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EDITORIAL

Gastric Acid and Enteric Infections: Souring on the Use of PPIs

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Gastric acid is important for maintaining homeostasis within the gastrointestinal tract by facilitating protein digestion and the absorption of dietary calcium and iron, and by reducing the counts of enteric infectious agents. This defense mechanism is most important for persons living in or visiting regions of the world where personal and food hygiene are substandard. Reductions in gastric acid secretion associated with nutritional deficiencies in developing countries are partially responsible for the high local rates of infectious diarrhea and cholera. There is growing scientific evidence that pharmacologic reductions in gastric acid concentrations, in particular by proton-pump inhibitors (PPIs), approximately doubles the risk of acquiring enteric infection from infectious pathogens present in contaminated foods that are ingested [1]. The successes achieved in the PPI era regarding acid-related disorders including reflux esophagitis has led to overuse of this drug class. The problem of overuse has increased since PPIs became available over the counter without prescription. Patients are often given a PPI on admission to the hospital as a routine measure, and in many cases the drug is continued after discharge. Primary care physicians and the general public should be advised on the proper long-term use of PPIs [2].

Enteric pathogens differ in terms of their susceptibility to low gastric pH. Susceptibility to gastric acid directly determines the expected inoculum size for an orally ingested enteric pathogen to produce illness. For the organisms exhibiting higher levels of acid susceptibility, most infections that develop require initial replication in the presence of food or less commonly in water prior to reaching infectious inoculum size. Only the more acid-resistant organisms commonly show direct person-to-person spread [3].

For most of the enteric pathogens, antecedent PPI use or preexistent hypochlorhydria enhances susceptibility to diarrheal disease, in particular due to *Vibrio cholerae* infection, which is among the most acid-susceptible enteric pathogens. In a study conducted in the USA, adult volunteers experimentally challenged with virulent strains of *Vibrio cholerae* only developed cholera after the gastric pH in the volunteers were raised by antacid drugs [4]. Vegetative cells of *Clostridium difficile* are susceptible to gastric acid at pH ≤ 5, whereas spores of this antibiotic-associated pathogen are resistant to gastric acid even at very low pH levels. Nontyphoid salmonellosis is particularly common in infants and the elderly who have decreased gastric acid secretion. For organisms that require a low inoculum, gastric acid suppression may not be essential for the development of infection although a recent study suggested that norovirus infection could be facilitated by prior PPI use [5]. In Table 1, important infectious causes of diarrhea are listed according to degree of known acid susceptibility, along with a perspective on how this property predicts the inoculum size required for disease development and how acid susceptibility influences the epidemiology of disease. Finally, the table provides published evidence that PPI use predisposes to enteric infection listed by the pathogen.

In this issue of *Digestive Diseases and Sciences*, Yasutomi et al. [6] examined the mechanisms whereby the proton-pump inhibitor, lansoprazole (laz), facilitated intestinal infection in a mouse model of bacterial colitis. The authors used the murine pathogen, *Citrobacter rodentium*, an indole-positive gram-negative bacterium that produces an attaching and effacing intestinal lesion similar to that of the human pathogens, Shiga toxin-producing *Escherichia (E.) coli*, and enteropathogenic *E. coli*. Laz was administered to the mice daily for 7 days by intraperitoneal injection before

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Table 1 Description of important enteric pathogens according susceptibility to gastric acid, with a perspective on how this influences epidemiology of infectious diarrhea, followed by a comment on available evidence that PPI use facilitates the infection

Degree of acid susceptibility	Enteric pathogens	Dose usually required to produce illness	Characteristic epidemiology		Evidence antacids predispose to infection [6]
			Foodborne	Person-to-person	
High (most strains unable to survive gastric pH ≥ 4)	*V. cholerae*	Millions of viable bacteria	To produce cholera, a large inoculum must be ingested in contaminated water or food	Does not normally occur	Patients in endemic areas have a high rate of hypochlorhydria. To infect healthy volunteers, gastric acid must be first neutralized
	C. difficile (vegetative cells)	Very large, uncertain if disease can be produced with normal gastric acidity	Unlikely	Occurs in patients with reduced gastric acid	A number of studies show that PPI use predisposes to *C. difficile* infection
Moderate (most strains unable survive exposure to pH ≤ 2.5)	*Salmonella*	500–100,000 viable bacteria	95% of cases are secondary to foodborne disease	Can occur but not commonly	A number of studies show that PPI use predisposes to *Salmonella* infection
	Campylobacter	500–100,000 viable bacteria	Most common source undercooked poultry	Can occur but not commonly	A number of studies show that PPI use predisposes to *Campylobacter* infection
Low (most strains able to survive exposure to pH ≤ 2.5)	*Shigella* Noroviruses	≤ 100 viable organisms	Common causes of foodborne illness from food mishandled by an infected food handler	Very common: the two most communicable pathogens, usually spread from persons who are excreting the pathogens, can spread from the environment	PPI use can increase susceptibility to enteric infection although the effect is less dramatic than for organisms showing greater susceptibility to gastric acid
	C. difficile spores	Low inoculum required in the susceptible host	Probably occurs	Most commonly spread from an infected person to another susceptible host via a contaminated environment, often in a hospital or nursing home	A number of studies show that PPI use predisposes to *C. difficile* infection

inoculation with 10^4 to 10^6 colony-forming units (CFUs) of *Citrobacter* by oral gavage. Enteric infection was confirmed by tissue histology and the measurement of inflammatory cytokines, combined with measurements of intraluminal pH, microbial composition, and selected metabolites from contents obtained from several locations of the gut. In challenged mice given laz, a reduction in pH was present only in the stomach. The laz-treated but not the untreated and challenged control mice developed colitis. Also, in the laz-treated mice, a greater number of the *Citrobacter* were present in the cecum compared with control mice. Laz administration altered the composition of the microbiota of the ileum with a reduction in abundance of *Clostridiales*, while not altering the composition of the fecal microbiota. Butyrate and propionate concentrations in the ileum of laz-treated mice were reduced, whereas fecal levels matched values in the control mice. No characteristic immune cell distributions in mesenteric lymph node tissues or gene expression profiles in small intestinal tissue were seen in the laz-treated mice. The authors interpreted these results as being consistent with the hypothesis that an increase in intragastric pH due to PPI treatment was solely responsible for of the increase in the abundance of pathogenic bacteria in the lower gut and the subsequent development of colitis and not other PPI-induced intestinal changes.

This ambitious study furthers knowledge in the area of susceptibility to infection with enteric pathogens providing strong evidence of the importance of the suppression of gastric acid secretion in the enabling of acid-susceptible bacteria to survive the gastric milieu in the facilitation of enteric infection. The study furthermore looks at other factors that could explain the enhancement of pathogenicity of an orally ingested pro-inflammatory bacterial pathogen in the face of PPI therapy, attempting to exclude extragastric pH alterations, changes in the metabolite production of the endogenous microbiota or the host response as an explanation for enhancement of the success of enteric infection.

The existing scientific data certainly support the conclusion of this study; most believe that protection in the normally acidic stomach explains the enhancement of enteric infection in people receiving PPIs. The present study extends the observations of Tennant et al. [7] who studied the effects of gastric acid neutralization in a similar mouse model of enteric infection. The authors in the Tannant publication arrived at the same conclusions using antacid agents as well as genetically hypochlorhydric mice challenged with *Yersinia*, *Salmonella*, or *Citrobacter*. *Citrobacter,* a member of the family Enterobacteriaceae that produces pathogenic lesions of the gut resembling an enteric infection of humans, is not a human pathogen. Studies of experimental infection in mice using a variety of human pathogens that differed in acid susceptibility include an enteropathogenic *E. coli* (EPEC) strain that produces the attaching an effacing lesion also produced by *Citrobacter* [8], *Yersinia,* and *Salmonella* [7].

More research is needed on the characterization of the microbiota and the metabolites that they produce before concluding that PPI enhancement of enteric infection relates solely to gastric acid secretory mechanisms. Yasutomi et al. reported that anaerobic *Clostridia*-type bacteria were inhibited in the ileum of laz-treated mice. Spore-forming *Clostridialis* is among the most biologically active class of the intestinal microbiota providing colonization resistance through which intestinal bacterial pathogens are inhibited [9], which may have contributed to the increase in *Citrobacter* abundance reported in the study. Also, the authors apparently only studied the microbiota composition at the order or genus level, ignoring events that can occur at the strain level. The reduced levels of butyrate and propionate seen in the ileum of laz-treated mice in the Yasutomi paper may have contributed to disease pathogenesis. Short-chain fatty acids, especially butyrate, influence host physiology and bacterial fitness or virulence. Changes in virulence characteristics are affected by these organic acids in experimental infection caused by attaching and effacing *E. coli,* including bacterial adherence and formation of fimbriae [10]. The reduced level of SCFA in the ileum seen in the study reviewed could have altered the virulence of the *Citrobacter* as it entered the colon.

PPIs double the risk of acquiring a foodborne diarrheal disease. For persons planning trips to developing regions of Latin America, Africa and Southern Asia, avoidance of this class of drugs is critical to their travel health. In these regions, foods are often contaminated with pathogenic bacteria and viruses. A majority of travelers' diarrhea is caused by bacterial pathogens, while bacteria are responsible for < 10% of cases of diarrhea in the USA. For their patients planning high-risk trips, physicians should consider stopping or suspending their PPIs or to use a nighttime H_2 receptor antagonist during the travel. Every effort should be made to maintain acidic gastric pH at mealtimes for international travelers.

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