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MICROBIOTA AND GASTRIC DISEASES IN 2022

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Abstract – *Helicobacter pylori* is the most dominant and clinically relevant member of the human gastric microbiota that it may be considered a natural member of it as only a small proportion of *H. pylori*-colonized humans develop disease. At phylum level, the gastric microbiota is mainly comprised of Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria and Fusobacteria, both in *H. pylori*-positive and -negative individuals, but with different percentages of relative abundance. *Helicobacter* is the major genera followed by *Streptococus*, *Prevotella*, *Neisseria*, *Veillonella*, *Fusobacterium*, and *Haemophilus* in the *H. pylori*-colonized stomach of humans, whilst *Streptococcus* and *Prevotella* are the most predominant in the *H. pylori*-negative stomach. *Helicobacter*, *Streptococcus*, *Prevotella*, and *Fusobacterium* are among the most predominant genera colonizing the human stomach, when transcriptionally active bacteria were studied.
The papers published between 2021 and 2022 confirmed the *H. pylori* dominance in the non-atrophic stomach microbiome and a progressive dysbiosis occurred as result of the cascade of histological changes toward gastric carcinogenesis, but a unique gastric cancer associated microbiome profile has not been consistently identified. Colonization with bacteria other than *H. pylori* may contribute to perpetuating chronic inflammation and to increasing gastric cancer risk.

Keywords: *Helicobacter pylori*, Gastric microbiome, Gastric diseases.

Abbreviations: SG: superficial gastritis, AG: atrophic gastric, CAG: corpus atrophic gastritis, CG: chronic gastritis, FGPs: fundic gland polyps, GC: gastric cancer, EGC: early GC, GERD: gastroesophageal reflux disease, IM: intestinal metaplasia, LGIN: low-grade intraepithelial neoplastic, MALT: Mucosa Associated Lymphoma Tissue, PPIs: proton pump inhibitors.

INTRODUCTION

For a long time, bacteriologist thought that the human stomach was a sterile organ, however, thanks to Marshall and Warren[1], they confirmed a stable colonization of *Helicobacter pylori* in the stomach despite the acidic environment. This bacterium was considered the only one able to survive in this hostile environment. Moreover, culture was the main tool of microbial research[2] and when some microbes grew in the culture of gastric fluid, they were considered transient luminal microbes[3]. However, the presence of *H. pylori* suggested that other bacteria might be able to tolerate the harsh acidic conditions.

WHAT WAS KNOWN ABOUT THE GASTRIC MICROBIOME BEFORE 2022?

Since the first studies assessing the gastric microbiome[4] it was clear that humans showed a great stability of the gastric microbiota at the phylum level. Most of the studies confirmed

the presence of 5 major phyla present in all human and non-human primate related studies associated with the composition of the gastric microbiota[5]. The 5 phyla present are: Proteobacteria, Bacteroidetes, Firmicutes, Fusobacteria, and Actinobacteria[5].

A consistent finding in most of the published studies of the gastric microbiota has been minor qualitative differences in the composition of the gastric microbiota and most of those differences are associated with the colonization of the gastric mucosa with *H. pylori*. In contrast, major quantitative differences have been reported in the composition of the gastric microbiota but always associated with the presence/absence of *H. pylori*[5,6].

The composition of the gastric microbiota has small variations, linked to gender, age, geographic origin, Body Mass Index, diet, or current treatment. Most of the differences in the gastric microbiota composition are associated with alterations in acid production related to *H. pylori* infection, acid suppression therapy, and changes in the gastric epithelium due to atrophy, intestinal metaplasia (IM) or gastric cancer (GC).

WHAT IS KNOWN OF THE GASTRIC MICROBIOME IN 2022?

During 2022, several papers were published about the gastric microbiome and the role of *H. pylori* in the development of peptic ulcer disease, gastric adenocarcinoma and Mucosa Associated Lymphoma Tissue (MALT) lymphoma. The potential role, of non-*H. pylori* bacteria in the development of different gastric diseases and in particular GC was also studied.

CONFIRMATION OF THE QUALITATIVE AND QUANTITATIVE COMPOSITION OF THE GASTRIC MICROBIOME

Nowadays we know that the human stomach is not sterile but harbors many bacteria, although they are fewer in number than in the small and large intestine (only 10^2-10^4 CFUs per mL comparing to 10^{10}-10^{12} CFUs per mL in the colon)[7].

H. pylori is the dominant and most clinically relevant member of the human gastric microbiome, being as high as 72% of the cultivable gastric bacteria and 97% of transcriptionally active taxa[7]. As only a small proportion of *H. pylori*-infected humans develop a clinical disease, it may be considered a natural member of the gastric microbiome[7].

Some scholars[3] have shown heterogeneity of the gastric microbiome, which may be due to different sample types, different gastric pathologies, inter-individual variability, individual ethnicity, or even the use of different sequencing approaches.

As mentioned, at phylum level, the gastric microbiome is mainly composed of Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria and Fusobacteria[8,9], representing over 95% of all phyla[10]. Proteobacteria, Bacteroidetes, Actinobacteria and Firmicutes were detected as the most frequent by shotgun metagenomic sequencing[11].

Helicobacter genus was recently reclassified in a new phylum, firstly named Epsilonbacteraeota[12], and finally Campylobacterota[13]. So, *Helicobacter* can be classified in the Proteobacteria, the Epsilonbacteraeota or the Campylobacterota phyla depending on the database used for microbiome studies. Firmicutes, Proteobacteria, and Bacteroidetes, followed by Actinobacteria, Cyanobacteria, Omnitrophicaeota, Epsilonbacteraeota, Fusobacteria, and Patescibacteria were the most frequent bacterial phyla detected in a study of Conti et al[14].

The relative abundance of Proteobacteria and Firmicutes were significantly different among the different gastric sites studied (antrum, corpus and cardia). In patients with chronic gastritis (CG), members of Proteobacteria were predominant in the corpus, whereas those Proteobacteria and Firmicutes were at comparable levels in the antrum and cardia[10]. *Firmicutes* were significantly more frequent in cases of corpus atrophic gastritis (CAG) than in controls whilst Bacteroidetes, Fusobacteria, Patescibacteria and Spirochaetes were less abundant in CAG cases than in controls[14].

As previously mentioned, the gastric microbiome has small variations according with the studies published and those variations are mainly described below.

HELICOBACTER PYLORI INFECTION

The gastric microbiome is mainly dominated by the same phyla in *H. pylori*-positive and -negative individuals, but with different percentages of relative abundance[7,15]. Alpha diversity scores were negatively associated with the presence of *H. pylori*[3].

The composition of the gastric microbiome in *H. pylori*-colonized subjects may be influenced by disease: dyspeptic versus non-dyspeptic patients, different degrees of inflammation and pathology[7]. Moreover, *H. pylori* gastric infection may impact the microbiome in other areas of the gastrointestinal tract including the oral cavity, oesophagus, duodenum and colon[7].

In the *H. pylori*-colonized stomach, *Helicobacter* is the major genera (40% to 99%) followed by *Streptococcus*, *Prevotella*, *Neisseria*, *Veillonella*, *Fusobacterium*, and *Haemophilus*. The genera *Helicobacter*, *Streptococcus*, *Prevotella*, and *Fusobacterium* are among the most predominant, when the transcriptionally active bacteria were studied[16]. *Streptococcus* and *Prevotella* are among the most predominant genera in the *H. pylori*-negative stomach[16].

H. pylori infection may influence the presence of other gastric microbes as chronic infection affect the gastric physiology, including luminal pH and mucin structure. However, it is not completely defined to what extent *H. pylori* infection alters the composition of the gastric microbiome or there are other environmental conditions, such as oxygen levels or pH that can also influence bacterial community structure[7].

The gastric microbiome was also studied by metagenomic shotgun sequencing of stomach in swab samples showing that 55 microbial pathways were enriched in the *H. pylori*-positive group, whilst only 2 were more abundant in the *H. pylori* negative group (dTDP-L-rhamnose biosynthesis and tetrapyrrole biosynthesis)[11].

HELICOBACTER PYLORI ERADICATION

It is well known that eradication of *H. pylori* infection changes the diversity of gastric microbiome[3]. The impact on gastric acid secretion may alter the gastrointestinal microbiome and the host health status. Near complete normalization of the gastric microbiome two months after antibiotic eradication of *H. pylori* in both children and adults was described in most studies but not in al[17.] Overall, non- *H. pylori* bacteria remained within the stomach following *H. pylori* elimination[7].

It is known that *H. pylori* eradication therapy is not always successful in preventing GC and persistence of gastric inflammation, and progression of gastric precancerous lesions could be explained by the colonization with other bacteria[16]. A cluster of oral commensal bacteria including *Peptostreptococcus, Streptococcus, Parvimonas, Prevotella, Rothia*, and *Granulicatella*[3] were associated with the emergence and persistence of atrophic gastric (AG) and IM one year following *H. pylori* eradication. Watanabe et al[18] studied paired biopsy samples at pre- and post-eradication of *H. pylori*-infected patients with early GC (EGC) treated by endoscopic resection and found that *H. pylori*-positive patients exhibited low richness and evenness of bacteria with the deletion of several genera, including *Blautia*, *Ralstonia*, *Faecalibacterium*, *Methylobacterium*, and *Megamonas* with *H. pylori* eradication partially restoring microbial diversity after a median 13 months follow-up, although the microbial communities clustered into three separate groups: *H. pylori*-negative, pre-eradication, and post-eradication[18].

The gastric microbiome was also shown to influence *H. pylori* eradication effectiveness according to the study of Niu et al[19]. Patients who did not respond to quadruple therapy (bismuth plus esomeprazole, amoxicillin and clarithromycin for 14 days) were compared with those in which eradication was achieved and found that, although the phyla were the same, microbial diversity decreased, significantly lower species abundance in the treatment failure group compared with the successful group. *Rhodococcus*, *Lactobacillus*, and *Sphingomonas* were significantly enriched in the successful group[19].

There is still a debate regarding whether universal eradication of *H. pylori* has any beneficial effects or potentially some negative effects, including childhood asthma and other atopic disorders[3], antibiotic-associated diarrhea, including severe *Clostridioides difficile*-associated diarrhea[20]. Therefore, universal eradication of *H. pylori* should be based on each individual patient benefit-risk ratio[20].

ACID SUPPRESSION THERAPY

Differential levels of acid secretion in the stomach contribute to colonization by non-*H. pylori* microbes. Hypochlorhydria is a long-term consequence of chronic *H. pylori* infection, with a decrease in gastric pH due to *H. pylori*-induced suppression of the gastric proton pump or the atrophy. When there is high acid production, *H. pylori* colonizes the gastric antrum and leads to antrum-predominant gastritis, however, when low acid production exists the location of gastritis is dominant in the corpus[10].

The use of proton pump inhibitors (PPIs) to control GERD is wildly used in adult patients and currently ~60% of adults are using them[21]. Long term treatment with acid-blocking agents has lasting effects on the gastric microbiome. PPI treatment promotes bacterial growth, with a higher number of cultivable non-*H. pylori* bacterial in the stomach. PPI induces a higher diversity of bacterial species in the stomach with an increased abundance of Firmicutes and Fusobacteria and a decrease in Bacteroidetes. At the genus level, *Streptococcae* increased in number following PPI consumption[7].

GASTRIC PATHOLOGY SUCH AS ATROPHY, IM AND GC

H. pylori is recognized as a class I carcinogen for GC. Infection with this bacterium can initiate chronic gastric inflammation in the stomach, destroying the hydrochloric acid-secreting glands, which can progress to precancerous lesions, such as AG and IM[3].

In an insulin-gastrin transgenic mouse model, mice infected with *H. pylori* and commensal flora developed more severe gastric lesions than *H. pylori*-infected germ-free mice. Moreover, mice with commensal flora had earlier development of gastrointestinal intraepithelial neoplastic[3]. In contrast, a recent systemic review did not find significant differences in the microbiome profiles between individuals with superficial gastritis (SG), AG, and IM, although some of the studies included were small and underpowered[3].

Bacterial abundance and diversity were significantly lower in gastric microbiota from CAG patients compared to controls, with Firmicutes being more frequent in cases, whilst Bacteroidetes and Fusobacteria were higher in controls[14]. Moreover, the genus *Streptococcus* was positively correlated with severe OLGA/OLGIM stages linked to a higher risk of GC[14].

Deng et al[10] studied microbiome in different anatomical locations of the stomach during the progression from gastritis to GC: the antrum and the corpus of patients with GC were different than CG patients, being strongly associated to the *H. pylori* infection status. Alpha diversity and species richness were similar between CG and GC, independently from *H. pylori* status. Proteobacteria levels were slightly higher in *H. pylori* positive specimens in both the antrum and corpus, but important changes also occurred at the order level.

Gastric microbiome dysbiosis occurred in gastric carcinogenesis according to a systematic review[22]. GC group showed lower species number and Simpson index, higher abundance of Firmicutes at the phylum level and of *Streptococcus* and *Lactobacillus* at the genus level compared with non-cancer group. The relative abundance of other phyla or genera did not change. Subgroup analyses indicated that the source of samples was the major reason of inter-study heterogeneity[22].

The microbial microenvironment in CG, fundic gland polyps (FGPs), low-grade intraepithelial neoplastic (LGIN) and EGC was studied by Li et al[8] and found that the microbiome in gastric LGIN seems to be like EGC in terms of functional prediction. Neoplastic lesions showed a significant difference to CG or FGPs according to beta diversity. *Paracoccus*, *Blautia*, *Barnesiella*, *Lactobacillus*, *Thauera*, *Collinsella* were significantly enriched in gastric neoplastic mucosa (LGIN and EGC) compared to non-neoplastic tissues (CG and FGPs). In contrast, *Pseudomonas* and *Kingella* decreased in neoplastic tissue. FGPs showed a distinctive microbial network system that negatively interacted with *Helicobacter*[8].

Some scholars[16] described enriched microbiota of GC patients with *Lactobacillus*, *Clostridium* and *Rhodococcus*, *Fusobacterium* or *Staphylococcus*, and *Veillonella*. *Streptococcus* and *Prevotella* have been reported as both enriched and depleted in the gastric microbiota of GC patients. Importantly, *Lactobacillus*, *Clostridium*, *Fusobacterium*, and *Veillonella*, have been identified in the transcriptionally active GC microbiota[16].

Firmicutes were more frequent and Proteobacteria less frequent both in the IM and EGC when comparing to controls[9]. Relative frequency of *H. pylori*, when present, was much higher in the controls (83%) than in the other groups (IM 1%, EGC 27%). Two bacteria were shown to progressively increase from controls to IM then to cancer: *Gemella* from 1.48 to 3.9%; and *Streptococcus* from 19.3 to 33.7%[9]. The lipopolysaccharide and ubiquinol biosynthesis pathways were more abundant in IM, whilst the sugar degradation pathways were under-represented in IM[23].

Although some studies[16] suggested a shift in the structure, composition, and functions of the gastric microbiome from CG to GC a unique GC-associated microbiome profile has not been consistently identified. Colonization with bacteria other than *H. pylori* may contribute to perpetuating chronic inflammation and to increasing GC risk.

TUMOUR AND NON-TUMOUR TISSUES

The gastric microbiome was studied within the neoplastic stomach comparing tumour and non-tumour tissues[16]. Bacterial richness gradually decreased from normal tissue to the tumour periphery to the tumour tissue[16]. Moreover, *H. pylori* abundance decreased in the tumour tissue compared with non-neoplastic areas, suggesting that non-*H. pylori* bacteria may play a role in the development of GC[3]. These findings agree with previously reported reduction of *H. pylori* colonization at later steps of carcinogenesis by Correa and Piazuelo[24].

ROLE OF NON *H. PYLORI* BACTERIA IN GASTRIC DISEASES

In the pathogenesis of gastric diseases, a diverse collection of microorganisms, including viruses and fungi, may play a synergistic or antagonistic role[25]. As previously mentioned, colonization of the stomach by *H. pylori* modulates the acidity of the stomach and, as a result may promote the development of gastric diseases and in particular GC, due to the interaction between the resident microbes, the environment, and host immune response. Gastric colonization of non-*H. pylori* bacteria may represent an additional risk factor for the development of GC, independent of the *H. pylori* carcinogenic role[26].

Fusobacterium nucleatum is known to play a role in the progression of colorectal cancer and approximately one-third of resected cancer tissues from patients undergoing gastrectomy were positive for this bacterium according to Hsieh et al[27]. Colonization increased in late-stage cancer patients and was associated with poorer outcomes among patients also positive for *H. pylori*[27]. A higher relative abundance of *Actinobacteria* species showed a significantly increased risk of GC in a Korean population[28] and *Propionibacterium acnes* significantly increased in GC tissues, especially in *H. pylori*-negative tissues[29].

GASTRIC MICROBIOME IN *H. PYLORI*-NEGATIVE GC OR MALT LYMPHOMA

The gastric microbiome of *H. pylori* negative patients with GC was studied by Deng et al[10] who reported no important differences in microbiome profiles between CG and GC at the phylum level, while major changes occur at lower taxonomic levels[10]. IM and dysplasia had similar microbial profiles in *H. pylori*-negative GC patients with lower diversity than SG group; GC patients had the lowest bacterial richness[30]. Burkholderiaceae abundance continuously increased, while Streptococcaceae and Prevotellaceae abundance decreased, across precancerous lesion stages from AG to dysplasia[30].

Lower alpha diversity was also observed in *H. pylori*-negative MALT lymphoma patients, compared with controls[31]. *Burkholderia* and *Sphingomonas* genera were more abundant while *Prevotella* and *Veillonella* were less abundant in MALT lymphoma patients. Functional prediction showed that "replication and repair", "translation," and "nucleotide metabolism" gene pathways were down regulated in MALT lymphoma patients[31].

In conclusion, the relationship between the gastric microbiota and GC should be clarified, overall, the associative *vs.* causative role and further prospective longitudinal studies including large numbers of well-characterized and controlled patients are needed[16].

VARIATIONS IN GASTRIC MICROBIOTA ARE NOT ASSOCIATED WITH: AGE, GENDER, ETHNICITY, OR TYPE OF FOOD INGESTED

Most of the papers published between 2021 and 2022 confirmed minor variations associated with age, gender, ethnicity or type of food ingested. Eradication treatment supplemented with probiotics showed enrichment of *Bifidobacterium* in gastric mucosa and *Lactobacillus* in gastric juice, whilst *Fusobacterium* and *Campylobacter* decreased[17]. Microbial diversity was similar to *H. pylori*-negative subjects. The diversity, community structure, and composition of gastric microbiome was altered by probiotics monotherapy increasing *Bifidobacterium* and *Lactobacillus*. *Fusobacterium*, a potentially pathogenic bacteria, increased after probiotic monotherapy[17].

CONCLUSIONS

In summary the results of the papers published between 2021 and 2022 confirmed *H. pylori* dominancy in the non-atrophic stomach microbiota with a progressive dysbiosis occurring as a result of the cascade of histological changes towards gastric carcinogenesis. Some authors suggested that specific modulation of these bacteria might change GC risk[9]. Microbial communities in GC and in CG are distinct, but a consistent GC associated microbiota profile has not been identified. Multiple aspects, such as the descriptive nature of studies, the inclusion of low numbers of patients, differences in technical procedures for sampling, approaches to bioinformatics data analysis, the environmental and genetic background associated with the geographic origin of patients may influence the results obtained[16].

Conflict of Interest

The authors declare no conflict of interest.

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