ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2022 February 21; 28(7): 693-774

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 28 Number 7 February 21, 2022

World Journal of Gastroenterology

Weekly Volume 28 Number 7 February 21, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Madhusudana Girija Sanal, MBBS, PhD, Academic Fellow, Assistant Professor, Department of Molecular and Cellular Medicine, Institute of Liver and Biliary Scieneces, New Delhi 110070, Delhi, India. sanalmg@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for *WJG* as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The *WJG*'s CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE

February 21, 2022

INSTRUCTIONS TO AUTHORS

https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS

https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS

https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT

https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE

https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION

https://www.f6publishing.com

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2022 February 21; 28(7): 766-774

DOI: 10.3748/wjg.v28.i7.766

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LETTER TO THE EDITOR

Gastrointestinal microbiome and *Helicobacter pylori*: Eradicate, leave it as it is, or take a personalized benefit–risk approach?

Stanislav Sitkin, Leonid Lazebnik, Elena Avalueva, Svetlana Kononova, Timur Vakhitov

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mincione G, Wen XL, Xiao Y

Received: August 13, 2021
Peer-review started: August 13, 2021
First decision: September 4, 2021
Revised: September 17, 2021
Accepted: January 20, 2022
Article in press: January 20, 2022
Published online: February 21, 2022

Stanislav Sitkin, Elena Avalueva, Department of Internal Diseases, Gastroenterology and Dietetics, North-Western State Medical University Named After I.I. Mechnikov, St. Petersburg 191015, Russia

Stanislav Sitkin, Svetlana Kononova, Timur Vakhitov, Non-Infectious Disease Metabolomics Group, Institute of Experimental Medicine, St. Petersburg 197376, Russia

Stanislav Sitkin, Epigenetics and Metagenomics Group, Institute of Perinatology and Pediatrics, Almazov National Medical Research Centre, St. Petersburg 197341, Russia

Leonid Lazebnik, Department of Outpatient Therapy, A.I. Yevdokimov Moscow State University of Medicine and Dentistry, Moscow 127473, Russia

Svetlana Kononova, Institute of Protein Research, Russian Academy of Sciences, Pushchino, Moscow region 142290, Russia

Corresponding author: Stanislav Sitkin, MD, PhD, Associate Professor, Senior Researcher, Department of Internal Diseases, Gastroenterology and Dietetics, North-Western State Medical University named after I.I. Mechnikov, Kirochnaya Street, 41, St. Petersburg 191015, Russia. drsitkin@gmail.com

Abstract

Helicobacter pylori (*H. pylori*) is generally regarded as a human pathogen and a class 1 carcinogen, etiologically related to gastric and duodenal ulcers, gastric cancer, and mucosa-associated lymphoid tissue lymphoma. However, *H. pylori* can also be regarded as a commensal symbiont. Unlike other pathogenic/opportunistic bacteria, *H. pylori* colonization in infancy is facilitated by T helper type 2 immunity and leads to the development of immune tolerance. Fucosylated gastric mucin glycans, which are an important part of the innate and adaptive immune system, mediate the adhesion of *H. pylori* to the surface of the gastric epithelium, contributing to successful colonization. *H. pylori* may have beneficial effects on the host by regulating gastrointestinal (GI) microbiota and protecting against some allergic and autoimmune disorders and inflammatory bowel disease. The potential protective role against inflammatory bowel disease may be related to both modulation of the gut microbiota and the immunomodulatory properties of *H. pylori*. The inverse association between *H. pylori* and some potentially proinflammatory and/or procarcinogenic bacteria may suggest it regulates the GI microbiota. Eradication of *H. pylori* can cause various adverse effects and alter the GI microbiota, leading to short-term or long-term dysbiosis.

Overall, studies have shown that gastric Actinobacteria decrease after *H. pylori* eradication, Proteobacteria increase during short-term follow-up and then return to baseline levels, and Enterobacteriaceae and *Enterococcus* increase in the short-term and interim follow-up. Various gastric mucosal bacteria (*Actinomyces*, *Granulicatella*, *Parvimonas*, *Peptostreptococcus*, *Prevotella*, *Rothia*, *Streptococcus*, *Rhodococcus*, and *Lactobacillus*) may contribute to precancerous gastric lesions and cancer itself after *H. pylori* eradication. *H. pylori* eradication can also lead to dysbiosis of the gut microbiota, with increased Proteobacteria and decreased Bacteroidetes and Actinobacteria. The increase in gut Proteobacteria may contribute to adverse effects during and after eradication. The decrease in Actinobacteria, which are pivotal in the maintenance of gut homeostasis, can persist for > 6 mo after *H. pylori* eradication. Furthermore, *H. pylori* eradication can alter the metabolism of gastric and intestinal bacteria. Given the available data, eradication cannot be an unconditional recommendation in every case of *H. pylori* infection, and the decision to eradicate *H. pylori* should be based on an assessment of the benefit–risk ratio for the individual patient. Thus, the current guidelines based on the unconditional "test-and-treat" strategy should be revised. The most cautious and careful approach should be taken in elderly patients with multiple eradication failures since repeated eradication can cause antibiotic-associated diarrhea, including severe *Clostridioides difficile*-associated diarrhea and colitis and antibiotic-associated hemorrhagic colitis due to *Klebsiella oxytoca*. Furthermore, since eradication therapy with antibiotics and proton pump inhibitors can lead to serious adverse effects and/or dysbiosis of the GI microbiota, supplementation of probiotics, prebiotics, and microbial metabolites (*e.g.*, butyrate + inulin) should be considered to decrease the negative effects of eradication.

Key Words: *Helicobacter pylori*; Eradication; Gastrointestinal microbiota; Dysbiosis; Fucosylated glycan; Inflammatory bowel disease

Core Tip: *Helicobacter pylori* (*H. pylori*) is generally regarded as a human pathogen, but it can act as a commensal symbiont. *H. pylori* colonization may have beneficial effects on the host by regulating gastrointestinal microbiota and protecting against some allergic and autoimmune disorders and inflammatory bowel disease. *H. pylori* eradication can cause various adverse effects and alter the gastrointestinal microbiota, leading to dysbiosis. Therefore, eradication cannot be an unconditional recommendation in every case of *H. pylori* infection, and the therapeutic decision should be based on a personalized assessment of the benefit *vs* risk.

Citation: Sitkin S, Lazebnik L, Avalueva E, Kononova S, Vakhitov T. Gastrointestinal microbiome and *Helicobacter pylori*: Eradicate, leave it as it is, or take a personalized benefit–risk approach? *World J Gastroenterol* 2022; 28(7): 766-774
URL: https://www.wjgnet.com/1007-9327/full/v28/i7/766.htm
DOI: https://dx.doi.org/10.3748/wjg.v28.i7.766

TO THE EDITOR

We read with great interest the article by Niu *et al*[1], which showed that the effectiveness of quadruple *Helicobacter pylori* (*H. pylori*) eradication therapy containing bismuth depended on the gastric microbiota, and a high rate of *H. pylori* eradication was associated with the presence of *Rhodococcus*, *Lactobacillus*, and *Sphingomonas*, which were significantly enriched in the gastric mucosa in the successful eradication group[1]. The role of lactobacilli, mainly beneficial bacteria, in *H. pylori* infection, including eradication, has been well studied[2]. However, the authors showed for the first time the importance of *Rhodococcus* and *Sphingomonas*, which are more likely to be opportunistic or pathobiont species with unclear functions in the human gastrointestinal (GI) tract[3,4], in successful eradication of *H. pylori*[1]. It is noteworthy that in gastric cancer (GC), when the abundance of *H. pylori* decreased, several taxa (including *Rhodococcus* and *Lactobacillus*, discussed by Niu *et al*[1]) in the gastric mucosa significantly increased, which may indicate their potential involvement in GC after *H. pylori* infection[5]. In addition, *H. pylori* was negatively correlated with some opportunistic bacteria/pathobionts such as *Haemophilus*, *Streptococcus*, *Neisseria*, and *Fusobacterium* in the success group[1]. The results obtained by Niu *et al*[1] may suggest that *H. pylori* competes not so much with beneficial bacteria as with pathobionts, and eradication may ultimately worsen the gastric microbiota.

Indeed, not only does the composition of the gastric microbiota affect *H. pylori* eradication, but eradication significantly affects the microbiota of both the stomach and intestine, which can lead to marked and long-term dysbiotic changes. Dysbiosis of the microbiota after *H. pylori* eradication can be caused by many factors: by the action of antibiotics and proton pump inhibitors; by the loss of *H. pylori* leading to changes in the immune response of the GI mucosa; and by changes in the microenvironment of the GI tract, including those in microbial metabolic pathways and changes in gastric acidity associated with both pharmacotherapy and loss of *H. pylori*[6,7]. Features of the dysbiotic changes, their duration, and the rate of restoration of the disturbed microbiota vary greatly in different studies.

Diverse effects of H. pylori eradication on gastric and intestinal microbiota

Recent studies have demonstrated not only short-term but also long-term (≥ 6 mo) changes in the gastric microbiota after *H. pylori* eradication. In about half of cases (52.3%), eradication led to the predominance of proinflammatory *Acinetobacter* in gastric corpus mucosa with a decrease in microbial diversity in patients with endoscopic follow-up for > 1 year[8]. An earlier study showed that *Acinetobacter* was enriched in patients with persistent gastric inflammation 1 year after *H. pylori* eradication[9]. Moreover, some bacteria in the gastric mucosa (*Actinomyces*, *Granulicatella*, *Parvimonas*, *Peptostreptococcus*, *Prevotella*, *Rothia*, and *Streptococcus*), which are predominantly of oral origin, were associated with precancerous gastric lesions (atrophy and/or intestinal metaplasia) 1 year after *H. pylori* eradication[9]. *Actinomyces*, whose abundance can increase in the absence of *H. pylori*, might significantly increase the risk of GC [10]. Thus, some studies demonstrated a contribution of various gastric bacteria to precancerous gastric lesions after *H. pylori* eradication[9]. In general, Actinobacteria decreased after *H. pylori* eradication, Proteobacteria increased during short-term follow-up and then returned to baseline levels, and Enterobacteriaceae and *Enterococcus* increased in the short-term and interim follow-up[11]. Alternatively, it has been shown that in regions with high GC risk, *H. pylori* is one of the main factors in gastric dysbiosis and successful eradication can lead to the restoration of gastric microbiota[12].

H. pylori eradication also affects the gut microbiota. Bismuth quadruple therapy leads to short-term dysbiosis of the gut microbiota with an increased abundance of Proteobacteria and decreased abundances of Bacteroidetes and Actinobacteria. The increase in gut Proteobacteria may contribute to adverse effects during eradication therapy[13]. In another study, *H. pylori* eradication was associated with significant alterations in the gut microbiota that did not completely recover 6 wk after treatment [7]. In general, there was a decrease in Actinobacteria, which are pivotal in the maintenance of gut homeostasis, compared with baseline throughout the follow-up (> 6 mo) after eradication[11]. Furthermore, eradication therapy alters microbial functional pathways and the metabolism of gastric and gut bacteria[9,14].

Conversely, other studies showed that successful *H. pylori* eradication exerts beneficial effects on gut microbiota, including increased probiotic *Bifidobacterium* and downregulation of drug-resistance mechanisms[12]. Liou *et al*[15] generally confirmed the long-term safety of *H. pylori* eradication therapy but reported incomplete restoration of microbial diversity after 1 year and clinically irrelevant but significant increases in body mass index (BMI) and body weight at that time.

Interestingly, an increase in body weight/body mass index after *H. pylori* eradication had been identified earlier[16]. Suggested mechanisms of this effect range from an improvement in the symptoms of postprandial dyspepsia[16] to changes in the regulation of leptin and ghrelin[17] mediated by antibiotic-associated changes in the microbiota (especially by the imbalance between bacterial producers of lactate and acetate)[18]. In general, however, the data in various studies are contradictory and indicate weight gain, weight loss, or the absence of an effect of *H. pylori* eradication on body weight; this may be due to differences in the characteristics of the studied populations, such as age, nosology, and composition of the GI microbiota[19]. Further in-depth study of the microbiome-mediated effects of *H. pylori* and eradication therapy on human host metabolism, including nutrient uptake, energy homeostasis, bodyweight, hormone secretion, lipid profile, and glucose homeostasis/glycemic control, will provide clinically important findings for the management of *H. pylori* infection.

H. pylori status and the human gut microbiome

The presence or absence of gastric *H. pylori* can significantly affect the gut microbiota. For example, Nitrospirae were found exclusively in *H. pylori*-negative patients. The role of this phylum, containing nitrite-oxidizing bacteria, in the human microbiome is unclear. In a study by Wang *et al*[20], Nitrospirae were found in the gastric mucosa in all patients with GC but not in patients with chronic gastritis. The authors suggested that these bacteria may be involved in carcinogenesis through enhanced production of N-nitroso compounds. A recent study demonstrated a possible pathogenetic link between enriched colonic Nitrospirae and drug-resistant epilepsy, implying that Nitrospirae can increase nitrite toxicity and cause blood-brain barrier dysfunction[21].

Proinflammatory *Bacteroides ovatus* and *Fusobacterium varium*, associated with ulcerative colitis and adenomatous polyps[22,23] as well as trimethylamine-producing *Clostridium* sp. AT5[24] were enriched in *H. pylori*-negative samples, while *Bacteroides plebeius*, characteristic of the healthy groups (*vs* patients with adenomatous polyps)[23] and butyrate-producing *Eubacterium ramulus* were enriched in *H. pylori*-positive samples[7].

Conversely, *Butyricimonas* spp., including *Butyricimonas virosa*, associated with bacteremia in patients with GI cancer (colon and duodenal adenocarcinomas) and diverticulitis[25] as well as *Bacteroides coprophilus*, specifically enriched in ankylosing spondylitis[26], were enriched in *H. pylori*-positive individuals[7]. Proinflammatory *Prevotella copri*, associated with rheumatoid arthritis and microscopic colitis as well as *Enterobacter cloacae* and *Klebsiella pneumoniae*, pathogens commonly associated with hospital infections, were also enriched in *H. pylori*-positive individuals[27]. Moreover, gut microbial vitamin B_{12} biosynthesis was significantly lower in *H. pylori*-positive individuals compared with *H. pylori* -negative individuals[27]. Dash *et al*[28] showed that the gut microbiota of *H. pylori*-infected individuals was characterized by a significantly increased abundance of *Succinivibrio*, Coriobacteriaceae, Enterococcaceae and Rikenellaceae as well as *Candida glabrata* and other unclassified fungi. The authors suggested a possible role for these *H. pylori*-associated changes in the gut microbiota in intestinal barrier disruption and development of colorectal carcinoma[28].

Potential protective and regulatory role of commensal H. pylori

Currently, *H. pylori* is generally regarded as a human pathogen and a class 1 carcinogen[29], responsible for 15% of the total cancer burden globally and up to 89% of all GC cases[30]. *H. pylori* is etiologically related to gastric and duodenal ulcers and mucosa-associated lymphoid tissue lymphoma. According to current guidelines, it is almost always subject to unconditional eradication based on the "test-and-treat" strategy[31]. However, although *H. pylori* is present in > 50% of the world's population, sequelae of infection occur in only 20% of infected individuals, and malignant complications, such as GC, occur in < 3% of infected people[7]. Therefore, there is also an alternative point of view that *H. pylori* is a commensal symbiont[32,33]. Back in 1998, Blaser[32] wrote that, "*H. pylori* can thus be regarded as indigenous or 'normal' flora, which most humans acquire within the first few years of childhood and then carry for life."

Unlike other pathogenic/opportunistic bacteria, *H. pylori* colonization of newborns/infants is facilitated by T helper type 2 immunity and leads to the development of immune tolerance[34]. Most likely, the co-evolution of *H. pylori* and the human host over millennia has led to the fact that this bacterium is considered a commensal symbiont, not a pathogen, by the host's immune system. This is indirectly confirmed by the fact that α1,2-fucosylated glycans of the GI epithelium, which are an important part of the innate and adaptive immune system (they create a symbiotic environment for the host and microbiota and protect against pathogens), mediate the adhesion of *H. pylori* to the surface of the gastric epithelium, contributing to successful colonization[35]. As a result, early colonization of *H. pylori* can have a positive effect on the host, for example on the regulation of the hormones leptin and ghrelin as well as on protection against some allergic (*e.g.*, asthma) and autoimmune diseases and against inflammatory bowel disease (IBD)[36,34]. The inverse association between *H. pylori* and some potentially proinflammatory and/or procarcinogenic bacteria found in various studies[20,22-24] may suggest a regulatory function of *H. pylori* toward the GI microbiota. The available evidence for beneficial effects of *H. pylori* toward the GI microbiota, as well as potential protective effects against certain diseases, should not be ignored by the gastroenterological community.

Presence of *H. pylori* infection and reduced risk of IBD: Is there a causal relationship? The potential protective role of *H. pylori* in the development of IBD, shown in some studies[37], may be related to both modulation of the gut microbiota and the immunomodulatory properties of *H. pylori*. An inverse association between *H. pylori* and potentially proinflammatory microbes (*Bacteroides ovatus*, *Fusobacterium varium*, *Rhodococcus*, *Sphingomonas*) supports a microbiome-modulating mechanism, while an immunomodulatory mechanism of protection against IBD may involve the activation of colonic mucus production by *H. pylori via* the NLRP3/caspase-1/interleukin-18 axis[38].

We suggest another possibility for the association between *H. pylori* infection and IBD, a non-causal relationship, which relates to the fucosylation status of host mucin glycans in the GIT. Individuals with a non-functional α(1,2)-fucosyltransferase 2 (*FUT2*) gene (they are termed non-secretors), who have loss-of-function mutations, cannot express α(1,2)-fucosylated glycans in the GI mucosa. Non-secretors (about 20% of the population) are more susceptible to infection by some pathogens (*Escherichia coli*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Candida albicans*) and have aberrant gut microbiota, with a reduction of beneficial *Bifidobacterium* spp. The *FUT2* non-secretor phenotype increases susceptibility to Crohn's disease, ulcerative colitis, primary sclerosing cholangitis, celiac disease, psoriasis, Behçet's disease, type 1 diabetes, and so on but at the same time protects against *H. pylori*, which requires fucosylated glycans in the gastric mucosa for adhesion[35,39,40].

A recent study showed that patients with ulcerative colitis and Crohn's disease had decreased *FUT2* expression and α1,2-fucosylation in the colon[41]. In addition, *Fut2* deficiency in the intestinal epithelium exacerbated colitis in epithelium-specific *Fut2* knockout ($Fut2^{\Delta IEC}$) mice, promoted the release of proinflammatory cytokines, and aggravated epithelial barrier damage[41]. The authors demonstrated for the first time that epithelium-specific *Fut2* deficiency increased susceptibility to IBD through modulation of the gut microbiome and microbiota-mediated lysophosphatidylcholine generation. Lysophosphatidylcholine may have deleterious effects on the colon by promoting the release of proinflammatory cytokines, damaging the tight junctions and epithelial barrier in the colon epithelium, and exacerbating colonic inflammation in $Fut2^{\Delta IEC}$ mice[41].

In turn, upregulation of *FUT2*-mediated fucosylation in the intestinal epithelium, for example by exogenous L-fucose, can protect the intestinal barrier, enhance tight junctions, and alleviate intestinal inflammation[42]. Similar to the colon, increased expression of the fucosyltransferase genes *FUT2* and *FUT1* in the gastric epithelium promotes *H. pylori* adhesion and ultimately infection[43]. Thus, we suggest that increased expression of *FUT2* in the gastrointestinal mucosa can simultaneously mediate both *H. pylori* infection and protection against IBD *via* an *H. pylori*-independent mechanism. In this case, a causal relationship between the presence of *H. pylori* and a reduced risk of IBD is unlikely. However, it cannot be ruled out that *H. pylori* mediates the protective effect of fucosylation against IBD by modulation of the gut microbiota or through an immunomodulatory mechanism[38].

Concluding remarks

Given the available data, eradication cannot be an unconditional recommendation in every case of *H. pylori* infection, as in the vast majority of people *H. pylori* is most likely a commensal[32,33], possibly beneficial in mutualistic interaction with the host (for example protecting against some allergic and autoimmune diseases[36]). We join the opinion of Chen *et al*[7] that the decision to eradicate *H. pylori* should be based on an assessment of the benefit–risk ratio for the individual patient. We also support the position of Miller and Williams[44] that "universal eradication" of *H. pylori* may cause more harm than good for the infected persons. Thus, the current guidelines based on the unconditional "test-and-treat" strategy[31] should be revised, including to reduce the excessive number of indications for eradication and to avoid empirical eradication therapy without a previous diagnostic test for *H. pylori* infection.

It may be worth recommending unconditional eradication only in patients with concomitant mucosa-associated lymphoid tissue lymphoma[45] and/or in individuals at high risk of GC, for example in groups of high familial (hereditary) risk[46] or in high-risk areas/populations where eradication effectively reduces the risk of GC[47]. In the latter case, the advisability of such an approach is unquestionable, if it is evidence-based. For example, a recent systematic review and meta-analysis provided moderate-certainty evidence that searching for and eradicating *H. pylori* can reduce the subsequent incidence of GC and death from GC in healthy asymptomatic infected people; the risk of GC decreased by 46% after eradication therapy[48]. However, the authors concluded that as all but one of the eligible trials were conducted in East Asian populations (in China, Japan, or South Korea), and the only trial conducted in a non-Asian population (in Colombia) did not demonstrate any benefit of such an approach, the results of the systematic review cannot be extrapolated to populations outside East Asia [48].

A well-known paradox, the low incidence of GC in some regions of Africa, Asia (*e.g.*, in India), and Latin America with a high prevalence of *H. pylori* infection, also requires in-depth study; this is called the African[49] or Asian/Indian enigma[50]. Although the existence of this phenomenon is sometimes disputed[51], studies have shown that *H. pylori* alone is most likely not enough for the development of GC, even with a high prevalence of highly pathogenic strains. Therefore, it is necessary to take into account not only the virulence factors of *H. pylori* and the oncogenic potential of specific strains of *H. pylori* but also the genetics and ethnicity of the human host population, their dietary habits (including antioxidant and sodium levels), smoking, alcohol consumption, socioeconomic status, and coinfection (parasitoses/helminthiases) modulating the potentially protective T helper type 2 immune response[49,50].

An important factor influencing the serious consequences of *H. pylori* infection appears to be the co-evolution of *H. pylori* and the human host. A recent study demonstrated that the African human ancestry showed clear signs of co-evolution with *H. pylori*, while the European ancestry was maladapted. The Asian ancestry was intermediate but closer to the African ancestry[52]. This supports the hypothesis that *H. pylori* is a commensal symbiont rather than a human pathogen. Hopefully, a series of international prevalence surveys to investigate age-specific prevalence of *H. pylori* in areas of low and high GC risk, namely ENIGMA, recently launched under the auspices of the International Agency for Research on Cancer in Africa (Uganda), Asia (Iran), and Latin America (Chile, Costa Rica), will shed light on the regional characteristics of *H. pylori* infection and identify markers for GC risk stratification to offer reasonable preventive interventions for different populations[53].

In addition, *H. pylori* eradication is likely to be recommended in patients with cancer who are on therapy with immune checkpoint inhibitors or vaccine-based immunotherapy, for example in patients with non-small-cell lung cancer[54].

In patients with diseases negatively associated with *H. pylori*, such as IBD, microscopic colitis, celiac disease, asthma, multiple sclerosis, Barrett's esophagus, esophageal adenocarcinoma, eosinophilic esophagitis, and so on, eradication should be carried out with caution, carefully weighing the risk-to-benefit in each case. Even though *H. pylori* eradication did not affect either the healing rate or the recurrence rate of pre-existing gastroesophageal reflux disease, the possibility of developing new erosive gastroesophageal reflux disease after eradication should always be kept in mind[55].

The most cautious and careful approach should be taken in elderly patients with multiple eradication failures since repeated eradication (second-/third-line therapies) can cause antibiotic-associated diarrhea, including severe *Clostridioides difficile*-associated diarrhea and colitis[56] and antibiotic-associated hemorrhagic colitis due to *Klebsiella oxytoca*[57]. In this regard, we support the recent

conclusion of the American Gastroenterological Association experts that, "after multiple failed eradication attempts, the potential benefits of *H. pylori* eradication should be weighed carefully against the likelihood of adverse effects and inconvenience of repeated high-dose acid suppression and antibiotic exposure, particularly among individuals who are not at an identifiably higher risk of complications from persistent *H. pylori* infection (*e.g.*, GC, peptic ulcer disease); in such scenarios, a shared decision-making approach should be seriously considered, especially in the elderly, those with frailty, and those with intolerance to antibiotics" (Best Practice Advice #9)[30].

Furthermore, since eradication therapy with antibiotics and proton pump inhibitors can lead to serious adverse effects and/or long-term dysbiotic changes in the GI microbiota, the supplementation of probiotics[58-61], prebiotics, and microbial metabolites (*e.g.*, butyrate + inulin)[62] to reduce the negative effects of eradication should be considered[7]. In addition, alternative eradication regimens with limited or no antibiotic use, for example phage-based regimens[63], autoprobiotics[64], and natural agents and methods including traditional Chinese medicine[65], should be proposed, developed, and explored in future studies.

ACKNOWLEDGEMENTS

The authors are grateful to Dr. James Allen for editing a draft of this manuscript.

FOOTNOTES

Author contributions: Sitkin S contributed to the conception, review of literature, and drafting of the manuscript; All authors contributed to the writing and editing of the manuscript and approved the final version of the manuscript.

Supported by the Russian Science Foundation, No. 20-65-47026.

Conflict-of-interest statement: The authors declare no conflict of interest.

Country/Territory of origin: Russia

ORCID number: Stanislav Sitkin 0000-0003-0331-0963; Leonid Lazebnik 0000-0001-8736-5851; Elena Avalueva 0000-0001-6011-0998; Svetlana Kononova 0000-0002-7373-7797; Timur Vakhitov 0000-0001-8221-6910.

Corresponding Author's Membership in Professional Societies: European Crohn's and Colitis Organisation (ECCO), Member ID: 37495.

S-Editor: Wang LL
L-Editor: Filipodia
P-Editor: Wang LL

REFERENCES

1 **Niu ZY**, Li SZ, Shi YY, Xue Y. Effect of gastric microbiota on quadruple *Helicobacter pylori* eradication therapy containing bismuth. *World J Gastroenterol* 2021; **27**: 3913-3924 [PMID: 34321854 DOI: 10.3748/wjg.v27.i25.3913]

2 **Chen YH**, Tsai WH, Wu HY, Chen CY, Yeh WL, Chen YH, Hsu HY, Chen WW, Chen YW, Chang WW, Lin TL, Lai HC, Lin YH, Lai CH. Probiotic *Lactobacillus* spp. act Against *Helicobacter pylori*-induced Inflammation. *J Clin Med* 2019; **8** [PMID: 30646625 DOI: 10.3390/jcm8010090]

3 **Lepage P**, Häsler R, Spehlmann ME, Rehman A, Zvirbliene A, Begun A, Ott S, Kupcinskas L, Doré J, Raedler A, Schreiber S. Twin study indicates loss of interaction between microbiota and mucosa of patients with ulcerative colitis. *Gastroenterology* 2011; **141**: 227-236 [PMID: 21621540 DOI: 10.1053/j.gastro.2011.04.011]

4 **Richard ML**, Liguori G, Lamas B, Brandi G, da Costa G, Hoffmann TW, Pierluigi Di Simone M, Calabrese C, Poggioli G, Langella P, Campieri M, Sokol H. Mucosa-associated microbiota dysbiosis in colitis associated cancer. *Gut Microbes* 2018; **9**: 131-142 [PMID: 28914591 DOI: 10.1080/19490976.2017.1379637]

5 **Ferreira RM**, Pereira-Marques J, Pinto-Ribeiro I, Costa JL, Carneiro F, Machado JC, Figueiredo C. Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota. *Gut* 2018; **67**: 226-236 [PMID: 29102920 DOI: 10.1136/gutjnl-2017-314205]

6 **Lopetuso LR**, Napoli M, Rizzatti G, Scaldaferri F, Franceschi F, Gasbarrini A. Considering gut microbiota disturbance in the management of Helicobacter pylori infection. *Expert Rev Gastroenterol Hepatol* 2018; **12**: 899-906 [PMID: 30040500 DOI: 10.1080/17474124.2018.1503946]

7 **Chen L**, Xu W, Lee A, He J, Huang B, Zheng W, Su T, Lai S, Long Y, Chu H, Chen Y, Wang L, Wang K, Si J, Chen S. The impact of Helicobacter pylori infection, eradication therapy and probiotic supplementation on gut microenvironment homeostasis: An open-label, randomized clinical trial. *EBioMedicine* 2018; **35**: 87-96 [PMID: 30145102 DOI: 10.1016/j.ebiom.2018.08.028]

8 **Shin CM**, Kim N, Park JH, Lee DH. Changes in Gastric Corpus Microbiota With Age and After *Helicobacter pylori* Eradication: A Long-Term Follow-Up Study. *Front Microbiol* 2020; **11**: 621879 [PMID: 33633697 DOI: 10.3389/fmicb.2020.621879]

9 **Sung JJY**, Coker OO, Chu E, Szeto CH, Luk STY, Lau HCH, Yu J. Gastric microbes associated with gastric inflammation, atrophy and intestinal metaplasia 1 year after *Helicobacter pylori* eradication. *Gut* 2020; **69**: 1572-1580 [PMID: 31974133 DOI: 10.1136/gutjnl-2019-319826]

10 **Gunathilake M**, Lee J, Choi IJ, Kim YI, Kim J. Association between bacteria other than Helicobacter pylori and the risk of gastric cancer. *Helicobacter* 2021; **26**: e12836 [PMID: 34268831 DOI: 10.1111/hel.12836]

11 **Chen CC**, Liou JM, Lee YC, Hong TC, El-Omar EM, Wu MS. The interplay between *Helicobacter pylori* and gastrointestinal microbiota. *Gut Microbes* 2021; **13**: 1-22 [PMID: 33938378 DOI: 10.1080/19490976.2021.1909459]

12 **Guo Y**, Zhang Y, Gerhard M, Gao JJ, Mejias-Luque R, Zhang L, Vieth M, Ma JL, Bajbouj M, Suchanek S, Liu WD, Ulm K, Quante M, Li ZX, Zhou T, Schmid R, Classen M, Li WQ, You WC, Pan KF. Effect of *Helicobacter pylori* on gastrointestinal microbiota: a population-based study in Linqu, a high-risk area of gastric cancer. *Gut* 2020; **69**: 1598-1607 [PMID: 31857433 DOI: 10.1136/gutjnl-2019-319696]

13 **Hsu PI**, Pan CY, Kao JY, Tsay FW, Peng NJ, Kao SS, Wang HM, Tsai TJ, Wu DC, Chen CL, Tsai KW; Taiwan Acid-related Disease (TARD) Study Group. Helicobacter pylori eradication with bismuth quadruple therapy leads to dysbiosis of gut microbiota with an increased relative abundance of Proteobacteria and decreased relative abundances of Bacteroidetes and Actinobacteria. *Helicobacter* 2018; **23**: e12498 [PMID: 29897654 DOI: 10.1111/hel.12498]

14 **Maiti KS**, Apolonski A. Monitoring the Reaction of the Body State to Antibiotic Treatment against *Helicobacter pylori via* Infrared Spectroscopy: A Case Study. *Molecules* 2021; **26** [PMID: 34200454 DOI: 10.3390/molecules26113474]

15 **Liou JM**, Chen CC, Chang CM, Fang YJ, Bair MJ, Chen PY, Chang CY, Hsu YC, Chen MJ, Lee JY, Yang TH, Luo JC, Chen CY, Hsu WF, Chen YN, Wu JY, Lin JT, Lu TP, Chuang EY, El-Omar EM, Wu MS; Taiwan Gastrointestinal Disease and Helicobacter Consortium. Long-term changes of gut microbiota, antibiotic resistance, and metabolic parameters after Helicobacter pylori eradication: a multicentre, open-label, randomised trial. *Lancet Infect Dis* 2019; **19**: 1109-1120 [PMID: 31559966 DOI: 10.1016/S1473-3099(19)30272-5]

16 **Lane JA**, Murray LJ, Harvey IM, Donovan JL, Nair P, Harvey RF. Randomised clinical trial: Helicobacter pylori eradication is associated with a significantly increased body mass index in a placebo-controlled study. *Aliment Pharmacol Ther* 2011; **33**: 922-929 [PMID: 21366634 DOI: 10.1111/j.1365-2036.2011.04610.x]

17 **Francois F**, Roper J, Joseph N, Pei Z, Chhada A, Shak JR, de Perez AZ, Perez-Perez GI, Blaser MJ. The effect of H. pylori eradication on meal-associated changes in plasma ghrelin and leptin. *BMC Gastroenterol* 2011; **11**: 37 [PMID: 21489301 DOI: 10.1186/1471-230X-11-37]

18 **Martín-Núñez GM**, Cornejo-Pareja I, Clemente-Postigo M, Tinahones FJ, Moreno-Indias I. *Helicobacter pylori* Eradication Therapy Affect the Gut Microbiota and Ghrelin Levels. *Front Med (Lausanne)* 2021; **8**: 712908 [PMID: 34458288 DOI: 10.3389/fmed.2021.712908]

19 **Martin-Nuñez GM**, Cornejo-Pareja I, Clemente-Postigo M, Tinahones FJ. Gut Microbiota: The Missing Link Between Helicobacter pylori Infection and Metabolic Disorders? *Front Endocrinol (Lausanne)* 2021; **12**: 639856 [DOI: 10.3389/fendo.2021.639856]

20 **Wang L**, Zhou J, Xin Y, Geng C, Tian Z, Yu X, Dong Q. Bacterial overgrowth and diversification of microbiota in gastric cancer. *Eur J Gastroenterol Hepatol* 2016; **28**: 261-266 [PMID: 26657453 DOI: 10.1097/MEG.0000000000000542]

21 **Gong X**, Liu X, Chen C, Lin J, Li A, Guo K, An D, Zhou D, Hong Z. Alteration of Gut Microbiota in Patients With Epilepsy and the Potential Index as a Biomarker. *Front Microbiol* 2020; **11**: 517797 [PMID: 33042045 DOI: 10.3389/fmicb.2020.517797]

22 **Sasaki M**, Klapproth JM. The role of bacteria in the pathogenesis of ulcerative colitis. *J Signal Transduct* 2012; **2012**: 704953 [PMID: 22619714 DOI: 10.1155/2012/704953]

23 **Wei PL**, Hung CS, Kao YW, Lin YC, Lee CY, Chang TH, Shia BC, Lin JC. Classification of Changes in the Fecal Microbiota Associated with Colonic Adenomatous Polyps Using a Long-Read Sequencing Platform. *Genes (Basel)* 2020; **11** [PMID: 33233735 DOI: 10.3390/genes11111374]

24 **Rath S**, Heidrich B, Pieper DH, Vital M. Uncovering the trimethylamine-producing bacteria of the human gut microbiota. *Microbiome* 2017; **5**: 54 [PMID: 28506279 DOI: 10.1186/s40168-017-0271-9]

25 **Enemchukwu CU**, Ben-Faras H, Gialanella P, Szymczak WA, Nosanchuk JD, Madaline TF. Butyricimonas virosa bacteraemia and bowel disease: case report and review. *New Microbes New Infect* 2016; **13**: 34-36 [PMID: 27408738 DOI: 10.1016/j.nmni.2016.05.004]

26 **Zhou C**, Zhao H, Xiao XY, Chen BD, Guo RJ, Wang Q, Chen H, Zhao LD, Zhang CC, Jiao YH, Ju YM, Yang HX, Fei YY, Wang L, Shen M, Li H, Wang XH, Lu X, Yang B, Liu JJ, Li J, Peng LY, Zheng WJ, Zhang CY, Zhou JX, Wu QJ, Yang YJ, Su JM, Shi Q, Wu D, Zhang W, Zhang FC, Jia HJ, Liu DP, Jie ZY, Zhang X. Metagenomic profiling of the pro-inflammatory gut microbiota in ankylosing spondylitis. *J Autoimmun* 2020; **107**: 102360 [PMID: 31806420 DOI: 10.1016/j.jaut.2019.102360]

27 **Wang D**, Li Y, Zhong H, Ding Q, Lin Y, Tang S, Zong Y, Wang Q, Zhang X, Yang H, Wang R, Liu X. Alterations in the human gut microbiome associated with Helicobacter pylori infection. *FEBS Open Bio* 2019; **9**: 1552-1560 [PMID: 31250988 DOI: 10.1002/2211-5463.12694]

28 **Dash NR**, Khoder G, Nada AM, Al Bataineh MT. Exploring the impact of Helicobacter pylori on gut microbiome composition. *PLoS One* 2019; **14**: e0218274 [PMID: 31211818 DOI: 10.1371/journal.pone.0218274]

29 **Takahashi-Kanemitsu A**, Knight CT, Hatakeyama M. Molecular anatomy and pathogenic actions of Helicobacter pylori CagA that underpin gastric carcinogenesis. *Cell Mol Immunol* 2020; **17**: 50-63 [PMID: 31804619 DOI: 10.1038/s41423-019-0339-5]

30 **Shah SC**, Iyer PG, Moss SF. AGA Clinical Practice Update on the Management of Refractory Helicobacter pylori Infection: Expert Review. *Gastroenterology* 2021; **160**: 1831-1841 [PMID: 33524402 DOI: 10.1053/j.gastro.2020.11.059]

31 **Malfertheiner P**, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M, Selgrad M, Suerbaum S, Sugano K, El-Omar EM; European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. *Gut* 2017; **66**: 6-30 [PMID: 27707777 DOI: 10.1136/gutjnl-2016-312288]

32 **Blaser MJ**. Helicobacter pylori and gastric diseases. *BMJ* 1998; **316**: 1507-1510 [PMID: 9582144 DOI: 10.1136/bmj.316.7143.1507]

33 **Reshetnyak VI**, Burmistrov AI, Maev IV. *Helicobacter pylori*: Commensal, symbiont or pathogen? *World J Gastroenterol* 2021; **27**: 545-560 [PMID: 33642828 DOI: 10.3748/wjg.v27.i7.545]

34 **Kononova S**, Litvinova E, Vakhitov T, Skalinskaya M, Sitkin S. Acceptive Immunity: The Role of Fucosylated Glycans in Human Host-Microbiome Interactions. *Int J Mol Sci* 2021; **22** [PMID: 33917768 DOI: 10.3390/ijms22083854]

35 **Goto Y**, Uematsu S, Kiyono H. Epithelial glycosylation in gut homeostasis and inflammation. *Nat Immunol* 2016; **17**: 1244-1251 [PMID: 27760104 DOI: 10.1038/ni.3587]

36 **Bravo D**, Hoare A, Soto C, Valenzuela MA, Quest AF. *Helicobacter pylori* in human health and disease: Mechanisms for local gastric and systemic effects. *World J Gastroenterol* 2018; **24**: 3071-3089 [PMID: 30065554 DOI: 10.3748/wjg.v24.i28.3071]

37 **Papamichael K**, Konstantopoulos P, Mantzaris GJ. Helicobacter pylori infection and inflammatory bowel disease: is there a link? *World J Gastroenterol* 2014; **20**: 6374-6385 [PMID: 24914359 DOI: 10.3748/wjg.v20.i21.6374]

38 **Engler DB**, Leonardi I, Hartung ML, Kyburz A, Spath S, Becher B, Rogler G, Müller A. Helicobacter pylori-specific protection against inflammatory bowel disease requires the NLRP3 inflammasome and IL-18. *Inflamm Bowel Dis* 2015; **21**: 854-861 [PMID: 25742401 DOI: 10.1097/MIB.0000000000000318]

39 **Zhou F**, Zhu Q, Zheng PF, Feng YL. Association of Fucosyltransferase 2 Gene Variant with Inflammatory Bowel Diseases: A Meta-Analysis. *Med Sci Monit* 2019; **25**: 184-192 [PMID: 30615603 DOI: 10.12659/MSM.911857]

40 **Giampaoli O**, Conta G, Calvani R, Miccheli A. Can the FUT2 *Non-secretor* Phenotype Associated With Gut Microbiota Increase the Children Susceptibility for Type 1 Diabetes? *Front Nutr* 2020; **7**: 606171 [PMID: 33425974 DOI: 10.3389/fnut.2020.606171]

41 **Tang X**, Wang W, Hong G, Duan C, Zhu S, Tian Y, Han C, Qian W, Lin R, Hou X. Gut microbiota-mediated lysophosphatidylcholine generation promotes colitis in intestinal epithelium-specific Fut2 deficiency. *J Biomed Sci* 2021; **28**: 20 [PMID: 33722220 DOI: 10.1186/s12929-021-00711-z]

42 **Li Y**, Jiang Y, Zhang L, Qian W, Hou X, Lin R. Exogenous l-fucose protects the intestinal mucosal barrier depending on upregulation of FUT2-mediated fucosylation of intestinal epithelial cells. *FASEB J* 2021; **35**: e21699 [PMID: 34151459 DOI: 10.1096/fj.202002446RRRR]

43 **Fan R**, Han X, Gong Y, He L, Xue Z, Yang Y, Sun L, Fan D, You Y, Meng F, Yan X, Zhang M, Zhang J. Alterations of Fucosyltransferase Genes and Fucosylated Glycans in Gastric Epithelial Cells Infected with *Helicobacter pylori*. *Pathogens* 2021; **10** [PMID: 33557187 DOI: 10.3390/pathogens10020168]

44 **Miller AK**, Williams SM. Helicobacter pylori infection causes both protective and deleterious effects in human health and disease. *Genes Immun* 2021; **22**: 218-226 [PMID: 34244666 DOI: 10.1038/s41435-021-00146-4]

45 **Salar A**. Gastric MALT lymphoma and Helicobacter pylori. *Med Clin (Barc)* 2019; **152**: 65-71 [PMID: 30424932 DOI: 10.1016/j.medcli.2018.09.006]

46 **Choi IJ**, Kim CG, Lee JY, Kim YI, Kook MC, Park B, Joo J. Family History of Gastric Cancer and *Helicobacter pylori* Treatment. *N Engl J Med* 2020; **382**: 427-436 [PMID: 31995688 DOI: 10.1056/NEJMoa1909666]

47 **Sugimoto M**, Murata M, Yamaoka Y. Chemoprevention of gastric cancer development after *Helicobacter pylori* eradication therapy in an East Asian population: Meta-analysis. *World J Gastroenterol* 2020; **26**: 1820-1840 [PMID: 32351296 DOI: 10.3748/wjg.v26.i15.1820]

48 **Ford AC**, Yuan Y, Forman D, Hunt R, Moayyedi P. Helicobacter pylori eradication for the prevention of gastric neoplasia. *Cochrane Database Syst Rev* 2020; **7**: CD005583 [PMID: 32628791 DOI: 10.1002/14651858.CD005583.pub3]

49 **Smith S**, Fowora M, Pellicano R. Infections with *Helicobacter pylori* and challenges encountered in Africa. *World J Gastroenterol* 2019; **25**: 3183-3195 [PMID: 31333310 DOI: 10.3748/wjg.v25.i25.3183]

50 **Misra V**, Pandey R, Misra SP, Dwivedi M. Helicobacter pylori and gastric cancer: Indian enigma. *World J Gastroenterol* 2014; **20**: 1503-1509 [PMID: 24587625 DOI: 10.3748/wjg.v20.i6.1503]

51 **Graham DY**, Lu H, Yamaoka Y. African, Asian or Indian enigma, the East Asian Helicobacter pylori: facts or medical myths. *J Dig Dis* 2009; **10**: 77-84 [PMID: 19426388 DOI: 10.1111/j.1751-2980.2009.00368.x]

52 **Cavadas B**, Leite M, Pedro N, Magalhães AC, Melo J, Correia M, Máximo V, Camacho R, Fonseca NA, Figueiredo C, Pereira L. Shedding Light on the African Enigma: In Vitro Testing of *Homo sapiens-Helicobacter pylori* Coevolution. *Microorganisms* 2021; **9** [PMID: 33503840 DOI: 10.3390/microorganisms9020240]

53 **Herrero R**, Heise K, Acevedo J, Cook P, Gonzalez C, Gahona J, Cortés R, Collado L, Beltrán ME, Cikutovic M, Gonzalez P, Murillo R, Leja M, Megraud F, Hernandez ML, Barbier S, Park JY, Ferreccio C; ENIGMA Chile study group. Regional variations in Helicobacter pylori infection, gastric atrophy and gastric cancer risk: The ENIGMA study in Chile. *PLoS One* 2020; **15**: e0237515 [PMID: 32898138 DOI: 10.1371/journal.pone.0237515]

54 **Oster P**, Vaillant L, Riva E, McMillan B, Begka C, Truntzer C, Richard C, Leblond MM, Messaoudene M, Machremi E, Limagne E, Ghiringhelli F, Routy B, Verdeil G, Velin D. *Helicobacter pylori* infection has a detrimental impact on the efficacy of cancer immunotherapies. *Gut* 2021 [PMID: 34253574 DOI: 10.1136/gutjnl-2020-323392]

55 **Zhao Y**, Li Y, Hu J, Wang X, Ren M, Lu G, Lu X, Zhang D, He S. The Effect of Helicobacter pylori Eradication in Patients with Gastroesophageal Reflux Disease: A Meta-Analysis of Randomized Controlled Studies. *Dig Dis* 2020; **38**: 261-268 [PMID: 32396919 DOI: 10.1159/000504086]

56 **Nei T**, Hagiwara J, Takiguchi T, Yokobori S, Shiei K, Yokota H, Senoh M, Kato H. Fatal fulminant Clostridioides difficile colitis caused by Helicobacter pylori eradication therapy; a case report. *J Infect Chemother* 2020; **26**: 305-308 [PMID: 31822448 DOI: 10.1016/j.jiac.2019.10.021]

57 **Tanaka K**, Fujiya M, Sakatani A, Fujibayashi S, Nomura Y, Ueno N, Kashima S, Goto T, Sasajima J, Moriichi K, Okumura T. Second-line therapy for Helicobacter pylori eradication causing antibiotic-associated hemorrhagic colitis. *Ann Clin Microbiol Antimicrob* 2017; **16**: 54 [PMID: 28806959 DOI: 10.1186/s12941-017-0230-0]

58 **Franceschi F**, Cazzato A, Nista EC, Scarpellini E, Roccarina D, Gigante G, Gasbarrini G, Gasbarrini A. Role of probiotics in patients with Helicobacter pylori infection. *Helicobacter* 2007; **12** Suppl 2: 59-63 [PMID: 17991178 DOI: 10.1111/j.1523-5378.2007.00565.x]

59 **Iarovenko II**, Golofeevskiĭ VIu, Sitkin SI. The new possibilities for improving peptic ulcer therapy with the use of probiotic drugs. *Voen Med Zh* 2007; **328**: 17-22 [PMID: 17580472]

60 **Goderska K**, Agudo Pena S, Alarcon T. Helicobacter pylori treatment: antibiotics or probiotics. *Appl Microbiol Biotechnol* 2018; **102**: 1-7 [PMID: 29075827 DOI: 10.1007/s00253-017-8535-7]

61 **Wu L**, Wang Z, Sun G, Peng L, Lu Z, Yan B, Huang K, Yang Y. Effects of anti-H. pylori triple therapy and a probiotic complex on intestinal microbiota in duodenal ulcer. *Sci Rep* 2019; **9**: 12874 [PMID: 31492912 DOI: 10.1038/s41598-019-49415-3]

62 **Butorova LI**, Ardatskaya MD, Osadchuk MA, Kadnikova NG, Lukianova EI, Plavnik RG, Sayutina EV, Topchiy TB, Tuayeva EM. [Comparison of clinical-metabolic efficacy of pre- and probiotics in the conducted optimized protocols of eradication therapy of Helicobacter pylori infection]. *Ter Arkh* 2020; **92**: 64-69 [PMID: 32598700 DOI: 10.26442/00403660.2020.04.000647]

63 **Cuomo P**, Papaianni M, Fulgione A, Guerra F, Capparelli R, Medaglia C. An Innovative Approach to Control *H. pylori*-Induced Persistent Inflammation and Colonization. *Microorganisms* 2020; **8** [PMID: 32785064 DOI: 10.3390/microorganisms8081214]

64 **Suvorov A**, Karaseva A, Kotyleva M, Kondratenko Y, Lavrenova N, Korobeynikov A, Kozyrev P, Kramskaya T, Leontieva G, Kudryavtsev I, Guo D, Lapidus A, Ermolenko E. Autoprobiotics as an Approach for Restoration of Personalised Microbiota. *Front Microbiol* 2018; **9**: 1869 [PMID: 30258408 DOI: 10.3389/fmicb.2018.01869]

65 **Li Y**, Li X, Tan Z. An overview of traditional Chinese medicine therapy for Helicobacter pylori-related gastritis. *Helicobacter* 2021; **26**: e12799 [PMID: 33765344 DOI: 10.1111/hel.12799]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com