



been demonstrated to exhibit such inhibitory activity on *H. pylori* include lactic acid from *Lactobacillus acidophilus* LB, *Lactobacillus johnsonii* La 1, *Lactobacillus salivarius* and *Lactobacillus casei*, bacteriocins from *Wissella confusa*, *Lactobacillus lactis*, and *Bacillus subtilis*.^{10,11} Another metabolite, reuterin, produced by *Lactobacillus reuteri* ATCC 55730, has also been suggested to suppress *H. pylori* load in humans.^{10,11}

Probiotics may also inhibit adhesion of *H. pylori* to the gastric epithelium, a step in which the pathogen achieves to interact with epithelial cells to effect inflammatory processes and other associated diseases.^{10,11} The mechanism of adhesion inhibition could be by direct competition, like in the case of *Weissella confusa* strain PL9001.¹⁰ Another mechanism can be by changing the structure of adhesion sites, like how neuraminidase activity expressed by *Saccharomyces boulardii* could remove surface α -2,3-linked sialic acid (ligand of *H. pylori* adhesin), thereby inhibiting adhesion of *H. pylori* to duodenal epithelial cells.¹⁰ Antimicrobial substances of certain strains such as *Lactobacillus acidophilus* LB and *Lactobacillus johnsonii* La1 can also play a part in exerting their anti-adhesion activity.¹⁰ The last mechanism found to be related to probiotics' effect on *H. pylori* is in the regulation of mucin expression. Studies on *Lactobacillus plantarum* strain 299v, *Lactobacillus rhamnosus* GG and *Bifidobacterium bifidum* BF-1 have shown that these strains have the capacity to enhance gene expression of various mucin genes, therefore promoting the strengthening of the gastric mucosal barrier that serves as a defence against the adhesion of *H. pylori*, among many pathogenic bacteria.^{10,11}

With such mechanistic findings of probiotics, how does it translate to clinical efficacy? Studies conducted are generally on bifidobacteria, lactobacilli and *Saccharomyces boulardii* and many meta-analyses have been performed to address this question. A meta-analysis pooling results of studies on lactobacilli and bifidobacteria as a whole have shown that these probiotics improved *H. pylori* eradication rates and decreased incidence of side effects¹²; however these findings need to be interpreted carefully, given that effects of probiotics are understood to be strain-specific. One meta-analysis by McFarland et al¹⁰ examining single-strain probiotics for the eradication of *H. pylori* and prevention of adverse events found *Saccharomyces boulardii* to be

significantly effective as an adjunct for *H. pylori* eradication, reducing adverse events (including antibiotic-associated diarrhoea) associated with eradication therapy, which *Lactobacillus rhamnosus* GG was the only other strain that reduced incidence of associated antibiotic-associated diarrhoea. In another meta-analyses by Dang et al¹³, among studies investigating the effectiveness of single strain probiotic supplementation, 4 specific strains were found to be effective in improving *H. pylori* eradication rates. These strains were *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus gasseri* and *Bifidobacterium infantis* 2036. An interesting observation by the authors were that probiotic supplementation is only found to be useful in eradication regimens that yielded eradication rates of less than 80%. In terms of the impact of probiotics on side effects experienced from eradication therapy, this was not reported in one-third of the trials included in the analysis. With the data available, it was found that only *Saccharomyces boulardii* showed a significant reduction in side effects experienced from eradication therapy.¹³

Meta-analyses have also been performed with consideration of the duration and type of *H. pylori* eradication therapy received by patients. Wang et al reported that their analyses found *Lactobacillus acidophilus*, *Saccharomyces boulardii* and probiotic mixtures containing *Lactobacillus*, *Bifidobacterium* and *Enterococcus* to be significant in enhancing efficacy of 7-day, 10-day and 14-day triple therapy. Probiotic mixtures of *Lactobacillus*, *Bifidobacterium* and *Enterococcus* were also found to be significant in improving eradication rates of 10-day sequential therapy and 7-day quadruple therapy.¹⁴ As a whole, probiotics were reported to significantly reduce the incidence of adverse events related to eradication therapy as well, by as much as 50%.

With growing interest in the positive impact of probiotics in the management of *H. pylori* infection, the encouraging results thus far is just the beginning. The challenge in elucidating the effects of probiotics in *H. pylori* management lies in the differences in the data captured by studies, e.g. the types of probiotic strains and combinations used, incidence of adverse events, etc. Many questions remain to be answered, in terms of the optimal dosages of probiotic strains, duration of use, timing of use (before, during or extending beyond eradication regimens).



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Message from the Editor

20th Edition

What are FGIDs & are they common patient complaints in your practice?

Dr Kewin Siah, a consultant of the division of Gastroenterology & Hepatology at NUH has kindly shared a case-based article on Functional Gastrointestinal Disorders from an Asian perspective involving 11 centres in Asia.

The role of probiotics in gestational diabetes mellitus & *Helicobacter pylori* management are also worthy of your "Read" time in this newsletter.

God bless!

Melvin Wong
Editor-in-chief

The Asian Functional Gastrointestinal Disorder: Time for Probiotic Trials in Asian Functional Bowel Phenotypes

By **Dr Kewin Siah**

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Case Study A:

Mr. A is a 30-year-old Chinese school teacher who complains of frequent "gastritis" after meals. There is otherwise no heartburn or regurgitation symptoms. He had normal gastroscopy with negative CLO test the year before. He has been diagnosed with functional dyspepsia by his doctor. He came to see you because he has been having more severe upper abdominal pain. He is currently on antacids and proton pump inhibitors. On further history, he claimed that he opened his bowel every 1 to 2 days with occasional hard stools and straining.

What is your diagnosis and how would you manage him?

Case Study B:

Miss B is a 45-year-old lady who is currently unemployed. She previously worked as an accountant but had to stop working because of her bowel problems. She suffers from regular epigastric discomfort and fullness. She described an irregular bowel habit with worse bowel urgency

symptoms right after spicy or oily food. There were a few occasions that she suffered from bowel incontinence. She went to see a surgeon, her colonoscopy was normal and she was started on the charcoal pill. Now she does not eat out and has been staying at home for 1 year. She came to see you today because she said that her abdominal pain is getting worse.

What is your diagnosis and how would you manage her?

Functional gastrointestinal disorders (FGIDs) are common diseases affecting a large proportion of the population. There are no biomarkers that can reliably distinguish FGIDs from other gastrointestinal diseases. The current subclassification system by the Rome committee was developed initially through a process of expert clinical observations, systematic reviews and Delphi consensus building. However, the poor representation of Asian experts on the committee and its ever-changing classification make it difficult for Asian physicians to understand and diagnose FGIDs with confidence.

In 2017, a group of Asian FGIDs experts performed a study that was carried out in 11 centers (Bangkok, Guangzhou, Hyderabad, Ipoh, Jakarta, Lucknow, Manila, Seoul, Singapore, Taipei, and Wuhan) across Asia to identify FGIDs symptom clusters in Asia. A total of 1805 FGIDs patients completed the study. In this large cohort of Asian patients, nine dominant symptom clusters were identified. The result was published in Gut last year.¹

Asian FGIDs Symptom Clusters¹

Factors	Symptom Clusters
F1	Constipation and anorectal pain
F2	Diarrhoea and abdominal pain
F3	Meal-related bowel symptoms
F4	Diarrhoea, urgency and incontinence
F5	Bloating, fullness, belching and flatulence
F6	Globus, odynophagia and dysphagia
F7	Constipation and upper abdominal pain
F8	Nausea, vomiting and regurgitation
F9	Chest pain and heartburn

There were 5 bowel-related symptoms clusters.

- Two anorectal factors:
 - F1: The feeling of obstructed defecation with anorectal pain or pressure associated with straining, tensing, difficulty relaxing to allow stool to pass and a need to manually evacuate stool
 - F4: Diarrhoea with urgency and incontinence
- Three bowel factors with Irritable Bowel Syndrome(IBS)-like symptoms:
 - F2: Abdominal pain or discomfort started with more frequent or looser stools with improvement of symptom after bowel movement

F3: Epigastric pain or burning affected by eating, which was better after bowel movement or passing gas, and preceded by a change in the number of bowel movements
 F7: Upper abdominal pain or discomfort associated with passing less frequent or passing harder stools

F7 Constipation and upper abdominal pain

F7 represents a unique constipation symptom cluster. Patients suffer from this cluster often present with either mid or upper abdominal pain. Bouchoucha et al studied the relationship between pain localization and FGIDs. They reported that IBS-C was associated with left flank pain and Functional Constipation was more likely to report pain in the right hypochondrium.²

In our case study, Mr. A was suffering from upper abdominal pain secondary to chronic constipation. Patients often refer to epigastric pain as pain in the upper gastrointestinal system; in particular, the stomach. It is important to highlight the association as this may help clinicians to avoid misdiagnosing these patients as having dyspepsia or gallbladder disease and to avert inappropriate invasive investigations and surgery. Identifying the constipation-type bowel disturbance in this group may allow for a therapeutic trial of laxatives or prokinetics to demonstrate impaired intestinal transit as a putative pathophysiology. For a full and comprehensive review of chronic constipation management at the primary care level, I refer the readers to the paper by Prof Gwee Kok Ann Primary Care Management of Chronic Constipation in Asia: The ANMA Chronic Constipation Tool published by Journal Neurogastroenterol Motility 2013.³



Important Constipation History:

Alert Symptoms

- Bloating or fullness
- Difficult to pass stools
- Need for laxative
- Constipation symptoms*

*Constipation Symptoms

- Straining
- Bristol Stool Form types 1, 2 or 3
- Sensation of incomplete evacuation
- Sensation of infrequent defecations
- Anorectal blockage
- Digitation



F3 Meal-related bowel symptoms

Many patients attribute their symptoms to food-triggers. Patients report that their symptoms worsen after eating certain foods. This phenomenon is often described as Irritable Bowel Syndrome-Functional Dyspepsia (IBS-FD) overlap in the literature. The fine print of the Rome III FD criteria requires that patients with epigastric pain must not report relief with passing stool or flatus, presumably to avoid misdiagnosing potential IBS as FD. A pronounced gastro-colic reflex could account for the meal association, while the pain relief after defecation points to its origin in the colon. It is important to take a proper food history from Miss B. A suitable diet management might include the following measures: a diet low in fermentable oligo-, di- and monosaccharides and polyols (FODMAPs), limitation or exclusion of gas-producing foods and/or lactose and gluten and fiber supplementation in selected cases. Foods associated with an increase in intestinal gas and flatulence include alcohol, apricots, bagels, bananas, beans, Brussels sprouts, caffeine, carrots, celery, onions, pretzels, prunes, raisins and wheat germ, and should be avoided.

Usefulness of Probiotics in Asian FGIDs Symptom Clusters?

Frankly speaking, due to the strict criteria of research methodology, the above 2 cases would not be qualified for the traditional IBS-C or IBS-D studies. New studies need to be done to check the efficacy of probiotics in each of the new Asian FGIDs symptom clusters. In my own experience, probiotics may be useful in treating the urgency symptom of meal-related bowel phenotype as well as gas symptom clusters with bloating, fullness, belching and flatulence. More studies are needed to elucidate the role of IBS in idiopathic constipation.

The classical ROME diagnostic criteria may not encompass all the FGIDs symptom clusters that we see in our Asian clinic. The Asian FGIDs enable us to make a more detailed classification of local patients and hopefully more effective treatment in the future. A consideration needs to be made regarding how Asian FGIDs patients normally present. It is important to encourage physicians to take a broader approach to history taking, encompassing a detailed bowel history, meal association, and overlap between different FGIDs.

Should women with gestational diabetes mellitus use probiotics?

By **Prof. Dr. Paul Enck**
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Gestational diabetes mellitus (GDM) is one of the most frequent metabolic complications of pregnancy and its prevalence is up to 12% in developed countries. Nowadays, several studies are investigating new therapies for glucose control that may complement diet, exercise, and pharmacological therapies. Among them, probiotics potentially represent a novel way to improve maternal metabolic and pregnancy outcomes. However, there are scarce randomized controlled trials (RCTs) to date that have directly investigated the glycemic effects of probiotics among women with GDM. In addition, the studies that have been completed have reported a mix of positive and null outcomes. Noticeably, studies that investigate the effect of probiotics when taken after diagnosis of GDM are scarce.

A recent double-blind placebo-controlled RCT, which was led by Dr. Mehran Mesgari Abbasi from the Drug Applied Research Centre at Tabriz University of Medical Sciences in Iran, found that a probiotic capsule taken once daily for 8 weeks may affect glucose metabolism and weight gain among pregnant women with GDM.⁴

Briefly, 64 pregnant women with GDM were randomized to a daily probiotic (*Lactobacillus acidophilus* LA-5, *Bifidobacterium* BB-12, *Streptococcus thermophilus* STY-31 and *Lactobacillus delbrueckii bulgaricus* LBY-27 at a target dose of $> 4 \times 10^9$ colony-forming units) or placebo capsule along with dietary advice for 8 consecutive weeks. Fasting blood samples were collected before and after the intervention. Primary outcomes were the women's trend of weight gain and glucose metabolism indices, which included fasting blood glucose, fasting serum insulin, homeostasis model assessment insulin resistance (HOMA-IR) index, and quantitative insulin sensitivity check (QUICKI) index.

In the last 2 weeks of the study, the weight gain in the probiotic group was significantly lower than in the placebo group. Regarding glucose metabolism indices, fasting blood glucose and HOMA-IR index in the probiotic group significantly decreased over the study period. However, the post-intervention insulin sensitivity index in the probiotic group was not significantly different

from placebo.

In conclusion, probiotic supplementation seems to have a beneficial effect on weight gain and glucose metabolism among pregnant women with GDM. However, whether the outcomes in maternal metabolic parameters detected in this study can translate to clinically meaningful outcomes deserves further randomized trials. With more study, researchers may fully elucidate the potential effect of probiotics among this important obstetric group at risk of future metabolic syndrome.

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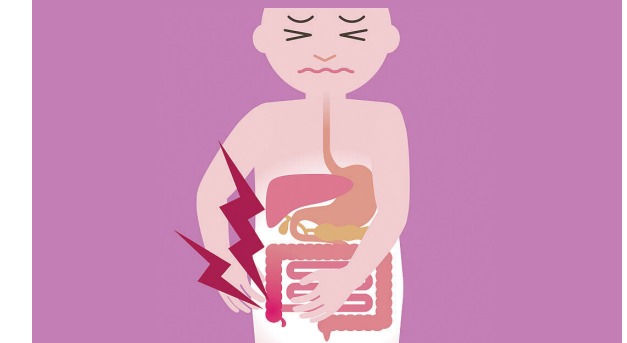


Research Updates

Appendix may have important function, new research suggests

The human appendix, a narrow pouch that projects off the caecum in the digestive system, has a notorious reputation for its tendency to become inflamed (appendicitis), often resulting in surgical removal. Although it is widely viewed as a vestigial organ with little known function, recent research suggests that the appendix may serve an important purpose. In particular, it may serve as a reservoir for beneficial gut bacteria.

Retrieved from: *Midwestern University. "Appendix may have important function, new research suggests." ScienceDaily. ScienceDaily, 9 January 2017.*



Probiotics: An option for *Helicobacter pylori* management?

By **Tay Jia Yuan**, Executive Editor

Helicobacter pylori infection is a common chronic bacterial infection worldwide, affecting about 30% of children and 60% of adults.^{5,6} With colonisation by *H. pylori* having a role in development of peptic ulcer disease and gastric malignancies such as gastric adenocarcinoma and lymphoma involving mucosa-associated lymphoid tissue, its eradication is a goal in therapy for affected patients.^{5,7,8} Increasing evidence is also showing a relationship between *H. pylori* and unexplained iron deficiency anaemia, idiopathic thrombocytopenic purpura and vitamin B12 deficiency.^{8,9} Spontaneous clearance of *H. pylori* is relatively rare once the pathogen is acquired.⁸ In Singapore, seroprevalence rate of *H. pylori* stands at 31%.⁷ Concern over *H. pylori* management also stems from the trend of increasing antibiotic resistance to agents currently recommended for eradication therapy, thereby decreasing the efficacy of these regimens.^{5,7,9} It should be noted that antibiotic resistance patterns vary across different geographical regions too. It was reported that the local *H. pylori* resistance profile in the time periods of 2000-2002 and 2012-2014 showed an upward trend in the resistance rate to clarithromycin (7.9% to 17.1%), metronidazole (24.8% to 48.2%) and levofloxacin (5.0 to 14.7%), while resistance to amoxicillin (3.0% to 4.1%) and tetracycline (5.0% to 7.6%) remained low.⁷

Apart from the sensitivity profile of *H. pylori* strain to the treatment regimens, patient adherence and tolerance to side effects are also contributing factors to successful eradication.⁵ With these concerns surrounding management of *H. pylori* infection, many are looking into the potential of probiotics to complement and enhance the effect of eradication regimens. Studies looking into the effect of probiotics against *H. pylori* infection have shed light on various mechanisms of action of some common bacterial strains. Adverse effects of eradication regimens, like diarrhoea or colitis, have been suggested to be ameliorated by probiotics, by restoring the normal microbiota.¹⁰ One potential effect of probiotics is in its immunomodulating mechanism, by diminishing cytokine reactions triggered by *H. pylori*, with current evidence focused on lactobacilli, like *Lactobacillus bulgaricus*, *Lactobacillus acidophilus* and *Lactobacillus plantarum* B7.^{10,11} Antimicrobial substances secreted by probiotics have also been proposed to be a mechanism through which growth of *H. pylori* is inhibited. Secretory products that have