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Helicobacter pylori Infection and Small Intestinal Bacterial Overgrowth–More than what meets the eye

Helicobacter pylori infection, small intestinal overgrowth, overlap

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Abstract

Helicobacter 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 Helicobacter pylori infection (HPI). The review article explores the available evidence on the relationship between HPI 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; over lap; diagnosis and tretament

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Core Tip: The article explores the coexistence of small intestinal bacterial overgrowth (SIBO) in patients with Helicobacter pylori infection (HPI) 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 HPI.

INTRODUCTION

The concentration of microbiota increases as we traverse down the gastrointestinal tract, reaching amounts of up to 10^{11} bacteria per gram of stool in the colon. Compared with the colon, the small bowel normally has lower levels of microbial colonization. Excess of bacteria in the small intestine causing gastrointestinal symptoms is known as small intestine 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 infection (HPI), the gram negative bacteria hydrolyzes urea into ammonia and carbonic acid in the stomach. The ammonia byproduct buffers gastric acid, raising stomach pH to protect the bacteria and allow further proliferation. With time, atrophy of the gastric mucosa occurs, permitting further multiplication of the bacteria. The preferred treatment of HPI includes a course of proton pump inhibitor (PPI) therapy which further raises gastric pH [3] and antibiotic agents which may also cause dysbiosis and consequent gastrointestinal symptoms.[4,5]

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

EPIDEMIOLOGY:

HPI affects more than half of the adult population worldwide with a United States prevalence rate 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 is 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] HPI is however 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 HPI was explored in a 2017 study which tested 109 patients for HPI and SIBO. 19 of 36 or 52.8% of HPI patients were found to have concurrent SIBO. Whereas only 16 of 73 or 21.9% of patients without HPI met criteria for SIBO. This data suggests the occurrence of SIBO is 2 fold greater in HPI than uninfected patients. [7] These findings are supported by a 2018 study which found 53% or 62 of 116 patients with concurrent HPI and SIBO. [14]

Several associations have been made between SIBO, HPI and a variety of pathologies (Figure 1). In comparison trials, both SIBO and HPI appear more common in cirrhosis [15], Fabry's disease [16] and Parkinson's disease [17]. Independent reviews of HPI 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 HPI does not. [15] Inversely, the treatment of HPI has been documented to improve chronic spontaneous urticaria [18] and rosacea [19] but the treatment of SIBO has not.

PATHOGENESIS:

In the general population, gastric secretions are strongly acidic with a pH range of 1 to 2. In non-HPI individuals, daily 20mg omeprazole has shown to increase gastric pH by 2 to a pH range of 3 to 4. During HPI, 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 1,000 fold. [22] These bacteria are predominantly gram negative anaerobes which produce a gas with the fermentation of carbohydrates. [2] This gas fermentation allows for the detection of HPI by urea breath test and the detection of SIBO by hydrogen breath test. With that said, both bacterial load and the gas they produce contribute to the non-specific constellation of gastrointestinal complaints described during SIBO and HPI.

PPI's 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] Most studies have not however found a correlation between 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 HPI exists, evidence for this is lacking. 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 HPI 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 HPI. [3] SIBO symptoms documented in up to two thirds of patients include flatulence, bloating, abdominal cramping, diarrhea. Some studies also suggest nausea and constipation. [2] HPI too is frequently reported with flatulence, bloating, abdominal

cramping, and nausea. [3] This significant symptom overlap between reported symptoms of SIBO and HPI might, in some patients, be due to co-existence of both conditions.

DIAGNOSIS:

Testing for HPI is clinically indicated in patients with dyspepsia, atrophic gastritis, unexplained iron deficiency anemia, current or past history of peptic ulcer disease, chronic non-steroidal anti-inflammatory use, gastric cancer or gastric mucosa associated lymphoid tissue lymphoma or idiopathic thrombocytopenic purpura. [3,12,26] Confirmation of HPI 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 biopsy and urea breath tests so should be discontinued prior to testing. [24] 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 HPI should be documented after one month by urea breath test or stool antigen testing. [24-26]

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. With that said, evidence behind both testing and treatment for SIBO is currently low and recommendations remain conditional. [2]

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 75g glucose or 10g 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 minutes 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 co-infection implicated between HPI and SIBO further research is needed to determine if co-treatment of both pathologies is preferred over first eliminating HPI 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 overall success of therapy to be 70.8%. [29] 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 HPI treatment regimens and might serve as a solution to treating co-infection..

Multiple HPI treatment regimens are acceptable for initial infection. Considerations such as penicillin allergy, previous macrolide exposure or high local resistance impact treatment choices. [26] 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 day course of bismuth quadruple therapy consisting of bismuth, tetracycline, PPI and metronidazole. [3] A recent meta-analysis from 2021 however suggest 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. [30] When primary treatment fails, salvage therapy should be tailored to not include previously attempted antibiotics. [26] Based on current

guidelines, bismuth quadruple therapy or levofloxacin containing regimens are preferred salvage therapy options. [3]

Helicobacter pylori is however frequently resistant to metronidazole with highly variable local resistance rates between 10-90%. [30,31] One study comparing treatment eradication in HPI 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 rifaximin containing regimens are acceptable, further studies are required to determine the best treatment option.

CONCLUSION

Based on current literature review, SIBO appears to have an elevated prevalence in patients with HPI compared to the general population. [7,14] While the "test and treat" strategy [13] for HPI in patients with dyspepsia has been validated, no clear recommendations currently exist for testing/treating SIBO in patients with HPI. Several extra-gastrointestinal conditions appear to be associated with both SIBO and HPI [15-21] and dysbiosis due to the attempted treatment for HPI may be related to the microbiome mediated pro-inflammatory state. It is therefore important to recognize the signs and symptoms of HPI and treat the infection as well as the associated dysbiosis as persistence of gastrointestinal symptoms despite eradication of HPI could suggest coinfection of SIBO.

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