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# Relationship Between Helicobacter Pylori Gastritis And Iron Deficiency Anemia In Children

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**ABSTRACT**

Data from several countries reported a high prevalence of both H. pylori infection and anemia in children. Several studies tried to find the association between H. pylori gastritis and iron deficiency anemia (IDA) in both pediatric and adult populations, but the results remain inconclusive. Knowing that H. pylori gastritis and IDA in children have a long term complication, finding the relationship between the two may be beneficial to eradicate both. This is an observational analytic with cross-sectional design study in children 2 to 18 years old, who were diagnosed with H. pylori and non H. pylori gastritis based on esophagoduodenoscopy (EGD) and Campylobacter-like organism (CLO) tests. A total of 63 children (33 H. pylori and 30 non H. pylori gastritis) with a median age of 12 years (range 2-18 years old) were enrolled between August until December 2021. Blood specimens were then taken for complete blood count and iron profile examination. There were 26 samples (41.3%) who were anemic (11 children with H. pylori gastritis and 15 children with non H. pylori gastritis). There were only 5 (7.9%) children with IDA (1 child with H. pylori and 4 children with non H. pylori gastritis). Based on statistical analysis, there was no significant difference in IDA incidence in children with H. pylori and non H. pylori gastritis (p=0.183). It is concluded that H. pylori gastritis is not associated with iron deficiency anemia in children.



## 1. Introduction

Gastritis is an inflammatory process in the mucosa and submucosa of the gaster in response to injury (which can be acute or chronic) and causes mucosal atrophy and epithelial metaplasia [1]. Gastritis occurs because aggressive factors are more dominant than defensive factors, which include mucosal microcirculation, surface epithelial cells, prostaglandins, phospholipids, mucus, bicarbonate, and gastrointestinal motility. While aggressive factors consist of stomach acid, pepsin, biliary reflux, nicotine, alcohol, non-steroid anti-inflammatory drugs (NSAIDs), corticosteroids, free radicals, and Helicobacter pylori (H. pylori) infection [2]. Helicobacter pylori infection occurs all over the world and can cause infection in childhood which may last a lifetime if not eradicated. Studies in several countries reported that the prevalence rate of H. pylori infection in children is quite high [3]. In developing countries, it is estimated that around 65% of children

are infected with H. pylori [4]. H. pylori infection in children can manifest as gastrointestinal and extraintestinal problem, including iron deficiency anemia (IDA).

Based on data published by the World Health Organization (WHO) in 2015, the prevalence of anemia in children aged 6 months to 5 years was 42.6% (95% CI: 37-47), with a total of 273.2 million children under five years old with anemia (95% CI: 241.8–303.7) [5]. Iron deficiency is known as one of the main causes of anemia in developing countries, with an estimated prevalence of around 40-50% in children under five years old [6], [7]. In Indonesia, the prevalence of anemia occurs in around 20-40% children (predominantly due to iron deficiency) and is associated with long-term outcomes of decreased cognitive function and mortality in children [5]. Iron deficiency anemia has several phases starting from iron depletion, iron deficiency erythropoiesis, and the final phase is iron deficiency anemia.

The relationship between H. pylori gastritis and IDA has been studied in both children and adults but the results remain inconclusive. A systematic review of the relationship between H. pylori infection and IDA carried out by [4] noted that most of the studies reviewed reported a significant association between H. pylori infection and IDA in the pediatric population. However, several studies still show contradictory results, so it was concluded that further cohort studies are needed to strengthen the relationship between H. pylori infection and IDA in the pediatric population. Whereas a cohort-retrospective study in America between 1998 – 2004 with a sample of 523 adults divided into two groups (H. pylori positive and H. pylori negative) showed that there was no association between IDA and H. pylori infection in the study population [8]. Due to the high estimated incidence of H. pylori infection and IDA in developing countries such as Indonesia, proving whether there is a relationship between H. pylori gastritis and IDA in the pediatric population may be beneficial to eradicate both.

## 2. Methodology

This was a cross sectional analytic observation study carried out between August and December 2021 at Columbia Asia Hospital, Medan, Indonesia.

### *2.1 Research Subjects*

All patients were children aged 2 to 18 years with H pylori or non H pylori gastritis confirmed by esophagoduodenoscopy (EGD) and Campylobacter-like organism (CLO) test done by qualified consultant pediatric gastroenterohepatologist. The sampling method was non-randomized consecutive sampling in which all samples were recruited sequentially. All samples must not consume proton pump inhibitor (PPI), histamin-2 receptor antagonist (H2RA), bismuth, sucralfate, antibiotics, nor iron supplementation within 4 weeks before EGD and blood examination to be included in this study. Sample with history of gastrointestinal bleeding, blood transfusion within 3 months before examination, known other hematological disease (thalassemia, hemophilia, leukemia), child with chronic diseases such as malnutrition, metabolic diseases, chronic kidney disease, systemic lupus erythematosus, immune suppressed, and malignancy were excluded. There were 33 gastritis H pylori children and 30 gastritis non H pylori who are eligible for this study.

### *2.2 Procedure*

Patient was identified according to the inclusion criteria. Data including age, gender, nutritional status, past medical history, medication history, related physical examination, any previous laboratory result, and patient's diagnosis were recorded. All patients which were not excluded will be approached to participate in this study and upon the signed agreement of parent or guardian of the patient, blood sample were then taken for complete blood count and iron profile examination. Laboratory examination was done by Prodia

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laboratory which had qualified ISO 9001:2008. Samples were considered to have iron depletion if there were at least 2 of mean corpuscular volume (MCV) < 80fL, serum iron (SI) < 50µg/dL, ferritrin <12 µg/L. Anemia classification used was in accordance to the WHO classification according to age. Iron deficiency anemia was termed if the sample with anemia also had iron depletion.

### *2.3 Data Analysis*

Data collected were processed and analyzed using computer software SPSS version 23.0. Univariate analysis was used to describe the characteristics of the sample. Categorical data are presented in terms of frequency and percentage. As the data are not normally distributed, numerical data are presented in both mean (standard deviation) and median (ranges). Bivariate analysis assessed the relationship between categorical variables using chi-square test. For bivariate that did not meet the chi-square rule, an alternative Fisher's exact test was used. As for analysis of the numerical independent variables with the categorical dependent variable, the independent T test was used if the data is normally distributed and the Mann Whitney test if the data is not normally distributed. Statistical analysis was performed with 95% confidence interval and a p value <0.05 was considered statistically significant.

### *2.4 Ethical Consideration*

This study was approved by the Health Research Ethics Committee Universitas Sumatera Utara (No. 917/KEP USU/2021).

## 3. Results

### *3.1 Characteristics of Research Subjects*

There were 33 children with H. pylori positive and 30 H. pylori negative gastritis. In both groups, the subjects had good socioeconomic status with the combined income of both parents more than 2 times the regional minimum wage. Only 5 from H. pylori and 2 from non H. pylori gastritis were undernourished but none was severely undernourished. There was no statistically significant differences in the characteristics of the two study groups based on gender, age, weight, height, ethnicity, education or occupation of the father and mother, socioeconomic status, or nutritional status in the sample population. The demographic characteristic of the research subjects is presented in Table 1.

**Table 1.** Characteristics of subjects based on incidence of H. pylori gastritis

| Characteristics | *H. pylori* | |
|---|---|---|
| | **Positive (n=33)** | **Negative (n=30)** |
| Gender, n (%) | | |
| Boy | 12 (36,4) | 12 (40,0) |
| Girl | 21 (63,6) | 18 (60,0) |
| Age, years | | |
| Mean (SD) | 11,1 (3,8) | 11,7 (3,7) |
| Median (min – max) | 12,1 (2,8 - 17,8) | 11,9 (4,4-17,5) |
| Weight, kg | | |
| Mean (SD) | 36,8 (17,0) | 37,5 (11,6) |
| Median (min – max) | 35,0 (9,0-85,0) | 36,0 (17,0-60,0) |
| Height, cm | | |
| Mean (SD) | 135,2 (21,7) | 138,2 (16,7) |
| Median (min – max) | 140,0 (84,0-168,0) | 144,5 (104,0-170,0) |
| Ethnic, n (%) | | |
| Aceh | 4 (12,1) | 4 (13,3) |
| Batak | 16 (48,5) | 12 (40,0) |
| Java | 4 (12,1) | 3 (10,0) |
| Malay | 4 (12,1) | 9 (30,0) |

| Characteristics | *H. pylori* | |
|---|---|---|
| | Positive (n=33) | Negative (n=30) |
| Minang | 4 (12,1) | 1 (3,3) |
| Chinese | 1 (3,0) | 1 (3,3) |
| Father's education, n (%) | | |
| High school | 6 (18,2) | 8 (26,7) |
| University | 27 (81,8) | 22 (73,3) |
| Mother's education, n (%) | | |
| High school | 3 (9,1) | 2 (6,7) |
| University | 30 (90,9) | 28 (93,3) |
| Father's occupation, n (%) | | |
| Employee | 18 (54,5) | 20 (66,7) |
| Farmer | 3 (9,1) | 2 (6,7) |
| Civil servant | 3 (9,1) | 2 (6,7) |
| Army/police | 2 (6,1) | 2 (6,1) |
| Entrepreneur | 7 (21,2) | 5 (16,7) |
| Mother's occupation, n (%) | | |
| Housewife | 5 (15,2) | 5 (16,7) |
| Employee | 16 (48,5) | 14 (46,7) |
| Farmer | 4 (12,1) | 1 (3,3) |
| Civil servant | 3 (9,1) | 3 (10) |
| Entrepreneur | 5 (15,2) | 5 (16,7) |
| Socio-economic, n (%) | | |
| < 2x regional minimum wage | 4 (12,1) | 5 (16,7) |
| > 2x regional minimum wage | 29 (87,9) | 25 (83,3) |
| Nutritional status, n (%) | | |
| Undernourished | 5 (15,2) | 2 (6,7) |
| Normal weight | 14 (42,4) | 14 (46,7) |
| Overweight | 14 (42,4) | 14 (46,7) |

### *3.2 Hemoglobin, MCV, Serum Iron, Ferritin and Iron Depletion Levels*

Using statistical analysis, no significant differences were found in hemoglobin, MCV, serum iron, ferritin, and iron depletion status between H. pylori and non H. pylori gastritits in this study.

**Table 2.** Hemoglobin and MCV based on the incidence of H. pylori gastritis

| | Hemoglobin, g/dL | | p | MCV, fL | | p |
|---|---|---|---|---|---|---|
| | Mean (SD) | Median (min-max) | | Mean (SD) | Median (min-max) | |
| *H. pylori* | | | | | | |
| Positive (n=33) | 12,4 (2,0) | 12,5 (8,7-15,7) | 0,210[a] | 82,5 (5,2) | 81,2 (74,2-92,2) | 0,885[b] |
| Negative (n=30) | 11,8 (1,5) | 12,0 (9,2-14,8) | | 82,6 (4,7) | 82,5 (72,5-90,6) | |

[a]Independent T, [b]Mann Whitney

**Table 3.** Serum iron and ferritin based on the incidence of H. pylori gastritis

| | Serum iron, µg/dL | | p | Ferritin, µg/L | | p |
|---|---|---|---|---|---|---|
| | Mean (SD) | Median (min-max) | | Mean (SD) | Median (min-max) | |
| *H. pylori* | | | | | | |
| Positive (n=33) | 68,3 (34,9) | 65,0 (18,0-212,0) | 0,989[a] | 65,0 (47,2) | 56,9 (5,2-185,2) | 0,815[a] |
| Negative (n=30) | 65,5 (31,1) | 72,5 (17,0-147,0) | | 58,0 (33,5) | 60,2 (7,9-172,5) | |

[a]Mann Whitney

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**Table 4.** Iron depletion status based on the incidence of H. pylori gastritis

| | Iron depletion, n (%) | | p |
|---|---|---|---|
| | Yes | No | |
| *H. pylori* | | | |
| Positifve (n=33) | 10 (30,3) | 23 (69,7) | 0,593[a] |
| Negative (n=30) | 11 (36,7) | 19 (63,3) | |

[a]Chi Square

### *3.3 Helicobacter pylori Gastritis and Anemia*

Of the 33 children with positive H. pylori gastritis, 11 (33.3%) had anemia. Meanwhile, out of 30 children with negative H. pylori gastritis, 15 (50%) had anemia. Chi Square test showed that there was no significant relationship between the incidence of H. pylori gastritis and anemia (p = 0.180).

**Table 5.** Anemia status based on the incidence of H. pylori gastritis

| | **Anemia** | | **p** |
|---|---|---|---|
| | **Positive (n=26)** | **Negative (n=37)** | |
| *H. pylori*, n (%) | | | |
| Positive | 11 (33,3) | 22 (66,7) | 0,180[a] |
| Negative | 15 (50,0) | 15 (50,0) | |

[a]Chi Square

### *3.4 Helicobacter pylori Gastritis and Iron Deficiency Anemia*

Of the 33 children with H. pylori gastritis, only 1 person (3%) had IDA. Meanwhile, out of 30 children with non H. pylori gastritis, 4 (13.3%) had IDA. Analysis using Fischer's Exact test showed that there was no significant relationship between the incidence of H. pylori and IDA (p = 0.183).

**Table 6.** Iron deficiency anemia status based on the incidence of H. pylori gastritis

| | **Iron deficiency anemia** | | **p** |
|---|---|---|---|
| | **Positive (n=5)** | **Negative (n=58)** | |
| *H. pylori*, n (%) | | | |
| Positive | 1 (3,0) | 32 (97,0) | 0,183[a] |
| Negative | 4 (13,3) | 26 (86,7) | |

[a]Fischer's Exact

## 4. Discussion

Gastritis is an inflammatory process in the mucosa and submucosa of the gaster in response to injury which can be acute or chronic. The diagnosis of gastritis is confirmed histopathologically by endoscopy and biopsy. In this cross-sectional study of 63 children diagnosed as gastritis with EGD, there were 33 children with H. pylori gastritis and 30 children with negative H. pylori based on CLO examination. The CLO test is a highly specific invasive diagnostic test for H. pylori by detecting urease activity in H. pylori through endoscopy [4]. Literatures suggest that the main etiology of gastritis in children is H. pylori infection [9]. A systematic review even estimated that H. pylori infection occurs in about 65% of children in developing countries [4]. This is consistent with the result of this study where the incidence of H. pylori gastritis was quite high (52%). The results of previous studies regarding the prevalence of H. pylori infection in several teaching hospitals in Indonesia stated an average prevalence of H. pylori gastritis of 10.2%, but with wide range of between 8-55% among several centers [10].

Subject characteristics between the H. pylori and non H. pylori gastritis groups in this study had no significant differences in terms of gender, age, ethnicity, nutritional status as well as education, occupation, and parents' socioeconomic status. The mean age of the sample was 11 years and the median was 12 years

with an age range of 2-18 years. It is to be noted that there was a 2 years old child who was diagnosed as H. pylori gastritis in this study, which is in accordance with study of [11] in Ireland who also found H. pylori infection in children between 2 to 4 years old. There was no severely undernourished child in this study. All parents graduated high school and most of them were university educated, with 54 out of 63 families considered to have good socioeconomic status with a combined monthly income of both parents more than 2x minimum regional wage.

In this study, the median (min-max) of hemoglobin level in the H. pylori gastritis group was 12.5 (8.7-15.7) g/dL and 12.0 (9.2-14.8) g/dL for non H. pylori gastritis. From the result of statistical analysis, there was no significant difference of hemoglobin level between the H. pylori and non H. pylori gastritis group (p=0.210). It is known that iron deficiency is the main cause of anemia in children [6]. Iron is an important micronutrient for the growth and development of children because it plays a role in various metabolic processes, including oxygen transport and DNA synthesis. Iron deficiency anemia develop gradually, with the first phase is iron depletion (marked by low serum ferritin), followed by iron deficiency erythropoiesis (marked by decreased serum iron (SI) level and increased total iron binding capacity (TIBC) with normal hematocrit values). The last phase is iron deficiency anemia when the hemoglobin value is lower than normal and characteristically patient will have microcytic anemia with low MCV level [7]. In this study, MCV, SI, and serum ferritin were assessed to determine whether the samples were in a state of iron depletion, which was diagnosed when at least 2 of 3 conditions were found, which were MCV <80fL, SI <50µg/dL, and ferritin <12µg/L. The median MCV values of the two groups were found to be within normal limit, 81.2 (74.2-92.2) fL for H. pylori gastritis and 82.5 (72.5-90.6) fL for non H. pylori gastritis group and the result of statistical analysis found no significant difference between H. pylori and non H. pylori gastritis group (p=0.885). Serum iron is a measure of the amount of iron circulating in the blood that is bound to transferrin (90%) and ferritin (10%). The median SI in the H. pylori gastritis was 65 (18-212) µg/dL while in the non H. pylori group was 72.5 (17-147) µg/dL which was still above the normal value set for this study (> 50µg /dL). SI levels in the two groups also did not statistically significant different (p=0.989). Serum ferritin is the most important intracellular iron storage protein in the body. Ferritin in blood serum correlates with the total amount of body iron stores. However, serum ferritin is also a marker of inflammation so it can be increased in patients with other infections. In this study, the median serum ferritin level in the H. pylori gastritis group was 56.89 (5.16-185.21) µ/L and in the non H. pylori group was 60.16 (7.99-172.48) µ/L. These results were also within normal limits of our preset level of >12µ/L and the difference between the two groups was not statistically different (p=0.815).

Even though the median numbers of MCV, SI, and ferritin were within normal range, but from individual assessment, it was noted that a fairly high number of children were iron depleted in this study. Iron depletion was found in 10 (30.3%) children with H. pylori gastritis and 11 (36.7%) children with non H. pylori gastritis. However, from the result of statistical analysis, there was no significant difference between iron depletion conditions in the H. pylori and non H. pylori gastritis group. Hence, H. pylori gastritis does not correlate with iron depletion in this study. This result is different from a study in Korea which showed H. pylori infection contributed to iron depletion even without the presence of gastrointestinal bleeding [12]. A study by [13] regarding gastric histopathology, iron status, and IDA in children with H. pylori infection also stated that H. pylori infection is associated with low serum iron levels.

Patients were evaluated as anemia or not based on Hb level in accordance with WHO classification (anemia if the Hb level for children aged 6 months – 5 years < 11.0 g/dl, 5 – 11 years old < 11.5 g/dl and for children aged over 12 years < 12.0 g/dl) [6]. There were 26 children (41.3%) who met the criteria for anemia (11 children with H. pylori gastritis and 15 children with non-H. pylori gastritis). Statistical analysis

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showed that there was no significant difference between the incidence of anemia in children with H. pylori gastritis compared to non H. pylori gastritis (p=0.180). The high incidence of anemia in this study is similar to data published by WHO in 2015 (42.6% anemia was found in children aged 6 months - 5 years) [5]. The data from household survey in Indonesia in 2008 stated that 31.4% children under 5 and 20.6% of children 5-12 years old had anemia [14]. This should be a concern because anemia can lead to low cognitive abilities and behavioral disturbances in children [15].

In this study, patients were considered to have IDA if they had anemia (according to WHO classification) and were iron depleted. Using this criteria, a total of 5 (7.9%) children had IDA (1 child with H. pylori gastritis and 4 children with non H. pylori gastritis). Based on the statistical analysis, there was also no significant difference of IDA in patients with H. pylori and non H. pylori gastritis (p=0.183). This is similar to a case-control study in Iran by [16], which involved a group of children with and without H. pylori infection who were anemic and not anemic and concluded that H. pylori infection was not associated with IDA in the pediatric population. Similar results were also found in a retrospective cohort study in America [8]. However, a systematic review by [4] which reviewed 14 case reports, 24 epidemiological observational studies, 7 uncontrolled clinical studies, and 16 RCTs published from January 1991 to October 2014, described that most of the studies reviewed reported a significant relationship between H. pylori infection and IDA in the pediatric population. Likewise the systematic review and meta-analysis of [17] stated that H. pylori infection can be considered as a risk factor for depletion of iron reserves and IDA, especially in high-risk groups, such as growing children. Helicobacter pylori infected individual had an increased risk of IDA events with a pooled odds ratio (OR) of 2.8 (95% CI 1.9-4.2). Other studies reported that patients with iron-refractory IDA (anemia that does not improve with iron supplementation) experience improvement of anemia after being treated with H. pylori eradication therapy [18], [19].

The cause of IDA in H. pylori gastritis is considered multifactorial with suspected mechanisms in the form of (1) increased iron loss through active bleeding due to gastritis by H. pylori infection [17], (2) autoimmune atrophic gastritis [18], (3) gastric cancer [20], (4) decreased iron absorption as a result of chronic pan-gastritis [21], and (5) iron utilization by bacteria [22]. Chronic occult gastrointestinal bleeding was reported to occur in patients with H. pylori infection in a study in Alaska and was suspected as a mechanism for the occurrence of IDA, but this was not proven in other studies [17]. The level of gastric acidity plays a role in iron reduction from ferric to ferrous form which is important in the process of binding iron to luminal mucin in the process of iron absorption. Autoimmune atrophic gastritis or chronic pan-gastritis which alter this process can result in decreased absorption of iron [16]. However, both of these are chronic conditions and associated with progressive disease, so it may not yet manifest in pediatric gastritis as is in this study. The incidence of gastric cancer is also uncommon in the pediatric population.

It is known that most bacteria including H. pylori require iron to grow. The results of this study found no association between the incidence of H. pylori gastritis and IDA or iron depletion, indicating that the possibility of iron utilization by H. pylori is not significant for the incidence of IDA in the pediatric population. From a study in Korea, differences in the proteonomic profile of H. pylori strains isolated from patients with IDA and non IDA showed that polymorphism of certain H. pylori strains might be a determinant of iron depletion conditions in the host [23]. Study by [13] showed that CagA strain H. pylori inversely correlated with the concentration of gastric ascorbic acid (which assist the process of iron absorption), although the CagA strain is not directly associated with the incidence of IDA in children. A study by Ciacci et al however, showed that impaired iron absorption in H. pylori infection is not associated with CagA strain H. pylori [24]. Several other studies also showed that CagA strain H. pylori did not increase the risk of IDA [25], [26].

Regulation of iron uptake by H. pylori was thought to be different from other bacteria due to the habitat of H. pylori in the gaster (where iron reserves are not available continuously), so that it is assumed that H. pylori depends on host lactoferrin for iron. Mucosal lactoferrin levels were found to be higher in adolescents with H. pylori infection who had IDA than those without IDA and eradication of H. pylori reduced mucosal lactoferrin levels. So it is suspected that IDA in patients with H. pylori infection is the result of lactoferrin iron sequestration in the gastric mucosa and iron uptake by bacteria which may be mediated by overexpression of the H. pylori napA gene which can induce inflammation of the gastric epithelium. However, Hong et al study found no significant correlation between the expression of H. pylori napA and the incidence of IDA [27]. Gene mutation of pfr H. pylori which causes overproduction of H. pylori ferritin protein (pfr) is also thought to play a role in causing iron depletion but was not proven to be significant in the incidence of IDA [28].

This study has several limitations, such as (1) other causes of iron depletion, such as inadequate iron intake, worm infections, occult gastrointestinal bleeding were not adequately excluded in this study, (2) H. pylori strain was not examined in this study. The strengths of this study are (1) the pediatric subjects in this study were diagnosed as gastritis using EGD and followed by CLO test to confirm the diagnosis of H. pylori and non H pylori gastritis by a qualified consultant pediatric gastroenterohepatologist, (2) iron depletion was diagnosed with a minimun of at least 2 of 3 parameters of MCV, SI, and ferritin, (3) to the author's knowledge, this is a pioneer study that examine the relationship between H. pylori gastritis and IDA in Indonesia, which is significant because the prevalence of both is quite high in the country.

## 5. Conclusion

Of the 33 children with H. pylori gastritis and 30 children with non-H. pylori gastritis, iron deficiency anemia was found in 1 child (0.03%) with H. pylori gastritis and 4 children (0.13%) with non H. pylori gastritis. Based on statistical analysis, there was no significant association between H. pylori gastritis and IDA in children (p=0.183). Hence, it is concluded that H. pylori gastritis is not associated with iron deficiency anemia in children.

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