Relationship between Helicobacter pylori infection and iron deficiency anemia in children: A review article

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Abstract

Background: One of the greatest prevalent chronic illnesses, Helicobacter pylori (H. pylori), affects around 50% of people globally. Early infancy is when this virus is most often contracted, particularly in developing nations. The frequency of H. pylori varies greatly across nations; in underdeveloped nations, 50% of children are infected by the time they become 10 years old. The beginning of several Gastro intestinal tract pathologies, including active persistent gastritis, peptic ulcers, gastric carcinoma, extra-gastric symptoms, thrombocytopenic purpura, and anemia owing to inadequate iron reserves iron deficiency anemia (IDA), is discovered to be related with H. Pylori infections. A link between anemia and H. pylori infections is supported by a variety of data from epidemiological and clinical research.

Objectives: To highlight connection between Helicobacter pylori infections and IDA in children, and to explore the mechanism of this association.

Conclusion: Infection with Helicobacter pylori is substantially linked with iron deficiency anemia in children.

Keywords: Helicobacter pylori; IDA; iron deficiency.

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Introduction

over than 50% of the worldwide people is thought to be affected by the prevalent stomach infection Helicobacter pylori (H. pylori), which is linked to a number of gastropathies like persistent gastritis, peptic ulcers, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric carcinoma **(Hooi et al., 2017).** With over than 50% of the worldwide people (Around 30% of children's and 60% of elderly) infected, it is the greatest prevalent infectious human pathogen and is linked to 90 percent of duodenal ulceration and 70 percent of benign gastric ulceration. A HP positive group had a 1.7–5.3 times greater relative risk of developing gastric carcinoma than an HP negative group**(Choi, 2016).**

Regarding to WHO, iron insufficiency affects over 25% of the global population, making it the most prevalent micronutrient deficit globally and one of the most significant public health issues. Preschoolers and women of reproductive age are most likely to suffer from iron insufficiency, especially in areas of Asia and Africa where there is little availability to foods high in iron.Despite increases in public health awareness, a rise in the breastfeeding rate, and the provision of iron-fortified foods in diets, the incidence of IDA is still high in infants and young children. These data highlight the need of ongoing monitoring, early identification, and management for iron insufficiency in children, especially in high risk populations **(Roganović and Starinac, 2018)**.

Anemia is a discovery that requires more research rather than being regarded as a diagnosis. In youngsters, it is often brought on by slower red blood cells (RBCs) development or faster RBCs turnover. Most kids with mild anemia don't exhibit any symptoms or indicators. Some people may exhibit pallor, agitation, or palpitations together with shortness of breath. Tachycardia, tachypnea, and heart failure may be detected during physical examinations, particularly in kids with severe or acute anemia**(Abo El-Naga et al., 2020).**

Numerous extra-gastric conditions, likeIDA, chronic idiopathic purpura, stunted development, and type 2 diabetes are linked to Helicobacter pylori. Although the magnitude of the interactions has not been established, some investigations suggested aconnection with H. pylori infections and anemia, ID, and IDA **(Pacifico et al., 2014)**.Thorough investigations and meta-analysis that were done to investigate the incidence of low iron reserves in H. pylori-infected individuals compared to healthy people, and to compare the effects of H. pylori cure plus iron medication on ferritin and

hemoglobin concentrations compared to iron medication. Lately, five meta-analyses involving both young and adult'spatients have demonstrated a connection between infection with H. pylori and IDA.

Regarding to recent investigation, H. pylori infection is linked with a higher probability of iron reserves to be depleted. A combination of iron treatment and H. pylori eradication therapy may help raising ferritin and hemoglobin levels **(Malfertheiner et al. 2017)**. This review's objective was to provide proof of the connection between childhood IDA and H. pylori infection.

Evidence based association

The connection between H. pylori infection and IDA was first noted in 1991 by Blecker et al. who successfully treated a female patient aged fifteen with IDA who had been diagnosed with anemia-related syncope and H. pylori-induced persistent active bleeding gastritis without the use of iron supplementation **(Tsay and Hsu, 2018)**.

Although a few studies failed to find this connection, the correlation between Infection with H. pylori and unexplained IDA has been revealed in young and adults'groups. Qu et al. recently a performed meta-analysis of 15 case-control investigations to look at the connection between IDA and Infection with H. pylori. In five trials, Infection with H. pylori was identified by endoscopy and histological analysis; patients with stomach cancer and peptic ulcer illness were excluded from these investigations. The other 10 trials used urea breath testing or serology to confirm H. pylori infections. The odds ratio (OR) for IDA in individuals with Infection with H. pylori was 2.2 (95% confidence interval [CI]: 1.5-3.2), according to the data. Numerous trialshave revealed that IDA recovery with H. pylori clearance that was effective without the use of iron supplementation **(Qu et al., 2010).**

Forty-four patients randomly allocated into two groups underwent a blinded randomized controlled interventional trial. 22 people in group 1 had Hb less than 11g/d and were identified with IDA. 22 youngsters in Group 2 seemed to be in good health. In comparison to healthy kids, children with IDA and children with refractory IDA had a considerably greater prevalence of Helicobacter pylori infections, according to the authors. This reveals that H.pylori may be one of the main reasons of IDA and refractory IDA **(Abo El-Naga et al., 2020)**.

In line with the earlier work, Abou-Taleb et al. conducted prospective case-control research with 200 school-aged IDA patients and 50 nonanemic, matched ageand gender nonanemic controls. Of

them, 6 (12%) controls and 72 (36%) children with IDA exhibited positive levels for H. pylori specific IgG (P = 0.036). Significantly negative correlations between the Hb level, MCV, HCT, and serum ferritin were found in the H. pylori IgG antibody titer. They showed a strong correlation between IDA and positive H. pylori serology in children of school age. **(Abou-Taleb et al., 2017).**

Hassan et al. in their evaluation of 60 individuals split into two groups, Group I was composed of 30 individuals with hemoglobin (Hb) levels less than 11g/dL who had iron deficiency anemia. Group II consists of 30 healthy kids (control Group). They discovered that all CBC values were considerably lower in cases than in controls. Serum iron, ferritin, and TIBC levels considerably decreased in cases compared to controls. They discovered that there was much more evidence of H pylori antigen in stool samples from patients compared to controls. p-value of 0.002 compares 63.3 percent to 23.3 percent. **(Hassan et al., 2020).**

In recent case-controlled research, **Elkhalifa et al.** tested H. pylori infection's impact on complete blood counts (CBC). As a control group, 50 healthy volunteers were involved, whereas 130 recruited persons with proven H. pylori infection made up the case group. According to this study , patients with H. pylori infections had considerably lower median values of RBCs, Hb, HCT, and MCV than the control group. Infected Patients with H. pylori had substantial impacts on certain hematological markers.**(Elkhalifa et al., 2021)**.

Similarly**, Hammoodi et al.**analyzesthe connection between H. pylori and IDA in kids aged 6 to 12 years old.50 IDA-positive children and 50 matched age and gender, non-anemic controls were evaluated. The findings showed that IDA and H. pylori infection were statistically significantly associated. IDA sufferers were 12 percent more likely than healthy (control) group to have H. pylori antigen in their feces **(Hammoodi et al., 2019)**.

Gilbert et al. analyzed the results of 105 children aged 5 to 15 years (35 cases and 70 controls) revealed that Hb values in kids with H. pylori infections were smaller than those in kids with H.pylori IgG-negative kids. They claimed that the development of anemia in children is strongly correlated with seropositivity of H. pylori infection (**Gilbert et al., 2019**).

Mechanism of association

Iron deficiency anemia is caused by H. pylori in various different ways. First, hemorrhagic gastritis, peptic ulcers, and stomach cancers may all contribute to increased iron loss. Second, it has been shown that the H. pylori CagA protein takes involved in the acquisition of iron

from interstitial holotransferrin. As the bacterium grows, H. pylori is better able to absorb iron. Third, because of gland atrophy, corporal gastritis caused by H. pylori may reduce acid production, which lowers dietary iron absorption **(Tsay and Hsu, 2018)**.

As evidence that H. pylori effectivelyinteracts with the host for the accessible iron, Flores et al. shows how the bacteria can change the intracellular ironconcentrationwithin gastric epithelial cells. They also proposed that the breakdown of lysosomal ferritin may help the pathogenicity of the bacteria and contribute to its retention in the human stomachs**(Flores et al., 2017).**Xu et al, in a retrospective investigation, Infection with H. pylori and IDA are significantly correlated, with ORs of 1.39 for medium to extreme anemia and 1.05 for mild anemia. **(Xu et al., 2017)**.

While Katu et al. revealed how H. pylori genetic traits may affect whether infants and adolescents develop IDA, **(Kato et al., 2017)**. In fact, they discovered that IDA patients had greater expression levels of the sialic acid-binding (sab) and vacuolating cytotoxin gene A (vacA) than healthy individuals did. Maruyama et al. convincingly had showed how H. pylori removal may stop preclinical IDA in elderly people and reduce weight loss **(Ražuka-Ebela et al., 2018)**.

Hepcidin, a tiny protein in charge of controlling iron recycling and the iron balances of the body, was the subject of research by Azab et al. The liver produces hepcidin, which controls the release of iron by macrophages and the absorption of iron from enterocytes. Hepcidin serum levels are increased by H. pylori infections, which blunt the effects of iron treatment. **(Azab et al., 2013)**. H. pylori's capacity to get iron from human transferrin and lactoferrin was established by Senkovich et al. In contrast to strains from people without IDA, Yokota et al. found that several single nucleotide polymorphisms (SNPs) in the H. pylori neutrophileffect activating protein were more prevalent in strains from IDA patients. These polymorphisms in H. pylori cause it to ingest iron more quickly than other strains. The environment in which inorganic iron dissolves best is one that is quite acidic, therefore H. pylori infections may decrease the absorption of dietary iron.**(Gravina et al., 2018)**.

Patients with refractory IDA and those infected with CagA-positive strains had enhanced blood concentrations of TNF, a pro-inflammatory cytokine that may contribute to anemia. Other potential contribute to IDA in infectedpeople with H.pylori include aspirin usage concurrently

with non-steroidal anti-inflammatory medication treatment or persistent or acute hemorrhage brought on by erosive gastritis **(Gravina et al., 2018)**.

In conclusion, as shown in (Table 1), multiple investigations have definitely shown the connection between H. pylori and IDA. In individuals with unexplained IDA, current internationaland national recommendations advise treating H. pylori. **(Tsay and Hsu, 2018)**.

Table 1. Observational investigations on the connection between iron reserves and Helicobacter pylori

Study	Study design	Participants	H.Pylori detection	Results
Xia et al.(2012)	Cross-sectional	Girls (12–18 years old; n=1037)	Identification of stool antigens and serum IgG antibodies	The IDA group showed a 46.9% incidence of H. pylori infections, compared to a 28.1% incidence in the non-anemic group.
Darvishi et al.(2014)	Cross-sectional	70 healthy, non-anemic children and 64 children with an IDA diagnostic	Serum IgG antibodies	A positive H. pylori infection was present in 80.3% of IDA patients and 14% of non-anemic controls, with a statistically substantial variation.
Hoseinzadeh et al. (2010)	Cross-sectional	100 IDA children aged 7- 12 years	Serum IgG Antibodies	H. pylori antibody value was inversely correlated with serum ferritin and iron
Gilbert et al. (2019)	Retrospective case-control	105 Children Aged 5-15 Years (35 were cases and 70 were the controls)	Serum IgG antibodies	Children with H. pylori infections showed lower levels of hemoglobin than kids whose IgG tests were negative for the disease.

Table 2. Clinical studies examining how anti-Helicobacter pylori medication affects anemia

Study	Study design	H.Pylori detection	Results
El-Aziz Awad et al.(2014)	Anti-H. pylori and Iron taken orally (n = 20) make up group (A). Anti-H. pylori (n = 20) in group (B). Iron taken orally (Group C; n = 20)	H. pylori serum IgG antibodies	In children groups who got anti-HP treatment, either in conjunction with iron or alone, iron parameters considerably improved.
Cardenas et al.(2011).	Oral iron and anti-H. pylori (n = 32) make up group (A). Sequential anti-H. pylori in group (B) (n = 29) Group 1 contains Oral Iron (n = 23). (C). group (D) with just placebos (n = 26)	IgG antibodies to H. pylori in urine and l3C-labeled urea breath tests	When compared to children who had their illness not cleared up, they discovered that those who did saw a 3-fold larger median variation in serum ferritin from baseline.
Gessner et al. (2006)	Dietary iron and anti-H. pylori in group (A) (n = 79). Dietary iron (Group (B)) (n = 113)	l3C-Iabeled urea breath tests	Insufficiency or moderate anemia was detected in a group with a great incidence of H. pylori, and these conditions persisted up to 14 months after the start of management.
Choe et al. (2001)	Anti-H. pylori group (A) (n = 12) Oral iron in Group (B) (n = 9)	Rapid urease test and histology	Substantial enhances in iron measures after H. pylori treating, but no substantial differences in patients just taking oral iron treatment
Sarker et al. (2008).	Group (A): oral iron and anti-H. pylori (n = 50). Anti-H. pylori group (B) (n = 50). Iron taken orally, group (C) (n = 49) Placebos exclusively in Group (D) (n = 51)	l3C-Iabeled urea breath tests	Young Bangladeshi children with IDA/ID are not caused by H. pylori, and iron supplementation is not ineffective as a therapy for either condition.

Effect of eliminating H Pylori on refractory or inexplicable IDA

Nearly 15% of cases of IDA are refractory or unexplained. It is a diagnostic and evaluative challenge that makes use of a variety of tests, including endoscopies for the whole gastrointestinal spectrum and stool testing for parasite infestations. When the endoscopygut workup is unable to identify the etiology of IDA, the condition is referred to as "unexplained IDA." On the other hand, a significant number of patients are referred to as having "refractory IDA"

if they do not improve after receiving iron supplementation for 4-6 weeks at a daily intake of at least 100 mg iron.

El Demerdash et al. 104 people with iron deficiency anemia and 70 healthy controls made up the case-controlled trial. Patients with H. pylori infection had their hematological response to triple therapy and iron medication (n = 32) or iron medication alone (n = 32) evaluated. More individuals with unexplained iron deficiency anemia had H. pylori (61.5 percent). Only the infection with H. pylori and median corpuscular volume were significantly correlated among the several hematological parameters examined (p-value 0.046). Additionally, there was a substantialconnection between getting triple treatment and iron supplements as opposed to receiving iron aloneand improvements in the hematologic indicators [hemoglobin (p-value <0.001), median corpuscular volume (p-value <0.001), iron (p-value <0.001), and serum ferritin (p-value <0.001). **(El Demerdash et al., 2018)**.

Hudak et al. conducted a recent systematic review and meta-analysis to look a person's likelihood of having lower iron reserves than someone who isn't affected with Helicobacter pylori. Additionally, they compared the effects of iron treatment alone to iron medication combined with anti-H. pylori eradication medication on ferritin and hemoglobin values. The incidence of IDA was raised by H. pylori (14 observational studies), iron deficit (combined OR 1.33; 95% 30 trials; CI 1.15-1.54), and anemia (combined OR 1.15; 95% 23 trials; CI 1.00-1.32) compared to uninfected people. Ferritin concentrations were greater with iron medication coupled with anti-H. pylori clearance medication compared with iron medication alone, according to meta-analyses of seven RCTs They claimed that adding H. pylori eradication to iron treatment would help raise ferritin and hemoglobin levels. **(Hudak et al., 2017)**.

Other trials, however, did not demonstrate as pronounced increases in the indicators of iron insufficiency as seen in (**Table 2**).

In contrast to previous studies, **Sarker et al.** 200 randomly selected HP-infected kids (positive urea breath test) 2-week anti-H. pylori therapy with 90 days of oral ferrous sulfate, 2-week anti-H. pylori treatment alone, 90 days of iron supplements alone, or placebo were given to children with IDA who were 2 to 5 years old; iron was given as a negative control to uninfected children with IDA. It seems that H. pylori infection is neither a reason of iron shortage nor a factor in the treatment failure of iron supplements in this situation

since it did not limit the response to iron. **(Sarker et al., 2008)**.

Conclusion

According to the available data, H. pylori infection is linked to a higher prevalence of IDA in kids. Additionally, investigation for H.pylori infection specially in children with refractory or unexplaned iron deficiency anemia with adding H. pylori eradication medication to iron therapy for those children may be advantageous.

Conflict of Interest:

No conflict of interest.

Abbreviations

IDA : iron deficiency anemia

ID: iron deficiency

HP: helicobacter pylori

MALT:mucosa-associated lymphoid tissue

WHO : World Health Organization.

RBC : Red blood cells

OR : odds ratio

CI : confidence interval

MCV : Mean corpuscular volume

HCT : hematocrit

CBC : complete blood count

Sab : sialic acid-binding

vacA: vacuolating cytotoxin gene A

CagA : cytotoxin- associated gene A

TNF : tumor necrosis factor

MCHC: Mean corpuscular hemoglobin concentration

SNPs : single nucleotide polymorphisms

IgG : immunoglobulinG

References:

- **Abou-Taleb A, Allam A ,Elsamman MK (2017).** Association between Helicobacter pylori Infection and Iron Deficiency Anemia among School-Age Children in Sohag University Hospital, Upper Egypt .Open Journal of Blood Diseases, 7: 36-46.
- **Cardenas VM, Prieto-Jimenez CA, Mulla ZD, Rivera JO, Dominguez DC, Graham DY, et al. (2011).** *Helicobacter pylori*eradication and change in markers of iron stores amongnon-iron deficient children in El Paso, Texas: an etiologicintervention study. J PediatricGastroenterol Nutr,52(3):326–329.
- **Choe YH, Kwon YS, Jung MK, Kang SK, Hwang TS, Hong YC (2001).** *Helicobacter pylori*-associated iron-deficiency anemia inadolescent female athletes. J Pediatr, 34(4): 100-136
- **Choi YJ (2016).** Specific Conditions: Diagnosis of H. pylori Infection in Case of Upper

Gastrointestinal Bleeding. Helicobacter pylori: Springer, 12(3): 157-162

- **Darvishi M , Ziari K, Mohebi H (2014).** Association between Iron Deficiency Anemia and Helicobacter Pylori Infection among Children under Six Years in Iran, ActaMedicaIranica, 53: 220-228.

- **El-Aziz Awad M-D, Amin SM, Abdou SM (2014).** Assessment ofdiagnostic and therapeutic approaches of *Helicobacterpylori*-associated iron deficiency and anemia in children withdyspeptic symptoms. J Egypt SocParasitol**,**44(3):695–708.

- **El-Demerdash DM, Ibrahim H, Hassan DM, Moustafa H, Tawfik NM (2018).** Helicobacter pylori associated to unexplained or refractory iron deficiency anemia: An Egyptian single- center experience. Hematology, transfusion, and cell therapy**,** 40:219-225.

- **Flores SE,Aitchison A, Day AS, Keenan JI (2017).** Helicobacter pylori infection perturbs iron homeostasis in gastric epithelial cells. PLoS One**,**12: 184026.

- **Gessner BD, Baggett HC, Muth PT, Dunaway E, Gold BD, Feng Z, et al. (2006).** A controlled, household randomized, open-label trial of the effect that treatment of *Helicobacter pylori* infection has on iron deficiency in children in rural Alaska. J Infect Dis**,**193(4): 537–633.

- **Gilbert R, Ngeiywa M, Rono S (2019).** Association Between Seropositivity of Helicobacter pylori Infection and Anemia Amongst Children Aged 5-15 Years in Western Highlands of Kenya. In: Journal of Health and Medical Sciences**,** 2(3): 248-255.

- **Gravina AG, Zagari RM, De Musis C, Romano L, Loguercio C, Romano M (2018).** *Helicobacter pylori* and extragastric diseases: A review. *World J Gastroenterol***,** 24(29): 3204-3221

- **Hammoodi MS, Al-Ani MH (2019).** Coexistence of iron deficiency anemia with Helicobacter pylori infection among children aged 6 to 12 years

in Erbil city. The Medical Journal of Tikrit University, 25(2): 121-130

- **Hassan MA, Kasem IA, Ali ASM (2020).** Correlation Between Helicobacter Pylori Infection and Iron Deficiency Anemia in School-Aged Children. The Egyptian Journal of Hospital Medicine, 81 (2):1489-1498.
- **Hooi JKY, Lai WY, Ng WK, (2017).** Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis.Gastroenterol,153(2):420–429.
- **Hoseinzadeh M, Khosravi A, Sayemiri K (2010).** The antibody titers to Helicobacter pylori in 7 - 12 year old iron deficiency anemic children, in Ilam. J Res Med Sci, 15(6):324-330 .
- **Hudak L, Jaraisy A, Haj S (2017).** An updated systematic review and meta-analysis on the association between Helicobacter pylori infection and iron deficiency anemia. Helicobacter, 22:123-303
- **Kato S, Osaki T, Kamiya S, Zhang XS, Blaser MJ (2017).** Helicobacter pylori sabA gene is associated with iron deficiency anemia in childhood and adolescence,12: 184-046.
- **Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, et al. (2017).** Management of Helicobacter pylori infection-the Maastricht V/Florence consensus report. Gut, 66:6–30.
- **Pacifico L, Osborn J, Tromba V (2014).** Helicobacter pylori infection and extra gastric disorders in children: A critical update. World J Gastroenterol, 20(6): 1379-1401.
- **Qu XH, Huang XL, Xiong P, Zhu CY, Huang YL, Lu LG, et al. (2010).** Does *Helicobacter pylori* infection play a role in iron deficiency anemia? A meta-analysis. *WorldJ Gastroenterol*2010, 16(7): 886-896.
- **Ražuka-Ebela D, Giupponi B, Franceschi F (2018).** *Helicobacter pylori* and extra gastric diseases. *Helicobacter*, 23 (1): 125-202.
- **Sarker SA, Mahmud H, Davidsson L (2008).** Causal relationship of *Helicobacterpylori* with iron-deficiency anemia or

failure of iron supplementation in children.*Gastroenterology*, 135:1534– 1542.

- **Tsay F, Hsu P (2018).** H. pylori infection and extra-gastroduodenal diseases. Journal of Biomedical Science, 10 (2): 25-65

- **Xia W, Zhang X, Wang JJ, Sun CH, Wu LJ (2012).** Survey of anemia and *Helicobacter pylori* infection in adolescent girls in Suihua, China and enhancement of iron intervention effects by *H. pylori* eradication. *Br JNutr*, 108:357–362.

- **Xu MY, Cao B, Yuan BS, Yin J, Liu L, Lu QB(2017).** Association of anemia with Helicobacter pylori infection: a retrospective study. Sci Rep, 7: 134-340.