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STOMACH BUGS: WHAT'S NEW IN 2024

K. Lehr[1], C. Thon[1], M.P. Ebert[2], A. Link[1]

[1]Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University Hospital, Magdeburg, Germany
[2]Department of Medicine II, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

Corresponding Author: Alexander Link, MD, Ph.D; email: alexander.link@med.ovgu.de

Abstract – Many open questions remain about the microbes in the stomach, an environment long considered inhospitable. Our understanding of the gastric environment has been revolutionized over the last four decades by the identification of *Helicobacter pylori* (*H. pylori*). Despite significant advances, we are still unraveling the complex interactions within this ecosystem and identifying new microbial players in the acidic environment. In this review, we summarize the annual knowledge on the gastric microbiota published from 2023 to 2024, providing a comprehensive overview of the latest findings. Recent data shed light on the dynamics of the microbiome in the healthy state, as well as after *H. pylori* eradication and antibiotic resistance. Research on the microbiome in gastric cancer is revealing information about microbiota transitions during cancer progression and the potential role of the microbiome in assessing disease phenotype. The evidence surrounding *Fusobacterium nucleatum (F. nucleatum*) provides strong support for its clinical impact, although other bacteria and viruses also contribute. We look forward to further developments in this area, particularly in translating knowledge into clinical practice to improve the diagnosis and treatment of gastric diseases.

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

INTRODUCTION

Over the past 40 years, the stomach, once believed to be a sterile organ, has been shown to be colonized by the bacterium *Helicobacter pylori* (*H. pylori*). Initial progress in understanding the microbial environment of the stomach was facilitated by simple laboratory advancements and the dedication of generations of scientists[1]. Nevertheless, numerous questions remain regarding the physiological host-microbe interactions, the role of microbial species in healthy stomach function, and most notably, the involvement of these microbes in gastric diseases. Among these diseases, gastric cancer stands out as one of the deadliest cancers worldwide with still limited therapeutic options[2].

Unraveling the gaps related to the microbial environment of the stomach remains a priority. Given the rapid and continuous advancements in this field, it can be challenging to stay abreast of scientific developments. Therefore, it is crucial to obtain a summarized overview of the most relevant issues related to emerging topics in *H. pylori* and the gastric microbiome to stay updated with the most significant findings and identify key players in the acidic environment of the stomach.

Although our understanding of the microbial environment in the stomach has been revolutionized over the past four decades by the identification of *H. pylori* and other microbial flora, we are still unraveling the complex interactions and identifying new players in this acidic environment. In this review, we provide a comprehensive overview of recent findings on gastric microbiota reported from 2023 to 2024. We summarize the yearly advances in recent knowledge of the gastric microbiota, highlighting significant discoveries and ongoing research from the past year (Table 1).

TABLE 1. SUMMARY OF SELECTED PUBLICATIONS RELATED TO GASTRIC MICROBIOTA 2023-2024

Main topic	Reference	Main message
Healthy	Pivetta et al[5]	Gender-associated microbiome changes and autoimmune gastritis-related dynamics.
Stomach	Deissová et al[3]	Advantage of the V1-V2 primers to improve taxonomic richness and reproducibility.
	She et al[6]	Multi-organ microbiome analysis reveals microbial diversity, key species and interactions.
H. pylori	Sorini et al[8]	*H. pylori* colonization alters the gastric microbiome and immune cell landscape.
	Mannion et al[14]	Characterization of the gastric microbiome using whole genome sequencing.
	Dewayani et al[13]	Difference in microbiome associated with *H. pylori* resistance.
	Yu et al[7]	Microbial differences between symptomatic and asymptomatic individuals infected with *H. pylori*.
	Peng et al[12]	Microbiota-metabolite interactions and influence on the development of *H. pylori*-associated gastric lesions.
	Hua et al[9]	Virulent *H. pylori* infection and lower microbial richness associated with atrophic gastritis.
	Peng et al[10]	Effect of *H. pylori* eradication on oral *H. pylori* frequency and oral microbiota diversity.
	Nakano et al[37]	Changes in the gastric microbiota may influence early GC development after *H. pylori* infection.
MALT	Martin et al[15]	Characterization of microbial alterations in patients with MALT lymphoma.
Gastric cancer	Li et al[17]	*Fusobacterium*, *Leptotrichia* and several lactic acid bacteria are commonly enriched in GC.
	Lehr et al[19]	*Fusobacterium nucleatum* associated with worse prognosis in GC.
	Ai et al[18]	Increasing abundance of *Acinetobacter*, *Pasteurella*, *Streptomyces*, *Chlamydia* and Lysobacter during tumor progression.
	Oosterlinck et al[35]	Mucins influence the microbial microenvironment and are associated with prognosis in GC patients.
	Freitas et al[28]	AI-based microbiome data analysis for GC detection and prevention strategies.
	Byrd et al[22]	Diversity of oral cavity-derived microbes linked to microsatellite instability.
	Yue et al[24]	*Kytococcus sedentarius* and *Actinomyces oris interact* with methylation changes in immune genes and *Staphylococcus saccharolyticus* affects cell proliferation.
	Komori et al[21]	Changes in bacterial composition, including reduced diversity in saliva after GC resection.
	Abate et al[23]	No significant difference in microbial diversity and enrichment between the ancestry groups.
	Zhang et al[36]	The virome has a prognostic potential in GC.
	Lee et al[25]	Butyrate reduced PD-L1 and IL-10 expression in immune cells and inhibited GC tumor growth *in vivo*.
	Yu et al[26]	Restoring gut microbial butyrate enhances CD8+ T cell cytotoxicity thereby inhibiting GC development.
	Chen et al[27]	Metaproteome analysis of tongue coating proteins for diagnosis of patients at risk for GC.
	Kim et al[29]	Combined DNA methylation and gastric microbiome as a biomarkers for predicting *H. pylori*-negative GC.

METHODOLOGY

To provide readers with the most recent data published in the past year, we performed a systematic literature search of papers using the following terms: “microbiome”, “microbiota”, “virome”, “stomach”, “gastric cancer”, “gastritis”. The identified papers were screened by the

authors to identify potentially the most emerging original scientific papers with translational and clinical relevance published between April 2023 and March 2024 or directly related to the topic of interest.

STOMACH MICROBIOTA IN A HEALTHY STATE

The composition and function of the gastric microbiota in a healthy state play a crucial role in maintaining gastrointestinal homeostasis. However, it is critical to use the best available methodology and consider the influencing factors to understand the full picture. The selection of primers plays a decisive role in microbiome analysis as it significantly influences the quality and outcome of the results. Deissová et al[3] analyzed the microbiome from esophageal, gastric, and duodenal biopsies using 16S rRNA amplicon sequencing. They employed the commonly used V4 primers along with primers for the V1-V2 region. When using the V4 primers, approximately 70% of amplicon sequence variants aligned with the human genome. In contrast, the V1-V2 primers showed no off-target amplification[3].

In addition to technical aspects, many other factors may impact microbial dynamics[4]. One aspect that remains open is the impact of gender on the stomach environment. Pivetta et al[5] investigated the relationship between gender and microbiome in healthy patients and subjects with autoimmune gastritis. They found that women with healthy stomachs had higher bacterial abundance, but less microbial diversity compared to men. Gender differences in taxa abundance were found at both the phylum and genus levels. In autoimmune gastritis, likely due to hypochlorhydria and the non-acidic intragastric environment, autoimmune atrophic gastritis was associated with a reversal of gender differences in gastric bacterial abundance and reduced biodiversity in males, showing a greater degree of dysbiosis in terms of reduced biodiversity in males.

Recent research has shed light on the diversity and dynamics of these microbial communities, revealing their major contributions to digestion, nutrient absorption, immune modulation, and carcinogenesis (Figure 1). Key microbial species, such as *H. pylori*, have been studied for their symbiotic or pathogenic roles in gastric health. Meanwhile, interest is not only focused on the few microorganisms well described so far but also on the microbial community and their interactions with each other and the host. She et al[6] examined the microbiome across various human organs

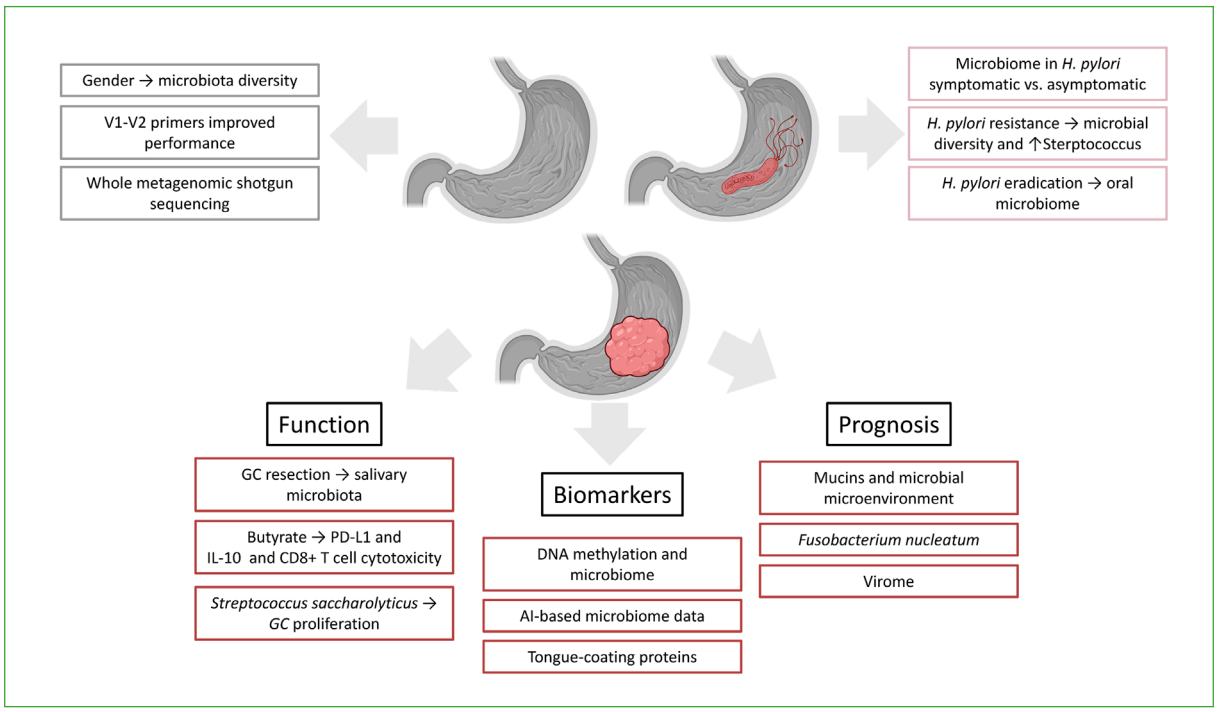

Figure 1. Summary of selected publications related to gastric microbiota 2023-2024.

using 16S full-length sequencing in 1608 samples from 53 sites of 7 organs, including the stomach. They analyzed microbial changes within organs and identified distinct signature microbes, their functional traits, and site-specific interactions. They found significant microbial diversity between organs and identified key microbial species coexisting in different organs. Notable microbial heterogeneity was observed between paired mucosa-lumen samples from the stomach, small intestine, and large intestine. Additionally, they provided the mapping of inter-organ microbial relationships along the digestive tract.

HELICOBACTER PYLORI AND MICROBIOME

H. pylori is a chronic infectious disease that dramatically impacts microbial structure and function. This chapter outlines several aspects of the interplay between *H. pylori* and the gastric microbiome.

H. pylori is, in most cases, an asymptomatic infection, but if there is a difference in microbiome between symptomatic and asymptomatic patients, it remains to be answered. Yu et al[7] examined the microbiome of these patients (n=31) and found that their gastric microbiota was similar to that of symptomatic patients at the phylum and genus levels but differed from uninfected patients. Asymptomatic *H. pylori* infection (HPI) patients showed significantly reduced microbial diversity and richness compared to uninfected individuals. The authors identified Sphingomonas to be differentially abundant between symptomatic and asymptomatic HPI (AUC 0.79), suggesting that microbiome composition and interspecies interactions might influence the presence of gastric symptoms[7].

To characterize the immunological impact of asymptomatic *H. pylori* infection, Sorini et al[8] investigated the microbiome and immune response. As expected, they observed substantial changes in gastric microbiome composition and immune cell profiles compared to non-infected individuals. Asymptomatic HPI showed almost no type 2 innate lymphoid cells (ILC2) and a predominance of ILC3s. Furthermore, there was a notable increase in NKp44+ natural killer cells relative to total ILCs, correlating with specific microbial taxa. Additionally, CD11c+ myeloid cells, activated CD4+ T cells, and B cells were expanded in HPI patients[8]. This shows a clear influence of HPI on the immune system of asymptomatic patients.

Hua et al[9] investigated the potential microbial differences in patients with atrophic and non-atrophic gastritis and correlated them with the serological type of HPI. As expected, patients with atrophic gastritis were more likely to be infected with more virulent *H. pylori* strains and had significantly lower gastric microbiota richness than patients with non-atrophic gastritis. They observed a symbiotic shift between Helicobacter and non-Helicobacter species in relation to atrophic gastritis. They also found that bile reflux promoted the colonization of oral microbiota in the stomach.

The question of the potential impact of *H. pylori* eradication on the gastric microbiome remains of interest. Peng et al[10] analyzed the effects of vonoprazan-amoxicillin dual therapy with probiotic supplementation for *H. pylori* eradication on oral microbiota. The authors analyzed tongue coating samples from 60 patients at three different time points and healthy subjects using 16S rRNA sequencing. Although *H. pylori* was identified in both *H. pylori*-positive and negative groups, eradication substantially reduced its presence. Overall, the vonoprazan-based dual therapy, but not probiotic supplementation, significantly affected oral microbial diversity, structure, and function, showing a suppressive impact on the proliferation of Firmicutes and Lactobacillus[10].

The impact of *H. pylori* eradication has been further investigated by Nakano et al[11] in early gastric cancer (GC) patients compared to non-cancer patients. They observed no significant differences in alpha diversity and mean abundance at the phylum level. However, at the genus level, the early GC group had significantly lower mean abundances of unclassified *Oxalobacteraceae*, *Capnocytophaga*, and *Haemophilus* than the non-GC group, but the cohort may be too small to make any functional valid conclusions[11].

Peng et al[12] analyzed the influence of HPI on the gastric microbiome and metabolites in patients with successfully and unsuccessfully eradicated *H. pylori*. The authors found that *H. pylori* eradication resulted in significant differences in 81 metabolites. Different metabolites were negatively associated with the microbiota of biopsies, such as glycerophospholipids and *H. pylori*, and were reversed following successful eradication. They further showed negative correlations

between glycosylceramides and *Fusobacterium*, *Streptococcus*, and *Gemella* in *H. pylori*-positive biopsies, highlighting the potential value of metabolites in understanding the microbial physiology of the stomach[12].

Dewayani et al[13] evaluated the influence of *H. pylori* resistance on the microbiome alteration of the stomach. In a cohort of 69 patients with predominant metronidazole resistance, they observed elevated α-diversity under multidrug resistance conditions. Triple-resistance evaluated using E-test was associated with relatively lower *H. pylori* and increased Streptococcus abundance[13].

Most studies continue to implement 16S rRNA sequencing, but more advanced sequencing techniques may provide a more comprehensive view of microbial composition. Mannion et al[14] investigated gastric biopsies of patients with and without high GC risk and with and without HPI using whole metagenomic shotgun sequencing (WMS). They found that the most common taxa were bacteria, non-human eukaryotes, and viral genera. These included *Staphylococcus*, *Streptococcus*, *Bacillus*, *Aspergillus*, and *Siphoviridae.* The *H. pylori*-positive samples were dominated by these bacteria. In comparison to 16S rRNA sequencing and cultivation methods, WMS allowed the identification of a greater diversity of bacterial taxa performed on the same biopsies. As expected, *H. pylori*-positive samples were enriched for *H. pylori*-virulence factors, such as vacA, cagA, and urease, while *H. pylori*-negative samples were enriched for carbohydrate and amino acid metabolism genes. Nevertheless, further research is needed to evaluate the overall benefit of WMS for stomach microbiome research[14].

STOMACH MICROBIOTA IN MALT

Changes in the microbiome in mucosa-associated lymphoid tissue (MALT) lymphoma and their influence on the microbiota were examined by Martin et al[15]. While there were no changes in diversity, MALT was associated with a higher abundance of *Actinobacillus*, Lactobacillus, and *Chryseobacterium*, whereas *Veillonella*, *Atopobium*, *Leptotrichia*, *Catonella*, *Filifactor*, and *Escherichia/Shigella* were more abundant in controls. Patients in remission had higher *Haemophilus* and *Moraxella*, whereas *Atopobium* and *Actinomyces* were more abundant in refractory patients. Whether those species functionally contribute to lymphogenesis or to the clinical phenotype, however, needs further investigation[15].

STOMACH MICROBIOTA IN GASTRIC CANCER

Understanding the microbial function and its interaction with the host may be of the greatest value in understanding gastric carcinogenesis. With a decline in global *H. pylori* infection[16], we may be able to see new signals that would provide an additional view on *H. pylori*-associated and *H. pylori* non-related gastric cancers.

In a meta-analysis of nine different studies involving mainly Chinese patients, Li et al[17] discovered that certain microbes, such as *Fusobacterium*, *Leptotrichia*, and various lactic acid bacteria were frequently and significantly enriched in GC patients compared with patients with gastritis. These microbes showed a strong ability to differentiate GC samples from gastritis. Oral microbes were more abundant in GC patients than in patients in precancerous stages. Furthermore, a comparison between the gastric fluid microbiome and the gastric mucosa indicated a convergent dysbiosis in progressive gastric disease[17].

The changes in the microbiota associated with the progression of gastric disease were further investigated by Ai et al[18]. The authors found that the gastric tissue microbiome comprises over 1400 genera, with seventeen core genera identified. Among these, *Helicobacter* and *Lysobacter* were significantly enriched in normal tissue, while Pseudomonas was enriched in tumorous tissues. Interestingly, *Acinetobacter*, *Pasteurella*, *Streptomyces*, *Chlamydia*, and *Lysobacter* showed a significant increase during tumor development and exhibited strong intra- and inter-correlative relationships with each other or with other genera (25). The results for Helicobacter are well established and could also be validated in two other recent publications, in Lehr et al[19] with tumor tissue at the DNA level and in Nikitina et al[20] with tumor biopsies at DNA and RNA levels.

However, it is not only tumor progression that influences the microbiome, but treatment also has an effect, as the study by Komori et al[21] shows. The authors analyzed saliva and gastric fluid samples from patients who had undergone gastrectomy and found that the number of bacterial species in the salivary microbiota decreased, and the bacterial composition changed after the resection of GC. In addition, they identified several bacterial genera in the salivary microbiota that differed significantly, some of which also showed similar changes in the gastric fluid microbiota. These results suggest that changes in the gastric environment affect the oral microbiota, emphasizing the close relationship between the oral and gastric fluid microbiota[21].

The work of Byrd et al[22] also clearly shows this relationship. The diversity of microbes originating from the oral cavity was linked to microsatellite instability (MSI), which is associated with higher tumor immunity and mutational burden in patients with colorectal cancer (CRC) and GC. Overall, the results suggest that the intratumoral microbiota may vary according to MSI status and influence the tumor microenvironment[22].

Recent efforts have been made to assess the human microbiota as a whole, including its genetics and regional and ethnic diversity. Abate et al[23] analyzed 1042 GC patients using next-generation sequencing data from an institutional Integrated Mutation Profiling of Actionable Cancer Targets assay and The Cancer Genome Atlas (TCGA) group. They examined genomic alterations and microbial profiles in patients of African, European, and Asian ancestry and assessed 8023 genomic alterations. Patients of African descent had significantly more CCNE1 alterations and fewer KRAS alterations, while patients of East Asian descent had significantly fewer alterations in the PI3K pathway compared to other groups, but microbial diversity and enrichment did not differ significantly between the ancestry groups[23].

However, current efforts are being made to go beyond the description of microbial alterations. Yue et al[24] showed that *H. pylori* and other cancer-associated microorganisms are associated with the development, progression, or prognosis of gastric adenocarcinoma. *Kytococcus sedentarius* and *Actinomyces oris* showed significant interactions with methylation changes in immune genes and were associated with prognosis. Mechanistic *in vitro* experiments confirmed that *Staphylococcus saccharolyticus* can promote the proliferation and cloning of gastric cells by modulating the expression of the ZNF215 gene. Their data suggest that the bidirectional mediation effect between intratumoral microorganisms and host epigenetics plays a critical role in the distant metastasis of cancer cells and the deterioration of survival in the tumor microenvironment of patients with GC[24].

Lee et al[25] studied the gut microbiome of GC patients to reverse immunosuppression in their immune and cancer cells by modulating microbiome metabolites. They measured the levels of PD-L1 and IL-10 in peripheral blood immune cells of GC patients and their microbiome from stool samples. PD-L1 and IL-10 levels were higher in immune cells from GC patients compared to healthy controls, and immunosuppressive factors were increased in immune and tumor cells from GC patients. Faecalibacterium and Bifidobacterium were less abundant in the gut flora of GC patients. Butyrate, one of the most important microbial metabolites, inhibited PD-L1 and IL-10 expression in immune cells and tumor growth in mice. These data suggest that restoring the gut microbiome and its metabolic functions has potential therapeutic implications for suppressing tumor growth and reversing immunosuppression in GC patients[25].

Yu et al[26] provided further evidence for the importance of butyrate in GC. In their study, they analyzed the composition of the gut microbiota and the levels of SCFA in the blood and stool of healthy individuals and GC patients. They found that GC patients had significantly fewer SCFA-producing bacteria compared to healthy controls. Antibiotic-pretreated mice transplanted with the fecal microbiota of GC patients developed more tumors and had lower butyrate levels during GC induction. Supplementation of butyrate during GC induction resulted in fewer tumors and an increase in IFN-γ+ CD8+ T cells. *In vitro* studies using GC cells and co-cultured CD8+ T cells showed that butyrate enhanced the cytotoxic function of CD8+ T cells against GC cells. These results suggest that the recovery of butyrate from the gut microbiome enhances the cytotoxicity of CD8+ T cells, thereby inhibiting the development of GC. Taken together, the recent research demonstrates once again that the microbiota and its metabolites are not bystanders in the progression of GC and that their role goes far beyond the role of *H. pylori* in the development of GC[26].

Given the emerging understanding of the interaction between GC and the microbiota, there is a need for practical insights from research that can be translated into clinical practice. One example would be new diagnostic tools for clinicians, preferably in a non-invasive manner without the

need for time-consuming endoscopy. The relationship between GC and oral microbiota may be one of the options for diagnostic development. Chen et al[27] performed a metaproteomics-based study of tongue-coating samples, which are a critical environment for oral microorganisms. Tongue-coating proteins were extracted and identified from 180 GC patients and 185 non-GC patients from five research centers in China. A machine learning model identified individuals at high risk for GC based on microbial proteins in the tongue coating. In GC patients, the human keratins KRT2 and KRT9 and the ABC transporter COG1136 were downregulated in the microbiota, indicating a reduced defense capacity of the tongue mucosa. A machine learning model using 50 microbial proteins from the tongue mucosa identified individuals at high risk for GC and achieved an AUC of 0.91 in the validation cohort. These results characterize changes in tongue-coating proteins in GC patients and highlight tongue-coating proteins as promising indicators for identifying high-risk groups for GC[27].

The study by Freitas et al[28], similar to that of Chen et al[27], aimed to use a machine learning-based method to identify cancer types but using tissue-specific microbial information for prediction. Algorithms were trained using samples to classify five cancer types: head and neck, esophagus, stomach, colon, and rectum. The results showed that the difficulty of accurately classifying samples increased as the specificity of the cancer site increased. The models performed well in predicting head and neck, stomach, and colorectal cancer, with over 90% accuracy for colorectal cancer in all studies. However, they often confuse rectal cancers with CRC and esophageal cancers with head and neck and stomach cancers. This suggests that cancers in anatomically adjacent areas are more difficult to identify due to microbial similarities. Despite these challenges, microbiome data, as well as metaproteomic data analysis using machine learning, hold promise for advancing cancer detection and prevention strategies, potentially reducing the burden of disease[28].

Despite the general enthusiasm for AI-based modalities, there have also been elegant studies exploring the diagnostic potential without AI tools. Kim et al al[29] investigated the potential of a combined DNA methylation and gastric microbiome signature to predict *H. pylori*-negative GC. Both DNA methylation and the gastric microbiome are associated with GC, but their combined predictive role has never been investigated. Methylation levels were significantly higher in GC patients than in controls. Higher TWIST1 methylation was an independent predictor of *H. pylori*-negative GC. The combination of TWIST1 methylation and GC microbiome index was significantly associated with *H. pylori*-negative GC. Thus, the combined TWIST1 methylation and GC microbiome index may serve as a biomarker for predicting *H. pylori*-negative GC[29].

In addition to the need for diagnostic tools, there is an emerging need to identify clinically relevant microbiome data that can impact clinical practice and patient care, such as assessing disease progression, prognosis, or predicting treatment response. A known interaction between microbial alterations (specifically *Fusobacterium nucleatum*) and prognosis has been reported for CRC[30], but there is also seminal evidence for an association between *F. nucleatum* and prognosis in GC[31]. These findings were recently confirmed by Hsieh et al[32] in a GC patient cohort from Taiwan, who also demonstrated that the combination of *F. nucleatum* infection and high tumor mutational burden serves as a potent biomarker for poor prognosis[32]. While *F. nucleatum* status was determined by qPCR in previous studies, Lehr et al [19] recently performed 16S rRNA sequencing to evaluate the association between the microbiome and prognosis in GC patients. They observed that the presence of *F. nucleatum* in tumor tissue, but not in adjacent tissue, was associated with worse overall survival regardless of GC classification. Whether targeting *F. nucleatum* may have therapeutic options remains to be answered, however, *F. nucleatum* has been reported to be associated with immune checkpoint blockade in lung cancer[33] and emerging data on *F. nucleatum* in CRC are also on the way.

For example, Wang et al[34] observed a significant (25.5%) improvement in disease-free survival in patients with CRC with pre-resection antibiotics targeting anaerobic bacteria. For studies in mice, a liposome-encapsulated silver-tinidazole antibiotic complex (LipoAgTNZ) was developed to eliminate tumor-associated bacteria in primary tumors and liver metastases without causing dysbiosis of the gut microbiome. CRC mouse models colonized with *F. nucleatum spp*. or *Escherichia coli Nissle spp*. responded to LipoAgTNZ therapy, resulting in long-term survival of more than 70% in two *F. nucleatum*-infected CRC models. Antibiotic treatment generated microbial neoantigens that induced anti-tumor CD8+ T cells. Heterologous and homologous

bacterial epitopes contributed to immunogenicity and induced T lymphocytes to recognize both infected and non-infected tumors. This strategy could be used to target tumor-associated bacteria to induce antitumor immunity and pave the way for microbiome immunotherapeutic interventions[34].

Another interesting aspect of the prognosis of GC is provided by the study of Oosterlinck et al[35] which aimed to identify mucin microbiome signatures that shape the tumor microenvironment in GC and their association with clinical outcomes. They showed that poor survival was associated with GC characterized by an intestinal mucin environment or high MUC13 expression, whereas tumors with higher levels of gastric MUC5AC or MUC6 had a more favorable outcome. Oral taxa, such as *Neisseria*, *Prevotella,* and *Veillonella* were centrally associated with tumors exhibiting intestinal and mixed phenotypes and were associated with MUC13 overexpression, suggesting their potential role as drivers of MUC13 signaling in GC. Enrichment of oral or intestinal microbes varied by mucin phenotype, with intestinal mucin phenotype tumors favoring the establishment of pro-inflammatory oral taxa, forming strong co-occurrence networks[35].

The aforementioned studies have provided evidence for bacteria and their influence on prognosis, but virome is also gaining increasing attention. Zhang et al[36] characterized the virome of tissue samples from 31 cancer types, including GC. Viral DNA was found at low levels in tissues from the major human cancers, with significant differences in the composition of the viral community between the different cancers. In addition, Cox regression analyses for GC and other cancers revealed a strong correlation between tissue viral composition/abundance and patient survival. Virus-associated prognostic signatures were identified for these cancers, and differences in their interaction with dominant bacteria in tissues were found in patients with different survival risks[36].

FUTURE DIRECTIONS AND CONCLUDING REMARKS

Understanding the microbial role of the stomach and gastric disease, in particular in gastric carcinogenesis, remains one of the most relevant challenges in translational research. The recent data support the current suggestion that the microbiome is one of the key elements in gastric carcinogenesis. In this review, we have gathered the most recent research related to the gastric microbiome to provide readers with a brief insight into this topic. Besides the studies that allow a better mapping of the microbiome:host interaction, there are also highly important data on the microbiome from sequencing with higher resolution using whole genome sequencing. Furthermore, the new data provide additional aspects of microbiome dynamics after eradication or the presence of antibiotic resistance in individuals with HPI. Research on the microbiome in GC is likely to provide the most interesting information on the transition of the microbiota during GC and, more interestingly, the role of the microbiome in assessing prognosis. Besides *H. pylori*, the data on *F. nucleatum* provide the strongest evidence to date for the clinical impact, but other bacteria and viruses are likely to play a role in this interaction. It is with great hope and excitement that we look forward to further developments in this field, in particular, the translation of knowledge into clinical practice to benefit our patients with diagnostic and therapeutic advances.

Conflict of Interest

AL received speaker fee from Janssen and Luvos and advisory fee from Ferring. Other authors declare no potential conflicts of interest.

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Ethics Statement

Not applicable due to the type of study.

Authors' Contribution

KL: drafting, graphic design, critical revision, editing and final approval of the final version; CT: drafting, critical revision, editing and final approval of the final version; MPE: critical revision and final approval of the manuscript; AL: conception and design of the study, literature review and analysis, drafting, critical revision, editing and final approval of the final version, guarantor of the study.

ORCID ID

Konrad Lehr: 0000-0003-3213-8138
Cosima Thon: 0000-0002-8954-6119
Alexander Link: 0000-0002-9514-4562

AI Statement

AI was not used for paper selection or manuscript writing. However, Deepl was used to identify spelling and writing errors in the final version.

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