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# ***Helicobacter pylori* Infection, Gastric Physiology and Micronutrient deficiency (Iron and Vitamin C) in Children in Developing Countries**

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/58375>

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## **1. Introduction**

At least half the world's population are infected by *Helicobacter pylori* (*H. pylori*), making it the most widespread infection in the world [1]. Although infection occurs worldwide, there are significant differences in the prevalence of infection both within and between countries [2-4]. The overall prevalence of *H. pylori* infection in developed countries is lower than that in developing countries [3, 5]. The increased infection rate in developing countries is likely due to poor sanitary and/or living conditions. In such communities the incidence of *H. pylori* infection in infancy is also high [6, 7], and has also been associated with malnutrition and growth faltering [8]. Epidemiological data suggest the prevalence of *H. pylori* infection in children under 10 years resident in developed countries to be 0 to 5% compared to 13 to 60% in their developing country counterparts [9]. The age at which this bacterium is acquired seems to influence the possible pathologic outcome of the infection - people infected at an early age are likely to develop more intense inflammation that may be followed by atrophic gastritis with a higher risk of gastric ulcer, gastric cancer or both. Acquisition at an older age brings different gastric changes that are more likely to result in duodenal ulcer. Individuals infected with *H. pylori* have a 10 to 20% lifetime risk of developing peptic ulcers and a 1 to 2% risk of acquiring stomach cancer [10]

*H. pylori* infection also exerts diverse effects of gastric physiology - it may increase or reduce gastric acid secretion or result in no overall change in the acid output [11]. It is important to know why *H. pylori* infection produces different aberrations in gastric physiology, and consequently gastric or duodenal ulcer or gastric cancer. *H. pylori* infection has also been suggested to be associated with a variety of conditions outside of the alimentary tract. The list

of the proposed 'extragastric' association continues to grow despite the fact that *H. pylori* is a non-invasive organism and as such the infections are essentially confined to the surface of gastric-type mucosa. In an initial overview of the non-gastrointestinal manifestations of *H. pylori* [12], some biological plausibility has been suggested that underlie its association with iron deficiency anemia (IDA); cross sectional studies have demonstrated a relatively strong association. [13]

In this chapter, we will review and update the consequence of *H. pylori* infection, its role on the gastric acid secretion and some other conditions, notably IDA and iron absorption in children. The relationship between *H. pylori* infection and vitamin C levels in the blood and gastric juice will also be reviewed.

## 2. Consequences of initial *H. pylori* infection in children

There are not enough studies on the natural history of gastric infections in childhood years. In older children and adolescents, and adults it appears that *H. pylori* infection and the accompanying gastritis are lifelong unless specific eradication therapies are employed. However, several epidemiological studies, using serology [14, [15] and breath tests ([16, 17] as indirect markers of gastric infection reported spontaneous clearance in the pre-school aged children. Current evidence suggests that the overwhelming majority of *H. pylori* infected children and adolescents develop a chronic-active, antral- predominant gastritis) [18]. There is a single report suggesting the potential for *H. pylori* colonization of stomach of children without mucosal inflammation in antrum or gastric fundus [19]. Although, infection with the Cag A-positive strain was associated with more pronounced changes in the gastric physiology, limited studies in children reported no association between Cag A status and the severity of gastritis [20].

Some studies reported pan-gastritis involving both body and antrum in children infected with *H. pylori* [21, 22]. However, a formal mapping study to delineate the extent and the severity of bacterial colonization of the stomach, as well as the accompanying host cells mucosal inflammatory response to infection is lacking. To date there are not enough studies in children evaluating the healing of mucosal inflammation following eradication therapy. There are indirect evidences to suggest that resolution of inflammatory response may occur more rapidly in children than had been reported for adults [23]. In France, Ganga-Zandzou and colleagues prospectively monitored the consequences of untreated *H. pylori* infection in a group of asymptomatic children [24]. Although the density of bacterial colonization was not changed, there was both marked antral nodularity and more severe mucosal inflammation in the antrum over the 2-year follow-up of the children. However, there is the lack for comparable studies in other pediatric population, e.g. among those residing in developing countries and a greater length of follow-up. Further studies are needed to delineate the inflammatory and immune responses during development in order to provide additional insights into the interactions between the *H. pylori* and the host in such populations.

## **2.1. *H. pylori* infection and gastric acid perturbation**

Acid secretion by the gastric parietal cell is regulated by paracrine, endocrine, and neural pathways. The physiological stimuli for acid secretion include histamine, acetylcholine, and gastrin, each of which binds to receptors located on the basolateral plasma membranes of the cells. The antral region of stomach contains G cells which release hormone gastrin. When meal is ingested, the protein component stimulates G cell to release Gastrin, which travels through the bloodstream to parietal cells in the body region (fundus) to secrete acid [25]. Gastrin directly does not stimulate parietal cells but stimulates the adjacent enterochromaffin-like cell (ECL cells) to release histamine, which in turn stimulates the parietal cells. Stimulation of acid secretion typically involves an activation of a cAMP-dependent protein kinase cascade that triggers the translocation and insertion of the proton pump enzyme, H,K-ATPase, into the apical plasma membrane parietal cells [26]. As the acid accumulates and overcome the buffering effects of the food, the fall in intragastric pH inhibits further release of gastrin and thus prevents secretion of excessive amount of acids (negative feedback control).

*Helicobacter pylori* infection exerts diverse effects on gastric physiology. In acute *H. pylori* infection transient hypochlorhydria in adults is well documented [27, 28]. However, the relationship between chronic *H. pylori* infection and gastric acid secretion is not fully understood. It may increase gastric acid secretion, reduce it or results no overall changes in acid output. [11]. These alterations in acid secretion depend on the degree and distribution of gastritis caused by the infection [29, 30]. In subjects with an antral predominant gastritis, without atrophy, acid secretion is normal or increased. This is the pattern of gastritis seen in patients who develop duodenal ulceration. When gastritis is body predominant, a situation leading to gastric atrophy, *H. pylori* infection leads to markedly reduced acid secretion or achlorhydria which is also seen in patients who develop non-cardiac gastric cancer. Finally, when gastritis is mixed antral or body, *H. pylori* may have no effect on acid secretion.

## **2.2. *H. pylori* infection and increased acid output (hyperchlorhydria)**

*H. pylori* infection in the antral region of the stomach disrupts the negative feedback control of gastrin release, resulting in inappropriately high and sustained levels of gastrin following meal [31, 32]. In those subjects, the gastritis is non-atrophic and, therefore, the increased gastrin release stimulates the healthy body region of stomach to secrete excessive amounts of acid [33, 34]. The increased amount of acid output produced by this pattern of gastritis results in an increased duodenal acid load damaging the duodenal mucosa, which may eventually result in ulcer formation [35]. Eradicating *H. pylori* infection in subjects with this type of gastritis leads to lowering of serum gastrin with concomitant reductions in acid output.

## **2.3. *H. pylori* infection and low acid output (hypochlorhydria)**

In subjects with atrophic gastritis or body predominant gastritis, there also is increased gastrin release, but that is not accompanied with increased acid secretion. In such subjects, acid secretion is reduced or completely absent (achlorhydria) [36, 37]. The low acid secretion,

despite increased gastrin levels, indicates markedly impaired ability of oxyntic mucosa to secrete acid in response to gastrin. Following eradication of *H. pylori* infection in patients with this pattern of gastritis, there is recovery in acid secretion [36, 37]. However, the degree of recovery in acid outputs is variable – acid output resumes to normal level in some patients while very small increase occurs in others [36]. The recovery in acid outputs following eradication of infection coincides with the disappearance of organism as well as resolution of inflammation of the body mucosa. However, there is little evidence of resolution of the atrophy of body mucosa. Capurso *et al.* [23] observed that both pangastritis and pangastritis-induced hypochlorhydria were more prevalent in adult patients with *H. pylori* who had anemia than in those who did not have anemia.

### 3. Role of *H. pylori* infection in gastric acid perturbation in children

There are only a few pediatric case reports on gastric acid secretion in *H. pylori* infection. Several studies in the pre-*H. pylori* era [38, 39] and very recently [40] studies observed the maximal acid output higher in children with duodenal ulcer than in the children without peptic-ulcer disease. However, no study has examined the relationship between gastric acid secretion and *H. pylori* infection in asymptomatic young children living in developing countries. The effect of *H. pylori* on gastric acid production can be examined by studying individuals with and without infection or, more directly by examining before and after eradication of *H. pylori* [41]. In an attempt to see if *H. pylori* infection is associated with gastric acid perturbation in Bangladeshi children, basal gastric acid output (GAO-B) and stimulated gastric acid output (GAO-S) just before and after pentagastrin stimulation in age matched *H. pylori*-infected and non-infected children were measured. Experiments were repeated in infected children 8 weeks after completing a 2-week course of anti-*H. pylori* therapy to evaluate the influence of *H. pylori* on gastric acid secretion. Comparison of acid output between infected and non-infected children both before and after eradication therapy is shown in Table 1. Both the basal acid output (GAO-B) and the stimulated gastric acid outputs (GAO-S) were significantly lower in *H. pylori* infected children compared to *H. pylori* negative group. The mean GAO-B and GAO-S of the infected children were estimated to be 30% and 50% respectively of that of non-infected children. Successful eradication therapy was associated with a significant rise of both the basal and the stimulated acid output values reaching equivalence to those in the *H. pylori*-negative children. Improvement of GAO following anti-*H. pylori* therapy suggests a causal link of *H. pylori* infection and depressed GAO in this population. Whether the observed reversibility of acid secretion to normal level within a relatively short term period of eradication therapy was associated with recovery from corpus gastritis is not known as gastric biopsy for histological examination was not performed. It is also important to know the acid secretory status after a long term period of eradication in settings with possibilities of having re-infection by the organism as a consequence of poor hygiene and environmental contamination.



	Non-infected (n=30)	p	Infected before treatment (n=30)	p	Infected after treatment (n=28)
Basal Acid Output (BAO)	0.23 ± 0.30	0.06	0.62 ± 0.9	NS	0.65 ± 0.65
Stimulated Acid Output	2.04 ± 1.4	0.001	3.4 ± 2.5	NS	3.3 ± 2.1

**Table 1.** Comparison of acid outputs (mMol/h between infected and non-infected children along with effect of anti-*H. pylori* therapy

#### 4. Potential mechanisms of *H. pylori*-induced hypochlorhydria

*H. pylori* induced hypochlorhydria might be due to the bacterium releasing some substances that can directly inhibit acid secretion. Several candidate substances have been identified, which inhibits parietal cell function *in vitro*, but the evidence for involvement of these substances for the *in-vivo* effects remains weak. *H. pylori* infection also produces ammonia, which may uncouple the proton pump [42]. But the ammonia produced by *H. pylori* infection in hypochlorhydric subjects is relatively small [43]. Another problem in attributing the impairment of oxyntic mucosal function to the presence of *H. pylori* organisms is that density of colonization of the gastric mucosa with the organism is similar or lower in subjects with hypochlorhydria than in subjects with normal or high acid secretion [36]. Therefore, current knowledge precludes attributing impaired function of oxyntic mucosa as a direct effect of some bacterial factor.

An alternative explanation for the impaired acid secretory function is infection-induced inflammation of the oxyntic mucosa, since the severity of inflammation of the body mucosa is more marked in subjects with *H. pylori* associated hypochlorhydria than in subjects with *H. pylori* infection with normal or increased acid secretion [44]. This raises the possibility that a product of inflammatory response following infection might inhibit acid secretion.

The molecular mechanisms underlying *H. pylori*-induced hypochlorhydria is not completely understood. However, it has been shown that *H. pylori*-induced pro-inflammatory factors, such as interleukin-1 $\beta$ , may contribute to hypochlorhydria [26, 45]. The increased production of this cytokines may be important because it is very potent inhibitor of acid secretion [46] and and may play a role in chronic *H. pylori*-induced hypochlorhydria. Polymorphisms in IL-1 $\beta$  gene cluster may control the extent and the duration of hypochlorhydria with initial *H. pylori* infection [47], which has been noted to be linked to increased risk for atrophy and consequently gastric cancer [48]. It is possible that inflammatory factors, such as IL-1 $\beta$  cause an inhibition of acid secretion from parietal cells via paracrine pathways. Using freshly isolated rabbit gastric glands and culture parietal cells, Fang and colleague observed that Vac-A toxin treatments inhibits gastric acid secretion by preventing the recruitment of gastric H, K-adenosine triphosphatase (H, K-ATPase), the parietal cell enzyme mediating acid secretion. [49]. This was the first evidence that *H. pylori* Vac-A toxin impairs gastric parietal cell physiology by disrupting the apical membrane cycloskeletal linkers of the gastric parietal cells. Studies in animal models as well as epidemiologic studies of *H. pylori* isolates from humans have

suggested that VacA toxin enhances the ability of *H. pylori* to colonize in the stomach and contributes to the development of symptomatic diseases (15).

#### **4.1. Potential consequences of *H. pylori* induced hypochlorhydria**

*H. pylori*, by producing hypochlorhydria or impaired gastric barrier may contribute to childhood malnutrition in developing countries through malabsorption or increased susceptibility to enteric infections [50]. Several observations demonstrated a correlation between *H. pylori* and malabsorption of essential nutrients; epidemiological studies have shown an association between *H. pylori* infection and iron deficiency anemia, while the absorption of some vitamins such as vitamin B12, vitamin A, vitamin C, folic acid and Vitamin E may also be affected by the infection [51]. The main mechanism related to malabsorption of these components is the modified intragastric pH (hypo or achlorhydria) due to *H. pylori* infection. On the other hand, *H. pylori* eradication has been shown to improve serum level of iron and vitamin B12, and some effects on Vitamin A and Vitamin E absorption as well as late effects on ghrelin levels [51].

### **5. *H. pylori* infection and iron deficiency anemia**

#### **5.1. Iron deficiency and iron deficiency anemia**

Iron deficiency (ID) and iron deficiency anemia (IDA) are major public health problems, especially in children and women of childbearing age in developing countries [52], and is considered one of the ten leading global risks factors in terms of its attributable disease burden [53]. It has been estimated that globally approximately 1.6 billion people, representing 25% of the total population are anemic [54]. ID is considered to account for 50% of identified anemia, and 800,000 deaths worldwide can be attributed to IDA. Deficiency of this trace element has adverse implications on health at all stages of life. When iron deficiency occurs during critical windows of brain development, the resultant cognitive deficits may be irreversible and unresponsive to subsequent improvements in the iron status [55]. In adults, ID and IDA can adversely impact physical work capacity and work productivity - variables that may have a detrimental impact on their economic potential [56].

#### **5.2. *H. pylori* and iron deficiency anemia**

Several reports have demonstrated an association between *H. pylori* infection and anemia, ID, and IDA, although the mechanisms of the interactions have not been well defined [13, 57-60]. A few case reports indicate that successful eradication of *H. pylori* results in improving iron status and anemia [61-63]. Other studies implicate *H. pylori* as a cause of IDA, refractory to oral iron treatment (refractory iron deficiency or sideropenic anemia); similarly eradication of *H. pylori* has resulted in improved iron status in children [58, 64-67]. Overall, these findings suggest that a substantial proportion of global ID and IDA might be attributed to *H. pylori* infection, leading to a recommendation by some for *H. pylori* eradication therapy in infected

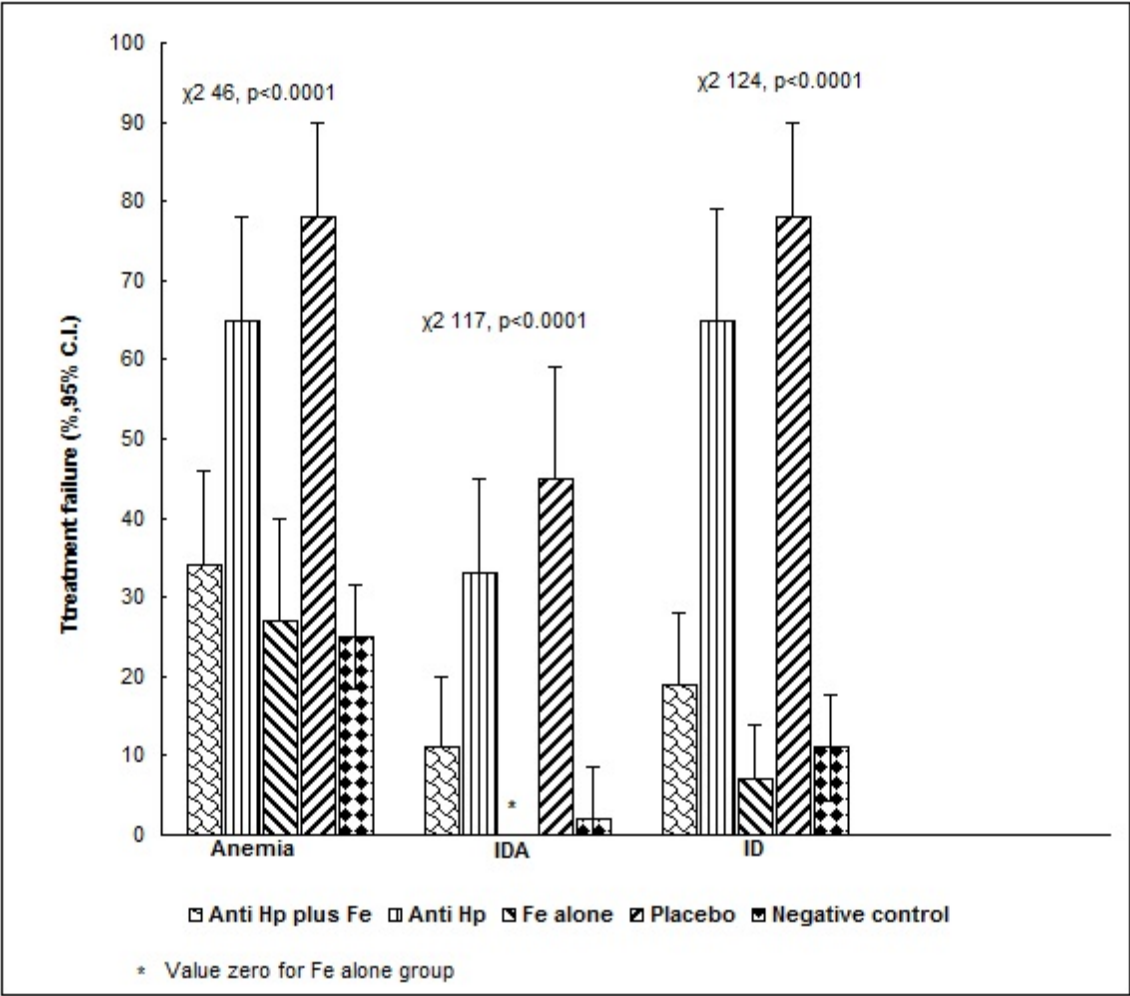
individuals with unexplained IDA [68]. However, methodological limitations, including small sample sizes and lacks of control groups, among others, do not allow conclusive interpretation of the results. No previous study has examined whether or not active *H. pylori* infection is causally linked to IDA in young children living in less developed countries. Although the mechanisms for *H. pylori*-associated IDA is not fully understood, *H. pylori*-induced chronic pan gastritis with resultant achlor- or hypo-chlorhydria [41, 69] and reduced ascorbic acid secretion in the gastric mucosa [70, 71] may lead to reduced iron absorption since they are essential for alimentary iron absorption; they not only convert ferric iron to the ferrous form, which maintains solubility at the alkaline pH of the duodenum, but also chelates with ferric chloride that is also stable at a pH >3. Uptake of iron by *H. pylori* is also suggested [72]. Whether *H. pylori* is a cause or associated with ID or IDA is not fully elucidated.

In Bangladesh, a randomized controlled community based study was conducted to determine whether or not *H. pylori* is a cause of IDA or a reason for treatment failure of iron supplementation in children with IDA [73]. The population consisted of 260 children, 2-5 years (200 *H. pylori* infected, detected by positive urea breath test [UBT], and 60 uninfected) with IDA. IDA was defined as a combination of low hemoglobin (Hb <110 g/L) and a low serum ferritin (SF <12 µg/L) plus elevated serum transferrin receptor (sTfR >8.3 mg/L) [74]. ID was defined as Hb <110 g/L and SF <12 µg/L, or sTfR >8.3 mg/L. They were randomly assigned to one of 4 regimens: (i) 2-week course of anti-*H. pylori* (anti-*H. pylori*) triple therapy (amoxicillin 15mg/kg.dose and clarithromycin 7.5mg/kg.dose, both administered twice daily; and a single 20 mg dose of omeprazole per day) plus a 90-day course of oral ferrous sulfate in elixir (3 mg/kg elemental iron daily) (anti-*H. pylori* therapy plus iron); (ii) a 2-week's anti-*H. pylori* therapy plus placebo for iron for 90 days (anti-*H. pylori* alone); (iii) 2-week's course of placebo for anti-*H. pylori* therapy but ferrous sulfate (3 mg/kg for 90 days) (Fe alone); and (iv) 2-week's placebos for anti-*H. pylori* therapy and a 90-day course of placebo for iron (positive control). For precisely determining the role of *H. pylori* infection in the treatment failure of iron supplementation, the study included a fifth group of children with IDA but without *H. pylori* infection (negative control), who were treated with open iron therapy alone for 90 days. Iron status was reassessed after 90 days in all children; those with continued IDA/ID were given a 60-day course of ferrous sulfate.

The results of the study indicated that iron status, as reevaluated on day-90, improved in all groups. However, the improvement was significantly higher among 3 groups receiving iron (anti-*H. pylori* plus iron, iron alone or negative control receiving iron). A greater proportion of infected children receiving iron experienced correction of IDA than those receiving placebo or anti-*H. pylori* alone (68% for anti-*H. pylori* plus iron, 76% for iron alone, 25% for placebo and 36% for anti-*H. pylori* alone,  $F=49$ ,  $p<0.0001$  (Figure 1). The results suggest no role of anti-*H. pylori* in IDA. Regarding ID, iron therapy had the most pronounced effect - correction occurred in 100% of children receiving iron compared to only 50% of children receiving anti-*H. pylori* alone or placebo. It is important to note that compared to placebo or iron therapy, anti-*H. pylori* therapy did not improve iron status or decrease IDA and ID prevalence. Therefore, the study concluded that *H. pylori* is neither causally linked with IDA nor is a reason for treatment failure of iron supplementation in children. The findings were in contrast with



a randomized controlled trial by Choe and colleague who showed that treatment of the infection was associated with a more rapid response to oral iron compared with iron supplementation alone, and that *H. pylori* eradication led to enhanced iron metabolism even in those not receiving oral iron therapy, suggesting a causal relationship between *H. pylori* infection and IDA [62]. A recent meta-analysis of 12 case reports and series, 19 observational epidemiologic studies and 6 interventional trials, concluded *H. pylori* infection to be a major risk factor for iron deficiency or IDA especially in high-risk groups [75]. Several other meta-analyses of randomized controlled clinical trials suggested that treatment of *H. pylori* infection could be effective in improving anemia and iron statue in IDA patients infected by *H. pylori*, particularly in patients with moderate or severe anemia [76], [77], [78]. Although an association between the pathogenesis of IDA and *H. pylori* infection has been well recognized, a causal link is yet to be established.



**Figure 1.** Treatment failure (%) of anemia, IDA, and ID in children receiving different therapies. \*Value of zero for the Fe-alone group (Adapted from Sarker et. al. 2008)

### 5.3. *H. pylori* and iron absorption

Non-heme iron absorption requires an acidic milieu. Non-water-soluble iron compounds, e.g. ferrous and ferric pyrophosphate are often used in the fortification programs because they cause no unacceptable organoleptic changes in the fortified food. However, these compounds need gastric acid for their solubilization and absorption. Therefore, if gastric acid output is compromised as a consequence of *H. pylori* infection in a large proportion of the target population, the effect of food fortification programs using ferrous fumarate might be less than expected due to reduced absorption of iron from fortified foods. Keeping this in mind, a study was conducted in 12 Bangladeshi children to measure iron absorption from a non-water-soluble iron compound (ferrous fumarate) and from a water-soluble iron compound (ferrous sulfate) before and after treatment of their *H. pylori* infections. For comparison, 12 uninfected age matched children were studied in parallel; all children had IDA [79]. Iron absorption from ferrous fumarate was compared with that from a highly bioavailable, water-soluble iron compound (ferrous sulfate) in a randomized, crossover study using a double stable-isotope technique. Incorporation of  $^{57}\text{Fe}$  and  $^{58}\text{Fe}$  into erythrocytes 14 days after administration was used as an index of iron absorption [80]. The study noted geometric mean of iron absorption from ferrous sulfate and ferrous fumarate to be 19.7% and 5.3% respectively ( $P < 0.0001$ ;  $n = 12$ ) before treatment and 22.5% and 6.4% respectively after treatment ( $P < 0.0001$ ;  $n = 11$ ) of *H. pylori*-infected children (Table 2). The corresponding values for uninfected children were 15.6% and 5.4% ( $P < 0.001$ ;  $n = 12$ ). Geometric mean relative absorption (absorption of ferrous fumarate compared to ferrous sulfate) was 26.9% and 34.8% in *H. pylori*-infected and uninfected children respectively, and 28.3% in *H. pylori*-infected children after treatment. The results clearly indicate that iron absorption from ferrous fumarate was significantly lower than that from ferrous sulfate in both *H. pylori*-infected and uninfected Bangladeshi children and also that *H. pylori* infection, *per se*, does not influence iron absorption in young children. The efficacy of ferrous fumarate in iron fortification programs to prevent iron deficiency in young children should, therefore, be further evaluated. The results of iron absorption tests may rule out the possibility of *H. pylori* induced hypochlorhydria in interfering iron absorption in Bangladeshi children.

#### 5.3.1. Mechanism of IDA

The interaction between *H. pylori* and iron metabolism, based on clinical, ferrokinetic and microbiological evidences has generated increasing interest. Iron is an essential micronutrient for virtually all organisms, and *H. pylorus* is no exception. *H. pylori* may cause iron deficiency anemia by competing with the host for the acquisition of alimentary iron. In the stomach, ingested food provides iron in heme and nonheme forms. The low pH and the digestive enzymes in the stomach release iron from ligands to the gastric lumen. *H. pylori* and the host both compete for the free iron by deploying mechanisms specifically devised to sequester and facilitate the acquisition of iron as well as other essential metals. *H. pylori* seems particularly adept at competing for iron [81]; it has been established that *H. pylori* competes for iron in murine hosts to an extent so as to cause iron deficiency when the dietary iron intake is poor [82]. In order to ensure a sufficient supply of iron from the environment, *H. pylori* cells display

	<i>H. pylori</i> -infected children before treatment (n=12)			<i>H. pylori</i> -infected children after treatment (n=11)			Uninfected children (n=12)		
	Ferrous fumarate	Ferrous sulfate	Relative absorption	Ferrous fumarate	Ferrous sulfate	Relative absorption	Ferrous fumarate	Ferrous sulfate	Relative absorption
		%			%			%	
Geometric mean	5.3	19.7	26.9	6.4	22.5	28.3	5.4	15.6	34.8
+1SD	13.5	32.9	49.0	12.9	33.0	47.7	12.7	30.1	64.3
-1SD	2.1	11.8	14.8	3.2	15.4	16.8	2.3	8.1	18.8
<i>P</i> <sup>1</sup>	<0.0001			<0.0001			<0.001		

<sup>1</sup>P value for iron absorption from ferrous fumarate compared with that from ferrous sulfate within each group.

Adapted from Sarker et al. 2004

**Table 2.** Fractional iron absorption from ferrous fumarate and ferrous sulfate in uninfected children with iron deficiency anemia (IDA) and in *Helicobacter pylori* infected children with IDA before and after treatment

a repertoire of high-affinity iron-uptake systems. It seems that *H. pylori* strains isolated from patients with IDA demonstrates enhanced iron-uptake activity and may be more adept at competing with the host for iron [83]. So far, little is known about how *H. pylori* cells acquire iron bound to host-binding proteins. *In-vitro* studies indicate that human lactoferrin (LF) supports full growth of *H. pylori* in media lacking other iron sources [72]. LF is released from neutrophil, which captures iron from transferrin in conditions with iron-poor state (hypoferremia) and has been observed to be abundant in human stomach resection specimens from patients with superficial or atrophic gastritis [84], [84]. The iron uptake by *H. pylori* via a specific human LF receptor may thus play a major role in the virulence of *H. pylori* infection in its uptake of iron. A 70-kDa LF-binding protein from the outer membrane proteins of *H. pylori* was identified in bacterium grown in an iron-starved medium, implicating the protein in iron uptake [85]. Comparative binding experiments with bovine or human LF, and with transferrin of horse, bovine or human origin indicated that this protein is highly specific for human LF. By means of this LF-binding protein, *H. pylori* is able to by-pass the human hypoferremic defensive response -a phenomenon when total extracellular iron is reduced in the host limiting bacterial growth. Further *in vivo* studies demonstrated increased concentration of LF in the biopsy specimen [86] and in the gastric juice [86] of patients with *H. pylori*-related gastritis, and also that LF tissue levels correlate significantly with the degree of inflammation of the gastric mucosa. Two outer membrane proteins, FrpB1 and FrpB2 have also been implicated in hemoglobin binding [81]. In keeping with this, the ability of *H. pylori* to use hemoglobin as an

iron source is well documented [87]. Several iron-repressible outer membrane proteins from *H. pylori*, including FrpB1, seem to be responsible for heme utilization [88]

#### 5.4. *H. pylori* and vitamin C

Ascorbic acid is the reduced form of the vitamin, which can act as a potent antioxidant for neutralizing nitrite-derived mutagens protecting against gastric carcinogenesis [90]. Vitamin C is first absorbed and then is actively secreted, mainly in the antral mucosa, from plasma into gastric juice. Once there, it is able to react with nitrosating agents preventing N-nitroso compounds formation; however, vitamin C in the stomach interacts with iron improving its absorption. In children, *H. pylori* infection was associated with reduced gastric juice ascorbic acid concentration, and the effect was more pronounced in patients with the CagA positive strain [20]. In adults, *H. pylori* infection is also recognized to lower the concentration of vitamin C in gastric juice as evident from a study involving randomly chosen 25-74 years old men and women of north Glasgow, UK. Compared to the non-infected, the *H. pylori* infected had 20% lower concentration of vitamin C in their plasma. [91]. The mechanism whereby *H. pylori* infection lowers vitamin C concentration in gastric juice is unclear, but there are several possibilities. Infection has been associated with significant reduction of gastric juice vitamin C concentration due to chronic gastritis and/or *H. pylori* oxidase activity [92]. Study in Korean children also demonstrated significant negative correlation between vitamin C level in gastric juice and the degree of active and chronic inflammation in the antral mucosa. Vitamin C levels in whole blood, plasma, and gastric juice and the gastric juice pH were also closely related to the severity of *H. pylori* infection and the histologic changes in the stomach in those children [93]. *H. pylori* has been noted to potentiate the polymorphonuclear leukocyte oxidative burst [94], accompanied by a considerable production of reactive oxygen metabolites. Within the microcirculation of the gastric mucosa ascorbic acid may be consumed during scavenging of these reactive oxygen metabolites as vitamin C is the first line of defense against the oxygen free radical damage in the human body [95]. Low level of Vitamin C may be a consequence of an irreversible inactivation of the ingested vitamin C in the intestinal lumen prior to its absorption. Studies have demonstrated that *H. pylori* produces reductions in stomach vitamin C due to its degradation to dehydroascorbic acid (DHAA) - a metabolite that may be oxidized afterwards irreversibly to 2,3- Diketo- 1-gluconic acid. DHAA is unstable at high pH values, and thus hypochlorhydria or achlorhydria may reduce the stability even further and thus the bioavailability of this vitamin.

In developing countries, low intake of vitamin C-enriched food is associated with higher prevalence of *H. pylori* infection, and together will lead to significantly reduced systemic availability of this vitamin. Therefore, prolonged *H. pylori* infection, as it is frequent in developing countries, may impact absorption of several micronutrients including vitamin C. The impact of *H. pylori* infection on the prevalence of micronutrient malnutrition is not currently known, but it is known that there is a strong correlation of both high prevalence of *H. pylori* infection and micronutrient deficiency in developing regions. Various fortification programs are being carried out in developing regions using iron and/or zinc sources e.g. electrolytic iron, ferric pyrophosphate, and zinc oxide. They need secretion of an adequate

amount of hydrochloric acid for optimal absorption. Higher prevalence of *H. pylori* infection is associated with low levels of vitamin C in serum and in gastric juice in children [20]; however, there is no consensus about the usefulness of vitamin C supplementation in the management of *H. pylori* infection. In review of the current literature, it may be concluded that high concentration of vitamin C in gastric juice might inactivate *H. pylori* urease [98], the key enzyme for survival of the pathogen and its colonization into acidic stomach. However, it is not certain if vitamin C will be useful in regions with high prevalence of iron and/or zinc deficiency as well as high *H. pylori* contamination rates.

## 6. Conclusion

The combination of micronutrient deficiency and more frequent enteric infections consequent to *H. pylori*-induced hypochlorhydria is likely to have a profound impact on health of children in developing countries with high prevalence of *H. pylori* and lower intake of reliable nutritional sources of bioavailable iron and ascorbic acid. Thus, prevention of *H. pylori* infection could potentially have an important impact on iron deficiency anemia or other micronutrient deficiencies in the developing world.

## Acknowledgements

I gratefully acknowledge Dr. Mohammed Abdus Salam, Director, Research & Clinical Administration and Strategy, icddr,b for his review and valuable comments.

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