

The Relationship of Interleukin-8 Levels in Children's Gastritis 1

with and without Helicobacter Pylori Infections

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Abstract

Background: Gastritis is a gastrointestinal health problem that often occurs and is divided into acute and chronic gastritis. Where the main cause of chronic gastritis is *Helicobacter pylori* infection. The number of Interleukin-8 (IL-8) expressed by gaster epithelial cells in response to *Helicobacter pylori* is sufficient to induce neutrophil chemotaxis, which is associated with a variety of gastrointestinal diseases including gastritis, peptic ulcer cells, gaster carcinoma and gastric mucosa sufficient to induce neutrophil chemotaxis, which is associated with various gastrointestinal diseases including gastritis, peptic ulcer cells, gastric carcinoma and gastric mucosa sufficient to induce neutrophil chemotaxis, which is associated with various gastrointestinal diseases including gastritis, peptic ulcer cells, gastric carcinoma and gastric mucosa-associated lymphoid-tissue lymphoma. **Objective:** To analysis the relationship of IL-8 levels in pediatric gastritis with and without *Helicobacter pylori* infection. **Method:** A cross sectional study was conducted In outpatient and inpatient department in three centers from March until April 2020. The diagnosis of *Helicobacter pylori* gastritis was confirmed by CLO test. Blood sample was taken from subjects to evaluate interleukin-8 level. **Result:** 60 subjects with gastrointestinal complaints were reviewed. Subjects were divided into 2 groups based on CLO test, 29 subjects with *Helicobacter pylori* infection and 31 subjects without *Helicobacter pylori* infection. From the analysis, mean IL-8 value was 25,86 pg/ul and 10,99 pg/ul in helicobacter and non-helicobacter group respectively (p<0,001). **Conclusion:** There are differences levels of IL-8 value between *Helicobacter pylori* gastritis and non *Helicobacter pylori* gastritis in children.

Keyword: gastritis, *Helicobacter pylori*, interleukin-8

Introduction

Gastritis is one of the most common gastrointestinal health problems. Gastritis can be divided into acute gastritis and chronic gastritis. Most children with chronic gastritis have secondary inflammation or mucosal ulcers. The leading cause of chronic gastritis is *H. Pylori* bacterial infection. *H. Pylori* infection is associated with various gastrointestinal diseases, including gastritis, peptic ulcers, gastric carcinoma, and gastric mucosa-associated lymphoid tissue lymphoma.^{1,2} *H. pylori* can cause gastritis in infected children with non-specific clinical manifestations.² In developing countries, the prevalence of *H. pylori* infection in children under 10 years is about 80%, while in developed countries, it is about 10%.^{2,3}

H. Pylori infection causes gastric mucosal inflammation so that the gastric epithelium releases interleukin-1 β , interleukin-2, interleukin-6, interleukin-8, and tumor necrosis factor- α . Interleukin-8 or Human Neutrophil Activating Factor (NAF-1) is the most important neutrophil-activating chemokine expressed in gastric epithelial cells associated with the recruitment of neutrophils toxic metabolites and lysosomal enzymes are released neutrophils creates gastric mucosal damage.⁴⁻⁶ *H. pylori* trigger systemic and local humoral responses that produce antibodies. These antibodies do not function to clear pathogens but instead cause tissue damage by destroying the H + / K + -ATPase parietal cells that produce gastric acid, causing corpus atrophy achlorhydria conditions.⁷⁻⁹

Research on the relationship of IL-8 level expression between gastritis patients with or without *H. Pylori* infection at H. Adam Malik Hospital, University of North Sumatera Hospital, and Satellite Education Hospital but still no interleukin-8 level difference noted. So, the author wants to study the interleukin-8 level

differences in gastritis patients with *H. pylori* and without *H. pylori*.

Method

Our cross sectional analytic study was conducted at Gastroenterology Polyclinic and Ward in H. Adam Malik Medan Hospital, Universitas Sumatera Utara Hospital, and Satellite Education Hospital Medan in March – April 2020 after obtaining ethical clearance from Universitas Sumatera Utara, with inclusion criteria: children 2 – 18 years old with suspected gastritis or diagnosed with gastritis and willing to join and agree to follow our study procedures. Patients using proton pump inhibitor (PPI), H2 receptor antagonist, antibiotic or non-steroid anti-inflammatory drugs (NSAID) within 14 days, malignancy, immunosuppression disease, gastric bleeding, patients with a history of gastric operation, and history with other infection that not related to gastritis infection are excluded. The subject appropriate with inclusion criteria will be noted, perform HpSA test, urea breath test or campylobacter like organism (CLO) test and interleukin-8 in standardized laboratory. All the data will noted and analysed statistically by using SPSS version 23 with descriptive study, comparison of unpaired group with T-test and if distributed unnormal the data will be analyse with Mann Whitney test. Data normality will use Saphiro Wilk test. The significance of the statistical test results was determined based on a P value <0.05 with a 95% confidence interval. (figure 1)

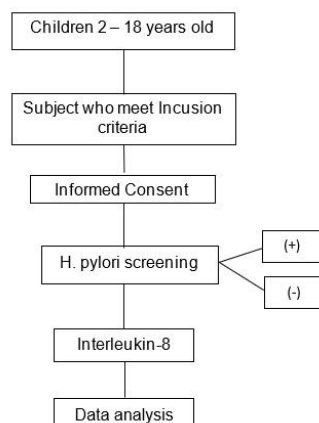


Figure 1. Subject recruitment

Result

Our study was followed by 60 children with gastritis symptoms who met the inclusion and exclusion criteria. Endoscopic examination results showed 29 children with positive *H. pylori* and 31 children with negative *H. pylori*. Our study found female 60% with mean age 11,57 years old, youngest 2,8 years old and oldest 17,5 years old. Mean body weight 36,42 years old and mean body length 136,6 years old. We found Bataknesse was the most in ethnic group, majority of children education level primary and secondary school. Majority of parent's educational level and occupation were college and entrepreneur. Most cases with good socioeconomic status 88,3%, family history 44,7%, and abdominal pain 56,7% (table 1).

Subject Characteristic	n = 60
Gender, n (%)	
Male	24 (40)
Female	36 (60)
Age, n (%)	
Mean	11,57
Median	12,6
SD	3,58
Min Max	2,8 - 17,5
Body Weight, mean (SD), kg	
Mean	36,42
Median	35
SD	11,72
Min Max	9 - 60
Body Height, mean (SD), cm	
Mean	136,6
Median	141,5
SD	18,52
Min Max	84 - 167
Ethnic Group, n (%)	
Acehnese	8 (13,3)
Bataknese	25 (41,7)
Indianese	1 (1,7)
Javanese	7 (11,7)
Melayunese	9 (15)
Minangnese	7 (11,7)
Papuanese	2 (3,3)
Chineese	1 (1,7)
Child educational level, n (%)	
Kindergarten	4 (6,7)
Primary school	21 (35)
Secondary school	21 (35)
Senior high school	10 (16,7)
College	4 (6,7)
Father educational level, n (%)	
Senior high school	12 (20)
College	48 (80)
Mother educational level, n (%)	
Senior high school	4 (6,7)
College	56 (93,3)
Father's occupation, n (%)	
Private employee	32 (53,3)
Farmer	3 (5)
Government employee	6 (10)
Army/ police	3 (5)
Entrepreneur	16 (26,7)
Mother's occupation, n (%)	
Private employee	22 (36,7)
Farmer	5 (8,3)
Government employee	11 (18,3)
Entrepreneur	13 (21,7)
Housewife	9 (15)
Socioeconomic status, n (%)	
Scant	7 (11,7)
Good	53 (88,3)
Clinical manifestation, n (%)	
Nausea	3 (5)
Vomitus	11 (18,3)
Haematemesis	12 (20)
Abdominal pain	34 (56,7)
Family history, n (%)	
Yes	40 (44,7)
No	20 (33,3)

Table 1. Subject characteristic

We analyze the data that show in table 2. We found female greater both in positive and negative *H. pylori* with 62,1% and 58,1%. We perform Chi square test and found no significant proportion different in gender group ($p=0,752$). Mean age in positive *H. pylori* group 11,35 years old while negative *H. pylori* 11,78 years old and when we perform Mann-Whitney test we also found no significant different in mean age with *H. pylori* ($p=0,706$). In ethnic group we found Bataknese was the greatest among other with 41,4% in positive *H.*

pylori and 41,9% in negative H. pylori. We performed Kruskal Wallis and found no significant different in ethnic group ($p=0,744$). Good socioeconomic status found higher both in two groups with 89,7% in positive H. pylori and 87,1% in negative H. pylori, and when we analyze with Fischer's exact test we found no significant difference between two groups ($p=1,000$). The highest level of children's education in the two groups was secondary school 37,9% in positive H. pylori and 35,5% primary school in negative H. pylori. We found no significant difference in children's educational level both in the two study groups ($p = 0.981$) after analyzed with Kruskal Wallis test.

Subject Characteristic	H. pylori		P
	Positive n = 29	Negative n = 31	
Gender, n (%)			
Male	11 (37,9)	13 (41,9)	0,752 ^a
Female	18 (62,1)	18 (58,1)	
Age, n (%), Mean (SD), years	11,35 (3,81)	11,78 (3,41)	0,706 ^o
Body weight, n (%), Mean (SD), kg	36,38 (13,96)	36,47 (9,39)	0,977 ^c
Ethnic Group, n (%)			
Acehnese	4 (13,8)	4 (12,9)	0,744 ^a
Batakese	12 (41,4)	13 (41,9)	
Indiense	1 (3,4)	0 (0)	
Javanese	3 (10,3)	4 (12,9)	
Melayunese	4 (13,8)	5 (16,1)	
Minangnese	3 (10,3)	4 (12,9)	
Papuanese	2 (6,9)	0	
Chinese	0	1 (3,2)	
Socioeconomic status, n (%)			
Scant	3 (10,3)	4 (12,9)	1,000 ^c
Good	(89,7)	27 (87,1)	
Child educational level, n (%)			
Kindergarten	2 (6,9)	2 (6,5)	0,981 ^a
Primary school	10 (34,5)	11 (35,5)	
Secondary school	11 (37,9)	10 (32,3)	
Senior high school	4 (13,8)	6 (19,4)	
College	2 (6,9)	2 (6,5)	
Father educational level, n (%)			
Senior high school	5 (17,2)	7 (22,6)	0,605 ^a
College	24 (82,8)	24 (77,4)	
Mother educational level, n (%)			
Senior high school	2 (6,9)	2 (6,5)	1,000 ^c
College	27 (93,1)	29 (93,5)	
Father's occupation, n (%)			
Private employee	14 (48,3)	18 (58,1)	0,784 ^a
Farmer	2 (6,9)	1 (3,2)	
Government employee	4 (13,8)	2 (6,5)	
Army/ police	1 (3,4)	2 (6,5)	
Entrepreneur	8 (27,6)	8 (25,8)	
Mother's occupation, n (%)			
Private employee	8 (27,6)	14 (45,2)	0,366 ^a
Farmer	4 (13,8)	1 (3,2)	
Government employee	7 (24,1)	4 (12,9)	
Entrepreneur	6 (20,7)	7 (22,6)	
Housewife	4 (13,8)	5 (16,1)	
Family history, n (%)			
Yes	21 (72,4)	19 (61,3)	0,361 ^a
No	8 (27,6)	12 (38,7)	
Clinical manifestation, n (%)			
Nausea	0	3 (9,7)	0,135 ^a
Vomitus	8 (27,6)	3 (9,7)	
Haematemesis	5 (17,2)	7 (22,6)	
Abdominal pain	16 (55,2)	18 (58,1)	

^aChi square, ^bMann Whitney, ^cT Independent, ^dKruskal Wallis, ^eFischer's Exact

Table 2. Subject Characteristic Study base on H. pylori infection

The majority of the father's and mother's education level is college, both in two groups. There was no significant difference in education level, both in two groups ($p > 0.05$). We found private employees were the most between the two groups from father's and mother's occupation and there was no significant difference in the father and mother's type of work in the two study groups ($p > 0.05$). We also found 72,4% in the positive H. pylori group, and 61,3% in negative H. pylori had a previous family history with no significant difference analyzed with Chi-square ($p = 0.361$). The most clinical manifestation of both two groups was abdominal pain, with 55,2% in the positive H. pylori group and 58,1% in the negative H. pylori group. There was no significant difference in clinical symptoms between the two groups with the Kruskal Wallis test ($p = 0.135$). In the interleukin-8 level, we found that the mean level of interleukin-8 in positive H. Pylori was 25,86 pg/ μ l (SD = 2.12 pg / μ l) and in negative H. pylori was 10,99 pg/ μ l (SD = 2.26 pg / μ l). When we performed the Mann Whitney test, we found a significant difference in the mean levels of interleukin-8 between the two groups with $p < 0.001$ (table 3 and figure 2).

	H. pylori		p^a
	(+) n = 29	(-) n = 31	
Interleukin 8, pg/ μ l			
Mean	25,86	10,99	<0,001
Median	16,61	10,41	
SD	29,34	3,99	
Min – max	10,05 – 128	5,57 – 19,64	

^aMann Whitney

Table 3. Interleukin-8 level difference

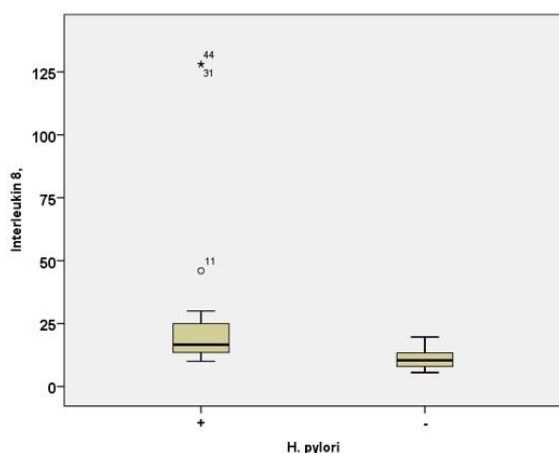


Figure 2. Boxplot of Interleukin-8 value

Discussion

H. Pylori are bacteria that cause gastritis, a microaerophilic bacteria, and live in a unique environment, under the mucus of the stomach wall, which is acidic, have the urease enzyme which can break down urea into ammonia that has alkaline nature, thus creating a microenvironment that allows these germs to survive.^{1,2} Most people with gastritis might well recover, depending on how many factors are affected, but gastritis symptoms can recur at any time. In general, gastritis with minimal signs will respond well to the treatment given but in some cases, gastritis can become a serious case and can even become a life-threatening emergency.¹⁰ Diagnostic tests for H. pylori infection are used to determine the presence of infection before administering treatment, to observe whether eradication has been achieved after antibiotics treatments and epidemiological studies, such as endoscopy and biopsy followed by histological examination, culture, urease

test, and PCR, serology, HpSA or C-Urea Breath Test.^{2,11} The prevalence of *H. pylori* infection in developing countries is higher than in developed countries. The prevalence in developed countries is around 30-40%, while in developing countries, it is 80-90%. The prevalence of *H. pylori* in adults and children in low to middle income countries and industrialized countries varies widely.^{12,13} Seroepidemiological studies in Indonesia show a prevalence of 36% to 46.1%, with the youngest age is 5 months. In the young age group under 5 years, 5.3-15.4% have been infected, and it is suspected that infection at an early age plays a role as a risk factor for malignant degeneration at a later age.^{14,15}

Interleukin-8 is an important factor that causes neutrophil influx to infected cells. Interleukin-8 is a chemokine produced by monocytes, T lymphocytes, neutrophils, vascular endothelial cells, dermal fibroblasts, keratinocytes, hepatocytes, and human gastric cancer cells. In humans, interleukin-8 is encoded by the interleukin-8 gene. Interleukin-8 is chemotactic against T lymphocytes and basophils, and neutrophils in vitro. Also, Interleukin-8 can induce neutrophils to release lysosome enzymes. Interleukin-8 is undetectable in normal adult plasma.¹⁶ In vivo and in vitro studies have shown an increase in Interleukin-8 levels associated with *H. pylori* infection. The amount of Interleukin-8 expressed by gastric epithelial cells in response to *H. pylori* is sufficient to induce neutrophil chemotaxis.¹⁷ In vivo and in vitro studies showed an increase in interleukin-8 levels associated with *H. pylori* infection on which the induction of interleukin-8 expression was mediated through NF- κ B and protein activator-1 (AP-1).^{18,19} *H. pylori* will directly upregulate the expression of messenger RNA from Interleukin-8 and Interleukin-8 protein in epithelial cells.²⁰⁻²³

The *H. pylori* strain expresses three virulence factors. One of the most researched virulence factors is the CagA protein encoded by the *cagA* gene. Infection by strains that produce *cagA* is associated with higher production of interleukin-8 (IL-8) and a more severe degree of inflammation.²³ Interleukin-8 as a novel cytokine that activates neutrophils in patients infected with *H. pylori*. Interleukin-8 is a potential mediator of the inflammatory response. As a potential chemotactic, Interleukin-8 can activate polymorphonuclear leukocyte degranulation (PMN), respiratory burst and 5-lipoxygenase pathway, Interleukin-8 is produced by various immune and non-immune cells including monocytes / macrophages, endothelial cells, fibroblasts, hepatocytes and PMN. *H. pylori* strains containing *cag*-PAI (producing *cagA*) elicited a stronger interleukin-8 response than those that did not.²⁴ Several studies on the relationship between *cagA* status, gastric mucosal Interleukin-8 levels and the degree of mucosal inflammation have shown multiple results. Yamaoka et al. found severe level severity in positive *H. pylori* than in negative ones. PMN and MN infiltration was heavier in the *cagA* positive strain. Gaseous mucosal Interleukin-8 levels were associated with a significant degree of severity in the *CagA* positive strain. *CagA* positive was strongly related to high gastric mucosal Interleukin-8 levels. MN cell infiltration was significantly correlated with IL-8 levels.²⁵ Xuan et al. (2005) found higher levels of mucosal Interleukin-8 with the ELISA method in severe degrees of gastritis (neutrophil infiltration, mononuclear infiltration and atrophy).²⁶ Andersen et al. found that interleukin-8 and interleukin-10 were significantly elevated in the more severe degrees of inflammation and higher levels of *H. pylori* density.²⁷ Holck et al. reported a significant association between Interleukin-8 and Interleukin-10 with gastritis and *H. pylori* density. The cytokines activity of interleukin-8 and interleukin-10 is increased in patients infected with *H. pylori*. Interleukin-8 was found to be elevated in half of *H. pylori* patients, compared with 25% in patients not infected with *H. pylori*.²⁸

Reports from various countries around the world a decade after the bacteria discovery of *H. pylori* states that *H. pylori* bacteria cause 95% of duodenal ulcers and 85% of gastric ulcers. *H. pylori* has been classified as a class 1 carcinogen in humans by the International Agency for Research on Cancer Consensus Group since 1994. Approximately 50% of the world's population is infected with *H. pylori*.²⁹ Our study found that there is a difference in interleukin-8 levels between *H. pylori* gastritis and non-*H. pylori* gastritis in children.

Conclusion

The main cause of chronic gastritis is the infection of *H. pylori*, and interleukin-8 is one of the important factors causing gastritis caused by *H. Pylori*. There were no significant differences in the mean age of children, ethnicity, socioeconomics, education, family history, and symptoms in both groups positive *H. pylori* and negative. There was a significant difference in the mean levels of interleukin-8 (IL-8) in children with positive *H. pylori* infection.

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Conflicts of interest

The author declares that there is no conflicts of interest.

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