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Review articles

Frequency and immunological consequences of *Helicobacter pylori* and intestinal parasite co-infections: A brief review

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ABSTRACT. *Helicobacter pylori* is a Gram-negative, spiral bacterium capable of colonizing the gastric mucosa. Infections caused by this microorganism often lead to the development of various gastrointestinal complaints. Simultaneous human colonization by *H. pylori* and intestinal parasites is a common phenomenon. Moreover, the two groups of pathogens share the similar predisposing factors. The presence of parasites together with *H. pylori* can significantly influence the modulation of the host immune response. During *H. pylori* infection, strong polarization of Th_1 cells is observed. The presence of protozoa, also contributing to the recruitment of Th_1 cells, may well aggravate this response and exacerbate gastric mucosal damage. In contrast, intestinal helminth infection is associated with the polarization of lymphocytes towards Th_2; their presence enhances the regenerative processes within the digestive tract and lowers the host overresponse. A literature review suggests that co-infection with intestinal helminths may serve as a buffering mechanism against the effects of *H. pylori* and/or protozoan infection, alleviating the Th_1-dependent response and protecting against inflammations within the gastrointestinal tract.

Key words: co-infection, *Helicobacter pylori*, helminths, protozoa

Helicobacter pylori infections

Helicobacter pylori is a Gram-negative, microaerophilic, spiral bacterium capable of colonizing the gastric mucosa. Chronic infections with this microorganism can contribute to the development of various gastrointestinal complaints, including gastritis, gastric and duodenal ulcers, gastric cancers or MALT lymphomas [1]. This bacterium has the ability to express various virulence factors that initiate and enhance the progression of these diseases. The CagA (cytotoxin-associated gene A) oncoprotein is associated with immortalization of gastric mucosal cells, tight junction destruction, the initiation of loss of cell-cell contact and extracellular matrix remodeling. Another well-characterized virulence factor of *H. pylori* is VacA (vacuolating cytotoxin A), which contributes to cell apoptosis, promotes inflammation and inhibits the proliferation of T and B cells. In addition, strains of this pathogen produce large amounts of urease, an enzyme associated with the alkalization of the local environment, as well as outer membrane proteins (OMPs) that enable rapid and efficient colonization of the gastric mucosa [2].

The prevalence of *H. pylori* infection has changed over the years with an observed downward trend in most countries [3]. The risk factors for acquiring this microorganism include age, with most cases observed during early childhood, weakened immune status, low socioeconomic and education status, consumption of contaminated water sources and the presence of *H. pylori* infection in other family members [4]. The infection most likely spreads through three routes: oral-oral, gastro-oral and fecal-oral. Transmission of bacteria from person to person appears to be a major mechanism for the spread of these microorganisms. On the other hand, environmental reservoirs, including contaminated water and food or infected animals, also appear to be possible [3,5]. Because *H. pylori* very often colonizes people with low hygiene and socioeconomic status, it is important to know the risk factors and organisms commonly observed in co-existing infections, such as intestinal parasites [6].

H. pylori and intestinal parasites co-infections

Infections caused by soil parasites, both protozoa and helminths, are the most common infections observed in people living in developing countries [7]. This is due to the ease of transmission of these etiological agents in high temperature and humidity conditions, reduced hygiene, over-population and consumption of contaminated water and food [8,9]. In the endemic areas of developing countries, polyparasitism or co-infections with several types of gastrointestinal parasites is frequently observed. This phenomenon is especially common among young people [7,9]. The presence of intestinal parasites generates many negative

Table 1. *H. pylori* and intestinal parasites prevalence and co-infection rate

Country [reference]	*H. pylori* diagnostic method	Population studied	Number of subjects	Prevalence and co-infection rate of infectious agent (%)
Venezuela [6]	Serologic, SAT	Adults (16-84 y) Children (3m-15y)	151 167	76,4% (243/318) *H. pylori* **Co-infections: 70.8% (172/243) with poliparasitism, 18.9% (46/243) with monoparasitism**
Uganda [15]	SAT, Culture	Children (0-12 y)	427	44.3% (189/427) *H. pylori* 20.1% (86/427) *G. lamblia* **30.2% (57/189) co-infected**
Mexico [16]	Serology	Children (< 18 y)	120	43.75% (21/48) *H. pylori* without parasites **57.1% (8/14) *H. pylori* with 1 parasite** **52.9% (9/17) *H. pylori* with 2 parasites** **50% (11/22) *H. pylori* with >2 parasites**
		Adults (> 19 y)	188	80.4% (78/97) *H. pylori* without parasites **71.9% (23/32) *H. pylori* with 1 parasite** **61.5% (16/26) *H. pylori* with 2 parasites** **54.5% (18/33) *H. pylori* with >2 parasites**
Colombia [17]	Serology	Children from Tumaco (1-6 y)	105 110	93,1% (148/159) *H. pylori* (both regions) 84% (92/110) infected with protozoa 54% (59/110) infected with helminths **45% (49/110) co-infected both with protozoa and helminths**
		Children from Pasto (1-6 y)	54 101	93.1% (148/159) *H. pylori* (both regions) 72% (73/101) infected with protozoa 25% (25/101) infected with helminths **21% (21/101) co-infected both with protozoa and helminths**
China [19]	Gastric biopsy	Adults with *B. hominis* monoinfection (57.2 ± 10.3 y)	26	**73.1 % (19/26) *H. pylori* co-infected with *B. hominis***
		Control adults without *B. hominis* (56.8 ± 11.2 y)	38	39.5% (15/38) *H. pylori* monoinfection
Iran [20]	SAT	Children with recurrent abdominal pain (< 18 y)	68	54.4% (37/68) *H. pylori* **29.7% (11/37) co-infected with *G. lamblia*** **10.8% (4/37) co-infected with *E. histolytica/ E. dispar***
Egypt [22]	SAT	Adults (15-60 y)	206	69.4% (143/206) *H. pylori* **51.4% (70/140) co-infected with *G. lamblia* or *E. histolytica***
Turkey [23]	Serologic, SAT	Children with recurrent abdominal pain (3-15 y)	98	49% (48/98) *H. pylori* 30,6% (30/98) *G. lamblia* **45.8% (22/48) co-infected**
		Healthy control children (3-15 y)	88	45.5% (40/88) *H. pylori* 20.4% (18/88) *G. lamblia* **15% (6/40) co-infected**

SAT: stool antigen test

health consequences, i.e. damage to host tissue, reduced nutrient absorption and malnutrition, or immune modulation [8]. Protozoa are single-celled organisms and can therefore rapidly grow in the host organism, leading to the development of complications such as malaise, fatigue, malnutrition, epigastric pain, inflammation or the digestive tract ulceration [10]. These parasites cause high mortality, especially in children, and often co-exist with functional impairment of the immune system, for example during AIDS/ HIV [8]. The most common gastrointestinal protozoa include *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium parvum*, *Cyclospora cayetanensis*, *Dientamoeba fragilis*, *Blastocystis hominis*, *Isospora belli* and *Micromonospora* [8,10]. Helminths are multicellular and capable of surviving in the host organism for decades. Unlike the fast-growing protozoa that promote Th_1 polarization, helminth infections contribute to Th_2 recruitment. Thus, their presence is linked with immune suppression and enhancement of the regenerative processes within the digestive tract [7,11]. There are three classes of intestinal helminths: nematodes (*Ascaris lumbricoides*, *Ancylostoma duodenale*, *Necator americanus*, *Trichuris trichiura, Strongyloides stercoralis, Enterobius vermicularis, Toxocara canis/cati*), cestodes (*Taenia solium/saginata*, *Echinococcus granulosus/multilocularis*) and trematodes (*Fasciolopsis buski*, *Heterophes heteropes* and *Echnostoma ilocanum*) [8,12].

Colonization of humans by *H. pylori* and intestinal parasites is very common. In addition, the two groups share similar predisposing factors. Therefore, a determination of the frequency of co-infection and the effect of these organisms on immune system function is an important factor in public health promotion.

To our knowledge, there are only two studies reporting the relationship between *H. pylori* and intestinal parasites in Europe. The presence of *G. lamblia* was detected in 6.5% (9/137) of an Italian population with irritable bowel syndrome (IBS) and dyspepsia, eight cases of which were associated with *H. pylori* [13]. Another study found the co-infection rate with *G. lamblia* to be 44.6% (25/56) in Portugalete children with positive *H. pylori* status [14]. Due to the relatively small body of data on the incidence of intestinal parasites and *H. pylori* co-infections in developed countries, this review focuses on the prevalence of these pathogens in developing areas.

Many studies have shown a significant relationship between the presence of *H. pylori* and intestinal parasites (Table 1). Studies using the stool antigen test (SAT) detection method found the incidence of *H. pylori* infection to range from 44.3% in Ugandan children [15] to 76.4% among the Venezuelan population [6]. Much higher values were achieved with serological detection in children and adults: 84.2% and 100% in Mexico [16] and 93.1% and 99% in Columbia [17], respectively. This indicates that the method of detecting active *H. pylori* infection using serological tests only is not sufficiently specific because of the risk of false positive results [18]. However, regardless of the method used to detect this bacterium, many *H. pylori* infections have been shown to be associated with infections caused by intestinal parasites.

Co-infections with protozoa

It has been observed that protozoa are often present in co-infections. In the Chinese population, the incidence of *H. pylori* was positively correlated with *Blastocystis hominis* infections, as patients infected with this parasite were more likely to have *H. pylori* in the bioptic samples (73.1%) than the uninfected control group (39.5 %) [19]. In children living in Ilham City with recurrent abdominal pain and positive *H. pylori* status, co-infections with *Giardia lamblia* and *Entamoeba histolytica/dispar* were reported in 29.7% and 10.8% of cases, respectively [20]. A group of the same researchers in a subsequent experiment on a wider population, including children and adults, showed a similar incidence of these etiologic factors, i.e. 30.7% for *G. lamblia* and 12.7% for *E. histolytica/dispar* [21]. In the Tanta City district in Egypt, an even higher prevalence of co-infections with these protozoa was observed, with more than half of the subjects presenting co-infection of *H. pylori* with either *E. histolytica* or *G. lamblia* [22]. In children from sub-Saharan Africa, it has been documented that people infected with *G. lamblia* had a threefold higher chance of co-occurrence with *H. pylori* (12.2% vs. 30.2%). Moreover, the highest frequency of *G. lamblia* isolation was demonstrated by children aged one to five years (28.7%; 43/150) [15]. A comparative experiment involving children with recurrent abdominal pain and a control group revealed no difference in the detection of *H. pylori* or *G. lamblia*. However, it was noticed that in the

group of children with gastrointestinal disorders the co-infection rate was three times higher than in asymptomatic children (45.8% vs. 15%) [23].

These results may suggest that the presence of both pathogens may aggravate the progression of gastrointestinal ailments. Isaeva et al. [24] collected bioptic and bile samples from 160 patients suffering from chronic cholecystitis associated with chronic gastroduodenitis; the presence of *G. lamblia* was detected in 47.5 ± 3.95% of cases, and in the stomach in 29.09 ± 6.12% of individuals. A close relationship was observed between *G. lamblia* and *H. pylori* infections, as all isolated protozoa co-existed with this bacterial species. Elsewhere, the presence of *G. lamblia* trophozoites was verified in biopsies taken from 54 gastric cancer patients and 100 subjects with peptic ulcers. Protozoa were isolated in 14.9% (8/54) and 20% (7/35), respectively. A significant correlation was observed between the presence of *G. lamblia* in gastric samples and *H. pylori* status, as 6/7 persons with peptic ulcers and all cases with gastric cancer co-existed with these microorganisms [25]. *H. pylori* infection is suggested to affect the increased secretion of proinflammatory cytokines IL-2 and IFN-γ in the gastric environment, resulting in a reduction of gastric acid secretion [26]. Abnormalities in acid barrier function and the presence of chronic atrophic gastritis favor colonization of this organ by other microorganisms, including *G. lamblia* [27,28].

The hypothesis of *H. pylori*-dependent gastric acid suppression, however, is not entirely true. *H. pylori* infections can contribute to both reduction or increase of gastric acid production. In fact, increased gastric acid secretion is often observed in the course of peptic ulcer and *H. pylori* antrum colonization. In contrast, the presence of these bacteria in the corpus region promotes elevated pH in the gastric environment, a condition predisposing to the development of carcinogenesis [29]. Therefore, it appears that the effect of *H. pylori* on parasitic infection depends on the location of this bacterium within the stomach. While *H. pylori* may improve the colonization of this niche by acid-sensitive parasites during infection of the corpus region, a potentially inverse correlation is observed in the antrum localization of *H. pylori*.

Co-infections with helminths

It has been suggested that a relationship exists between *H. pylori* and intestinal helminths. The incidence of *H. pylori* in the Venezuelan population was significantly higher when concurred with multiple parasitic infections (70.8%) than during monoparasitosis (18.9%) or without parasitic infection (10.3%) [6]. In addition, the sero-prevalence of *H. pylori* was found to be almost twice as high in a group of children aged 0-5 years who were also infected by *Ascaris lumbricoides* than those who were not [6]; however, the opposite was observed in a Mexican population, where the amount of parasites was negatively correlated with *H. pylori* seroprevalence [16]. The discrepancies in the results obtained are probably determined by differences in the incidence of intestinal helminths. Fuenmayor-Boscán et al. [6] report a significantly higher rate of *H. pylori* and helminth co-infection (77.2–92.7%) than Torres et al. (< 5%) [16].

Hence, the presence of intestinal helminths may seem to play a key role in regulating the *H. pylori* infection. Whary et al. [17] have verified the presence of intestinal parasites and *H. pylori* in children and adults living in two Colombian areas, i.e. Pasto, with a high gastric cancer rate, and Tumaco, where a low level of gastric carcinogenesis is recorded. There were no differences in the *H. pylori* incidence between the two study groups. It has been shown, however, that prevalence of parasitic infections is higher in the Tumaco region (93%) than in the Pasto (76%). Moreover, the Tumaco residents demonstrate more than twice the prevalence of helminthic infections (54%) than those of Pasto (25%). Among them, *Ascaris lumbricoides* was detected in 35% (38/110) and 22% (22/101) while *Trichuris trichiura* was found in 43% (47/110) and 8% (8/101), respectively. Indirect determination of parasitic infection intensity by IgE level measurement showed that the level of this immunoglobulin was higher among people from Tumaco: i.e. more than fivefold higher in children and twice in adults.

There is also a link between *H. pylori* infection and schistosomosis. *Schistosoma* does not belong to the intestinal helminths group, but its presence in the host organism can significantly affect the functioning of the digestive tract. The mature forms of these parasites are located within the mesenteric venules where they produce eggs. Many eggs do not leave the body, and contribute to the granulomatous immune response, and over time, this reaction is silenced, leading to the chronic form of intestinal schistosomosis [30]. Du et al. [31] report no

difference in the incidence of *H. pylori* in patients with *Schistosoma japonicum* infection (53%) and non-infected cases (49.3%). In contrast, significantly lower incidence and titers of anti-CagA IgG antibodies were demonstrated in patients with co-infection (52.3%, 9.5 U/ml) than those without parasitic infection (75.8%, 18 U/ml). Moreover, the ratio of pepsinogen I/II was also higher during co-infection. These results suggest that the presence of parasites does not always affect the frequency of *H. pylori* infection, but may play an important role in modulating host response to ongoing infection, e.g. by affecting the host immune system.

Response of the immune system to ongoing infections

H. pylori infection induces the activation of innate and acquired response from the host immune system [4,32]. Th_1 and Th_2 cells play an important role in shaping this response with Th_1 dominating. These immune cells control the host cellular response, promote the secretion of proinflammatory cytokines IL-2 and INF-γ and reduce Th_2-dependent immune activity. Recruitment of Th_{17} cells, which are the source of cytokines IL-17A, IL-17F, IL-21 and IL-22, is also observed. These mediators are involved in antimicrobial activity directed against extracellular bacteria and fungi, and the pathogenesis of autoimmune diseases [4,33,34]. An increase in IL-17 secretion affects the production of IL-8, the chemoattractant proinflammatory cytokine which promotes the chemotaxis of neutrophils into gastric tissue [35]. Chronic neutrophil infiltration has a strong destructive effect on the mucosa, as these cells generate oxidative stress by reactive forms of oxygen and nitrogen. Immune cell clusters also contain histamine-releasing mast cells, which induce vasodilatation and the formation of edemas [32]. Despite the involvement of both Th_1 and Th_{17} cells in the *H. pylori* antimicrobial response, neither are capable of completely removing these microorganisms from the body; this is due to the fact that *H. pylori* promotes the recruitment of regulatory lymphocytes (Treg), which reduces the antibacterial host immune response and perpetuates the gastric mucosal infection [4].

Immunological response against protozoa

The presence of protozoa in the host organism results in a similar immune response with strong polarization of lymphocytes towards Th_1. Antimicrobial type 1 response is characterized by the secretion of proinflammatory cytokines IL-2, IL-12 and IFN-γ. Their presence contributes to host tissue damage. These symptoms are further influenced by the activation of cellular responses (macrophages and neutrophils) and cytotoxic lymphocytes (Tc) [36,37].

The development of gastritis, peptic ulcers, gastrointestinal metaplasia and gastric cancer in *H. pylori* infection are also dependent on the type 1 immune response [38]. For this reason, the presence of protozoa, which intensify this response, is likely to significantly aggravate these ailments. Such conclusions were drawn by Ek et al. [39], who indicate an increased risk of gastric oncogenesis in patients with *Toxoplasma gondii*. It cannot be excluded that intestinal protozoa, e.g. *G. lamblia*, *C. parvum* or *E. histolytica*, can also lead to the exacerbation of digestive system diseases [40]. The reverse tendency, and the suppression of hyperimmune response, have been implicated during *H. pylori* and *A. lumbricoides* co-infection [39].

Immunological response against helminths

The destruction of host tissues is a common phenomenon associated with helminthic infections [41]. Defense mechanisms, including highly toxic compounds, can significantly harm the host. However, as a result of host-parasite co-evolution, both organisms have developed co-existence mechanisms. This process of host-parasite matching is well described in helminths such as *A. lumbricoides* (roundworm) and *T. trichiura* (whipworm), and two species of hookworm: *N. americanus* and *A. duodenale* [42]. Unlike single-cell microorganisms that promote Th_1 polarization, helminth infections contribute to Th_2 recruitment [43–47]. These cells secrete cytokines IL-4, IL-5, IL-10 and IL-13, whose production is liked with suppression of the proinflammatory immune response and regeneration of damaged tissues. This process is conducive to the recruitment of eosinophils, alternative macrophage activation and blockage of Th_1-mediated response [12,41]. Eosinophils store many compounds involved in tissue repair and remodeling, including cytokines, growth factors, cationic proteins and matrix metalloproteases (MMPs) [48].

Alternatively activated macrophages (AAM/ M2) are larger and more multivacuolar than the classically activated macrophages (CAM/ M1), which protect against the development of infection but may contribute to the initiation of inflammatory processes. The specific properties of AAM include the ability to induce differentiation of Th_0 cells into Th_2 cells and activate eosinophils and eosinophil-dependent IgE production [11,41]. The mechanism responsible for Th_2 differentiation is not well understood, but it is suggested that the agents potentially involved in this process are TGF-β, anti-inflammatory cytokines produced by AAM. Their production correlates with the inhibition of IFN-γ secretion during primary stimulation and therefore promotes the shift in cell differentiation towards Th_2 [49]. It has been shown that AAM clusters express eosinophil chemoattractant agents: Ccl24 (eotaxin-2) and Ccl8. Their presence contributes to the increased influx of these cells and eosinophil-mediated IgE production [50]. In addition, AAM regulate the extracellular matrix turnover and scarring processes [11,41]. An important enzyme produced by AAM is arginase I (Arg I). Arg I-positive macrophages maintain balance between Treg and Th_{17} in the gastrointestinal mucosa and cause suppression of endotoxemia, neutrophilia, differentiation of M1 macrophages and Th_{17} cells, thus in turn suppressing the proinflammatory response [51].

The initial stages of helminth infection are associated with a strong host response. These mechanisms include both tissue reconstruction (tolerance) and defense processes [37]. For example, enhanced collagen synthesis contributes to both regeneration and parasite encapsulation [37,52]. During prolonged exposure of the host organism to helminthic antigens, a gradual decrease in proinflammatory activity and an increased response from the Treg cells occurs [11,45]. The immunomodulating pathways that regulate peripheral tolerance mechanisms rely on helminth-based IL-10 synthesis and the production of parasitic TGF-β analogs [38]. The synthesis of anti-inflammatory IL-10 and TGF-β is associated with the possibility of persistent host infection, reduced T cell activity, the suppression of tissue damage and a profibrinogenic effect [41]. The ability to induce anti-inflammatory cytokines and promote immune suppression has been demonstrated in parasites such as *Hymenolepis nana*, *Trichuris trichiura*, *Ascaris lumbricoides*, *Strongyloides stercoralis* and *Enterobius vermicularis* [53].

Many studies assessing the effect of helminths on Th_1-dependent response mitigation include a model parasitic organism, i.e. the intestinal nematode – *Heligmosomoides polygyrus* [11]. It has been shown that colonization with this parasite lowers IL-17A levels and increases the activity of type 2 (IL-4 and IL-10) immune responses, thus protecting against gastrointestinal mucosa inflammation [54]. A 5-month study of *H. pylori* and *Heligmosomoides polygyrus* co-infection on gastric mucosal ulceration and proliferative processes by Whary et al. [55] found that the co-existence of these organisms correlated with a reduction of gastric atrophy, dysplasia and *H. pylori*-mediated microflora changes. The presence of non-invasive (8/12) and invasive (2/12) gastric tumors was noted in individuals with *H. pylori* monoinfection. Oncogenesis detection was significantly lower in mice with co-infection, as four out of 10 subjects had non-invasive dysplasia, and no invasive neoplasms were identified. Similar observations were made by Fox et al. [56] during co-infection of *Helicobacter felis* and *H. polygyrus*. This contributed to the polarization of Th_1 towards Th_2 profile and the reduction of proinflammatory cytokines and chemokines, with the consequential alleviation of gastric atrophy .

To sum up, the development of gastritis, peptic ulcer, gastrointestinal metaplasia and gastric cancer in *H. pylori* infection are dependent on the type 1 immune response. It seems that the co-infections of *H. pylori* with protozoa may contribute to the strengthening of the pathogenesis within the gastrointestinal tract. This mechanism is conditioned by the recruitment of the same immune cells, i.e. Th_1 cells, by both types of micro-organisms. The activation of type 1 immune response promotes inflammatory and degenerative processes in the tissues of the digestive tract. The reverse relationship between *H. pylori* existence and inflammation of the gastrointestinal tract is observed during coinfection with intestinal helminths; their presence may lead to alleviation of the overactive immune response to *H. pylori* by suppressing the differentiation of M1 macrophages and Th_1 cells, and stimulating the regeneration and recruitment of AMM and Th_2 cells.

Polyparasitism, or co-infections with several types of gastrointestinal parasites, is often observed in developing countries, and simultaneous human colonization by *H. pylori* and intestinal parasites is

a common phenomenon. Moreover, predisposing factors are coincident in both groups of these pathogens, including low age, immunosuppression status, low socioeconomic and educational status, and consumption of contaminated water sources. During *H. pylori* infection, strong polarization of Th_1 cells is observed. These cells activate the processes involved in the elimination of microorganisms from the host organism, but they can also result in tissue damage. The development of *H. pylori*-mediated gastric mucosal inflammation, peptic ulcer and gastric cancer is strongly correlated with the promotion of the type 1 immune response. The presence of protozoa, which contribute to the recruitment of the same type of cells, is highly likely to intensify this response and exacerbate the damage to the gastric mucosa. The reverse tendency, and the polarization of lymphocytes towards Th_2 occurs during intestinal helminth infection. The presence of helminths enhances the regenerative processes within the digestive tract and ameliorates the host overresponse.

A review of the literature suggests that *H. pylori* and/or protozoan co-infection with intestinal helminths may be a buffering mechanism contributing to alleviation of the Th_1-dependent response and protecting against inflammation within the gastrointestinal tract. Still, more research is needed to understand the complexity and consequences of these interactions.

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