

## *Helicobacter pylori* and allergy: Update of research

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### Abstract

Recently a lot of literature has been published about the possible preventive action of *Helicobacter pylori* (*H. pylori*) against allergy. The present review summarizes research data about the association between *H. pylori* and allergic diseases, as well as discusses possible hypotheses about the preventive action of *H. pylori* against atopy. There is evidence from observational studies to support a weak inverse association between prevalence of *H. pylori* infection and allergy. However, confounders like some unidentified socioeconomic factors, antibiotic use and

others could bias the association. Although data from cohort studies point to a possible association of *H. pylori* with some of the allergic diseases, no definite proof for causal relationship has been clearly demonstrated yet. A biological mechanism proposed to explain the preventive action of *H. pylori* to allergy is reduced exposure to a major stimulus for the generation of Treg cells in individuals without *H. pylori* infection. In addition, *H. pylori* could be an indicator for changes in gut microbiome, reflecting the complex interaction between microbes and immune system.

**Key words:** *Helicobacter pylori*; Allergy; Atopy

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**Core tip:** Review summarizes research data about the association between *Helicobacter pylori* (*H. pylori*) and allergic diseases. Results from observational studies support a weak inverse association between prevalence of *H. pylori* and allergy. However, different confounders like unidentified socioeconomic factors, antibiotic use and others could bias the observed association. Further, no definite proof for causal relationship has been clearly demonstrated yet, although data from cohort studies point to a possible association of *H. pylori* with some of the allergic diseases. Finally, microbiological studies show that *H. pylori* could be an indicator for changes in gut microbiome during recent decades, reflecting the complex interaction between microbes and immune system.

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### INTRODUCTION

Although *Helicobacter pylori* (*H. pylori*) infection is supposed to be associated with gastric and duodenal

ulcer, gastric adenocarcinoma, MALT lymphoma and even recognized as grade-1 carcinogen<sup>[1-4]</sup>, only minority of infected patients will develop a serious disease. Moreover, some researchers even suggest possible preventive effect of *H. pylori* against several diseases like gastro-esophageal reflux disease and Barrett's adenocarcinoma, obesity, autoimmune diseases, allergy and others<sup>[5,6]</sup>.

The latest Maastricht consensus states that the evidence available shows no definite causative protective effect of *H. pylori* against asthma and atopy nor that its eradication causes or worsens them and further research is needed<sup>[7]</sup>. Thus, new data appear constantly about the possible role of bacterium in the development of allergic diseases. The present review summarizes research data about the association between *H. pylori* and allergic diseases.

## EVIDENCE FOR OPPOSITE PREVALENCE TREND BETWEEN *H. PYLORI* AND ALLERGIC DISEASES

The idea about a possible protective role of *H. pylori* against allergy has arisen observing opposite prevalence trends between *H. pylori* and allergic diseases, showing that the prevalence of *H. pylori* in industrialized countries is decreasing while the prevalence of asthma and other allergic diseases is increasing<sup>[6]</sup>.

Ironically, the first case-control studies showed a positive association between *H. pylori* infection and allergy. For example, in 1998 a study from Italy identified higher prevalence of *H. pylori* IgG antibodies among allergic patients compared to patients with inflammatory bowel disease<sup>[8]</sup>. Further, Figura *et al*<sup>[9]</sup> identified higher prevalence of anti-CagA antibodies in *H. pylori* infected persons with food allergy compared to controls (62.5% vs 28.0%, respectively;  $P = 0.03$ ). In addition, the mean IgE level to the most common alimentary antigens was increased in CagA-positive individuals compared to CagA-negative patients. This made the authors suggest that mucosal and inflammatory lesions found in individuals infected with CagA-positive *H. pylori* strains could increase the epithelial permeability and promote the passage of allergens, which, in atopic persons, could directly stimulate an IgE response.

Higher prevalence of *H. pylori* among patients with allergic diseases observed in some studies raised question about the role of inflammation (observed in the presence of *H. pylori* infection) in the development of allergy. A positive association between *H. pylori* and allergic diseases is still being discussed in respect to urticaria. Moreover, International guidelines in Urticaria state that in some cases of chronic spontaneous urticaria eradication of infections, such as *H. pylori*, bowel parasites and bacterial infections of the nasopharynx, have shown to provide a benefit in the management of the disease<sup>[10]</sup>.

One of the first well designed and controlled studies showing opposite prevalence trends between *H. pylori*

and atopy comes from Finland, demonstrating 3.5-fold increase of total and allergen-specific IgE antibody level in random population from 1973 to 1994 (OR = 5.12, 95%CI: 2.32-11.3)<sup>[11]</sup>. However, increase of IgE was observed mainly in the subgroup with no *H. pylori* antibodies, thus raising the hypothesis that *H. pylori* could influence the development of atopic diseases<sup>[11]</sup>.

A huge study from United States based on database containing information about asthma and *H. pylori* status in 7663 subjects showed an inverse association between cag-positive *H. pylori* strain and asthma (OR = 0.79, 95%CI: 0.63-0.99), with a stronger association in younger individuals<sup>[12]</sup>. An inverse association was found also with other allergic disorders (allergic rhinitis and sensitization to different allergens). Further, the authors tested the association in children up till 20 years of age ( $n = 7412$ ) and again found inverse association with wheezing, allergic rhinitis and eczema<sup>[13]</sup>.

Up to now many cross-sectional and case-control studies have been performed, thus, showing controversial results. Results are summarized in Tables 1 and 2.

Basing on the published studies, several meta-analyses have tested the association. Although in 2012 Wang *et al*<sup>[14]</sup> demonstrated no association between asthma and *H. pylori* infection, analyzing five studies with 770 cases and 785 controls (OR = 1.1, 95%CI: 0.82-1.24), another meta-analysis by the same authors showed pooled OR of all included studies (nine cross-sectional, seven case-control and three cohort studies) for asthma and *H. pylori* to be 0.81 (95%CI: 0.72-0.91); while pooled OR for asthma and *H. pylori* infection in cross-sectional studies was 0.84 (95%CI: 0.74-0.96), in case-control studies - 0.94 (95%CI: 0.79-1.12)<sup>[15]</sup>.

Similarly, Zhou *et al*<sup>[16]</sup> analyzing 14 studies with 28283 persons demonstrated a weak inverse association between *H. pylori* and asthma 0.84 (95%CI: 0.73-0.96). Taye *et al*<sup>[17]</sup> have performed meta-analysis of 16 studies ( $n = 21348$ ) about the association of atopy with *H. pylori*. The authors found an inverse association with atopy (OR = 0.82, 95%CI: 0.73-0.91) as well as with increased level of specific IgE (OR = 0.75, 95%CI: 0.62-0.92).

Detailed overview about case-control and cross-sectional studies, as well as meta-analysis of studies, has been recently published by Lionetti *et al*<sup>[18]</sup>. The authors concluded that pooled results of case-control studies showed a significant inverse association of *H. pylori* infection with atopy/allergic disease (or with atopy, but not with allergic disease), while pooled results of cross-sectional studies showed only a significant association between allergic disease and *H. pylori* infection.

However, the analysis and comparison of studies is complicated and should be evaluated with caution due to differences among study designs. The authors of the meta-analysis argue that different diagnostic criteria for allergic disease and atopy are used - in some studies asthma was diagnosed by physician tests or by symptoms, while in others the authors evaluated self-reported disease or used only laboratory tests<sup>[18]</sup>.

**Table 1 Association between *Helicobacter pylori* and allergy in cross-sectional studies**

Ref.	Country	Studied population	n	Age (yr)	<i>H. pylori</i> detection	Allergy diagnosis	Main finding: OR (95%CI) in relation to <i>H. pylori</i>
Lee <i>et al</i> <sup>[35]</sup>	South Korea	Routine check-up	3376	Adults	IgG	Physician diagnosed allergy; use of anti-allergic medication; IgE	No association with allergic disease: 1.05 (0.86-1.28); Inverse association with IgE hypersensitivity: 1.32 (0.98-1.31)
Zevit <i>et al</i> <sup>[46]</sup>	Israel	National referral laboratory	6959	5-18	UBT	Physician diagnosed asthma; use of anti-allergic medication	Inverse association with asthma: 0.82 (0.69-0.08)
Imamura <i>et al</i> <sup>[47]</sup>	Japan	Healthy volunteers	211	Adults	IgG	Specific IgE, polinosis symptoms	Inverse association with polinosis: 0.15 (0.05-0.48)
Fullerton <i>et al</i> <sup>[21]</sup>	United Kingdom	General population	2437	Adults	IgG	Symptoms of wheeze, hay fever; lung function tests; bronchial reactivity; SPT; IgE	No association with asthma: 1.09 (0.77-1.54), atopy: 0.92 (0.74-1.15); hay fever: 1.00 (0.79-1.26), wheeze: 0.94 (0.74-1.19)
Pfefferle <i>et al</i> <sup>[48]</sup>	Germany	Employees of two companies	500	Adults	SAT	Self-reported physician diagnosed allergy, use of anti-allergic medication specific skin sensitization	Inverse association with allergy diagnosis: 0.26 (0.08-0.84)
Chen <i>et al</i> <sup>[13]</sup>	United States	Data from health and nutrition examination survey	7412	3-19	IgG; CagA	Self-reported asthma	Inverse association with asthma: 0.69 (0.45-1.06) Subgroup < 5 yr: 0.58 (0.38-0.88); 3-13 yr: 0.14 (0.24-0.69)
Shiotani <i>et al</i> <sup>[49]</sup>	Japan	University students	1953	Adults	IgG	Self-reported atopic dermatitis, asthma, allergic rhinitis, urticaria	Inverse association with allergic diseases: 0.49 (0.27-0.89)
Baccioglu <i>et al</i> <sup>[50]</sup>	Turkey	Patients with upper gastrointestinal endoscopy	90	Adults	Gastric tissue microscopy	SPT, total IgE, questionnaire	No association with allergic disease: 1.0 (0.1-18.9) Inverse association with asthma/CagA <sup>+</sup> cases: 0.79 (0.63-0.99);
Chen <i>et al</i> <sup>[12]</sup>	United States	Data from health and nutrition examination survey	7663	Adults	CagA	Self-reported asthma, allergen-specific skin sensitization	Inverse association with allergic rhinitis/CagA <sup>+</sup> : 0.77 (0.62-0.96)
Herbarth <i>et al</i> <sup>[51]</sup>	Germany	School starters	3347	5-7	UBT	Eczema	Inverse association with eczema: OR 0.31
Kolho <i>et al</i> <sup>[52]</sup>	Finland	Patients with upper gastrointestinal endoscopy	97	5-15	Histology data	Specific IgE	No association with IgE, asthma, hay fever;
Jarvis <i>et al</i> <sup>[20]</sup>	United Kingdom	Health service registry	1121	Adults	IgG	Specific IgE, symptoms	Inverse association with sensitization to grass: 0.65 (0.43-0.99)
Uter <i>et al</i> <sup>[53]</sup>	Germany	University students	1368	18-20	IgG	Physician diagnosed asthma	No association with asthma: 0.99 (0.57-1.64)
McCune <i>et al</i> <sup>[54]</sup>	United Kingdom	Community-based population	3244	Adults	UBT	Use of asthma medication	Inverse association with asthma: 0.78 (0.59-1.05)

*H. pylori*: *Helicobacter pylori*; UBT: 13C-urea breath test; SAT: Stool antigen test; SPT: Skin prick test.

Further, difference between detection of active infection by urea breath test or stool antigen test and detection of *H. pylori* antibodies should be noted. In addition, the age of study population should also be taken into account since the time between *H. pylori* colonization and allergen sensitization is difficult to evaluate, therefore *H. pylori* negative adult patient could have been colonized since childhood and *vice versa*<sup>[18]</sup>.

Therefore we could conclude, that, although evidence from observational studies show an inverse association between allergic disease and *H. pylori*, the association is weak and not consistent.

## IS *H. PYLORI* TRULY INDEPENDENTLY INVERSELY ASSOCIATED WITH ALLERGIC DISEASE?

The idea about the inverse association of *H. pylori* with allergic diseases has been strongly criticized arguing, that *H. pylori* could be merely a marker of socio-economic status, known to be also associated with allergic disease<sup>[19]</sup>.

Although Blaser *et al*<sup>[6]</sup> report, that the inverse association between *H. pylori* and asthma was observed independent of socioeconomic status, age, gender,

**Table 2 Association between *Helicobacter pylori* and allergy in case-control studies**

Ref.	Country	Cases (n)	Controls (n)	Age (yr)	<i>H. pylori</i> detection	Allergy diagnosis	Main finding: OR (95%CI) in relation to <i>H. pylori</i> <sup>a</sup>
Pedullà <i>et al</i> <sup>[55]</sup>	Italy	Food allergy + atopic dermatitis (88)	Atopic dermatitis (202)	2-11.8	IgG, SAT	Physician diagnosed food allergy, IgE	Inverse association with food allergy: 0.32 (0.11-0.95)
Elitsur <i>et al</i> <sup>[56]</sup>	United States	Eosinophil esophagitis (62)	Esophagitis (268); idiopathic gastritis (480)	Children	Histology data	Upper endoscopy, histology data	Inverse association with eosinophil esophagitis: 0.096 (0.013-0.72)
Karimi <i>et al</i> <sup>[57]</sup>	Iran	Asthma (98)	Healthy children (98)	6-12	UBT	Physician diagnosed asthma	No association with asthma: <i>H. pylori</i> positivity 18% (cases) vs 23% (controls)
Reibman <i>et al</i> <sup>[58]</sup>	United States	Asthma (318)	Non-asthma controls (208)	Adults	IgG, CagA	Physician diagnosed asthma; IgE; spirometry	Inverse association with asthma for CagA <sup>+</sup> cases: 0.57 (0.36-0.89)
Konturek <i>et al</i> <sup>[59]</sup>	Germany	Food allergy (42)	Healthy controls (20)	Adults	UBT, IgG	Physician diagnosed food allergy; SPT, IgE, N-tele-methylhistamine urinary excretion	Inverse association with food allergy: <i>H. pylori</i> positivity 33% (cases) vs 40% (controls)
Annagür <i>et al</i> <sup>[60]</sup>	Turkey	Asthma (79)	Healthy children (36)	5-15	IgM and IgG	Pulmonary function tests, SPT, total IgE	No association with asthma: 1.69 (0.62-4.67)
Jaber <i>et al</i> <sup>[61]</sup>	Sauda Arabia	Asthma (220)	Asymptomatic children (543)	1-10	IgG	Physician diagnosed asthma	Inverse association with asthma: 0.84 (0.56-1.25)
Jun <i>et al</i> <sup>[62]</sup>	Japan	Asthma (46)	Peptic ulcer patients (48) + healthy controls (48)	Adults	IgG, CagA	Physician diagnosed asthma	No association with asthma: 1.20 (0.53-2.72)
Pessi <i>et al</i> <sup>[63]</sup>	Finland	Asthma (245)	Matched controls (405)	Adults	IgG	Physician diagnosed asthma	Inverse association with asthma: 0.86 (0.63-1.19)
Bartuzi <i>et al</i> <sup>[64]</sup>	Poland	Food allergy with GI symptoms (110)	Chronic gastritis (40)	Adults	Biopsy, histology	Physician diagnosed food allergy, IgE	In atopic patients <i>H. pylori</i> increases intensity of gastric inflammation
Tsang <i>et al</i> <sup>[65]</sup>	China	Asthma (90)	Healthy controls (97)	Adults	IgG	Physician diagnosed asthma	No association with asthma: 1.55 (0.87-2.78)
Corrado <i>et al</i> <sup>[66]</sup>	Italy	Atopic dermatitis (30) + atopic dermatitis with GI symptoms (30)	Asthma (30)	4-12	IgG; CagA	Physician diagnosed allergy	Positive association with atopic dermatitis compared to asthma: 56% and 37% (cases) vs 10% (controls)
Matricardi <i>et al</i> <sup>[67]</sup>	Italy	Atopic cases (240)	Non-atopic controls (240)	17-24	IgG	Physician diagnosed allergic rhinitis and asthma; IgE	Inverse association with atopy: 0.76 (0.47-1.24)
Figura <i>et al</i> <sup>[9]</sup>	Italy	Food allergy (38)	Matched controls (53)	4-12	IgG, CagA	Physician diagnosed food allergy; IgE	Positive association with food allergy in CagA <sup>+</sup> cases: 4.29
Corrado <i>et al</i> <sup>[8]</sup>	Norway	Food allergy (30) + asthma (30)	Inflammatory bowel disease (30)	5-14	IgG, CagA	Physician diagnosed food allergy and asthma	Positive association: 37% (cases) vs 10% controls

*H. pylori*: *Helicobacter pylori*; UBT: <sup>13</sup>C-urea breath test; SAT: Stool antigen test; SPT: Skin prick test; GI: Gastrointestinal.

ethnic background, smoking status, and hepatitis A infection, several studies indirectly suggest that other factors could influence the opposite prevalence trends and could play a role in the development of allergy.

For example, Jarvis *et al*<sup>[20]</sup> showed no association between presence of *H. pylori* antibodies and night cough, hay fever, wheezing within last 12 mo as well as sensitization to five allergens, after adjusting the patient sample for age, gender, area, number of siblings, social class. In addition, the authors observed a marked negative association of both hepatitis A and *H. pylori* with family size only in seropositive individuals (but not in those who were seronegative). This made authors

suggest that those without either infection are likely to have grown up in hygienic environments, possibly less overcrowded and with a better diet.

Similarly, a well-designed cross sectional study from United Kingdom (also controlled for social class) could identify only lower lung function in individuals with *H. pylori* seropositivity. However, after adjustment for either height or social class the size of the association was reduced. No association was observed with wheezing, chronic bronchitis, self-reported asthma, atopy or bronchial hyper-reactivity<sup>[21]</sup>.

No association with a group of infections was observed among Roma children living in poor hygienic



conditions compared to non-Roma children in Greece<sup>[22]</sup>. Although Roma children were found significantly more often seropositive for *Toxoplasma gondii*, hepatitis A, *H. pylori*, herpes simplex virus-1 (HSV-1), cytomegalovirus and Hepatitis B, no statistically significant differences were found between Roma and non-Roma children in respect to atopy or specific IgE level. Despite the higher numbers of exposure to infectious agents among Roma children, no protective effect for allergic disease development was evident. Even more, a positive association of the cumulative index of exposure to infections with atopy was found in the non-Roma children (OR = 1.38, 95%CI: 1.08-1.75) and in the total population (OR = 1.42, 95%CI: 1.11-1.83).

An interesting study on schoolchildren with similar genetic background but different socioeconomic environment (Finland and Russian Karelia) showed higher prevalence of allergen-specific IgE in Finnish children, while in Russian children higher prevalence of antibodies to coxsackivirus B4, *H. pylori*, *Toxoplasma gondii* and hepatitis A was detected. However, an inverse association between infections and prevalence of atopy was observed only in Russian Karelian children and the biggest effect was observed for enterovirus. However, the authors also hypothesised that some other factors could be associated with infections in Russian but not in Finnish populations are responsible for the effect<sup>[23]</sup>.

Finally, in Malaysia low *H. pylori* prevalence goes together with low prevalence of wheezing among 6-7 and 13-14 years old children (5.4% and 5.7%, respectively)<sup>[24]</sup>, therefore scientists have concluded that *H. pylori* is only a marker for poor hygiene<sup>[25]</sup>. Although no study has been performed yet comparing the prevalence of *H. pylori* among patients with and without asthma in Malaysia, Raj *et al*<sup>[26]</sup> consider that available data speak against the unique role for *H. pylori* infection as a protective factor against asthma.

To summarize, there is evidence that *H. pylori* could not be independently inversely associated with allergic disease, but just reflect changes in environment and/or diet. The inverse association between prevalence of *H. pylori* infection and allergic diseases observed in studies could also be biased by some other uncontrolled factors.

## POSSIBLE CAUSAL RELATIONSHIP BETWEEN *H. PYLORI* AND ALLERGIC DISEASE

Although a weak inverse association between *H. pylori* and allergy can be recognized, scientists argue that opposite prevalence, possibly evident from observational studies, does not mean a causal relationship<sup>[19]</sup>. However, demonstration of a possible causal relationship between *H. pylori* and allergy is extremely complicated.

A biological mechanism proposed to explain the preventive association of *H. pylori* to allergy is reduced exposure to a major stimulus for the generation of Treg cells in individuals without *H. pylori* infection<sup>[27]</sup>. One of

the latest ideas involves neutrophil-activating protein of *H. pylori* that could inhibit Th2-mediated bronchial inflammation in patients with allergic asthma<sup>[5]</sup>. Possible immunomodulatory properties of *H. pylori* are well described by Arnold *et al*<sup>[28]</sup>.

### Fulfilment of Bradford Hill criteria

Blaser *et al*<sup>[6]</sup> used Bradford Hill criteria to support the evidence about the inverse association between *H. pylori* and asthma. Hill's criteria consist of several conditions fulfillment of which can provide evidence of a causal relationship between an incidence (*H. pylori* prevalence) and a possible consequence (asthma)<sup>[29]</sup>.

To prove the causal link Blaser *et al*<sup>[6]</sup> mentioned the small but consistent trend demonstrated in several studies as well as the fact, that inverse causation is not likely and the decline is preceding the increase in asthma. However, although there is a weak trend showing inverse association between allergy and *H. pylori*, not all studies approve it. Further, Blaser *et al*<sup>[6]</sup> considered that the inverse association observed with early life asthma (not with long-standing asthma seen in adults) supported the role of *H. pylori*, since the effect of *H. pylori* might be less important in adult-onset asthma due to much more heterogeneous nature of adult asthma. However, confounding factors that could influence the association are not fully ruled out.

Further, one of the Bradford criteria states that there is no other likely explanation of disease - the more specific an association between a factor and an effect is, the bigger the probability of a causal relationship. However, at present allergologists consider asthma as a multifactorial disease associated with several other risk factors (like urban outdoor and indoor pollution, allergens, etc.) rather than *H. pylori* infection<sup>[30]</sup>. Therefore the fulfillment of Bradford Hill's criteria, demonstrated by Blaser *et al*<sup>[6]</sup>, should be interpreted with caution and should be considered only as one of the arguments for protection of *H. pylori* against asthma.

### Data from cohort studies

Since it is impossible to perform interventional studies to test the link between *H. pylori* and allergy, some knowledge about a possible causal association could be driven from cohort studies. However, it should be noted that such studies are not conclusive and they give only a better insight about a possible causality.

Holster *et al*<sup>[31]</sup> detected the presence of *H. pylori* antibodies in 7-9 years old children who were followed from birth and assessed by yearly questionnaires about allergic symptoms and possible risk factors. The authors observed no association between *H. pylori* and atopic dermatitis, allergic rhinitis and asthma. A borderline association was found only between *H. pylori* and wheezing. However, the authors admit, that they were not able to detect if *H. pylori* infection preceded the diagnosis of allergic disease, since presence of *H. pylori* infection was diagnosed only at the age of 7-9 years.

Further, a cohort study in Ethiopia followed children

since birth, detecting presence of allergic symptoms with questionnaires and performing allergic skin tests and *H. pylori* stool antigen tests at the age of one, three and five years. The sample was controlled for potential confounders. After three year follow-up the authors found only a borderline association with eczema<sup>[32]</sup>. Further, following the same cohort for five years an inverse association was observed only with eczema<sup>[33]</sup>. No association was observed with asthma or other allergic disease. Interestingly, that in the same cohort the association between paracetamol therapy and allergic symptoms was analyzed separately and an inverse association was observed between use of paracetamol and wheezing and eczema<sup>[34]</sup>.

#### **Development of allergy after *H. pylori* eradication**

Several studies demonstrated development of an allergic disease or increase of IgE after *H. pylori* eradication. Korean study demonstrated increased levels of IgE related, non IgE related allergy as well as subclinical raise of IgE levels in patients after *H. pylori* eradication compared to *H. pylori* positive patients without eradication and *H. pylori* negative controls<sup>[35]</sup>. However, this could also be related to the change in gastric acidity due to treatment with proton pump inhibitors, used together with eradication therapy. In addition, some patients continue use of acid lowering drugs even after eradication therapy.

#### **Data from animal studies**

Finally, a possible causal relationship can be demonstrated in animal models. One of the first studies showing causal relationship was the study by Arnold *et al.*<sup>[36]</sup>, showing that animals infected with *H. pylori* infection had lower airway hyper-responsiveness, tissue inflammation, and goblet cell metaplasia. Further studies supported the finding that *H. pylori* infection could protect mice from development of allergic asthma<sup>[37]</sup>. However, effect observed in animal models quite often is not observed also in humans.

## **H. PYLORI AS A PART OF COMPLEX INTERACTION BETWEEN MICROBES AND HUMAN IMMUNE SYSTEM**

#### ***H. pylori* and other infectious agents**

Blaser *et al.*<sup>[6]</sup> speculate, that *H. pylori* could be merely a marker for other phenomena, for example, early life antibiotic use could eliminate *H. pylori* as well as other microbes that actually could be the protective agents. Therefore, the question arises if *H. pylori* *per se* plays the crucial role in the development of allergy or it is just a marker of frequent infections or other factors, since several other microbes have been shown to be inversely associated with allergic disease<sup>[38]</sup>.

This could be indirectly supported by study, showing that seropositivity to *H. pylori* and Hepatitis A was

unrelated to atopic status, while multivariate analysis showed that both the effect of having two or more younger siblings (OR = 0.1, 95%CI: 0.03-0.8) and of acquiring measles up to the age of three (OR = 0.2, CI: 0.03-0.8) were significantly related to a lower risk of asthma<sup>[39]</sup>. The finding indicates that frequent infections observed more often in families with siblings are more important than *H. pylori* infection *per se*. Further, Janson *et al.*<sup>[40]</sup> demonstrated that combination of different infectious agents [hepatitis A, *H. pylori*, *Toxoplasmosis gondii*, HSV, Chlamydia pneumoniae, Epstein Barr virus (EBV) and cytomegalovirus] was an independent risk factor for atopy (OR = 1.43, 95%CI: 1.06-1.93), allergic asthma (OR = 1.82, 95%CI: 1.12-2.98), and allergic rhinitis (OR = 1.69, 95%CI: 1.21-2.37).

Importance of several pathogens (*Ascaris lumbricoides*, *T. gondii*, HSV and EBV) for prevention of atopy has been shown in a study by Alcantara-Neves *et al.*<sup>[41]</sup>: Children with three or fewer infection markers had a higher prevalence of specific IgE and skin prick test reactivity compared with those with four or more infection markers. On the contrary, isolated infections were not associated with the prevalence of atopic or non-atopic wheeze.

Therefore, evidence from studies suggests that *H. pylori* could be just a part of complex interaction between immune system and pathogens, as proposed by Janson *et al.*<sup>[40]</sup>.

#### ***H. pylori* as a part of gut microbiome**

This goes together with the idea that the increase in allergic diseases could be caused by changes in the composition of gut microflora due to global changes of environmental, socioeconomic and life style factors<sup>[27]</sup>. Data exist, showing lower diversity of microflora in allergic patients compared to healthy controls: A study in Sweden reports a lower diversity of the total microbiota at one month in infants with IgE-associated eczema<sup>[42]</sup>.

Although previously *H. pylori* was considered as the major inhabitant of stomach, at present up-to-date sequence based molecular methods have allowed identifying gastric microbiota more precisely. von Rosenvinge *et al.*<sup>[43]</sup> have shown that such phyla as *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria* and *Fusobacteria* dominate in gastric fluid samples. In a review Engstrand *et al.*<sup>[44]</sup> have also summarized that gastric micro-biota contains a large variety of genera including *Staphylococcus*, *Streptococcus*, *Pervotella*, *Lactobacillus* and some others, therefore *H. pylori* could be considered only a part of a complex microbial flora in the stomach.

Further, Rosenvinge has identified that treatment with proton pump inhibitors promotes bacterial overgrowth, while antibacterial treatment is associated with reduced bacterial diversity<sup>[43]</sup>. Decreased microbiota diversity in patients after *H. pylori* eradication therapy has been identified also by Jakobsson *et al.*<sup>[45]</sup>. Therefore, one can conclude, that after *H. pylori* eradication the diversity of gastric microflora decreases that could possibly be

associated with development of allergy.

Therefore we could hypothesise that loss of *H. pylori* results in a small (possibly significant) reduction of stimulation of immune system, as proposed by other authors<sup>[44]</sup>. Importance of other microorganisms should also be considered in the complex interaction between the human immune system and microbes. However, how *H. pylori* specifically and the entire human microbial ecosystem affect human health is still questionable.

## CONCLUSION

Evidence from observational studies supports a weak inverse association between prevalence of *H. pylori* infection and allergy. However, it could be biased by confounders like socioeconomic factors, antibiotic use and others. No definite proof for causal relationship has been clearly demonstrated yet, although data from cohort studies point to a possible association of *H. pylori* with some allergic diseases. In addition, *H. pylori* could be an indicator for changes in gut microbiome during recent decades, reflecting the complex interaction between microbes and immune system.

Summarizing the data, it seems that *H. pylori* infection alone cannot prevent development of allergy in all infected individuals, similarly like bacterium is not causing a serious gastrointestinal disease in all infected patients. In both conditions genetic and environmental factors (diet, other microbes, microflora, etc.) are of importance next to the recognized role of the bacterium.

Nevertheless, the intensive research in *H. pylori* field has brought a new insight into the interaction between microbes and immune system and the microbial - host relationship, supporting the idea that microbes could play a role in the development of allergy.

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