Risk Factors Associated with Helicobacter Pylori Infection in Children with Gastrointestinal Symptoms

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Abstract

Background: The main cause of peptic ulcer disease in children is *H. pylori*, which has also been proven as a carcinogen in human. With an estimated high prevalence and its chronic nature, it is important to determine the risk factors for *H. pylori* infection. Studies in adults have shown association of *H. pylori* infection with several risk factors, but research in children is still scarce.
Objective: To determine the risk factors associated with *H. pylori* infection in children with gastrointestinal symptoms.
Methods: This was a case-control study in children with gastrointestinal symptoms treated at H. Adam Malik General Hospital in Medan from September 2019 - June 2020. Diagnosis of *H. pylori* infection was made if one of the diagnostic tests was positive. Data was then collected from parents with a questionnaire guidance and was analysed to determine the association between the risk factors with the incidence of *H. pylori* infection.
Result: A total of 68 children (34 cases and 34 controls) met the criteria as sample. Age range of subjects was between 2-17 years with a median of 12.5 years. Routine hand washing (before eating, after defecation, and when hands were dirty) decreases the risk of *H. pylori* infection (P = 0.040; OR 0.2; 95% CI 0.4-1.04). History of bottle feeding beyond 2 years old increases the risk of *H. pylori* infection (P = 0.041; OR 3.59; 95% CI 1.01-12.73).
Conclusion: Routine hand washing and a history of bottle feeding beyond 2 years old are associated with the incidence of *H. pylori* infection.

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Keywords: *Helicobacter pylori;* risk factors; children; gastrointestinal

1. Introduction

Gastritis and peptic ulcers were initially associated with psychological factors. This theory was then shifted to stomach acid as the main cause of gastritis and ulcers. In 1983, Warren and Marshall proved that

Helicobacter pylori (*H. pylori*) can cause gastritis and peptic ulcers (Marshall and Warren, 1984). By 1994, *National Institutes of Health Consensus Development Conference* (NIHCDC) concluded that the leading cause of gastric ulcers in the pediatric population was *H. pylori*. The International Agency for Research on Cancer Working Group (IARCWG) of the World Health Organization (WHO), also in the same year, classified *H. pylori* as a group of carcinogens in humans (Crowley and Hussey, 2016).

Helicobacter pylori is slow-growing, gram-negative microaerophilic bacteria that colonize the gastric mucosa, with an estimated 65% of children in developing countries infected (Rowland et al., 2006). The prevalence of *H. pylori* infection, in patients with gastrointestinal symptoms who underwent endoscopic examinations in several hospitals in Indonesia between 2003 and 2004, was 10.2% (Syam, 2016). In other study, the prevalence rate differs among ethnic groups living in the same geographic area. It was then hypothesized that differences in socioeconomic status, personal hygiene, and number of family members as the probable cause. This was supported by data which showed the seroprevalence of *H. pylori* infection in Estonia in 1991 for children aged 11-15 years was 42.2%, decreasing to 28.2% in 2002 as the country became increasingly prosperous (Daugule et al., 2016).

Helicobacter pylori infection commonly occurs in early childhood. The manifestations of *H. pylori* infection in children include gastrointestinal and extraintestinal manifestations. Gastrointestinal manifestations include gastritis, gastric ulcers, gastroesophageal reflux, and gastric carcinoma. Extraintestinal manifestations include iron deficiency anemia, short stature, allergic and autoimmune diseases (Crowley and Hussey, 2016). Considering the morbidity attributable to *H. pylori* infection, analysis of the risk factors for *H. pylori* infection is warranted. Identification of risk factors will help in understanding its transmission and, furthermore, can reduce the incidence of chronic infections which can progress to recurrent abdominal pain and malignancy.

2. Methods

2.1. Subjects and Methods

This was an analytical observational study with a case-control design, carried out between September 2019 and July 2020. All patients were children aged 2 to 18 years with at least two complaints of gastrointestinal symptoms (recurring abdominal pain, flatulence, nausea, excessive belching and loss of appetite) within 2 months before the examination. All patients were tested with either one of *H. pylori* stool antigen (HPSA), urea breath test (UBT), or endoscopy with *Campylobacter*-like organism (CLO) test, also known as rapid urease test, to confirm the diagnosis of *H. pylori* infection. Patients with history of consumption of proton pump inhibitor (PPI), antibiotics, Histamine H-2 receptor antagonists (H2RA), bismuth, or sucralfate within 14 days prior to the diagnostic test for *H. pylori*, or patients with clinical symptoms and signs of acute abdomen who required emergency care were excluded.

The sampling method was non-randomized consecutive sampling in which all samples were recruited sequentially until the required sample size was met. Risk factors was recorded using questionnaire. Nutritional status was assessed by anthropometric examination using body weight over height according to Waterlow criteria (WHO 2006 for children aged 2-5 and CDC 2000 for children aged 5-18 years old) and divided into undernourished, normal, and overweight criteria (Waterlow, 1972). Parents's socioeconomic level was based on the regional minimum wage in Sumatera Utara Province (Badan Pusat Statistik, 2019). Ethnic of the subjects was based on the father's. Either active or passive smoker was included as a criteria for

cigarette smoke exposure. Hand washing habits were grouped into routine or rarely washing hands. Routine is when the child or caregiver (for children who cannot eat or wash themselves) almost always wash their hands before eating, after defecating, and when their hands are dirty.

All research subjects were asked for consent from parents after being given an explanation in advance about the purpose of this study. The study was conducted at H. Adam Malik General Hospital.

2.2. Research Ethics

This study was approved by the Health Research Ethical Committee of the Faculty of Medicine, Universitas Sumatera Utara/ H Adam Malik General Hospital no 939/tgl/kepk FK USU-RSUP HAM/2019.

2.3. Statistical Analysis

The collected data 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. Numerical data are presented in medians (ranges) because the data are not normally distributed. Bivariate analysis assesses 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 for data with 2x2 tables, whereas for data with 2xk tables, the variables were grouped into two groups and reanalyzed using similar procedure. Multivariate analysis was then performed using logistic regression tests on variables that had a p value <0.25 and were statistically significant with the incidence of *H. pylori* from the bivariate test analysis, to determine the risk factors that influence the incidence of *H. pylori* infection in children in this study. Statistical analyzes were performed with 95% confidence intervals and a p value <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of Research Subjects

The subjects involved in this study were 68 children (34 sample and 34 control) that met the inclusion and exclusion criteria. The mean age of the subjects was 12.5 years with an age range of 2-17 years. The mean body weight was 38 kg with a weight range from 9 to 85 kg and a mean height value was 143 cm with a range of 84 to 170 cm. Total of 9 (13.2%) children was undernourished and 27 (39.7%) children was overweight. Complete characteristic data are presented in Table 1.

Table 1. Characteristics of research subjects

Characteristics	**n = 68**
***H. pylori* diagnostic tests, n (%)**	
HPSA	8 (11.8)
UBT	10 (14.7)
Endoscopy (CLO)	50 (73.5)
Age (years), median (min-max)	12.5 (2-17)
2-9, n (%)	22 (32.4)
10-18, n (%)	46 (67.6)
Gender, n (%)	
Boy	26 (38.2)
Girl	42 (61.8)
Weight, median (min-max)	38 (9-85)
Height, median (min-max)	143 (84-170)

Nutritional status, n (%)	
Undernourished	9 (13.2)
Normal	32 (47.1)
Overweight	27 (39.7)
Ethnic, n (%)	
Batak	29 (42.6)
Minang	4 (5.9)
Aceh	7 (10.3)
Java	13 (19.1)
Malay	10 (14.7)
Chinese	4 (5.9)
India	1 (1.5)
Father's education, n (%)	
High school	10 (14.7)
University	58 (85.3)
Mother's education, n (%)	
High school	6 (8.8)
University	62 (91.2)
Father's occupation, n (%)	
Farmer	2 (2.9)
Civil servant	7 (10.3)
Employee	37 (54.4)
Entrepreneur	19 (27.9)
Army / police	3 (4.4)
Mother's occupation, n (%)	
Farmer	3 (4.4)
Civil servant	7 (10.3)
Employee	29 (42.6)
Entrepreneur	18 (26.5)
Housewife	11 (16.2)
Socio-economic, n (%)	
< 2x regional minimum wage	5 (7.4)
> 2x regional minimum wage	63 (92.6)
Family history of *H. pylori* infection, n (%)	
No	23 (33.8)
Yes	45 (66.2)
Cigarette smoke exposure, n (%)	
No	28 (41.2)
Yes	40 (58.8)
Hand washing habit, n (%)	
Rarely	10 (14.7)
Routine	58 (85.3)
Bottle feeding, n (%)	
Stop before 2 years old	15 (22.1)
Beyond 2 years old	53 (77.9)

3.2. Risk Factors and Incidence of H. pylori Infection

Hand washing habit significantly reduced the incidence of *H. pylori* infection with an odds ratio of 0.2 (95% CI = 0.40-1.04). History of bottle feeding beyond 2 years old significantly increased the incidence of *H. pylori* infection by 3.59 times (95% CI = 1.01-12.73).

Age, gender, nutritional status, father's ethnicity, father's and mother's education, father's and mother's occupation, socioeconomic level of parents, family history of *H. pylori* infection, and exposure to cigarette smoke did not have a statistically significant effect on the incidence of *H. pylori* infection (p value> 0.05). The details of these factors can be seen in Table 2.

Table 2. Relationship between risk factors and the incidence of *H. pylori* infection

Risk Factors		(-) *H. pylori*		(+) *H. pylori*		OR	95% CI		p value
		N	%	N	%		Min	Max	
Age	2-9 yrs	10	45.5	12	54.5	0.76	0.28	2.12	0.604 *
	10-18 yrs	24	52.2	22	47.8	1.00			
Gender	Girl	19	45.2	23	54.8	0.61	0.23	1.63	0.318 *
	Boy	15	57.7	11	42.3	1.00			
Nutritional status	Undernourished	3	33.3	6	66.7	0.45	0.10	1.98	0.476 **
	Not undernourished	31	52.5	28	47.5	1.00			
	Overweight	13	48.1	14	51.9				
	Normal	18	56.3	14	43.8				
Ethnic	Batak	14	48.3	15	51.7	0.89	0.34	2.32	0.806 *
	Not Batak	20	51.3	19	48.7	1.00			
	Minang	1	25.0	3	75.0				
	Aceh	4	57.1	3	42.9				
	Java	9	69.2	4	30.8				
	Malay	3	30.0	7	70.0				
	Chinese	3	75.0	1	25.0				
	India	0	0.0	1	100.0				
Father's education	High school	6	60.0	4	40.0	1.61	0.41	6.30	0.493 *
	University	28	48.3	30	51.7	1.00			
Mother's education	High school	3	50.0	3	50.0	1.00	0.19	5.34	1,000 **
	University	31	50.0	31	50.0	1.00			
Father's occupation	Employee	19	51.4	18	48.6	1.13	0.43	2.93	0.808 *
	Not employee	15	48.4	16	51.6	1.00			
	Civil servant	4	57.1	3	42.9				
	Farmer	1	50.0	1	50.0				
	Entrepreneur	8	42.1	11	57.9				
	Army/police	2	66.7	1	33.3				
Mother's occupation	Employees	15	51.7	14	48.3	1.13	0.43	2.95	0.806 *
	Not employees	19	48.7	20	51.3	1.00			
	Civil servants	3	42.9	4	57.1				
	Farmer	1	33.3	2	66.7				
	Entrepreneur	9	50.0	9	50.0				
	Housewife	6	54.5	5	45.5				
Parents's socio-economic	< 2x min wage	3	60.0	2	40.0	1.55	0.24	9.91	1,000 **
	> 2x min wage	31	49.2	32	50.8	1.00			
Family history of *H. pylori*	No	12	52.2	11	47.8	1.14	0.42	3.12	0.798 *
	Yes	22	48.9	23	51.1	1.00			

infection									
Cigarette	No	16	57.1	12	42.9	1.63	0.62	4.32	0.324 *
smoke	Yes	18	45.0	22	55.0	1.00			
exposure									
Hand washing	Rarely	2	20.0	8	80.0	0.20	0.04	1.04	0.040 *
habit	Routine	32	55.2	26	44.8	1.00			
Bottle feeding	< 2 years	11	73.3	4	26.7	3.59	1.01	12.73	0.041 *
	> 2 years	23	43.4	30	56.6	1.00			

* chi-square test ** Fisher's exact test

3.3. Multivariate Analysis Results

The variables that had a p value <0.25 and statistically significant for the incidence of *H. pylori* infection (hand washing habit and bottle feeding until more than 2 years old) were analysed by multivariate analysis using backward LR logistic regression test. The results are presented in Table 3.

Table 3. Logistic regression test results

	OR	95% CI		B	P value
		Min	Max		
Hand washing habit	0.05	0.00	0.55	-3,036	0.015
Bottle feeding > 2years old	12.86	1.55	106.81	2,554	0.018

4. Discussion

A total of 68 children with gastrointestinal symptoms, who were treated at H. Adam Malik General Hospital in Medan, were divided into two groups. The first was with *H. pylori* (+) infection and the second, control group, was without *H. pylori* infection. Each group consist of 34 children. The diagnosis of *H. pylori* infection was based on the results of one of the HPSA examinations (8 subjects), UBT (10 subjects), endoscopy and CLO (50 subjects). All of these diagnostic examination have a high sensitivity and sensitivity toward *H. pylori* infection (Koletzko S et al., 2011; Yanez et al., 2000; Glupczynski, 1998; Kato et al., 2003).

4.1. Age

The largest age group that participated in this study was 10-18 years old, consisted of 46 (67.6%) children. The incidence of *H. pylori* infection was almost equal in the 2-9 years old age group (54.5%) and in the 10-18 years old age group (47.8%). Hence, we can assume that *H. pylori* infection has occurred in young children which is in line with the result of a study in Ireland which showed that *H. pylori* infection has occurred in children between 2 to 4 years old (Rowland et al., 2006). A study in Latvia even found that the incidence *H. pylori* infection is highest in children under 5 years old (Daugule et al., 2016). Meanwhile, the results of studies in Uganda and China found that the incidence of *H. pylori* infection increases with increasing age of the child (Aitila et al., 2019; Ding et al., 2015).

4.2. Gender, Nutritional Status, and Parent's Education Level

A study in Taiwan, from a cross-sectional study, found no association between *H. pylori* infection and growth failure measured in body weight, height, and body mass index (Chi H et al., 2009). However, a

study in Turkey demonstrated that *H. pylori* infection can significantly impair growth in a group of children with low socioeconomic levels, presumably through mechanisms involving growth-related molecules (ghrelin) (Ozen et al., 2011).

From the results of our study, there were no significant differences between the incidence of *H. pylori* infection with gender, nutritional status, and parent's education level. This may be due to the disequilibrium of the sample, of which only 9 children (13%) who were malnourished. Majority of the subject's parent, 58 (85%) with father and 62 (91%) with mother, went to university, The rest have parents who had finished high school. Thus, conclusion from this can be bias and cannot be compared with studies in Vietnam and China that show the education level of parents (especially mothers) as a protective factor against the incidence of *H. pylori* infection to her child (Nguyen at al., 2017; Ding et al., 2015).

4.3. Parent's Occupation and Socioeconomic Status

Helicobacter pylori is transmitted via the faecal-oral route. Hence, socioeconomic is thought to play a role in *H. pylori* infection because it is related to sanitation (Aitila et al., 2019; Nguyen at al., 2017; Darnindro et al., 2015). The occupation of the parents of the subjects in this study were mostly employees (54.5% father and 42.6% mother). But from a socioeconomic perspective, the total income of both parents of 92% of the subjects was more than 2x the UMR (province minimum wage), which we categorized as middle and upper economic groups. From this study, there was no relationship between parent's occupation and socioeconomic status with the incidence of *H. pylori* infection.

4.4. Family History of H. pylori Infection

Of the total study subjects, 45 children (66.2%) had a family history of *H. pylori* infection. One possible explanation is that if there are family members who are infected, there will be an awareness to check other family members for the same disease. In this study, there was no statistically significant relationship between family history and the incidence of *H. pylori* infection in children. This is different from most other studies that have found an increased risk of *H. pylori* infection when there is a family history of infection, such as in studies in Vietnam, Ireland, China (Nguyen at al., 2017; Farrel et al., 2005; Ding et al., 2015).

4.5. Exposure to cigarette smoke

Secondhand smoke exposure is a debatable possible risk factor for *H. pylori* infection. Smoking itself is a major risk factor for peptic ulcer disease by stimulating gastric acid secretion and weakening the gastric mucosal barrier, thereby triggering gastric atrophy which in itself can also lead to malignancy. From a study in India and Brazil in adult subjects, it was found that smoking increases the risk of *H. pylori* infection (Mhaskar et al., 2013; Basilio et al., 2018). However, our study did not find statistically significant relationship between cigarette smoke exposure and the incidence of *H. pylori* infection in children.

4.6. Hand Washing Behavior

Transmission of *H. pylori* is via faecal-oral route, so the incidence of *H. pylori* infection is deemed to be associated with sanitation status and had been demonstrated in several studies, including a study in the adult population in Jakarta which found an association between environmental sanitation and *H. pylori* infection (Darnindro et al., 2015). The Vietnamese study also specifically found that not washing hands regularly after defecating was a risk factor for the incidence of *H. pylori* infection (Nguyen et al., 2017). From the multivariate regression results of a study, hand hygiene was also found to be a protective factor for the incidence of *H. pylori* infection (Ding et al., 2015).

The majority (85.3%) of the sample in this study routinely washed their hands with soap before

eating, after defecating, and when their hands were dirty. The behavior of washing hands itself is very subjective, so that in this study, we tried to reduce bias by explaining clearly in detail to parents (during the process of filling out the questionnaire) the parameters that had been determined, which was the habit of washing hands before eating, after defecating, and if hands were dirty. It should be emphasized that due to the fairly wide age range in the subjects of this study, we took note to include child's caregiver habit for children who could not take care of themselves. Hand washing behavior (p = 0.040) and history of bottle feeding beyond 2 years old (p = 0.041) were two risk factors that were found to be significantly associated with the incidence of *H. pylori* infection in this study.

4.7. History of Bottle Feeding

History of bottle feeding beyond 2 years old were stated as a risk factor from the results of a study in Ireland (Rowland et al., 2006). This is based on the principle of transmission of *H. pylori* via the faecal-oral route. *H. pylori* (in the form of coccoid) can be detected by the PCR in samples in contaminated mineral water, so it is possible that *H. pylori* can also be found in milk bottles that are not properly washed (Bahrami et al., 2013).

4.8. Research Limitations and Strengths

This study has several limitations including:

- Has a wide age range so that some research parameters can be bias. For example, the hand washing behavior is different between children aged 2 years and adolescent. The accuracy of history of bottle feeding beyond 2 years old is also doubtful in older children.
- Subjects are not normally distributed. The majority of the subjects are middle and upper socioeconomic groups with a minimum parental education was high school and the majority even university graduated.

The advantages of this research are:

- This is a pioneering study on the risk factors for *H. pylori* infection in children in Indonesia. Although similar studies have been published based on research results in other countries, until the time of this publication, in Indonesia there had only been research on adults.
- The diagnosis of *H. pylori* infection used one of the HPSA, UBT, and endoscopy (CLO) methods which have high sensitivity and specificity values (Koletzko S et al., 2011; Yanez et al., 2000; Glupczynski, 1998; Kato et al., 2003).

5. Conclusion

Hand washing behavior (before eating, after defecating, and if hands are dirty) and a history of bottle feeding beyond 2 years old are significantly associated with the incidence of *H. pylori* infection in children with gastrointestinal complaints. There are no association between age, sex, nutritional status, ethnicity, education and occupation of parents, socioeconomic status, family history of *H. pylori* infection, or exposure to cigarette smoke with the incidence of *H. pylori* infection in children.

Further research is needed with a sample population that is normally distributed from a socioeconomic perspective and a more specific age division.

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