

## Consequences of *Helicobacter pylori* infection in children

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### Abstract

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. If untreated, *H. pylori* infection is lifelong. Although *H. pylori* typically colonizes the human stomach for many decades without adverse consequences, children infected with *H. pylori* can manifest gastrointestinal diseases. Controversy persists regarding testing (and treating) for *H. pylori* infection in children with recurrent abdominal pain, chronic idiopathic thrombocytopenia, and poor growth. There is evidence of the role of *H. pylori* in childhood iron deficiency anemia, but the results are not conclusive. The possibility of an inverse relationship between *H. pylori* and gastroesophageal reflux disease, as well as childhood asthma, remains a controversial question. 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.

### INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is one of the most common chronic bacterial infections world-wide, and it is currently estimated that approximately half of the world's population is infected with the bacterium<sup>[1,2]</sup>. However, the prevalence of *H. pylori* is not homogeneous world-wide<sup>[1,3]</sup>. In western countries, the prevalence of infection has been decreasing during the past few decades<sup>[4-6]</sup>. *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<sup>[1]</sup>.

It is widely accepted that *H. pylori* infection is the main etiological factor for gastritis and peptic ulcer<sup>[3]</sup>. Its eradication is associated with healing of these diseases and significant reduction of ulcer recurrence and rebleeding<sup>[7,8]</sup>. Several studies have demonstrated that inflammation caused by *H. pylori* infection might contribute to the development of adenocarcinoma of the stomach; moreover, it has been involved in the development of low-grade B-cell lymphoma of gastric mucosa-associated lymphoid tissue

type (MALT)<sup>[3,9]</sup>. Recently, a potential role of *H. pylori* infection in other digestive diseases (gastroesophageal reflux disease; GERD) as well as several extra-intestinal pathologies [iron deficiency anemia (IDA), growth retardation, idiopathic thrombocytopenic purpura (ITP), asthma and allergic disorders] has been suggested<sup>[10]</sup>. The postulated role of *H. pylori* in the pathogenesis of extra-intestinal manifestations is based on the facts that: (1) local inflammation has systemic effects; (2) *H. pylori* gastric infection 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<sup>[11]</sup>.

The aim of this report is to provide a critical review of the available literature about digestive and extradigestive manifestations of *H. pylori* infection in children. Pertinent articles have been identified through a MEDLINE search. Studies published in English during the past two decades have been identified and reviewed.

## GASTRITIS AND PEPTIC ULCERS

During childhood, *H. pylori* is associated with predominant antral gastritis, and duodenal ulcers<sup>[12-14]</sup>. Successful eradication of *H. pylori* markedly reduces the rate of recurrence of duodenal ulcers in affected children<sup>[2,15,16]</sup>. Gastric ulcers are much less common in children than they are in adults<sup>[17]</sup>.

A pooled analysis of early reports (1983-1994) has demonstrated that the rate ratio of antral gastritis for children with *H. pylori* infection (compared with uninfected subjects) ranged from 1.9 to 71.0 (median, 4.6)<sup>[17]</sup>. The prevalence of *H. pylori* in children with duodenal ulcer was high (range, 33%-100%; median, 92%) compared with children with gastric ulcer (range, 11%-75%; median, 25%)<sup>[17]</sup>. Thus, there was strong evidence for an association between *H. pylori* infection and antral gastritis and duodenal ulcer in children; there was weak evidence for an association with gastric ulcer. Nevertheless, a subsequent retrospective study (1995-2001) from Japan has confirmed that the prevalence of *H. pylori* was very high in antral (nodular) gastritis and duodenal ulcer (98.5% and 83%, respectively), but it has also demonstrated that *H. pylori* was a definite risk factor for the development of gastric ulcer, although the prevalence of infection did not reach 50%<sup>[18]</sup>. *H. pylori* was significantly linked to duodenal and gastric ulcers in the age group 10-16 years, but not  $\leq 9$  years.

More recently, a decreasing proportion of *H. pylori*-positive peptic ulcers in adults has been observed, along with a decrease in the prevalence rate of the infection<sup>[19]</sup>. In children, there have been few data published in the literature to investigate the trend of *H. pylori* prevalence in peptic ulcer<sup>[20-23]</sup>. In a prospective European multicenter pilot study on the incidence of gastric and duodenal ulcer disease in children, Kalach *et al.*<sup>[20]</sup> have found that ulcers occurred in 10.6% of cases, with *H. pylori* infection in only 26.7% of these. From January 2001 to December 2002, information on 518 children was collected from the pe-

diatric European register for treatment of *H. pylori*<sup>[21]</sup>. At endoscopy, 454 children had *H. pylori*-associated gastritis and 64 had an ulcer (12.3%). However, this series included children from Russia and they had a significantly higher prevalence of peptic ulcer (35% *vs* 6.7% in the remainder of European children,  $P < 0.0001$ ; OR: 7.5; 95% CI: 4-13). Thus the prevalence of *H. pylori*-positive ulcers in children differed between countries, and this was not completely explained by the prevalence of the infection in the population studied<sup>[22]</sup>. In a retrospective review (1998-2006) of 619 Chinese children who had undergone upper endoscopy for investigation of upper gastrointestinal symptoms, Tam *et al.*<sup>[23]</sup> have found that 43 (6.9%) had peptic ulcer. Of these 43 patients, 37 and six had duodenal and gastric ulcer, respectively. The prevalence of *H. pylori* infection was 56.8% (21/37) in duodenal ulcer and 33.3% (2/6) in gastric ulcer. When they arbitrarily divided the study period into two, 1998-2001 and  $> 2002$ , no significant difference in the prevalence of *H. pylori* infection between the two periods was found.

## GASTRIC MALIGNANCIES

In relation to *H. pylori*-associated gastric malignancies in children, there have been a few cases of gastric MALT lymphoma<sup>[14,24,25]</sup>, but there have been no reports of adenocarcinoma.

There is evidence to support an association between long-standing *H. pylori* infection, gastric atrophy, and intestinal metaplasia with the development of intestinal-type and undifferentiated adenocarcinomas in adults<sup>[3]</sup>. It has been suggested that chronic gastritis, gastric atrophy, intestinal metaplasia and gastric cancer develop progressively, stepwise over decades, in predisposed individuals infected by *H. pylori*<sup>[26]</sup>. However, gastric atrophy and intestinal metaplasia have indeed been described in children living in countries with high gastric cancer incidence<sup>[27]</sup>, and they are sometimes found in very young subjects<sup>[28-30]</sup>. These findings provide support to the hypothesis that host genetic factors that affect the inflammatory and immune response to *H. pylori* infection might determine why some individuals infected with this bacterium develop precancerous lesions and gastric carcinoma while others do not<sup>[31,32]</sup>. Thus, it is probable that the prevalence of gastric atrophy and intestinal metaplasia varies according to the geographic/genetic origins as well as environmental factors<sup>[27-30,33-40]</sup>, as shown in Table 1. Yet, sampling problems exist. In fact, the non-systematic search during pediatric gastroscopy for these histological states might mask their true prevalence<sup>[32]</sup>. Most reported studies of the histological features of *H. pylori* infection in children have used either random biopsies<sup>[41]</sup> or a small number of targeted biopsies<sup>[29,34,42,43]</sup>, taken primarily from the antrum<sup>[29,44]</sup>. In most studies, the identification of atrophy has been focused on the presence of intestinal metaplasia or has been ill defined<sup>[29]</sup>.

In clinical practice, the updated Sydney system is widely used for grading gastric histopathological findings (density

Table 1 Prevalence of gastric atrophy in children

Author (yr)/country	Updated Sydney System	Mean age (range, yr)	No. of patients		Gastric atrophy and/or intestinal metaplasia (%)	
			<i>H. pylori</i> +	<i>H. pylori</i> -	<i>H. pylori</i> +	<i>H. pylori</i> -
Whitney <i>et al</i> <sup>[28]</sup> (2000)/USA	Yes	10.7 (1-21)	42	0	Antral: 16.6/0 Fundic: 2.3/0	-/-
Kolho <i>et al</i> <sup>[33]</sup> (2000)/Finland	Not reported	9.5 (2-16)	71	0	0/0	-/-
Campbell <i>et al</i> <sup>[34]</sup> (2001)/Gambia	Yes	1.4 (-/-)	21	16	0/0	0/0
Guiraldes <i>et al</i> <sup>[35]</sup> (2002)/Chile	No	12.2 (5-17)	59	14	0/0	0/0
Oztürk <i>et al</i> <sup>[36]</sup> (2003)/Turkey	Yes	12.2 (6-16)	18	9	Antral: 72.2/77.7	11.1/0
Guarner <i>et al</i> <sup>[29]</sup> (2003)/USA	Yes	- (1-17)	19	45	Antral: 52.6/15.7 Fundic: 0/5.2	22.2/0 0/0
Usta <i>et al</i> <sup>[37]</sup> (2004)/Turkey	Yes	11.8 (4-17)	175	0	2.2/1.1	-/-
Levine <i>et al</i> <sup>[38]</sup> (2004)/Israel	Not reported	14.2 (-/-)	55	40	0/0	2.5/0
Ricuarte <i>et al</i> <sup>[27]</sup> (2005)/Colombia, Korea	No	12.0 (4-18)	97	18	16.4	1
		14.0 (8-18)	10	48	0	0
Kato <i>et al</i> <sup>[39]</sup> (2006)/Japan	Yes	11.3 (1-16)	131	65	Antral: 51.9/4.6 Fundic: 34.8/0	10.8/4.6 8.3/4.2
Tutar <i>et al</i> <sup>[30]</sup> (2009)/Turkey	Yes	1.3 (0.1-2.0)	40	112	2.5/0	0/0
Kalach <i>et al</i> <sup>[40]</sup> (2009)/France	Yes	5.3 (0.1-17.7)	66	553	0/0	0.2/0.2

<sup>1</sup>Atrophic mucosa: 31% as intestinal metaplasia; 63% as pseudopyloric metaplasia; 6% as both. *H. pylori*: *Helicobacter pylori*.

of *H. pylori* organisms, acute and chronic inflammation, atrophy and intestinal metaplasia)<sup>[45]</sup>. Although this system has been validated in adult patients, interobserver variability is still a problem, primarily in the evaluation of mucosal atrophy<sup>[46,47]</sup>. Thus, further validation of atrophy parameters needs to be obtained for pediatric biopsy samples<sup>[29]</sup>. In contrast, metaplastic epithelium is easily detected by the pathologist, owing to the characteristic goblet cells<sup>[32]</sup>.

In adults, five gastric biopsy samples are recommended (two antral, two corporeal and one from the angulus)<sup>[45]</sup>, but no consensus is available about the optimal number and site location of gastric biopsies in children. Clinical practices in this domain are very heterogeneous, which could in part account for the different prevalence figures of atrophic gastritis in children<sup>[32]</sup>. Of note, in a study of 173 children from countries with high gastric cancer incidence, Ricuarte *et al*<sup>[27]</sup> emphasized the importance of biopsy site location for identifying the presence of corpus atrophy. In children, atrophy is only identified in biopsies taken near the normal antrum-corporum junction, which is consistent with the notion that atrophy progresses as an advancing antrum-corporum border<sup>[27]</sup>. Therefore, identification and characterization of the natural history of *H. pylori* gastritis requires, in addition to biopsies that target the antrum and the cardia, targeted biopsies to include the lesser and greater curvature of the corpus, starting just proximal to the anatomical junction of the antrum and corpus. Unfortunately, the sites recommended by the updated Sydney system can identify corpus atrophy only when it is extensive.

Studies from the 1990s have established that the development of low-grade gastric MALT lymphoma is strongly associated with chronic *H. pylori* gastritis. In two large series of adult patients, *H. pylori* was detected by histological examination in 92% and 100% of those with gastric MALT lymphoma<sup>[48,49]</sup>. Recognition of the responsiveness of MALT lymphoma to antibiotic therapy aimed at eradication of *H. pylori* has changed the approach to its manage-

ment. Remission rates in the literature range from 60% to 80%, although recurrence can be expected in 5% of cases<sup>[50-53]</sup>. MALT lymphoma occurs commonly in middle and old age; only a small number of cases have been reported in both immunocompetent and immunocompromised children<sup>[14,24,25]</sup>. Individual case reports have described the regression of MALT lymphoma after *H. pylori* eradication therapy alone<sup>[24,25]</sup>.

## FUNCTIONAL DYSPEPSIA

The role of *H. pylori* infection as a cause of non-ulcer or functional dyspepsia has been one of the most debated controversies in the medical community since the discovery of this bacterium.

Dyspepsia is very common in children with chronic or recurrent abdominal pain (RAP), with as many as 80% reporting this symptom<sup>[54]</sup>. The relation between RAP in childhood and *H. pylori* infection is not clear<sup>[17]</sup>. Pediatric studies are limited by the lack of a clear definition for RAP or by the use of nonspecific criteria for the diagnosis of chronic abdominal pain<sup>[54]</sup>. A pooled analysis of early reports (1983-1994) has demonstrated that prevalence rates of infection in children with RAP were inconsistent (range, 0%-81%; median, 22%), with lower rates (range, 0%-9%; median, 6%), in children who met Apley's criteria (i.e. at least three discrete episodes of abdominal pain of sufficient severity to interrupt normal daily activities or performance occurring over a period of  $\geq 3$  mo)<sup>[17]</sup>.

In adults, several controlled trials have shown a vague connection between *H. pylori* colonization and dyspeptic symptoms<sup>[55]</sup>. In children, controlled randomized treatment studies have been scant. The results of two uncontrolled trials have suggested improvement of clinical symptoms after treatment of *H. pylori* infection<sup>[56,57]</sup>. However, the double-blind, randomized placebo-controlled trial by Ashorn *et al*<sup>[58]</sup> has suggested that RAP is not an indication

for a test and treatment strategy for *H. pylori* infection in children. In fact, in that study, at 52 wk, dyspeptic symptoms improved to the same extent in the treatment group and in children who received placebo, irrespective of the healing of gastritis, which was more commonly achieved along with eradication<sup>[58]</sup>. Nonetheless, due to the limited number of patients who could finally be included, the results by Ashorn *et al.*<sup>[58]</sup> have to be interpreted with care. Large-scale multicenter trials performed in children are still needed to answer definitively the question whether a connection exists between *H. pylori* infection and RAP. Neither did the results of a very recent study give support for the use of *H. pylori* eradication in children with RAP<sup>[59]</sup>. Based on a meta-analysis of 38 studies between 1966 and 2009, the study by Spee *et al.*<sup>[59]</sup> has found no association between RAP (fulfilling Apley's criteria) and *H. pylori* infection in children. However, the authors have demonstrated that children who are referred to a gastroenterologist with unspecified abdominal pain (i.e. including children who do not fulfill Apley's criteria) or pain in the epigastric region are at 2-3-fold higher risk for *H. pylori* infection than children without these symptoms. Thus, these authors have postulated that unspecified abdominal pain in a hospital-based setting and epigastric pain in general might be associated with (acute) *H. pylori* infection. The potential for *H. pylori* to cause clinical symptoms that arise from gastric infection, in the absence of mucosal ulceration, requires additional studies using a strict study group definition. Functional dyspepsia and non-ulcer dyspepsia (i.e. epigastric pain in the absence of mucosal ulceration at esophago-gastro-duodenoscopy) must be evaluated as separate entities.

## GASTROESOPHAGEAL REFLUX DISEASE

The interaction between *H. pylori* infection and GERD has been widely debated in the literature over the past decade, and the hypothesis that eradication of *H. pylori* leads to increased GERD has been the subject of many publications with contradictory conclusions in children as well as in adults<sup>[38,60-76]</sup>. There are limited data in children because the prevalence of *H. pylori* infection is low and no randomized controlled trials have been conducted; therefore, inferences about the effects of *H. pylori* eradication and GERD need to be drawn from studies on adult patients<sup>[77]</sup>.

*H. pylori* has been found to be inversely correlated with the prevalence of GERD, and certain studies have shown aggravation of esophagitis after eradication<sup>[60-66]</sup>. Suggested mechanisms include presence of atrophic or significant body gastritis that leads to a post-eradication increase in acid output; decreased buffering as a result of elimination of *H. pylori*, which produces ammonia *via* bacterial urease; masking of reflux by acid neutralizing medications given for *H. pylori*-related disease; and increased appetite with weight-gain-mediated reflux. These observations are controversial, because several studies have not found an association between eradication of *H. pylori* and reflux disease<sup>[38, 66,70,74,78-80]</sup>.

Most studies aimed at evaluating the effect of *H. pylori* eradication on reflux in adults have used selected populations such as those with duodenal ulcer or patients with GERD before eradication<sup>[63,65,78,80]</sup>. The spectrum of risk factors found in adults, such as atrophic gastritis, duodenal ulcer, or significant esophagitis, might influence the outcome of the study. These factors are less common in children, therefore, these results might not be relevant to the decision to eradicate *H. pylori* when found in children<sup>[38]</sup>.

Dent has proposed that the effect of *H. pylori* eradication on GERD is most likely determined by the population studied<sup>[67]</sup>. Acid secretion in predominant antral gastritis with preserved body mucosa is hyper-responsive, thus enabling increased duodenal or esophageal injury. In these patients, eradication should improve or not affect GERD. This hypothesis is consistent with the results of other studies that have shown improvement in GERD symptoms in patients with duodenal ulcer<sup>[80,81]</sup>. However, in patients with atrophic gastritis or severe body gastritis, *H. pylori* eradication might result in increased acid secretion. Children and adolescents are more likely to behave like the first group, with predominant antral gastritis<sup>[38]</sup>.

The risks and benefits of *H. pylori* eradication are less well-defined for patients with gastritis alone, and vary according to the severity and pattern of gastritis<sup>[67]</sup>. Although this is the patient group most likely to develop reflux esophagitis<sup>[63]</sup>, the risks from this are outweighed by those of continued *H. pylori* infection. Reflux esophagitis following *H. pylori* eradication is believed to carry little risk and, in particular, not to lead to intestinal metaplasia. By contrast, the risks of continued *H. pylori* infection are relatively high in patients who have had an episode of chronic duodenal, gastric or gastroduodenal ulceration<sup>[67]</sup>. What is certain, is that *H. pylori* is a major risk factor for non-cardia gastric adenocarcinoma<sup>[82]</sup>, and children with this infection have at least a fivefold increased risk of developing stomach neoplasia in later life. This risk is likely to be reversed with *H. pylori* eradication<sup>[77]</sup>. In a study of high-risk adults, no reduction in gastric cancer risk at the end of 7.5 years of follow-up was observed in *H. pylori* carriers who had previously undergone eradication therapy<sup>[83]</sup>. However, in a subgroup analysis of patients who had no precancerous lesions at baseline, cancer risk was significantly reduced<sup>[83]</sup>. Additional studies have suggested that prevention of gastric cancer might be possible in infected individuals without precancerous lesions<sup>[84,85]</sup>. Therefore, children could well be the group to target in an effort to prevent the future development of gastric cancer.

## IRON DEFICIENCY ANEMIA

In addition to the already known causes of IDA, over the past two decades, an association between *H. pylori* and pediatric IDA has been established<sup>[86-92]</sup>. However, the issues of whether *H. pylori* infection is linked causally to IDA in children and whether treatment or resolution of *H. pylori* infection would improve iron stores or resolve IDA in children are still matters of great debate. In 1991,

**Table 2** Randomized trials of *Helicobacter pylori* eradication for iron deficiency anemia and iron deficiency in children

Author (yr)/country	No. of children with IDA/ <i>H. pylori</i>	Follow-up (No. of children)	Outcome	
			IDA	ID
Choe <i>et al</i> <sup>[89]</sup> (1999)/Korea	43/25	8 wk (18)	Hb increased with: eradication + iron, eradication + placebo <i>vs</i> iron + placebo ( <i>P</i> = 0.0086)	No significant differences in serum iron or ferritin
Sarker <i>et al</i> <sup>[106]</sup> (2008)/Bangladesh	260/200	3 mo (260)	IDA persisted with: eradication + iron, 11%; eradication alone, 33%; iron alone, 0%; placebo, 45%	ID persisted with: eradication + iron, 19%; eradication alone, 65%; iron alone, 7%; placebo, 78%
Gessner <i>et al</i> <sup>[105]</sup> (2006)/Alaska	219/219	14 mo (201)	IDA persisted with: eradication + iron, 22%; iron alone, 14%	ID persisted with: eradication + iron, 65%; iron alone, 72%
Fagan <i>et al</i> <sup>[104]</sup> (2009)/Alaska	219/219	40 mo (176)	IDA persisted with: eradication + iron, 5%; iron alone, 19%	ID persisted with: eradication + iron, 52%; iron alone, 58%

Hb: Hemoglobin; ID: Iron deficiency; IDA: Iron deficiency anemia; *H. pylori*: *Helicobacter pylori*.

an association between *H. pylori* infection and IDA due to microscopic blood loss was described in a 15-year-old girl with *H. pylori*-positive chronic active hemorrhagic gastritis, who showed no signs of gastrointestinal symptoms<sup>[88]</sup>. Two years later, Dufour *et al*<sup>[93]</sup> reported a 7-year-old child who presented with *H. pylori*-associated chronic antral gastritis without evidence of hemorrhage or clinical symptoms other than sideropenic anemia, which was refractory to oral iron administration and subsided after *H. pylori* eradication. These case reports were followed by other studies that have identified an association between *H. pylori* infection and pediatric unexplained or refractory IDA, and have indicated improvement of iron stores and anemia after successful *H. pylori* eradication<sup>[94-100]</sup>. Yet, some pediatric studies have implicated *H. pylori* as a cause of IDA that is refractory to oral iron treatment<sup>[94,95,99,100]</sup>. Thus, the above studies have supported a clinically significant influence of *H. pylori* infection on body iron stores and have led to a recommendation for *H. pylori* eradication in infected individuals with unexplained IDA<sup>[101-103]</sup>. However, small sample sizes, lack of control groups, and other methodological issues, including the use of validated measures of active *H. pylori* infection such as biopsy-related tests to confirm *H. pylori* infection, are among factors that have limited the interpretation and ability to generalize the importance of the results of these studies in children.

To the best of our knowledge, only four population-based randomized trials of the effect of *H. pylori* infection treatment on IDA have been performed in children<sup>[89,104-106]</sup>, as shown in Table 2. Three of them lacked true placebo groups<sup>[89,104,105]</sup>. Choe *et al*<sup>[89]</sup> have demonstrated a beneficial effect of *H. pylori* eradication therapy plus iron or placebo in increasing hemoglobin levels. However, no significant differences among study groups were found at 8 wk follow-up for serum iron level, total iron-binding capacity, and ferritin level. Sarker *et al*<sup>[106]</sup> have shown, in a relatively large cohort of Bangladeshi children with IDA, a similar improvement of IDA as well as iron deficiency, with anti-*H. pylori* therapy plus iron compared with iron therapy alone. Therefore, the improvement of iron status in children who receive combined therapy could be attributed to the effect of iron rather than anti-*H. pylori* therapy.

The findings from the Bangladeshi children corroborated well those of the study from rural Alaska, which showed that treatment and resolution of *H. pylori* infection did not substantially decrease levels of iron deficiency or mild anemia at 14 mo after treatment initiation, despite the relatively low rate of reinfection once the initial infection resolved<sup>[105]</sup>. When an additional follow-up evaluation at 40 mo after treatment initiation was performed, it was found that sustained resolution of *H. pylori* infection substantially reduced the prevalence of mild IDA but modestly improved iron status<sup>[104]</sup>.

How can *H. pylori* gastritis cause IDA? Several theoretical mechanisms have been proposed to explain the possible relationship between *H. pylori* infection and decreased iron stores. It appears that chronic gastrointestinal blood loss is not the likely culprit, because most published cases and case series have found no bleeding lesions at the time of endoscopy, and have reported negative testing for fecal occult blood<sup>[107]</sup>. 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. Non-heme iron accounts for 80% of dietary iron in industrialized countries<sup>[107]</sup>. Crucial to the effective 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<sup>[108]</sup>. 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<sup>[107,109]</sup>. Gastric acid hyposecretion results from atrophy of the gastric glands and fundic mucosa, which has been associated with chronic *H. pylori* infection<sup>[107]</sup>. It has been shown that adult patients with IDA and *H. pylori* infection are more likely to have a pattern of gastritis that involves the gastric corpus, with related decreases in gastric acid secretion and increases in intragastric pH that might impair iron absorption<sup>[110]</sup>. There are no comparable data in children.

Another hypothesized mechanism is that *H. pylori* might lead to IDA by sequestering and utilizing iron, thus

Table 3 Cross-sectional studies on the association between *Helicobacter pylori* infection and growth retardation

Author (yr)/country	Total No. of patients ( <i>H. pylori</i> +)	Age (range, yr)	Diagnostic test	Conclusion
Perri <i>et al</i> <sup>[114]</sup> (1997)/Italy	216 (49)	3-14	Urea breath test	<i>H. pylori</i> infection was associated with growth delay, and poor socioeconomic status
Oderda <i>et al</i> <sup>[115]</sup> (1998)/Italy	134 with short stature (27)	5-13	Serology	No association with short stature
	134 controls (18)	5-13		
Quiñonez <i>et al</i> <sup>[116]</sup> (1999)/Guatemala	211 (107)	5-10	Serology	No association with height for age and nutritional status
Choe <i>et al</i> <sup>[90]</sup> (2000)/Korea	375 (63)	10-15	Serology	<i>H. pylori</i> infection accompanied by IDA, rather than <i>H. pylori</i> infection <i>per se</i> , was associated with delayed pubertal growth
Richter <i>et al</i> <sup>[117]</sup> (2001)/Germany	3315 (213)	5-7	Urea breath test	<i>H. pylori</i> infection was associated with growth delay
Ertem <i>et al</i> <sup>[118]</sup> (2002)/Turkey	327 (162)	3-12	Urea breath test	<i>H. pylori</i> infection was associated with short stature independently of poor living standards
Sood <i>et al</i> <sup>[119]</sup> (2005)/UK	257 (97)	-	Urea breath test	No association with height and weight z scores, after adjustment for socioeconomic status and ethnicity
Süoglu <i>et al</i> <sup>[120]</sup> (2007)/Turkey	70 (35)	4-16	Endoscopy	<i>H. pylori</i> infection and IDA had a significant effect on height z scores, after adjustment for economic status
Mohammad <i>et al</i> <sup>[121]</sup> (2008)/Egypt	286 (208)	6-15	Urea breath test	<i>H. pylori</i> infection affected both body weight and height
Soylu <i>et al</i> <sup>[122]</sup> (2008)/Turkey	108 with dyspepsia (57)	7-17	Endoscopy	No association with anthropometry. But, dyspeptic children had worse nutritional status compared to controls, regardless of <i>H. pylori</i> status
	50 healthy controls	8-17		
Cherian <i>et al</i> <sup>[123]</sup> (2009)/Australia	182 (149)	< 16	Stool antigen	No association with BMI or other anthropometric measures
Gulcan <i>et al</i> <sup>[124]</sup> (2010)/Turkey	181 with RAP (121)	6-15	Endoscopy, 181	RAP associated with gastric mucosal injury had a negative effect on BMI independent of <i>H. pylori</i> infection
	309 asymptomatic (110)	6-15	Serology, 309	RAP originating from <i>H. pylori</i> infection affected both BMI and linear growth

BMI: Body mass index; RAP: Recurrent abdominal pain; IDA: Iron deficiency anemia; *H. pylori*: *Helicobacter pylori*.

competing with the human host<sup>[107]</sup>. Ferrokinetic studies have suggested the diversion of iron to some extramedullary focus, hypothesized but not proven to be *H. pylori*-associated gastric infection<sup>[95]</sup>. 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<sup>[111]</sup>. Another possible mechanism for IDA in *H. pylori*-infected subjects involves sequestration of iron in lactoferrin in the gastric mucosa, and uptake of iron by *H. pylori*. Lactoferrin is an iron-binding glycoprotein that is found in body fluids, and its secretion in the gastric mucosa seems to be influenced by some signal from *H. pylori*<sup>[112]</sup>. It appears that *H. pylori* then absorbs the iron from lactoferrin *via* a specific lactoferrin-binding protein that is expressed by *H. pylori*<sup>[107]</sup>. Lactoferrin levels in the gastric mucosa have been shown to be significantly higher in *H. pylori*-positive patients with IDA compared to those who are non-anemic *H. pylori*-negative, non-anemic *H. pylori*-positive, and *H. pylori*-negative with IDA<sup>[112]</sup>.

We conclude that future work in this area is needed. Randomized, double-blind, and placebo-controlled trials of sufficient size and power should evaluate the long-term effect of *H. pylori* eradication in children with IDA, who are living in developing as well as in developed countries. Additionally, these studies should evaluate the effect of *H. pylori* treatment among different pediatric populations, such as those with and without concurrent gastrointestinal symptoms, and those with a wide spectrum of IDA severity.

Based on our present knowledge, children with a first episode of IDA and no complications should be initially treated with iron supplementation alone, irrespective of *H. pylori* status<sup>[2]</sup>. Eradication of *H. pylori* could be considered in cases that are refractory to iron supplementation and in the case of frequent relapses, assuming that other causes, such as celiac disease and inflammatory bowel disease, have been excluded<sup>[2,102]</sup>. Of particular interest is the work by Memeo *et al*<sup>[113]</sup> who have shown the frequent occurrence of duodenal intraepithelial lymphocyte expansion in individuals with *H. pylori* gastritis, and the considerable overlap of the intraepithelial lymphocyte counts as well as the distribution patterns with those described for celiac disease and other small bowel diseases.

## GROWTH RETARDATION

The available evidence regarding *H. pylori* infection and its effect on growth in children is controversial. There have been many cross-sectional studies that point to either the presence or absence of such an association<sup>[90,114-124]</sup>, as shown in Table 3.

The Italian cross-sectional study by Perri *et al*<sup>[114]</sup> suggests that *H. pylori* infection (as diagnosed by urea breath test) is associated with growth delay in older children, poor socioeconomic conditions, and household overcrowding. The findings by Perri *et al*<sup>[114]</sup> are consistent with the hypothesis that *H. pylori* infection is one of the environmental factors capable of affecting growth. The cross-section-

al study by Richter *et al*<sup>[117]</sup> of a large number of 5-7-year-old preschool and school children suggests that *H. pylori* infection (as diagnosed by urea breath test) is associated in German children with growth delay, growth retardation, or both, despite similar socioeconomic status between *H. pylori*-positive and -negative children. Likewise, Ertem *et al*<sup>[118]</sup> also have suggested that *H. pylori* is associated with short stature through mechanisms that are independent of poor living conditions.

Other investigators have suggested that growth suppression reported in children with *H. pylori* infection could be due to socioeconomic, genetic and environmental factors. In their retrospective chart review of the growth parameters of children with dyspepsia referred to the Regional Paediatric Gastroenterology unit in Manchester, United Kingdom, Sood *et al*<sup>[119]</sup> found that children with dyspepsia and *H. pylori* infection (as diagnosed by urea breath test) were shorter and lighter than patients with similar symptoms but no infection. Sood *et al*<sup>[119]</sup> concluded that the differences in anthropometry might have been due to socioeconomic and ethnic factors rather than *H. pylori* infection. Yet, in a cross-sectional study of Turkish dyspeptic children who were evaluated by endoscopic gastric biopsy for *H. pylori* infection, as well as a control group of age and sex cross-matched children, Soyulu and Ozturk found that dyspeptic children with and without *H. pylori* infection had worse nutritional status compared to healthy controls<sup>[122]</sup>. The authors concluded that *H. pylori* infection as a major cause of dyspepsia might be considered to cause malnutrition secondary to decreased caloric intake associated with dyspepsia<sup>[122]</sup>.

In a case-control study of children aged 5-13 years whose height was below the third centile, matched with children of the same age and sex whose height was above the 25th centile, Oderda *et al*<sup>[115]</sup> found that *H. pylori* (diagnosed by serologic methods) was not a risk factor for short stature, and that reduced growth was related to genetic determinants such as parental height and to mixed genetic and environmental factors such as birth weight. Low socioeconomic status was also relevant<sup>[115]</sup>. In a cross-sectional study of children aged 5-10 years who were attending an all-girl public school in inner Guatemala City, Quiñonez *et al*<sup>[116]</sup> investigated the effect of *H. pylori* infection (diagnosed by serologic methods) on the anthropometric nutritional parameters (weight-for-height and height-for-age). After controlling for sociodemographic variables, the authors did not find significant differences in the nutritional parameters between infected and uninfected children. In another cross-sectional study of Turkish children aged 4-16 years who underwent upper gastrointestinal endoscopy for RAP and dyspeptic complaints, Süoglu *et al*<sup>[120]</sup> found that the effect of *H. pylori* infection on mean SD scores of height for age was statistically insignificant after correction for breast feeding, IDA and socioeconomic level. In contrast, even after controlling for socioeconomic level, *H. pylori* infection remained the single and most important variable that had an effect on mean weight SD score. Among *H. pylori*-positive as well

as -negative children<sup>[120]</sup>, IDA had no significant effect on anthropometric measurements *per se*. However, when *H. pylori* and IDA were present, mean weight was found to be significantly lower than that of the *H. pylori*-negative patients without IDA<sup>[120]</sup>.

There are also longitudinal studies that support the hypothesis that *H. pylori* infection might influence growth rate in children. Thomas *et al*<sup>[125]</sup> conducted two consecutive prospective, longitudinal cohort studies in Gambia, and found that, in both cohorts, children with early *H. pylori* colonization had lower values for both length- and weight-for-age Z scores than their peers in late infancy. No socioeconomic or demographic confounding variables were identified to explain this, and the weight deficit was no longer detectable when the children were aged 5-8 years. The authors concluded that *H. pylori* colonization at critical vulnerable ages might lead to malnutrition and growth retardation among infants in countries such as Gambia<sup>[125]</sup>. In the prospective, longitudinal study by Bravo *et al*<sup>[126]</sup>, 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 authors found significant slowing of growth velocity in children infected with *H. pylori*, independent of socioeconomic variables or overcrowding<sup>[126]</sup>. Likewise, Mera *et al*<sup>[127]</sup> prospectively investigated in Colombian children, in general good health, aged 1-5 years, whether a newly acquired *H. pylori* infection affected height and weight of children within 16 mo, by performing breath tests and anthropometry every 2-4 mo. The authors observed that the impact of a new infection on height growth velocity was more pronounced right after the infection was diagnosed and slowly ebbed, and continued to be significant for up to 6 mo after infection, and became borderline significant at 8 mo after infection. No catch-up growth was evident in infected children, with crowding retarding linear growth. Compared with uninfected children, newly infected children also experienced a significant, but small, decrease in weight at the first follow-up visit, which was not statistically significant at 4 mo after infection. There was no catch-up in weight. The authors concluded that *H. pylori* caused a non-transient negative effect on height and weight in affected children, regardless of age at the time of infection<sup>[127]</sup>.

Taken together, the results of these studies pointing to the presence or absence of an association between *H. pylori* and growth are subject to some potential limitations. First, most studies were cross-sectional or retrospective and therefore were unable to evaluate the possible effect of new infections on growth velocity. Second, the definition of socioeconomic status is complex and no set of parameters was fully descriptive in most studies. Third, some studies used serological methods to determine *H. pylori* infection. However, serology does not indicate whether there is active or past infection. Even in those patients who are treated and cured of their *H. pylori* infection, evidence of IgG antibodies may exist for several months

and possibly for years. Serological assays also have varying levels of sensitivity and specificity when used in different populations, particularly in children<sup>[128]</sup>. Fourth, in community-based studies, for example, in those that involve a blood specimen, participation rate is rarely more than 50%<sup>[116,129]</sup>. This might also be the case for studies that involve gastrointestinal endoscopy. As such, we have no information on the non-participating children in some of the above studies; thus, we cannot estimate if any bias was introduced in the results or the generalizability of their findings to other populations.

We conclude that future work in this area is needed to elucidate the importance of these factors. One would expect growth velocity to improve following *H. pylori* eradication, if the infection were the primary cause of growth suppression.

## IDIOPATHIC THROMBOCYTOPENIC PURPURA

ITP is an autoimmune disease that is characterized by a low circulating platelet count caused by the destruction of antibody-sensitized platelets in the reticuloendothelial system<sup>[130]</sup>. The mechanisms that trigger the production of platelet autoantibodies remain poorly understood. Persistent thrombocytopenia for > 6 mo defines the chronic form of this disorder (cITP)<sup>[130]</sup>. Lately, eradication of *H. pylori* from the gastric mucosa has been associated with an improvement of cITP.

Several studies in adults have reported improved platelet counts in *H. pylori*-positive patients following standard triple *H. pylori* eradication therapy<sup>[131-140]</sup>. A meta-analysis of 13 cohort reports in adult cITP, with combined data from 193 patients, has indicated an overall response rate of 52% of patients after *H. pylori* eradication therapy<sup>[141]</sup>. A recent systematic review of 25 published studies, with combined data from 696 adult patients with cITP, has demonstrated an overall response in platelet count after *H. pylori* eradication in 50.3% of patients (95% CI: 41.6%-59.0%)<sup>[142]</sup>. Cohorts from Japan and Italy<sup>[132,134,138,140]</sup> have reported higher response rates than from other countries<sup>[143,144]</sup>. Several theories, including direct antigen mimicry between *H. pylori* *cagA* and platelet glycoprotein antigens, *H. pylori* binding to von Willebrand factor, and the immunomodulatory effect of antibiotics (e.g. macrolides) used in *H. pylori* eradication, have been proposed to explain the platelet response to anti-*H. pylori* therapy<sup>[139,141]</sup>. It has also been postulated that platelet autoantibodies might be produced by autoreactive clonal B cells that are induced by chronic immunological stimulus by *H. pylori*<sup>[141,145]</sup>. The relative toxicity profiles of triple therapy compared to standard ITP therapy certainly make eradication an attractive and generally safe option in adults. However, large controlled clinical trials of adult patients from various ethnic backgrounds are necessary to determine the response rate and mechanism of platelet response to *H. pylori* eradication therapy<sup>[141]</sup>.

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<sup>[130,146]</sup>. 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 few, apparently contradictory studies with small sample sizes<sup>[147-153]</sup>. Yet, the results of pediatric studies are difficult to compare because the prevalence of *H. pylori* infection and diagnostic methods vary among them<sup>[154]</sup>. Of note, in children with cITP, no studies have assessed, at the initial as well as follow-up visits, *H. pylori* status by upper gastrointestinal endoscopy.

In a study from Taiwan, Jaing *et al.*<sup>[147]</sup> evaluated 22 cITP children, nine of whom were *H. pylori*-infected and were treated with a 1-wk course of triple therapy [including clarithromycin, amoxicillin, and proton pump inhibitors (PPIs)]. Of these nine patients, five (55.6%) 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. In a study from the Netherlands, Neefjes *et al.*<sup>[149]</sup> evaluated 47 children with cITP, three of whom were *H. pylori*-infected and were treated with a 2-wk course of the triple therapy mentioned above. Over a 6-mo follow-up, all three children achieved complete or partial remission. In a study from Iran, Hamidieh *et al.*<sup>[150]</sup> evaluated 31 cITP children, four of whom were *H. pylori*-infected and were treated with a 2-wk course of the same triple therapy. None of the four patients achieved complete or partial remission after *H. pylori* eradication. In a study from Japan, Hayashi *et al.*<sup>[148]</sup> evaluated 10 children with cITP, one of whom was *H. pylori*-infected and was treated with a 1-wk course of the same triple therapy. This child achieved complete remission throughout > 1 year of follow-up. In a study from Italy, Bisogno *et al.*<sup>[151]</sup> evaluated 25 children with cITP, nine of whom were *H. pylori*-infected and had *H. pylori* eradication following 1-2 courses of 2 wk of the same triple therapy. Over 6-mo follow-up, of these nine patients, three had an increase in platelet count after eradication therapy, and one had complete remission and two had partial, transient remission followed by relapse a few months later. Over the same follow-up period, no significant increase in platelet count was seen in the other six eradicated patients. In the same study, Bisogno *et al.*<sup>[151]</sup> also reported the platelet response in the 16 *H. pylori*-negative children with cITP. At 6-mo follow-up, two of these 16 patients achieved partial remission without any specific treatment. Yet, four of the *H. pylori*-negative children with cITP achieved spontaneous partial remission 1 year after diagnosis of *H. pylori* infection was excluded<sup>[151]</sup>. At latest follow-up, the remaining 10 *H. pylori*-negative children presented with a count above  $50 \times 10^9/L$  without any treatment. In another study from Italy, Loffredo *et al.*<sup>[152]</sup> evaluated 39 children (median age, 136 mo) with cITP, eight of whom were *H. pylori*-infected and had *H. pylori* eradication following 1-3 courses of 2 wk of the same triple therapy. Over 1-year follow-up, none of the eight patients achieved complete or partial remission after *H. pylori* eradication<sup>[152]</sup>.

Recently, Treepongkaruna *et al*<sup>[153]</sup> reported a multi-center randomized controlled trial of *H. pylori* eradication in 55 children with cITP. Of the 16 (29.1%) patients with cITP and *H. pylori* infection, seven were randomly treated with PPI-based triple therapy, while the remaining nine did not receive any specific treatment. If the first-line therapy failed to eradicate *H. pylori*, then second-line eradication therapy was used. Although eradication of *H. pylori* infection 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.

From the foregoing, whether antibiotic treatment of *H. pylori* infection should be considered in children with cITP is an unresolved question<sup>[154]</sup>. 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 relationship between *H. pylori* and cITP in children warrants further investigation with large randomized controlled trials of sufficient size and power and across different ethnic populations<sup>[154]</sup>.

## ASTHMA AND ALLERGIC DISORDERS

In industrialized countries, the incidence of asthma, especially childhood asthma, has risen in recent years<sup>[155]</sup>. Conversely, in developed countries, the rate of acquisition of *H. pylori* has decreased substantially over recent decades<sup>[3,9]</sup>. The lack of early exposure to *H. pylori* has been suggested to be an important determinant of asthma risk in childhood<sup>[156]</sup>. In a recent retrospective, cross-sectional study, using data from 3327 participants, aged 3-19 years, *H. pylori* seropositivity was found to be inversely associated with onset of asthma before 5 years of age and current asthma in children aged 3-13 years<sup>[157]</sup>. *H. pylori* seropositivity also was inversely related to recent wheezing, allergic rhinitis, and dermatitis, eczema, or rash.

Allergic diseases and asthma are caused by exaggerated T-helper 2 (Th2)-biased immune response in genetically susceptible individuals<sup>[158]</sup>. A number of recent studies have indicated that regulatory T cells (Tregs) play an important role in controlling such Th2-biased responses. Impaired expansion of natural and/or adaptive Tregs is hypothesized to lead to the development of allergy and asthma<sup>[158]</sup>. Increased numbers of Tregs have been reported in the *H. pylori*-infected human gastric mucosa<sup>[159,160]</sup>. Thus, the absence of early exposure to *H. pylori* might cause the loss of a metabolically active lymphoid compartment in the stomach, including Tregs, which ultimately could affect the activity of T cells present in other mucosal and cutaneous sites<sup>[156,160]</sup>. Although this is an undoubtedly interesting theory, future prospective, longitudinal studies are needed to test the strength of the association between *H. pylori* status and asthma risk in children from developed and developing countries<sup>[161]</sup>.

## CONCLUSION

Many areas of active scientific inquiry have been reported in

the recent literature about the disease spectrum of *H. pylori*. Several studies have demonstrated that *H. pylori* infection is not associated with specific symptomatology in children. Therefore, identification of children with *H. pylori*-associated gastritis on the basis of clinical presentation alone is not possible. Based on the best available evidence, testing for (and treating) *H. pylori* infection should be performed in children with endoscopically proven duodenal ulcer. Evidence from studies in adults supports the recommendation that testing for *H. pylori* should also be performed in children with a documented gastric ulcer. Endoscopy and biopsy are also recommended for children with persistent symptoms.

Pursuing *H. pylori* in asymptomatic children should be indicated for patients at increased risk of gastric cancer, for example, first-degree relatives of patients with gastric cancer, and individualized in populations at increased risk for gastric cancer, taking into consideration comorbid illness. Studies suggest that prevention of gastric cancer is possible in infected individuals with no precancerous lesions. Therefore, children might well be the group to target in an effort to prevent future development of gastric cancer.

Although dyspepsia and *H. pylori* infection are common in the general population, current data in the literature regarding a causal association between *H. pylori* gastritis and dyspepsia are conflicting. It is uncertain whether eradication of the infection leads to an improvement of symptoms. Randomized, placebo-controlled, double-blind trials with minimal loss to follow-up, strict group definition, and standardized and validated outcome measures are needed.

There is no compelling evidence to support routine testing in children with cITP, poor growth, and GERD. In children with refractory IDA, where other causes have been ruled out, testing for (and treating) *H. pylori* infection can be considered. Prospective, longitudinal studies are needed to test the strength of the newly reported association between *H. pylori* status and asthma risk in children. In the absence of these studies, there is little call to leave *H. pylori* infection untreated in patients with asthma and allergy. We believe that *H. pylori* eradication is strongly beneficial for curing peptic ulcer disease and gastric lymphoma and for prevention of gastric cancer, as well as other diseases that are putatively linked to infection, and it must be done in *H. pylori*-infected patients, whether or not they have asthma.

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