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TOPIC HIGHLIGHT

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

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, 324 00161 Rome, Italy
Claudio Chiesa, Institute of Translational Pharmacology, National Research Council, 100 00133 Rome, Italy
Author contributions: Pacifico L, Osborn JF, Tromba V and Chiesa C designed the study, analyzed the data and wrote the manuscript; Romaggioli S and Bascetta S collected the data; all authors participated in the critical review and in the final approval of the manuscript.
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.

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 concordant 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 transferrin 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 polymorphic 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-1β 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 decrease with age, and might explain the suggested age-dependent association 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 preadolescent 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 course 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 wk 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 wk. At 8 wk 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

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*[18] 1999, 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 wk 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*[56] 2000, 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*[17] 2001, 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*[62] 2005, Turkey; Clinical trial	140 *H. pylori*-infected children	SAT,^{14}C 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*[63] 2005, India; Randomized double-blind, placebo-controlled trial	169 asymptomatic children: 85 *H. pylori* –positive, 84 *H. pylori* -negative	^{13}C 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*[67] 2006, Alaska; Randomized controlled household open trial	219 children with ID and *H. pylori* infection	^{13}C 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 mo after treatment initiation for ID and anemia; In control group, 110, 109 and 107 children were, respectively, assessed 2, 8 and 14 mo after completion of iron supplementation for ID and anemia	At 14 mo, 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*[66] 2008, Bangladesh; Randomized double-blind, placebo controlled trial	200 asymptomatic children with *H. pylori* infection and IDA (n = 141) or ID (n = 59); 60 uninfected children with IDA (n = 49) or ID (n = 11)	^{13}C UBT	Regimen 1 (n = 50): 2-wk triple eradication therapy and 90-d ferrous sulfate; Regimen 2 (n = 50): 2-wk triple eradication therapy and 90-d placebo iron; Regimen 3 (n = 49): 2-wk placebo eradication therapy and 90-d ferrous sulfate; Regimen 4 (n = 51): 2-wk placebo eradication therapy and 90-d placebo iron; Uninfected controls: 90-d 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 mo 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*[68] 2009, Alaska; Randomized controlled household open trial	219 children with ID and *H. pylori* infection	^{13}C 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 mo after treatment initiation for ID and anemia; In control group, 110, 109,107 and 91 children were, respectively, assessed 2, 8 ,14 and 40 mo 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 mo, children without *H. pylori* demonstrated better resolution of outcomes

Duque *et al*[65] 2010, Mexico; Randomized placebo-controlled trial	69 children with ID/anemia: 33 *H. pylori*-infected in whom the organism was eradicated; 36 uninfected children	^{13}C 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*[44] 2011, Texas-United States; Randomized double-blind, placebo-controlled trial	110 asymptomatic children with *H. pylori*-infection	IgG antibodies, ^{13}C 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 mo 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*[64] 2012, 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 mo 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.

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 mo 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 $\geqslant$ 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 d. In addition, *H. pylori* status was assessed again at 90 d by urea breath testing and the analysis of children with successful eradication *vs* 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 mo[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 (RR = 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 re-

acted 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*[87] showed 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). 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 were observed in *H. pylori*-positive patients as compared with controls. Moreover, on a larger population of ITP patients, Veneri *et al*[89] 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).

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. pylori* infection	No. of infected children	No. of infected untreated children	Age of infected children, yr		Age of uninfected children, yr	PLT count (× 10^9/L) among treated *H. pylori*-positive/No. of children	PLT count (× 10^9/L) among *H. pylori*-negative/ No. of children	PLT count (× 10^9/L) among untreated *H. pylori*-positive/No. of children
Jaing *et al*[95] 2003, Taiwan	22	13/9	29 ± 26 mo	13/22	Stool antigen	9	0	5 (1-13.5)		8.7 (1.8-17.3)	< 50/9	50-99/3 < 50/10	-
Rajantie *et al*[96] 2003, Finland	17	7/10	3.9 (0.6-14.5) yr	NR	*H. pylori* antibodies and/ or ^{13}C UBT	0	0		3.8[2] (0.3-14.3)		-	-	-
Hayashi *et al*[97] 2005, Japan	10	6/4	4.2 ± 3.2 yr	NR	Stool antigen and/or ^{13}C UBT	2	1	9 (7-11)		9 (4-14)	50-99/1	50-99/4 < 50/4	< 50/1
Yetgin *et al*[98] 2005, Turkey	35	NR	⩾ 2 yr	NR	*H. pylori* antibodies and/ or histology/ ^{13}C UBT	11	0	NR	NR	NR	< 50/11	< 50/24	-
Loffredo *et al*[99] 2007, Italy	39	13/26	> 6 mo	-	*H. pylori* antibodies, ^{13}C UBT, or stool antigen	8	0		11[2] (4.4-17)		< 100/8	< 100/31	-
Neefjes *et al*[100] 2007, Netherlands	47	18/29	> 1 yr	-	Stool antigen	3	0		⩽ 16[2]		< 100/3	< 100/44	-
Wu *et al*[101] 2007, Taiwan	32	18/14	NR	32/32	Stool antigen	6	6	5.1[3] (1.9-9.8)		4.1[3] (0.2-13.5)	-	8.8 ± 11.3/26	5.5 ± 4.7/6
Bisogno *et al*[102] 2008, Italy	24	9/15	1.2 (0.6-24) yr	-	Stool antigen, ^{13}C 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	-
Hamidieh *et al*[103] 2008, Iran	31	14/17	2.3 ± 1.7 yr	NR	^{13}C UBT	4	0		8.9[2,3] (3.5-14)		100/1 < 50/3	NR	-
Treepongkaruna *et al*[105] 2009, Thailand	16	7/9	1.2-9.5 yr	9/16	^{13}C UBT	16[4]	9	7.4 -16.5			23 (3.0-84.0)/7	-	34 (3.0-86.0)/9
Ferrara *et al* 2009[104], 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 ± 3.8/8	33.5 ± 3.8/16	-
Russo *et al* 2011[106], Italy	37	12/25	> 1 yr	-	Stool antigen	37[4]	-	12.3 ± 4.3[5] 13.6 ± 2.9[6]	-	-	26.5 ± 22.3/33[5] 27.7 ± 22.3/4[6]	-	-

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; [3]Mean (range); [4]This series included only infected patients; [5]Children with successful eradication; [6]Children with unsuccessful eradication. PLT: Platelet; *H. pylori*: *Helicobacter pylori*; NR: Not reported.

In a study from Taiwan, Jaing *et al*[95] 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. 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.*

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 ($\times 10^9$/L) among treated *H. pylori*-positive with eradication success/No. of children	PLT count ($\times 10^9$/L) among treated *H. pylori*-positive with eradication failure/No. of children	PLT count ($\times 10^9$/L) among untreated *H. pylori*-positive/No. of children	PLT count ($\times 10^9$/L) among *H. pylori*-negative/No. of children
Jaing *et al*[95] 2003, Taiwan	6 mo	9/9	> 150/2 100-150/2 50-99/1 < 50/4	-	-	50-99/4 < 50/9
Hayashi *et al*[97] 2005, Japan	1 yr	1/1	> 150/1	-	NR	> 100/2 NR/6
Yetgin *et al*[98] 2005, Turkey	1 yr	9/11	< 50/9	< 50/2	-	NR
Loffredo *et al*[99] 2007, Italy	1 yr	7/8	NA	NA	-	< 100/31
Neefjes *et al*[100] 2007, Netherlands	6-9 mo	3/3	⩾ 100/3	-	-	51 ± 39.6/30
Wu *et al*[101] 2007, Taiwan	NR	-	-	-	88.2 ± 89.5/6[1]	64.9 ± 75.8/16[1] 132.7 ± 74.7/9[2]
Bisogno *et al*[102] 2008, Italy	6-50 mo	8/8	> 150/3 < 50/5	-	-	> 100/3 50-99/8 < 50/5
Hamidieh *et al*[103] 2008, Iran	6-11 mo	4/4	50-99/2 < 50/2	-	-	NR
Treepongkaruna *et al*[105] 2009, Thailand	6 mo	7/7	> 100/1 < 100/6	-	> 100/1 < 100/7	-
Ferrara *et al*[104] 2009, Italy	1 yr	8/8	⩾ 150/6 100-149/2	-	-	50-99/7 < 50/9
Russo *et al*[106] 2011, 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; [2]On therapy with intravenous immunoglobulin. PLT: Platelet; *H. pylori*: *Helicobacter pylori*; NR: Not reported.

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 × 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 × 10^9/L) or a partial response (rise of greater than 50 × 10^9/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-mo 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 ID anemic patients was lower than that in patients who were non-ID 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 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 asthma[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 hyperresponsiveness, 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 HbA_{1c} 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, the 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 be 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 *vs* 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 HbA_{1c} using data from 7417 participants in the National Health and Nutrition Examination Survey (NHANES) Ⅲ (aged ⩾ 18 years) and 6072 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 HbA_{1c} 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 HbA_{1c} 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 even more limited data on the therapeutic approach to *H. pylori* infection in 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 extragastric disorders of *H. pylori* infection, additional studies are needed to examine the strength of the evidence linking these disorders in children to *H. pylori*, and to better understand mechanisms on how *H. pylori* affects them 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.

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