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INVITED COMMENTARY

Antibiotics for Dyspepsia: Hp, SIBO, IMO, or Something Else?

Will Takakura[1]

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Since the dawn of humankind, the gastric pathogen *Helicobacter pylori* (Hp) has coexisted with humanity, migrating and dispersing throughout the globe following our footprints (or more precisely, our stomachs). Although Its contribution to gastric cancer pathogenesis is unquestioned, accounting for almost 75% of the global burden of gastric cancer [1], its involvement in non-ulcerative dyspepsia is somewhat disputed. A recent meta-analysis reported that the association of dyspepsia with Hp is rather modest with an OR = 1.18; 95% (CI 1.04–1.33) [2]. Nevertheless, for patients with dyspepsia, a routine test and treat strategy for Hp is commonly employed. As expected, the efficacy is somewhat modest with a NNT of 9 for symptom relief [3]. In practice, symptoms typically recur after treatment despite documented eradication of the organism, with symptom relief for over three months achieved in only 30% of patients [3]. There has always been a question as to whether the eradication of Hp is what improves symptoms or rather that the improvement is due to the modulation of other pathological gut microbes. The latter may explain the high symptom recurrence rate after Hp treatment given that the recurrence rate of Hp itself is low [4].

In this issue of *Digestive Diseases and Sciences*, Wang et al. evaluated the overlap between Hp and small intestinal bacterial overgrowth (SIBO) [5], a condition that is arguably associated with dyspepsia [6]. They studied 102 subjects who had undergone urea breath test and concomitantly performed a lactulose breath test. They found that both SIBO and intestinal methanogen overgrowth (IMO) were highly prevalent amongst those with Hp, with 49.1% vs 24.5%, respectively, ($P = 0.019$) for SIBO and 24.5% vs 8.2%, respectively, ($P = 0.027$) for IMO. In this population, symptoms assessed by the Gastrointestinal Symptom Rating Score (GSRS) was no different between those who were Hp positive vs Hp negative ($P = 0.21$). Nevertheless, within subjects with Hp, the GSRS were numerically higher for those with SIBO compared with those without SIBO or IMO (GSRS = 2, IQR 2; 3 vs GSRS = 2, IQR 1–2, $P = 0.102$), and significantly higher with IMO (GSRS = 2, IQR 2–3 vs GSRS = 2, IQR 1–2, $P = 0.02$).

These data are consistent with previous studies reporting a modest association between dyspepsia and Hp, with others reporting no association [2]. Furthermore, there have been similar studies published by other groups that reported that symptoms are more closely associated with higher levels of hydrogen as measured by the hydrogen breath test rather than urea levels as measured by the urea breath test [7]. These data suggest that symptoms may be more associated with SIBO or IMO in those infected with Hp. It is also very interesting, but somewhat expected, that Hp subjects experienced different types of symptoms based on whether or not they were positive for SIBO or IMO.

Lastly, Wang et al. showed the changes in symptoms for those who were prescribed bismuth quadruple therapy, reporting a 100% eradication rate for Hp, which is higher than expected. In this cohort, the GSRS score dropped from 2, IQR 1–3 to 0, IQR 0–1, $P < 0.001$. This appears to conflict with a recent meta-analysis showing that improvement in symptoms did not correlate with Hp eradication [3]. Perhaps the length of follow-up accounts for this difference; a longer follow-up may have seen a rebound in GSRS.

Given its short follow up duration, the authors did not assess symptom recurrence after 6 weeks. Future studies should follow patients for a longer duration (perhaps over 6 months), evaluating the rate of symptom recurrence in comparison to SIBO, IMO and Hp recurrence. A longitudinal study with a repeat course of antibiotics may help elucidate if the symptomatic improvement correlates best with Hp, SIBO, IMO, or some other bacterial dysbiosis with a normal lactulose breath test. Of note, Wang et al. also reported that patients with IMO and Hp had a larger reduction in GSRS compared with those without SIBO or IMO and Hp, suggesting that IMO may contribute more to

✉ Will Takakura
rtakakura826@gmail.com

[1] Division of Gastroenterology, Department of Medicine, University of Michigan, Ann Arbor, USA

symptom generation, though this study is not powered to make such conclusions.

There is some biological plausibility for dyspepsia causing SIBO. Functional dyspepsia can develop after an enteric infection; SIBO also appears to develop after a bout of infectious gastroenteritis such as with *Campylobacter jejuni* [8]. Cytolethal distending toxin B (CdtB) is one of the heterotrimeric toxins that are produced by many gram-negative pathogens that by molecular mimicry induce antibodies to vinculin, a cytoskeletal protein that localizes to the interstitial cells of Cajal (ICC) in some patients. Since the ICC are considered to be the intestinal pacemaker cells, vinculin antibodies are hypothesized to disrupt normal gastrointestinal motility and lead to SIBO. In human stomach, increased levels of anti-vinculin may be inversely associated with the number of gastric ICC [9]. Whether this decrease in ICC number leads to dysmotility and resultant SIBO/IMO and dyspepsia is not clear. Of course, given that these are associations, causality is merely inferred; it is equally plausible that SIBO and IMO are merely harmless consequences of dysmotility and that the antibiotics are treating another organism that are completely unrelated to SIBO or IMO. Future studies incorporating the testing of duodenal aspirates from dyspeptic patients with SIBO and IMO, and also using animal models, microfluidic devices, and *ex vivo* models, may better elucidate causality [10].

In summary, although it is commonplace to evaluate and treat for Hp, this practice has only been met with modest success. Since the eradication of Hp has not been consistently associated with improvement in dyspepsia, there may be other gut microbes that may be responsible for symptom generation. Since SIBO and IMO could be incorporated into plausible mechanisms, at least in a subset of this population, their involvement should be further investigated.

References

1. Amieva M, Peek RM Jr. Pathobiology of *Helicobacter pylori*-induced gastric cancer. *Gastroenterology.* 2016;150:64–78.
2. Ford AC, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. *Gut.* 2015;64:1049–1057.
3. Ford AC, Tsipotis E, Yuan Y, Leontiadis GI, Moayyedi P. Efficacy of *Helicobacter pylori* eradication therapy for functional dyspepsia: updated systematic review and meta-analysis. *Gut.* 2022. https://doi.org/10.1136/gutjnl-2021-326583.
4. Hu Y, Wan JH, Li XY, Zhu Y, Graham DY, Lu NH. Systematic review with meta-analysis: the global recurrence rate of *Helicobacter pylori*. *Aliment Pharmacol Ther.* 2017;46:773–779.
5. Wang X, Zhu D, Li S, Dai Y, Teng G, Wang W. The influence of *Helicobacter pylori* infection and eradication on small intestinal bacterial overgrowth and abdominal symptoms. *Dig Dis Sci.* 2023. https://doi.org/10.3389/fcimb.2023.1257817.
6. Gurusamy SR, Shah A, Talley NJ et al. Small intestinal bacterial overgrowth in functional dyspepsia: a systematic review and meta-analysis. *Am J Gastroenterol.* 2021;116:935–942.
7. Konrad P, Chojnacki J, Gasiorowska A, Rudnicki C, Kaczka A, Chojnacki C. Therapeutic efficacy of amoxicillin and rifaximin in patients with small intestinal bacterial overgrowth and *Helicobacter pylori* infection. *Prz Gastroenterol.* 2018;13:213–217.
8. Pimentel M, Morales W, Pokkunuri V et al. Autoimmunity links vinculin to the pathophysiology of chronic functional bowel changes following *Campylobacter jejuni* infection in a rat model. *Dig Dis Sci.* 2015;60:1195–1205.
9. Kim JH, Nam SJ, Park SC et al. Association between interstitial cells of Cajal and anti-vinculin antibody in human stomach. *Korean J Physiol Pharmacol.* 2020;24:185–191.
10. Taebnia N, Romling U, Lauschke VM. In vitro and ex vivo modeling of enteric bacterial infections. *Gut Microbes.* 2023;15:2158034.