checked data extraction, conducted the data analysis, and contributed to writing the paper.

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