Interrelation: gastric microbiota - acid-dependent diseases, and more…

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Abstract

Introduction. The relationship between gastric microbiota and acid-dependent diseases is currently not fully studied. The study is based on a review of the literature to analyze and reflect the available data on the interaction of gastric microbiota and acid-dependent diseases, as well as brain-gut diseases.

Methods. The survey was performed by analyzing data from Medscape, PubMed, Elsevier. The articles analyzed are in English, Romanian, Russian, published in the last 10 years. Data on the composition (landscape) of the gastric microbiota and their influence on acid-dependent diseases and digestive diseases in general were reflected.

Results. The research reflected that in addition to Helicobacter pylori infection, the landscape of the gastric microbiota in the acid stomach (with low pH) is not sterile and includes other types such as: Proteobacteria, Firmicutes, Actinobacteria, Bacteroidetes, Fusobacteria. At the same time, current methods document a bacterial load of 10^{10}-10^{12} CFU/mL in the colon, which is much higher than in the stomach, where it reaches 10^{2}-10^{4} CFU/mL. H. pylori influences the diversification of the non-H.pylori gastric microbiota; Decreased diversification increases the risk of carcinogenesis. The aspects of the role of H. pylori in functional dyspepsia, named after the Maastricht Consensus V - H. pylori dyspepsia, were also demonstrated.
The taxonomic profiles (Philum-level, Genus-level) of the gastric microbiota require the study of the interrelationships with acid-dependent diseases, as well as the feedback.

Conclusions. The study shows that the stomach is not a sterile organ and in addition to H. pylori there are 5 other types of gastric microbiota, which are interrelated with acid-dependent diseases and digestive disorders and vice versa. This issue requires a comprehensive approach.

Keywords: microbiota, H. pylori, acid-dependent diseases, interrelationships

Introduction

It is known that the nosological structure of acid-dependent diseases (ADD) includes:

- GERD - Gastro-Esophageal Reflux Disease
- Functional dyspepsia (DF) / H. pylori-dyspepsia
- Chronic gastritis / duodenitis
- GU/DU - Gastric Ulcer / Duodenal Ulcer - Peptic Ulcer Disease (PUD)
- NSAID-Gastroenteropathy
- Erosive-ulcerative lesions of the stomach and duodenum, associated with hyperparathyroidism
- Zollinger-Ellison syndrome
- Chronic pancreatitis [1,2].

The microbiota is a collection of microorganisms from the microbial community in the gastrointestinal tract.

Today, many functions have made it possible to interpret it as a truly independent organ - the 4th organ of the digestive system. The complex and dynamic diversity of the microbiota includes up to 10-100 trillion microbial cells in different parts of the body. [3]

In the gastrointestinal tract, current methods have documented a bacterial load

DOI: 10.15386/mpr-2510

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of 10^{10} - 10^{12} (CFU)/mL in the colon, which is much larger than in the stomach, where it reaches 10^2-10^4 CFU / mL [4].

Is there a stomach microbiota?

The history of discoveries

In 1875, German scientists discovered a spiral-shaped bacterium in the mucous membrane of the human stomach. The bacterium did not grow in culture (on artificial culture media known at the time), and this accidental discovery was forgotten.

In 1886, professor Valery Javorski of the Jagiellonian University in Kraków described bacteria with a characteristic spiral shape (Vibrio rugula) - assuming an etiological role in the pathogenesis of stomach diseases. However, this paper did not have much of an impact on the rest of the medical and scientific world, as it was written in Polish [5].

However, is there a stomach microbiota?

The stomach, with its low pH, has been considered a sterile organ for many years. The discovery of H. pylori in 1982 was revolutionary in many ways and challenged earlier concepts in digestive pathology [6].

"There is nothing more misleading than the obvious" (*Robin Warren)*

Barry Marshall and Robin Warren

The social impact of a Nobel Prize: Social impact of a Nobel Prize: The University of Western Australia

"This was not true, but it has become part of the folklore of the time. I've been told that bacteria are either contaminants or harmless diners" (Barry Marshall)

Helicobacter pylori (1983)

Markers of pathogenicity: *Cytotoxin-associated gene A* ***(Cag A)****, Bab A adhesin and vacuolating cytotoxin* ***(Vac A)*** [7].

Gram-negative bacterium, which has an S-shape, has 4-6 flagella at one end, which allows it to move in the gastric contents and contact the mucosal epithelium.

The most favorable conditions for *Hp* in the lumen of the stomach (antrum): high content of CO_2, urea $CO(NH_2)_2$ and pH from 3.0 to 6.0.

Vibrios Hp produce a number of substances with a direct cytotoxic effect on the mucous membrane; causes its inflammation, with the further extension of the process in the deep layers of the mucous membrane, lead to atrophy of the glandular apparatus [7].

However, the paradigm has changed: ... ***from pH → to Hp***.

Proof of the etiological significance of Hp for chronic gastritis:

1. Experiments with self-infection.
2. Animal experiments - models of Helicobacter pylori gastritis.
3. Hp bacterium:
    1. secretes a protein that activates neutrophils;
    2. induces cytokine secretion.
4. Hp eradication is accompanied by the reversibility of the morphological picture of gastritis [8,9].

Currently, the etiological role of *Hp* is considered to be demonstrated.

Hp infection occurs:

- fecal-oral route;
- oral-oral route;
- iatrogenic pathway.

The higher the standard of living of the population, the less *Hp* is detected, therefore in developing countries, *Hp* contamination reaches almost 100%, and in European countries - 70-80% [10].

Results

Regarding the development of non-atrophic gastritis associated with Hp (Kyoto Consensus, 2015):

- the inflammatory process develops in the antrum, then passes into the body and stomach fundus;
- Hp, due to its microvilli, as well as the activity of urease, enters the submucosal layer; - ammonia (cleavage of urea by Hp-urease) damages the epithelium and causes an inflammatory reaction by suppressing the defense factors;
- Hp inhibits cell differentiation and proliferation, creates conditions for apoptosis and therefore supports the inflammatory process [11].

For today the infectious agent - H. pylori - carcinogenic № 1 according to the IARC classification (Table I).

Table I. International **A**gency for **R**esearch on **C**ancer (IARC).

Tumor location Tumor type	Infectious agent - carcinogen 1 Groups by IARC classification
Stomach	*Helicobacter pylori*
Liver	HBV, HCV, Opisthorchis viverrini, Clonorchis, sinensis
Cervix uterine	HPV+/-HIV
Anogenital region	HPV+/-HIV
Nasopharynx	EBV
Oropharynx	HPV
Sarcoma Kaposi	HSV tip 8 +/- HIV
Non-Hodgkin's lymphoma	Helicobacter pylori, EBV +/- HIV, HCV, Human lymphotropic virus 1
Hodgkin's lymphoma	EBV +/- HIV
Bladder	Schistosoma haematobium

The second stage of the revolution was verified by the Kyoto Consensus on Gastritis, which confirmed the possibility of vital activity and the association with the pathology of the stomach of various bacteria, viruses and fungi (Kyoto global consensus report on Hellicobacter pylori gastritis) [11].

Recently, molecular methods have been developed based on the determination of 16S rRNA genes:

- fluorescent hybridization,
- dot blot hybridization with rRNA target probes,
- rDNA cloning,
- rRNA sequencing, which contributed to the identification and classification of stomach bacteria [12].

During sequencing, the nucleotide sequence of the 16S rRNA gene, which is present in the genome of all bacteria, is determined.

These studies found more than 10,000 types of microbes and showed that the set of microbial genes is 100 times larger than the set of genes in the human body, and their mass can reach almost 3% of the weight of the human body [13].

Non-Hp gastric microbiota

Regarding the non-Hp gastric microbiota, it is widely believed that H. pylori was the only microorganism capable of surviving in a hostile gastric environment - it has been assumed for the last 3 decades. [4] Studies of other cultures have been reported: Clostridium spp, Veillonella spp and Lactobacillus spp as the dominant species in a normal acid stomach. However, these methods underestimate the diversity of bacteria, as most of them could not be cultured [14].

Although some of the bacteria (Enterococcus, Streptococcus, Staphylococcus, Pseudomonas and Stomatococcus) live in the oral cavity and respiratory tract, documentation of Pseudomonas spp, other than P. aeruginosa, has led to the idea that there is a local microbiota in the gastric environment. Bik et al. analyzed stomach biopsy samples and identified 128 phylotypes, which are included in 5 different types of bacteria: - *Proteobacteria,* - *Firmicutes,* - *Actinobacteria,* - *Bacteroidetes,* - *Fusobacteria* [15]. The composition of the microbiota of the stomach 101-103 / 102-104 CFU / ml (compared to the small intestine1010-1012 CFU / ml): -healthy people

- Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria; Streptococcus- different from the oral and pharyngeal microbiota [16].

In 2013, Delgado et al. conducted the first study using a combination of classical cultivation and independent cultivation methods and found that the most common species belong to Streptococcus, Lactobacillus and Propionibacterium [4].

Japanese authors believe that stomach dysbiosis is a decrease in normal dominant strains and an increase in minor bacterial strains [18].

The relationship between Hp and another gastric microbiota

Studies on bacterial diversity in the stomach of H. pylori (+) versus H. pylori (-) remain controversial: H. pylori can change its own microclimate (produces NH_3 and urea bicarbonate, which can serve as a substrate for other microbial communities). A decrease in gastric secretion and thus an increase in gastric pH creates favorable ecological niches for the colonization of other microorganisms. H. pylori also induces the production of cytokines and antimicrobial peptides that cause chronic inflammation of the stomach and can inhibit other local microorganisms! [19].

Interestingly, other reports have shown that some species, such as Lactobacillus, have strong antagonistic effects and may inhibit the growth of H. pylori [20].

Similarly, Streptococcus mitis, a commensal bacterium found in the gastric environment, can inhibit the growth and conversion of H. pylori into cocoids [21].

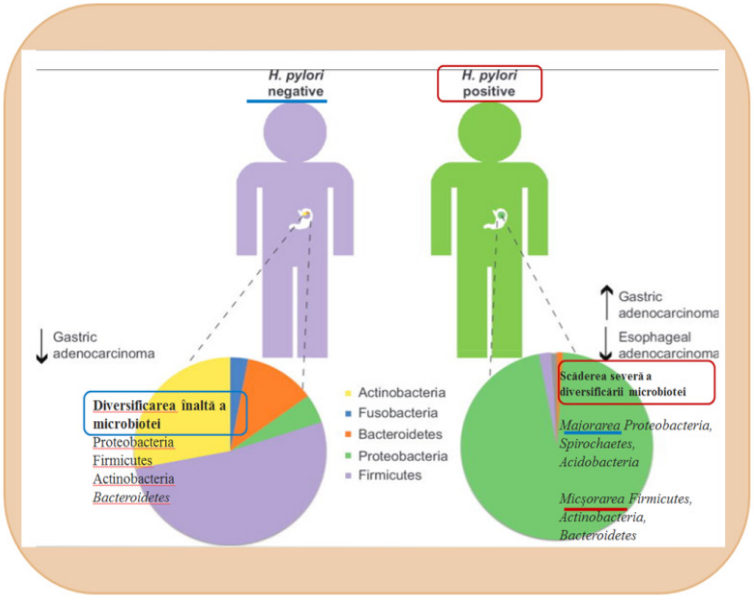

Figure 1. Adapted after Wroblewski et al. [17].

Stomach microbiota in ... the development of BAD

The etiological relationship between H. pylori "long-term" and chronic gastritis is well documented. ... it is thought that different communities of gastric microbes, such as the overrepresentation of the genus Streptococcus in the type Firmicutes, can also lead to gastritis, even in the absence of H. pylori [22].

The composition of the microbiota of the stomach (*H. pylori* dominates other species)

Percentage of reads (6 SD)						
	Firmicutes	Actinobacteria	Bacteroidetes	Proteobacteria	Fusobacteria	Others
Thrcat (n=6)	55,66 13,6	14,56 3,9	20,06 8,6	4,76 3,4	5,16 3,7	1
H. pylori negative stomach (n=3)	29,66 15,9	46,86 18,9	11,16 8,7	10,86 3,2	1,16 1,1	1
H. pylori positive stomach (n=3)	1,86 0,6	1,16 0,7	0,86 0,6	98,26 1,8	0,16 0,01	0,1
Feces (n=6)	8126 11,2	14,66 9,8	2,56 2,6	1,76 1,5	0	0,1

Figure 2. Adapted after Andersson et al. [23].

Among the different population groups (African-Americans, Latin Americans, Chinese and Europeans), the gastric microbiota had obvious similarities. At the same time, the total number of bacterial genera in the stomach reaches 85 [24].

Subsequent research has shown a significant correlation between the detection of streptococci (Streptococci) and PUD-peptic ulcer disease. Consequently, non-H.pylori microbiota may also play an important role in the pathogenesis of gastroduodenal diseases through complex mechanisms and interactions that remain to be fully elucidated … [25].

Stomach microbiota and carcinogenesis

Out of 100 people infected with H. pylori, stomach cancer develops in 2. Who are they? Those with a genotype that causes a high level of inflammatory response and its persistence.

H. pylori coevolved with humans for millennia and only 1-2% of persons infected with these bacteria actually develop severe complications, such as gastric cancer or MALT lymphoma. From this point of view, specific H. pylori strains, host genetic susceptibility, hyperglycemia, smoking, diet and other microbiota may also contribute to the outcome of infection [26].

Bacterial diversity decreases significantly from chronic gastritis to gastric cancer with an increase in the number of Pseudomonas (9 families represent 50% of the taxonomic units; an increase in Lactobacillus coleohominis and Lachnospiraceae) [27].

A possible link between autoimmune gastritis, hypochlorhydria and gastric cancer may be assumed (Figure 3).

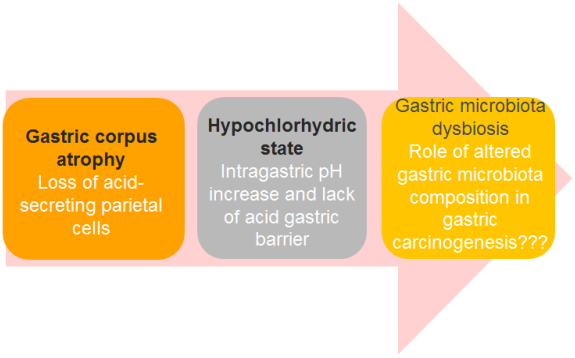

Figure 3. Adapted after Conti et al. [28].

This altered intragastric "microenvironment" may allow bacteria other than Hp to survive, possibly playing a key role in gastric carcinogenesis [28].

The role of H. pylori and non-H. microbiota pylori in FD development (?)

According to some studies, acute gastrointestinal infection appears to be a trigger for post-infectious irritable bowel syndrome and post-infectious functional dyspepsia (FD) [29].

The Maastricht V/Florence Consensus Report

The Maastricht Consensus-V continued to address the relationship between H. pylori gastritis and **functional dyspepsia**. It was concluded that H. pylori-induced gastritis is a separate diagnosis (this is in line with the provisions of the Kyoto Consensus) and may cause dyspeptic symptoms in some patients. Helicobacter pylori gastritis is an **organic** disease, as opposed to functional dyspepsia, which is a functional disease.

The Maastricht V consensus stated that the diagnosis of *true functional dyspepsia* should be made only in *the absence of H. pylori infection* or *after successful eradication* [2].

Dyspepsia associated with H. pylori infection

Does H. pylori gastritis cause dyspepsia? Gastritis associated with H. pylori is the cause of dyspepsia in a subgroup of patients (-recommendation rate: strong. -proof level: high. -concordance level: 100%). NNT * is 8. It takes at least 6 months (the time needed to cure gastritis) to see if the symptoms have resolved after eradication [11].

Eradication of Hp in most cases does not lead to the disappearance of dyspeptic symptoms in these patients.

In some patients with chronic Hp-associated gastritis, dyspeptic symptoms may disappear after successful eradication. But these patients should not be considered as patients suffering from FD, but as patients with dyspepsia associated with Hp-infection − *H. pylori dyspepsia* [11].

Thus, Maastrcht V says: *Statement 1*: Gastric microbiota includes other microbes beyond H. pylori; *Statement 2*: The composition of a health gastric microbiota and how H. pylori affects this microbiota have not yet been fully defined.(lev. of evidence: 2c, gr. of recommendation: B) [2].

H. pylori - side effects of eradication

Increased severe esophageal diseases associated with a decrease in Hp infections (Figure 4) [30].

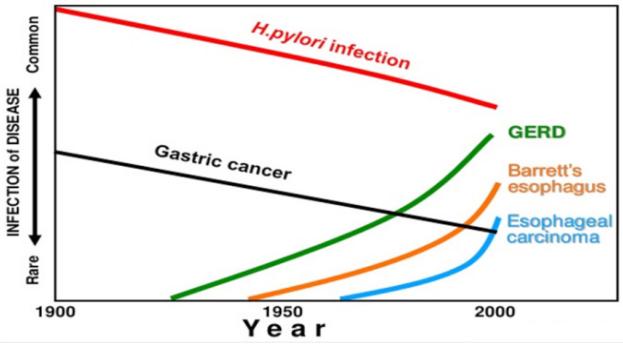

Figure 4. H. pylori prevalence and GERD (adapted after Blaser [30]).

There is growing evidence of possible protective effects of H. pylori and other gastric bacteria. The loss of the local microbiota could lead to an increase in modern allergic and metabolic diseases, as reflected in the hypothesis of "endangered microbiota". From this point of view, several studies have shown that the presence of H. pylori in the gastric environment is inversely associated with esophageal adenocarcinoma, asthma and obesity. Current lines of research are investigating the possible benefits of infecting people with benign H. pylori strains [30].

The treatment of acid-dependent diseases also influences the stomach microbiota: long-term use of PPI (which immobilizes and inhibits the growth of H. pylori) also changes the condition of the stomach microbiota (obviously depends on the secretory function); the importance of other microorganisms found in the stomach in relation to ADD has not been unequivocally proven [31].

Today we can confidently say that Hp as one of the representatives of "slow infections" is not a new threat or an old friend, and the eradication of an infectious disease is considered a fragment of the protocol for treating patients with Hp associated with pathology (comorbidity) [2].

Houston Consensus Conference on Testing for Helicobacter pylori Infection states: *Statement 1*: We recommend treating all patients with active H. pylori infection (100% agree / totally agree, grade 1A); *Statement 3*: We recommend that all patients with uninvestigated dyspepsia be tested for H. pylori infection (100% agree / totally agree, grade 1A) [32].

Regarding the concretization of some moments, we are waiting for what the Consensus Report ***Maastricht VI*** Florence will say (Updated: (27-28 Sept. 2021) Malfertheiner et al. Manuscript in preparation) [33].

The interrelationships between H. pylori and COVID-19 infection should be noted: the new coronavirus (SARS CoV-2) is known to bind to ACE-2 receptors to enter the cell. These receptors are widely expressed in the gut, and the 2019 coronavirus can induce gastrointestinal symptoms through these receptors during the disease. Helicobacter pylori is known to increase the expression of ACE-2 receptors in the gastrointestinal tract. The results showed that the signs of abdominal pain and diarrhea were strongly correlated with the presence of Helicobacter pylori in patients with CoViD-19. We believe that this effect is mediated by ACE-2 receptors [34]. This was the first study in the literature in which the relationship between H. pylori and COVID-19 is being explored. The results show that H. pylori exacerbates diarrhea and abdominal pain in COVID-19 infection due to overexpression of ACE-2 receptors, causing more viruses to enter the gastrointestinal tract.

PUD's Non-Rhetorical Question Reflected by Peter Malfertheiner-*Peptic Ulcer: Closed Chapter? ...* however, new challenges have arisen with an increase in treatment failure due to increased antibiotic resistance of H. pylori. The treatment of bleeding caused by peptic ulcer remains an important clinical problem. *The PUD section has shrunk and diversified - but not closed!* [35].

H. pylori: what's new in 2021? Helicobacter pylori infection - a pattern of dysbiosis [36]. Probiotics, when combined with antibiotics, reduce the risk of colonization by MDR bacteria in the gastrointestinal tract [37].

Noting the role of H. pylori in deseases and symptoms Colm O'Morain says "*The only good bug is a dead one*" (uegweek 2021).

"... doubt on the scientific understanding of the thinking activity of Homo Sapiens. A person has two eyes, two arms, two legs and two brains: one pulses in the head, the other is active in the stomach. " − Michael Gershon [38].

Conclusion

Recent studies have shown that the stomach is not a sterile organ. In parallel with H. pylori there is also the non-Hp gastric microbiota represented by 5 different types of bacteria: - *Proteobacteria,* - *Firmicutes,* - *Actinobacteria,* - *Bacteroidetes,* - *Fusobacteria,* which also influence the evolution of acid-dependent diseases.

The question remains open… Non-H. pylori microbiota may also play an important role in the pathogenesis of gastroduodenal diseases through complex mechanisms and interactions that remain to be fully elucidated.

References

1. Polunina TV. Terapie combinată a bolilor acidodependente. РМЖ №.13, 2013, P. 691. Полунина Т.В. Комбинированная терапия кислотозависимых заболеваний. РМЖ. №.13, 2013, P. 691.
2. Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, et al. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report Gut 2017;66:6-30.
3. Ursell LK, Metcalf JL, Parfrey LW, Knight R. Defining the human microbiome. Nutr Rev. 2012;70 Suppl 1(Suppl 1):S38-S44.
4. Delgado S, Cabrera-Rubio R, Mira A, Suárez A, Mayo B. Microbiological survey of the human gastric ecosystem using culturing and pyrosequencing methods. Microb Ecol. 2013;65:763-772.
5. Blaser MJ. An endangered species in the stomach. Sci Am. 2005;292:38-45.
6. Petra CV, Rus A, Dumitrașcu DL. Gastric microbiota: tracing the culprit. Clujul Med. 2017;90:369-376.
7. Backert S, Neddermann M, Maubach G, Naumann M. Pathogenesis of Helicobacter pylori infection. Helicobacter. 2016;21 Suppl 1:19–25.
8. Warren JR, Marshall BJ. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet. 1983;1:1273-1275.
9. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984;1:1311-1315.
10. Mégraud F. H pylori antibiotic resistance: prevalence, importance, and advances in testing. Gut. 2004;53:1374-1384.
11. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al. Kyoto global consensus report on Hellicobacter pylori gastritis. Gut. 2015;64:1353-1367.
12. Fraher MH, O'Toole PW, Quigley EM. Techniques used to characterize the gut microbiota: a guide for the clinician. Nat Rev Gastroenterol Hepatol. 2012;9:312–322.
13. Kharitonova LA, Grigoriev KI, Borzakova SN. Human microbiote: how a new scientific paradigm changes medical practice. Eksperimental'naia i klinicheskaia gastroenterologiia (Experimental and clinical gastroenterology) 2019;161(1):55–63. DOI: 10.31146/1682-8658-ecg-161-1-55-63
14. Zilberstein B, Quintanilha AG, Santos MA, Pajecki D, Moura EG, Alves PR, et al. Digestive tract microbiota in healthy volunteers. Clinics (Sao Paulo). 2007;62:47–54.
15. Bik EM, Eckburg PB, Gill SR, Nelson KE, Purdom EA, Francois F, et al. Molecular analysis of the bacterial microbiota in the human stomach. Proc Natl Acad Sci U S A. 2006;103:732–737.
16. Yang I, Woltemate S, Piazuelo MB, Bravo LE, Yepez MC, Romero-Gallo J, et al. Different gastric microbiota compositions in two human population with high and low gastric cancer risk in Colombia. Sci Rep. 2016;6:18594.
17. Wroblewski LE, Peek RM Jr, Coburn LA. The Role of the Microbiome in Gastrointestinal Cancer. Gastroenterol Clin North Am. 2016;45:543-556.
18. Iizasa H, Ishihara S, Richardo T, Kanehiro Y, Yoshiyama H. Dysbiotic infection in the stomach. World J Gastroenterol. 2015;21:11450–11457.
19. Mustapha P, Paris I, Garcia M, Tran CT, Cremniter J, Garnier M, et al. Chemokines and antimicrobial peptides have a cag-dependent early response to Helicobacter pylori infection in primary human gastric epithelial cells. Infect Immun. 2014;82:2881–2889.
20. Delgado S, Leite AM, Ruas-Madiedo P, Mayo B. Probiotic and technological properties of Lactobacillus spp. strains from the human stomach in the search for potential candidates against gastric microbial dysbiosis. Front Microbiol. 2015;5:766.
21. Khosravi Y, Dieye Y, Loke MF, Goh KL, Vadivelu J. Streptococcus mitis induces conversion of Helicobacter pylori to coccoid cells during co-culture in vitro. PLoS One. 2014;9:e112214.
22. Engstrand L, Lindberg M. Helicobacter pylori and the gastric microbiota. Best Pract Res Clin Gastroenterol. 2013;27:39-45.
23. Andersson AF, Lindberg M, Jakobsson H, Bäckhed F, Nyrén P, Engstrand L. Comparative analysis of human gut microbiota by barcoded pyrosequencing. PLoS One. 2008;3: e2836.
24. Cao L, Yu J. Effect of Helicobacter pylori Infection on the Composition of Gastric Microbiota in the Development of Gastric Cancer. Gastrointest Tumors. 2015;2:14–25.
25. Khosravi Y, Dieye Y, Poh BH, Ng CG, Loke MF, Goh KL, et al. Culturable bacterial microbiota of the stomach of Helicobacter pylori positive and negative gastric disease patients. ScientificWorldJournal. 2014;2014:610421.
26. Raei N, Behrouz B, Zahri S, Latifi-Navid S. Helicobacter pylori Infection and Dietary Factors Act Synergistically to Promote Gastric Cancer. Asian Pac J Cancer Prev. 2016;17:917–921.
27. Aviles-Jimenez F, Vazquez-Jimenez F, Medrano-Guzman R, Mantilla A, Torres J. Stomach microbiota composition varies between patiens with non-atrophic gastritis and patients with intestinal type of gastric cancer. Sci Rep. 2014;4:4202.
28. Conti C, Annibale B, Lahner E. Autoimmune Gastritis and Gastric Microbiota. Microorganisms. 2020;8:1827
29. Futagami S, Itoh T, Sakamoto C. Systematic review with meta-analysis: post-infectious functional dyspepsia. Aliment Pharmacol Ther. 2015;41:177–188.
30. Blaser MJ. Disappearing microbiota: Helicobacter pylori protection against esophageal adenocarcinoma. Cancer Prev Res (Phila). 2008;1:308–311.
31. Ohara T, Goshi S, Taneike I, Tamura Y, Zhang HM, Yamamoto T. Inhibitory action of a novel proton pump inhibitor, rabeprazole, and its thioether derivative against the growth and motility of clarithromycin-resistant Helicobacter pylori. Helicobacter. 2001;6:125-129.
32. El-Serag BE, Kao JK, Kanwal F, Gilger M, LoVecchio F, Moss SF, et al. Houston Consensus Conference on Testing for Helicobacter pylori Infection in the United States. Clin

Gastroenterol Hepatol. 2018;16:992-1002.e6.

33. International-Symposium-on-H-Pylori-Consensus-Report-Maastricht-VI-Florence report Maastricht VI Florence. Sept. 2021. Available from: https://www.en.fondazione-menarini.it/Home/Events/International-Symposium-on-H-Pylori-Consensus-Report-Maastricht-VI-Florence/780/Presentation
34. Balamtekin N, Artuk C, Arslan M, Gülşen M. The Effect of Helicobacter pylori on the Presentation and Clinical Course of Coronavirus Disease 2019 Infection. J Pediatr Gastroenterol Nutr. 2021;72:511–513.
35. Malfertheiner P, Schultz C. Peptic Ulcer: Chapter Closed? Dig Dis. 2020;38:112–116.
36. Rajilic-Stojanovic M. H. Pylori as a model of dysbiosis. 2021
37. Wieërs G, Verbelen V, Van Den Driessche M, Melnik E, Vanheule G, Marot JC, et al. Do Probiotics During In-Hospital Antibiotic Treatment Prevent Colonization of Gut Microbiota With Multi-Drug-Resistant Bacteria? A Randomized Placebo-Controlled Trial Comparing Saccharomyces to a Mixture of Lactobacillus, Bifidobacterium, and Saccharomyces. Front Public Health. 2021;8:578089.
38. Michael Gershon. The Second Brain. A Groundbreaking New Understanding of Nervous Disorders of the Stomach and Intestine, Scribd, 1998