REVIEW ARTICLE

Helicobacter pylori Infection and Gastric Microbiota

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Abstract

Owing to its strong acid production, the stomach was known to be a bacteria-free organ for many years. On the other hand, the presence of *Helicobacter pylori* (*H. pylori*) and other acid-resistant microbiota that are to persist in the stomach challenged this. It is now recognized that the existence of *H. pylori* and non-*H. pylori* species have been linked to the improvement of gastric disease; despite this, there is little published data on the interaction of gastric bacterial flora and the resultant effect on gastric health. The stomach has a unique microbiota including five major phyla, such as Firmicutes, Proteobacteria, Actinobacteria, Fusobacteria and Bacteroidetes. These phyla are identified in both *H. pylori*-infected and uninfected persons. The resident gastric microflora may mediate the role of *H. pylori* in the gastric diseases. This article aims to review previous studies that examine the impact of *H. pylori* infection and the effect of resident gastric microbiota on gut health and disease conditions.

Keywords: Gastric microbiota, *Helicobacter pylori*, Stomach.

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Background

The compound of human gastrointestinal microbiota tract has been well studied and a number of reports explaining the relationships between the diversity of microbiota in the human gastrointestinal tract and its influence on health and disease have been conducted.[1,2] The human gut microbiota includes about 100 trillion microbial substances comprising of many archaea, bacteria and viruses.[3] The development of the intestinal microbiome during the early stages of life affects the improvement of the mucosal immune system and an individual's susceptibility to some diseases.[3] The gastric was known to be a sterile organ owing to its strong acid production; however, the discovery of *Helicobacter pylori* (*H. pylori*) in 1982 followed by additional microbiota being identified in the stomach changed this notion.[4] Interest and research in the stomach's microbial community has expanded in recent years due to improvements in culture-independent methods.[5]

Helicobacter pylori is a microaerophilic gram-negative bacteria with spiral shaped and placed within the order of Campylobacterales.[6] It is a major human gastric pathogen that resides in more than 50% of the world's population.[6] Although more than 80% of the infected people remain asymptomatic,[7] in others it is capable of developing several gastric diseases such gastric cancer, peptic ulcers and chronic gastritis.[8,9] In the Elazig Province of East of Turkey, the prevalence of *H. pylori* infection was 76.1% in adults and 66.3% in children.[10,11] It was thought that the existence of *H. pylori* in the stomach inhibited the colonization of other non-*H. pylori* bacterial flora.[1] Nevertheless, recent studies have reported a wider image of the gastric microbiota that is not limited to *H. pylori*.[12,13]

Gastric Microbiota in Association with *H. pylori* Infection

Although non-*H. pylori* species have been related to the improvement of gastric disorders, the published information on the gastric bacterial flora are very limited.[14] Detection of the gastric microbiota is often dependent on the cultivation of gastric juice or mucosal biopsies[15] where reports have detected several genera of the Actinobacteria, Firmicutes, Fusobacteria, and Proteobacteria, as well as yeasts.[16,17]

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The gastric microbiota in a healthy population has a similar compound at both the genera level and phyla irrespective of geographical area and ethnicity.[1,5] Recent advances have shown that the gastric microbiota composition is diverse in *H. pylori*-infected and uninfected individuals. However, certain genera were at higher proportion in *H. pylori*-infected individuals.[12] In contrast to this, Bik et al.[18] suggested that no statistically significant discrepancy in the diversity of gastric microbiota between *H. pylori* positive and negative patients was found. However, in this study, 7 *H. pylori*-uninfected individuals identified by traditional methods were actually had *H. pylori*-positive results when tested using the DNA-based techniques.[18] Others have reported inconsistent properties of gastric microbiota in *H. pylori*-positive patients[21] (Table 1).

For *H. pylori*-negative subjects, a highly different gastric microbiota was present that included the 5 major phyla: Actinobacteria, Firmicutes, Bacteroidetes, Fusobacteria, and Proteobacteria; these studies used PCR and sequence-based techniques.[18,19,22] In strong agreement, the sequencing of 1,833 bacterial isolates obtained from gastric biopsies of 23 healthy adults also exhibited the same 5 major phyla. These came from a highly diverse bacterial community totaling 128 phylotypes

Table 1: Distribution of gastric microbiota in humans

Country	*Study population (number of subjects)*	*Type of samples, method*	*Distribution of gastric microbiota*	*References*
United States	23 adults (13 Caucasians, 5 Hispanics, and 5 African Americans)	Gastric biopsies, 16S rDNA clone library	Overall gastric microbiota: Proteobacteria (952 clones) Firmicutes (464 clones) Bacteroidetes (193 clones) Actinobacteria (164 clones) Fusobacteria (56 clones) Top 5 genera: *Streptococcus* (299 clones) *Prevotella* (139 clones) *Rothia* (95 clones) *Fusobacterium* (45 clones) *Veillonella* (41 clones) No. of phylotypes: HP+ve = 60 phylotypes HP−ve = 143 phylotypes	Bik et al.[18]
Sweden	6 adults (healthy individuals)	Gastric biopsies, 454 pyrosequencing	HP−ve = 262 phylotypes: Most prominent phylotypes were *Streptococcus, Actinomyces, Prevotella, Gemella* HP+ve = 93–97% of the reads belong to Proteobacteria	Andersson et al.[19]
Sweden	6 gastric cancer	Gastric biopsies, T-RFLP, 16S rRNA cloning and sequencing	102 phylotypes were identified including 5 phyla: Firmicutes (61% relative abundance) Bacteroidetes (11% relative abundance) Actinobacteria (7% relative abundance) Proteobacteria (6% relative abundance) Fusobacteria (3% relative abundance) Highly presented genera: Firmicutes: *Streptococcus, Lactobacillus, Veillonella, Prevotella* Bacteroidetes: different species of *Prevotella* Proteobacteria: alpha-, beta-, gamma-, delta-, and Epsilonproteobacteria, *Neisseria, Haemophilus*	Dicksved et al.[20]
Chinese	10 adults (5 normal, 5 gastritis)	Gastric biopsies, Cloning and sequencing of 16S rRNA	Clone percentage from normal and gastritis biopsies (average): Firmicutes: 22% in normal, 41% in gastritis Proteobacteria: 37% in normal, 20% in gastritis Bacteroidetes: 28% in normal, 25% in gastritis Actinobacteria: 8% in normal, 8% in gastritis Fusobacteria: 4% in normal, 6% in gastritis Overall top 5 genera: *Streptococcus* (254 clones) *Prevotella* (243 clones) Neisseriae (175 clones) *Haemophilus* (122 clones) *Porphyromonas* (68 clones)	Li et al.[21]
Puerto Rica, Venezuela, and United States	12 adults (10 Amerindians, 2 immigrants to the United States)	Gastric biopsies, PhyloChip (DNA microarray)	Phyla identified in HP+ve ($n = 8$): Proteobacteria (classes Alpha, Delta, Epsilonproteobacteria) Acidobacteria Spirochaetae Phyla identified in HP−ve ($n = 4$): Actinobacteria Firmicutes Bacteroidetes	Maldonado-Contrerase et al.[22]

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Country	*Study population (number of subjects)*	*Type of samples, method*	*Distribution of gastric microbiota*	*References*
			Fusobacteria	
			Proteobacteria (classes Beta and Gammaproteobacteria)	
Chinese	103 patients with dyspeptic symptoms	Gastric biopsies, MALDI-TOF MS	In 65% of HP+ve patients, 201 non-HP bacterial isolates were identified. The dominant species were:	Hu et al.[14]
			Streptococcus	
			Neisseria	
			Rothia	
			Staphylococcus	
Spain	12 healthy persons	Gastric biopsies and gastric juice, Culture nested PCR pyrosequencing of 16S rRNA	Most abundant phylum:	Delgado et al.[5]
			Firmicutes	
			Proteobacteria	
			Actinobacteria	
			4 main genera identified:	
			Propionibacterium	
			Lactobacillus	
			Streptococcus	
			Staphylococcus	
Korean	31 patients (11 noncardia GC, 10 intestinal metaplasia, 10 chronic gastritis)	Gastric biopsies, 454 pyrosequencing	Dominant phyla identified:	Eun et al.[23]
			Chronic gastritis—Epsilonproteobacteria (contain *H. pylori*)	
			Gastric cancer—Bacilli (Streptococci and Lactobacilli)	
Spain	51 children	Gastric biopsies, V4-16S ribosomal RNA gene high-throughput sequencing	HP+ve ($n = 18$):	Llorca et al.[24]
			Higher abundance of *Helicobacter* genus (66.3%)	
			Abundant of Epsilonproteobacteria	
			HP-ve ($n = 33$):	
			0.45% *Helicobacter* genus	
			Abundant of gamma- and betaproteobacteria	

from 8 bacterial phyla.[18,25] The gastric microbiome in *H. pylori*-negative subjects was mostly predominated by the same phylum, however, with diverse percent abundances: with 52.6% of Proteobacteria, 26.4% of Firmicutes, 12% of Bacteroidetes and 6.4% of Actinobacteria.[24] In other studies, the most abundant phyla of Firmicutes, Bacteroidetes, and Actinobacteria were found in *H. pylori*-negative subjects.[26] The common genera observed in *H. pylori*-negative individuals includes *Gemella*, *Prevotella*, and *Streptococcus*.[19]

Like *H. pylori*-negative individuals, *H. pylori*-positive humans' stomach were also abundant with Proteobacteria, Firmicutes, and Actinobacteria.[19] However, in samples from 3 *H. pylori*-positive individuals, *H. pylori* was the dominant species and accounted for more than 90% of all sequence reads using 454 pyrosequencing technology.[19] Here, only 33 phylotypes were identified, which was 229 fewer than were found in *H. pylori*-negative individuals[19] This suggests that *H. pylori*-colonized individuals harbor a significantly lower diversity of gastric microbiota and may suggest some inhibitory effects on the colonization of non-*H. pylori* gastric bacteria. This is also suggested in other studies where *H. pylori* dominates the gastric microbiota and results in a reduced bacterial diversity. The *H. pylori* eradication yielded a restoration of microbiota in the gastric environment where the abundance of *Helicobacter* in pretreatment and posttreatment was 83.7 and 6.88%, respectively, and the relative abundance of non-*H. pylori* Proteobacteria raised from 4.55 to 51.7%.[27] It also appears that the relative abundance changes with Proteobacteria, Spirochaetes, and Acidobacteria increasing, and Actinobacteria, Bacteroidetes, and Firmicutes decreasing in *H. pylori*-positive individuals.[28] A total of 44 phyla were identified from 12 corpus biopsy samples from 8 *H. pylori*-positive individuals with the most common being Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes.[22] This was performed using high-density 16S rRNA gene microarray (PhyloChip).[22] Again and in agreement with the above study, the relative abundance of Acidobacteria, Proteobacteria, and Spirochaetes increased while Actinobacteria, Bacteroidetes, and Firmicutes decreased in *H. pylori*-positive samples. In *H. pylori*-positive pediatric patients, the major phylum were Proteobacteria (69.3%), Firmicutes (14.3%), Bacteroidetes (8.2%), and Actinobacteria (6%).[29] The higher percentage of Proteobacteria is likely to be due to the presence of *Helicobacter* genus in these samples. It has also been shown that the compound of microbiota between *H. pylori*-negative controls and *H. pylori* positive individuals were diversities in the total number of anaerobes and clostridia.[30]

Gastric Microbiota Compositions in Patients with Gastric Diseases

The above highlights the alterations in the microbiota composition in relation to the infection with *H. pylori.*[31] Below we discuss the compound of the gastric microbiota in *H. pylori*-infected and

uninfected patients with gastric disorders (e.g. peptic ulcer, chronic gastritis, and gastric cancer).[31]

A study by Eun et al.[23] suggested that differences exist in the compound of gastric microbiota in people with chronic gastritis, precancerous lesions and gastric cancer. The same authors also reported that the gastric flora may also partially influence the impact of *H. pylori* infection in carcinogenesis.[23] Diversities in the gastric microbiota in healthy individuals are unlikely to be due to ethnicity or geographical region because these factors have been shown to have a similar gastric microbiota composition.[1]

Chronic Gastritis

In *H. pylori*-positive individuals with antral gastritis, the abundancy of phyla Proteobacteria was decreased and Firmicutes was increased compared to *H. pylori*-negative subjects.[21] In patients with atrophic gastritis, *Streptococcus* increased whilst *Prevotella* decreased when compared to healthy subjects.[1] In addition, those with chronic gastritis showed a higher rate of bacterial growth than individuals not having gastritis.[12] This was performed on gastric samples from 50 individuals having chronic gastritis and 53 samples without chronic gastritis.[12] By using matrix assisted laser desorption ionization-time of flight (MALDI-TOF), the species that were significantly associated with gastritis from mucosa samples were *H. pylori*, *Streptococcus mitis*, *Neisseria flavencens*, and *Nieseria perlava* and species associated with gastritis from gastric juice samples were *S. oralsi*, *Rothia mufilaginosa*, and *Nieseria perlava*.[12] The dominant species associated with gastritis such as *Neisseria*, *Rothia*, *Staphylococcus* and *Streptococcus* were identified and varied from the acid resistant bacterial species as indicated earlier in healthy individuals.[14,32]

Peptic Ulcer Disease

A study demonstrated that despite being no significant differences between uninfected and *H. pylori*-infected persons, the isolation of streptococci was related to the presence of peptic ulcers.[33] This analysis was performed using molecular methods such as MALDI-TOF MS biotyping and 16S rRNA sequencing on samples obtained from 215 Malaysian patients.[33] In China the common species identified from *H. pylori*-positive gastric biopsy specimens were *Streptococcus*, *Neisseria*, *Rothia*, and *Staphylococcus* using the MALDI-TOF MS technique.[14] These isolated bacteria are more acid-susceptible and differed from *H. pylori*-negative volunteers. In addition, the *H. pylori*-positive individuals with gastric ulcers, a much lower prevalence of non-*H. pylori* species were identified compared to those with nonulcer dyspepsia.[14]

Gastric Cancer

Gastric cancer has various risk factors which includes *H. pylori* infection, host genetic and environmental factors. *H. pylori* infection is a well-studied risk factor for gastric adenocarcinoma; however, cancer risks can alter greatly between different populations that have a relatively similar *H. pylori* prevalence.[34] One of the possible factors is the interaction of different *H. pylori* strains and the compound of gastric microbiota.[4] The different in gastric microbiota composition between two populations within the same country with different risks of gastric cancer has been indicated in a previous study.[4] They found that operational taxonomic units (OTUs) identified as *Leptotrichia wadei* and a genus *Veillonella* were greatly abundant in those with high gastric cancer risks (Túquerres town).[4] Those with a lower gastric cancer risk had a high abundance of OTU's assigned to *Staphylococcus*, *Neisseria flavescens*, a member of family Porphyromonadaceae, *Flavobacterium* and *Rothia* sp. (Tumaco town).[4]

Gastric Microbiota Compositions in Animal Studies

Recent studies in a diverse range of animal models (mice,[35–37] Mongolian gerbils,[38,39] dogs,[40] Eastern oysters,[41] horses,[42,43] and yellow catfish[44]) have reported the potential role of the gastric microbiota in different animal species.[36,45,46] Several papers have reported the effect of bacterial infection on gastric mucin expression. Muc1 expression in the stomach of mice showed a decrease level in acute and chronic *H. pylori* infection.[47] In *Helicobacter felis*-infected mice, increased Muc4 and Muc5b gene expressions were observed, while the expression of Muc5ac was unaltered or had decreased in level of expression.[48,49]

In germ-free INS-GAS mice the supplementation of just 3 species of commensal gastric and intestinal microbiota (ASF519 *Bacteroides* spp., ASF356 *Clostridium* spp. and ASF361 *Lactobacillus murinus*) in conjunction with *H. pylori* infection were adequate to stimulate gastric neoplasia to the same extent as observed in mice harboring a complex microbiota.[45] Significantly, these genera are enhanced in the stomach of patients with premalignant and malignant lesions.[50] The contributory role to the constitution of the gastric microbiota in stimulating disease has been further supported by successfully delaying the beginning of gastric cancer in INS-GAS mice using antibiotic therapy that was undependent upon the presence of *H. pylori*.[50,51]

Earlier studies have reported that the whole or individual microbiota can either contribute to noxious effects by the carcinogenic nitrosamines formation under hypochlorhydric conditions[52] or show positively influences, by decreasing the pro-inflammatory cytokines secretion,[53–56] improving the healing of gastric ulcer,[46,57] or inactivating the growth and colonization of *H. pylori*.[53,58]

The gastric microbiota has been shown to be altered by the infection of *H. pylori* in both gerbils and mice.[36,39,59] Helminth infections are at higher prevalence in children infected with *H. pylori* and were showed to decrease the survival-time risk for gastric adenocarcinoma.[60] In rodent models, co-infection with helminth did not decrease the grade of *Helicobacter*-caused inflammation but did delay the improvement to premalignant gastric lesions.[60]

The effect of *Heligmosomoides polygyrus* co-infection with *H. pylori* in INS-GAS mice showed that despite having similar gastric inflammation and increased levels of proinflammatory mRNA, FoxP3+ cells in the corpus increased, *H. pylori*-related gastric atrophy and dysplasia were decreased, and *H. pylori*-caused alterations in the gastric flora was prevented.[60]

Conclusion

In spite of the fact that major improvements in research techniques have been made to figure out the correlation between *H. pylori* and the gastric microbiota in the incidence of gastric cancer, ongoing and future studies should be required in well-designed human populations. Research needs to be conducted to compare the variations of the gastric microbiota composition in uninfected and *H. pylori*-infected patients with and without different gastric diseases and to enhance the knowledge of the microbiota composition, diversity, and dynamics along with species interactions and mechanism driving/functional phyla in

the onset and prevention of gastric diseases, including gastric cancers.

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