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What do we know about benefits of *H. pylori* treatment in childhood?

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Policy analysis shows that *H. pylori* test and treat strategies targeting adults at moderate to high risk of *H. pylori*-induced disease is likely to be cost-effective for preventing digestive diseases responsible for a large global disease burden. Little is known, however, about health benefits to children from eliminating this infection. We conducted a systematic review of the evidence regarding health benefits to children from treatment to eliminate *H. pylori* infection.

We systematically searched Ovid MEDLINE for pertinent review articles published through 2012. We excluded reviews focused on treatment efficacy and scrutinized reference lists of selected reviews to identify additional eligible reviews.

Fifteen reviews met specified inclusion criteria. Overall, they show that few reported studies investigating pediatric health effects of treatment for *H. pylori* infection were well designed with adequate statistical power. Thus, there is insufficient evidence for drawing conclusions about health benefits to children from treatment to eliminate *H. pylori* infection.

Introduction

H. pylori infection occurs worldwide and is usually acquired in early childhood.[1] This infection typically goes undetected at onset because it does not induce a specific constellation of symptoms.[1-3] While *H. pylori* infection can persist indefinitely without treatment, evidence suggests that acute infection can occur and resolve spontaneously before the development of detectable antibodies.[3,4] Chronic *H. pylori* infection is nearly always accompanied by chronic gastritis[2-4] and is involved in the pathogenesis of duodenal ulcers, gastric ulcers, and more rarely, gastric carcinoma.[1-4] Chronic gastritis and peptic ulcer disease are more common in older and low-income populations.[4] Chronic *H. pylori*-associated gastritis is generally asymptomatic, particularly in children. Symptomatic disease associated with *H. pylori* infection generally arises from long-term infection and occurs primarily in adults.[2-4]

Various studies have investigated hypotheses pertaining to *H. pylori* infection as a cause of a wide variety of extragastric diseases in children such as otitis media, upper respiratory tract infections, periodontal disease, food allergies, sudden infant death syndrome, idiopathic thrombocytopenic purpura, and short stature.[1,5] At present, there is no clear evidence that *H. pylori* plays a role in the pathogenesis of any of these conditions.[1,6] Studies of the relationship of *H. pylori* infection to iron deficiency in children have had inconsistent results.

In 2011, the European and North American Societies for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN and NASPGHAN) released updated guidelines for the management of *H. pylori* infection in children. These guidelines, developed using a systematic evaluation of the evidence, comprised recommendations to pediatricians for investigating gastrointestinal symptoms. The guidelines state that a "test and treat" approach, a strategy that uses a noninvasive test rather than upper gastrointestinal endoscopy to diagnose *H. pylori* infection and treat patients with positive results, is not recommended for pediatric patients, with the exception of specified circumstances.[6] Unlike guidelines for adult populations, testing for *H. pylori* is not recommended for children presenting with functional abdominal pain.[6] A test and treat strategy is recommended, however, for children who have first-degree relatives with a history of gastric cancer.[6] The guidelines also recommend that testing for *H. pylori* infection be considered in children with refractory iron-deficiency anemia after other causes have been ruled-out.[6] The identification of treatment regimens that are effective at eliminating pediatric *H. pylori* infections remains a challenge, particularly for high-prevalence populations, which often experience high frequencies of antimicrobial resistance and treatment failure.[7-10] The 2011 guidelines recommend monitoring the local prevalence of antibiotic-resistant *H. pylori* strains in children and adolescents and tailoring treatment regimens accordingly.[6]

Policy analysis shows that *H. pylori* test and treat strategies targeting adults at moderate to high risk of *H. pylori*-induced disease is likely to be cost-effective for preventing digestive diseases responsible for a large global disease burden. Little is known, however, about health benefits to children from eliminating this infection. We conducted a systematic review of the evidence regarding health benefits to children from treatment to eliminate *H. pylori* infection.

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Methods

We conducted a systematic search in Ovid MEDLINE from the starting year of this database (1946) through October 2012 to identify scholarly publications pertaining to the health benefits to children from treatment to eliminate *H. pylori* infection. For efficiency, we limited our search to published review articles and assessed details pertaining to individuals studies as reported in the published reviews; when details were lacking, we reviewed the original study reports.

Search strategy:

(1) Malnutrition and/or Anemia and/or Iron-Deficiency and/or Inflammation and/or Asthma and/or Purpura, Thrombocytopenic, Idiopathic and/or Abdominal Pain and/or recurrent abdominal pain and/or Ferritins and/or Hemoglobins and/or Platelet Aggregation and/or Platelet-Rich Plasma
(2) Anthropometry and/or body weights and measures and/or body mass index and/or body size and/or body height and/or body weight and/or waist circumference and/or skinfold thickness and/or waist-hip ratio
(3) Gastric Mucosa [Immunology, Microbiology, Parasitology, Virology]
(4) Gastrointestinal Diseases and/or Digestive System [Pathology] and/or Diarrhea and/or Parasites and/or Comorbidity and/or Vomiting and/or Gastroenteritis
(5) Anti-Bacterial Agents and/or Anti-Ulcer Agents
(6) Atrophy [Complications, Etiology, Microbiology, Therapy]
(7) Treatment Outcome
(8) One or 2 or 3 or 4 or 5 or 6 or 7
(9) exp *Helicobacter pylori*
(10) Eight and 9
(11) Search results were limited to "all child (0 to 18 years)," English language, "review articles"

Review articles were scrutinized for relevant information regarding health effects of treatment to eliminate *H. pylori* in children. Reference lists of identified reviews were scrutinized to identify other relevant reviews. We did not consider the elimination of *H. pylori* infection in and of itself to be a health benefit, thus reviews restricted to assessing the efficacy of particular treatment regimens were excluded. We classified the studies summarized in the review articles by the type of health outcomes investigated. We present study details in tables for the more frequently investigated health outcomes and provide a narrative summary of the less commonly investigated outcomes. Studies that examined multiple health outcomes are repeated in the relevant tables.

Results

Our systematic search identified 43 published reviews, of which 15 met the inclusion criteria. The most common treatment outcomes evaluated across the studies summarized in these review articles, other than clearance of *H. pylori*, were symptom relief, improvement of antral gastritis, and markers of iron deficiency. Health outcomes investigated sufficiently for tabular presentation include peptic ulcer disease, symptoms and/or recurrent abdominal pain, gastresophageal reflux, iron deficiency and/or anemia, and idiopathic thrombocytopenic purpura (ITP). Health outcomes summarized in narrative form include growth, mucosa-associated lymphoid tissue (MALT), and levels of pepsinogen, gastrin and ghrelin. Common limitations across studies were small sample size, poor statistical precision, lack of defined subject selection criteria, and substantial losses to follow-up.

Peptic ulcer disease

Identified studies of effects of treatment to eliminate *H. pylori* infection on peptic ulcer disease in children varied in design, study quality and the age range of subjects. Common limitations included inadequate sample size, poor statistical precision, lack of control group, non-randomized treatment allocations, use of subjective symptom scoring, failure to use blinding, and failure to control for potential confounding factors. Studies show that the frequency of peptic ulcer disease diagnosed via upper gastrointestinal endoscopy is low in children with *H. pylori* infection relative to *H. pylori*–positive adults.[1,6] In a meta-analysis of 45 studies of varied design the median prevalence of *H. pylori* infection was 92% (range, 33–100%) in children with duodenal ulcers and 25% (range, 11–75%) in children with gastric ulcers.[11] This meta-analysis showed high prevalence of *H. pylori* infection in children with antral gastritis and duodenal ulcer. In *H. pylori*-positive children presenting with peptic ulcers, ulcer healing was observed following treatment to eliminate *H. pylori* in controlled and uncontrolled trials in Ireland, Japan, Canada, China, Italy, Russia and Sweden (**Table 1**). These studies indicated that treatment to eliminate *H. pylori* might improve symptoms in children with peptic ulcer disease.

While the existing literature suggests that treatment to eliminate *H. pylori* infection may result in healing of peptic ulcers and relief of associated symptoms in children, a large proportion of these studies were not optimally designed for estimating these effects. Additional evidence of the benefits of *H. pylori* elimination on pediatric peptic ulcer disease should be generated by studies designed to better control for potential confounding factors at the design and analytical stages. Given that the standard of care requires treatment to eliminate *H. pylori* infection in children with peptic ulcer disease, observational studies can be conducted to estimate the effect of successful *H. pylori* elimination on improving symptoms and preventing recurrence. For valid estimation of such effects, studies of sufficient size for adequate statistical precision should collect data on factors that may influence the course of disease in the absence of *H. pylori* infection in order to control for confounding. Further, the use of standardized symptom assessment tools will improve the validity of studies focused on symptom improvement and allow for comparisons across studies. Analytical methods such as multivariable regression modeling should be employed to estimate measures of association and 95% confidence intervals, adjusted for potential confounders (**Table 1**).

Dyspeptic symptoms and/or recurrent abdominal pain

All of the identified studies pertaining to dyspeptic symptoms in children (**Table 2**) were conducted in hospital settings and restricted to patients with documented *H. pylori* infection.

Table 1. Studies of improvement after treatment to eliminate *H. pylori* among children with gastric or duodenal lesions

Location, Author, Year	Study Design	Age Range (years)	Baseline Sample Size	Follow-up Intervals (months)	Treatment Regimen [n]	Diagnostic Category [n]	Of Subjects with Outcome Data	
							% With *H. pylori* Eliminated	% With Improvement
Ireland, Goggin, 1998[12-14]	Uncontrolled trial	10–14	16	6, 12, 18, 24, 30, 36	1 antibiotic (M, A, T)+B [15]	Duodenal Ulcer [15]	100 [15/15]	100 [15/15]
						Antral Nodularity [13]	100 [13/13]	[11/13]
						Acute Duodenitis [4]	100 [4/4]	ND
						Chronic Duodenitis [5]	100 [5/5]	ND
Canada, Israel,1993[11,15]	Uncontrolled trial	4–16	29	3–8	Combination of A, B, M [29]	Duodenal Ulcer [29]	66 [8/12]	66 [8/12]
Canada, Drumm,1988[11,16]	Uncontrolled trial	10–18	20	1.75, 4, 24	B+Am [20]	Antral Gastritis [20]	75 [12/16]	75 [12/16]
						Duodenal Ulcer [10]	80 [8/10]	90 [9/10]
Canada, Dohil,1997[8,17,18]	Uncontrolled trial	9–16	15	6–8	M,O, C [15]	Antral Gastritis [15]	93 [14/15]	87 [13/15]
Italy, Oderda,1989[11,19]	Uncontrolled trial	8–18	42	1, 3	A [42]	Chronic Gastritis [42]	26 [8/30]	26 [8/30]
Italy, Oderda,1992[11,20]	Uncontrolled trial	1–18	63	1, 6, 12,18	A, Tin [63]	Total	80 [16/20]	
						Histological Gastritis [63]	80 [16/20]	89 [16/18]
						Duodenal Ulcer [13]	ND	ND
						Gastric Ulcer [11]	ND	ND
						Esophagitis [4]	ND	ND
						Normal Endoscopic Appearance [16]	ND	ND
Italy, De Giacomo, 1990[11,21-23]	Controlled trial	5–18	48	2–20	A, B [19]	Chronic Gastritis [19]	84 [16/19]	72 [13/18]
						Peptic Ulcers [2]	100 [2/2]	100 [2/2]
Japan, Kato, 1997[18,24]	Uncontrolled trial	8–16	22	1, 3, 6	O, A ± C [22]	Chronic Gastritis [22]	82 [18/22]	77 [17/22]
						Active Ulcer [10]	90 [9/10]	90 [9/10]
						Antral Nodularity [19]	79 [15/19]	84 [16/19]
Israel, Moshkowitz, 1998[18,25]	Uncontrolled trial	10–19	35	1	Tx Naïve (O, C, and [M or T]) [27]	Total	89 [24/27]	89 [24/27]
						Nodular Gastritis [13]	91 [10/11]	91 [10/11]
						Gastritis and Duodenitis [14]	91 [10/11]	91 [10/11]
						Duodenal Ulcer [6]	80 [4/5]	80 [4/5]
					Failed previous Tx (M, B) [8]	Total	13 [1/8]	13 [1/8]
						Nodular Gastritis [13]	33 [1/3]	33 [1/3]
						Gastritis and Duodenitis [14]	0 [0/4]	0 [0/4]
						Duodenal Ulcer [6]	0 [0/1]	0 [0/1]

HP, *H. pylori*; RCT, randomized controlled trial; C, culture; H, histology; RUT, rapid urea test; S, serology; A, amoxycillin; Am, ampicillin; B, bismuth subcitrate; C, clarithromycin; Cm, cimetidine; O, omeprazole; M, metronidazole; T, tetracycline; Tin, tinidazole; P, placebo; Tx, Treatment

Table 1. Studies of improvement after treatment to eliminate *H. pylori* among children with gastric or duodenal lesions (continued)

Location, Author, Year	Study Design	Age Range (years)	Baseline Sample Size	Follow-up Intervals (months)	Treatment Regimen [n]	Diagnostic Category [n]	Of Subjects with Outcome Data	
							% With *H. pylori* Eliminated	% With Improvement
China, Yeung,1990[8,26]	RCT	4–16	23	1.5, 3, 6	A+Cm [23]	Duodenal Ulcer [23]	35 [7/20]	75 [15/20]
Russia, Shcherbakov, 2001[6,27]	RCT, open	5–15	106	1-week, 1.5	Proprietary O+A+M [36]	Duodenal Ulcer [106]	89 [32/36]	100 [36/36]
					Generic O+A+M [35]		80 [28/35]	100 [36/36]
					R+A+M [35]		74 [26/35]	94 [33/35]
Finland, Ashorn, 2004[5,13,28]	RCT, double-blind	Mean 12.1	20	3, 6, > 12	O, A, C [10]	Antral Gastritis [20]	80 [8/10]	70 [7/10]
					O, P [10]		0 [0/10]	10 [1/10]

HP, *H. pylori*; RCT, randomized controlled trial; C, culture; H, histology; RUT, rapid urea test; S, serology; A, amoxycillin; Am, ampicillin; B, bismuth subcitrate; C, clarithromycin; Cm, cimetidine; O, omeprazole; M, metronidazole; T, tetracycline; Tin, tinidazole; P, placebo; Tx, Treatment

Gastric biopsies were examined for *H. pylori* by histology, urease staining, or culture. The age of participants ranged from 2 to 17 y and sample sizes ranged from 13 to 201. Common limitations included: small sample size; large losses to follow-up; uncertain validity of methods for assessing symptoms; use of serology to classify post-treatment infection status; failure to control for potential confounders. Several studies assessed gastritis severity before and after treatment but few examined this in relation to measures of clinical improvement.

Among Irish children with recurrent abdominal pain, Goggin et al. (1998) observed that the frequency and severity of abdominal pain decreased in all subjects 8 weeks after completion of treatment to eliminate *H. pylori*; symptoms that improved included vomiting, nocturnal awakening, and gastrointestinal bleeding.[13,14] Drumm et al. (1988) reported that Canadian children with antral gastritis and associated duodenal ulcers showed signs of improvement in clinical symptoms and antral inflammation as soon as 1 week following successful treatment of *H. pylori* infection.[11]

In a study of Italian children by Oderda et al. (1992), and reviewed by Macarthur (1995), those with gastritis who were treated to eliminate *H. pylori* showed improvement or complete resolution of symptoms at two weeks after treatment; at the 3-mo follow-up, mild abdominal pain recurred in those whose infection was not successfully cleared (3 of 22, 14%) and in one child who remained infection free (1 of 8, 13%).[11,19] In another study of Italian children with dyspeptic symptoms, De Giacomo et al. (1990) reported improvement of clinical symptoms, reduction of mean gastritis scores, and histological improvement in children who eliminated *H. pylori* infection . Conversely, in children who remained *H. pylori*-positive, gastritis persisted.[11,21,22]

In a study of Russian children with peptic ulcer disease, Shcherbakov et al. (2001) allocated children to one of three treatment arms, with regimens consisting of two antibiotics (metronidazole and amoxicillin) and one of three PPIs (proprietary omeprazole, generic omeprazole or ranitidine). The authors reported that all three regimens led to rapid symptom relief during the first week; however, two children in the ranitidine treatment arm experienced ulcer relapses that resulted in the recurrence of epigastric pain, heartburn and nausea. Treatment to eliminate *H. pylori* was effective in 81% (86 of 106) of the children enrolled in the study (74% (26 of 35) on the ranitidine regimen, 89% (32 of 36) on the proprietary omeprazole regimen, and in 80% (28 of 35) on the generic omeprazole regimen).[27]

In contrast, Cucchiara et al. (1996) observed that a 3-drug regimen used to treat *H. pylori* infection improved symptoms in Italian children regardless of *H. pylori* elimination,[22,29] noting similar proportions showing symptom improvement 6 mo after treatment in those who eliminated *H. pylori* infection (30 of 47) and those who did not (6 of 9). In a meta-analysis of 5 case-control studies of the association between *H. pylori* infection prevalence and recurrent abdominal pain, Macarthur (1999) reported a summary OR of 0.74 (95% CI: 0.50–1.1);[30] however, the study-specific odds ratios (OR) for this association ranged widely from 0.32 to 1.8 and 5 studies are too few for adequate assessment of the homogeneity assumed for valid estimation of the summary OR.

The existing evidence leaves doubt regarding the role of *H. pylori* infection in nonulcer dyspepsia and recurrent abdominal pain. Improvement in symptoms following treatment to eliminate *H. pylori* has been documented in several studies[1,6,11,13,31]; however, the quality of the current evidence makes it difficult to determine the extent to which elimination of *H. pylori* is responsible for the improvement noted. Studies designed to investigate benefits of eliminating *H. pylori* on dyspeptic symptoms and recurrent abdominal pain should compare changes in symptom profiles before and after anti-*H. pylori* therapy in children with successful elimination of *H. pylori* to those with persistent infection, while controlling for potentially confounding factors that influence the persistence of symptoms.

Table 2. Studies of symptomatic response to treatment to eliminate *H. pylori* among children with dyspeptic symptoms or recurrent abdominal pain

Location, Author, Year	Study Design	Age Range (years)	Baseline Sample Size	Follow-up Intervals (months)	Treatment Regimen [n]	Diagnostic Category [n]	Of Subjects with Outcome Data	
							% With *H. pylori* Eliminated	% With Symptom Improvement
Ireland, Goggin, 1998[12-14]	Uncontrolled trial	10–14	16	26–62	1 antibiotic (M, A, T)+B [15]	Abdominal Pain [15]	100 [15/15]	100 [15/15]
						Nocturnal Awakening [13]	100 [13/13]	100 [13/13]
						Vomiting [3]	100 [3/3]	100 [3/3]
						Melaena [6]	100 [6/6]	100 [6/6]
Italy, Oderda, 1989[11,19]	Uncontrolled trial	8–18	42	0.5–3	A	Non-ulcer Dyspepsia [42]	85 [34/40]	95 [38/40]
Italy, Oderda, 1992[11,20]	Uncontrolled trial	1–18	63	1	A, Tin [63]	Abdominal Pain [63]	87 [54/63]	ND
				6			91 [31/34]‡	85 [29/34]
				12			100 [22/22]‡	82 [18/22]
				18			80 [16/20]‡	85 [17/20]
Italy, Oderda, 2004[5,9]	Uncontrolled trial		43	6, 12–24		Epigastric pain [33]	74 [31/42]	82 [27/33]
						Heartburn and acid regurgitation [17]		100 [17/17]
						Fasting pain [19]		84 [16/19]
						Nocturnal pain [15]		93 [14/15]
Italy, De Giacomo, 1990[11,21,22]	Uncontrolled trial	5–17	48	2–20	B, A [19]	Chronic Gastritis [19]	84 [16/19]	74 [14/19]
						Peptic Ulcer [2]	100 [2/2]	100 [2/2]
India, Das, 2003[32,33]	Uncontrolled trial	3–12	65	6	O, C, M [65]	Recurrent Abdominal Pain [65]	ND	83 [54/65]
Turkey, Ozgenc, 2003[34,35]	Uncontrolled trial	5.5–18	33	1	O, A, C [33]	Chronic Gastritis [33]	88 [29/33]	85 [28/33]
Sweden, Casswall, 1998[18,36]	Uncontrolled trial	4.7–17	30	1	O, C, M [30]	Gastritis [30]	91 [29/32]	83 [25/30]
England, Uc, 2002[13,37]	Uncontrolled trial	7–20	16	2–24	C, A, PPI [16]	Nodular Antral Gastritis [16]	100 [16/16]	Reduction of total symptom scores
Switzerland†, Frank, 2000[13,38]	Uncontrolled trial	2–15	73	1–1.5	O, A, C [22]	Recurrent Abdominal Pain [73]	100 [19/19]	79 [15/19]
Russia, Shcherbakov, 2001[6,27]	RCT, open	5–15	106	1.5	Proprietary O+A+M [36]	Epigastric pain, heartburn and nausea [106]	81 [86/106]	98 [104/106]
					Generic O+A+M [35]			
					R+A+M [35]			
Finland, Ashorn,(1994)[39,40]	Uncontrolled trial	4–16	21	4, 18	B, Tin [21]	Abdominal pain and dyspeptic symptoms [21]	67 [14/21]	71 [15/21] ††
						Epigastric pain [9]	ND	ND
						Periumbilical pain [7]	ND	ND
						Diffuse pain [5]	ND	ND

† Included 5 Swiss children and 24 non-Swiss children; †† Reported no statistical differences between those who eliminated the H. pylori infection and those who remained H. pylori-positive; ‡ proportion of children who were followed successfully; ND, no data in report; O, omeprazole; L, Lanzoprazole; R, ranitidine; RCT, randomized controlled trial; PPI, proton pump inhibitor; HP, H. pylori¬¬; A, amoxicillin; Am, ampicillin; B, bismuth subcitrate; C, clarithromycin; Cm, cimetidine; O, omeprazole; M, metronidazole; T, tetracycline; Tin, tinidazole; +, positive; -, negative.

Table 2. Studies of symptomatic response to treatment to eliminate *H. pylori* among children with dyspeptic symptoms or recurrent abdominal pain (continued)

Location, Author, Year	Study Design	Age Range (years)	Baseline Sample Size	Follow-up Intervals (months)	Treatment Regimen [n]	Diagnostic Category [n]	Of Subjects with Outcome Data	
							% With *H. pylori* Eliminated	% With Symptom Improvement
Canada, Drumm, 1988[11,16,22,23]	Uncontrolled trial	10–17.5	16	1 week	B+Am [16]	Epigastric pain [10]	75 [12/16]	56 [9/16]
						Nocturnal pain [7]		
						Recurrent vomiting [2]		
					Post-Treatment Comparison [16]	Eliminated *HP* [12]		75 [9/12]
						Remained *HP*+ [4]		0 [0/4]
Isreal, Heldenberg, 1995[22,33,41]	Uncontrolled trial	Mean 9.2	80	2, 8	B, A, M [43]	Recurrent Abdominal Pain	85 [27/34]	100 [34/34]
Italy, Cucchiara, 1996[18,22]	Uncontrolled trial	0.5–13	56	1,6	B, Tin, A for 1 week [26]	Non-ulcer dyspepsia [56]	85 [19/22]	86 [19/22]
					B, Tin, A for 4 weeks [30]		88 [22/25]	84 [21/25]
Ireland, Farrell,2005[42]	Uncontrolled trial	≤ 14 (Mean 9.0)	39	6, 12	PPI, M, and C or A [39]	Upper abdominal pain; Non-ulcer dyspepsia [39]	90 [35/39]	67 [26/39]
						Nausea [12]		
						Vomiting [24]		
						Heartburn [12]		
Finland, Ashorn, 2004[5,13,28]	RCT, double-blind	Mean 12.1	20	3, 6, > 12	O, A, C [10]	Abdominal pain [9]	80 [8/10]	67 [6/9]
						Heartburn [4]		50 [2/4]
						Acid regurgitation [4]		50 [2/4]
						Nausea [7]		86 [6/7]
					O, P [10]	Abdominal pain [10]	0 [0/10]	50 [5/10]
						Heartburn [6]		83 [5/6]
						Acid regurgitation [6]		83 [5/6]
						Nausea [5]		60 [3/5]

† Included 5 Swiss children and 24 non-Swiss children; †† Reported no statistical differences between those who eliminated the H. pylori infection and those who remained H. pylori-positive; ‡ proportion of children who were followed successfully; ND, no data in report; O, omeprazole; L, Lanzoprazole; R, ranitidine; RCT, randomized controlled trial; PPI, proton pump inhibitor; HP, H. pylori¬¬; A, amoxicillin; Am, ampicillin; B, bismuth subcitrate; C, clarithromycin; Cm, cimetidine; O, omeprazole; M, metronidazole; T, tetracycline; Tin, tinidazole; +, positive; -, negative.

Iron Deficiency and/or Anemia

The relationship between *H. pylori* infection and iron deficiency (ID) or iron deficiency anemia (IDA) was investigated in several studies identified for this review.[1,13] Some of the identified studies showed that elimination of *H. pylori* was followed by improvements in mean hemoglobin levels, while others did not show clear improvement in varied markers of iron deficiency. It should be noted that most of the studies that showed a beneficial effect were small trials, including some without control groups (**Table 3**).

Choe et al. (2000) conducted a randomized placebo-controlled trial to compare the effects of three *H. pylori* treatment regimens on iron status in 22 South Korean adolescent females with sideropenic refractory anemia who had *H. pylori*-associated antral gastritis without evidence of hemorrhage or clinical symptoms.[43] Subjects were randomly allocated to one of three treatment arms: iron supplementation only, treatment to eliminate *H. pylori*, or both. Iron status was measured at 1 and 3 mo after treatment. Mean levels of hemoglobin and serum ferritin increased 3 mo following treatment in those who received *H. pylori* therapy only relative to those receiving iron supplementation with placebo (p-value = 0.009).

In Bangladesh, Sarker et al. (2008) observed mean hemoglobin, serum ferritin, and soluble transferrin receptors in children with IDA or ID before and after completion of a randomly assigned treatment regimen.[44] Children were randomly allocated to one of four treatment arms: (1) iron supplementation and

Table 3. Studies of response to treatment to eliminate *H. pylori* among children with iron deficiency or anemia

Location, Author, Year	Study Design	Age Range (years)	Baseline Sample Size	Follow-up Intervals (months)	Treatment Group [n]	Diagnostic Category [n]	Outcome of Interest	Of Subjects with Outcome Data	
								% With *H. pylori* Eliminated	Measures of Improvement
Italy, Barabino, 1999[13,50,51]	Uncontrolled trial	4–14	4	2–11	*HP* treatment and iron supplementation [4]	IDA [4]	Percent with improved measures of anemia	100 [4/4]	100 [4/4]
Japan, Konno, 2000[50-52]	Uncontrolled trial	13–15	6	27–50	*HP* treatment [6]	IDA [6]	Percent with improved measures of anemia	100 [6/6]	100 [6/6]
United States, Fagan, 2009[13,46] (update from ref. 45)	RCT	7–11	237	40	*HP* treatment [106]	ID [44]	Median increase in serum ferritin (μg/L) and hemoglobin (g/L) levels	38 [32/85]	Ferritin: 4.3 Hemoglobin: 4.0
						Anemia [26]			
					Control [113]	ID [53]		1 [1/91]	**Ferritin: 2.9** **Hemoglobin: 3.0**
						Anemia [19]			
					Post-treatment comparison [176]	Eliminated HP [33]			Ferritin: 6.6 Hemoglobin: 4.0
						Remained *HP*+ [143]			Ferritin: 3.0 Hemoglobin: 3.0
Greece, Kostaki, 2003[50,51,53]	Uncontrolled trial	9–13	3	3–12	*HP* treatment	IDA and chronic gastritis	Percent with improved hemoglobin levels	100 [3/3]	100 [3/3]
Italy, Russo-Mancuso, 2003[51,54]	Uncontrolled trial	4–18	9	6–24	*HP* treatment and iron supplementation [9]	Recurrent/ unresponsive IDA [9]	Percent with improved hemoglobin levels	100 [9/9]	100 [9/9]
Turkey, Kurekci, 2005[6,51,55]	Uncontrolled trial	6–16	140	1	*HP* treatment	IDA [18]	Change in mean hemoglobin (g/dl) and ferritin (ng/ml) levels	78 [14/18]	Hemoglobin: 10.4 to 12.0 Ferritin: 7.0 to 21.1
						ID [36]		92 [33/36]	Hemoglobin: 12.9 to 13.0 Ferritin: 7.6 to 16.9
						Normal [86]		86 [74/86]	Hemoglobin: 13.2 to 13.2 Ferritin: 30.2 to 37.6
South Korea, Choe, 1999[56]	Controlled trial	10–17	25	1, 2	*HP* treatment and iron supplementation [8]	IDA [25]	Change in mean hemoglobin (g/dL) and ferritin (ng/dL) levels	83 [5/6]	Hemoglobin: 6.9 to 11.0 Ferritin: 4.6 to 8.3
					HP treatment and placebo [7]			100 [5/5]	Hemoglobin: 8.9 to 10.6 Ferritin: 6.9 to 6.8
					Iron supplementation and placebo [7]			0 [0/7]	Hemoglobin: 7.7 to 8.6 Ferritin: 5.1 to 3.3

†† Information comes from English abstract (Lin, 2005) and review by Huang et al., 2010 48, rather than original Chinese publication. +, positive; -, negative

Table 3. Studies of response to treatment to eliminate *H. pylori* among children with iron deficiency or anemia (continued)

Location, Author, Year	Study Design	Age Range (years)	Baseline Sample Size	Follow-up Intervals (months)	Treatment Group [n]	Diagnostic Category [n]	Outcome of Interest	Of Subjects with Outcome Data	
								% With *H. pylori* Eliminated	Measures of Improvement
South Korea, Choe, 2000[43,50,51]	Uncontrolled Trial	15–17	14	1–2	*HP* treatment and iron supplementation [14]	*HP*+ with IDA [14]	Change in mean hemoglobin (g/dl) and ferritin (μg/l) levels	92 [11/12]	Hemoglobin: 8.6 to 11.3 Ferritin: 4.3 to 17.5
United States, Gessner, 2006[13,45,51]	RCT	7–11	219	2, 8, 14	*HP* treatment + iron supplementation [106]	ID [94]	Percent of ID and *HP*+ with improvement in ID and anemia	68 [63/93]	35 [33/94]
						Anemia [29]			28 [8/29]
					Iron supplementation [113]	ID [107]		4 [4/107]	28 [30/107]
						Anemia [20]			25 [5/20]
					HP treatment + iron supplementation [106]		Change in mean hemoglobin (g/dL) and ferritin (ug/L) levels		Hemoglobin: 0.24 Ferritin: 2.3
					Iron supplementation [113]				Hemoglobin: 0.12 Ferritin: 1.7
					Post-treatment comparison [37]	Eliminated HP [22]			Hemoglobin: 0.27 Ferritin: 3.9
						Remained *HP*+ [15]			Hemoglobin: 0.11 Ferritin: 1.6
Bangladesh, Sarker, 2008[13,44]	RCT	2–5	200	3	*HP* treatment and iron supplementation [50]	IDA and ID	Mean difference in hemoglobin (g/L), serum ferritin (mg/mL) and serum transferrin (mg/mL) levels in each treatment group vs. *HP*- group	67 [32/47]	Hemoglobin: 16 vs. 21 Serum ferritin: 53 vs. 43 Serum transferrin: 5.4 vs.5.5
					HP treatment [50]			64 [31/49]	Hemoglobin: 7 vs. 21 Serum ferritin: 10 vs. 43 Serum transferrin: 1.3 vs.5.5
					Iron supplementation [49]			18 [8/45]	Hemoglobin: 17 vs. 21 Serum ferritin: 48 vs. 43 Serum transferrin: 5.2 vs.5.5
					Placebo [51]			7 [4/49]	Hemoglobin: 9 vs. 21 Serum ferritin: 8 vs. 43 Serum transferritin: 1.8 vs.5.5
India, Vijayan, 2007[57]	RCT	≥ 13	22	1	*HP* therapy and iron supplementation [11]	Anemia	Change in mean hemoglobin (g/dL) and ferritin (ng/mL) levels	ND	Hemoglobin: 7.4 to 10.4 Ferritin: 30.5 to 116.9
					Iron supplementation [11]				Hemoglobin: 6.4 to 7.5 Ferritin: 27.2 to 52.5

†† Information comes from English abstract (Lin, 2005) and review by Huang et al., 2010 48, rather than original Chinese publication. +, positive; -, negative

Table 3. Studies of response to treatment to eliminate *H. pylori* among children with iron deficiency or anemia (continued)

Location, Author, Year	Study Design	Age Range (years)	Baseline Sample Size	Follow-up Intervals (months)	Treatment Group [n]	Diagnostic Category [n]	Outcome of Interest	Of Subjects with Outcome Data	
								% With *H. pylori* Eliminated	Measures of Improvement
China, Lin, 2005[48,58]††	RCT, open	6–12	68	2	*HP* therapy and iron supplementation [35]	Anemia	Mean increase in hemoglobin, serum iron and serum ferritin levels	ND	- Increased levels of hemoglobin, serum iron and serum ferritin from baseline - Mean levels higher than control group
					Iron supplementation and placebo [33]				- Increased levels of hemoglobin, serum iron and serum ferritin from baseline
China, Huang, 2005[48]††	Uncontrolled trial	2–7	58	2	*HP* therapy	Anemia	Weighted mean difference in hemoglobin (g/L) and serum ferritin (mg/L)	ND	Hemoglobin: 9.7 Serum ferritin: 5.8
United States/ Mexico, Cardenas, 2011[49]	RCT, double-blind	3–10	110	8	Per protocol: *HP* therapy and iron supplementation [28]	Normal [110]	Mean difference† in hemoglobin (g/dL) and serum ferritin (mg/L)	50 [14/28][59]	Hemoglobin: 0.3 (0.1–0.5) TSAT: 2.2 (-1.2–5.5) Serum ferritin:5.6 (0.4–10.8)
					HP therapy and placebo [23]			57 [13/23][59]	Hemoglobin: 0.2 (-0.1–0.5) TSAT: 0.4 (-3.0–4.1) Serum ferritin: 3.8 (-2.1–9.7)
					Iron and placebo [20]			20 [4/20][59]	Hemoglobin: 0.4 (0.1–0.7) TSAT: 3.4 (-0.4–7.2) Serum ferritin: 3.6 (-2.5–9.6)
					Placebo [19]			11 [2/19][59]	Hemoglobin: 0.3 (-0.0–0.6) TSAT: 2.4 (-0.6–5.4) Serum ferritin: 4.8 (0.5–9.2)
					Intention to treat: *HP* therapy and iron supplementation [32]			44 [14/32][59]	Hemoglobin: 0.2 (0.0–0.4) TSAT: 2.2 (-1.2–5.5) Serum ferritin:5.6 (0.4–10.8)
					HP therapy and placebo [29]			45 [13/29][59]	Hemoglobin: 0.1 (-0.1–0.4) TSAT: 0.1 (-3.1–3.2) Serum ferritin: 3.5 (-1.1–8.0)
					Iron and placebo [23]			17 [4/23][59]	Hemoglobin: 0.3 (0.0–0.6) TSAT: 3.3 (-0.2–6.7) Serum ferritin: 3.5 (-1.5–8.6)
					Placebo [26]			8 [2/26][59]	Hemoglobin: 0.2 (-0.0–0.5) TSAT: 1.8 (-1.5–5.2) Serum ferritin: 1.3 (-3.6–6.2)

†† Information comes from English abstract (Lin, 2005) and review by Huang et al., 2010 48, rather than original Chinese publication. +, positive; -, negative

Table 4. Trials included in published meta-analyses of the effect of treatment to eliminate *H. pylori* on iron deficiency or anemia in children

Location, Author, Year, Study Design	Age Range (years)	Baseline Sample size	Follow-up Interval (months)	Definitions of Iron Deficiency and Anemia	Treatment Group [n]	Diagnostic Category [n]	Change in mean hemoglobin (g/dL) and ferritin (ng/dL) levels
Trials included by Qu et al. (2010)[47] Estimated summary weighted mean difference in: Hemoglobin: 0.65 g/L (95% CI: -1.52, 2.82) Serum ferritin: 0.70 μg/L (95% CI: -1.01, 2.41)							
South Korea Choe, 1999[56] RCT, blinded	10–17	25	2	SF < 12 ng/ml TSAT < 15%	*HP* therapy and iron supplementation [8]	IDA [25]	Hemoglobin: 6.9 to 11.0 Ferritin: 4.6 to 8.3
					HP therapy and Placebo [7]		Hemoglobin: 8.9 to 10.6 Ferritin: 6.9 to 6.8
					Iron supplementation and Placebo [7]		Hemoglobin: 7.7 to 8.6 Ferritin: 5.1 to 3.3
United States Gessner, 2006[45] RCT, open-label	7–11	201	14	SF < 10 μg/L Hb < 11.5 g/dL	*HP* therapy and iron supplementation [106]	ID [94]	Hemoglobin: 0.24 Ferritin: 2.3
						Anemia [29]	
					Iron supplementation [113]	ID [107]	Hemoglobin: 0.12 Ferritin: 1.7
						Anemia [20]	
India Vijayan, 2007[57] RCT	≥ 13	22	1	Hb < 11 g/dL	*HP* therapy and iron supplementation [11]	Anemia [22]	Hemoglobin: 7.4 to 10.4 Ferritin: 30.5 to 116.9
					Iron supplementation [11]		Hemoglobin: 6.4 to 7.5 Ferritin: 27.2 to 52.5
Bangladesh Sarker, 2008[44] RCT, double-blinded	2–5	200	3	Hb < 110 g/L SF < 12 μg/L sTfR > 8.3 mg/L	*HP* therapy and Iron supplementation [50]	IDA or ID [200]	Hemoglobin: 16 vs. 21 Serum ferritin: 53 vs. 43
					HP therapy [50]		Hemoglobin: 7 vs. 21 Serum ferritin: 10 vs. 43
					Iron [49]		Hemoglobin: 17 vs. 21 Serum ferritin: 48 vs. 43
					Placebo [51]		Hemoglobin: 9 vs. 21 Serum ferritin: 8 vs. 43
Trials included by Huang et al. (2010)[48] Estimated summary weighted mean difference in: Hemoglobin: 11.77 g/L (95% CI: 2.40, 21.15) Serum ferritin: 15.11 μg/L (95% CI: 7.8, 22.35)							
South Korea Choe, 1999[56] RCT, double-blinded	10–17	25	2	SF < 12 ng/ml TSAT < 15%	*HP* therapy and iron supplementation [8]	IDA [25]	Hemoglobin: 6.9 to 11.0 Ferritin: 4.6 to 8.3
					HP therapy and Placebo [7]		Hemoglobin: 8.9 to 10.6 Ferritin: 6.9 to 6.8
					Iron supplementation and Placebo [7]		Hemoglobin: 7.7 to 8.6 Ferritin: 5.1 to 3.3

HP, H. pylori; Hb, hemoglobin; SF, serum ferritin; sTfR, soluble transferrin receptor; TSAT, transferrin saturation. †† Information comes from English abstract (Lin, 2005) and review by Huang et al., 2010 48, rather than original Chinese publication.

Table 4. Trials included in published meta-analyses of the effect of treatment to eliminate *H. pylori* on iron deficiency or anemia in children (continued)

Location, Author, Year, Study Design	Age Range (years)	Baseline Sample size	Follow-up Interval (months)	Definitions of Iron Deficiency and Anemia	Treatment Group [n]	Diagnostic Category [n]	Change in mean hemoglobin (g/dL) and ferritin (ng/dL) levels
China Lin, 2005[58]†† RCT, open label	6–12	68	2	ND	*HP* therapy and iron supplementation [35]	IDA [68]	(not available)
					Iron supplementation and Placebo [33]		
China Huang, 2005†† Uncontrolled trial	2–7	58	2	ND	*HP* therapy [58]	Anemia [58]	Hemoglobin: 9.7 Serum ferritin: 5.8
India Vijayan, 2007[57] RCT	≥ 13	22	1	Hb < 11 g/dL	*HP* therapy and iron supplementation [11]	Anemia [22]	Hemoglobin: 7.4 to 10.4 Ferritin: 30.5 to 116.9
					Iron supplementation [11]		Hemoglobin: 6.4 to 7.5 Ferritin: 27.2 to 52.5
Bangladesh Sarker, 2008[44] RCT, double blinded	2–5	200	3	Hb < 110 g/L SF < 12 μg/L sTfR > 8.3 mg/L	*HP* therapy and Iron supplementation [50]	IDA or ID [200]	Hemoglobin: 16 vs. 21 Serum ferritin: 53 vs. 43
					HP therapy [50]		Hemoglobin: 7 vs. 21 Serum ferritin: 10 vs. 43
					Iron [49]		Hemoglobin: 17 vs. 21 Serum ferritin: 48 vs. 43
					Placebo [51]		Hemoglobin: 9 vs. 21 Serum ferritin: 8 vs. 43

HP, H. pylori; Hb, hemoglobin; SF, serum ferritin; sTfR, soluble transferrin receptor; TSAT, transferrin saturation. †† Information comes from English abstract (Lin, 2005) and review by Huang et al., 2010 48, rather than original Chinese publication.

H. pylori therapy, (2) *H. pylori* therapy and placebo, (3) iron supplementation and placebo, and (4) placebo. The authors reported that there were no detectable differences in mean levels of hemoglobin, serum ferritin, and soluble transferrin receptors among treatment groups at the 90-d follow-up or between children who remained *H. pylori*-positive and those who eliminated the infection.

Gessner et al. (2006) conducted a trial that included 219 Alaska Native children aged 7–11 y with both ID and *H. pylori* infection.[45] In household groups, children were randomly assigned to one of two treatment arms: iron supplementation alone or iron supplementation with treatment to eliminate *H. pylori*. Iron status was measured at 1, 2, and 14 mo after treatment. *H. pylori*-positive children were treated again if the infection had not cleared two months after treatment. The authors reported that they did not detect meaningful differences between the groups in the prevalence of ID at 2 mo (32% in the antimicrobial treatment plus iron group; 39% in the iron only group) or 14 mo (65% in the antimicrobial treatment plus iron group; 72% in the iron only group) after treatment. Fagan et al. (2009) re-examined these children 40 mo after treatment and reported that elimination of *H. pylori* infection was associated with reduced prevalence of mild IDA (IDA persisted in only 1 *H. pylori*-negative child) and modestly improved iron status.[46] The authors also reported some improvement in ID among those who remained *H. pylori*-positive.

The inconsistent age distributions of the identified studies complicate comparison validity due to lifespan variation in iron requirements and susceptibility to ID. Additional design inconsistencies include varied follow-up intervals and diverse *H. pylori* detection methods that influence the accuracy of classifying *H. pylori* status before and after treatment. Further limitations of these analyses include small sample sizes and limited generalizability given that the available studies were geographically restricted to Bangladesh, India, South Korea, China, and Alaska.

Two recent meta-analyses of studies that examined the effect of treatment to eliminate *H. pylori* on IDA reported conflicting results for children (**Table 4**). Both of these meta-analyses generated summary estimates of the average change in hemoglobin and serum ferritin concentration before and after treatment using the weighted mean difference in subgroups defined by age and treatment regimen. Qu et al. (2010) evaluated 15 observational studies and 5 randomized controlled trials of *H. pylori* treatment and iron supplementation

(of which 4 randomized clinical trials were restricted to pediatric populations).[47] In contrast to studies of adults and adolescents, from which estimated summary weighted mean differences were 25.03 g/L (95% CI: 9.69, 40.37) for hemoglogin and 4.79 μg/L (95% CI: 2.53, 27.05) for serum ferritin, in children estimated summary weighted mean differences were just 0.65 g/L (95% CI: -1.52, 2.82) for hemoglobin and 0.70 μg/L (95% CI: -1.01, 2.41) for serum ferritin. Huang et al. (2010) evaluated 8 randomized controlled trials of *H. pylori* treatment and iron supplementation (4 of which were restricted to pediatric populations, though not the same set of 4 assessed by Qu et al.).[48] This meta-analysis estimated summary weighted mean differences in children of 11.77 g/L (95% CI: 2.40, 21.15) for hemoglobin and 5.93 μg/L (95% CI: 4.53, 7.32) for serum ferritin; the corresponding estimates for adults were 15.11 g/L (95% CI: 7.87, 22.35 g/L) for hemoglobin and 15.08 μg/L (95% CI: 11.49, 18.67) for serum ferritin. Huang et al. (2010) concluded that *H. pylori* treatment plus iron is more effective than iron alone for the treatment of IDA. **Table 4** shows that the drastically different conclusions of the two meta-analyses result from the selection of distinct sets of studies. Of note, the meta-analysis by Huang et al. excludes the large trial conducted in Alaska.

In a recent double-blind intervention trial, 110 asymptomatic *H. pylori*-positive 3- to-10 y old children with normal iron levels from El Paso, Texas were randomly assigned to one of four treatment arms: quadruple therapy plus iron supplementation, quadruple or sequential therapy only, iron supplementation only, or placebo.[49] *H. pylori* infection status was determined by measuring anti-*H. pylori* IgG antibodies in the urine and confirmed using the urea breath test. Hemoglobin, transferrin saturation, and serum ferritin levels were measured at baseline and 8 mo post-treatment. *H. pylori* infection status was measured approximately 45 d post-treatment. An increase in serum ferritin levels was observed among children who eliminated *H. pylori* infection (mean difference 7.7 ng/mL, 95% CI: 2.7, 12.8) when compared with those who remained *H. pylori*-positive (1.9 ng/mL, 95% CI: 1.7, 5.6), after adjustment for age, sex, baseline level of each marker of iron stores, days of follow-up, and batch (defined as a group of 10 or more children who received the medication at a given date based on the time the medicine shipments arrived). The authors reported that the average change in serum ferritin levels from baseline was 3 times higher in children whose infection cleared relative to those who remained infected (p-value < 0.05). However, the adjusted mean levels of transferrin saturation and hemoglobin were similar for children who eliminated *H. pylori* infection (2.3%, 95% CI: -0.1, 0.5 for transferrin, and 0.3 g/dL 95% CI: 0.1, 0.5 for hemoglobin) and those who remained *H. pylori*-positive (2.0%, 95% CI: -1.1, 5.4 for transferrin, and 0.3 g/dL, 95% CI: 0.0, 0.5 for hemoglobin). Intention-to-treat and per-protocol analyses were conducted to evaluate the effect of random allocation to treatment arms, neither of which yielded clear evidence of an effect on iron stores.

In summary, the identified studies on the effect in children of treatment to eliminate *H. pylori* on indicators of iron deficiency are of inconsistent quality and yield inconsistent results. In addition, there is a need for investigation of this effect in pediatric populations from diverse geographic locations. The reviewed epidemiologic evidence supports current recommendations from expert guidelines that children with a first episode of IDA and no complications should be treated only with iron supplementation, regardless of their *H. pylori* infection status.[6,13,14]

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease in which antiplatelet antibodies accelerate the destruction of platelets.[13] There have been inconsistent reports of a relationship between elimination of *H. pylori* and improvement of chronic-ITP.[13,60,61] Several mechanisms have been proposed to explain how platelets may respond to *H. pylori* therapy.[60,62] These mechanisms include molecular mimicry, platelet aggregation, T-helper 1 (Th1) type immune response (since both *H. pylori* infection and ITP are associated with a Th1 response), and the role of CagA (cytotoxin-associated gene A) protein and other *H. pylori*-related factors.[60]

There is limited epidemiologic evidence pertaining to the role of *H. pylori* therapy in improvement of ITP and therefore the potential for *H. pylori* eradication to benefit ITP patients remains uncertain (**Table 5**). In three studies conducted in the Netherlands and one in Japan, all children with chronic ITP who were treated for *H. pylori* infection achieved complete or partial remission of ITP. Conversely, in studies conducted in Iran and Italy, children did not achieve complete or partial remission during the follow-up period. In studies conducted in Italy, Thailand, and Turkey, platelet recovery rates were similar for children with chronic ITP who received *H. pylori* therapy compared with children with chronic ITP who were not given treatment to eliminate *H. pylori*. In studies conducted in Taiwan and Italy, mean platelet counts increased in children with chronic ITP who were treated for *H. pylori* infection. It should be noted that spontaneous platelet count increases in *H. pylori*-negative children with chronic ITP were observed in an Italian study (**Table 5**).

In the clinical trial conducted by Bisogno et al. (2008), which included 24 Italian children with chronic ITP, the authors found that 6 mo after *H. pylori* therapy, of the eight children who were *H. pylori*-positive at baseline, three had an increased platelet count, one showing complete remission (rise in platelet count above 150×10^9 per L relative to baseline) and two showing partial remission (rise in platelet count of 50 to 150×10^9 per L with an increase $>30 \times 10^9$ per L over the baseline).[63] The two children who achieved partial remission relapsed a few months later.[63] No increase in platelet counts was observed in 5 other children who eliminated *H. pylori*.[63] Bisogno et al. (2008) also measured the platelet response in 16 *H. pylori*-negative children with chronic-ITP who did not receive *H. pylori* therapy; two of these children achieved partial remission at the 6-mo follow-up.[63] One year following *H. pylori* classification, 4 of the children with chronic ITP who were *H. pylori*-negative at baseline had achieved partial remission and the remaining 10 had a platelet count greater than 50×10^9 per L.[63] In a multicenter study from Italy, Ruso et al. (2011) observed that successful *H. pylori* treatment was followed by platelet count increases in 39% (13 of 33) of *H. pylori*-positive

Table 5. Studies of response to treatment to eliminate *H. pylori* among children with idiopathic thrombocytopenic purpura (ITP)

Location, Author, Year	Study Design	Age Range (years)	Baseline Sample Size	Follow-up Intervals (months)	Treatment Group [n]	Diagnostic Category [n]	Outcome of Interest	Of Those with Follow-Up Data:	
								% with *H. pylori* Eliminated	Measures of Improvement
Netherlands, Neefjes, 2007[13,61,64]	Clinical trial	≤ 16	47	3, 6–9	*HP* treatment [3]	*HP*+ with chronic ITP [3]	Percent with complete (increase in PLT count > 150 × 10^9/L) or partial (increase in PLT count > 50 × 10^9/L) remission of ITP	100 [3/3]	100 [3/3]
Japan, Hayashi, 2005[13,61,65]	Clinical trial	4–14	10	12–25	*HP* treatment [1]	*HP*+ with chronic ITP [1]	Percent with improved median PLT count	100 [1/1]	100 [1/1]
					Post-treatment comparison [1]	*HP*+ baseline [1]	Change in median PLT count		6.5 × 10^4/μL
						Eliminated *HP* [1]			21.5 × 10^4/μL
Iran, Hamidieh, 2008[13,61,66]	Clinical trial	3–14	31	6–11	*HP* treatment [4]	*HP*+ with chronic ITP [4]	Percent with complete (increase in PLT count > 150 × 10^9/L) or partial (increase in PLT count > 50 × 10^9/L) remission of ITP	100 [4/4]	0 [0/4]
Italy, Loffredo, 2007[13,61,67]	Clinical trial	4–17	39	6, 12	*HP* treatment [8]	*HP*+ with chronic ITP [8]	Percent with improved PLT count	88 [7/8]	0 [0/8]
					Post-treatment comparison [38]	Eliminated *HP* [7]	Change in median platelet count (mmc)		33x10^3 to 80.9 × 10^3
						HP- at baseline [31]			43.5 × 10^3 to 84.6 × 10^3
Thailand, Treepongkaruna, 2009[13,61,62,68]	Multicenter RCT	4–18	55	6	*HP* treatment and prednisolone [7]	*HP*+ with chronic ITP [16]	Percent with PLT recovery (PLT count over 100 x10^9/L for 3 mo)	100 [7/7]	14 [1/7]
					Prednisolone [9]			0 [0/7]	14 [1/7]
Turkey, Gursel, 2010[69]	Multicenter RCT	6–15	45	1	*HP* treatment [30]	*HP*+ with dyspepsia [30]	Change in maximum PLT rich plasma aggregation values (%) induced by 10 μmol/L adenosine phosphate	100 [30/30]	62.76 ± 13.89 to 78.16 ± 15.21
					Control [15]	*HP*- with dyspepsia [15]			80.93 ± 10.84
Taiwan, Jaing, 2003[13,61,70]	Clinical trial	1–17	22	16	*HP* treatment [9]	*HP*+ with chronic ITP [9]	Percent with complete (increase in PLT count > 150 × 10^9/L) or partial (increase in PLT count > 50 × 10^9/L) remission of ITP	100 [9/9]	56 [5/9]
Italy, Russo, 2011[61,62]	Prospective control multicenter study	< 18	244	6–12	*HP* treatment [37]	*HP*+ with ITP [55]	Percent with complete (increase in PLT count > 150 × 10^9/L) or partial (increase in PLT count > 50 × 10^9/L) remission of ITP	89 [33/37]	39 [13/33]
						HP- with ITP [166]			10 [17/166]

HP, H. pylori; PLT, platelet; +, positive; -, negative.

Table 5. Studies of response to treatment to eliminate *H. pylori* among children with idiopathic thrombocytopenic purpura (ITP) (continued)

Location, Author, Year	Study Design	Age Range (years)	Baseline Sample Size	Follow-up Intervals (months)	Treatment Group [n]	Diagnostic Category [n]	Outcome of Interest	Of Those with Follow-Up Data:	
								% with *H. pylori* Eliminated	Measures of Improvement
Italy, Ferrara, 2009[61,69,71]	Clinical trial	5–11	24	12	Pre- *HP* treatment comparison [24]	*HP*+ with chronic ITP [8]	PLT count in *HP*+ patients relative to *HP*- patients before and after *HP* eradication therapy	100 [8/8]	33 ± 2.8 x 10^9/L
						HP- with chronic ITP [16]			34 ± 5.8 x 10^9/L
					Post- *HP* treatment comparison	Eliminated *HP* [8]			315 ± 7.1 x 10^9/L
						HP- at baseline [16]			44 ± 2.1 x 10^9/L
						Eliminated *HP* [8]	Percent with PLT recovery		75 [6/8]
Italy, Bisogno, 2008[13,63,72]	Clinical trial	1.5–14	36	6–50	*HP* treatment [8]	*HP*+ with chronic ITP [8]	Percent with complete (increase in PLT count > 150 × 10^9/L) or partial (increase in PLT count > 50 × 10^9/L)) remission of ITP	100 [8/8]	38 [3/8]
						HP- with chronic ITP [16]			63 [10/16]

HP, H. pylori; PLT, platelet; +, positive; -, negative.

children with chronic ITP and they also observed spontaneous remission in 10% (17 of 166) of *H. pylori*-negative children with chronic ITP.[61]

Common limitations of these studies were small sample sizes, low prevalence of *H. pylori* infection, lack of control groups, and short follow-up periods. Variation in *H. pylori* treatment protocols and methods for evaluating platelet response makes comparisons across studies difficult. In summary, the benefit of treatment to eliminate *H. pylori* in children with chronic ITP is unclear.

Gastresophageal Reflux Disease (GERD)

Studies have investigated opposing hypothesizes regarding causal or protective effects on GERD of treatment to eliminate *H. pylori* in children.[73] All relevant reports identified by this review had inconclusive results.[74-76]

Levine et al. (2004) evaluated 95 Israeli children with epigastric pain and GERD symptoms and reported that they observed no association between *H. pylori* treatment and improvement of symptoms.[6,74] More specifically, a similar distribution of GERD symptoms was observed before and after *H. pylori* treatment, and the mean decrease from baseline in symptom severity scores after *H. pylori* treatment were similar across comparison groups (*H. pylori*-negative at baseline, *H. pylori*-positive after therapy, and *H. pylori*-negative after therapy).[77] Pollet et al. (2004) studied 43 neurologically impaired *H. pylori*-positive children using endoscopy to diagnose reflux esophagitis.[78] Children were examined endoscopically again 4–6 weeks after treatment. At the time of the first endoscopy, 14 of the 43 children had esophagitis.[78] *H. pylori* infection was successfully eliminated in all 14 children who had esophagitis and in 19 of 29 children who had a normal esophagus.[78] Of the 14 children with esophagitis, only four had persistent esophagitis at the follow-up exam, while one of the 29 children with a normal esophagus at baseline had esophagitis at the follow-up exam.[78] Gold (2001) evaluated 90 children undergoing upper endoscopy and obtained biopsies from the stomach and esophagus.[75] The author reported that the subgroup of children who eliminated *H. pylori* infection experienced a resolution of both esophageal and gastric disease at the 6-mo follow-up exam.[75]

These three reports do not provide clear evidence for or against an effect of treatment to eliminate *H. pylori* on GERD in children. These studies are limited by their small sample sizes and lack of a randomized, controlled design. Observational studies do not add evidence of an association between *H. pylori* infection and reflux esophagitis. It should also be noted that studies evaluating reflux as an outcome are prone to misclassification due to the absence of a valid scale specific to children.

H. pylori Treatment and Effects on Growth

H. pylori infection in children can produce gastric lesions that weaken or destroy the gastric acid barrier,[1] interfering with micronutrient absorption, appetite, metabolism, and related factors, and thereby inhibiting growth.[79-81] A small number of studies have investigated the impact of treatment to eliminate *H. pylori* infection on growth.[79-81]

Chimonas et al. (2006) investigated 650 Alaskan children (aged 7–11 y) and reported that they found no association between elimination of *H. pylori* infection and growth outcomes, low ferritin, IDA, or ID in children treated with iron alone or iron plus antimicrobial therapy.[82] At 2, 8, and 14 mo after treatment, children who were *H. pylori*-negative showed little evidence of improvement in any of the measured growth parameters (height, weight, and body mass index) relative to persistently *H. pylori*-positive children.[82] Improvement in iron deficiency over the 14-mo period was not accompanied by clear increases in growth relative to persistent iron deficiency.[82]

Sood et al. (2005) compared the height, weight, and body mass index (BMI) of 97 *H. pylori*-positive children (mean age 11.49 ± 3.3) with dyspepsia to 160 *H. pylori*-negative children (mean age 10.96 ± 3.1) with dyspepsia.[83] Differences in mean scores for height (cm), weight (kilograms), and BMI standard deviation scores (SDs) were estimated based on the 1990 UK growth reference charts. Differences in mean scores were adjusted for socioeconomic deprivation and ethnicity. The authors reported that *H. pylori* infection was minimally associated with adjusted mean height, weight, or BMI scores in dyspeptic children. Comparing *H. pylori*-positive children who were treated for the infection to *H. pylori*-negative children, the adjusted mean height score difference was 0.33 SDs (95% CI: -0.03, 0.69), the adjusted mean weight score difference was 0.33 SDs (95% CI: -0.07, 0.72), and the adjusted BMI score difference was 0.27 SDs (95% CI: -0.11, 0.66).

In a therapeutic intervention study of children aged 4–8 y at baseline in the Andean region of Colombia, Goodman et al. (2011) and Mera et al. (2012) evaluated effects of eliminating *H. pylori* on growth. Goodman et al. (2011) reported that children who were *H. pylori*-positive positive at baseline, eliminated the infection after treatment, and remained negative throughout follow-up had higher growth velocity on average than children who were persistently *H. pylori*-positive.[79] The children who remained infection free accumulated an average gain of 0.66 cm (95% CI: 0.24, 1.05) relative to children whose infection persisted over an average follow-up of 2.5 y, independent of age, sex, and height. Mera et al. (2012) compared growth in communities where *H. pylori*-positive children received treatment to eliminate the infection to growth in communities where no intervention was offered.[81] At the end of an average follow-up of 3.7 y, children from the community that received treatment were 1.1 kg (95% CI: 0.64, 1.64) heavier on average than children from the non-intervention community, after adjusting for age, sex, father's education, number of siblings, cohort, follow-up time, *H. pylori* status, and the interaction between *H. pylori* status and follow-up time. Children from the community that received treatment were also 2.98 cm (95% CI: 2.04, 3.94) taller on average than children from the non-intervention community, after adjusting for age, sex, father's education, number of siblings, and presence of helminthes or protozoa in the stool.

Yang et al. (2012) evaluated 204 Taiwanese children aged 4 to 12 y. At baseline, 51 children tested *H. pylori*-positive and received treatment to eliminate the infection. Body weight and height were measured at baseline and 6 and 12 mo after *H. pylori* treatment, and children who received treatment were compared with those who tested *H. pylori*-negative at baseline.[84] Yang et al. (2012) reported that one year after treatment to eliminate *H. pylori*, children for whom treatment was successful had a higher average increase in weight (5.84 ± 3.37 kg vs. 4.84 ± 2.85 kg, p-value = 0.04) and height (8.00 ± 2.78 cm vs. 5.85 ± 1.81 cm, *P*-value < 0.001) than children who were *H. pylori*-negative at baseline.[84] *H. pylori*-positive children whose treatment did not eliminate the infection had a higher average gain in height (7.20 ± 2.85 cm vs. 5.85 ± 1.81 cm, *P*-value = 0.01) than children who were *H. pylori*-negative at baseline. Little difference was observed in the average increase in body weight between children with and without *H. pylori* infection at one year of follow-up (5.03 ± 2.77 kg vs. 4.84 ± 2.35 kg, *P*-value = 0.78) (**Table 6**).

In summary, there is insufficient evidence to conclude that children's growth may benefit from being treated for *H. pylori* infection. Given the potentially profound impact on children worldwide, further research should assess the effect of offering treatment to eliminate *H. pylori* infection during age periods of rapid growth such as early childhood and puberty. In pursuit of this goal, cohort studies that follow children to identify factors that influence growth could be targeted for inclusion of a component aimed at assessing the impact of eliminating *H. pylori* infection.

Mucosa-Associated Lymphoid Tissue (MALT)

Evidence of an effect of *H. pylori* infection on MALT in childhood was presented in a report by Ohno et al. (2006) on two cases in Japanese children.[85,86] A 14-y-old boy with gastric MALT with local invasion and lymph node involvement was seropositive for *H. pylori*. The boy did not complete treatment to eliminate *H. pylori* due to adverse effects; the MALT lesion spontaneously regressed over the next 24 mo without any treatment for lymphoma. This patient was followed up for 10 y and showed no signs of relapse. A 6-y-old boy with gastric MALT and *H. pylori* gastritis was treated for *H. pylori* infection. The treatment successfully eliminated the infection and the MALT lesion fully resolved. The patient was followed for 3 y and showed no signs of relapse.

Other Conditions

Oderda et al. (1992) measured serum pepsinogen I, serum gastrin and serum *H. pylori* IgG levels in 63 *H. pylori*-positive Italian children (aged 1–18 y) with abdominal pain.[20] Elimination of *H. pylori* was associated with an average decrease in serum pepsinogen I, serum gastrin and serum IgG levels. However, persisting or recurrent *H. pylori* infection was associated with a rise in serum IgG but not with pepsinogen I or gastrin levels.[20,23]

A small body of evidence on changes in ghrelin levels in children after treatment to eliminate *H. pylori* was reviewed systematically by Nweneka and Prentice (2011).[87] Pacifico et al. (2008) reported that elimination of *H. pylori* was associated with a decrease in circulating ghrelin levels and an increase in leptin levels and BMI in prepubescent children with

Table 6. Studies of response to treatment to eliminate *H. pylori* among children with gastresophageal reflux (GER)

Location, Author, Year	Study Design	Age Range (years)	Baseline Sample Size	Follow-up intervals (months)	Treatment Regimen [n]	Diagnostic Category [n]	Outcome of Interest	Of those with follow-up data	
								% with *H. pylori* eliminated	Measures of Response to Treatment
Israel, Levine, 2004[74,77]	Clinical trial	8–19	119	Mean 11.2	*HP* treatment [55]	*HP* negative at baseline [40]	Percent with improved reflux	86 [44/51]	30 [12/40]
						Eliminated *HP* [44]			34 [15/44]
						Remained *HP*+ [11]			36 [4/11]
						HP negative at baseline [40]	Percent with worsening reflux		12 [5/40]
						Eliminated *HP* [44]			18 [8/44]
						Remained *HP*+ [11]			36 [4/11]
						HP negative at baseline [40]	Mean decrease in severity score for epigastric pain		2.25 ± 0.58
						Eliminated *HP* [44]			2.4 ± 0.62
						Remained *HP*+ [11]			2.45 ± 0.52
France Pollet, 2004[76,78]	Clinical trial	3–22	78	4–6	*HP* treatment [78]	Esophagitis [14]	Percent with esophagitis	100 [43/43]	29 [4/14]
						Normal esophagus [29]			3 [1/29]
United States Gold, 2003[74,75]	Cohort	ND	90	6	*HP* treatment [ND]	*HP* cagA + [ND]	Frequency of esophageal and gastric disease	ND	Higher frequencies in children infected with *HP* cagA+ strains relative to cagA- strains
						HP cagA – [ND]			
					Post-treatment [ND]	Eliminated *HP* [ND]			Resolution of esophageal and gastric disease

HP, H. pylori; ND, no data provided in report; +, positive; -, negative.

H. pylori-associated gastritis at 6 and 12 mo follow-up.[62,88]

Yang et al. (2012) investigated whether *H. pylori* eradication restores growth while improving serum acylated ghrelin levels.[84] The authors reported that serum acylated ghrelin levels appeared to increase after treatment to eliminate *H. pylori* regardless of successful clearance of the infection. On average, children whose infection was eliminated had increased serum acylated ghrelin levels compared with baseline levels; mean post-treatment levels compared with baseline were 88.2 ± 17.3 pg/mL vs. 44.2 ± 38.1 pg/mL (*P*-value < 0.001) at 6 mo and 87.7 ± 38.0 pg/mL vs. 44.2 ± 38.1 pg/mL (*P*-value < 0.001) at 12 mo. At the same time, children whose treatment was not successful at eliminating *H. pylori* also had increased post treatment levels compared with baseline; for this group, mean post-treatment levels compared with baseline were 93.2 ± 31.6 pg/mL vs. 37.2 ± 30.9 pg/mL (*P*-value < 0.001) at 6 mo and 80.6 ± 28.8 pg/mL vs. 37.2 ± 30.9 pg/mL (*P*-value = 0.003) at 12 mo.

In summary, a small body of evidence indicates that ghrelin levels in children increase after treatment to eliminate *H. pylori.* Additional studies are needed to verify this observation across diverse populations of children, and if valid, to investigate whether these changes result from elimination of *H. pylori* or other effects of *H. pylori* treatment regimens.

Conclusion

We identified a modest body of studies yielding evidence regarding benefits to children from treatment to eliminate *H. pylori*. Few of these studies were adequately designed to obtain valid results and even fewer had sufficient statistical power for precise estimation of effects. Overall, there is insufficient evidence to draw solid conclusions about health benefits from treating *H. pylori* infection in pediatric populations. Researchers conducting clinical trials aimed at assessing effects on children's health of eliminating *H. pylori* should design multicenter trials when needed for adequate numbers of subjects; such trials should include observational analysis to compare outcomes in

children whose infection is eliminated to those with persistent infection while controlling for factors that influence the outcome of interest as potential confounders. Additional evidence of value would come from cohort studies that enroll children who have been treated for *H. pylori* infection to compare children whose infection is eliminated to those with persistent or recurrent infection on growth, iron deficiency indicators and other health outcomes of interest.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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