

Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection

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SUMMARY

Background

The use of proton pump inhibitors (PPIs) is increasing worldwide. Suppression of gastric acid alters the susceptibility to enteric bacterial pathogens.

Aim

This systematic review was undertaken to examine the relationship between PPI use and susceptibility to enteric infections by a specific pathogen based on published literature and to discuss the potential mechanisms of PPI enhanced pathogenesis of enteric infections.

Methods

PubMed, OVID Medline Databases were searched. Search terms included proton pump inhibitors and mechanisms of, actions of, gastric acid, enteric infections, diarrhoea, *Clostridium difficile*, *Salmonella*, *Shigella* and *Campylobacter*.

Results

The use of PPIs increases gastric pH, encourages growth of the gut microflora, increases bacterial translocation and alters various immunomodulatory and anti-inflammatory effects. Enteric pathogens show variable gastric acid pH susceptibility and acid tolerance levels. By multiple mechanisms, PPIs appear to increase susceptibility to the following bacterial enteropathogens: *Salmonella*, *Campylobacter jejuni*, invasive strains of *Escherichia coli*, vegetative cells of *Clostridium difficile*, *Vibrio cholerae* and *Listeria*. We describe the available evidence for enhanced susceptibility to enteric infection caused by *Salmonella*, *Campylobacter* and *C. difficile* by PPI use, with adjusted relative risk ranges of 4.2–8.3 (two studies); 3.5–11.7 (four studies); and 1.2–5.0 (17 of 27 studies) for the three respective organisms.

Conclusions

Severe hypochlorhydria generated by PPI use leads to bacterial colonisation and increased susceptibility to enteric bacterial infection. The clinical implication of chronic PPI use among hospitalized patients placed on antibiotics and travellers departing for areas with high incidence of diarrhoea should be considered by their physicians.

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INTRODUCTION

Proton pump inhibitors (PPIs) are the major treatment for many gastroesophageal diseases. Omeprazole (1988), lansoprazole (1995), pantoprazole (1997), rabeprazole (1999) and esomeprazole (2001) are the widely used PPIs clinically and omeprazole is available over-the-counter without a prescription in many countries. According to one report, PPIs are the third most prescribed medications in United States with 13.9 billion dollar sales per year. With the widespread use of PPIs worldwide, the authors of this review have attempted to put the added risk for acquisition of enteric infection in PPI-treated people into perspective based on the published literature.

Bacterial colonisation by exogenous enteric microbes is kept in check by a number of host defence mechanisms such as gastric acid, host gut microflora, local gut immunity, intestinal motility, intestinal secretion and epithelial barrier.¹ These forces work synergistically in maintaining intestinal homeostasis. A compromise in host defences may influence susceptibility to various enteric pathogens. In this review we will discuss the association of PPI treatment and enhanced susceptibility to enteric infection with an emphasis on potential mechanisms.

METHODS

A comprehensive literature search was undertaken in PubMed and Ovid Medline Databases as of May 1, 2011. A literature search was undertaken using the key words: proton pump inhibitors and mechanisms of, actions of, gastric acid, enteric infections, diarrhoea, *Clostridium difficile*, *Salmonella*, *Shigella*, *Campylobacter*, *Vibrio cholerae* and *Listeria*. For each enteric infection by a particular pathogen, studies evaluating its association with proton pump inhibitors were explored. For initial selection, studies were eligible if they referred to any aspect of antacid/antisecretory therapy and enteric infection by any organism. We then restricted our search for studies having independent data on PPIs use and its relevance to the particular enteric infection. In addition, a manual search of the full text for the relevant review articles and original studies was performed to identify additional data.

An example of one such search strategy which we applied for *Salmonella* and proton pump inhibitors in PubMed was (“salmonella”[MeSH Terms] OR “salmonella”[All Fields]) AND (“proton pump inhibitors”[MeSH Terms] OR (“proton”[All Fields] AND “pump”[All Fields] AND “inhibitors”[All Fields]) OR “proton pump inhibitors”[All Fields] OR (“proton”[All

Fields] AND “pump”[All Fields] AND “inhibitor”[All Fields]) OR “proton pump inhibitor”[All Fields] OR “proton pump inhibitors”[Pharmacological Action]). This search strategy yielded 15 studies, of which three met our criteria and we found an additional study by reviewing the references of the selected studies. A similar search was undertaken in Ovid Medline database and for other enteric infections.

As the main focus of this review was to evaluate the role of PPIs in enteric infections, while preparing the evidence table, studies not categorising antacid/antisecretory therapy and not assessing individual role of PPIs were excluded. Only studies assessing the independent role of proton pump inhibitors were included in our evidence tables. Additional details on association of other antacid agents studied, salient features of the study and potential bias were mentioned in the comments section of the tables presented. Each selected study was evaluated by both the authors to determine its inclusion for the review. We included no date restrictions and selected studies published in English language in peer-reviewed journals. Case reports and case series were not included in our review.

GASTRIC ACID AND PPI USE

Gastric acid, secreted by the parietal cells in the stomach, plays a vital role in the local defence of the gut against ingested organisms. Parietal cell acid secretion is regulated by three major neuro-hormonal pathways. Neuronal secretion is regulated by acetylcholine and hormonal secretion is regulated by gastrin and histamine. All the signalling pathways finally converge on $H^+ - K^+$ ATPase, the proton pump of the parietal cell, secreting gastric acid. Parietal cells secrete hydrochloric acid at a concentration of pH 0.8 and maintain a median daily pH in human stomach around 1.4.² Gastric acid secretion demonstrates a circadian rhythm, with a rise in gastric acid secretion during the day with the greatest rate of secretion during the evening followed by gradual decrease during the night.³ The 24-h integrated intra-gastric acidity in fasted or fed subjects is similar. Gastric acid secretion is influenced by several factors such as food, gender, smoking, stress, ulcer disease, *Helicobacter pylori* gastric infection and hormonal factors.⁴ Gastric acid at pH < 4 has a powerful bactericidal effect, capable of killing exogenous acid sensitive bacteria introduced into the stomach usually within 15 min.⁵ Any increase in the gastric pH above 4 causes a state of hypochlorhydria and potentially increases the susceptibility to various microbes, allowing at least 50% of ingested bacteria to survive the gastric trap.⁶

Proton pump inhibitors selectively inhibit the gastric $H^+ - K^+$ ATPase and hence gastric acid secretion. All PPIs irreversibly inhibit the gastric $H^+ - K^+$ ATPase by binding to alpha subunit of the proton pump. Both basal and stimulated secretion of gastric acid is inhibited, independent of the nature of parietal cell stimulation. All PPIs are more or less similar in efficacy and potency. The slight difference observed among them is attributed to their different pharmacokinetic properties. PPIs are most commonly used for gastroesophageal reflux disease (GERD) and peptic ulcers. The efficacy of PPIs is generally evaluated by the degree of acid suppression measured either as mean/median 24-h intra-gastric pH or the duration of time during which a PPI maintains intra-gastric pH above a certain threshold. For peptic ulcers, the target threshold is $pH > 3$ and for GERD the threshold is $pH > 4$, as these pH strongly correlates with healing of these conditions.⁷ So while prescribing PPIs for these conditions, physicians aim to achieve this therapeutic threshold pH. Importantly, a $pH > 4$ is also observed to be a watershed line for acquisition of various enteric infections.

There have been studies evaluating the relative efficacy of different PPIs using various drug formulations, dose schedules and routes of administration under various conditions for treating peptic ulcer or GERD. At therapeutic doses, the PPIs generally cause the gastric pH to be greater than 4.⁸ Among esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg for treatment of GERD, esomeprazole 40 mg provides more effective intra-gastric acid control by having the longest duration of acid control (14.1 h after single daily dose for 5 days) and having the highest 24-h median intra-gastric pH.^{8, 9} The efficacy of different PPIs also depends on the various dosing schedules such as lansoprazole 30 mg BD provide more effective acid suppression than esomeprazole 40 mg OD but less than esomeprazole 40 mg BD.¹⁰ Esomeprazole 20 mg OD appeared to be more effective than rabeprazole 10 mg but less than rabeprazole 20 mg among healthy subjects.^{11, 12} Among healthy volunteers, studies evaluating the effect of PPIs on 24-h intra-gastric pH found that omeprazole 40 mg OD caused a median 24-h intra-gastric pH of 4.9 after 1 week,¹³ pantoprazole 40 mg caused a mean 24-h pH of 4.0 after 1 week,¹⁴ lansoprazole 30 mg OD produced a mean 24-h pH of 4.5 while 30 mg BD dose produced a pH 5.0 after 5 days,¹⁵ rabeprazole 20 mg OD produced median 24-h pH of 4.7 and 40 mg OD caused a pH of 5.0 after 1 week.¹⁶ Esomeprazole 40 mg BD produced a

higher median 24-h pH of 6.1 with median intra-gastric 24-h $pH > 4$ for 21 h after 5 days of ingestion among healthy volunteers.¹⁷ Pantoprazole 40 mg BD, in comparison, produced a median intra-gastric 24-h $pH > 4$ for 16.8 h. The duration of time when the intra-gastric pH remains greater than 4 is vital for the overall therapeutic efficacy of PPIs. The duration of reduced gastric acid may be influenced by PPI dose. Esomeprazole 40 mg OD produced a mean 24-h $pH > 4$ for 14.1 h as opposed to 20 mg BD dose which produced a mean 24-h $pH > 4$ for 17.5 h.¹⁸ In addition to PPI use, gastric pH is also influenced by usage of other medications, meals and existence of co-morbid conditions. These differences in the efficacies of various PPIs certainly can influence the susceptibility to enteric infections. In a large pharmaco-epidemiologic study by Howell *et al.*,¹⁹ the risk of nosocomial *C. difficile* infection (CDI) increased with increasing levels of acid suppression. The study demonstrated increased risk of CDI among patients taking PPI more frequently than daily as compared with taking daily PPI.

GUT MICROFLORA AND PPI USE

Gut microflora has metabolic, trophic and protective functions which make them host friendly or host deleterious depending upon their location in the gut, their numbers and the presence of virulence properties. Endogenous bacteria of the lower gastrointestinal tract provide homeostatic protection from ingested pathogens.¹ PPIs are implicated in the disruption of the gut ecology and causing altered bacterial growth ranging from abnormal bacterial counts²⁰ to overt small intestine bacterial overgrowth (SIBO).²¹ Both faecal and oropharyngeal type of microbes have been observed to contribute to small bowel bacterial overgrowth. This may be related to the lack of destruction of bacteria swallowed from the oropharynx or to the ascending colonisation from the intestine.²² Upper gut colonisation by enteric pathogens relate to the degree of hypochlorhydria and organism virulence including acid-resistance.^{22, 23} Gastric acid, once believed to affect only upper gut flora, influences lower intestinal microflora also. Bacteria in both small and large bowel increase in number in gastric hypochlorhydric conditions.²⁴ Severe hypochlorhydria induced by PPIs can thus modulate the microflora in stomach, in small intestine as well as in lower intestine, potentially increasing the susceptibility to infection by enteric pathogens that have a predilection for different regions of the gut. PPIs have also been shown to retard gastrointestinal motility,²⁵ delay gastric

emptying rate²⁶ and decreased gastric mucus viscosity,²⁷ all of which may have direct effects on gut microflora and survival of enteric pathogens.

BACTERIAL TRANSLOCATION AND PPI USE

In bacterial translocation enteric microbes are able to escape local gut defences and cross the epithelial barrier.²⁸ Animal model studies have shown a relationship between hypochlorhydria by gastric acid inhibitors and increased bacterial translocation.^{29, 30} While assessing PPIs in a triple therapy regimen for eradication of *H. pylori*, omeprazole was shown to facilitate macromolecular transport by widening the intra-epithelial spacing and increasing the permeability of gastric mucosa.³¹ Translocation across the intestinal epithelial barrier can be further encouraged by the use of PPIs through a several fold increase in gastric and small bowel microflora, secondary to reduced gastric acidity and impaired gut motility.²⁸ Studies assessing the effect of PPI on bacterial translocation have been limited to animal studies and human studies are needed.

ANTI-INFLAMMATORY EFFECTS OF PPI USE

In vitro studies involving various PPIs have shown a wide range of immunomodulatory and anti-inflammatory effects. *In vitro* studies have shown that omeprazole exerts significant anti-oxidant effects against HOCl- and iron- and copper-driven oxidant damage.³² Pantoprazole, omeprazole and lansoprazole showed hydroxyl ion scavenger activity at higher concentrations.³³ Among the inflammatory cells, neutrophils are particularly susceptible to PPI therapy, resulting in inhibition of neutrophil's bactericidal activity.^{34–36}

As with non-enteric infectious diseases, inflammatory response against gastrointestinal pathogens is regulated by complex multi-step processes involving microbial products, chemo-attractants, cytokines and interleukins, adhesion molecules and leucocytes.

Proton pump inhibitors have been shown to affect: chemotactic migration of neutrophils in response to formyl-MLP (formyl-methionyl-leucyl-phenylalanine), a potent chemo-attractant in bacteria^{36, 37}; phagocytosis of microorganisms³⁸; and neutrophil-endothelium expression of adhesion molecules.³⁹ These important negative effects of PPIs on neutrophil's function may relate to alteration of v-type of H⁺ ATPases on neutrophils,⁴⁰ inhibition of IL-8 derived immune response or inhibition of formyl-MLP-induced elevation of the cytosolic calcium concentration in polymorphonuclear neutrophils.⁴¹

INCREASED HOST SUSCEPTIBILITY TO ENTERIC INFECTION BY USE OF PPI

Bacterial enteropathogens differ as to their acid resistance and pathogenic potential in the face of potent anti-acid drugs. They will be considered separately here. See Tables 1–4 for the scientific evidence of an association between PPI use and specific enteric infection and for the cited references.

SALMONELLA INFECTIONS

Salmonella is an acid-sensitive microbe associated with consumption of eggs and poultry products and secondary to contact with cold blooded reptiles. Gianella *et al.*⁵ found a lack of survival of *S. paratyphi* and *S. enteritis* at pH < 3 whereas at pH > 4 no reduction in bacterial count was observed. Tennant *et al.*⁶ confirmed the same finding wherein a strain of *S. enterica serovar Typhimurium* hardly survived at pH < 3.5, but showed increased survival at pH above 3.5.

Additionally, therapy with PPIs may facilitate *Salmonella* infection by drug effects on neutrophils, which are the predominant inflammatory cells against nontyphoid *Salmonella* enteric infection. PPIs may also enhance susceptibility to *Salmonella* by facilitating the effects of *Salmonella* on the tight junctions in the intestinal epithelium.^{42, 43} PPI action on resident intestinal microflora, pro-inflammatory cytokines and other local mechanisms could influence the pathogenicity of strains of *Salmonella*. See Table 1 for data on the association of PPI use and infection by *Salmonella* and references for the various studies. A clear association was found between PPI use and increased susceptibility to *Salmonella* gastroenteritis in two case control studies with adjusted relative risk ranging from 4.2 to 8.3.

CAMPYLOBACTER JEJUNI INFECTIONS

C. jejuni is a poultry- and travel-associated enteric pathogen. The organism is more susceptible to gastric acid than *Salmonella*.⁴⁴ Waterman and Small⁴⁵ recovered very few colonies of *C. jejuni* on exposure to acidified Luria-Bertani broth at a relative high pH of 4 and 5. However *C. jejuni* showed increased survival at pH 6, a pH possibly seen with high doses of PPIs. See Table 2 for data on the association of PPI use and alteration of host susceptibility to strains of *C. jejuni* along with published references on the topic. Four studies, all case-control evaluations, showed an association between *Campylobacter* diarrhoea and PPI use with adjusted relative risk ranging from 3.5 to 11.7.

Table 1 Published studies of the relationship between use of PPIs and development of non-typhoid <i>Salmonella</i> gastroenteritis			
Reference	Study description	Strength of association (with 95% CI)*†	Comments
(83)	Nested case control study: 374 cases and 2000 controls	The article established CI for bacterial diarrhoea, not specifically for the subgroup with <i>Salmonella</i> infection	A relative risk of 1.6 (1.0–2.4) was reported between PPI use and bacterial gastroenteritis in general. Among the 374 total diarrhoea cases in the study, 136 (36.4%) cases were caused by <i>Salmonella</i> .
(84)	Case control study: 167 <i>S. enteritidis</i> , 193 <i>S. typhimurium</i> cases and 3119 controls	<i>S. enteritidis</i> : 4.2 (2.2–7.9) <i>S. typhimurium</i> : 8.3 (4.3–15.9)	Population attributable risk was also observed to be very high for PPIs.
(85)	Case control study: 6414 cases and 50 000 controls	The article established CI for bacterial diarrhoea, not for the subgroup with <i>Salmonella</i>	A relative risk of 2.9 (2.5–3.5) was reported between PPI use and bacterial gastroenteritis in general. Among the 6414 total diarrhoea cases in the study, 1885 (29.4%) cases were caused by <i>Salmonella</i> .
(86)	Case control study: 573 cases and 3409 controls	4.3 (2.9–6.5)	The association was reported for PPI use and recurrent cases of <i>Salmonella</i> gastroenteritis.

CI, confidence interval; PPI, proton pump inhibitor.

* Strength of association: multivariate odds ratio or relative risk is reported wherever possible rather than univariate values.

† Values were rounded to nearest first decimal wherever necessary.

DIARRHOEAGENIC *ESCHERICHIA COLI*

Diarrhoea-producing *E. coli* strains show decreased survival at pH < 3.5.⁵ Strains of *E. coli* appear to be more acid stable than strains of *Salmonella* in complex media. However, the minimum pH supporting bacterial proliferation is 4.4 for strains of *E. coli* compared with 4.0 for strains of *Salmonella*.⁴⁶ Also, *E. coli* are equipped with multiple complex pH dependent acid tolerance strategies, enabling them to survive in the acidic pH of the stomach.⁴⁷ A high gastric pH created by PPIs may facilitate the pathogenesis of *E. coli* diarrhoea. In an adult volunteer challenge study, invasive *E. coli* produced diarrhoea only when the organisms were administered after neutralising gastric acid with sodium bicarbonate showing the importance of reducing gastric acidity in the development of diarrhoea caused by this organism.⁴⁸ More studies are needed to specifically determine the association of PPI use and susceptibility to the various diarrhoea-producing *E. coli* strains including enterotoxigenic *E. coli* (ETEC), common in travellers, Shiga toxin producing *E. coli* (STEC), an important food-borne pathogen, and enteroaggregative *E. coli* (EAEC), an important cause of paediatric diarrhoea, travellers' diarrhoea and AIDS-associated diarrhoea.

CLOSTRIDIUM DIFFICILE

C. difficile is the most commonly identified cause of nosocomial diarrhoea. The association between PPIs and CDI has been better studied than potential associations between PPI use and other enteric infections. *C. difficile* exists in two forms: an acid-sensitive vegetative form and an acid-resistant spore form. Both vegetative bacteria and spores are excreted in the faeces of infected people with vegetative forms generally found in 10-fold greater numbers than spores.⁴⁹ Based on the observations from *in vitro* studies⁴⁹ and animal models,^{50, 51} most ingested vegetative cells fail to survive normal gastric acidity. The spores, however, survive in low gastric pH and readily pass into the small bowel. The spores then germinate in the small bowel under favourable conditions liberating the toxigenic vegetative forms.

Vegetative cells of *C. difficile* are important in the pathogenesis of CDI. Jump *et al.*⁴⁹ showed that vegetative *C. difficile* can remain viable for up to 6 h on moist surfaces in room air. So along with spores, vegetative forms of *C. difficile* are also a potential source of infection. Vegetative forms have shown to survive

Table 2 | Published studies of the relationship between *Campylobacter jejuni* diarrhoea and use of PPIs

Reference	Study description	Strength of association (with 95% CI)*†	Comments
(87)	Case control study: 211 cases and 422 controls	11.7 (2.5–54.0)	Omeprazole use within 1 month before infection showed the strongest association.
(88)	Case control study: 313 cases and 512 controls	3.5 (1.1–12.0)	Foreign travel explained 25% of cases of <i>Campylobacter</i> diarrhoea
(83)	Nested case control study: 374 cases and 2000 controls	The article established CI for bacterial diarrhoea, not for the subgroup with <i>Campylobacter</i>	A relative risk of 1.6 (1.0–2.4) was reported between PPI use and bacterial gastroenteritis in general. Among the 374 total diarrhoea cases in the study, 201 (53.7%) cases were caused by <i>Campylobacter</i> .
(85)	Case control study: 6414 cases and 50 000 controls	The article established CI for bacterial diarrhoea, not for the subgroup with <i>Campylobacter</i>	A relative risk of 2.9 (2.5–3.5) was reported between PPI use and bacterial gastroenteritis in general. Among the 6414 total diarrhoea cases in the study, 4124 (64.3%) cases were caused by <i>Campylobacter</i> .
(86)	Case control study: 1446 cases and 3409 controls	4.5 (3.3–6.1)	PPI use and recurrent cases of <i>Campylobacter</i> gastroenteritis were associated.
(89)	Case control study: 1,019 cases and 3119 controls	4.3 (2.9–6.2)	For elderly patients, the OR was observed to be 2.9 (1.5–5.7).

CI, confidence interval; PPI, proton pump inhibitor.

* Strength of association: multivariate odds ratio (OR) or relative risk is reported wherever possible rather than univariate values.

† Values were rounded to nearest first decimal wherever necessary.

in gastric contents at pH > 5 allowing them to directly colonise the intestinal tracts of susceptible hosts.⁴⁹ Spores are considered to be the major vector for transmission of CDI. The timing and the factors needed for the initiation of germination of *C. difficile* spores are not clearly understood. In a hamster model, 80% of *C. difficile* spores germinate in the small intestine within 1 h of intra-gastric ingestion with germination being related to exposure to bile salts.⁵⁰ A mouse model demonstrated initiation of germination in the small intestine and caecum. In the presence of bile salts and amino acids, germination was observed in the stomach.⁵¹ Bile salts have been detected in the gastric contents of patients with GERD and also in normal people.⁵² *In vitro* studies show that the minimum concentration of bile salts required for germination of *C. difficile* spores is 0.1 mmol/L and 10 mmol/L for sodium taurocholate and chenodeoxycholate, respectively,⁵³ such concentrations have been observed in

GERD patients.^{54–56} Under conditions of high pH induced by PPIs and in the presence of bile salts in the stomach, the intra-gastric milieu could be favourable for propagation of *C. difficile* vegetative cells and for conversion of spores to vegetative cells promoting the development of CDI.

Antibiotics are the most common host risk factors for CDI whereby the normal microbiota in the gut is altered eliminating the homeostatic influence of the flora and providing opportunity for growth of *C. difficile*. Prior antibiotic use is more important in the development of CDI than PPI use.^{19, 57–59} Antibiotics and PPIs used concurrently, a common situation in clinical settings, appear to work together in an additive fashion for increasing the susceptibility to CDI. Among the other mechanisms which can be speculated are the action of PPI on H⁺– K⁺ ATPases found in the colon⁶⁰ and the immunological actions of PPI as discussed earlier. To date, 27 published studies have been conducted evaluat-

ing an association between the use of PPIs and enhanced susceptibility to CDI. Most of the studies were hospital-based except for five studies looking at community-associated CDI. Seventeen studies identified a significant association of PPI use with higher rates of development of CDI (adjusted relative risk ranging from 1.2 to 5.0), while ten studies failed to show an association. See Table 3 for specific studies examining the relationship between PPI use and development of CDI. Three retrospective cohort studies found an association between PPI use and development of recurrent CDI (RCDI) (adjusted relative risk range from 1.4 to 4.2).^{61–63} See Table 4 for studies examining the relationship between PPI use and development of RCDI.

SHIGELLA

Shigellosis is a common form of dysenteric diarrhoea. The low inoculum size needed for infection explains the propensity of the organism to be spread from person-to-person. *Shigella* strains are often more acid resistant than strains of *Salmonella* and can survive in acidic complex media.^{46, 64} Strains of *Shigella* can survive exposure to acid in the stomach trap, which is different than many other bacterial organisms.⁶⁵ There have been no studies evaluating the association between shigellosis and PPI use. However, it is unlikely that PPI use would increase susceptibility to infection by *Shigella* strains due to their low inoculum requirements and relative acid resistance.

VIBRIO CHOLERAE 01

V. cholerae, the cause of cholera and an important cause of dehydrating diarrhoea in endemic areas of the developing countries, is very acid sensitive.⁶⁶ Studies have provided evidence that those experiencing cholera in endemic areas are preselected based on their reduced basal gastric hydrochloric acid.^{67–69} In human challenge studies, a strain of *V. cholerae* produced disease only after first reducing gastric acidity of the volunteers.⁷⁰ One study carried out in 1989, which examined an outbreak in Thailand, showed an increased association of antacid use among the cholera cases.⁷¹ More studies are needed to directly link PPI use with enhanced susceptibility to cholera.

LISTERIA

Strains of *Listeria* show various degrees of susceptibility to gastric acid. In general, *Listeria* is susceptible to a pH ≤ 2 with increased survival at pH ≥ 5 .^{72, 73} Strains of *Listeria* have been isolated from the stools

of patients receiving H₂ blockers.⁷⁴ In an outbreak of *Listeria* infection, enhanced susceptibility to the organism was associated with cimetidine treatment.⁷⁵ While no studies have been carried out to look at PPI use and increased susceptibility to infection by strains of *Listeria*, it is likely that people on PPIs will be more susceptible to this organism that is capable of causing fatal disease in the elderly or in the immunocompromised patients.

DISCUSSION AND CONCLUSIONS

In spite of clear evidence that reduced gastric acidity facilitates intestinal infection by bacterial enteropathogens, the magnitude of the enhanced susceptibility to diarrhoea by chronic PPI use is not clear. Decreased gastric acidity caused by PPI use has important implications for the survival of intestinal bacteria including enteropathogenic forms with potential to colonise, invade or inflame the intestine. For *Salmonella* and *C. jejuni* strains, the relatively few published studies report a significant association of enteric infection with PPI use. This association is best studied for CDI which has the greatest importance for hospitalized persons or for people confined to nursing homes and other facilities. Not all studies have shown an association of PPI use and increased susceptibility to CDI. The studies failing to show an association between PPI use and CDI involved predominantly patients ≥ 65 years of age. It is likely that in persons of advanced age with their high rate of underlying hypochlorhydria⁷⁶ and presence of co-morbid diseases, the addition of PPI may not confer important additional risk.

In this review, we have proposed potential mechanisms to help in understanding the association between PPI use and CDI. The incidence of CDI is increasing rapidly due to two important reasons – increasing virulence of *C. difficile* strains and increasing host vulnerability with a rapidly growing elderly and infirm population.⁷⁷

It is common for hospitalized patients to receive PPIs prophylactically to prevent gastric complications including GI bleeding. PPI are probably overused and may be associated with significant health-care expenditure.⁷⁸ Prevention of stress ulcers in hospitalized patients and treatment of functional dyspepsia are common indications for this class of drugs.⁷⁹ A short course of PPI may be very helpful in selected patients but discontinuing PPI therapy should be considered in patients who are asymptomatic or about to receive broad-spectrum antibiotics known to have important

Table 3 Published studies of the relationship between CDI and use of PPIs				
Reference	Type of study	Study description	Strength of association (with 95% CI*†)	Comments
(90)	Hospital based	Case control study: 126 cases and 126 controls	0.9 (0.5-1.5)‡	An association between PPI use and CDI was not seen in a group of elderly subjects.
(91)	Hospital based	Case control study: 27 cases and 27 controls	3.0 (0.8-11.0)	H ₂ blockers§ were also evaluated and showed no significant association.
(92)	Hospital based	Case control study: 160 cases and 160 controls	2.5 (1.5-4.2)	PPI use the preceding 8 weeks was associated with increase in CDI risk.
(93)	Hospital based	Cohort study: 1,187 subjects	2.1 (1.2-3.5)	H ₂ blockers were also evaluated and showed no significant association.
(93)	Hospital based	Case control study: 94 cases and 94 controls	2.7 (1.4-5.2)	Patients in the hospital who received PPIs were at increased risk for CDI.
(94)	Community based	Case control study: 1,233 cases and 12,330 controls	2.9 (2.4-3.4)	H ₂ blockers were also evaluated and showed significant association.
(95)	Hospital based	Case control study: 203 cases and 203 controls	2.4 (1.3-4.4)	Hospital outbreak of CDI was studied.
(96)	Hospital based	Case control study: 50 cases and 200 controls	3.4 (1.7-6.8)	H ₂ blockers were also evaluated and showed no significant association.
(59)	Hospital based	Retrospective cohort study: 5,619 subjects	1.0 (0.8-1.3)	H ₂ blockers were also evaluated and showed no significant association.
(97)	Community based	Case control study: 317 cases and 3,167 controls	3.5 (2.3-5.2)	Cases of CDI were identified by first identifying oral use of vancomycin.
(98)	Hospital-based	Case control study: 64 cases and 128 controls	5.0 (1.3-19.4)	Hospital outbreak of CDI cases was studied.
(99)	Community based	Population based nested case control study: 1389 cases and 12 303 controls	0.9 (0.8-1.1)	Study in old age patients, age ≥ 66 years.
(57)	Hospital based	Case control study: 155 cases and 153 controls	1.9 (1.1-3.3)	PPI use in the preceding 3 months was associated with increase in CDI risk.
(100)	Hospital based	Case control study: 640 cases and 650 controls	1.7 (1.4-2.2)	Study in African American and Hispanics population.
(58)	Hospital based	Cohort study: 827 subjects	0.9 (0.6-1.4)	Mean duration of PPI use was 8.9 days. H ₂ blockers were also evaluated and showed no significant association.
(101)	Hospital based	Retrospective cohort study: 36 086 subjects	1.6 (1.3-2.1)	H ₂ blockers were also evaluated and showed significant association.
(102)	Hospital based	Nested Case control study: 382 cases and 1,528 controls	4.1 (3.2-5.2)	H ₂ blockers were also evaluated showing significant association.
(103)	Hospital based	Case control study: 122 cases and 244 controls	2.8 (1.7-4.5)	H ₂ blockers were also evaluated and showed no significant association.
(104)	Hospital based	Case control study: 184 cases and 184 controls	0.8 (0.5-1.4)‡	H ₂ blockers were also evaluated and showed no significant association.
(105)	Hospital based	Case control study: 94 cases and 94 controls	3.6 (1.7-8.3)	Environmental factors were controlled between case and control subjects. H ₂ blockers were also evaluated and showed no significant association.

Table 3 (Continued)				
Reference	Type of study	Study description	Strength of association (with 95% CI*†)	Comments
(106)	Hospital based	Case control study: 1142 cases and 3351 controls	1.2 (1.03-1.5)	Use of PPI in the 60 days before index date was associated with increased risk of CDI.
(107)	Hospital based	Retrospective cohort study: 14 719 subjects	2.0 (1.4-2.7)	The increased risk of acquiring CDI with PPI use in the hospital relates to the frequency of CDI in the population.
(108)	Community based	Nested case control study: 836 cases and 8360 controls	1.6 (1.3-2.0)	H ₂ blockers were also evaluated and showed significant association. Older age patients, age ≥ 65 years studied.
(109)	Community based	Case control study: 40 cases and 112 controls	1.1 (0.1-7.2)‡	The study reported only 2 cases of PPI users among cases of CDI.
(110)	Hospital based	Case control study: 45 cases and 90 controls	1.1 (0.5-2.6)	The various risk factors for hospital acquired CDI were evaluated.
(111)	Hospital based	Prospective Case control study: 93 cases and 76 controls	1.1 (0.5-2.6)	Studied the risk factors for CDI in an endemic setting.
(19)	Hospital based	Cohort study: 1 01 796 subjects	For daily PPI use: 1.7 (1.4-2.2) More frequent than daily PPI use: 2.4 (1.8-3.1)	H ₂ blockers were also evaluated and showed significant association The authors identified the combination of acid suppression and antibiotic exposure as the principal risk factors for CDI.

CI, confidence interval; PPI, proton pump inhibitor; CDI, *C. difficile* infection.

* Strength of association: multivariate odds ratio (OR) or relative risk is reported wherever possible rather than univariate values.

† Values were rounded to nearest first decimal wherever necessary.

‡ Calculated from the data given in the study article.

§ Type 2 histamine receptor blockers.

effects on gut flora. Non-pharmacological measures such as watchful observation (many cases of dyspepsia resolve on their own), life style modifications such as eating smaller meals well before sleep, weight reduction, smoking cessation and stress reduction⁷⁹ may be useful in many cases. The Public Health Agency of Canada has issued an advisory on their website that PPIs may increase the risk of CDI.

There are other recommendations for decreasing CDI in the hospital. Thachil J *et al.*⁸⁰ suggested having a 'hospital antacid policy' to prevent irrational drug use and to withhold PPI while the patient receive broad-spectrum antibiotics during hospital admissions. Metz⁸¹ recommended giving the lowest effective dose of PPIs in hospitalized patients while providing optimal hygiene

measures such as enteric precautions and strict and effective hand washing, limiting unnecessary antibiotic exposure. Heidelbaugh JJ *et al.*⁷⁸ suggested using pharmacy-driven step-down orders and prescribing on demand PPI therapy only after ascertaining its rationale through case by case evaluation.

Patients on PPIs should be informed that they are more susceptible to bacterial diarrhoea and they should exercise care in eating higher risk foods such as poorly cooked ground beef, unpasteurized milk or cheese or moist foods served at room temperature at restaurants. These people may also be at considerable risk of acquiring various enteric infections during travel to tropical and semi-tropical regions of the developing world. The International Society of Travel Medicine identified PPI

Table 4 | Published studies of the relationship between RCDI and use of PPIs

Reference	Type of study	Study description	Strength of association (with 95% CI*†)	Comments
(61)	Hospital based	Retrospective cohort study: 140 subjects	4.2 (1.7–10.4)	RCDI was defined as the return of signs and symptoms after complete resolution, with a positive result for <i>C. difficile</i> toxins A and B (by ELISA), within 90 days after the end of therapy.
(62)	Hospital based	Retrospective cohort study: 1166 subjects	1.4 (1.1–1.8)	RCDI defined by a positive toxin finding in the 15 to 90 days after incident CDI. H ₂ blockers‡ were also evaluated and showed no significant association.
(63)	Hospital based	Retrospective cohort study: 125 subjects	3.5 (1.6–7.7)	RCDI was defined as diarrhea recurrence after complete resolution, with a positive result for cytotoxin A (ELISA), within 90 days after the end of therapy.

CI, confidence interval; PPI, proton pump inhibitor; RCDI, recurrent *Clostridium difficile* infection.

* Strength of association: multivariate odds ratio or relative risk is reported wherever possible rather than univariate values.

† Values were rounded to nearest first decimal wherever necessary.

‡ Type 2 histamine receptor blockers.

use as a risk factor for developing travellers' diarrhoea and suggested that consideration be given to administering daily chemoprophylaxis to prevent illness in PPI users during travel to high risk areas of Latin America, Africa or Southern Asia.⁸²

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