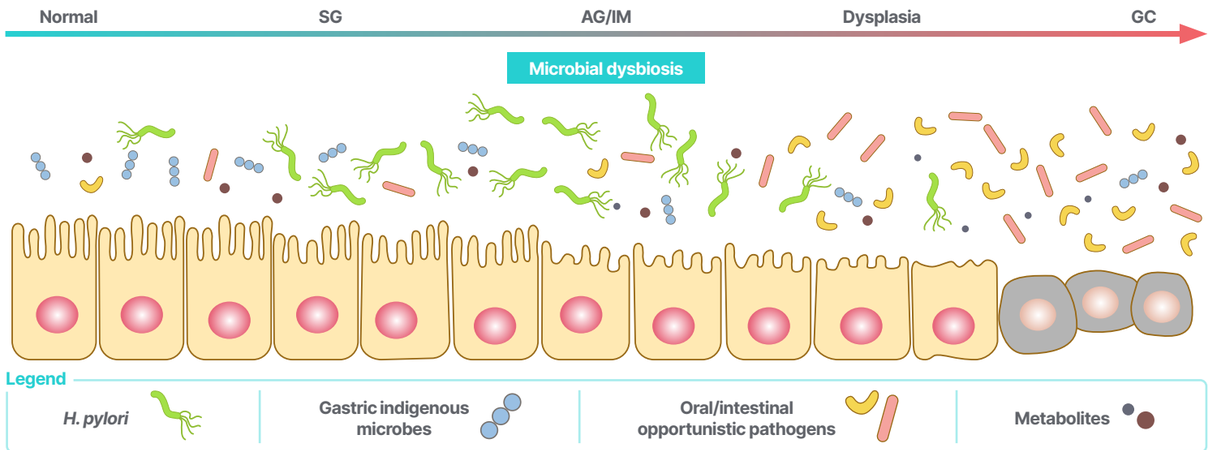
The Microbiota in Gastric Cancer: What Do We Know?

Citation: EMJ Gastroenterol. 2024; https://doi.org/10.33590/emjgastroenterol/WSET2915.

EMJ European Medical Journal

Microbial dysbiosis in gastric carcinogenesis[1,2]

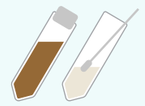
- *Helicobacter pylori* is recognised as a Class 1 carcinogen by the WHO. While it infects approximately 50% of the global population, only <3% of *H. pylori*-infected patients eventually develop GC.
- *H. pylori* initiates GC in a 'hit and run' manner by neutralising the gastric acidic environment via urease activity.
- Elevated gastric pH might facilitate the overgrowth of opportunistic microbes within the gastric niche. Colonisation of *H. pylori* has been linked to significantly reduced alpha and beta diversities in the gastric mucosa.
- The intestinal and gastric mucosal microbiota of patients with GC is often enriched in *Streptococcus, Lactobacillus,* and *Fusobacterium,* but study results remain heterogeneous.



Diagnostic microbial biomarkers

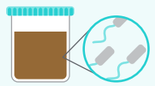
Early diagnosis of GC is crucial to increase patient survival, and the microbiota represents a new avenue for GC diagnosis.

Panels of gastric microbial signatures and a microbial dysbiosis index based on levels of enriched or depleted microbes, have been used to distinguish GC from superficial gastritis.[3,4]



Collecting gastric mucosal samples remains invasive and resource-demanding; non-invasive approaches for GC diagnosis can include collecting oral or gastric fluid samples.

Microbial biomarkers in the saliva can distinguish GC from non-malignant lesions with high accuracy.[5]

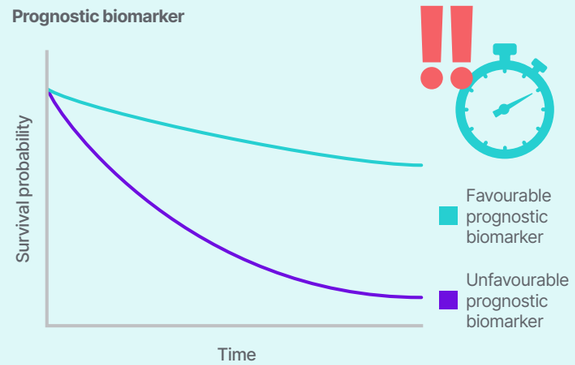


A large-scale multicentre study reported a panel of faecal microbial signatures (*Streptococcus anginosus* and *Streptococcus constellatus*) that accurately detected both early and later stages of GC.[6]

Prognostic microbial biomarkers

Microbial signatures can be used to predict outcomes of patients with GC, allowing clinicians to select more appropriate therapeutics.

- Higher abundance of *Methylobacterium*, *Prevotella,* and *Fusobacterium* in GC tumour tissues is associated with poorer overall survival.[7]
- *Halomonas* and *Shewanella* are enriched in gastric mucosa of patients with poor prognosis.[8]
- *Collinsella, Blautia, Anaerostipes,* and *Dorea* are more abundant in patients with advanced GC than in those with early GC.[9]

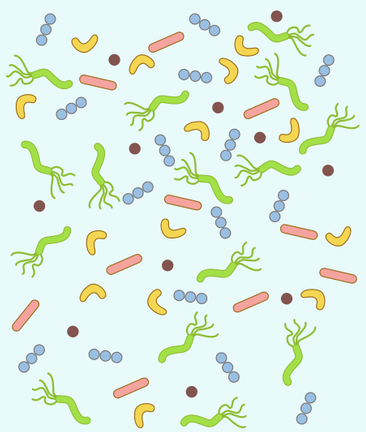


Therapeutic potential of gastric bacteria

Targeted regulation of microbiome

- Probiotics are commonly used as adjuvants in *H. pylori* eradication. However, *H. pylori* infection has been identified as a favourable factor for GC immunotherapy by shaping the "hot" TME, with higher densities of PD-L1+ immune cells and non-exhausted CD8+ T cells in TME found in *H. pylori*–positive GC.[10]
- Probiotics with beneficial bacteria, like *Clostridium butyricum* and *Lactobacillus,* can reduce post-operative inflammation in patients undergoing gastrectomy and enhance immunity.[2]

Gut microbiome



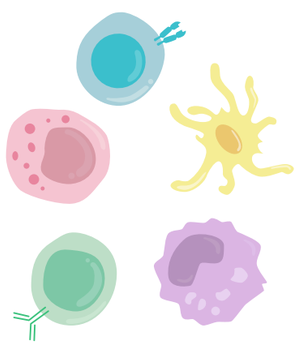
Enhancing chemotherapy and radiotherapy

- Faecal microbiota transplantation prior to chemotherapy could improve patient response and survival.[11]
- Butyrate-producing bacteria increase the efficacy of oxaliplatin.[12]
- Bacteria producing short-chain fatty acids demonstrate protective effects against radiotherapy-induced injury.[13]

Enhancing immunotherapy

Response rates of patients with advanced GC to immunotherapy vary from 10–26%.[2] The gut microbiota, associated with the gastric immune microenvironment, could modulate the response to immunotherapy.

- Higher abundance of *Lactobacillus* is associated with better response to immune checkpoint blockade and survival in patients with GC.[14]
- *Methylobacterium* is negatively correlated with the production of TGF-β and intratumoural infiltration of CD8+ tissue-resident memory T cells.[7]
- Enriched *Stenotrophomonas* and *Selenomona* are correlated with increased infiltration of immunosuppressive cells into the GC TME, like regulatory T cells and plasmacytoid dendritic cells.[15]



Future directions

Currently, translating microbial biomarkers into clinical practice for GC faces challenges:[2]

- unknown confounders affecting a patient's microbiota;

- lack of established sampling guidelines; and
- lack of consensus on the appropriate timing, location, and manner in which microbial biomarkers should be used.

Large-scale multicentre studies with standardised methodologies are needed to better understand the dynamic microbial landscape in gastric carcinogenesis.

Further research is needed to determine the dosage and safety of microbiota-targeting approaches before clinical application.

Abbreviations

AG: atrophic gastritis; GC: gastric cancer; IM: intestinal metaplasia; SG: superficial gastritis; TME: tumour microenvironment; WHO: World Health Organization

References

1. Shin WS et al. Cancers (Basel). 2023;15(20):4993.
2. Zeng R et al. Gut. 2024; DOI:10.1136/gutjnl-2024-332815 .
3. Liu D et al. BMC Microbiol. 2022;22:184.
4. Wu Z-F et al. A comparison of tumor-associated and non-tumor-associated gastric microbiota in gastric cancer patients. Dig Dis Sci. 2021;66:1673-82.
5. Huang K et al. Front Cell Infect Microbiol. 2021;11:640309.
6. Zhou C-B et al. Gastroenterology. 2022;162:1933-47.
7. Peng R et al. Cancer Immunol Res. 2022;10:1224-40.
8. Yang J et al. Cancer Science. 2023;114:1075-85.
9. Chen C et al. Appl Microbiol Biotechnol. 2022;106:6671-87.
10. Jia K et al. Innovation (Camb). 2024;5.
11. de Clercq NC et al. Clin Cancer Res. 2021;27:3784-92.
12. He Y et al. Cell Metab. 2021;33:988-1000.
13. Yi Y et al. Exp Hematol Oncol. 2023;12:48.
14. Han Z et al. Clin Transl Med. 2023;13:e1312.
15. Ling Z et al. Front Immunol. 2019;10:533.