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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Rajesh Kumar Rajnish, MBBS, MS, Assistant Professor, Department of Orthopaedics, All India Institute of Medical Sciences, Bilaspur, Bilaspur 174001, Himachal Pradesh, India. duktiraj@gmail.com

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Helicobacter pylori infection and small intestinal bacterial overgrowth—more than what meets the eye

Murali Dharan, David Wozny

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Murali Dharan, Department of Gastroenterology and Hepatology, University of Connecticut Health Center, Farmington, CT 06030, United States

David Wozny, Department of Primary Care and Internal Medicine, University of Connecticut, Farmington, CT 06030, United States

Corresponding author: Murali Dharan, FASGE, MRCP, Assistant Professor, Department of Gastroenterology and Hepatology, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06030, United States. dharan@uchc.edu

Abstract

Helicobacter pylori (*H. pylori*) infection is very common and affects a significant proportion of the world population. In contrast, the prevalence of small intestinal bacterial overgrowth (SIBO) in the general population is not well understood. There can be coexistence of both disease states in a given patient and their clinical symptoms may also overlap with one and another. There is no clear clinical guidelines for testing for and treating SIBO in patients with *H. pylori* infection. This review article explores the available evidence on the relationship between *H. pylori* infection and SIBO, diagnosis and treatment of these entities and also comments on associated non-gastrointestinal conditions.

Key Words: *Helicobacter pylori* infection; Small intestinal bacterial overgrowth; Overlap; Diagnosis; Treatment

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Core Tip: This article explores the coexistence of small intestinal bacterial overgrowth (SIBO) in patients with *Helicobacter pylori* (*H. pylori*) infection including epidemiology and pathophysiologic mechanisms. It also reviews diagnosis and treatment of these entities and highlights current knowledge gaps and areas of future research. Currently, there are no guidelines for evaluation and management of co-existent SIBO in *H. pylori* infection.

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INTRODUCTION

The concentration of microbiota increases as we traverse down the gastrointestinal tract, reaching up to 10^{11} bacteria *per* gram of stool in the colon. Compared with the colon, the small intestine normally has lower levels of microbial colonization. Excess bacteria in the small intestine that cause gastrointestinal symptoms are known as small intestinal bacterial overgrowth (SIBO). It has been postulated that SIBO occurs due to impaired gastric motility and/or acidity allowing for bacterial multiplication and enhanced colonization[1,2].

During active *Helicobacter pylori* (*H. pylori*) infection, gram-negative bacteria hydrolyze urea into ammonia and carbonic acid in the stomach. The ammonia byproduct buffers gastric acid leading to an increase in stomach pH to protect the organism and allow further proliferation. Over time, atrophy of the gastric mucosa occurs permitting further multiplication of the bacteria. The preferred treatment of *H. pylori* infection includes a course of proton pump inhibitor (PPI) therapy, which further raises gastric pH[3] and antibiotic agents, and may also cause dysbiosis and consequent gastrointestinal symptoms[4, 5].

Both mucosal atrophy and gastric pH alterations have been proposed to predispose patients to SIBO [1,2,6]. However, SIBO rates in patients with active or recent *H. pylori* infection have not been widely studied and no universal guidelines exist regarding testing for the detection of SIBO either concurrently with *H. pylori* infection or posttreatment[7]. This article highlights available evidence on the relationship between *H. pylori* infection and SIBO as well as their association with other pathologies.

EPIDEMIOLOGY

H. pylori infection affects more than half of the adult population worldwide with a prevalence rate in the United States between 20% and 40%[8]. Due to testing variability, the prevalence of SIBO in the general population is less well understood[9]. Studies have suggested an association of SIBO with altered anatomy, hypochlorhydria, dysmotility, immune deficiencies, small intestinal disease and PPI use[9,10]. The correlation between PPI and SIBO has been well established[11]. One meta-analysis of 19 eligible studies from 1994-2016 included 7055 subjects and found a 3-fold increased risk of SIBO in patients who had received PPI therapy[6].

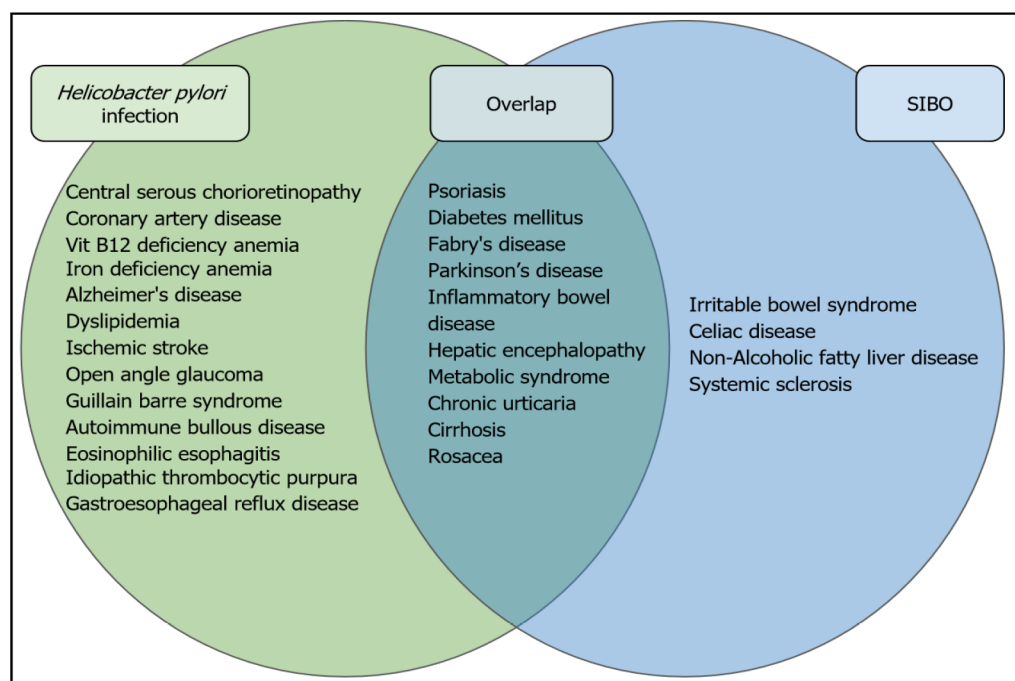
PPI therapy is often prescribed for patients complaining of dyspepsia, a common complaint known to affect up to 21% of the world's population[12]. *H. pylori* infection is also more common in patients with dyspepsia[3,12]. Dyspepsia is often treated with over-the-counter medications, empiric PPI therapy or sometimes antibiotic therapy[13]. Antibiotic therapy is known to disrupt the natural microbiome and predispose patients to dysbiosis[4] and potentially SIBO.

The association of SIBO with *H. pylori* infection was explored in a 2017 study that tested 109 patients for *H. pylori* infection and SIBO. Nineteen of 36 or 52.8% of *H. pylori* infection patients were found to have concurrent SIBO. However, only 16 of 73 or 21.9% of patients without *H. pylori* infection met the criteria for SIBO. These data suggest that the occurrence of SIBO is 2-fold greater in *H. pylori* infection patients than in uninfected patients[7]. These findings are supported by a 2018 study that found 53% or 62 of 116 patients with concurrent *H. pylori* infection and SIBO[14].

Several studies have reported an association between SIBO, *H. pylori* infection and a variety of pathologies (Figure 1). In comparison trials, both SIBO and *H. pylori* infection appear more common in cirrhosis[15], Fabry's disease[16] and Parkinson's disease[17]. Independent reviews of *H. pylori* infection and SIBO show overlapping higher incidence in patients with diabetes mellitus, metabolic syndrome, hepatic encephalopathy, chronic urticaria, psoriasis and rosacea when compared to the general population[18-21]. In patients with cirrhosis and hepatic encephalopathy, the eradication of SIBO appears to improve encephalopathic symptoms; however, the treatment of *H. pylori* infection does not [15]. Inversely, the treatment of *H. pylori* infection has been documented to improve chronic spontaneous urticaria[18] and rosacea[19] but the treatment of SIBO has not.

PATHOGENESIS (MECHANISMS)

In the general population, gastric secretions are strongly acidic with a pH range of 1 to 2. In non-*H. pylori* infection individuals, daily administration of 20 mg omeprazole has been shown to increase



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Figure 1 *Helicobacter pylori* infection, small intestinal bacterial overgrowth and their associated pathologies. Studies comparing small intestinal bacterial overgrowth (SIBO) and *Helicobacter pylori* infection in patients with hepatic encephalopathy 15, Fabry disease 16, Parkinson's Disease 17, Chronic urticarial 18, and Rosacea 19. Extra-gastric manifestations of *Helicobacter pylori* infection 20. Extra-gastric manifestations of SIBO 21. SIBO: Small intestinal bacterial overgrowth.

gastric pH by 2 to a pH range of 3 to 4. During *H. pylori* infection, individuals receiving this same dose of omeprazole showed increased stomach pH by a total of 4 to a pH range of 5 to 6[1]. Within the pH range of 5 to 6, enteric bacterial load can increase by as much as 1000-fold[22]. These bacteria are predominantly gram-negative anaerobes that produce gas with the fermentation of carbohydrates[2]. This gas fermentation allows for the detection of *H. pylori* infection by the urea breath test and the detection of SIBO by the hydrogen breath test. With that said, both bacterial load and the gas they produce contribute to the nonspecific constellation of gastrointestinal complaints described in SIBO and *H. pylori* infection.

PPIs are one of the most commonly prescribed medications for the treatment of several gastrointestinal symptoms. Numerous studies have shown an association between PPI use and SIBO[1, 6,11]. However, most studies have not found a correlation between the timing of PPI use and SIBO[2].

Antibiotic-induced dysbiosis has been well documented[4]. While the theoretical possibility of SIBO after eradication therapy for *H. pylori* infection exists, there is a lack of evidence. Interestingly, recurrence of SIBO following antibiotic therapy for the treatment of bacterial overgrowth is well recognized[2]. It remains unclear whether this is due to regrowth of the primary microbiome or due to alteration of the gastrointestinal flora, known as dysbiosis, following antibiotic therapy.

CLINICAL PRESENTATION

The symptoms of SIBO and *H. pylori* infection are largely due to malabsorption of nutrients, inflammation and immune activation as a result of a high bacterial load and its byproducts. Although no single symptom is attributed to all cases of bacterial overgrowth, dyspepsia appears to be the most commonly reported in both SIBO[23] and *H. pylori* infection[3]. In up to two-thirds of patients with SIBO, symptoms include flatulence, bloating, abdominal cramping and diarrhea. Some studies have also reported nausea and constipation[2]. *H. pylori* infection is also frequently reported with flatulence, bloating, abdominal cramping and nausea[3]. This significant symptom overlap between reported symptoms of SIBO and *H. pylori* infection might, in some patients, be due to the coexistence of both conditions.

DIAGNOSIS

Testing for *H. pylori* infection is clinically indicated in patients with dyspepsia, unexplained iron deficiency anemia, current or past history of peptic ulcer disease, chronic nonsteroidal anti-inflammatory use, gastric cancer or gastric mucosa-associated lymphoid tissue lymphoma or idiopathic thrombocytopenic purpura[3,12,24,25]. Confirmation of *H. pylori* infection can be performed directly on biopsy specimens collected during endoscopy, by stool antigen test or by urea breath test. PPI therapy can impair the accuracy of these tests and should be discontinued prior to testing[23]. Stool antigen testing, however, maintains a high level of sensitivity 94% (95%CI: 93-95) and specificity 97% (95%CI: 96-98) regardless of PPI use[25]. Following treatment, clearance of *H. pylori* infection should be documented after 1 mo by the urea breath test or stool antigen testing[25,26].

Due in large part to a lack of international testing standards for the diagnosis of SIBO, there is a large amount of uncertainty regarding the prevalence of this condition. In 2020, the American College of Gastroenterology (ACG) first published SIBO-related clinical guidelines on diagnosis and treatment. However, evidence behind both testing and treatment for SIBO is currently low and recommendations remain conditional[2].

The diagnosis of SIBO can be made by direct small bowel aspirate or a less invasive hydrogen breath test. The ACG cites a collation study of literature from the North American Consensus for the diagnostic threshold of SIBO on direct small bowel aspirate as a bacterial count of $> 10^3$ colony forming units *per* milliliter[27]. Alternatively, the less invasive hydrogen breath test is performed by ingestion of a fixed quantity of carbohydrate, such as 75 g glucose or 10 g lactulose, and measuring exhaled hydrogen. The recommended diagnostic threshold for SIBO is a rise of at least 20 parts *per* million (ppm) in exhaled hydrogen above baseline within 90 min of ingestion of either glucose or lactulose[2]. Based on a systematic review, the sensitivity of hydrogen breath testing using lactulose substrate ranges from 31% to 68% and specificity 44% to 100% compared to glucose substrate with a sensitivity range from 20% to 93% and specificity of 30% to 86%[28].

TREATMENT

Given the potential for coinfection with both *H. pylori* infection and SIBO, further research is needed to determine if co-treatment of both pathologies is preferred over first eliminating *H. pylori* infection before treating SIBO. For the treatment of SIBO, the most widely studied agent remains oral rifaximin. In 2017, a meta-analysis of 32 trials using rifaximin in the treatment of SIBO found the overall success of therapy to be 70.8%[27]. Alternately, studies have proposed the use of amoxicillin-clavulanate, ciprofloxacin, doxycycline, tetracycline, metronidazole, neomycin or trimethoprim-sulfamethoxazole[2]. These alternative antibiotics share some overlap with currently accepted *H. pylori* infection treatment regimens and might serve as a solution to treating coinfection.

Multiple *H. pylori* infection treatment regimens are acceptable for initial infection. Considerations such as penicillin allergy, previous macrolide exposure or high local resistance may impact treatment choices[25]. In areas where clarithromycin resistance is low, the ACG 2017 preferred treatment regimen is triple therapy with PPI, clarithromycin and amoxicillin or metronidazole. Where clarithromycin resistance is high, an alternative first-line regimen is a 10-14 d course of bismuth quadruple therapy consisting of bismuth, tetracycline, PPI and metronidazole[3]. A recent meta-analysis from 2021, however, suggests that regardless of local clarithromycin resistance, levofloxacin triple therapy with PPI, amoxicillin and levofloxacin has the highest overall composite eradication rate of 88.5% in Western countries[29]. When primary treatment fails, salvage therapy should be tailored to not include previously attempted antibiotics[25]. Based on current guidelines, bismuth quadruple therapy or levofloxacin-containing regimens are preferred salvage therapy options[3].

However, *H. pylori* is frequently resistant to metronidazole, with highly variable local resistance rates between 10%-90%[29,30]. One study comparing treatment eradication in *H. pylori* infection and SIBO coinfection suggests nearly equivalent eradication rates when substituting rifaximin (59.4% eradication) for metronidazole (63% eradication) when using triple therapy[14]. Although these findings suggest that rifaximin-containing regimens are acceptable, further studies are required to determine the best treatment option.

CONCLUSION

Based on the current literature review, SIBO appears to have an increased prevalence in patients with *H. pylori* infection compared to the general population[7,14]. While the “test and treat” strategy[13] for *H. pylori* infection in patients with dyspepsia has been validated, no clear recommendations currently exist for testing/treating SIBO in patients with *H. pylori* infection. Several extra gastrointestinal conditions appear to be associated with both SIBO[15-18] and *H. pylori* infection[19-21] and dysbiosis due to the attempted treatment for *H. pylori* infection may be related to the microbiome-mediated pro-inflam-

matory state. It is therefore important to recognize the signs and symptoms of *H. pylori* infection and treat the infection as well as the associated dysbiosis bearing in mind that persistence of gastrointestinal symptoms despite eradication of *H. pylori* infection could suggest coexisting SIBO.

FOOTNOTES

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ORCID number: Murali Dharan 0000-0002-9764-0068; David Wozny 0000-0002-1842-1511.

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