



Might helicobacter pylori play a role in allergic or cross-reaction related disorders?

Enzo Ierardi , Giuseppe Losurdo , Floriana Giorgio & Alfredo Di Leo

To cite this article: Enzo Ierardi , Giuseppe Losurdo , Floriana Giorgio & Alfredo Di Leo (2020): Might helicobacter pylori play a role in allergic or cross-reaction related disorders?, Expert Review of Gastroenterology & Hepatology, DOI: [10.1080/17474124.2020.1780119](https://doi.org/10.1080/17474124.2020.1780119)

To link to this article: <https://doi.org/10.1080/17474124.2020.1780119>



Accepted author version posted online: 08 Jun 2020.
Published online: 16 Jun 2020.



Submit your article to this journal [↗](#)



Article views: 3



View related articles [↗](#)



View Crossmark data [↗](#)

EDITORIAL



Might *helicobacter pylori* play a role in allergic or cross-reaction related disorders?

Enzo Ierardi, Giuseppe Losurdo, Floriana Giorgio and Alfredo Di Leo

Gastroenterology Section, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy

KEYWORDS *Helicobacter pylori*; allergy; atopy; cross-reaction; asthma

1. Introduction

Helicobacter pylori (*H. pylori*) is the most common cause of major gastric benign (chronic active gastritis, peptic ulcer) and malignant disorders (gastric carcinoma, mucosal associated lymphoid tissue lymphoma) [1,2]. However, a link between *H. pylori* and a large series of extra-intestinal disorders [3] has been ascertained even if with different levels of evidence. Pure atopic reactions, such as urticaria or asthma, have been hypothesized to be associated with *H. pylori* and this relationship will be herein discussed.

2. Body

A cross-reaction between some components of *H. pylori* and the immune system has been demonstrated. A representative example could be autoimmune gastritis, in which the similarity of H⁺,K⁺-ATPase and bacterial epitopes may lead to the production of antibodies against parietal cells, thus suggesting that bacterial infection may be the trigger of a successive autoimmune mucosal inflammation [4]. Moreover, it has been hypothesized that an infection in childhood with a spontaneous bacterial clearance might be the basis of this event [5].

A suitable example of a positive association between *H. pylori* and atopy is represented by chronic spontaneous urticaria, a skin disorder characterized by recurrent itchy wheals within a period of almost 6 months. A meta-analysis demonstrated that the prevalence of *H. pylori* infection was greater in chronic urticaria patients than in controls (odd ratio = 1.66) [6]. Moreover, the same study reported that spontaneous remission of symptoms occurred more frequently in *H. pylori* negative than in positive patients. An additional remarkable result showed that bacterium eradication doubled the possibility of clinical remission [7].

Several hypotheses have been formulated to explain these findings. In detail, a 21–35 kDa mixed proteic component of *H. pylori* might stimulate the degranulation of human mast cells [8]. Moreover, some bacterial genes, such as *cagA*, *vacA* and *nap* might codify for specific proteins triggering immune responses, thus enhancing pro-inflammatory pathways [9,10].

Nevertheless, the paradigm of cross reactions might only be partially applied to atopic disorders. In fact, it seems that *H. pylori* infection fulfills the main features of the so-called

'hygiene hypothesis'. According to this theory, formulated in 1989 by Strachan, the improvement of hygienic conditions in Western countries has led to a minor exposure to infective agents during childhood [11]. As a consequence, this might have impaired the priming and development of the immune system, thus causing the diffusion of allergic and autoimmune disorders [12]. Therefore, the decline of *H. pylori* spreading might be hypothesized as a possible background for the diffusion of atopic diseases. Furthermore, interventions such as cesarean delivery, changes in breastfeeding formulas and early antibiotics use have caused a disappearance of ancestral human microbiota [13], in whose context *H. pylori* could be even considered as a component. Further, considering that the acquisition of *H. pylori* could occur in early stages of life, presumably by maternal acquisition, this event could not be considered as an environmental exposure, thus supporting the hygiene hypothesis. *H. pylori* might be protective against allergic disorders. A mechanistic explanation for this phenomenon could be that a persistent gastric infection is associated with dendritic cell activation and induction of T-regulatory lymphocytes, which in turn, results in an increased tolerance toward environmental antigens [12]. Evidences supporting possible mechanisms of the protective role of *H. pylori* in asthma are provided by studies of basic science in animal models. In this regard, the bacterium has been demonstrated to powerfully re-program dendritic cells (DCs) toward a tolerance-promoting phenotype, thus inducing the production of regulatory Foxp3 + T lymphocytes, which are protective against atopy [14]. On the other hand, in *H. pylori* infected mice, it has been shown that DC depletion has led to down-regulation of T-regulatory cells with improved airway inflammation [15]. In addition, it has been proven that the urease produced by the bacterium activated NLRP3, a component of cytoplasmic inflammasome in DC and stimulates the TLR2/NLRP3/IL-18 axis, which is a well known pathway protecting against asthma [16]. Additionally, the immune response mediated by Th1 versus Th2 may explain the balance between *H. pylori* infection and atopy. It is known that the bacterium may elicit a Th1-dependent immune response, over Th2 [17] and express high levels of tumor necrosis factor alpha in the gastric mucosa [18]. This event could prevent the development of a Th2-mediated response, which drives the onset of allergic diseases. In this perspective, *Helicobacter pylori*

neutrophil-activating protein (HP-NAP) is able in vitro to elicit IL-12 and IL-23 production via agonistic interaction with toll-like receptor 2, and to promote Th1 polarization of allergen-specific T-cell responses. Indeed, in a murine model, administration of HP-NAP was able to reduce eosinophilia, IgE and Th2 cytokine levels in bronchoalveolar lavage [19]. Similarly, in ovalbumin (OVA)-induced allergic asthma animal model, HP-NAP reduced the levels of IL-4 and IL-13 (two mediators of atopic response), as well as that of total IgE [20].

These basic data parallel human epidemiologic studies. Indeed, the National Health and Nutrition Examination Survey (NHANES III) 1999–2000 study performed cross-sectional analyses to assess the association between *H. pylori* and childhood asthma. Bacterial seropositivity was inversely associated with the onset of asthma, especially in the first 5 years of age (odds ratio = 0.58). In addition, *H. pylori* seropositivity was also inversely related to recent wheezing, allergic rhinitis, dermatitis, eczema, or rash [21]. Further meta-analyses confirmed an inverse correlation of *H. pylori* infection with atopy [22]. However, these data show a meta-analytic heterogeneity as a relevant drawback due to the different methods for both *H. pylori* infection and atopy appraisal. On the other hand, few studies supported an opposite deduction and stated that wheezing and allergen specific antibodies were more commonly found in *H. pylori* [23] and anti-*cagA* positive subjects [24].

Indeed, the bacterium has inhabited the human stomach for several millennia, and evolutionary and environmental stimuli might have induced a mutual adaptation between guest and host [25,26]. Thus, the possible inhibitory role in asthma onset could represent a 'strategy' by which the germ may promote its survival in humans, creating a 'symbiotic process'.

On these bases, the lesson is difficult to interpret. The hypotheses are quite dissimilar, and results are conflicting. Doubtless, when approaching the field of atopic disorders, it is crucial to remember that each disease has a complex pathogenesis and it is impossible to encase under the same umbrella atopic dermatitis, asthma and urticaria for the truthful differences in clinical manifestations and pathogenetic pathways. In other words, they could be considered as 'distant relatives' and therefore, it is pretentious to assert that *H. pylori* could be a common ancestor.

The results of evidence-based medicine could advocate two main considerations. The first one is that only some disorders, such as chronic urticaria or immune thrombocytopenic purpura, may benefit from *H. pylori* eradication. In this case, the literature might encourage the treatment of the bacterium, together with specific dermatological or hematological therapy. In this regard, we must note that the pathogenesis of these conditions is complex and multiple predisposing factors are involved. On the other hand, it is known that *H. pylori* eradication may improve, but not always suppress both disorders. The second consideration is based on the hypothesis that *H. pylori* infection might alter the composition of gut microbiota, and this event may be a trigger for the onset of atopic diseases [27]. Indeed, the bacterium may increase the diversity index of microbiota composition by inducing a shift from an enterotype

characterized by *Bacteroides*, to one dominated by *Prevotella* [28]. Moreover, *Fusobacterium*, *Neisseria*, *Prevotella*, *Veillonella* and *Rothia* have been positively associated with the presence of *H. pylori* and related gastric lesions [29]. These evidences have stimulated studies to demonstrate that the eradication of the bacterium may permit the restoration of the microbiota composition. In a recent study, *H. pylori* eradication induced an increase of *Bifidobacteria* and an enrichment of some potentially beneficial gut bacteria such as *Blautia* and *Lachnospirillum* [30]. Furthermore, the microbiota composition of children with *H. pylori* eradication was comparable to non-infected individuals [31]. Therefore, it is reasonable to speculate that a multifaceted pathogenetic mechanism may occur in atopic diseases and novel strategies aiming to modulate the imbalance of microbiota may play a key role [32]. Accordingly, an intervention on the triple bound *H. pylori*-microbiota-atopy could be invoked to explain this mutual relationship and design future interventional trials aimed to microbiota handling.

In conclusion, despite the fact that *H. pylori* role has been recognized in both cross reactions and atopy, it needs to be framed in a context characterized by multifactorial events developing over time. Bacterium eradication has been proven to be useful in urticaria, while it seems to exert a protective role in asthma. Lastly, its interaction with intestinal microbiota composition suggests the possibility of an intervention on the triple bound *H. pylori*-microbiota-atopy. Our hope is to expect future studies to bring further elements of translational medicine.

Acknowledgments

Mrs. Mary Paulene Butts for linguistic revisions.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (***) to readers.

1. Ierardi E, Goni E, Losurdo G, et al. *Helicobacter pylori* and non-malignant diseases. *Helicobacter*. 2014;19(Suppl 1):27–31.
2. Gasbarrini G, Genta RM, Anti M, et al. Update on *Helicobacter pylori* research. Malignancies. *Eur J Gastroenterol Hepatol*. 1997;9(6):621–623.

3. Gravina AG, Zagari RM, De Musis C, et al. *Helicobacter pylori* and extragastric diseases: a review. *World J Gastroenterol*. 2018;24(29):3204–3221.
4. Claeys D, Faller G, Appelmelk BJ, et al. The gastric H⁺,K⁺-ATPase is a major autoantigen in chronic *Helicobacter pylori* gastritis with body mucosa atrophy. *Gastroenterology*. 1998;115(2):340–347.
- **Seminal paper describing the role of *Helicobacter* in induction of autoimmune gastritis.**
5. Ierardi E, Francavilla R, Balzano T, et al. Autoantibodies reacting with gastric antigens in *Helicobacter pylori* associated body gastritis of dyspeptic children. *Ital J Gastroenterol Hepatol*. 1998;30(5):478–480.
6. Gu H, Li L, Gu M, et al. Association between *Helicobacter pylori* infection and chronic urticaria: a meta-analysis. *Gastroenterol Res Pract*. 2015;2015:486974.
7. Kim HJ, Kim YJ, Lee HJ, et al. Systematic review and meta-analysis: effect of *Helicobacter pylori* eradication on chronic spontaneous urticaria. *Helicobacter*. 2019;24(6):e12661.
- **A relevant meta-analysis exploring the relationship between *Helicobacter* and urticaria.**
8. Tan RJ, Sun HQ, Zhang W, et al. A 21-35 kDa mixed protein component from *Helicobacter pylori* activates mast cells effectively in chronic spontaneous urticaria. *Helicobacter*. 2016 Dec;21(6):565–574.
9. Supajatura V, Ushio H, Wada A, et al. Cutting edge: vacA, a vacuolating cytotoxin of *Helicobacter pylori*, directly activates mast cells for migration and production of proinflammatory cytokines. *J Immunol*. 2002;168:2603-2607.
10. Tsai CC, Kuo TY, Hong ZW, et al. *Helicobacter pylori* neutrophil activating protein induces release of histamine and interleukin-6 through G protein-mediated MAPKs and PI3K/Akt pathways in HMC-1 cells. *Virulence*. 2015;6:755-765.
11. Strachan DP. Hay fever, hygiene, and household size. *BMJ*. 1989;299(6710):1259–1260.
12. Miftahussurur M, Nusi IA, Graham DY, et al. *Helicobacter*, hygiene, atopy, and asthma. *Front Microbiol*. 2017;8:1034.
- **Interesting systematic review about the relationship between *Helicobacter* and allergic disorders.**
13. Blaser MJ, Falkow S. What are the consequences of the disappearing human microbiota? *Nat Rev Microbiol*. 2009;7(12):887–894.
14. Oertli M, Müller A. *Helicobacter pylori* targets dendritic cells to induce immune tolerance, promote persistence and confer protection against allergic asthma. *Gut Microbes*. 2012;3(6):566–571.
15. Oertli M, Sundquist M, Hitzler I, et al. DC-derived IL-18 drives Treg differentiation, murine *Helicobacter pylori*-specific immune tolerance, and asthma protection. *J Clin Invest*. 2012;122(3):1082–1096.
16. Koch KN, Hartung ML, Urban S, et al. *Helicobacter* urease-induced activation of the TLR2/NLRP3/IL-18 axis protects against asthma. *J Clin Invest*. 2015;125(8):3297–3302.
17. Luzza F, Parrello T, Sebkova L, et al. Expression of proinflammatory and Th1 but not Th2 cytokines is enhanced in gastric mucosa of *Helicobacter pylori* infected children. *Dig Liver Dis*. 2001;33(1):14–20.
18. Ierardi E, Monno RA, Gentile A, et al. *Helicobacter Heilmannii* gastritis: a histological and immunohistochemical trait. *J Clin Pathol*. 2001;54(10):774–777.
19. Codolo G, Mazzi P, Amedei A, et al. The neutrophil-activating protein of *Helicobacter pylori* down-modulates Th2 inflammation in ovalbumin-induced allergic asthma. *Cell Microbiol*. 2008;10(11):2355–2363.
20. Zhou S, Huang Y, Liang B, et al. Systemic and mucosal pre-administration of recombinant *Helicobacter pylori* neutrophil-activating protein prevents ovalbumin-induced allergic asthma in mice. *FEMS Microbiol Lett*. 2017;364(2):pii: fnw288.
21. Chen Y, Blaser MJ. *Helicobacter pylori* colonization is inversely associated with childhood asthma. *J Infect Dis*. 2008;198(4):553–560.
- **Large epidemiological study investigating the link between *Helicobacter* and asthma.**
22. Lionetti E, Leonardi S, Lanzafame A, et al. *Helicobacter pylori* infection and atopic diseases: is there a relationship? A systematic review and meta-analysis. *World J Gastroenterol*. 2014;20(46):17635–17647.
23. Jarvis D, Luczynska C, Chinn S, et al. The association of hepatitis A and *Helicobacter pylori* with sensitization to common allergens, asthma and hay fever in a population of young British adults. *Allergy*. 2004;59(10):1063–1067.
24. Jun ZJ, Lei Y, Shimizu Y, et al. High seroprevalence of *Helicobacter pylori* in chronic bronchitis among Chinese population. *Tohoku J Exp Med*. 2006;208(4):327–331.
25. Abadi AT, Ierardi E, Lee YY. Why do we still have *Helicobacter Pylori* in our stomachs. *Malays J Med Sci*. 2015;22(5):70–75.
26. Blaser MJ, Atherton JC. *Helicobacter pylori* persistence: biology and disease. *J Clin Invest*. 2004;113(3):321–333.
27. Borbet TC, Zhang X, Müller A, et al. The role of the changing human microbiome in the asthma pandemic. *J Allergy Clin Immunol*. 2019;144(6):1457–1466.
- **This review sheds a new light on the role of microbiota in modulating the immune response and its role in asthma onset, with a particular eye on *Helicobacter*.**
28. Frost F, Kacprowski T, Rühlemann M, et al. *Helicobacter pylori* infection associates with fecal microbiota composition and diversity. *Sci Rep*. 2019;9(1):20100.
29. Guo Y, Zhang Y, Gerhard M, et al. Effect of *Helicobacter pylori* on gastrointestinal microbiota: a population-based study in Linqu, a high-risk area of gastric cancer. *Gut*. 2019 Dec 19;pii: gutjnl-2019-319696. [Epub ahead of print]. DOI:10.1136/gutjnl-2019-319696
30. He C, Peng C, Wang H, et al. The eradication of *Helicobacter pylori* restores rather than disturbs the gastrointestinal microbiota in asymptomatic young adults. *Helicobacter*. 2019;24(4):e12590.
31. Serrano CA, Pierre R, Van Der Pol WJ, et al. Eradication of *Helicobacter pylori* in children restores the structure of the gastric bacterial community to that of noninfected children. *Gastroenterology*. 2019;157(6):1673–1675.
32. Musso P, Chiappini E, Bernardini R. Human microbiome and allergic diseases in children: pathogenetic role and therapeutic options. *Curr Pediatr Rev*. 2019 Oct 25;15. [Epub ahead of print]. DOI:10.2174/1573396315666191025110849