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REVIEW

Suicide journey of *H. pylori* through gastric carcinogenesis: the role of non-*H. pylori* microbiome and potential consequences for clinical practice

Paulo Pimentel de Assumpção[1] · Taíssa Maíra Thomaz Araújo[1] · Paula Baraúna de Assumpção[2] · Williams Fernandes Barra[1] · André Salim Khayat[1] · Carolina Baraúna Assumpção[3,4] · Geraldo Ishak[1,5] · Diana Noronha Nunes[6] · Emmanuel Dias-Neto[6] · Luiz Gonzaga Vaz Coelho[7]

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Abstract

Despite being one of the most studied cancer-related infections, the relationship between *Helicobacter pylori* infection and gastric adenocarcinoma (GC) remains, in some points, obscure. Based on a critical analysis of the available literature regarding stomach microbiota, we aimed to shed light to a possible new interpretation of the current understanding about the *Helicobacter pylori*-related GC carcinogenesis. We analyzed data from the literature on *Helicobacter pylori* and other potential carcinogenic pathogens, in both benignant conditions and gastric adenocarcinoma. *Helicobacter pylori* is the dominant microorganism in benignant conditions as non-complicated gastritis. In atrophic gastritis, metaplasia and, mainly, in gastric adenocarcinoma, a strong reduction in *Helicobacter pylori* abundance, and increased occurrence of other microorganisms is strongly demonstrated by metagenomic experiments. While causing peptic disease and keeping the stomach's high acidity, *Helicobacter pylori* infection avoids gastric infection by carcinogenic intestinal microbiota. Nevertheless, *Helicobacter pylori* persistence may also provoke an atrophic gastritis, a condition that causes its own decline, due to a microenvironment modification, including reduced acidity, resulting in *Helicobacter pylori* substitution by a cancer-prone microbiota. This new interpretation might result in a dramatic modification on clinical management of *Helicobacter pylori*-related gastric disease.

Keywords *Helicobacter pylori* · Gastric cancer · Microbiota · Dysbiosis · Carcinogenesis

Gastric cancer burden

Gastric cancer (GC) remains one of the most lethal human cancers in the world. Despite a reduction of incidence, mainly in developed populations, GC is still the third cause of cancer-related deaths [1]. The most important factors attributed to the decrease in GC incidence are the use of refrigerators that allows better food preservation and improvement in sanitary conditions that reduces exposure to *Helicobacter pylori* infection, the main cause of GC [2–4].

H. pylori infection is associated with GC risk, as demonstrated by bold epidemiological data [2, 5, 6]. Nevertheless,

✉ Paulo Pimentel de Assumpção
assumpcaopp@gmail.com

[1] Núcleo de Pesquisas em Oncologia, Universidade Federal do Pará, Rua dos Mundurucus, 4487, Guamá, Belém, Pará 66073-000, Brazil

[2] Programa de Pós-Graduação em Génetica e Biologia Molecular, Universidade Federal do Pará, Rua Augusto Corrêa, 01, Guamá, Belém, Pará 66075-110, Brazil

[3] Departamento de Cirurgia Oncológica, Hospital Alemão Oswaldo Cruz, Rua Treze de Maio, 1815, Bela Vista, São Paulo, São Paulo 01327-001, Brazil

[4] Departamento de Cirurgia Oncológica, Alameda dos Lírios, Hospital Geral de Guarulhos, 300, Parque Cecap, Guarulhos, São Paulo 07190-012, Brazil

[5] Hospital Universitário João de Barros Barreto, Universidade Federal do Pará, Rua dos Mundurucus, 4487, Guamá, Belém, Pará 66073-000, Brazil

[6] Laboratório de Genômica Médica, AC Camargo Cancer Center, Rua Tamandaré, 753, Liberdade, São Paulo, São Paulo 04002-010, Brazil

[7] Instituto Alfa de Gastroenterologia do Hospital das Clínicas, Universidade Federal de Minas Gerais, Avenida Alfredo Balena 110, Santa Efigênia, 30130-100, 31270-901, Belo Horizonte, Minas Gerais, Brazil

treatment of *H. pylori* infection does not appear to be totally effective in avoiding the progression of all pre-neoplastic lesions [7–10]. In extensive atrophic gastritis, and particularly intestinal metaplasia, *H. pylori* eradication seems to have low impact. Equally, treatment of *H. pylori* infection in GC patients has no effect on cancer evolution [7–10].

These data suggest that the role of treatment of *H. pylori* infection as a strategy of reducing the GC burden appears to be restricted to a normal gastric mucosa condition or a rather incipient pre-neoplastic state. The advent of the pathological recognizable advanced pre-cancerous lesions appears to reduce the benefit of *H. pylori* elimination, with the aim of avoiding GC development.

Different diseases are caused by the same agent

Peptic duodenal ulcer disease, as well as GC, is caused by chronic *H. pylori* infection [11–13]. However, these diseases are almost always mutually exclusive [14–16]. Peptic disease occurs in a highly acidic environment, whereas GC is characterized by a much less acidic state [14, 17]. Additionally, patients with peptic duodenal ulcers have a lower risk for GC than the general population [3, 18, 19]. Eradication of this bacterium cures both duodenal ulcer and *H. pylori*-induced gastritis, but it has no impact in already established GC [7–10].

Regardless of the eradication efficacy in controlling these diseases, an important observation is the relationship between the presence of both, the disease and the bacterium. It might be perplexing that conventional investigation of *H. pylori* in pre-neoplastic lesions and GC is usually negative in clinical practice.

Even after the advent of next-generation sequencing (NGS) technologies, it remains strongly evident that the amount of *H. pylori* DNA is much higher in non-malignant gastric mucosa than in pre-malignant lesions or any stage of GC [20–24], strengthening the hypothesis of *H. pylori* decline along gastric carcinogenesis.

Although *H. pylori* infection is thought to cause two quite different diseases in the same organ [11–13], the contrasting environment necessary for the development of each disease [14], the different responses to *H. pylori* eradication [7–10], and the absolute discrepancy of the bacterial load in each group of diseases [20, 23, 24] lead to a reflection on the ability of *H. pylori* to equally cause both conditions.

H. pylori detection is usually negative in pre-malignant gastric lesions and in GC

In clinical practice, the detection of active *H. pylori* infection depends on visualization of *H. pylori*-like bacteria (spiral shape) in gastric biopsies, and/or on urease-based tests [25, 26]. It is widely reported that the positivity rate of *H. pylori* tests is lower in patients with gastric cancer and in pre-malignant gastric lesions, as compared with those with gastritis and other peptic diseases. The most common explanation for this relies on a possible "false negative" result in those situations [3, 26–28].

After the investigation of the gastric microbiota by NGS, the low levels or even the absence of *H. pylori* DNA in both GC and pre-malignant lesion were strongly reinforced [20–24]. In benign conditions, *H. pylori* is the most frequent microorganism [29, 30], whereas in GC, and even in pre-neoplastic lesions, *H. pylori* infection appears to be replaced by other bacteria (Fig. 1) [20–24, 31]. In this scenario, gastric metatranscriptome studies may shed light on the functional role of *H. pylori* in benign and malignant diseases.

Previous studies of *H. pylori* biology demonstrate that the bacteria shape and urease production capabilities depend on a high acidity [32, 33], a condition that is absent in GC as well as in atrophy and intestinal metaplasia [34, 35]. In the less

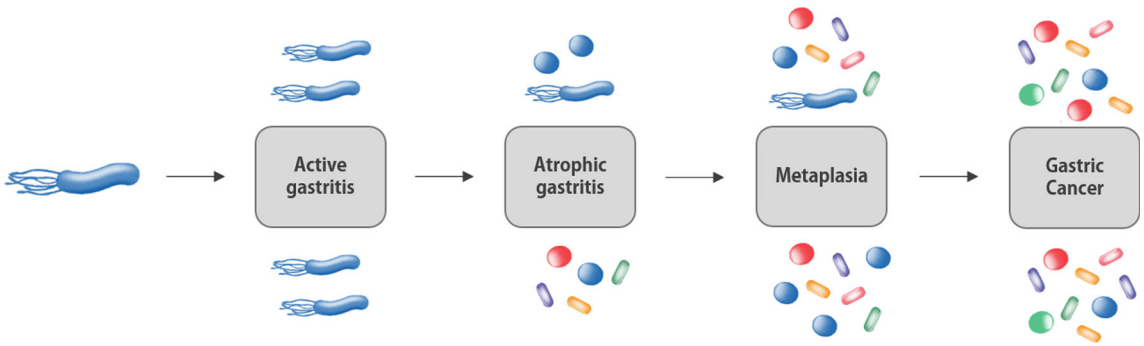

Fig. 1 Changes in gastric microbiota during GC carcinogenesis. Initially, *H. pylori* is the dominant bacterium in the stomach due to its ability to survive at acidic pH. In this condition, *H. pylori* initiates an inflammatory process (active gastritis) and with the persistence of inflammation, atrophic gastritis develops. The reduction of acid-secreting gastric parietal cells makes the environment more suitable for colonization by other bacteria and also appears to lead to an alteration in the morphology of *H. pylori* to a coccoid shape. Thus, in advanced pre-neoplastic lesions, such as extensive atrophy and intestinal metaplasia, and in gastric cancer, potentially genotoxic bacteria other than *H. pylori* dominate the bacterial community of the stomach

acidic conditions such as found in pre-malignant lesions and GC, *H. pylori* adopts a coccoid shape and has a reduced urease production, which precludes its identification by conventional tests [36] (Fig. 1). The virulence potential of the coccoid-shaped *H. pylori*, as well as its capability of returning to the spiral morphology, remains to be determined [37–41].

H. pylori and gastric cancer: the villain and/or the guardian

H. pylori infection causes gastritis, and in certain cases, atrophic gastritis develops, either by a failure of the tissue stem cells in replacing gastric epithelia, due to a high proliferative state and enhanced cellular turn over, or as a consequence of a host immune response [42–46]. At this point, a deep modification of the stomach environment might occur, leading to a broader spectrum of events that could favor GC development. The acidity that favors *H. pylori* as a dominant microorganism in gastric mucosa, due to its ability to survive in that hostile condition, constitutes an impairment for the survival and development of many other bacteria derived from the upper or the lower digestive tracts. However, alterations that lead to a less acidic gastric pH allow the colonization by a different microbiota [20, 22, 23]. This new dominant microbiota appears to be more capable to support the subsequent gastric carcinogenic in the second stage of the neoplastic development [20].

As the gastric atrophy results in a reduced production of acid, and consequently decreasing in load of *H. pylori* and modification of its expression pattern, including *H. pylori* production of immunogenic proteins at lower pH, the gastric environment scenario changes dramatically, and a cascade of subsequent events is activated [20, 29, 37, 40, 41].

At this point, in a clinical setting, *H. pylori* investigation tends to be negative and will parallel a higher stomach pH. Simultaneously, the microbiota translocation from other sources will take place and start a gastric dysbiosis [20, 29]. Nevertheless, in clinical practice, avoiding medicines that would additionally increase gastric pH, and attention to a new gastric microbial colonization, is yet not a common place for most generalists.

The replacement of *H. pylori*-dominated microbiota appears to be the determinant to GC carcinogenesis [20, 29, 47]. In other words, at this point, reduction of *H. pylori* burden from the gastric microbiota, and maintenance of a higher stomach pH, would favor GC development, which is frontally antagonist to the current clinical interpretation and practice.

In short, in addition to causing peptic disease such as non-atrophic gastritis, and maintaining the stomach's high acidity, *H. pylori* infection would help avoiding gastric microbiota replacement, therefore protecting the host against GC. Nevertheless, *H. pylori* persistence might also provoke a condition that causes its own decline and substitution by a cancer-prone microbiota, characterizing a suicide trajectory that leads to GC development in the absence of the usual *H. pylori* infection (Fig. 2).

With respect to experimental data, most of the available information (including the data that pushed World Health Organization to classify *H. pylori* as a Group I carcinogen) [48] were derived from pre-NGS studies. *Helicobacter felis*, a species closely related to *H. pylori*, trigger gastric mucosa modifications, resulting in intestinal metaplasia and finally GC [49–51]. Nevertheless, it is unknown whether a new microbiota developed along the process and favored GC development. In strengthening this hypothesis, it is difficult for germ-free animals to reproduce experimental GC after infection by *H. felis*, suggesting that an additional microbiota is necessary for the final steps of GC carcinogenesis [47].

The two phases of the GC carcinogenesis pathway

Correa and Piazuelo [52] proposed a cascade of events related to intestinal-type GC carcinogenesis that is widely accepted. The contribution of Correa to the understanding of intestinal-type GC carcinogenesis is unquestionable, including the role of atrophic gastritis and intestinal metaplasia as conditions that favor GC occurrence. Nevertheless, the causal link between *H. pylori* and GC development is less sustainable.

As discussed above, *H. pylori* infection causes only non-malignant conditions, and seems to be partially substituted by other cancer-related microorganisms, to allow GC emergence and development.

The Correa's cascade, in the light of current knowledge, should be revisited, maybe linking the *H. pylori* infection exclusively to a pre-malignant phase, and the replacement of

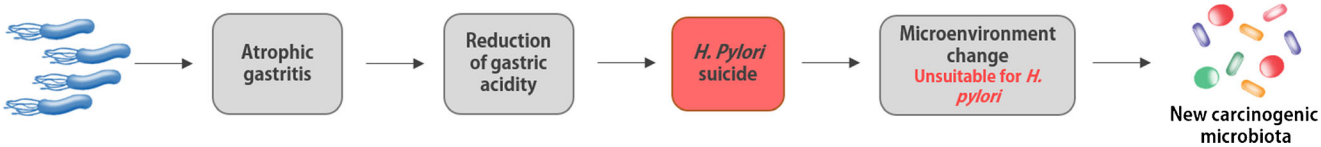

Fig. 2 The suicide journey of *H. pylori*. Gastric atrophy caused by *H. pylori* leads to a reduction of acid-secreting gastric parietal cells, thus increasing stomach pH. This environmental change allows colonization of the stomach by a new carcinogenic microbiota but is unfavorable for *H. pylori* survival

H. pylori infection by a microbiota translocation to play a more relevant role in GC development.

Since most patients infected by *H. pylori* never develop gastric cancer [2, 53, 54], similarly, the interactions among the new dominant microbiota, host-defense, and, probably, genetic and environmental factors, might trigger or not the evolution to gastric adenocarcinoma.

The implication of this new interpretation of the role of *H. pylori* infection in GC carcinogenesis is tremendous, including indications for the eradication of *H. pylori* infection according to the ongoing pathologic condition of the mucosa, and the role of proton pump inhibitors (PPI), that might contribute to GC carcinogenesis in a scenario of gastric atrophy and low acidity. Figure 3 summarizes the cascade of events necessary to GC occurrence and the role of *H. pylori* infection in each stage of the process.

Clinical implications

Much more than a new look at older information, the hypothesis presented here suggests potential modifications to critical clinical decisions, as the current management that aims to treat pre-malignant conditions might end up favoring GC carcinogenesis by both *H. pylori* eradication and reduction of gastric acidity, leading to an *H. pylori*-independent stage of GC carcinogenesis.

The current clinical practice includes the broad use of PPI and the eradication of *H. pylori* infection, even in the presence of pre-malignant lesions, which is nevertheless an unproven benefit in avoiding progress to GC [2, 5, 6, 55, 56].

Among the potential clinical implications of this two-stage GC model, indications for *H. pylori* treatment, PPI prescriptions, and new microbiota management should be discussed. Preliminarily, avoiding *H. pylori* infection and its early eradication (before gastric atrophy occurrence) should be the best preventive measure to control the gastric cancer burden. Additionally, if extensive atrophy with and without intestinal metaplasia is already present, PPI should not be prescribed, and investigation and treatment of the new carcinogenic microbiota might be addressed (Fig. 4).

We might also speculate that a lateral beneficial effect of using antibiotics to treat *H. pylori* could be the off-target reduction of carcinogenic non-*Helicobacter* microorganisms, eventually misinterpreted as a secondary prevention, due to *H. pylori* treatment.

If this hypothesis is confirmed, treatment of the cancer-prone gastric microbiota infection poses a challenging task for the near future. The best moment at which to eradicate *H. pylori* would also need to be determined. Indeed, management of gastric dysbiosis might be a landmark in sporadic GC control, providing additional contributions to the already recognized benefits of *H. pylori* primary prevention and better food preservation.

Nevertheless, we must emphasize that the substitution of the *H. pylori* dominant microbiota by a different microbiota may not be the determinant event of gastric carcinogenesis. The microenvironment modification accompanying the

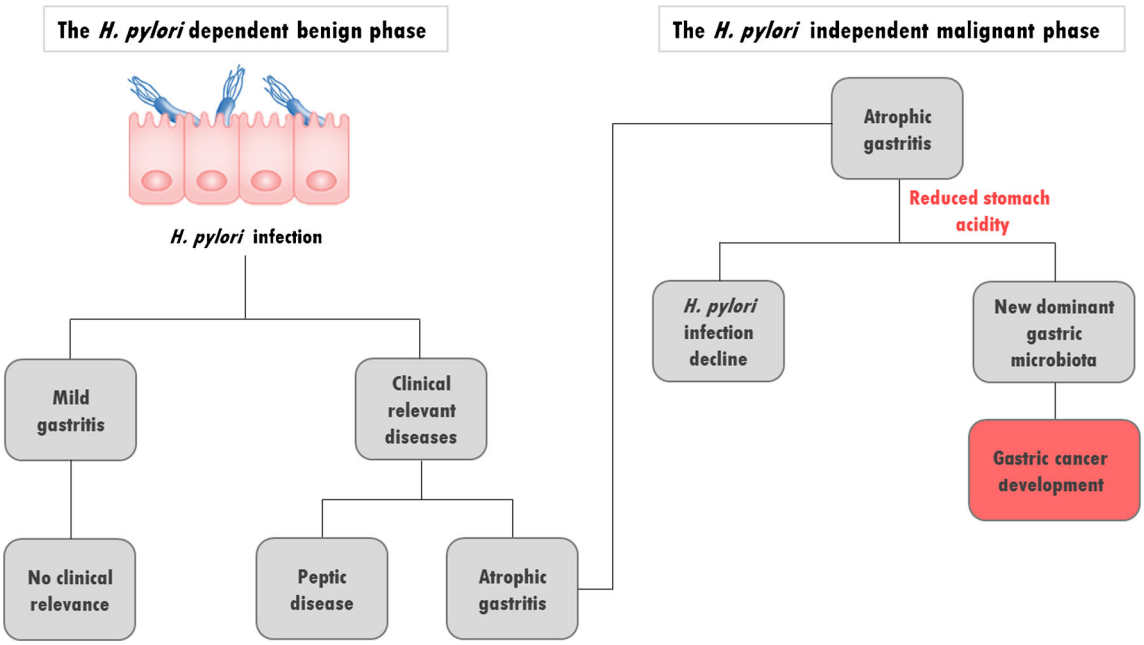

Fig. 3 The *H. pylori* dependent and independent phases. During the benign phase, *H. pylori* is responsible for the onset of benign conditions. Once atrophic gastritis develops, a second phase might occur in which the stomach acidity decreases, reducing *H. pylori* abundance, and allowing new carcinogenic microbiota to colonize the stomach, which in turn facilitates gastric cancer development (the malignant phase)

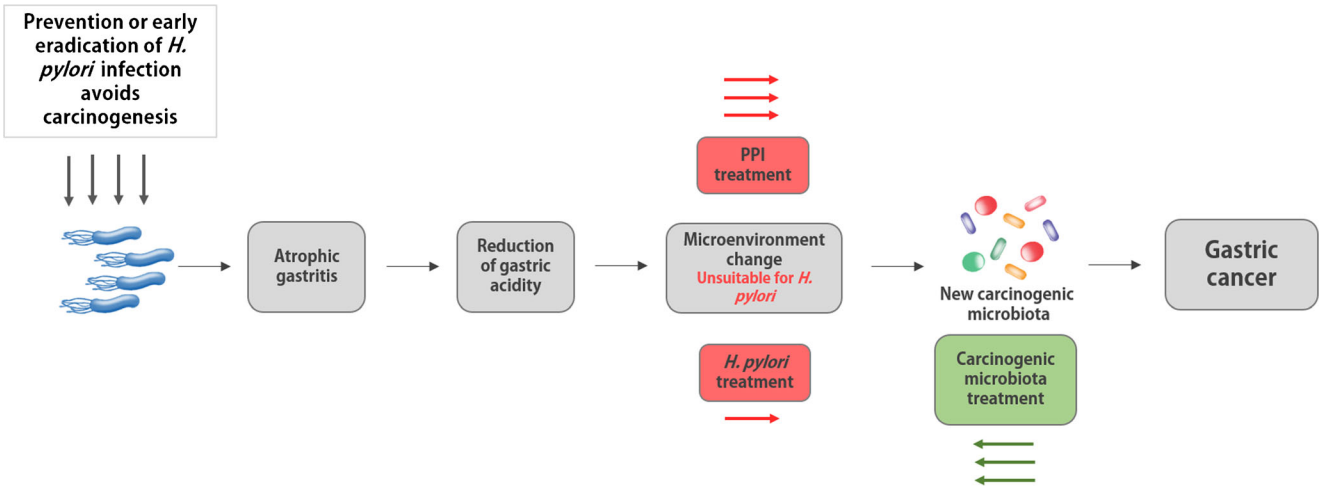

Fig. 4 Two-phase GC carcinogenesis model and its potential clinical implications. Prevention of *H. pylori* infection or eradication before atrophic gastritis onset would avoid the carcinogenic process. The establishment of atrophic gastritis begins the second phase, which is characterized by increased gastric pH and modification of microbiota. At this point, clinical interventions intended to protect against gastric cancer should target the new carcinogenic microbiota instead of the eradication of *H. pylori* and use of PPI

progression of carcinogenesis may be caused by yet unknown factors, and the microbiota modification might just be related, but not causative. Accordingly, the new microbiota should be a passenger event, secondary to the microenvironment modification, but not a driver event causing cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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