**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

**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\cite{1-4}, only minority of infected patients will develop a serious disease. Moreover, some researchers even suggest possible preventive effect of \textit{H. pylori} against several diseases like gastroesophageal reflux disease and Barret’s adenocarcinoma, obesity, autoimmune diseases, allergy and others\cite{5,6}.

The latest Maastricht consensus states that the evidence available shows no definite causative protective effect of \textit{H. pylori} against asthma and atopy nor that its eradication causes or worsens them and further research is needed\cite{7}. 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 \textit{H. pylori} and allergic diseases.

**EVIDENCE FOR OPPOSITE PREVALENCE TREND BETWEEN \textit{H. PYLORI} AND ALLERGIC DISEASES**

The idea about a possible protective role of \textit{H. pylori} against allergy has arisen observing opposite prevalence trends between \textit{H. pylori} and allergic diseases, showing that the prevalence of \textit{H. pylori} in industrialized countries is decreasing while the prevalence of asthma and other allergic diseases is increasing\cite{6}.

Ironically, the first case-control studies showed a positive association between \textit{H. pylori} infection and allergy. For example, in 1998 a study from Italy identified higher prevalence of \textit{H. pylori} IgG antibodies among allergic patients compared to patients with inflammatory bowel disease\cite{8}. Further, Figura et al\cite{9} identified higher prevalence of anti-CagA antibodies in \textit{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 \textit{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 \textit{H. pylori} among patients with allergic diseases observed in some studies raised question about the role of inflammation (observed in the presence of \textit{H. pylori} infection) in the development of allergy. A positive association between \textit{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 \textit{H. pylori}, bowel parasites and bacterial infections of the nasopharynx, have shown to provide a benefit in the management of the disease\cite{10}.

One of the first well designed and controlled studies showing opposite prevalence trends between \textit{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)\cite{11}. However, increase of IgE was observed mainly in the subgroup with no \textit{H. pylori} antibodies, thus raising the hypothesis that \textit{H. pylori} could influence the development of atopic diseases\cite{11}.

A huge study from United States based on database containing information about asthma and \textit{H. pylori} status in 7663 subjects showed an inverse association between cag-positive \textit{H. pylori} strain and asthma (OR = 0.79, 95%CI: 0.63-0.99), with a stronger association in younger individuals\cite{12}. 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\cite{13}.

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\cite{14} demonstrated no association between asthma and \textit{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 \textit{H. pylori} to be 0.81 (95%CI: 0.72-0.91); while pooled OR for asthma and \textit{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)\cite{15}.

Similarly, Zhou et al\cite{16} analyzing 14 studies with 28283 persons demonstrated a weak inverse association between \textit{H. pylori} and asthma 0.84 (95%CI: 0.73-0.96). Taye et al\cite{17} have performed meta-analysis of 16 studies (\( n = 21348 \)) about the association of atopy with \textit{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\cite{18}. The authors concluded that pooled results of case-control studies showed a significant inverse association of \textit{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 \textit{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\cite{18}.
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\(^{18}\).

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.

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

| Ref.  | Country     | Studied population                  | n  | Age (yr) | H. pylori detection | Allergy diagnosis                  | Main finding: OR (95%CI) in relation to *H. pylori* |
|-------|-------------|------------------------------------|----|----------|---------------------|------------------------------------|--------------------------------------------------|
| Lee et al\(^{[48]}\) | 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 et al\(^{[49]}\) | Israel      | National referral laboratory        | 6959 | 5-18     | UBT                 | Physician diagnosed asthma; use of anti-allergic medication | Inverse association with asthma: 0.82 (0.69-0.98) |
| Imamura et al\(^{[50]}\) | Japan       | Healthy volunteers                  | 211  | Adults   | IgG                 | Specific IgE, polinosis symptoms | Inverse association with polinosis: 0.15 (0.05-0.48) |
| Fullerton et al\(^{[51]}\) | United Kingdom  | General population                  | 2437 | Adults   | IgG                 | Symptoms of wheeze, 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 et al\(^{[52]}\) | 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 et al\(^{[53]}\) | 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 (0.02-0.69) |
| Shiotani et al\(^{[54]}\) | 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 et al\(^{[55]}\) | 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\(^+\) cases: 0.79 (0.63-0.99) |
| Chen et al\(^{[56]}\) | 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\(^+\): 0.77 (0.62-0.96) |
| Herbarth et al\(^{[57]}\) | Germany     | School starters                     | 3347 | 5-7      | UBT                 | Eczema                            | Inverse association with eczema: OR 0.31 |
| Kolho et al\(^{[58]}\) | Finland     | Patients with upper gastrointestinal endoscopy | 97   | 5-15     | Histology data      | Specific IgE                       | No association with IgE, asthma, hay fever; Inverse association with sensitization to grass: 0.65 (0.43-0.99) |
| Jarvis et al\(^{[59]}\) | United Kingdom  | Health service registry             | 1121 | Adults   | IgG                 | Specific IgE, symptoms             | |
| Uter et al\(^{[60]}\) | Germany     | University students                | 1368 | 18-20    | IgG                 | Physician diagnosed asthma         | No association with asthma: 0.99 (0.57-1.64) Inverse association with asthma: 0.78 (0.59-1.05) |
| McCune et al\(^{[61]}\) | United Kingdom  | Community-based population          | 3244 | Adults   | UBT                 | Use of asthma medication           | |

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

**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\(^{19}\).

Although Blaser et al\(^{[62]}\) 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) | H. pylori detection | Allergy diagnosis | Main finding: OR (95%CI) in relation to H. pylori* |
|------|---------|-----------|--------------|----------|---------------------|-------------------|-------------------------------------------------|
| Pedullà et al[20] | 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 et al[21] | 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 et al[22] | Iran | Asthma (98) | Healthy children (98) | 6-12 | UBT | Physician diagnosed asthma | No association with asthma: H. pylori positivity 18% (cases) vs 23% (controls) |
| Reibman et al[23] | United States | Asthma (318) | Non-asthma controls (208) | Adults | IgG, CagA | Physician diagnosed asthma; IgE; spirometry | Inverse association with asthma for CagA+: cases: 0.57 (0.36-0.89) |
| Konturek et al[24] | 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: H. pylori positivity 33% (cases) vs 40% (controls) |
| Annagür et al[25] | 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 et al[26] | Sauda Arabia | Asthma (220) | Asymptomatic children (543) | 1-10 | IgG | Physician diagnosed asthma | Inverse association with asthma: 0.84 (0.56-1.25) |
| Jun et al[27] | 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 et al[28] | Finland | Asthma (245) | Matched controls (405) | Adults | IgG | Physician diagnosed asthma | Inverse association with asthma: 0.86 (0.63-1.19) In atopic patients H. pylori increases intensity of gastric inflammation |
| Bartuzi et al[29] | Poland | Food allergy with GI symptoms (110) | Chronic gastritis (40) | Adults | Biopsy, histology | Physician diagnosed food allergy, IgE | No association with asthma: 1.53 (0.87-2.78) |
| Tsang et al[30] | China | Asthma (90) | Healthy controls (97) | Adults | IgG | Physician diagnosed asthma | Inverse association with asthma: 1.56 (0.87-2.78) |
| Corrado et al[31] | 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) Inverse association with atopy: 0.76 (0.47-1.24) |
| Matricardi et al[32] | Italy | Atopic cases (240) | Non-atopic controls (240) | 17-24 | IgG | Physician diagnosed allergic rhinitis and asthma; IgE | No association with asthma: 1.56 (0.87-2.78) |
| Figura et al[33] | Italy | Food allergy (36) | Matched controls (53) | 4-12 | IgG, CagA | Physician diagnosed food allergy; IgE | Positive association with food allergy in CagA+: cases: 4.29 Positive association: 37% (cases) vs 10% controls |
| Corrado et al[34] | Norway | Food allergy (30) + asthma (30) | Inflammatory bowel disease (30) | 5-14 | IgG, CagA | Physician diagnosed food allergy and asthma | Positive association with food allergy in CagA+: cases: 4.29 Positive association: 37% (cases) vs 10% controls |

H. pylori: Helicobacter pylori; UBT: 13C-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[35] 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[21].

No association with a group of infections was observed among Roma children living in poor hygienic
conditions compared to non-Roma children in Greece\textsuperscript{[22]}. 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 coxsackievirus 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\textsuperscript{[23]}. 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)\textsuperscript{[26]}, therefore scientists have concluded that H. pylori is only a marker for poor hygiene\textsuperscript{[26]}. Although no study has been performed yet comparing the prevalence of H. pylori among patients with and without asthma in Malaysia, Raj et al\textsuperscript{[26]} 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\textsuperscript{[30]}. 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\textsuperscript{[27]}. One of the latest ideas involves neutrophil-activating protein of H. pylori that could inhibit Th2-mediated bronchial inflammation in patients with allergic asthma\textsuperscript{[31]}. Possible immunomodulatory properties of H. pylori are well described by Arnold et al\textsuperscript{[28]}.

Fulfilment of Bradford Hill criteria

Blaser et al\textsuperscript{[6]} 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)\textsuperscript{[29]}.

To prove the causal link Blaser et al\textsuperscript{[6]} 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\textsuperscript{[6]} 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\textsuperscript{[26]}. Therefore the fulfillment of Bradford Hill’s criteria, demonstrated by Blaser et al\textsuperscript{[6]}, 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\textsuperscript{[31]} 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, there and five years. The sample was controlled for potential confounders. After three year follow-up the authors found only a borderline association with eczema\cite{32}. Further, following the same cohort for five years an inverse association was observed only with eczema\cite{33}. 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\cite{34}.

**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\cite{35}. 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\cite{36}, 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\cite{37}. However, effect observed in animal models quite often is not observed also in humans.

**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\cite{27}. 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\cite{39}. 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\cite{40} have shown that such phyla as Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria and Fusobacteria dominate in gastric fluid samples. In a review Engstrand et al\cite{44} have also summarized that gastric micro-biota contains a large variety of genera including Staphylococcus, Streptococcus, Pseudomonas, 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\cite{39}. Decreased microbiota diversity in patients after H. pylori eradication therapy has been identified also by Jakobsson et al\cite{45}. Therefore, one can conclude, that after H. pylori eradication the diversity of gastric microflora decreases that could possibly be 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\cite{40}. 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\cite{40} demonstrated that combination of different infectious agents [hepatitis A, H. pylori, Toxoplasmosis gondii, HSV, Chlamydia pneumoniae, Ebstein 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\cite{41}: 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\cite{40}.

**H. pylori as a part of complex interaction between microbes and human immune system**

**H. pylori and other infectious agents**

Blaser et al\cite{36} 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\cite{38}.

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