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***Helicobacter pylori* infection and extragastric disorders in children: A critical update**

Pacifico L *et al*.Extragastric *H. pylori* in children

Lucia Pacifico, John F Osborn, Valeria Tromba, Sara Romaggioli, Stefano Bascetta, Claudio Chiesa

**Lucia Pacifico, Valeria Tromba, Sara Romaggioli, Stefano Bascetta,** Department of Pediatrics, Sapienza University of Rome, 324 00161-Rome, Italy

**John F Osborn,** Department of Health Sciences and Infectious Diseases, Sapienza University of Rome, 00161-Rome, Italy

**Claudio Chiesa,** Institute of Translational Pharmacology, National Research Council, 100 00133-Rome, Italy

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**Correspondence to: Claudio Chiesa, MD,** Institute of Translational Pharmacology, National Research Council, Via Fosso del Cavaliere, 100 00133-Rome, Italy. claudio.chiesa@ift.cnr.it

**Telephone:** +39-6-49979215 **Fax:** +39-6-49979216

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**Abstract**

*Helicobacter pylori* (*H. pylori*) is a highly prevalent, serious and chronic infection that has been associated causally with a diverse spectrum of extragastric disorders including iron deficiency anemia, chronic idiopathic thrombocytopenic purpura, growth retardation, and diabetes mellitus. The inverse relation of *H. pylori* prevalence and the increase in allergies, as reported from epidemiological studies, has stimulated research for elucidating potential underlying pathophysiological mechanisms. Although *H. pylori* is most frequently acquired during childhood in both developed and developing countries, clinicians are less familiar with the pediatric literature in the field. A better understanding of the *H. pylori* disease spectrum in childhood should lead to clearer recommendations about testing for and treating *H. pylori* infection in children who are more likely to develop clinical sequelae. A further clinical challenge is whether the progressive decrease of *H. pylori* in the last decades, abetted by modern clinical practices, may have other health consequences.

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**Key words**: *Helicobacter pylori*; Children; Iron deficiency anemia; Chronic idiopathic thrombocytopenic purpura; Growth retardation; Asthma; Allergy; Diabetes mellitus

**Core tip**: It is widely accepted that *Helicobacter pylori* (*H. pylori*)infection is a key pathogen for gastroduodenal diseases. Recently, the body of literature concerning a possible association between *H. pylori* infection and extragastric disorders has grown rapidly. Although *H. pylori* is most frequently acquired during childhood in both developed and developing countries, clinicians are less familiar with the pediatric literature in the field. This review attempts to highlight the main reported associations of *H. pylori* with extragastric disorders in children (including iron deficiency anemia, chronic idiopathic thrombocytopenic purpura, growth retardation, asthma and allergic disorders, and diabetes mellitus).

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**INTRODUCTION**

Although evidence is emerging that the prevalence of *Helicobacter pylori* (*H. pylori*) is declining in all age groups, the understanding of its disease spectrum continues to evolve. *H. pylori* infection is acquired early in life (almost always before the age of 10 years), and in the absence of antibiotic therapy, it generally persists for life[1]. *H. pylori* typically colonizes the human stomach for many decades without adverse consequences; however, children infected with *H. pylori* can manifest gastrointestinal diseases[2]. Recently, *H. pylori* has been associated with the development of extragastric disorders including iron deficiency anemia (IDA), chronic idiopathic thrombocytopenic purpura (cITP), growth retardation, and diabetes mellitus (DM). The postulated role of *H. pylori* in the pathogenesis of extragastric disorders is based on the facts: (1) local inflammation has systemic effects; (2) *H. pylori* is a chronic process that lasts for several decades; and (3) persistent infection induces a chronic inflammatory and immune response that is able to induce lesions both locally and remote to the primary site of infection[3]. Conversely, a growing body of literature suggests that the absence of *H. pylori* might also be associated with an increased risk of various diseases such as asthma and allergic diseases[4]. An absence of *H. pylori* could indicate that an individual was never colonized or that the organism was present in earlier life and subsequently eradicated [4]. The idea that *H. pylori* might actually confer benefit to humans has engendered considerable controversy among investigators.

The aim of this report is to provide a critical review of the available literature about extragastric disorders associated with *H. pylori* infection in children. Potential beneficial aspects of *H. pylori* in asthma and allergic diseases are also critically addressed in this review. To identify all publications, the medical terms “*Helicobacter* “ and “children” were used in MEDLINE search. Studies published in English during the past two decades were selected.

**IRON DEFICIENCY ANEMIA**

The role of *H. pylori* in the causation of IDA is of considerable current interest. Recently, four meta-analyses including both pediatric and adult patients have shown an association between *H. pylori* infection and IDA[5-8]. Based on the results of these studies, the last Maastricht Florence Consensus Report recommends to search and treat *H. pylori* infection in IDA after exclusion of bleeding sources in the gastrointestinal tract[9].

***Biological mechanisms***

How can *H. pylori* gastritis cause iron deficiency (ID) or IDA? The biological mechanism explaining the relationship between *H. pylori* infection and decreased iron stores is not fully understood. It seems that several pathways are involved separately or in combination[5]. One of the possible explanations of this relationship is the loss of iron from the human gastrointestinal tract which is induced by the infection. However, it appears that chronic gastrointestinal blood loss is not the likely culprit, because most published case reports and case series[10-16] describing patients with IDA and *H. pylori-*associated gastritis have found no bleeding lesions at the time of endoscopy. Testing for fecal occult blood was negative and anti-*H. pylori* eradication treatment was associated with resolution of IDA[10-16]. In the intervention *H. pylori* therapeutic trials of Choe *et al*[17,18] that were conducted among children with *H. pylori*-associated IDA, no evidence of hemorrhage in the gastric and duodenal mucosa was observed among the participants, except one patient who was excluded from the trial, and the stool examinations for occult blood of all the participants were negative.

Another explanation for a relationship between *H. pylori* infection and IDA involves the possible effect of *H. pylori* gastritis on gastric acid secretion and iron absorption. Dietary iron is available as heme iron, which is readily absorbed, or non-heme iron, in which bioavailability is dependent on a variety of factors. Non-heme iron accounts for 80% of dietary iron in industrialized countries[16]. Crucial to the effective solubility and absorption of non-heme iron is hydrochloric acid in acid secretions. Reduction of the ferric to ferrous form is dependent upon the pH of the gastric juice, and reduction to the ferrous form facilitates membrane transport[19]. In a recent non-endoscopic study involving age-matched asymptomatic *H. pylori*-infected and noninfected preschool Bangladeshi children, Sarker *et al*[20] showed that both the basal and the stimulated acid outputs were markedly reduced in *H. pylori*-infected children compared with the noninfected children. *H. pylori* eradication was associated with significant increase in both the basal and the stimulated gastric acid secretions reaching levels similar to those in the noninfected children[20]. These results suggest that the reduced acid secretion was a consequence of the *H. pylori* infection and/or the inflammation it induced, impairing the function of the acid secreting corpus mucosa. The findings are concordance with an earlier study in Gambian children that reported a correlation between *H. pylori* infection and hypochlorhydria as determined by a noninvasive test for gastric acid secretions (measurement of change in urine acid output before and after a feed)[21]. Very recently, the relation between gastric juice pH and ID has been investigated in Chilean *H. pylori*-infected children undergoing gastrointestinal endoscopy[22]. *H. pylori* was significantly more frequent in children with hypochlorhydria (pH > 4) compared with those with gastric juice pH ≤ 4. Additionally, the study identified that *H. pylori*-infected children with hypochlorhydria in the absence of corpus atrophy have significantly reduced serum iron and transferring saturation. Importantly, hypochlorhydria in the absence of *H. pylori* infection was not associated with these changes, suggesting a combination of both *H. pylori* and hypochlorhydria is etiologically important in ID[22]. The mechanisms of *H. pylori-*induced hypochlorhydria in children in the absence of gastric atrophy are not well understood. *H. pylori* may induce hypochlorhydria through increased gastric interleukin(IL)-1β and tumor necrosis factor (TNF)-α[23,24], which inhibit acid secretion, induce parietal cell apoptosis, and decrease enterochromaffin-like cell histamine release[25,26]. In the study of Takashima *et al*[27] in gerbils, gastric acid hyposecretion in the *H. pylori*-infected groups returned to control levels after injection of recombinant IL-1 receptor antagonist. In a very recent study, Queiroz *et al*[28] demonstrated that in Brazilian *H. pylori-*infected children without common known causes of ID/IDA, increased gastric IL-1β concentration, but not TNF-α, was an independent, significant predictor of low blood concentration of ferritin and hemoglobin (Hb). In the group of the *H. pylori*-positive youngest children, the Hb and hematocrit (Ht) values were lower in carriers of *IL1RN* polimorphic alleles than in children with wild genotype. The high production of IL-1β in the former group may account for a more severe hypochlorhydria in the acute phase of *H.pylori* infection that is mainly acquired in early childhood. IL-1 β would also participate in the impairment of iron absorption by upregulating hepcidin as demonstrated *in vivo*[29,30]. However, in a recent study, Schwarz *et al*[31 did not observe associations between the serum concentrations of hepcidin and *H. pylori* infection].

An important promoter of iron absorption is ascorbic acid, which appears to act in two ways: by promoting reduction to the ferrous form, and by forming an absorbable molecular complex with ferric iron, which is insoluble at pH > 5[16,32]. In a study involving children with gastrointestinal complaints, Baysoy *et al*[33] found that *H. pylori* gastritis was associated with a decrease in the gastric juice ascorbic acid level. Infection with cytotoxin-associated gene A (CagA)-positive strains was associated with a greater decrease in gastric juice ascorbic acid than infection with CagA-negative strains. However, the gastric juice ascorbic acid levels of patients with *H. pylori* and anemia were not different from those of non-anemic patients with *H. pylori*[33].

Another hypothesized mechanism is that *H. pylori* might lead to IDA by sequestering and utilizing iron, thus competing with the human host[16]. Like many bacteria, *H. pylori* requires iron as a growth factor, and it possesses a 19-kDa iron-binding protein that resembles ferritin, which has been considered to play a role in storage of excess iron sequestered by the bacterium[34].

Another possible mechanism for IDA in *H. pylori*-infected subjects involves lactoferrin sequestration in the *H. pylori*-infected gastric mucosa, especially in the cardiac and pyloric glands and neutrophils within surface epithelium[35,36]. Lactoferrin is an iron-binding glycoprotein that is found in various body fluids such as milk, lacrimae, pituita, saliva, and urine[37,38], and its secretion in the gastric mucosa seems to be controlled by some signal transmitted from *H. pylori* close to the glands[36]. It appears that *H. pylori* then absorbs the iron from lactoferrin via a highly specific lactoferrin-binding protein that is expressed by *H. pylori*[39]. Choe *et al*[36]reported a study on 101 adolescents with unexplained epigastric pain and /or ID, which found lactoferrin levels in the gastric mucosa to be significantly higher in *H. pylori*-positive patients with IDA compared to those who were non-anemic *H. pylori*-negative, non-anemic *H. pylori*-positive, and *H. pylori*-negative with IDA. Furthermore, when lactoferrin and Hb levels were compared before and after *H. pylori* eradication in adolescents with *H. pylori* gastritis and coexisting IDA, lactoferrin levels decreased and Hb levels increased significantly after eradication[36]. In contrast, this association could not be established in other pediatric studies. Dogan *et al*[40] determined the lactoferrin levels in the gastric tissue of 61 children with recurrent abdominal pain of whom 45 and 16 were *H. pylori-*positive and –negative, respectively. The increase in lactoferrin in *H. pylori*-positive cases agreed with the previous study by Choe *et al*[36], but, conversely, Hb, Ht, and ferritin levels in these cases did not differ significantly. These results did not support the hypothesis that anemia is caused by loss of iron to *H. pylori* via lactoferrin in the gastric tissue of *H. pylori*-positive cases. The Authors concluded that the increase of lactoferrin in the gastric tissue of *H. pylori*-positive cases is dependent upon inflammation[40].

Studies regarding the involvement of *H. pylori* CagA strains in the alteration of the hosts’ iron stores are controversial. Data generated from a large population-based study could not establish a risk excess for the reduction in the serum ferritin (SF) levels according to CagA seropositivity among German adults[41]. Ciacci *et al*[42] showed that impaired iron absorption in *H. pylori*-infected adult (> 17 years) patients was not related to infection with CagA positive strains. Baysoy *et al*[33] also found no association between *H. pylori* CagA-positive strains and IDA in children. In contrast, recent data from a cross-sectional study conducted among Israeli Arab children found a higher prevalence of low SF (< 10 ng/mL) among those with CagA-positive strains than CagA-negative strains and *H. pylori*-negative subjects[43]. Of interest, a recent double-blind randomized intervention trial on non-iron- deficient 3-to 10-year-old children in El Paso, Texas, showed that eradication of *H. pylori* infection by CagA-negative strains was associated with a larger SF increase[44]. However, because the observations on CagA-negative strains were based on fewer observations, the Authors were cautious about drawing definite conclusions[44]. In view of above findings, more studies are needed in this area, in particular in children.

Finally, one cannot exclude the possibility that a molecule produced by *H. pylori* may exert an inhibitory effect on the duodenal mucosal cells which are directly responsible for iron absorption, without even crossing the duodenal mucosal barrier[45].

Whatever the mechanism by which *H. pylori* induces a decrease in the iron stores of the host, why does only a small proportion of the population develop IDA despite worldwide *H. pylori* infection? Individuals with increased demands of iron needed for growth and tissue building are thought to be more likely to develop IDA associated with *H. pylori* infection. Most surveys focusing on *H. pylori*–associated IDA were carried out in school-age children or at puberty when children are more vulnerable to ID because of their high demand of iron during the growth spurt and, in females, menstrual blood loss.

***Observational epidemiologic studies in children***

Observational epidemiologic studies conducted among school-age children and adolescents have found an association between *H. pylori* infection and increased prevalence of ID or IDA[17,46-49]. However, there are others that have not[50-55] . Differences in the study design, inclusion criteria, number of infected children, and ethnicity could explain the discrepancies among the studies. In addition, there are fewer studies evaluating the role of *H. pylori* in the development of ID/IDA in children undergoing upper gastrointestinal endoscopy[56-59], which allow an accurate diagnosis of *H. pylori* infection as well as the exclusion of other common causes of ID such as gastrointestinal bleeding, peptic ulcer disease, extensive erosions, and celiac disease.

It has been also suggested that the lack of association could be a result of age-confounding. A study carried out among 7- to 11-year old children from 10 predominantly Alaska Native villages in southwestern Alaska[48] showed that the association between ID and *H. pylori* infection was modified by age, with the strongest association in children who were aged 9 years or more. In this age group, ID was 3.7-4 times more prevalent among *H. pylori*–infected than –uninfected children. Likewise, an age-dependent association between *H. pylori* and IDA was reported among South Korean children[60]; *H. pylori* infection did not seem to contribute to ID in adolescents under 15 years of age, but played an important role in iron depletion in the subjects above 16 years of age. In a study examining Israeli Arab children and infants[61], there was no association between *H. pylori* positivity and anemia, but when stratified by age group, *H. pylori* positivity was significantly associated with a 2.8-fold increased prevalence of anemia in school-age children, while among infants, the prevalence ratio was only 1.2 .

The increased risk in older children seems biologically plausible. Older children are likely to have been infected for longer than younger children, allowing more time for ID to develop. Furthermore, older children may be less likely to have ID related to other causes, such as insufficient dietary intake, leaving *H. pylori* infection to account for a greater proportion of ID[48]. Finally, it is also possible that with increasing age and progression of severity of the gastritis, secretion of gastric acid might decreases with age, and might explain the suggested age-dependent between *H. pylori* and depletion in iron stores.

***Clinical and interventional trials in children***

The most convincing evidence of cause-and-effect relation between IDA and *H. pylori* infection in children is the demonstration of the beneficial effects of *H. pylori* eradication on pre-existing IDA. The beneficial effect of *H. pylori* eradication has been assessed in a number of clinical and interventional trials. Small sample sizes, poor case or control definitions, lack of control groups, short follow-up periods, and other methodologic issues, including the use of validated measures to confirm active *H. pylori* infection, are among factors that limit the interpretation and ability to generalize the relevance of the results of these trials (Table 1).

The earliest study was a randomized placebo-controlled trial which was carried out among 43 Korean pre-adolescent children and adolescents with IDA[18], who underwent gastroduodenal endoscopy. Of these, 22 patients with confirmed *H. pylori* infection were randomly assigned to one of three treatment groups: eight were given oral ferrous sulfate and a 2-wk of *H. pylori* triple therapy, seven were given placebo for iron and a 2-wk course of triple therapy, and seven were given oral ferrous sulfate and a 2-wk course of placebo. At 8 wks after the end of the 2-wk treatment regimen, a significant increase in Hb level was seen among children of the first two groups who received *H. pylori* eradication therapy, as compared with the third group who received only iron supplementation.

An open therapeutic trial was conducted among 21 Korean adolescent girls with IDA refractory to oral iron therapy, who underwent gastroduodenal endoscopy[56]. Of these, the 13 patients with confirmed *H. pylori* infection were given a 2-wk course of triple therapy and a 6-wk course of oral ferrous sulfate. After eradication of *H. pylori*, the mean levels of Hb and SF showed an important increase. An additional open therapeutic trial from Korea was conducted among 22 children who exhibited IDA and underwent gastroduodenal endoscopy[17]. Of these, the 12 patients with confirmed *H. pylori* infection received a 2-wk course of triple therapy without iron supplementation, while the 10 *H. pylori*-negative patients were given oral ferrous sulfate for 10 wks. At 8 wks after the end of the 2-wk regimen, significant increases in Hb, iron, and SF levels were observed only in children who received eradication therapy.

The study of Kurekci *et al*[62] carried out in Turkey, investigated whether the eradication of *H. pylori* (as assessed by stool antigen test and urea breath testing) without iron supplementation can lead to the resolution of ID and IDA. Children with *H. pylori* infection were divided into three groups: ID, IDA, and *H. pylori* infection with neither ID nor IDA. All the participants received only eradication therapy. The values of Hb and mean corpuscular volume increased significantly in children with IDA compared with baseline values, after *H. pylori* eradication therapy. SF levels increased significantly after *H. pylori* eradication therapy in all groups. The authors emphasized that resolution of both ID and IDA associated with *H. pylori* eradication may be achieved by *H. pylori* eradication treatment alone. However, all participants received *H. pylori* eradication therapy without a control group.

A randomized, double-blind, placebo-controlled trial carried out in India[63] examined the antagonistic effect of asymptomatic *H. pylori* infection in children on the response to iron supplementation. One hundred and sixty nine children aged 1-10 years from an urban poor community underwent urea breath testing for *H. pylori* and haematologic tests at baseline and after 8 wk. Both *H. pylori*-positive and –negative children were randomly assigned to receive ferrous fumarate syrup or placebo for 8 wk. It was found that asymptomatic *H. pylori* infection was not associated with higher rates of anemia or ID, but had a significant adverse effect on response to iron supplementation among children. These results were complemented by the randomized, double-blind, controlled trial carried out in Chinese adolescent girls by Xia *et al*[64] who investigated whether treatment of *H. pylori* infection can influence response to oral iron supplementation. Eighty participants with IDA and a co-existing serological diagnosis of *H. pylori* infection were assigned randomly to the intervention (*n =* 37) and control (*n =* 43) groups. Subjects in the intervention group received oral iron supplementation for 12 wk and a 2-wk course of triple eradication therapy, whereas those in the control group received oral iron supplementation alone for 12 wk. A total of 73 participants (31 in the intervention group and 42 in the control group) returned at the end of trial. Follow-up assessments of *H. pylori* infection were conducted 4 wk after completion of the triple therapy using an *H. pylori* stool antigen test, while iron status was reassessed 3 months after conclusion of the 12-wk regimen through determination of Hb, SF, and serum transferrin receptor. Results showed that subjects who underwent *H. pylori* treatment had significantly higher improvement in Hb and SF values, compared to subjects who were untreated for *H. pylori*.

A trial was carried out in Mexico City by Duque *et al*[65] to evaluate the iron status of 33 school-age children with ID or IDA, who eradicated *H. pylori* infection (diagnosed by urea breath test) and were randomized to daily supplementation with ferrous sulfate (*n =* 17) or placebo (*n =* 16) for 12 wk. Thirty six school-age children without *H. pylori* infection received daily supplementation with ferrous sulfate for 12 wk. Children in whom eradication of *H. pylori* was achieved and iron supplementation was given had, on average, a larger Hb concentration than children without *H. pylori* infection at baseline who received oral supplementation. This difference was not observed in the group for whom eradication of *H. pylori* was achieved and who received the placebo supplementation. It was suggested that both interventions -*H. pylori* eradication and iron supplementation-are necessary in school -age children with ID or IDA.

The double-blind randomized trial carried out by Cardenas *et al*[44] in El Paso, Texas, investigated whether eradication of *H. pylori* (as diagnosed by urea breath test) among non-iron deficient, asymptomatic 3-to 10-year-olds was followed by changes in markers of iron stores (including SF, transferrin saturation, and Hb levels) at ≥ 6 mo of follow-up. Children were randomly assigned to one of following 4 arms: both quadruple eradication and iron supplementation, either quadruple sequential eradication or iron supplementation, or placebo only. In neither intention-to-treat (*n =* 110) nor per protocol (*n =* 90) analyses was there evidence of a statistically significant effect of any of the treatments on the change of levels of the markers of iron stores. However, non-iron deficient children who had their infection eradicated at follow-up had a 3-fold increased average change from baseline SF compared with that of children who remained infected. The above findings by Cardenas *et al*[44] are important. The study population was free of ID, and thus the implications go beyond those affected with iron-deficiency malnutrition but are important to the larger *H. pylori*-infected population. Their findings also strengthen the case for a causal relation by which the changes in levels of iron stores appeared subsequent to changes in *H. pylori* infection status.

Sarker *et al*[66] completed a population-based, randomized, double-blind, and placebo-controlled trial to evaluate the response of iron plus anti-*H. pylori* therapy in children with IDA (*n =* 200). The trial was performed in Bangladesh, an area highly endemic for ID and *H. pylori* infection. Results showed no additional benefit of *H. pylori* eradication on ID compared to iron treatment alone at 90 days. In addition, *H. pylori* status was assessed again at 90 days by urea breath testing and the analysis of children with successful eradication versus persisting infection showed no difference in ID.

Gessner *et al*[67] performed in western Alaska, another highly prevalent *H. pylori* infection area, a large therapeutic, controlled, household-randomized, open-label trial in 7-11-year-old children (*n =* 219). Eligible were children with *H. pylori* infection (as diagnosed by urea breath testing) and having ID [defined as SF level < 22.5 pmol/L (< 10 µg/L)], without being treated with iron supplementation. The intervention group comprised 106 children (79 households) who received 6-wk iron sulfate and a concurrent 2-wk *H. pylori* eradication therapy. The control group (113 children from 89 households) received only 6-wk iron sulfate therapy. There was no difference between the intervention group and control group regarding SF level, Hb level, rate of ID, and rate of anemia [defined as Hb level < 115 g/L (< 11.5 g/dL)] up to 14 mo after treatment initiation. The authors hypothesized that 14 mo was too early to resolve *H. pylori*-induced gastric damage, and therefore out of the 219 children initially enrolled 176 were re-evaluated in a follow-up study performed at 40-month[68]. Re-infection occurred among 52% of children who had initially cleared their infection. However, *H. pylori*–negative children had lower prevalence of ID [(RR = 0.62; 95%CI: 0.38–1.01) and ID and anemia (R = 0.62; 95%CI: 0.03–1.50), compared with *H. pylori*–positive children[68]. It was concluded that the resolution of *H. pylori* infection for > 14 mo modestly reduced the prevalence of ID and substantially reduced the prevalence of ID and anemia.

On the basis of the above clinical and interventional trials, *H. pylori* infection may be considered a risk factor for IDA in subjects with large demands for iron and poor dietary patterns[69]. However, the relationship between *H. pylori* and ID may be stronger than that reported, since most of the above mentioned trials were performed in geographical areas where both ID and *H. pylori* infection are highly prevalent, and where many factors such as malnutrition, vitamin deficits, chronic parasitic infections, and malaria may have blunted the overall effect of *H. pylori* eradication[70]. In this setting, poor response to *H. pylori* eradication should be viewed with caution. Thus further large and well-controlled trials among children living in areas with high prevalences of *H. pylori* infection and ID, will be of value in documenting the extent to which early infection and subsequent gastrointestinal changes lead to inadequately reversible hematologic changes. Additional studies should also evaluate the effect of treatment among other populations with ID, such as those with low prevalences of *H. pylori* infection, more severe anemia, or concurrent gastrointestinal symptoms.

It has been long established that anemia and IDA in children are negatively correlated with cognitive development and school performance[71,72]. Recently, Muhsen *et al*[73]have retrospectively examined the association between *H. pylori* infection and cognitive development among Israeli Arab school age children from different socioeconomic backgrounds. *H. pylori* infection was determined by an Elisa kit for detection of *H. pylori* antigen in stool samples. Data on socioeconomic factors and nutritional covariates were collected through maternal interviews and from medical records. *H. pylori* infection in children living in the high socioeconomic village was independently associated with impaired cognitive function at early school age assessed by both full-scale Intelligence Quotient (IQ) score and reduced non-verbal IQ and verbal IQ scores[73]. In the low socioeconomic village an association between *H. pylori* infection and cognitive impairment was not observed, probably due to high levels of *H. pylori* infection[74]. This retrospective study, however, cannot draw conclusions regarding a causal association between *H. pylori* and IQ scores because the small sample size limited the precision of the effect estimates, and limited the ability to assess the role of the duration of *H. pylori* infection and the duration of anemia on cognitive development. Given the association of *H. pylori* infection with IDA, further investigations on direct or indirect effects of *H. pylori* infection on cognitive impairment in children would be challenging and require large longitudinal birth cohorts to be examined for cognitive function at school age[74].

**CHRONIC IDIOPATHIC THROMBOCYTOPENIC PURPURA**

cITP is an autoimmune disease characterized by autoantibody-mediated platelet destruction lasting more than 6 mo[75]. The disorder affects both children and adults. Factors triggering platelet autoantibody formation remain poorly understood. An association with infectious disease inducing autoimmune disorders in a proportion of patients has been suggested[76]. Recently, it has been suggested that *H. pylori* may play a role in the pathogenesis of cITP, since partial or even complete remission of thrombocytopenia has been reported in some patients after eradication of *H. pylori*[77-80].

***Biological mechanisms***

Several hypotheses have been proposed regarding the mechanism by which *H. pylori* might induce the development of ITP. One is that antibodies to *H. pylori* components cross-react with platelet surface antigens. In this regard, it has been proposed that the CagA antigen of *H. pylori* could be responsible for the cross-mimicry between *H. pylori* and platelet glycoproteins. This hypothesis was not confirmed by Michel *et al*[81], who showed that platelet eluates from three *H. pylori*–positive ITP patients that reacted with glycoprotein IIb/IIIa or glycoprotein Ib failed to recognize *H. pylori* antigens. Conversely, Takahashi *et al*[82] showed that eluates of platelet-associated immunoglobulin G from twelve (9 *H. pylori*-positive and 3 *H. pylori*-negative) out of the 18 ITP patients recognized *H. pylori* CagA protein, and that in three completely responsive patients, levels of anti-CagA antibody in platelet eluates declined after eradication therapy. Likewise, Franceschi *et al*[83] noted the disappearance of anti-CagA antibodies in eight patients who were successfully treated with eradication therapy. This hypothesis could explain the observed variability in treatment effect in different studies because it is known that the ratio of CagA-positive strains of *H. pylori* varies greatly from country to country[84].

Another potential mechanism is modulation of the host’s immune system by *H. pylori* in a manner that promotes the emergence of autoreactive B cells[85]. However, no significant difference between *H. pylori*–positive and *H. pylori*–negative individuals has been found for non–organ-specific autoantibody responses, such as anti-nuclear, anti-microsome, or anti–smooth muscle antibodies[86]. In a recent paper, Asahi *et al* showed that that the platelet recovery observed in ITP patients after *H. pylori* eradication is associated with modulation of the monocyte Fcγ receptor balance toward the inhibitory Fcγ receptor IIB (FcγRIIB)[87]. In fact, circulating monocytes from *H. pylori*–infected ITP patients exhibited an activated phenotype with enhanced phagocytic capacity and low levels of the inhibitory FcγRIIB. Interestingly, this phenotype reverted to that of *H. pylori*–uninfected ITP patients after the eradication of *H. pylori*, but only in the responders[87]. In addition, this change in monocyte phenotype preceded the improvements in autoimmune and platelet kinetic parameters. Potential patient selection bias has to be considered when interpreting the results of that study. Many patients had relatively long disease duration and had been treated with prednisolone and/or splenectomy. In addition, the high frequency of splenectomized patients in the *H. pylori–*negative group might have affected the phenotypic and functional properties of circulating monocytes. Another limitation was the use of peripheral blood monocytes instead of macrophages in the reticuloendothelial system in the analysis. Genetic influences may also be implied in the development of thrombocytopenia in *H. pylori* infection. Veneri *et al*[88] analyzed the correlation between *H. pylori* infection and HLA class II alleles in 39 adult ITP patients by comparing the frequency of the HLA-DR/-DQ antigens in these patients with that of 150 healthy bone marrow donors, matched for gender and age. The frequency of HLA-DRB1\*11 and HLA -DQB1\*03 alleles were significantly lower in ITP patients than in healthy controls. None of the other alleles (HLA-DRB1\*1, \*15, \*16, \*03, \*04, \*12, \*13, \*14, \*07, \*08, \*0910, \*1001; and -DQB1\*02, \*04, \*05, \*06) was differently expressed in ITP patients and healthy controls. The 39 patients were then compared for the presence of *H. pylori* infection: 24 patients were *H. pylori*–positive and 15 patients were *H. pylori*–negative. *H. pylori*–negative patients showed HLA-DRB1\*03 frequency significantly higher and HLA -DRB1\*11, \*14 and HLA -DQB1\*03 frequencies significantly lower than in *H. pylori*–positive patients. No significant differences in any of the class II alleles was observed in *H.* *pylori*–positive patients as compared with controls. Moreover, on a larger population of ITP patients[89], Veneri *et al*[88] observed that the HLA-DQB1\*03 pattern was associated with a higher probability of platelet response to eradication treatment. Despite these suggestive findings, a note of caution should be introduced. The complexity of the HLA system, the variability of *H. pylori* strains, and the yet not well defined pathophysiology of ITP makes this type of investigation very complicated[90]. A higher prevalence of other class II alleles among ITP patients has been described in some human races[91], although other studies failed to demonstrate a statistically significant association[92,93].

***Effects of H.pylori eradication in children with cITP***

According to the Maastricht IV Consensus Conference, cITP is one of the two extragastric disorders for which *H. pylori* infection detection and eradication are indicated, the other being unexplained IDA[9]. In children, the natural history of cITP is clearly different from that observed in adults. Spontaneous recovery occurs in one third of childhood cITP cases from several months to many years after their diagnosis, whereas only 5% of adults recover[75,94]. Thus, the effects of *H. pylori* eradication in childhood cITP could be different from those in adults. The issue of whether *H. pylori* eradication has a beneficial effect on the course of cITP in children has been the subject of a few apparently contradictory studies with small sample sizes[95-106] and the predominant use of observational data from retrospective series[95-104]. To the best of our knowledge, only one randomized controlled trial (RCT) concerning *H. pylori* eradication in children with cITP has been published[105]. It is important to remark that this was a very small trial. Additionally, the results of pediatric studies are difficult to compare because the prevalence of *H. pylori* infection and diagnostic methods vary among them. It is well known that the geographic variation in prevalence rate of *H. pylori* infection in children with cITP likely reflects the variation in the prevalence of *H. pylori* infection in the general populations of different countries, which is declining during the last decades in industrialized countries[84]. It is also important to note that most of the studies in children with cITP have investigated the presence of *H. pylori* infection using techniques such as serology, urea breath testing, or detection of *H. pylori* antigen in stool specimens (Table 2). Only one small case series has also assessed the *H. pylori* status by upper gastrointestinal endoscopy[98]. Other variables included differences in ages of patients, protocol eligibility (*i.e.* criteria for patient eligibility, eradication schedule, platelet count threshold at enrollment, and platelet response cut-off), previous and concomitant therapies, duration of the disease, and follow-up (Tables 2 and 3).

In a study from Taiwan, Jaing *et al* were the first to report successful *H. pylori* eradication in 9 infected children with cITP, among whom five were in complete or partial remission over a median of 16 mo follow-up, while four showed no improvement in platelet counts during 8-19 mo follow-up[95]. One potential criticism of the study was that their results in *H. pylori*-positive patients might have been biased due to spontaneous recovery, since those patients who showed the greatest increases in the number of platelets were younger and had a shorter duration of thrombocytopenia than the others. No spontaneous recovery was observed after 6 mo of follow-up in the remaining 13 *H. pylori* -negative children. In a study from Italy involving 24 cITP children (8 *H. pylori* -positive, and 16 *H. pylori* -negative), Ferrara *et al*[104] reported that six and two of the *H. pylori* -positive children had, respectively, complete and partial remission after the 1-year follow-up after eradication therapy. No significant increase in platelet counts was observed in the 16 uninfected patients over the follow-up period. In a very small cohort of Japanese children, Hayashi *et al*[97] evaluated 10 children with cITP, of whom two and eight were *H. pylori*-positive and –negative, respectively. One *H. pylori*-positive child received eradication therapy, and achieved a significant platelet recovery throughout a follow-up period of more than 1 year. In the same cohort, Hayashi *et al*[97] also showed that two of the eight *H. pylori*-negative children had a significant rise in platelet counts during the follow-up period. In a study from the Netherlands, Neefjes *et al*[100] followed-up for 6-9 mo 33 children with cITP, three of whom were *H. pylori*-infected and were treated. Though all three children initially responded to eradication treatment, in two of them a downward trend in platelet count was discernible at the end of the study period. Therefore, with a relatively short follow-up period the authors could not exclude the possibility that the platelet response was only transient. However, none of the 30 *H. pylori* -negative children achieved spontaneous complete or partial remission during 6 mo of follow-up[100].

By contrast, in a study from Turkey, Yetgin *et al*[98] were unable to see, over a 1-year follow-up, any response of platelet count (> 50 x 10 9 /L) to eradication therapy in the 11 *H. pylori*-positive children with cITP. Likewise, in a study from Iran, Hamidiet *et al*[103] reported that none of the four *H. pylori*-positive children achieved a complete response (rise of platelet count above 100 x 109/L) or a partial response (rise of greater than 50 x 109/L relative to baseline) after *H. pylori* eradication during 6 to 11 mo of follow-up. Regrettably, in both studies by Yetgin *et al*[98] and Hamidiet *et al*[103], follow-up and platelet count responses in the *H. pylori*-negative cITP children were not reported. Furthermore, the use of different thresholds to define platelet response to eradication therapy in the two cohorts suggests caution in the generalizability of results. Further doubts were cast on the role of *H. pylori* in cITP by the report from Rajantie and Klemola[96], who were unable to diagnose *H. pylori* infection in any of the Finnish children with cITP they studied using a combination of urea breath test, serology, and stool antigen test. In a study from Italy, Loffredo *et al*[99] evaluated 39 children with cITP, eight of whom were *H. pylori*-infected and had *H. pylori* eradication. Over a 1-year follow-up, the platelet counts did not show any trend towards improvement in the infected children and were similar to those of the uninfected patients. In a subsequent study from Italy, Bisogno *et al*[102] reported a platelet response after *H. pylori* eradication in three out of eight children but two of the three patients had a relapse of cITP later. In addition, after 12 to 50 mo of follow-up, 10 of the 16 *H. pylori*-negative patients had a partial response without any specific treatment. Therefore, Bisogno *et al*[102] concluded that it is difficult to demonstrate the role of *H. pylori* infection in cITP occurring in pediatric age. More recently, in a prospective, controlled, multicenter study from Italy, Russo *et al*[106] evaluated 203 children with cITP, of whom 37 were *H. pylori*-infected, received *H. pylori* eradication therapy and completed a 1-year follow-up. Eradication was successful in 33 (89%) of the thirty seven *H. pylori*-positive patients. Platelet recovery was demonstrated in 13 of the thirty three patients after eradication (39%), whereas spontaneous remission was observed in 17 (10%) of the 166 *H. pylori*-negative patients. Finally, in a study from Thailand, Treepongkaruma *et al*[105] reported a multicenter RCT concerning *H. pylori* eradication in 55 children with cITP. Of the 16 patients with cITP and *H. pylori* infection, seven were randomly selected and treated while the remaining nine did not receive any specific treatment. Although eradication of *H. pylori* was successful in all patients in the treated group, the platelet recovery rate was not significantly different between the *H. pylori* treatment group and control group during the 6-month period.

In conclusion, in view of the published evidence in children with cITP and the sporadic benefit of *H. pylori* eradication on the platelet response, the identification of a pediatric subpopulation that might most benefit from *H. pylori* screening and eradication represents the challenge of the near future. Further evidence from RCTs enrolling a large number of children with cITP across different ethnic populations are required not only to assess the efficacy of eradication therapy but also to allow further immunologic investigation of the mechanisms behind the response to eradication therapy[80].

# **EFFECT OF *H. PYLORI* ON GROWTH**

# The available evidence regarding *H. pylori* infection and its effect on growth in children remains controversial. Acute and chronic infections may impair linear growth by interfering with micronutrient absorption, appetite, metabolism, and related factors[107]. However, human growth is also dictated by factors such as diet, socioeconomic status, other infections, and genetics[108]. Thus, accurately estimating the effect of *H. pylori* infection on growth is challenging due to the number of potential confounders, many of which are inadequately controlled in studies. There have been many cross-sectional studies[46,57,109-127] that point to either the presence or absence of an association between *H. pylori* and decreased height, weight, or growth. These studies all are limited by the inability to establish temporal precedence[128,129]. Does infection precede growth retardation, or are both events related to a third independent event, such as nutritional deficiency?

# ***Longitudinal studies of growth patterns and H. pylori status***

# Because of this temporal ambiguity, a number of longitudinal studies have been performed to prospectively follow-up changes in growth patterns subsequent to changes in *H. pylori* status over time. Thomas *et al*[130] conducted two consecutive prospective, longitudinal cohort studies in a rural community in the Gambia, and found that, in both cohorts, children with early *H. pylori* colonization (as detected by sequential urea breath tests) had lower values for both length- and weight-for-age *z*-scores than their peers in late infancy. The association between *H. pylori* colonization in early infancy and growth faltering remained significant after accounting for local growth patterns, season of birth, and level of diarrheal disease in the analysis. The deterioration in growth performance was transient, and follow-up measurements taken several years later failed to reveal any persistent growth effect subsequent to early *H. pylori* colonization, suggesting that catch-up growth occurred naturally in the Gambian community. Nonetheless, in view of the temporal association between *H. pylori* colonization and the onset of growth faltering, the authors concluded that *H. pylori* colonization in early infancy might predispose to the development of malnutrition and growth faltering among infants in countries such as the Gambia[130].

# In the prospective, longitudinal study by Bravo *et al*[128], lower-middle class children from Colombia, in general good health, aged 1-5 years, who tested negative by urea breath test at baseline, were monitored over the following 2.5 years for anthropometric measurements every 2 mo, and for *H. pylori* by urea breath test every 4 mo. The deceleration of growth velocity took place 1 to 2 mo after the onset of infection, and after adjusting for age the slower growth rate was a fairly constant 0.042 ± 0.014 cm/mo (*P* = 0.003) less than that of uninfected children. The effect of *H. pylori* infection on growth velocity (0.5 cm/year) led to an accumulated growth deficit, which was not compensated after the infection had been established for more than 6 mo. No interactions between growth velocity, *H. pylori* status and the time of exposure, or other socioeconomic variables were observed. As expected[131], a limitation of this study was the high intrasubject variability of growth velocity.

# In a cohort of urban Colombian preschool children, in good general health, with a median follow-up of about 500 d, Mera *et al*[132] prospectively investigated whether a newly acquired *H. pylori* infection had transient or permanent effects on growth. Breath tests and anthropometric measurements were performed every 2 to 4 mo. The authors observed that the impact of a new infection on growth velocity was more pronounced during the first 4 mo after infection. There was no height catch-up in infected children, with crowding retarding linear growth, and after 8 mo, an infected child had a cumulative difference of 0.24 cm (95%CI: 0.22-0.26) compared with an uninfected child. Newly infected children experienced a significant, but small, decrease in weight at the first visit compared with uninfected children, which became non statistically significant at 4 mo after infection, mostly because of the tendency of weight measurements to have large variability. After 6 and 8 mo, the effect disappeared completely. There was no interaction or relationship with age; the effect was the same regardless of age at time of infection.

# Egorov *et al*[133] prospectively assessed the potential effects of new *H. pylori* infection (defined as positive fecal antigen test and negative serology) on linear and ponderal growth in low socioeconomic status young children living in poor suburbs of Quito, Ecuador. Normally nourished, mildly and substantially malnourished children (defined using weight-for-age *z*-scores at recruitment) formed one-third each of the study population. Six height and weight measurements were collected during one year. The main finding of this study was that new *H. pylori* infections were associated with reduced linear growth in young children. The estimated deficit in the average growth velocity during one year of follow-up in children with new infections compared to non-infected controls was almost 1 cm/year. There was no evidence of catch-up growth in children with *H. pylori* infection. Thus the results of this study provides further evidence of detrimental developmental effects of *H. pylori* in young children living in poor economic conditions. The detrimental effect of new *H. pylori* infection on linear growth velocity in these Ecuadorian children was almost twice the 0.5 cm/year effect observed in Colombian children[128]. This discrepancy may be explained by different source populations. Of note, a strength of the study by Egorov *et al*[133] is the use of a socioeconomically homogeneous source population. The effect of *H. pylori* on ponderal growth in these Ecuadorian children was small and non-significant.

# Goodman *et al*[129] prospectively evaluated the effect of *H. pylori* on growth among school-age children in the Colombian Andes by comparing growth velocity in the presence and absence of *H. pylori* infection during a mean follow-up of 2.5 years. *H. pylori*- positive children grew on average 0.022 cm/mo (95%CI: 0.008-0.035) slower than *H. pylori*-negative children independently of age, gender, and time elapsed since baseline. The result was not appreciably altered by adjustment for socio-environmental factors including presence of intestinal parasites, community of residence, mother’s and father’s education, number of siblings, residential stability, type of housing, number of people in the house, number of rooms in the house, and household density. A subsequent study[134] conducted in two cohorts of school-age Andean children who were followed-up for an average length of 3.7 years, reported the long-term effect of acquiring or clearing *H. pylori* infection. After nearly 4 years of observation, through a multivariate height-based growth model (including variables such as age and the square of age, gender, father’s education, number of siblings, visit number, type of cohort, *H. pylori* status, and the interaction between *H. pylori* status and visit number), the authors estimated that children at an average age of 10.1 years who were not infected with *H. pylori* were 1.1 cm taller on average compared with positive children of the same age[134]. Children who were always *H. pylori*-positive were 1.76 cm shorter by the end of the observation period than those who were always negative, and 1.45 cm shorter than those who cleared the infection, after adjustment for initial values and all other covariates.

# Taken together, the results of all these studies point to the presence of an association between *H. pylori* and growth. None-the-less, additional studies are needed to provide more information about the clinical and therapeutic outcome of this apparent association in diverse pediatric populations with different *H. pylori* prevalences and risk factors.

## ***Biological mechanisms***

## The mechanisms by which *H. pylori* infection may affect growth are largely unknown, but possible mechanisms such as dyspepsia and hypochlorhydria have been proposed. It has been suggested that *H. pylori* infection may reduce food intake because of its association with dyspepsia[135]. Nevertheless, most infected subjects remain asymptomatic and the proportion of children with dyspeptic symptoms may be similar among infected and noninfected children[119]. Though Sood *et al*[119] suggested that children with dyspepsia and H. pylori infection were shorter and lighter compared to children without the infection, this was not significant after adjusting for confounding factors such as socioeconomic status and ethnic differences between the two groups of patients. *H. pylori* infection causes hypochlorhydria and the loss of the protecting barrier in the stomach, thus with an attendant vulnerability to enteric infections, which may, in turn, cause diarrheal diseases. However, three cohort studies exploring the association between *H. pylori* infection and diarrhea have yielded conflicting results[136-138].

## Additionally*,* *H. pylori* infection has been reported to impair growth owing to IDA. In a study that included adolescents in South Korea, Choe *et al*[46] found that the height-for-age mean was less in those who had *H. pylori* infection and IDA. The authors concluded that infection, together with IDA, more than infection *per se*, may affect growth. Süoglu *et al*[57] in a study comprising a population 4–16 years of age found that the mean height-for-age *z*-score in *H. pylori*-infected and iron-deficiency anemic patients was lower than that in patients who were non–iron-deficiency anemic and negative for *H. pylori* infection.

## Finally*,* *H. pylori* gastritis may affect the production of hormones that control appetite and satiety such as ghrelin. Ghrelin, a 28-amino acid peptide, possesses strong growth hormone-releasing activity and plays both central and peripheral roles in food intake, gastric motility, and acid secretion[139]. This peptide also contributes to the regulation of both somatic growth and adipose tissue mass and is therefore a short- as well as long-term regulator of body weight. The majority of circulating ghrelin is produced in the mammalian gastric mucosa by enteroendocrine cells/oxyntic glands, the X/A-like cells[140]. Thus, there exists the possibility that chronic persistent damage of the gastric mucosa, such as *H. pylori* chronic gastritis, might affect ghrelin production, leading to changes in food intake and body weight. It has been speculated that following *H. pylori* infection, an increase in gastric ghrelin secretion leads to increased plasma ghrelin levels, resulting in increased appetite, weight gain and thus obesity[141,142]. It is said that *H. pylori* is factor that prevents putting on weight[143]. However, in adults, there are contradictory reports on the relationship between *H. pylori* infection and ghrelin as well as on the influence of *H. pylori* eradication on ghrelin concentrations[141,142,144-147]. Some studies have demonstrated that *H. pylori* infection decreased ghrelin secretion[142,148], whereas other studies have reported that *H. pylori* infection had no effect on plasma ghrelin levels[149,150]. Although ghrelin is known to induce weight gain, in a study with 6 wk of follow-up after *H. pylori* eradication, plasma ghrelin was increased, but median body mass index (BMI) was unchanged[141]. In another study, 12 wk following *H. pylori* eradication, plasma ghrelin was increased in some subjects and reduced in others [145]. This controversy may be caused by different length of follow-up, or different ghrelin profiles (total, acylated, des-acyl ghrelin, and the ratio of acylated/des-acyl ghrelin).

## There have been few studies evaluating the relationship between ghrelin and *H. pylori* infection in children[151-154], with conflicting results on the influence of eradication of *H. pylori* on childhood growth and ghrelin levels. Plonka *et al*[151] showed that both serum (total) ghrelin and leptin concentrations were significantly reduced in *H. pylori-*infected children when compared with those in *H. pylori-*negative children. However, no information was given on the histological findings as well as on the association between *H. pylori* status and anthropometric measures. In a study involving prepubertal children, we found that serum (total) ghrelin concentrations were inversely related to the severity of *H. pylori*-associated gastritis[152]. In these youngsters, at the 12-mo follow-up, eradication of *H. pylori* infection was associated with a significant increase in BMI, lean and fat mass along with a significant decrease in circulating ghrelin levels and an increase in leptin levels[152]. Although there is evidence that ghrelin and leptin exert opposite actions in nutrient intake and metabolic balance[155,156], in our clinical setting including children with *H. pylori*-associated gastritis (without atrophic changes or long-term history of gastritis), ghrelin and leptin responses appeared to be independent of one another[152]. In a study involving children with *H. pylori*-associated functional dyspepsia, Deng *et al*[154] found that at the 2-mo follow-up the plasma (total) ghrelin and gastric mRNA levels increased significantly in those patients for whom *H. pylori* treatment was successful and were not significantly different in those patients for whom the *H. pylori* treatment failed. In addition, the BMI of the two groups did not differ significantly 2 mo before and after the *H. pylori* treatment. Yang *et al*[153] showed that *H. pylori*-infected children had low serum acylated ghrelin levels,and decreased body weight and height. After the 1-year of follow-up, successful eradication of *H. pylori* restored ghrelin levels and improved childhood growth[153]. Methodological issues including the use of validated measures to confirm active *H. pylori* infections, different ghrelin profiles, different length of follow-up, and differences in populations may partially account for differing metabolic and anthropometric findings across pediatric studies. Based on these observations, the role of *H. pylori* in the context of gut-brain interaction and weight gain has to be better defined in adults as well as in children.

**ASTHMA AND ALLERGIC DISORDERS**

The severity and incidence of asthma have increased drastically in the developed nations of the world over the last decades. Though the underlying reason is still unknown, clinical, epidemiological and experimental evidence indicate that infectious diseases can influence the development of allergic disorders[157]. In a case-control study, Matricardi *et al*[158] showed that atopy was inversely related to markers of infections transmitted through the orofecal route or borne by contaminated hands or foods (Toxoplasma gondii, H. pylori*,* hepatitis A virus) but not to those mainly transmitted through other routes (measles, mumps, rubella, chickenpox, cytomegalovirus, herpes simplex virus type 1). These data supported the “hygiene” hypothesis that in humans inadequate stimulation by commensals or pathogens of gut-associated lymphoid tissue, a critical site for maturation of the mucosal immunity, enhances the risk of atopy. At the immunological level, this hypothesis proposes that early life exposure to microbial antigens is required for the normal maturation of the immune system and the generation of protective regulatory T- cell responses. This notion has been recently revised by Blaser and Falkow[159], who suggest that the important factor in modern allergic and metabolic diseases might not be our decreased exposure to the microorganisms in food, air, water or soil, as has been postulated by the “hygiene hypothesis”, but instead could reflect the specific loss of our ancestral microorganisms due to modern health practices (including exposure to antibiotics) and lifestyle changes. According to the “disappearing microbiota “hypothesis, alterations in human macroecology have progressively affected the composition of our indigenous microbiota, which in turn has affected human physiology and, ultimately, disease risk. Thus the loss of our ancestral indigenous organisms is not entirely beneficial and has consequences that might include post-modern conditions such as asthma(and obesity). As such, it is plausible to consider *H. pylori*, the ancient dominant member of the gastric niche[160], since it has been progressively disappearing[161-163] from individuals in developed countries during the twentieth century, with secondary alterations in gastric secretory, hormonal and immune physiology[164,165]. Further, the disappearance of *H. pylori* has preceded the rise in asthma[166], but are they related? Several studies have shown negative associations of *H. pylori* with asthma, allergy, and atopic diseases[158,167-175], and more specifically with the pediatric onset of these diseases[4,165,172,176-178]. However, others have challenged the validity of these associations[179-184].

***Biological mechanisms***

There have been several attempts to try to explain the influence of *H. pylori* in this regard. Allergic diseases are driven by T cells that produce T-helper type 2 (Th2) cytokines and are inhibited by Th1 responses. One of the suggested underlying molecular mechanisms of this possible preventive effect of *H. pylori* is that the neutrophil-activating protein of *H. pylori* (HP-NAP) not only plays a key role in driving Th1 inflammation, but is also able to inhibit Th2-mediated bronchial inflammation of allergic bronchial asthm[185]. Amedei *et al*[186] showed that the addition of HP-NAP to allergen-induced T-cell lines derived from allergic asthmatic patients led to a drastic increase in interferon-γ producing T cells and to a decrease in IL-4-secreting cells, thus resulting in a redirection of the immune response from Th2 to a Th1 phenotype. Furthermore, in a mouse model of allergic asthma, both systemic and mucosal administration of HP-NAP exherted a powerful anti-Th2 activity by strongly inhibiting the development of airway eosinophilia and bronchial inflammation[185,187]. Likewise, HP-NAP treatment strongly affected the lung cytokine release. Systemic HP-NAP also significantly resulted in the reduction of total serum IgE responses[185,187]. Based on these properties, NAP was identified as a candidate for vaccination as a preventive strategy against allergic diseases[186] and NAP might be a critical molecule of *H.pylori* with a beneficial effect in allergic diseases[185,187].

Another hypothetical explanation for the inverse association between *H. pylori* and asthma is that high levels of regulatory T cells (Tregs) associated with *H. pylori* infection may contribute to the prevention of allergic diseases, while impaired expansion of natural and/or adaptive Tregs might lead to the development of allergy and asthma[188].In support of this, a number of studies have indicated that Tregs play an important role in controlling exaggerated Th2-biased immune responses[188], and that *H. pylori*-positive people have higher levels of gastric Tregs than those without the organism[189,190]. Arnold *et al*[191] utilized mouse models of allergic airway disease to experimentally examine a possible inverse correlation between *H. pylori* and asthma. *H. pylori* infection efficiently protected mice from airway hyper-responsiveness, tissue inflammation and goblet cell metaplasia that are hallmarks of asthma, and prevented allergen-induced pulmonary and bronchoalveolar infiltration with eosinophils, Th2 cells, and Th17 cells. Protection against asthma was most robust in mice infected neonatally and was abrogated by antibiotic eradication of *H. pylori*. Asthma protection in infected mice was attributable to an increase in highly suppressive Tregs in the lungs and impaired maturation of lung-infiltrating dendritic cells. Systemic Tregs depletion abolished asthma protection, whereas the adoptive transfer of purified Treg populations was sufficient to transfer protection from infected donor mice to uninfected recipients. Thus, these mouse models of *H. pylori*–mediated asthma protection provide experimental support for the “disappearing microbiota” hypothesis[159], which postulates that the asthma and allergy epidemic of modern societies is a direct consequence of the disappearance of our ancestral indigenous microflora, which included *H. pylori*.

Several large cross-sectional and case-control studies have demonstrated an inverse relationship between asthma and *H. pylori* especially for CagA-positive strains and early onset asthma and allergic rhinitis[165,171,173-175]. However, others have reported no associations[179,192,193].

Future prospective, longitudinal studies are needed to test the strength of the association between *H. pylori* status and asthma in children from developed and developing countries[183]. Research is also needed to identify the potential factors that may modify such association[194].

**DIABETES MELLITUS**

The relationship between DM and *H. pylori* infection is controversial[195]. According to some studies there is a high prevalence of *H. pylori* infection in patients with either type I[196-199] or type II[200-203] DM which is correlated with the duration of DM[197,199], the presence of dyspeptic symptom [203,204], age[196,198], gender[205], BMI[205], blood pressure[205], fasting glucose levels[205] and HbA1c values[205]. The mechanism by which *H. pylori* infection increases the risk of diabetes may involve inflammation or dyspepsia. Infection with *H. pylori* has been found to be correlated with elevated levels of C reactive protein (CRP)[206], IL-6, and TNF-α[207], which are markers of inflammation implicated in insulin resistance and development of diabetes[208]. Elevated levels of inflammatory cytokines may lead to phosphorylation of serine residues on the insulin receptor substrate, which prevents its interaction with insulin receptors, inhibiting insulin action[208]. Furthermore, the presence of Gram-negative bacteria, such as *H. pylori*, in the gut microbiota leads to increased production of lipopolysaccharide, which also activates innate inflammatory processes [209]. An alternative hypothesis is that gastroduodenal conditions resulting from *H. pylori* infection could delay gastric emptying[210], which has been postulated to cause poor glucose control in insulin-dependent children with diabetes[211].

On the other hand, other studies have not found a higher prevalence of *H. pylori* in diabetic patients and have not supported any correlation between metabolic control and infection[212-216]. The presence of micro-angiopathy in patients with DM may be a negative factor for colonization by *H. pylori*, because micro-vascular changes in the gastric mucosa may create an unfavourable environment for the establishment or survival of *H. pylori*[205]. In these cases the results may be also explained by the higher number of antibiotics taken by diabetics and, thus, a more frequent occasional clearance of the infection.

The above conflicting results may be explained by considering that most previous studies attempting to clarify the association between *H. pylori* infection and DM were limited by cross-sectional analyses. To date, there is only one prospective study which overcame methodological limitations of previous cross-sectional studies by examining the impact of *H. pylori* infection on development of diabetes over a 10-year follow-up period[217]. Recently, in fact, in a large prospective cohort of community-dwelling elderly Latinos followed up for 10 years, Jeon *et al*[217] showed that individuals who were seropositive for *H. pylori* at enrollment were 2.7 times more likely at any given time to develop DM than seronegative individuals (HR = 2.69; 95%CI: 1.10-6.60), after adjustment for multiple factors, including age, gender, ethnicity, education, and cardiometabolic risk factors. Thus, this study by Jeon *et al*[217] was able to establish the relative timing of seropositivity and development of DM, giving more credence to a potential causal relationship. However, several issues must be considered in interpreting these results. First, similar studies need to repeated in other populations to ensure that the findings are related to the presence of infection itself and are not a peculiarity of the *H. pylori-*infected subjects in their community (*i.e.*, due to particular dietary or living habits that may be linked to vulnerability to infection and diabetes). Second, findings in elderly individuals may not be generalizable to younger individuals considering that a younger population has a shorter history of infection. Third, only a small percentage of the population was seronegative for *H. pylori* (7%), which limited the power of the study. Finally, evaluation of the *H. pylori* infection status depended solely on the detection of *H. pylori* IgG antibody without further laboratory assessment such as urease breath testing. The presence of the *H. pylori* antibody does not distinguish recent versus historic *H. pylori* infection.

The prevalence of *H. pylori* infection and its relation with glycemic control was also studied by a few researchers in pediatric patients, with discordant results. Some authors have found a high prevalence of infection in such patients [198,199,211] and an influence on metabolic control[218,219]. On the other hand, other studies have described the lack of any difference in the prevalence between diabetic and control children[212,220-222], and have shown no difference in HbA1c, disease duration, and daily insulin requirement in type 1 diabetic children with and without *H. pylori* infection[220,221,223]. Taking these conflicting results into account, a recent study assessing the association between *H. pylori* and levels of HbA1c using data from 7,417 participants in the National Health and Nutrition Examination Survey (NHANES) III (aged ≥ 18 years) and 6,072 participants in NHANES 1999-2000[224] is noteworthy. There was a significant interaction between *H. pylori* and age, such that glucose intolerance was found to increase the risk of *H. pylori* colonization only after 18 years, a finding that persisted when subjects who had known diabetes or were insulin users were excluded. The most plausible hypothesis is that *H. pylori* directly or indirectly increases levels of HbA1c in adulthood, particularly in obese individuals. In fact, when the population of older individuals was stratified on the basis of BMI (< 25 and ≥ 25), there was a positive association between *H. pylori* positivity and HbA1c levels only among those with higher BMI.

Also, issues such as the effectiveness of eradication regimens for *H. pylori* infection in diabetic children and the influence of *H. pylori* eradication on the control of DM, remain to be elucidated. There are few data on the effects *H. pylori* eradication on metabolic control in children with type 1 DM, providing conflicting results[211,219,220,223]. There are still more limited data on the therapeutic approach to *H. pylori* infectionin diabetic children, as only one non-randomized study with a small sample size is available[223]. In that study the eradication rates of *H. pylori* with standard triple therapy in a group of type 1 diabetic children and a group of non-diabetic children matched for gender and age, were similar.

**CONCLUSION**

Though there is an important pediatric literature on some extradigestive manifestations of *H. pylori* infection, additional studies are needed to examine the strength of the evidence linking these manifestations in children to *H. pylori*, and to better understand mechanisms on how *H. pylori* affects extragastric disorders in childhood. According to the new guidelines of Maastrich IV consensus[9], IDA is an extragastric disorder for which *H. pylori* infection detection and eradication are indicated. However, large and well-controlled trials are needed among symptomatic and asymptomatic children with IDA living in areas with high as well as low prevalences of *H. pylori* infection. Likewise, although the new guidelines are to search and treat *H. pylori* infection in patients with cITP, RCTs enrolling a large number of children across different ethnic populations are required. Despite the strong association between *H. pylori* and growth, further studies are needed to provide more information about the clinical and therapeutic outcome of this apparent association in diverse pediatric populations with different *H. pylori* prevalences and risk factors. Furthermore, longitudinal studies are of paramount importance to test the strength of the association of *H. pylori* status with asthma and allergic disorders in children from developed and developing countries, and to identify the potential factors that may modify this association. Issues such as the effectiveness of eradication regimens for *H. pylori* infection in diabetic children and the influence of *H. pylori* eradication on the control of DM, remain also to be elucidated.

**REFERENCES**

1 **Chiesa C**, Pacifico L, Anania C, Poggiogalle E, Chiarelli F, Osborn JF. Helicobacter pylori therapy in children: overview and challenges. *Int J Immunopathol Pharmacol* 2010; **23**: 405-416 [PMID: 20646336]

2 **Pacifico L**, Anania C, Osborn JF, Ferraro F, Chiesa C. Consequences of Helicobacter pylori infection in children. *World J Gastroenterol* 2010; **16**: 5181-5194 [PMID: 21049552 DOI: 10.3748/wjg.v16.i41.5181]

3 **Realdi G**, Dore MP, Fastame L. Extradigestive manifestations of Helicobacter pylori infection: fact and fiction. *Dig Dis Sci* 1999; **44**: 229-236 [PMID: 10063905]

4 **Cover TL**, Blaser MJ. Helicobacter pylori in health and disease. *Gastroenterology* 2009; **136**: 1863-1873 [PMID: 19457415 DOI: 10.1053/j.gastro.2009.01.073]

5 **Muhsen K**, Cohen D. Helicobacter pylori infection and iron stores: a systematic review and meta-analysis. *Helicobacter* 2008; **13**: 323-340 [PMID: 19250507 DOI: 10.1111]

6 **Qu XH**, Huang XL, Xiong P, Zhu CY, Huang YL, Lu LG, Sun X, Rong L, Zhong L, Sun DY, Lin H, Cai MC, Chen ZW, Hu B, Wu LM, Jiang YB, Yan WL. Does Helicobacter pylori infection play a role in iron deficiency anemia? A meta-analysis. *World J Gastroenterol* 2010; **16**: 886-896 [PMID: 20143469 DOI: 10.3748/wjg.v16.i7.886]

7 **Huang X**, Qu X, Yan W, Huang Y, Cai M, Hu B, Wu L, Lin H, Chen Z, Zhu C, Lu L, Sun X, Rong L, Jiang Y, Sun D, Zhong L, Xiong P. Iron deficiency anaemia can be improved after eradication of Helicobacter pylori. *Postgrad Med J* 2010; **86**: 272-278 [PMID: 20448223 DOI: 10.1136/pgmj.2009.089987]

8 **Yuan W**, Li Yumin D, Yang L. Iron deficiency anemia in Helicobacter pylori infection: meta-analysis of randomized controlled trials. *Scand J Gastroenterol* 2010; **45**: 665-676 [PMID: 20201716 DOI: 0.3109/00365521003663670]

9 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]

10 **Dufour C**, Brisigotti M, Fabretti G, Luxardo P, Mori PG, Barabino A. Helicobacter pylori gastric infection and sideropenic refractory anemia. *J Pediatr Gastroenterol Nutr* 1993; **17**: 225-227 [PMID: 8229554 DOI: 10.1097/00005176-199308000-00018]

11 **Carnicer J**, Badía R, Argemí J. Helicobacter pylori gastritis and sideropenic refractory anemia. *J Pediatr Gastroenterol Nutr* 1997; **25**: 441 [PMID: 9327380 DOI: 10.1097/00005176-199710000-00017]

12 **Barabino A**, Dufour C, Marino CE, Claudiani F, De Alessandri A. Unexplained refractory iron-deficiency anemia associated with Helicobacter pylori gastric infection in children: further clinical evidence. *J Pediatr Gastroenterol Nutr* 1999; **28**: 116-119 [PMID: 9890483 DOI: 10.1097/00005176-199901000-00027]

13 **Konno M**, Muraoka S, Takahashi M, Imai T. Iron-deficiency anemia associated with Helicobacter pylori gastritis. *J Pediatr Gastroenterol Nutr* 2000; **31**: 52-56 [PMID: 10896071 DOI: 10.1097/00005176-200007000-00012]

14 **Ashorn M**, Ruuska T, Mäkipernaa A. Helicobacter pylori and iron deficiency anaemia in children. *Scand J Gastroenterol* 2001; **36**: 701-705 [PMID: 11444468 DOI: 10.1080/003655201300191950]

15 **Kostaki M**, Fessatou S, Karpathios T. Refractory iron-deficiency anaemia due to silent Helicobacter pylori gastritis in children. *Eur J Pediatr* 2003; **162**: 177-179 [PMID: 12655422 DOI: 10.1007/s00431-002-1139-x]

16 **DuBois S**, Kearney DJ. Iron-deficiency anemia and Helicobacter pylori infection: a review of the evidence. *Am J Gastroenterol* 2005; **100**: 453-459 [PMID: 15667507 DOI: 10.1111/j.1572-0241.2005.30252.x]

17 **Choe YH**, Kwon YS, Jung MK, Kang SK, Hwang TS, Hong YC. Helicobacter pylori-associated iron-deficiency anemia in adolescent female athletes. *J Pediatr* 2001; **139**: 100-104 [PMID: 11445801 DOI: 10.1067/mpd.2001.114700]

18 **Choe YH**, Kim SK, Son BK, Lee DH, Hong YC, Pai SH. Randomized placebo-controlled trial of Helicobacter pylori eradication for iron-deficiency anemia in preadolescent children and adolescents. *Helicobacter* 1999; **4**: 135-139 [PMID: 10382128 DOI: 10.1046/j.1523-5378.1999.98066.x]

19 **Lombard M**, Chua E, O'Toole P. Regulation of intestinal non-haem iron absorption. *Gut* 1997; **40**: 435-439 [PMID: 9176066 DOI: 10.1136/gut.40.4.435]

20 **Sarker SA**, Sultana S, Sattar S, Ahmed T, Beglinger C, Gyr N, Fuchs GJ. Influence of Helicobacter pylori infection on gastric acid secretion in pre-school Bangladeshi children. *Helicobacter* 2012; **17**: 333-339 [PMID: 22967116 DOI: 10.1111/j.1523-5378]

21 **Dale A**, Thomas JE, Darboe MK, Coward WA, Harding M, Weaver LT. Helicobacter pylori infection, gastric acid secretion, and infant growth. *J Pediatr Gastroenterol Nutr* 1998; **26**: 393-397 [PMID: 9552134]

22 **Harris PR**, Serrano CA, Villagrán A, Walker MM, Thomson M, Duarte I, Windle HJ, Crabtree JE. Helicobacter pylori-associated hypochlorhydria in children, and development of iron deficiency. *J Clin Pathol* 2013; **66**: 343-347 [PMID: 23268321 DOI: 10.1136/jclinpath-2012-201243]

23 **Guiraldes E**, Duarte I, Peña A, Godoy A, Espinosa MN, Bravo R, Larraín F, Schultz M, Harris P. Proinflammatory cytokine expression in gastric tissue from children with Helicobacter pylori-associated gastritis. *J Pediatr Gastroenterol Nutr* 2001; **33**: 127-132 [PMID: 11568511]

24 **Crabtree JE**, Shallcross TM, Heatley RV, Wyatt JI. Mucosal tumour necrosis factor alpha and interleukin-6 in patients with Helicobacter pylori associated gastritis. *Gut* 1991; **32**: 1473-1477 [PMID: 1773951 DOI: 10.1136/gut.32.12.1473]

25 **Neu B**, Randlkofer P, Neuhofer M, Voland P, Mayerhofer A, Gerhard M, Schepp W, Prinz C. Helicobacter pylori induces apoptosis of rat gastric parietal cells. *Am J Physiol Gastrointest Liver Physiol* 2002; **283**: G309-G318 [PMID: 12121877 DOI: 10.1152/ajpgi.00546.2001]

26 **Amieva MR**, El-Omar EM. Host-bacterial interactions in Helicobacter pylori infection. *Gastroenterology* 2008; **134**: 306-323 [PMID: 18166359 DOI: 10.1053/j.gastro]

27 **Takashima M**, Furuta T, Hanai H, Sugimura H, Kaneko E. Effects of Helicobacter pylori infection on gastric acid secretion and serum gastrin levels in Mongolian gerbils. *Gut* 2001; **48**: 765-773 [PMID: 11358893 DOI: 10.1136/gut.48.6.765]

28 **Queiroz DM**, Rocha AM, Melo FF, Rocha GA, Teixeira KN, Carvalho SD, Bittencourt PF, Castro LP, Crabtree JE. Increased gastric IL-1β concentration and iron deficiency parameters in H. pylori infected children. *PLoS One* 2013; **8**: e57420 [PMID: 23451225 DOI: 10.1371/journal.pone.0057420]

29 **Inamura J**, Ikuta K, Jimbo J, Shindo M, Sato K, Torimoto Y, Kohgo Y. Upregulation of hepcidin by interleukin-1beta in human hepatoma cell lines. *Hepatol Res* 2005; **33**: 198-205 [PMID: 16198622]

30 **Lee P**, Peng H, Gelbart T, Wang L, Beutler E. Regulation of hepcidin transcription by interleukin-1 and interleukin-6. *Proc Natl Acad Sci U S A* 2005; **102**: 1906-1910 [PMID: 15684062 DOI: 10.1073/pnas.0409808102]

31 **Schwarz P**, Kübler JA, Strnad P, Müller K, Barth TF, Gerloff A, Feick P, Peyssonnaux C, Vaulont S, Adler G, Kulaksiz H. Hepcidin is localised in gastric parietal cells, regulates acid secretion and is induced by Helicobacter pylori infection. *Gut* 2012; **61**: 193-201 [PMID: 21757452 DOI: 10.1136/gut.2011.241208]

32 **Charlton RW**, Bothwell TH. Iron absorption. *Annu Rev Med* 1983; **34**: 55-68 [PMID: 6344777 DOI: 10.1146/annurev.me.34.020183.000415]

33 **Baysoy G**, Ertem D, Ademoğlu E, Kotiloğlu E, Keskin S, Pehlivanoğlu E. Gastric histopathology, iron status and iron deficiency anemia in children with Helicobacter pylori infection. *J Pediatr Gastroenterol Nutr* 2004; **38**: 146-151 [PMID: 14734875]

34 **Doig P**, Austin JW, Trust TJ. The Helicobacter pylori 19.6-kilodalton protein is an iron-containing protein resembling ferritin. *J Bacteriol* 1993; **175**: 557-560 [PMID: 8419304]

35 **Luqmani YA**, Campbell TA, Bennett C, Coombes RC, Paterson IM. Expression of lactoferrin in human stomach. *Int J Cancer* 1991; **49**: 684-687 [PMID: 1937955 DOI: 10.1002/ijc.2910490510]

36 **Choe YH**, Oh YJ, Lee NG, Imoto I, Adachi Y, Toyoda N, Gabazza EC. Lactoferrin sequestration and its contribution to iron-deficiency anemia in Helicobacter pylori-infected gastric mucosa. *J Gastroenterol Hepatol* 2003; **18**: 980-985 [PMID: 12859729 DOI: 10.1046/j.1440-1746.2003.03098.x]

37 **Levay PF**, Viljoen M. Lactoferrin: a general review. *Haematologica* ; **80**: 252-267 [PMID: 7672721]

38 **Lönnerdal B**, Iyer S. Lactoferrin: molecular structure and biological function. *Annu Rev Nutr* 1995; **15**: 93-110 [PMID: 8527233 DOI: 10.1146/annurev.nu.15.070195]

39 **Dhaenens L**, Szczebara F, Husson MO. Identification, characterization, and immunogenicity of the lactoferrin-binding protein from Helicobacter pylori. *Infect Immun* 1997; **65**: 514-518 [PMID: 9009306]

40 **Doğan Y**, Erkan T, Önal Z, Usta M, Doğusoy G, Çokuğraş FÇ, Kutlu T. Lactoferrin levels in the gastric tissue of Helicobacter pylori-positive and -negative patients and its effect on anemia. *Mediators Inflamm* 2012; **2012**: 214581 [PMID: 22529520 DOI: 10.1155/2012/214581]

41 **Berg G**, Bode G, Blettner M, Boeing H, Brenner H. Helicobacter pylori infection and serum ferritin: A population-based study among 1806 adults in Germany. *Am J Gastroenterol* 2001; **96**: 1014-1018 [PMID: 11316140 DOI: 10.1111/j.1572-0241]

42 **Ciacci C**, Sabbatini F, Cavallaro R, Castiglione F, Di Bella S, Iovino P, Palumbo A, Tortora R, Amoruso D, Mazzacca G. Helicobacter pylori impairs iron absorption in infected individuals. *Dig Liver Dis* 2004; **36**: 455-460 [PMID: 15285524 DOI: 10.1016/j.dld.2004.02.008]

43 **Muhsen K**, Barak M, Shifnaidel L, Nir A, Bassal R, Cohen D. Helicobacter pylori infection is associated with low serum ferritin levels in Israeli Arab children: a seroepidemiologic study. *J Pediatr Gastroenterol Nutr* 2009; **49**: 262-264 [PMID: 19525869 DOI: 10.1097/MPG.0b013e31818f0a0d]

44 **Cardenas VM**, Prieto-Jimenez CA, Mulla ZD, Rivera JO, Dominguez DC, Graham DY, Ortiz M. Helicobacter pylori eradication and change in markers of iron stores among non-iron-deficient children in El Paso, Texas: an etiologic intervention study. *J Pediatr Gastroenterol Nutr* 2011; **52**: 326-332 [PMID: 21336159 DOI: 10.1097/MPG.0b013e3182054123]

45 Hershko C. Reply to commentary: Hepcidin mimetics from microorganisms? A possible explanation for the effect of Helicobacter pylori on iron homeostasis. Blood Cells Mol Dis 2007; 38: 56 [DOI: 10.1016/j.bcmd.2006.10.002]

46 **Choe YH**, Kim SK, Hong YC. Helicobacter pylori infection with iron deficiency anaemia and subnormal growth at puberty. *Arch Dis Child* 2000; **82**: 136-140 [PMID: 10648367 DOI: 10.1136/adc.82.2.136]

47 **Seo JK**, Ko JS, Choi KD. Serum ferritin and Helicobacter pylori infection in children: a sero-epidemiologic study in Korea. *J Gastroenterol Hepatol* 2002; **17**: 754-757 [PMID: 12121504 DOI: 10.1046/j.1440-1746.2002.02797.x]

48 **Baggett HC**, Parkinson AJ, Muth PT, Gold BD, Gessner BD. Endemic iron deficiency associated with Helicobacter pylori infection among school-aged children in Alaska. *Pediatrics* 2006; **117**: e396-e404 [PMID: 16452320 DOI: 10.1542/peds.2005-1129]

49 **Fraser AG**, Scragg R, Schaaf D, Metcalf P, Grant CC. Helicobacter pylori infection and iron deficiency in teenage females in New Zealand. *N Z Med J* 2010; **123**: 38-45 [PMID: 20581894]

50 **Choi JW**. Does Helicobacter pylori infection relate to iron deficiency anaemia in prepubescent children under 12 years of age? *Acta Paediatr* 2003; **92**: 970-972 [PMID: 12948075 DOI: 10.1111/j.1651-2227.2003.tb00633.x]

51 **Haghi-Ashtiani MT**, Monajemzadeh M, Motamed F, Mahjoub F, Sharifan M, Shahsiah R, Kashef N. Anemia in children with and without Helicobacter pylori infection. *Arch Med Res* 2008; **39**: 536-540 [PMID: 18514100 DOI: 10.1016/j.arcmed]

52 **Santos IS**, Boccio J, Davidsson L, Hernandez-Triana M, Huanca-Sardinas E, Janjetic M, Moya-Camarena SY, Paez-Valery MC, Ruiz-Alvarez V, Valencia ME, Valle NC, Vargas-Pinto G, Solano L, Thomas J. Helicobacter pylori is not associated with anaemia in Latin America: results from Argentina, Brazil, Bolivia, Cuba, Mexico and Venezuela. *Public Health Nutr* 2009; **12**: 1862-1870 [PMID: 19257919 DOI: 10.1017/S1368980009004789]

53 **Janjetic MA**, Goldman CG, Balcarce NE, Rua EC, González AB, Fuda JA, Meseri EI, Torti HE, Barrado J, Zubillaga MB, López LB, Boccio JR. Iron, zinc, and copper nutritional status in children infected with Helicobacter pylori. *J Pediatr Gastroenterol Nutr* 2010; **51**: 85-89 [PMID: 20410842 DOI: 10.1097/MPG]

54 **Araf LN**, Pereira CA, Machado RS, Raguza D, Kawakami E. Helicobacter pylori and iron-deficiency anemia in adolescents in Brazil. *J Pediatr Gastroenterol Nutr* 2010; **51**: 477-480 [PMID: 20562724 DOI: 10.1097/MPG.0b013e3181d40cd7]

55 **Vendt N**, Kool P, Teesalu K, Lillemäe K, Maaroos HI, Oona M. Iron deficiency and Helicobacter pylori infection in children. *Acta Paediatr* 2011; **100**: 1239-1243 [PMID: 21434997 DOI: 10.1111/j.1651-2227.2011.02281.x]

56 **Choe YH**, Lee JE, Kim SK. Effect of helicobacter pylori eradication on sideropenic refractory anaemia in adolescent girls with Helicobacter pylori infection. *Acta Paediatr* 2000; **89**: 154-157 [PMID: 10709883 DOI: 10.1111/j.1651-2227.2000.tb01208.x]

57 **Süoglu OD**, Gökçe S, Saglam AT, Sökücü S, Saner G. Association of Helicobacter pylori infection with gastroduodenal disease, epidemiologic factors and iron-deficiency anemia in Turkish children undergoing endoscopy, and impact on growth. *Pediatr Int* 2007; **49**: 858-863 [PMID: 18045286 DOI: 10.1111/j.1442-200X.2007.02444.x]

58 **Gulen H**, Kasirga E, Yildirim SA, Kader S, Sahin G, Ayhan S. Diagnostic yield of upper gastrointestinal endoscopy in the evaluation of iron deficiency anemia in older children and adolescents. *Pediatr Hematol Oncol* 2011; **28**: 694-701 [PMID: 21728721 DOI: 10.3109/08880018.2011.572145]

59 **Queiroz DM**, Harris PR, Sanderson IR, Windle HJ, Walker MM, Rocha AM, Rocha GA, Carvalho SD, Bittencourt PF, de Castro LP, Villagrán A, Serrano C, Kelleher D, Crabtree JE. Iron status and Helicobacter pylori infection in symptomatic children: an international multi-centered study. *PLoS One* 2013; **8**: e68833 [PMID: 23861946 DOI: 10.1371/journal.pone.0068833]

60 **Choi JW**. Association between Helicobacter pylori infection and iron deficiency varies according to age in healthy adolescents. *Acta Haematol* 2007; **117**: 197-199 [PMID: 17199079 DOI: 10.1159/000098272]

61 **Muhsen K**, Barak M, Henig C, Alpert G, Ornoy A, Cohen D. Is the association between Helicobacter pylori infection and anemia age dependent? *Helicobacter* 2010; **15**: 467-472 [PMID: 21083753 DOI: 10.1111/j.1523-5378.2010.00793.x]

62 **Kurekci AE**, Atay AA, Sarici SU, Yesilkaya E, Senses Z, Okutan V, Ozcan O. Is there a relationship between childhood Helicobacter pylori infection and iron deficiency anemia? *J Trop Pediatr* 2005; **51**: 166-169 [PMID: 15855306 DOI: 10.1093/tropej/fmi015]

63 **Mahalanabis D**, Islam MA, Shaikh S, Chakrabarty M, Kurpad AV, Mukherjee S, Sen B, Khaled MA, Vermund SH. Haematological response to iron supplementation is reduced in children with asymptomatic Helicobacter pylori infection. *Br J Nutr* 2005; **94**: 969-975 [PMID: 16351775 DOI: 10.1079/BJN20051586]

64 **Xia W**, Zhang X, Wang J, Sun C, Wu L. Survey of anaemia and Helicobacter pylori infection in adolescent girls in Suihua, China and enhancement of iron intervention effects by H. pylori eradication. *Br J Nutr* 2012; **108**: 357-362 [PMID: 22004585 DOI: 10.1017/S0007114511005666]

65 **Duque X**, Moran S, Mera R, Medina M, Martinez H, Mendoza ME, Torres J, Correa P. Effect of eradication of Helicobacter pylori and iron supplementation on the iron status of children with iron deficiency. *Arch Med Res* 2010; **41**: 38-45 [PMID: 20430253 DOI: 10.1016/j.arcmed.2009.11.006]

66 **Sarker SA**, Mahmud H, Davidsson L, Alam NH, Ahmed T, Alam N, Salam MA, Beglinger C, Gyr N, Fuchs GJ. Causal relationship of Helicobacter pylori with iron-deficiency anemia or failure of iron supplementation in children. *Gastroenterology* 2008; **135**: 1534-1542 [PMID: 18775429 DOI: 10.1053/j.gastro.2008.07.030]

67 **Gessner BD**, Baggett HC, Muth PT, Dunaway E, Gold BD, Feng Z, Parkinson AJ. A controlled, household-randomized, open-label trial of the effect that treatment of Helicobacter pylori infection has on iron deficiency in children in rural Alaska. *J Infect Dis* 2006; **193**: 537-546 [PMID: 16425133 DOI: 10.1086/499604]

68 **Fagan RP**, Dunaway CE, Bruden DL, Parkinson AJ, Gessner BD. Controlled, household-randomized, open-label trial of the effect of treatment of Helicobacter pylori infection on iron deficiency among children in rural Alaska: results at 40 months. *J Infect Dis* 2009; **199**: 652-660 [PMID: 19125674 DOI: 10.1086/596659]

69 **Fernández-Bañares F**, Monzón H, Forné M. A short review of malabsorption and anemia. *World J Gastroenterol* 2009; **15**: 4644-4652 [PMID: 19787827 DOI: 10.3748/wjg.15.4644]

70 **Jamieson JA**, Kuhnlein HV. The paradox of anemia with high meat intake: a review of the multifactorial etiology of anemia in the Inuit of North America. *Nutr Rev* 2008; **66**: 256-271 [PMID: 18454812 DOI: 10.1111/j.1753-4887.2008.00030.x]

71 **Lozoff B**, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. *N Engl J Med* 1991; **325**: 687-694 [PMID: 1870641 DOI: 10.1056/NEJM199109053251004]

72 **Lozoff B**, Jimenez E, Smith JB. Double burden of iron deficiency in infancy and low socioeconomic status: a longitudinal analysis of cognitive test scores to age 19 years. *Arch Pediatr Adolesc Med* 2006; **160**: 1108-1113 [PMID: 17088512 DOI: 10.1001/archpedi.160.11.1108]

73 **Muhsen K**, Ornoy A, Akawi A, Alpert G, Cohen D. An association between Helicobacter pylori infection and cognitive function in children at early school age: a community-based study. *BMC Pediatr* 2011; **11**: 43 [PMID: 21612616 DOI: 10.1186/1471-2431-11-43]

74 [**Queiroz DM**](http://www.ncbi.nlm.nih.gov/pubmed?term=Queiroz%20DM%5BAuthor%5D&cauthor=true&cauthor_uid=23988829), [Rocha AM](http://www.ncbi.nlm.nih.gov/pubmed?term=Rocha%20AM%5BAuthor%5D&cauthor=true&cauthor_uid=23988829), [Crabtree JE](http://www.ncbi.nlm.nih.gov/pubmed?term=Crabtree%20JE%5BAuthor%5D&cauthor=true&cauthor_uid=23988829). Unintended consequences of Helicobacter pylori infection in children in developing countries: Iron deficiency, diarrhea, and growth retardation. *Gut Microbes* 2013; [Epub ahead of print] [PMID: 23988829 DOI: 10.4161/gmic.26277]

75 **Blanchette VS**, Price V. Childhood chronic immune thrombocytopenic purpura: unresolved issues. *J Pediatr Hematol Oncol* 2003; **25 Suppl 1**: S28-S33 [PMID: 14668636 DOI: 10.1097/00043426-200312001-00007]

76 **Stasi R**, Willis F, Shannon MS, Gordon-Smith EC. Infectious causes of chronic immune thrombocytopenia. *Hematol Oncol Clin North Am* 2009; **23**: 1275-1297 [PMID: 19932434 DOI: 10.1016/j.hoc.2009.08.009]

77 **Jackson S**, Beck PL, Pineo GF, Poon MC. Helicobacter pylori eradication: novel therapy for immune thrombocytopenic purpura? A review of the literature. *Am J Hematol* 2005; **78**: 142-150 [PMID: 15682423 DOI: 10.1002/ajh.20250]

78 **Franchini M**, Cruciani M, Mengoli C, Pizzolo G, Veneri D. Effect of Helicobacter pylori eradication on platelet count in idiopathic thrombocytopenic purpura: a systematic review and meta-analysis. *J Antimicrob Chemother* 2007; **60**: 237-246 [PMID: 17561502 DOI: 10.1093/jac/dkm195]

79 **Arnold DM**, Bernotas A, Nazi I, Stasi R, Kuwana M, Liu Y, Kelton JG, Crowther MA. Platelet count response to H. pylori treatment in patients with immune thrombocytopenic purpura with and without H. pylori infection: a systematic review. *Haematologica* 2009; **94**: 850-856 [PMID: 19483158 DOI: 10.3324/haematol]

80 **Stasi R**, Sarpatwari A, Segal JB, Osborn J, Evangelista ML, Cooper N, Provan D, Newland A, Amadori S, Bussel JB. Effects of eradication of Helicobacter pylori infection in patients with immune thrombocytopenic purpura: a systematic review. *Blood* 2009; **113**: 1231-1240 [PMID: 18945961 DOI: 10.1182/blood-2008-07-167155]

81 **Michel M**, Khellaf M, Desforges L, Lee K, Schaeffer A, Godeau B, Bierling P. Autoimmune thrombocytopenic Purpura and Helicobacter pylori infection. *Arch Intern Med* 2002; **162**: 1033-1036 [PMID: 11996614 DOI: 10.1001/archinte.162.9.1033]

82 **Takahashi T**, Yujiri T, Shinohara K, Inoue Y, Sato Y, Fujii Y, Okubo M, Zaitsu Y, Ariyoshi K, Nakamura Y, Nawata R, Oka Y, Shirai M, Tanizawa Y. Molecular mimicry by Helicobacter pylori CagA protein may be involved in the pathogenesis of H. pylori-associated chronic idiopathic thrombocytopenic purpura. *Br J Haematol* 2004; **124**: 91-96 [PMID: 14675413 DOI: 10.1046/j.1365-2141.2003.04735.x]

83 **Franceschi F**, Christodoulides N, Kroll MH, Genta RM. Helicobacter pylori and idiopathic thrombocytopenic purpura. *Ann Intern Med* 2004; **140**: 766-767 [PMID: 15126268 DOI: 10.7326/0003-4819-140-9-200405040-00028]

84 **Franchini M**, Vescovi PP, Garofano M, Veneri D. Helicobacter pylori-associated idiopathic thrombocytopenic purpura: a narrative review. *Semin Thromb Hemost* 2012; **38**: 463-468 [PMID: 22753098 DOI: 10.1055/s-0032-1305781]

85 **Yamanishi S**, Iizumi T, Watanabe E, Shimizu M, Kamiya S, Nagata K, Kumagai Y, Fukunaga Y, Takahashi H. Implications for induction of autoimmunity via activation of B-1 cells by Helicobacter pylori urease. *Infect Immun* 2006; **74**: 248-256 [PMID: 16368978 DOI: 10.1128/IAI.74.1.248-256.2006]

86 **Pellicano R**, Touscoz GA, Smedile A, Berrutti M, Saracco G, Repici A, Ponzetto A, Rizzetto M. Prevalence of non-organ-specific autoantibodies in patients suffering from duodenal ulcer with and without Helicobacter pylori infection. *Dig Dis Sci* 2004; **49**: 395-398 [PMID: 15139486 DOI: 10.1023/B: DDAS.0000020491.78450.82]

87 **Asahi A**, Nishimoto T, Okazaki Y, Suzuki H, Masaoka T, Kawakami Y, Ikeda Y, Kuwana M. Helicobacter pylori eradication shifts monocyte Fcgamma receptor balance toward inhibitory FcgammaRIIB in immune thrombocytopenic purpura patients. *J Clin Invest* 2008; **118**: 2939-2949 [PMID: 18654664 DOI: 10.1172/JCI34496]

88 **Veneri D**, Gottardi M, Guizzardi E, Zanuso C, Krampera M, Franchini M. Idiopathic thrombocytopenic purpura, Helicobacter pylori infection, and HLA class II alleles. *Blood* 2002; **100**: 1925-196; author reply 1925-196; [PMID: 12211195 DOI: 10.1182/blood-2002-05-1348]

89 **Veneri D**, De Matteis G, Solero P, Federici F, Zanuso C, Guizzardi E, Arena S, Gaio M, Pontiero P, Ricetti MM, Franchini M. Analysis of B- and T-cell clonality and HLA class II alleles in patients with idiopathic thrombocytopenic purpura: correlation with Helicobacter pylori infection and response to eradication treatment. *Platelets* 2005; **16**: 307-311 [PMID: 16011982 DOI: 10.1080/09537100400015153]]

90 **Emilia G**, Luppi M, Morselli M, Longo G, Torelli G. Idiopathic thrombocytopenic purpura, Helicobacter pylori infection, and the HLA system. *Blood* 2002; **100**: 1926-1927

91 **Nomura S**, Matsuzaki T, Ozaki Y, Yamaoka M, Yoshimura C, Katsura K, Xie GL, Kagawa H, Ishida T, Fukuhara S. Clinical significance of HLA-DRB1\*0410 in Japanese patients with idiopathic thrombocytopenic purpura. *Blood* 1998; **91**: 3616-3622 [PMID: 9572996]

92 **Leung AY**, Hawkins BR, Chim CS, Kwong Y YL, Liang RH. Genetic analysis of HLA-typing in Chinese patients with idiopathic thrombocytopenic purpura. *Haematologica* 2001; **86**: 221-222 [PMID: 11224501]

93 **Gaiger A**, Neumeister A, Heinzl H, Pabinger I, Panzer S. HLA class-I and -II antigens in chronic idiopathic autoimmune thrombocytopenia. *Ann Hematol* 1994; **68**: 299-302 [PMID: 8038235]

94 **George JN**, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, Blanchette VS, Bussel JB, Cines DB, Kelton JG, Lichtin AE, McMillan R, Okerbloom JA, Regan DH, Warrier I. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 1996; **88**: 3-40 [PMID: 8704187]

95 **Jaing TH**, Yang CP, Hung IJ, Chiu CH, Chang KW. Efficacy of Helicobacter pylori eradication on platelet recovery in children with chronic idiopathic thrombocytopenic purpura. *Acta Paediatr* 2003; **92**: 1153-1157 [PMID: 14632330 DOI: 10.1111/j.1651-2227.2003.tb02476.x]

96 **Rajantie J**, Klemola T. Helicobacter pylori and idiopathic thrombocytopenic purpura in children. *Blood* 2003; **101**: 1660 [PMID: 12560248 DOI: 10.1182/blood-2002-10-3201]

97 **Hayashi H**, Okuda M, Aoyagi N, Yoshiyama M, Miyashiro E, Kounami S, Yoshikawa N. Helicobacter pylori infection in children with chronic idiopathic thrombocytopenic purpura. *Pediatr Int* 2005; **47**: 292-295 [PMID: 15910453 DOI: 10.1111/j.1442-200x.2005.02058.x]

98 **Yetgin S**, Demir H, Arslan D, Unal S, Koçak N. Autoimmune thrombocytopenic purpura and Helicobacter pylori infection effectivity during childhood. *Am J Hematol* 2005; **78**: 318 [PMID: 15795919 DOI: 10.1002/ajh.20302]

99 **Loffredo G**, Marzano MG, Migliorati R, Miele E, Menna F, Poggi V, Staiano A. The relationship between immune thrombocytopenic purpura and Helicobacter pylori infection in children: where is the truth? *Eur J Pediatr* 2007; **166**: 1067-1068 [PMID: 17136353 DOI: 10.1007/s00431-006-0344-4]

100 **Neefjes VM**, Heijboer H, Tamminga RY. H. pylori infection in childhood chronic immune thrombocytopenic purpura. *Haematologica* 2007; **92**: 576 [PMID: 17488677 DOI: 10.3324/haematol.10940]

101 **Wu KS**, Hsiao CC, Yu HR, Huang EY, Mai WL, Sheen JM. Helicobacter pylori infection and childhood idiopathic thrombocytopenic purpura. *Acta Paediatr Taiwan* 2007; **48**: 263-266 [PMID: 18254575]

102 **Bisogno G**, Errigo G, Rossetti F, Sainati L, Pusiol A, Da Dalt L, Colleselli P, Grotto P, Carli M. The role of Helicobacter pylori in children with chronic idiopathic thrombocytopenic purpura. *J Pediatr Hematol Oncol* 2008; **30**: 53-57 [PMID: 18176181 DOI: 10.1097/MPH.0b013e3181615613]

103 **Hamidieh AA**, Arzanian MT, Gachkar L, Pasha F. Helicobacter pylori infection in children with chronic idiopathic thrombocytopenic purpura. *J Pediatr Hematol Oncol* 2008; **30**: 96-97 [PMID: 18176194 DOI: 10.1097/MPH.0b013e3181615600]

104 **Capozzi L**, Russo R, Bertocco F, Ferrara D, Ferrara M. Effect on haematological and anthropometric parameters of iron supplementation in the first 2 years of life. Risks and benefits. *Hematology* 2011; **16**: 261-264 [PMID: 21902888 DOI: 10.1179/102453309X12473408860181]

105 **Treepongkaruna S**, Sirachainan N, Kanjanapongkul S, Winaichatsak A, Sirithorn S, Sumritsopak R, Chuansumrit A. Absence of platelet recovery following Helicobacter pylori eradication in childhood chronic idiopathic thrombocytopenic purpura: a multi-center randomized controlled trial. *Pediatr Blood Cancer* 2009; **53**: 72-77 [PMID: 19301380 DOI: 10.1002/pbc.21991]

106 **Russo G**, Miraglia V, Branciforte F, Matarese SM, Zecca M, Bisogno G, Parodi E, Amendola G, Giordano P, Jankovic M, Corti A, Nardi M, Farruggia P, Battisti L, Baronci C, Palazzi G, Tucci F, Ceppi S, Nobili B, Ramenghi U, De Mattia D, Notarangelo L. Effect of eradication of Helicobacter pylori in children with chronic immune thrombocytopenia: a prospective, controlled, multicenter study. *Pediatr Blood Cancer* 2011; **56**: 273-278 [PMID: 20830773 DOI: 10.1002/pbc.22770]

107 **Stephensen CB**. Burden of infection on growth failure. *J Nutr* 1999; **129**: 534S-538S [PMID: 10064326]

108 **Goodman KJ**, Joyce SL, Ismond KP. Extragastric diseases associated with Helicobacter pylori infection. *Curr Gastroenterol Rep* 2006; **8**: 458-464 [PMID: 17105683 DOI: 10.1007/s11894-006-0035-3]

109 **Clemens J**, Albert MJ, Rao M, Huda S, Qadri F, Van Loon FP, Pradhan B, Naficy A, Banik A. Sociodemographic, hygienic and nutritional correlates of Helicobacter pylori infection of young Bangladeshi children. *Pediatr Infect Dis J* 1996; **15**: 1113-1118 [PMID: 8970222 DOI: 10.1097/00006454-199612000-00012]

110 **Perri F**, Pastore M, Leandro G, Clemente R, Ghoos Y, Peeters M, Annese V, Quitadamo M, Latiano A, Rutgeerts P, Andriulli A. Helicobacter pylori infection and growth delay in older children. *Arch Dis Child* 1997; **77**: 46-49 [PMID: 9279151 DOI: 10.1136/adc.77.1.46]

111 **Goodman KJ**, Correa P, Tenganá Aux HJ, DeLany JP, Collazos T. Nutritional factors and Helicobacter pylori infection in Colombian children. *J Pediatr Gastroenterol Nutr* 1997; **25**: 507-515 [PMID: 9360204 DOI: 10.1097/00005176-199711000-00004]

112 **Kehrt R**, Becker M, Brösicke H, Krüger N, Helge H. Prevalence of Helicobacter pylori infection in Nicaraguan children with persistent diarrhea, diagnosed by the 13C-urea breath test. *J Pediatr Gastroenterol Nutr* 1997; **25**: 84-88 [PMID: 9226533 DOI: 10.1097/00005176-199707000-00014]

113 **Oderda G**, Palli D, Saieva C, Chiorboli E, Bona G. Short stature and Helicobacter pylori infection in italian children: prospective multicentre hospital based case-control study. The Italian Study Group on Short Stature and H pylori. *BMJ* 1998; **317**: 514-515 [PMID: 9712599 DOI: 10.1136/bmj.317.7157.514]

114 **Quiñonez JM**, Chew F, Torres O, Bégué RE. Nutritional status of Helicobacter pylori-infected children in Guatemala as compared with uninfected peers. *Am J Trop Med Hyg* 1999; **61**: 395-398 [PMID: 10497978]

115 **Castro-Rodríguez JA**, León-Barúa R, Penny M. Helicobacter pylori is not a determinant factor of persistent diarrhoea or malnutrition in Peruvian children. *Trans R Soc Trop Med Hyg* 1999; **93**: 537-539 [PMID: 10696416 DOI: 10.1016/S0035-9203(99)90372-3]

116 **Naficy AB**, Frenck RW, Abu-Elyazeed R, Kim Y, Rao MR, Savarino SJ, Wierzba TF, Hall E, Clemens JD. Seroepidemiology of Helicobacter pylori infection in a population of Egyptian children. *Int J Epidemiol* 2000; **29**: 928-932 [PMID: 11034980 DOI: 10.1093/ije/29.5.928]

117 **Richter T**, Richter T, List S, Müller DM, Deutscher J, Uhlig HH, Krumbiegel P, Herbarth O, Gutsmuths FJ, Kiess W. Five- to 7-year-old children with Helicobacter pylori infection are smaller than Helicobacter-negative children: a cross-sectional population-based study of 3,315 children. *J Pediatr Gastroenterol Nutr* 2001; **33**: 472-475 [PMID: 11698766 DOI: 10.1097/00005176-200110000-00010]

118 **Ertem D**, Pehlivanoglu E. Helicobacter pylori may influence height in children independent of socioeconomic factors. *J Pediatr Gastroenterol Nutr* 2002; **35**: 232-233 [PMID: 12187306 DOI: 10.1097/00005176-200208000-00028]

119 **Sood MR**, Joshi S, Akobeng AK, Mitchell J, Thomas AG. Growth in children with Helicobacter pylori infection and dyspepsia. *Arch Dis Child* 2005; **90**: 1025-1028 [PMID: 15956048 DOI: 10.1136/adc.2004.066803]

120 **Yang YJ**, Sheu BS, Lee SC, Yang HB, Wu JJ. Children of Helicobacter pylori-infected dyspeptic mothers are predisposed to H. pylori acquisition with subsequent iron deficiency and growth retardation. *Helicobacter* 2005; **10**: 249-255 [PMID: 15904483 DOI: 10.1111/j.1523-5378.2005.00317.x]

121 **Mohammad MA**, Hussein L, Coward A, Jackson SJ. Prevalence of Helicobacter pylori infection among Egyptian children: impact of social background and effect on growth. *Public Health Nutr* 2008; **11**: 230-236 [PMID: 17666124 DOI: 10.1017/S1368980007000481]

122 **Fialho AM**, Braga AB, Queiroz DM, Rodrigues MN, Herbster ID, Braga LL. The association between Helicobacter pylori infection and height in children from an urban community in north-east Brazil. *Ann Trop Paediatr* 2007; **27**: 55-61 [PMID: 17469733 DOI: 10.1179/146532807X170510]

123 **Braga AB**, Fialho AM, Rodrigues MN, Queiroz DM, Rocha AM, Braga LL. Helicobacter pylori colonization among children up to 6 years: results of a community-based study from Northeastern Brazil. *J Trop Pediatr* 2007; **53**: 393-397 [PMID: 17578847 DOI: 10.1093/tropej/fmm051]

124 **Soylu OB**, Ozturk Y. Helicobacter pylori infection: effect on malnutrition and growth failure in dyspeptic children. *Eur J Pediatr* 2008; **167**: 557-562 [PMID: 17618457 DOI: 10.1007/s00431-007-0552-6]

125 **Cherian S**, Forbes D, Sanfilippo F, Cook A, Burgner D. Helicobacter pylori, helminth infections and growth: a cross-sectional study in a high prevalence population. *Acta Paediatr* 2009; **98**: 860-864 [PMID: 19191761 DOI: 10.1111/j.1651-2227.2009.01221.x]

126 **Ferrara M**, Capozzi L, Russo R. Influence of Helicobacter pylori infection associated with iron deficiency anaemia on growth in pre-adolescent children. *Hematology* 2009; **14**: 173-176 [PMID: 19490764 DOI: 10.1179/102453309X402287]

127 **Gulcan M**, Ozen A, Karatepe HO, Gulcu D, Vitrinel A. Impact of H. pylori on growth: is the infection or mucosal disease related to growth impairment? *Dig Dis Sci* 2010; **55**: 2878-2886 [PMID: 20112067]

128 **Bravo LE**, Mera R, Reina JC, Pradilla A, Alzate A, Fontham E, Correa P. Impact of Helicobacter pylori infection on growth of children: a prospective cohort study. *J Pediatr Gastroenterol Nutr* 2003; **37**: 614-619 [PMID: 14581807 DOI: 10.1097/00005176-200311000-00021]

129 **Goodman KJ**, Correa P, Mera R, Yepez MC, Cerón C, Campo C, Guerrero N, Sierra MS, Bravo LE. Effect of Helicobacter pylori infection on growth velocity of school-age Andean children. *Epidemiology* 2011; **22**: 118-126 [PMID: 21068668 DOI: 10.1097/EDE]

130 **Thomas JE**, Dale A, Bunn JE, Harding M, Coward WA, Cole TJ, Weaver LT. Early Helicobacter pylori colonisation: the association with growth faltering in The Gambia. *Arch Dis Child* 2004; **89**: 1149-1154 [PMID: 15557054 DOI: 10.1136/adc.2002.015313]

131 Use and interpretation of anthropometric indicators of nutritional status. WHO Working Group. *Bull World Health Organ* 1986; **64**: 929-941 [PMID: 3493862]

132 **Mera RM**, Correa P, Fontham EE, Reina JC, Pradilla A, Alzate A, Bravo LE. Effects of a new Helicobacter pylori infection on height and weight in Colombian children. *Ann Epidemiol* 2006; **16**: 347-351 [PMID: 16246582 DOI: 10.1016/j.annepidem]

133 **Egorov AI**, Sempértegui F, Estrella B, Egas J, Naumova EN, Griffiths JK. The effect of Helicobacter pylori infection on growth velocity in young children from poor urban communities in Ecuador. *Int J Infect Dis* 2010; **14**: e788-e791 [PMID: 20638884 DOI: 10.1016/j.ijid.2010.03.013]]

134 **Mera RM**, Bravo LE, Goodman KJ, Yepez MC, Correa P. Long-term effects of clearing Helicobacter pylori on growth in school-age children. *Pediatr Infect Dis J* 2012; **31**: 263-266 [PMID: 22315005 DOI: 10.1097/INF.0b013e3182443fec]

135 **Patel P**, Mendall MA, Khulusi S, Northfield TC, Strachan DP. Helicobacter pylori infection in childhood: risk factors and effect on growth. *BMJ* 1994; **309**: 1119-1123 [PMID: 7987103 DOI: 10.1136/bmj.309.6962.1119]

136 **Isenbarger DW**, Bodhidatta L, Hoge CW, Nirdnoy W, Pitarangsi C, Umpawasiri U, Echeverria P. Prospective study of the incidence of diarrheal disease and Helicobacter pylori infection among children in an orphanage in Thailand. *Am J Trop Med Hyg* 1998; **59**: 796-800 [PMID: 9840601]

137 **Passaro DJ**, Taylor DN, Meza R, Cabrera L, Gilman RH, Parsonnet J. Acute Helicobacter pylori infection is followed by an increase in diarrheal disease among Peruvian children. *Pediatrics* 2001; **108**: E87 [PMID: 11694671 DOI: 10.1542]

138 **Rahman MM**, Mahalanabis D, Sarker SA, Bardhan PK, Alvarez JO, Hildebrand P, Beglinger C, Gyr K. Helicobacter pylori colonization in infants and young children is not necessarily associated with diarrhoea. *J Trop Pediatr* 1998; **44**: 283-287 [PMID: 9819491 DOI: 10.1093/tropej/44.5.283]

139 **van der Lely AJ**, Tschöp M, Heiman ML, Ghigo E. Biological, physiological, pathophysiological, and pharmacological aspects of ghrelin. *Endocr Rev* 2004; **25**: 426-457 [PMID: 15180951 DOI: 10.1210/er.2002-0029]

140 **Date Y**, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, Suganuma T, Matsukura S, Kangawa K, Nakazato M. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology* 2000; **141**: 4255-4261 [PMID: 11089560 DOI: 10.1210/en.141.11.4255]

141 **Nwokolo CU**, Freshwater DA, O'Hare P, Randeva HS. Plasma ghrelin following cure of Helicobacter pylori. *Gut* 2003; **52**: 637-640 [PMID: 12692045 DOI: 10.1136/gut.52.5.637]

142 **Tatsuguchi A**, Miyake K, Gudis K, Futagami S, Tsukui T, Wada K, Kishida T, Fukuda Y, Sugisaki Y, Sakamoto C. Effect of Helicobacter pylori infection on ghrelin expression in human gastric mucosa. *Am J Gastroenterol* 2004; **99**: 2121-2127 [PMID: 15554990 DOI: 10.1111/j.1572-0241.2004.30291.x]

143 **Loffeld RJ**. Helicobacter pylori, obesity and gastro-oesophageal reflux disease. Is there a relation? A personal view. *Neth J Med* 2005; **63**: 344-347 [PMID: 16244381]

144 **Isomoto H**, Ueno H, Saenko VA, Mondal MS, Nishi Y, Kawano N, Ohnita K, Mizuta Y, Ohtsuru A, Yamashita S, Nakazato M, Kohno S. Impact of Helicobacter pylori infection on gastric and plasma ghrelin dynamics in humans. *Am J Gastroenterol* 2005; **100**: 1711-1720 [PMID: 16086706 DOI: 10.1111/j.1572-0241.2005]

145 **Osawa H**, Kita H, Ohnishi H, Nakazato M, Date Y, Bowlus CL, Ishino Y, Watanabe E, Shiiya T, Ueno H, Hoshino H, Satoh K, Sugano K. Changes in plasma ghrelin levels, gastric ghrelin production, and body weight after Helicobacter pylori cure. *J Gastroenterol* 2006; **41**: 954-961 [PMID: 17096064]

146 **Murray CD**, Emmanuel AV. Ghrelin and Helicobacter pylori. *Gut* 2004; **53**: 315; author reply 315 [PMID: 14724174]

147 **Gokcel A**, Gumurdulu Y, Kayaselcuk F, Serin E, Ozer B, Ozsahin AK, Guvener N. Helicobacter pylori has no effect on plasma ghrelin levels. *Eur J Endocrinol* 2003; **148**: 423-426 [PMID: 12656662 DOI: 10.1530/eje.0.1480423]

148 **Osawa H**, Nakazato M, Date Y, Kita H, Ohnishi H, Ueno H, Shiiya T, Satoh K, Ishino Y, Sugano K. Impaired production of gastric ghrelin in chronic gastritis associated with Helicobacter pylori. *J Clin Endocrinol Metab* 2005; **90**: 10-16 [PMID: 15483107 DOI: 10.1210/jc.2004-1330]

149 **Isomoto H**, Ueno H, Nishi Y, Wen CY, Nakazato M, Kohno S. Impact of Helicobacter pylori infection on ghrelin and various neuroendocrine hormones in plasma. *World J Gastroenterol* 2005; **11**: 1644-1648 [PMID: 15786542]

150 **Cindoruk M**, Yetkin I, Deger SM, Karakan T, Kan E, Unal S. Influence of H pylori on plasma ghrelin in patients without atrophic gastritis. *World J Gastroenterol* 2007; **13**: 1595-1598 [PMID: 17461454]

151 **Plonka M**, Bielanski W, Konturek SJ, Targosz A, Sliwowski Z, Dobrzanska M, Kaminska A, Sito E, Konturek PC, Brzozowski T. Helicobacter pylori infection and serum gastrin, ghrelin and leptin in children of Polish shepherds. *Dig Liver Dis* 2006; **38**: 91-97 [PMID: 16293448 DOI: 10.1016/j.dld.2005.10.013]

152 **Pacifico L**, Anania C, Osborn JF, Ferrara E, Schiavo E, Bonamico M, Chiesa C. Long-term effects of Helicobacter pylori eradication on circulating ghrelin and leptin concentrations and body composition in prepubertal children. *Eur J Endocrinol* 2008; **158**: 323-332 [PMID: 18299465 DOI: 10.1530/EJE-07-0438]

153 **Yang YJ**, Sheu BS, Yang HB, Lu CC, Chuang CC. Eradication of Helicobacter pylori increases childhood growth and serum acylated ghrelin levels. *World J Gastroenterol* 2012; **18**: 2674-2681 [PMID: 22690077 DOI: 10.3748/wjg.v18.i21.2674]

154 **Deng ZH**, Chu B, Xu YZ, Zhang B, Jiang LR. Influence of Helicobacter pylori infection on ghrelin levels in children. *World J Gastroenterol* 2012; **18**: 5096-5100 [PMID: 23049220 DOI: 10.3748/wjg.v18.i36.5096]

155 **Nakazato M**, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K, Matsukura S. A role for ghrelin in the central regulation of feeding. *Nature* 2001; **409**: 194-198 [PMID: 11196643 DOI: 10.1038/35051587]

156 **Wren AM**, Seal LJ, Cohen MA, Brynes AE, Frost GS, Murphy KG, Dhillo WS, Ghatei MA, Bloom SR. Ghrelin enhances appetite and increases food intake in humans. *J Clin Endocrinol Metab* 2001; **86**: 5992 [PMID: 11739476 DOI: 10.1210/jc.86.12]

157 **Strachan DP**. Hay fever, hygiene, and household size. *BMJ* 1989; **299**: 1259-1260 [PMID: 2513902 DOI: 10.1136/bmj.299.6710.1259]

158 **Matricardi PM**, Rosmini F, Riondino S, Fortini M, Ferrigno L, Rapicetta M, Bonini S. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000; **320**: 412-417 [PMID: 10669445 DOI: 10.1136/bmj.320.7232.412]]

159 **Blaser MJ**, Falkow S. What are the consequences of the disappearing human microbiota? *Nat Rev Microbiol* 2009; **7**: 887-894 [PMID: 19898491 DOI: 10.1038/nrmicro2245]

160 **Linz B**, Balloux F, Moodley Y, Manica A, Liu H, Roumagnac P, Falush D, Stamer C, Prugnolle F, van der Merwe SW, Yamaoka Y, Graham DY, Perez-Trallero E, Wadstrom T, Suerbaum S, Achtman M. An African origin for the intimate association between humans and Helicobacter pylori. *Nature* 2007; **445**: 915-918 [PMID: 17287725 DOI: 10.1038/nature05562]

161 **Banatvala N**, Mayo K, Megraud F, Jennings R, Deeks JJ, Feldman RA. The cohort effect and Helicobacter pylori. *J Infect Dis* 1993; **168**: 219-221 [PMID: 8515114 DOI: 10.1093/infdis/168.1.219]

162 **Roosendaal R**, Kuipers EJ, Buitenwerf J, van Uffelen C, Meuwissen SG, van Kamp GJ, Vandenbroucke-Grauls CM. Helicobacter pylori and the birth cohort effect: evidence of a continuous decrease of infection rates in childhood. *Am J Gastroenterol* 1997; **92**: 1480-1482 [PMID: 9317067]

163 **Harvey RF**, Spence RW, Lane JA, Nair P, Murray LJ, Harvey IM, Donovan J. Relationship between the birth cohort pattern of Helicobacter pylori infection and the epidemiology of duodenal ulcer. *QJM* 2002; **95**: 519-525 [PMID: 12145391 DOI: 10.1093/qjmed/95.8.519]

164 **Blaser MJ**, Atherton JC. Helicobacter pylori persistence: biology and disease. *J Clin Invest* 2004; **113**: 321-333 [PMID: 14755326 DOI: 10.1172/JCI20925]

165 **Chen Y**, Blaser MJ. Helicobacter pylori colonization is inversely associated with childhood asthma. *J Infect Dis* 2008; **198**: 553-560 [PMID: 18598192 DOI: 10.1086/590158]

166 **Blaser MJ**, Chen Y, Reibman J. Does Helicobacter pylori protect against asthma and allergy? *Gut* 2008; **57**: 561-567 [PMID: 18194986 DOI: 10.1136/gut.2007.133462]

167 **Herbarth O**, Bauer M, Fritz GJ, Herbarth P, Rolle-Kampczyk U, Krumbiegel P, Richter M, Richter T. Helicobacter pylori colonisation and eczema. *J Epidemiol Community Health* 2007; **61**: 638-640 [PMID: 17568058 DOI: 10.1136/jech.2006]

168 **Linneberg A**, Ostergaard C, Tvede M, Andersen LP, Nielsen NH, Madsen F, Frølund L, Dirksen A, Jørgensen T. IgG antibodies against microorganisms and atopic disease in Danish adults: the Copenhagen Allergy Study. *J Allergy Clin Immunol* 2003; **111**: 847-853 [PMID: 12704368 DOI: 10.1067/mai.2003.1335]

169 **Kosunen TU**, Höök-Nikanne J, Salomaa A, Sarna S, Aromaa A, Haahtela T. Increase of allergen-specific immunoglobulin E antibodies from 1973 to 1994 in a Finnish population and a possible relationship to Helicobacter pylori infections. *Clin Exp Allergy* 2002; **32**: 373-378 [PMID: 11940066 DOI: 10.1046/j.1365-2222]

170 **Janson C**, Asbjornsdottir H, Birgisdottir A, Sigurjonsdottir RB, Gunnbjörnsdottir M, Gislason D, Olafsson I, Cook E, Jögi R, Gislason T, Thjodleifsson B. The effect of infectious burden on the prevalence of atopy and respiratory allergies in Iceland, Estonia, and Sweden. *J Allergy Clin Immunol* 2007; **120**: 673-679 [PMID: 17586034 DOI: 10.1016/j.jaci.2007.05.003]

171 **Shiotani A**, Miyanishi T, Kamada T, Haruma K. Helicobacter pylori infection and allergic diseases: epidemiological study in Japanese university students. *J Gastroenterol Hepatol* 2008; **23**: e29-e33 [PMID: 17725593 DOI: 10.1111/j.1440-1746]

172 **von Hertzen LC**, Laatikainen T, Mäkelä MJ, Jousilahti P, Kosunen TU, Petays T, Pussinen PJ, Haahtela T, Vartiainen E. Infectious burden as a determinant of atopy-- a comparison between adults in Finnish and Russian Karelia. *Int Arch Allergy Immunol* 2006; **140**: 89-95 [PMID: 16554659 DOI: 10.1159/000092251]

173 **Chen Y**, Blaser MJ. Inverse associations of Helicobacter pylori with asthma and allergy. *Arch Intern Med* 2007; **167**: 821-827 [PMID: 17452546 DOI: 10.1001/archinte]

174 **McCune A**, Lane A, Murray L, Harvey I, Nair P, Donovan J, Harvey R. Reduced risk of atopic disorders in adults with Helicobacter pylori infection. *Eur J Gastroenterol Hepatol* 2003; **15**: 637-640 [PMID: 12840675 DOI: 10.1097/01.meg]

175 **Reibman J**, Marmor M, Filner J, Fernandez-Beros ME, Rogers L, Perez-Perez GI, Blaser MJ. Asthma is inversely associated with Helicobacter pylori status in an urban population. *PLoS One* 2008; **3**: e4060 [PMID: 19112508 DOI: 10.1371/journal.pone.0004060]

176 **Konturek PC**, Rienecker H, Hahn EG, Raithel M. Helicobacter pylori as a protective factor against food allergy. *Med Sci Monit* 2008; **14**: CR452-CR458 [PMID: 18758415]

177 **Zevit N**, Balicer RD, Cohen HA, Karsh D, Niv Y, Shamir R. Inverse association between Helicobacter pylori and pediatric asthma in a high-prevalence population. *Helicobacter* 2012; **17**: 30-35 [PMID: 22221613 DOI: 10.1111/j.1523-5378.2011.00895.x]

178 **Amberbir A**, Medhin G, Erku W, Alem A, Simms R, Robinson K, Fogarty A, Britton J, Venn A, Davey G. Effects of Helicobacter pylori, geohelminth infection and selected commensal bacteria on the risk of allergic disease and sensitization in 3-year-old Ethiopian children. *Clin Exp Allergy* 2011; **41**: 1422-1430 [PMID: 21831135 DOI: 10.1111/j.1365-2222.2011.03831.x]

179 **Jarvis D**, Luczynska C, Chinn S, Burney P. 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**: 1063-1067 [PMID: 15355464 DOI: 10.1111/j.1398-9995.2004.00539.x]

180 **Annagür A**, Kendirli SG, Yilmaz M, Altintas DU, Inal A. Is there any relationship between asthma and asthma attack in children and atypical bacterial infections; Chlamydia pneumoniae, Mycoplasma pneumoniae and Helicobacter pylori. *J Trop Pediatr* 2007; **53**: 313-318 [PMID: 17535826 DOI: 10.1093/tropej]

181 **Roussos A**, Philippou N, Mantzaris GJ, Gourgoulianis KI. Respiratory diseases and Helicobacter pylori infection: is there a link? *Respiration* 2006; **73**: 708-714 [PMID: 16763382 DOI: 10.1159/000093816]

182 **Fullerton D**, Britton JR, Lewis SA, Pavord ID, McKeever TM, Fogarty AW. Helicobacter pylori and lung function, asthma, atopy and allergic disease--a population-based cross-sectional study in adults. *Int J Epidemiol* 2009; **38**: 419-426 [PMID: 19109248 DOI: 10.1093/ije/dyn348]

183 **Raj SM**, Choo KE, Noorizan AM, Lee YY, Graham DY. Evidence against Helicobacter pylori being related to childhood asthma. *J Infect Dis* 2009; **199**: 914-95; author reply 914-95; [PMID: 19434934 DOI: 10.1086/597066]

184 **Jun ZJ**, Lei Y, Shimizu Y, Dobashi K, Mori M. Helicobacter pylori seroprevalence in patients with mild asthma. *Tohoku J Exp Med* 2005; **207**: 287-291 [PMID: 16272799 DOI: 10.1620/tjem.207.287]

185 **D'Elios MM**, Codolo G, Amedei A, Mazzi P, Berton G, Zanotti G, Del Prete G, de Bernard M. Helicobacter pylori, asthma and allergy. *FEMS Immunol Med Microbiol* 2009; **56**: 1-8 [PMID: 19220467 DOI: 10.1111/j.1574-695X.2009.00537.x]

186 **Amedei A**, Cappon A, Codolo G, Cabrelle A, Polenghi A, Benagiano M, Tasca E, Azzurri A, D'Elios MM, Del Prete G, de Bernard M. The neutrophil-activating protein of Helicobacter pylori promotes Th1 immune responses. *J Clin Invest* 2006; **116**: 1092-1101 [PMID: 16543949 DOI: 10.1172/JCI27177]

187 **Codolo G**, Mazzi P, Amedei A, Del Prete G, Berton G, D'Elios MM, de Bernard M. The neutrophil-activating protein of Helicobacter pylori down-modulates Th2 inflammation in ovalbumin-induced allergic asthma. *Cell Microbiol* 2008; **10**: 2355-2363 [PMID: 18671823 DOI: 10.1111/j.1462-5822.2008.01217.x]

188 **Umetsu DT**, DeKruyff RH. The regulation of allergy and asthma. *Immunol Rev* 2006; **212**: 238-255 [PMID: 16903918 DOI: 10.1111/j.0105-2896.2006.00413.x]

189 [Lundgren A](http://www.ncbi.nlm.nih.gov/pubmed?term=Lundgren%20A%5BAuthor%5D&cauthor=true&cauthor_uid=16113278), [Trollmo C](http://www.ncbi.nlm.nih.gov/pubmed?term=Trollmo%20C%5BAuthor%5D&cauthor=true&cauthor_uid=16113278), [Edebo A](http://www.ncbi.nlm.nih.gov/pubmed?term=Edebo%20A%5BAuthor%5D&cauthor=true&cauthor_uid=16113278), [Svennerholm AM](http://www.ncbi.nlm.nih.gov/pubmed?term=Svennerholm%20AM%5BAuthor%5D&cauthor=true&cauthor_uid=16113278), [Lundin BS](http://www.ncbi.nlm.nih.gov/pubmed?term=Lundin%20BS%5BAuthor%5D&cauthor=true&cauthor_uid=16113278). Helicobacter pylori-specific CD4+ T cells home to and accumulate in the human Helicobacter pylori-infected gastric mucosa. *[Infect Immun](http://www.ncbi.nlm.nih.gov/pubmed/?term=lundgren+a%2Ctrollmo+c%2C2005" \o "Infection and immunity.)* 2005; **73:** 5612-5619 [PMID: 16113278 DOI: 10.1128/IAI.73.9.5612–5619.2005]

190 **Robinson K**, Kenefeck R, Pidgeon EL, Shakib S, Patel S, Polson RJ, Zaitoun AM, Atherton JC. Helicobacter pylori-induced peptic ulcer disease is associated with inadequate regulatory T cell responses. *Gut* 2008; **57**: 1375-1385 [PMID: 18467372 DOI: 10.1136/gut.2007.137539]

191 **Arnold IC**, Dehzad N, Reuter S, Martin H, Becher B, Taube C, Müller A. Helicobacter pylori infection prevents allergic asthma in mouse models through the induction of regulatory T cells. *J Clin Invest* 2011; **121**: 3088-3093 [PMID: 21737881 DOI: 10.1172/JCI45041]

192 **Tsang KW**, Lam WK, Chan KN, Hu W, Wu A, Kwok E, Zheng L, Wong BC, Lam SK. Helicobacter pylori sero-prevalence in asthma. *Respir Med* 2000; **94**: 756-759 [PMID: 10955750 DOI: 10.1053/rmed.2000.0817]

193 **Bodner C**, Anderson WJ, Reid TS, Godden DJ. Childhood exposure to infection and risk of adult onset wheeze and atopy. *Thorax* 2000; **55**: 383-387 [PMID: 10770819 DOI: 10.1136/thorax.55.5.383]

194 **Chen Y**, Blaser MJ. Reply to raj et Al. *J Infect Dis* 2009; **199**: 915-916 [PMID: 19239343 DOI: 10.1086/597067]

195 **Papamichael KX**, Papaioannou G, Karga H, Roussos A, Mantzaris GJ. Helicobacter pylori infection and endocrine disorders: is there a link? *World J Gastroenterol* 2009; **15**: 2701-2707 [PMID: 19522019 DOI: 10.3748/wjg.15.2701]

196 **Oldenburg B**, Diepersloot RJ, Hoekstra JB. High seroprevalence of Helicobacter pylori in diabetes mellitus patients. *Dig Dis Sci* 1996; **41**: 458-461 [PMID: 8617115 DOI: 10.1007/BF02282318]

197 **Gasbarrini A**, Ojetti V, Pitocco D, De Luca A, Franceschi F, Candelli M, Sanz Torre E, Pola P, Ghirlanda G, Gasbarrini G. Helicobacter pylori infection in patients affected by insulin-dependent diabetes mellitus. *Eur J Gastroenterol Hepatol* 1998; **10**: 469-472 [PMID: 9855061 DOI: 10.1097/00042737-199806000-00006]

198 **Salardi S**, Cacciari E, Menegatti M, Landi F, Mazzanti L, Stella FA, Pirazzoli P, Vaira D. Helicobacter pylori and type 1 diabetes mellitus in children. *J Pediatr Gastroenterol Nutr* 1999; **28**: 307-309 [PMID: 10067733 DOI: 10.1097/00005176-199903000-00017]

199 **Arslan D**, Kendirci M, Kurtoglu S, Kula M. Helicobacter pylori infection in children with insulin dependent diabetes mellitus. *J Pediatr Endocrinol Metab* 2000; **13**: 553-556 [PMID: 10803874 DOI: 10.1515/JPEM.2000.13.5.553]

200 **Perdichizzi G**, Bottari M, Pallio S, Fera MT, Carbone M, Barresi G. Gastric infection by Helicobacter pylori and antral gastritis in hyperglycemic obese and in diabetic subjects. *New Microbiol* 1996; **19**: 149-154 [PMID: 8722311]

201 **Senturk O**, Canturk Z, Cetinarslan B, Ercin C, Hulagu S, Canturk NZ. Prevalence and comparisons of five different diagnostic methods for Helicobacter pylori in diabetic patients. *Endocr Res* 2001; **27**: 179-189 [PMID: 11428709 DOI: 10.1081/ERC-100107179]

202 **Quatrini M**, Boarino V, Ghidoni A, Baldassarri AR, Bianchi PA, Bardella MT. Helicobacter pylori prevalence in patients with diabetes and its relationship to dyspeptic symptoms. *J Clin Gastroenterol* 2001; **32**: 215-217 [PMID: 11246346 DOI: 10.1097/00004836-200103000-00006]

203 **Gulcelik NE**, Kaya E, Demirbas B, Culha C, Koc G, Ozkaya M, Cakal E, Serter R, Aral Y. Helicobacter pylori prevalence in diabetic patients and its relationship with dyspepsia and autonomic neuropathy. *J Endocrinol Invest* 2005; **28**: 214-217 [PMID: 15952404]

204 **Gentile S**, Turco S, Oliviero B, Torella R. The role of autonomic neuropathy as a risk factor of Helicobacter pylori infection in dyspeptic patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 1998; **42**: 41-48 [PMID: 9884032 DOI: 10.1016/S0168-8227(98)00088-6]

205 **Quadri R**, Rossi C, Catalfamo E, Masoero G, Lombardo L, Della Monica P, Rovera L, Pera A, Cavello Perin P. Helicobacter pylori infection in type 2 diabetic patients. *Nutr Metab Cardiovasc Dis* 2000; **10**: 263-266 [PMID: 11213535]

206 **Diomedi M**, Stanzione P, Sallustio F, Leone G, Renna A, Misaggi G, Fontana C, Pasqualetti P, Pietroiusti A. Cytotoxin-associated Gene-A-positive Helicobacter pylori strains infection increases the risk of recurrent atherosclerotic stroke. *Helicobacter* 2008; **13**: 525-531 [PMID: 19166418 DOI: 10.1111/j.1523-5378.2008]

207 **Hamed SA**, Amine NF, Galal GM, Helal SR, Tag El-Din LM, Shawky OA, Ahmed EA, Abdel Rahman MS. Vascular risks and complications in diabetes mellitus: the role of helicobacter pylori infection. *J Stroke Cerebrovasc Dis* ; **17**: 86-94 [PMID: 18346651 DOI: 10.1016/j.jstrokecerebrovasdis.2007.10.006]

208 **Wellen KE**, Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest* 2005; **115**: 1111-1119 [PMID: 15864338 DOI: 10.1172/JCI25102]

209 **Manco M**, Putignani L, Bottazzo GF. Gut microbiota, lipopolysaccharides, and innate immunity in the pathogenesis of obesity and cardiovascular risk. *Endocr Rev* 2010; **31**: 817-844 [PMID: 20592272 DOI: 10.1210/er.2009-0030]

210 **Ojetti V**, Pellicano R, Fagoonee S, Migneco A, Berrutti M, Gasbarrini A. Helicobacter pylori infection and diabetes. *Minerva Med* 2010; **101**: 115-119 [PMID: 20467410]

211 **Burghen GA**, Murrell LR, Whitington GL, Klyce MK, Burstein S. Acid peptic disease in children with type I diabetes mellitus. A complicating relationship. *Am J Dis Child* 1992; **146**: 718-722 [PMID: 1595627]

212 **Dore MP**, Bilotta M, Malaty HM, Pacifico A, Maioli M, Graham DY, Realdi G. Diabetes mellitus and Helicobacter pylori infection. *Nutrition* 2000; **16**: 407-410 [PMID: 10869894 DOI: 10.1016/S0899-9007(00)00267-7]

213 **Ko GT**, Chan FK, Chan WB, Sung JJ, Tsoi CL, To KF, Lai CW, Cockram CS. Helicobacter pylori infection in Chinese subjects with type 2 diabetes. *Endocr Res* 2001; **27**: 171-177 [PMID: 11428708 DOI: 10.1081/ERC-100107178]

214 **Xia HH**, Talley NJ, Kam EP, Young LJ, Hammer J, Horowitz M. Helicobacter pylori infection is not associated with diabetes mellitus, nor with upper gastrointestinal symptoms in diabetes mellitus. *Am J Gastroenterol* 2001; **96**: 1039-1046 [PMID: 11316144 DOI: 10.1111/j.1572-0241.2001.03604.x]

215 **Anastasios R**, Goritsas C, Papamihail C, Trigidou R, Garzonis P, Ferti A. Helicobacter pylori infection in diabetic patients: prevalence and endoscopic findings. *Eur J Intern Med* 2002; **13**: 376 [PMID: 12225782 DOI: 10.1016/S0953-6205(02)00094-8]

216 **Oluyemi A**, Anomneze E, Smith S, Fasanmade O. Prevalence of a marker of active helicobacter pylori infection among patients with type 2 diabetes mellitus in Lagos, Nigeria. *BMC Res Notes* 2012; **5**: 284 [PMID: 22686510 DOI: 10.1186/1756-0500-5-284]

217 **Jeon CY**, Haan MN, Cheng C, Clayton ER, Mayeda ER, Miller JW, Aiello AE. Helicobacter pylori infection is associated with an increased rate of diabetes. *Diabetes Care* 2012; **35**: 520-525 [PMID: 22279028 DOI: 10.2337/dc11-1043]

218 **Begue RE**, Mirza A, Compton T, Gomez R, Vargas A. Helicobacter pylori infection and insulin requirement among children with type 1 diabetes mellitus. *Pediatrics* 1999; **103**: e83 [PMID: 10353980 DOI: 10.1542/peds.103.6.e83]

219 **Bégué RE**, Gómez R, Compton T, Vargas A. Effect of Helicobacter pylori eradication in the glycemia of children with type 1 diabetes: a preliminary study. *South Med J* 2002; **95**: 842-845 [PMID: 12190218 DOI: 10.1097/00007611-200295080-00012]

220 **Vazeou A**, Papadopoulou A, Booth IW, Bartsocas CS. Prevalence of gastrointestinal symptoms in children and adolescents with type 1 diabetes. *Diabetes Care* 2001; **24**: 962-964 [PMID: 11347770 DOI: 10.2337/diacare.24.5.962]

221 **Candelli M**, Rigante D, Marietti G, Nista EC, Crea F, Bartolozzi F, Schiavino A, Pignataro G, Silveri NG, Gasbarrini G, Gasbarrini A. Helicobacter pylori, gastrointestinal symptoms, and metabolic control in young type 1 diabetes mellitus patients. *Pediatrics* 2003; **111**: 800-803 [PMID: 12671115 DOI: 10.1542/peds]

222 **Barrio R**, Roldán MB, Alonso M, Cantón R, Camarero C. Helicobacter pylori infection with parietal cell antibodies in children and adolescents with insulin dependent diabetes mellitus. *J Pediatr Endocrinol Metab* 1997; **10**: 511-516 [PMID: 9401908 DOI: 10.1515/JPEM.1997.10.5.511]

223 **Candelli M**, Rigante D, Marietti G, Nista EC, Crea F, Schiavino A, Cammarota G, Pignataro G, Petrucci S, Gasbarrini G, Gasbarrini A. Helicobacter pylori eradication rate and glycemic control in young patients with type 1 diabetes. *J Pediatr Gastroenterol Nutr* 2004; **38**: 422-425 [PMID: 15085021 DOI: 10.1097/00005176-200404000-00010]

224 **Chen Y**, Blaser MJ. Association between gastric Helicobacter pylori colonization and glycated hemoglobin levels. *J Infect Dis* 2012; **205**: 1195-1202 [PMID: 22427676 DOI: 10.1093/infdis/jis106]

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**Table 1 Association between *Helicobacter pylori* and iron stores in children: clinical and intervention studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study and study design | Study population | *H. pylori*  detection | Intervention | Outcome:  evaluation | Outcome:  results |
| Choe *et al* 1999[18],  South Korea;  Randomized double-blind, placebo-controlled trial | 22 children with IDA  and *H. pylori* infection | EGDS | Group A (*n* =8):  2-wk triple eradication therapy and  10-wk oral ferrous sulfate;  Group B (*n* =5):  2-wk triple eradication therapy and  10-wk placebo iron;  Group C (*n* =7):  2-wk placebo eradication therapy and  10-wk oral ferrous sulfate | Follow-up of 18 children  (group A, *n =* 6; group B, *n =* 5;  group C, n =7):  changes in iron, Hb, SF, TIBC at  4 and 8 wks after the end of eradication therapy | At 8 wk, Hb significantly increased in all groups. No significant changes in iron, TIBC and SF occurred in any group |
| Choe *et al* 2000[56],  South Korea;  Open therapeutic trial | 13 adolescents with sideropenic refractory  anemia and *H. pylori*  antral gastritis | EGDS | All 13 children received 2-wk triple eradication therapy and  6-wk oral ferrous sulfate | Follow-up of 11 adolescents:  changes in Hb and SF 4 wk after  the end of eradication therapy | At 4 wk Hb and SF significantly increased |
| Choe *et al* 2001[17],  South Korea;  Open therapeutic trial | 21 adolescent athletes  with IDA and *H. pylori* infection | EGDS | 12 received 2-wk triple eradication therapy;  9 received 10-wk oral ferrous sulfate | Follow-up of 21 adolescents:  changes in iron, Hb, SF, TIBC 10  wk after the start of either therapy | Hb, iron, SF increased significantly only in the athletes who received eradication therapy |
| Kurekci *et al* 2005[62],  Turkey;  Clinical trial | 140 *H. pylori*-infected  children | SAT,14C UBT | All 140 children (18 with IDA,  36 with ID, 86 controls) received  2-wk triple eradication therapy | Follow-up of 140 children :  changes in Hb,SF, and MCV 4 wk after completion of eradication therapy | SF significantly increased in all groups; Hb and MCV values significantly increased only in IDA group |
| Mahalanabis *et al* 2005[63],  India;  Randomized double-blind, placebo-controlled trial | 169 asymptomatic  children:  85 *H. pylori –*positive,  84 *H. pylori* -negative | 13C UBT | 86 (42 *H. pylori*-positive, 44 *H. pylori*–negative) received 8-wk ferrous fumarate;  83 (43 *H. pylori*-positive, 40 *H. pylori*–negative) received 8-wk placebo | Follow-up of 84 iron supplemented (42 *H. pylori* -positive and 42–negative) and 83 placebo children  (43 *H.* *pylori*-positive and 40 –negative):  changes in Hb, Ht, and SF after 8 wk of iron supplementation or placebo | In iron-supplemented group, SF improved in both *H. pylori-*positive and –negative children, while Hb and Ht significantly increased only in those *H.pylori*-negative;  In the placebo group, no significant changes in Hb, Ht, and SF occurred regardless of *H. pylori* status |
| Gessner *et al* 2006[67],  Alaska;  Randomized controlled household open trial | 219 children with ID  and *H. pylori* infection | 13C UBT | 106 (intervention group) received 2-wk triple eradication therapy and  6-wk iron sulfate;  113 (control group) received 6-wk iron sulfate | In intervention group, 104, 94 and 94 children were, respectively, assessed 2, 8 and 14 months after treatment initiation for ID and anemia;  In control group, 110, 109 and 107 children were, respectively, assessed 2,8 and 14 months after completion of iron supplementation for ID and anemia | At 14 months, 65% and 72% of children in the intervention and control groups had, respectively, ID [AAR, 0.90 (95% CI,0.74-1.1)]; and 22% and 14% of children in the intervention and control groups had, respectively, anemia [AAR, 1.6 (95% CI, 0.86-2.9)].  Results were similar when children were compared by *H. pylori* infection status |
| Sarker *et al* 2008[66],  Bangladesh;  Randomized double-blind, placebo controlled trial | 200 asymptomatic  children with *H. pylori*  infection andIDA (*n =* 141) or ID (*n =* 59);  60 uninfected children  with IDA (*n =* 49) or ID (*n =* 11) | 13C UBT | Regimen 1 (*n =* 50):  2-wk triple eradication therapy and  90-day ferrous sulfate;  Regimen 2 (*n =* 50):  2-wk triple eradication therapy and  90-day placebo iron;  Regimen 3 (*n =* 49):  2-wk placebo eradication therapy and  90-day ferrous sulfate;  Regimen 4 (*n =* 51):  2-wk placebo eradication therapy and  90-day placebo iron;  Uninfected controls : 90-day iron therapy alone | Follow-up of 190 infected  (regimen 1, *n =* 47; regimen 2, *n =* 49; regimen 3, *n =* 45; regimen 4, *n =* 49) and 55 uninfected children:  changes in Hb, SF and sTfR 3 months after the initiation of therapy | Improvements in Hb, SF and sTfR were significantly greater in children who received iron therapy (regimens 1 and 3; negative control group) compared with the 2 other groups who did not receive iron (regimens 2 and 4);  No differences in Hb, SF and sTfR values between children who remained positive and those who eradicated *H. pylori* |
| Fagan *et al* 2009[68],  Alaska;  Randomized controlled household open trial | 219 children with ID  and *H. pylori* infection | 13C UBT | 106 (intervention group) received 2-wk triple eradication therapy and 6-wk iron sulfate;  113 (control group) received 6-wk iron sulfate | In intervention group, 104, 94, 94 and 85 children were, respectively, assessed 2, 8,14 and 40 months after treatment initiation for ID and anemia;  In control group, 110, 109,107 and 91 children were, respectively, assessed 2, 8 ,14 and 40 months after completion of iron supplementation for ID and anemia | Control and intervention groups had similar temporal trends regarding ID,anemia, and IDA.  When groups were compared according to *H. pylori* infection status at 40 months, children without *H. pylori* demonstrated better resolution of outcomes. |
| Duque *et al* 2010[65],  Mexico;  Randomized placebo- controlled trial | 69 children with ID/anemia:  33 H. pylori-infected in whom the organismwas eradicated;  36 uninfected children | 13C UBT | After completion of eradication,  17 received 12-wk ferrous sulfate,  16 children 12-wk placebo iron;  Uninfected controls : 12-wk ferrous sulfate. | Follow-up of 33 *H. pylori*-infected children in whom the organism was eradicated, and 36 uninfected children:  changes in Hb and SF after completion of the 12- wk regimen | Compared to uninfected iron-supplemented controls, only children who eradicated *H. pylori and* received iron supplementation showed an increased Hb concentration.  A significant SF increase occurred only in uninfected iron-supplemented controls compared to placebo group |
| Cardenas *et al* 2011[44],  Texas- United States;  Randomized double-blind, placebo-controlled trial | 110 asymptomatic  children with  *H. pylori*-infection | IgG antibodies,  13C UBT | 32 received both quadruple sequential therapy and 6-wk iron supplementation;  29 quadruple eradication only;  23 iron supplementation only;  26 placebo only | Intent-to-treat (*n =* 110) and per protocol (*n =* 90) analyses:  changes in Hb,SF, and TrS at 8 months from baseline | Intent-to-treat and per-protocol analyses revealed no differences across study arms in changes of iron stores. However, children who eradicated the infection had a statistically significant larger increase in SF than children who remained infected. |
| Xia *et al* 2012[64],  China;  Randomized double-blind, controlled trial | 80 adolescents  with IDA and *H. pylori* infection | IgG antibodies,  SAT | 37 (intervention group) received 2-wk triple eradication therapy and 12-wk iron supplementation;  43 (control group) received 12-wk iron supplementation alone | Follow-up of 74 children:  changes in Hb, SF, and sTfR 3 months after completion of the 12-wk regimen | Hb and SF values were increased only in the intervention group. sTfR was significantly decreased in both the intervention and control groups |

*H. pylori*: *Helicobacter pylori* IDA: Iron deficiency anemia; EGDS: Esophagogastroduodenoscopy; Hb: Hemoglobin; TIBC: Total iron-binding capacity; SF: Serum ferritin; SAT: Stool antigen test; UBT: Urea breath test; ID: Iron deficiency; MCV: Erythrocyte mean corpuscular volume; Ht: Hematocrit; ARR: Adjusted relative risk; sTfR: Serum transferrin receptor; TrS: Transferrin saturation.

**Table 2 Baseline clinical features of children with chronic idiopathic thrombocytopenic purpura**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | No. of patients | Male/  female | Disease  duration | Concomitant  therapy 1 | Diagnosis of *H. pylo****ri*** infection | No. of  infected  children | No. of  infected  untreated  children | Age of  infected  children, (yr ) |  | Age of uninfected  children, yr | PLT count  (x 109/L)  among treated *H. pylori* - positive/No. of children | PLT count  (x 109/L)  among *H. pylori* -negative/  No. of children | PLT count  (x 109/L)  among untreated  *H. pylori* -positive/  No. of children |
| Jaing *et al*  2003[95],  Taiwan | 22 | 13/9 | 29  ± 26 mo | 13/22 | Stool  antigen | 9 | 0 | 5.0  (1-13.5) |  | 8.7  (1.8-17.3) | < 50/9 | 50 -99/3  < 50/10 | - |
| Rajantie *et al*  2003[96],  Finland | 17 | 7/10 | 3.9  (0.6-14.5) yr | NR | *H. pylori* antibodies  and/or  13C UBT | 0 | 0 |  | 3.82  (0.3-14.3) |  | - | - | - |
| Hayashi *et al*  2005[97],  Japan | 10 | 6/4 | 4.2  ± 3.2 yr | NR | Stool antigen  and/or  13C UBT | 2 | 1 | 9.0  (7-11) |  | 9.0  (4-14) | 50 - 99/1 | 50 - 99/4  < 50/4 | < 50/1 |
| Yetgin *et al*  2005[98],  Turkey | 35 | NR | ≥ 2 yr | NR | *H. pylori* antibodies  and/or  histology/  13C UBT | 11 | 0 | NR | NR | NR | < 50/11 | < 50/24 | - |
| Loffredo *et al*  2007[99],  Italy | 39 | 13/26 | >6 mo | - | *H. pylori* antibodies,  13C UBT,  or stool antigen | 8 | 0 |  | 11 2  (4.4-17) |  | < 100/8 | < 100/31 | - |
| Neefjes *et al*  2007[100],  Netherlands | 47 | 18/29 | >1 yr | - | Stool antigen | 3 | 0 |  | ≤ 16 2 |  | < 100/3 | < 100/44 | - |
| Wu *et al*  2007[101],  Taiwan | 32 | 18/14 | NR | 32/32 | Stool antigen | 6 | 6 | 5.13  (1.9-9.8) |  | 4.1c  (0.2-13.5) | - | 8.8 ± 11.3 | 5.5 ± 4.7 |
| Bisogno *et al*  2008[102],  Italy | 24 | 9/15 | 1.2  (0.6-24) yr | - | Stool antigen,  13C UBT | 8 | 0 | 13.2  (4.6-25.1) | 12.5 2  (2-25.1) | 10.8  (2-16.5) | < 50/8 | 50 - 99/3  < 50/13 | - |
| Hamidiek *et al*  2008[103],  Iran | 31 | 14/17 | 2.3  ± 1.7 yr | NR | 13C UBT | 4 | 0 |  | 8.9 2,3  (3.5-14) |  | < 150 | < 150 | - |
| Treepongkaruna  *et al* 2009[104],  Thailand | 16 | 7/9 | 1.2-  9.5 yr | 9/16 | 13C UBT | 164 | 9 | 7.4 -16.5 |  |  | 23.0  (3.0-84.0) | - | 34.0  (3.0-86.0) |
| Ferrara *et al*  2009[105],  Italy | 24 | 14/10 | 1.8  (1.3-2.3) yr | - | Stool antigen | 8 | 0 | 7.5  (6.7-10.2) |  | 7.8  (5.4-10.7) | 29.8 ± 3.8 | 33.5 ± 3.8 | - |
| Russo *et al*  2011[106], Italy | 37 | 12/25 | > 1 yr | - | Stool antigen | 374 | - | 12.3 ± 4.35  13.6 ± 2.96 | - | - | 26.5 ± 22.3°  27.7 ± 22.3°° | - | - |

Results are given as mean plus or minus standard deviation, or as median (range), unless otherwise noted. 1 Concomitant therapy included steroids or other immunosuppressive therapies; 2 Age of all patients ; 3Mean (range); 4 This series included only infected patients ; 5Children with successful eradication; 6Children with unsuccessful eradication. PLT: Platelet; *H. pylori*: *Helicobacter pylori*; NR: Not reported.

**Table 3 Follow-up and platelet response to *Helicobacter pylori* eradication therapy among children with chronic idiopathic thrombocytopenic purpura**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Follow-up** | **Bacterial**  **eradication** | **PLT count (x109/L) among treated**  ***H. pylori* -positive with eradication success** **/No. of children** | **PLT count (x109/L) among treated** ***H. pylori* -positive with eradication failure** **/No. of children** | **PLT count (x109/L) among untreated *H. pylori* -positive/No. of children** | **PLT count (x109/L) among *H. pylori* -negative** **/No. of children** |
| **Jaing *et al***  **2003 [95],**  **Taiwan** | 6 mo | 9/9 | > 150/2  100 -150/2  50 - 99/1  < 50/4 | - | - | 50 - 99/4  < 50/9 |
| **Hayashi *et al***  **2005[97],**  **Japan** | 1 yr | 1/1 | > 150/1 | - | NR | > 100/2  NR/6 |
| **Yetgin *et al***  **2005[98],**  **Turkey** | 1 yr | 9/11 | < 50/9 | < 50/2 | - | NR |
| **Loffredo *et al***  **2007[99],**  **Italy** | 1 yr | 7/8 | NA | NA | - | < 100/31 |
| **Neefjes *et al***  **2007[100],**  **Netherlands** | 6- 9 mo | 3/3 | ≥ 100/3 | - | - | 51 ± 39.6/30 |
| **Wu *et al***  **2007[101],**  **Taiwan** | NR | - | - | - | 88.2 ± 89.5/61 | 64.9 ± 75.8/16**1**  132.7 ± 74.7/9**2** |
| **Bisogno *et al***  **2008[102],**  **Italy** | 6-50 mo | 8/8 | > 150/3  < 50/5 | - | - | > 100/3  50 - 99/8  < 50/5 |
| **Hamidiek *et al***  **2008[103],**  **Iran** | 6-11 mo | 4/4 | 50 - 99/2  < 50/2 | - | - | NR |
| **Treepongkaruna**  ***et al* 2009[104],**  **Thailand** | 6 mo | 7/7 | > 100/1  < 100/6 | - | > 100/1  < 100/7 | - |
| **Ferrara *et al***  **2009[105],**  **Italy** | 1 yr | 8/8 | ≥ 150/6  100 - 149/2 | - | - | 50 - 99/7  < 50/9 |
| **Russo *et al***  **2011[106], Italy** | 1 yr | 33/37 | > 150/7  50 - 149/6  < 50/20 | < 50/4 | - | - |

Results are given as mean plus or minus standard deviation, or as median (range), unless otherwise noted. 1 On therapy with high-dose methylprednisolone; 2On therapy with intravenous immunoglobulin. PLT: Platelet; *H. pylori*: *Helicobacter pylori*; NR: Not reported.