

Effectiveness of Probiotic on Eradication *Helicobacter Pylori* Gastritis in Children

Masitah Nasution^a, Supriatmo^b, Aridamuriany D Lubis^c, Gontar A Siregar^d,
Chairul Yoel^e, Rizky Adriansyah^f

^amasitahnasution.mn@gmail.com

^aResident of Paediatrics, Medical School, Universitas Sumatera Utara/ Adam Malik Hospital, Medan, Indonesia

^bDepartment of Paediatric, Medical School, Universitas Sumatera Utara/ Adam Malik Hospital, Medan, Indonesia

^cDepartment of Paediatrics, Medical School, Universitas Sumatera Utara/ Adam Malik Hospital, Medan, Indonesia

^dDepartment of Internal Medicine, Medical School, Universitas Sumatera Utara/ Adam Malik Hospital, Medan, Indonesia

^eDepartment of Paediatric, Medical School, Universitas Sumatera Utara/ Adam Malik Hospital, Medan, Indonesia

^fDepartment of Paediatrics, Medical School, Universitas Sumatera Utara/ Adam Malik Hospital, Medan, Indonesia

Abstract

Introduction : *Helicobacter pylori* (H. pylori) is one of causing intestinal and gastric ulcers and one of the factors that can cause gastric malignancy. The prevalence of H. pylori infection is more than 80% in developing countries. Probiotics have beneficial effects on health if administered in an adequate amount. The most commonly used as probiotics are Lactobacillus and Bifidobacteria. H.pylori colonization is interfered with by regular ingestion of L. acidophilus, and the value of urea breath test (UBT) decreased approximately 10% after four weeks of treatment. **Objective:** To assess the effectiveness of probiotic in eradication of H. pylori gastritis in children along with triple therapy **Material and Methods:** This clinical trial design in children with H. pylori gastritis in a network hospital in Medan. Sampling was carried out from August 2019 - April 2020 with randomization techniques and double-blind in children suffering from H. pylori gastritis based on history, physical examination, H. pylori stool antigen (HpSA) test and endoscopy. Mc Nemar test analysis was performed to assess the differential effectiveness of drugs in the two groups. **Result:** From 33 children who received probiotics 31 children eradicated and from 31 children who did not receive probiotics, 29 children were eradicated. From 33 children who received probiotics, 6 children had side effects. From 31 children who did not receive probiotics, 22 children had side effects such as nausea/vomiting, abdominal pain, and diarrhea. There was no significant difference between probiotics and triple therapy with only triple therapy ($p = 1,000$). But, there was a significant difference in reducing the side effects of nausea/vomiting and diarrhea in the probiotic group ($p = 0.015$). **Conclusion:** There were no significant differences between administering probiotics plus triple therapy with triple therapy only to eradicate H. pylori gastritis in children. However, there were significant differences in the probiotic group in reducing the symptoms of side effects.

Keywords: children, helicobacter pylori, triple therapy, gastritis, probiotics.

Introduction

Helicobacter pylori (H. pylori) is a species of bacterium which can be colonize in the human gastrointestinal tract and is one of the causes of intestinal and gastric ulcers, or one of the factors causing gastric malignancy.¹ The prevalence of infection caused by H. pylori, which is more than 80%, is found in developing countries. In contrast, in industrialized countries, it is much lower, and the prevalence is reported to be steadily decreasing.^{2,3} The prevalence estimation of H. pylori show a significant variation globally, with the rates varying from 15.1% in developed countries (Australia) to 87.7% in developing countries (Nigeria)⁴ while in Jakarta, the prevalence of gastritis due to H. pylori infection was 52.3% of 310 patients. In Yogyakarta in 2009 it was 22.2% of the total patients who underwent gastroscopy.⁵ In 2015, the prevalence of H. Pylori was estimated at approximately 4.4 billion individuals worldwide.⁴

One of the symptoms infection of H. Pylori is recurrent abdominal pain. The terminology of recurrent abdominal pain is when the patients have three episodes of severe stomach pain that disrupt daily activities

over three months or more.⁶ According to the ESPGHAN/ NASPGHAN Guidelines, the triple therapy in children is 14 days or triple therapy combined with bismuth is the best choice for eradicating *H. pylori* based on sensitivity test results of antimicrobial. If sensitivity testing is unavailable, the combination treatment of high-dose PPI-amoxicillin-metronidazole should be used with or without a combination of bismuth because clarithromycin is already highly resistant worldwide.⁷ In Indonesia, regimen therapy regimens using amoxicillin and clarithromycin are high priority for eradication because the combination of amoxicillin and clarithromycin showed a great result of 74.2%. The level of clarithromycin resistance in Indonesia much lower than other antibiotics (10% clarithromycin resistance, 20% amoxicillin, 62.7-100% metronidazole), and low eradication therapy failure (15%).^{5,6}

As live microorganisms, probiotics contribute well to health when given in adequate amounts.⁸ A Meta-analysis study suggests that probiotics plus triple therapy may help increase the eradication of *H. pylori* and reduce side effects related to treatment in children.⁹ Currently, there are many in vitro studies and/ or animal models showing that certain *Lactobacillus* strains can show an effect on the eradication of *H. pylori*.¹⁰ Double-blind RCT data involve of 20 adult volunteers found that in vivo *H. pylori* colonization was impaired by regular consumption of *L. acidophilus*, and the value of UBT will be decreased after four weeks of treatment approximately 10%.⁷ The author is interested in investigating whether probiotic supplementation could increase *H. pylori* eradication in children and to explore the dose and duration of supplementation.

Material and Method

The study was conducted at Gastroenterology Polyclinic H. Adam Malik Medan Hospital, University of North Sumatera Hospital, and Columbia Asia Hospital Medan in August 2019 – April 2020. The subject recruitment can be seen in figure 1. This is a prospective observational study. With inclusion criteria: children 2 – 18 years old with recurrent abdominal pain and had established with *H. pylori* diagnosis from the positive stool *H. pylori* stool antigen (HpSA) test and endoscopy and the patient's family signed to the informed consent. Patients with previously using PPI, H2 blocker antagonist, antibiotics and NSAIDs in the last 14 days are excluded and the patients with a history of gastric operation, gastric bleeding, hepatic cirrhosis, a renal failure that need dialysis, cardiac failure and early or advance gastric cancer also excluded. The subject who fulfil inclusion criteria will be randomized using randomized table and divided within treatment and control. The treatment group will get triple therapy plus probiotic, while the control group only gets triple therapy. The probiotic contains of *Lactobacillus acidophilus*, *Bifidobacterium longum*, dan *Streptococcus thermophilus* 1×10^9 CFU twice a day given after a day antibiotic treatment. The treatment subject will be followed for assessed and compared the success of treatment and the side effects of probiotics treatment for 4 weeks. Data will analyzed by using SPSS version 20 with bivariate analyses for the sample characteristic. Categorical data will shown as frequency and percent but numeric data will shown as rate and standard deviation. Chi-square will be used to assess probiotic effectiveness and to assess differences in side effects between the two groups. Fisher's exact test will be performed if the chi-square test did not meet the parametric requirements. P-value significant if < 0.05 .

Result

Figure 2 show the subject of recruitment and how the randomization of the study. All patients who fits with the inclusion criteria will be informed consent and perform the testing of HpSA and endoscopic procedure. From 84 patients, only 64 patients meet the criteria, and the sample randomized using a randomize table in which group 1 receive triple therapy plus probiotic LactoB® while group 2 receive triple therapy only. The treatment was given by the caregiver with a double blind method and during the treatment, all of the patients

were followed up to evaluate and assess the side effect of the treatment: nausea, vomitus, haematemesis and abdominal pain. After four weeks of treatment, the patients perform HpSA test. From this study, both of the recovery patients 93.9% vs 93.5% and unrecovered patients 6.1% vs 6.5%.

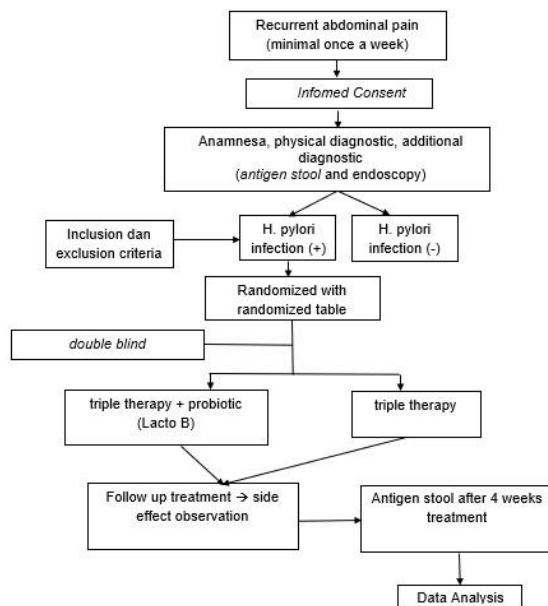


Fig. 1. Subject recruitment

Study characteristic is shown in table 1 between two groups triple therapy plus probiotic (group 1) vs triple therapy only (group 2). Female patients more than male patients both in two groups, with the most cases 6 – 18 years old. Body weight and body height mean between two groups are 37.99 kg and 137.91 cm vs 39.08 kg and 139.9 cm. BMI level 19.17 kg/m² vs 19.37 kg/m² and well nourished dominant between two groups. Batakneese ethnic are found the most. Parent's college educational levels are found the most between the two groups. A family history of gastritis was found greater between two groups. Abdominal pain is a complaint at most between the two groups.

Our study checked HpSA test and perform endoscopy study before and after treatment within standard therapy (triple therapy) plus probiotic and only standard therapy to evaluate the of *H. pylori*'s existences that we can see in table 2. Both from the study, we found that *H. pylori* still found among two groups 6.1 % vs 6.5% with eradication rate using Fischer's exact test with the result no significant difference between the two groups (figure 3, $p=1.000$). We perform Mc Nemar test to analyze comparison of *H. pylori* result between pretreatment and post treatment and we found a significant result in each group ($p<0.001$).

Our study also compares triple therapy's side effect plus probiotic and only triple therapy after 4 weeks of treatment (table 3). In triple therapy plus probiotic, we found 2 subjects experience nausea/ vomitus, bloating and diarrhea (6.1%) while in another group more prominent, 9 subjects experience nausea/ vomitus, diarrhea (29%) and 4 subjects experience bloating (12.9%), which statistically significant in nausea/ vomitus and diarrhea ($p=0.015$) while bloating not statistically significant ($p=0.419$).

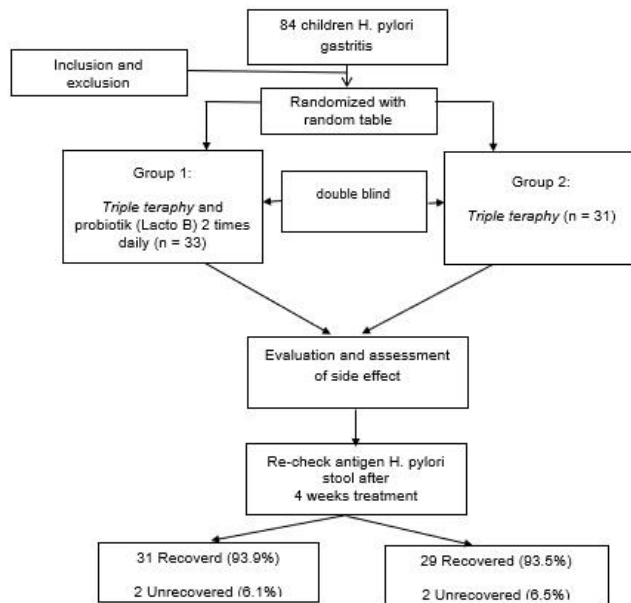


Fig. 2 Study profile

Discussion

H. pylori is negative gram of bacteria, spiral-shaped and often found on the gastric epithelium surface and is considered as bacterial infection that the most common appear in the world.¹¹ Clinically, all humans infected with this organism can have gastritis symptoms in the form of abdominal pain that can last for years and can develop into chronic inflammation. The infection of *H. pylori* is known to be associated with various risks of chronic gastritis, peptic ulcer disease (PUD) in the stomach and/ or duodenum, gastric mucosal-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma.¹¹

There are differences in the prevalence of *H. pylori* infection in various countries. In developed countries have lower prevalence rates. In Bangladesh, the mean prevalence of *H. pylori* was reported 92%, in India it was 79%, in Vietnam, it was 74.6%. In contrast, in countries that are considered developed, such as Australia, the seroprevalence rate is approximately 15.1%. The reported seroprevalence rate in East Asia was 59.6% in South Korea, 58.07% in China, 54.5% in Taiwan, and 39.3% in Japan. Meanwhile, in Southeast Asia, the reported prevalence rates were 57% in Thailand, 35.9% in Malaysia, and 31% in Singapore.¹²

Several studies have investigated the risk factors associated with *H. pylori* infection. The increased risk of disease was not associated with gender and age. Many studies reported no significant differences in *H. pylori* infection between both men and women, among adults and children.¹³ Socioeconomic factors have been associated with *H. pylori* infection, associated with lower socioeconomic status, considered to have a higher impact in developing *H. pylori* infection. Furthermore, there is an inverse relation between level of education and infection of *H. pylori*. It was found that individuals with low education levels have a higher risk than those who have higher education.¹³ Another related factor is residence, those who live in rural areas, at home, crowded homes, and having a source of contaminated drinking water are risk factors for infection of *H. pylori*.¹⁴ In our study, all of the risk factors are not statistically significant.

Tabel 1. Subject Characteristic

Subject Characteristic	Triple Therapy and antibiotic n = 33	Only Triple Therapy n = 31	p
Gender, n (%)			
Male	9 (27,3)	12 (38,7)	0.330 ^a
Female	24 (72,7)	19 (61,3)	
Age, n (%)			
2 – < 5 years old	2 (6,1)	1 (3,2)	0.535 ^b
5 – < 6 years old	1 (3)	0	
6 – 18 years old	30 (90,9)	30 (96,8)	
Body Weight, mean (SD), kg	37,99 (12,59)	39,08 (15,25)	0.707 ^c
Body Height, mean (SD), cm	137,91 (21,32)	139,90 (17,27)	0.968 ^c
IMT, mean (SD), kg/m ²	19,17 (2,90)	19,37 (4,15)	0.824 ^d
Nutritional status, n (%)			
Malnourished	10 (30,3)	14 (45,2)	0.304 ^b
Well nourished	21 (63,6)	13 (41,9)	
Overweight	2 (6,1)	3 (9,7)	
Obesity	0	1 (3,2)	
Ethnic Group, n (%)			
Aceh	6 (18,2)	3 (10)	0.263 ^b
Batak	15 (45,5)	12 (40)	
India	0	1 (3,3)	
Jawa	1 (3)	6 (20)	
Malayu	6 (18,2)	3 (9,7)	
Minang	3 (10)	3 (10)	
Papua	1 (3)	1 (3,3)	
Tionghoa	0	2 (6,7)	
Child educational level, n (%)			
Kindergarten	3 (9,1)	0	0.098 ^b
Primary school	9 (27,3)	15 (48,4)	
Secondary school	7 (21,2)	8 (25,8)	
Senior high school	12 (36,4)	5 (16,1)	
College	2 (6,1)	3 (9,7)	
Father educational level, n (%)			
Senior high school	6 (18,2)	5 (16,1)	0.828 ^a
College	27 (81,8)	26 (83,9)	
Mother educational level, n (%)			
Senior high school	2 (6,1)	3 (9,7)	0.677 ^a
College	31 (93,9)	28 (90,3)	
Father's occupation, n (%)			
Private employee	20 (60,6)	14 (45,2)	0.674 ^b
Farmer	2 (6,1)	1 (3,2)	
Government employee	4 (12,1)	5 (16,1)	
Army/ police	1 (3)	2 (6,5)	
Entrepreneur	6 (18,2)	9 (29)	
Mother's occupation, n (%)			
Private employee	11 (33,3)	11 (35,5)	0.982 ^b
Farmer	3 (9,1)	2 (6,5)	
Government employee	7 (21,2)	6 (19,4)	
Entrepreneur	9 (27,3)	8 (25,8)	
Housewife	3 (9,1)	4 (12,9)	
Socioeconomic status, n (%)			
Scant	4 (12,1)	4 (12,9)	1.000 ^a
Good	29 (87,9)	27 (87,1)	
Family history, n (%)			
Yes	24 (72,7)	23 (74,2)	0.894 ^a
No	9 (27,3)	8 (25,8)	
Clinical manifestation, n (%)			
Nausea	2 (6,1)	1 (3,2)	0.643 ^b
Vomitus	10 (30,3)	6 (19,4)	
Haematemesis	4 (12,1)	6 (19,4)	
Abdominal pain	17 (51,5)	18 (58,1)	

^a Chi Square, ^b Kruskal Wallis, ^c Mann Whitney, ^d T Independent, ^e Fischer's Exact

Table 2. H. pylori result on Pretreatment dan Post treatment

<i>Helicobacter pylori</i>	Triple Therapy with Probiotic n = 33	Triple Therapy without Probiotic n = 31	P
Pretreatment, n (%)			
Negative	0	0	-
Positive	33 (100)	31 (100)	
Post treatment, n (%)			p1=1.000 ^a
Negative	31 (93.9)	29 (93.5)	p2<0.001 ^b
Positive	2 (6.1)	2 (6.5)	p3<0.001 ^b

^aFischer's Exact, ^bMc Nemar, p1=probiotik vs non probiotik post treatment, p2=pre treatment vs post treatment on probiotic group, p3=pre treatment vs post treatment without probiotic

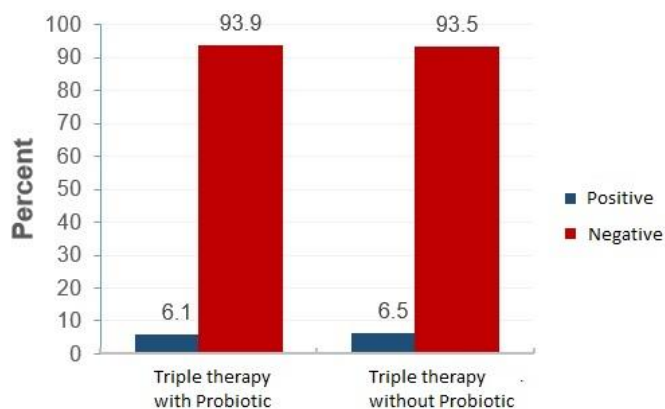


Figure 3. H. Pylori test result between Probiotic and Without Probiotic on post treatment

Table 3. Side effect between Probiotic group and without Probiotic

Side effect	Probiotic (+) n = 33	Probiotic (-) n = 31	p
Nausea/ vomitus	2 (6,1)	9 (29)	0,015 ^a
Bloating	2 (6,1)	4 (12,9)	0,419 ^b
Diarrhea	2 (6,1)	9 (29)	0,015 ^a

^aChi Square, ^bFischer's Exact

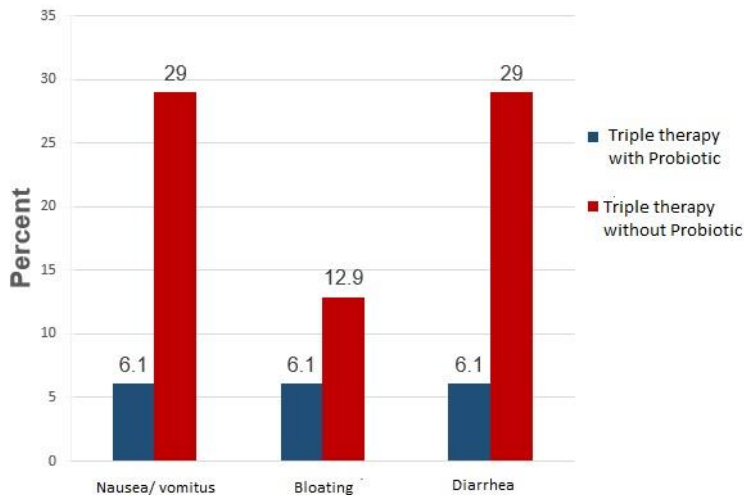


Figure 4. Side effect on post treatment between Probiotic and Without Probiotic

There are few studies on the relationship between clinical manifestations and infection of *H. pylori* in children than in adults. Several data reports that *H. pylori* infection in children is mostly asymptomatic or exhibits non-specific gastrointestinal symptoms^{15,16} and more frequently associated with gastritis than peptic ulcers. Gastritis often shows complaints of recurrent abdominal pain in children; therefore, complaints of recurrent abdominal pain in children are considered by some researchers as a clinical symptom associated with infection of *H. pylori* and difficult to distinguish gastritis with infection *H. pylori* or non infection of *H. pylori*. The clinical manifestations of *H. pylori* infection are: Recurrent abdominal pain (at least once a week), pain in the epigastric area, frequently vomit, decrease of body weight, growth disorder, iron deficiency anemia, recurrent diarrhea, and malnutrition.^{15,16}

There are various methods can be used to diagnose infection of *H. pylori*, both invasive and non-invasive. Invasive procedures include endoscopy and biopsy followed by histological examination, culture, urease test, and PCR, while non-invasive methods include serology and HpSA or C-Urea Breath Test. A combination of 2 or 3 types of tests will increase the sensitivity and specificity of the *H. pylori* diagnostic test.^{16,17} Our study choose HpSA and endoscopic procedure to diagnose the *H. pylori* infection.

Since the first guidelines for *H. pylori* infection in children were published, the first-line recommended treatment are the combination of a proton pump inhibitor (PPI) and two antibiotics (clarithromycin plus amoxicillin or metronidazole).¹⁸ The consensus of gastroenterologists in America and Europe recommends using 3 types of drugs consisting of PPIs and a combination of 2 antibiotics for 7 days : (1) PPI, metronidazole, and clarithromycin with eradication rate 87-92%, or (2) PPI, amoxicillin (if suspected metronidazole resistance) with eradication rate 70% or (3) PPI, amoxicillin, and metronidazole (if there is clarithromycin resistance).^{1,16,17} Meanwhile, in Indonesia, the eradication regimens treatment using a combination of amoxicillin and clarithromycin are still a top priority because eradication therapy using a combination of amoxicillin and clarithromycin shows a high eradication result 74.2%.^{5,6} We can see the recommendation treatment of *H. pylori* in table 4. Eradication is successful if a typical histological pattern is found, or the results of a biopsy tissue culture and HpSA or Urea Breath test negative. Non-invasive diagnostic tests are preferred to be done to confirm the successfulness of treatment. If the treatment given does not provide optimal results, culture and resistance testing are needed to determine the next antibiotic.¹⁸

Table 4. Recommendation for *H. pylori* treatment¹⁶

First Line Treatment	Drugs	Dosage
1.	Amoxicillin	50 mg/kgBW/day until 1 g bid
	Clarithromycin	15 mg/kgBW/day until 500 mg bid
	Proton pump inhibitor: omeprazole	1 mg/kgBW/day until 20 mg bid
2.	Amoxicillin	50 mg/kgBW/day until 1 g bid
	Metronidazole	20 mg/kgBW/day until 500 mg bid
	Proton pump inhibitor: omeprazole	1 mg/kgBW/day until 20 mg bid
3.	Clarithromycin	15 mg/kgBW/day until 500 mg bid
	Metronidazole	20 mg/kgBW/day until 500 mg bid
	Proton pump inhibitor: omeprazole	1 mg/kgBW/day until 20 mg bid

Probiotics are known to be living microorganisms that support beneficial effect for human health if given in proper amount.¹⁹ Many microbial species could potentially function as probiotics, like *Saccharomyces*, *Lactobacillus*, *Streptococcus*, *Bifidobacteria*, etc., of which *Bifidobacteria* and *Lactobacillus* are the most researched commonly.²⁰ Probiotics will stabilize the intestinal microflora by inhibiting the pathogens by attributed to their competitiveness for food and binding sites, immunomodulation, and production of antimicrobial substances. Beside the probiotic's antagonistic properties, probiotics have their own abilities surviving high pH and bile salts and colonizing gastrointestinal surfaces are critical to assign them among with the most promising and potential candidates of probiotic.²¹ Many kinds of research related to the antagonistic effect of probiotics against *H. pylori* have shown astonishing results in reducing the side effects of antibiotics, improving the *H. pylori* infection eradication, and reducing the cell's injury. Although not all probiotics strain is beneficial to improve the eradication of *H. pylori*'s treatment, several probiotics appear to minimize the disease and treatment side effects. Some research of *H. pylori* infection after the eradication using the conventional treatment, one-third of the children were re-infected after 2 years; so, using probiotics as an adjunct treatment or as a vaccine delivery tool would be very helpful.²¹⁻²⁵

Studies on probiotics' effect in minimizing the side effects of standard treatment of *H. pylori* have been increasing, usually due to their usefulness in accelerate compliance rate of the patients.²⁶ Research conducted by Ojetti et al. and Myllyluoma et al. found the effect of a combination of antibiotics and *L. reuteri* ATCC 55730, and found eradication rate of *H. pylori* the increase significantly; additionally, the reducing of side effects of antibiotics were also found.²¹ A research by Du et al. found the eradication of *H. pylori* improvement when using *L. acidophilus* combine with the triple therapy; and found that symptoms were not reduced using only probiotic.²⁵ Lionetti et al. found that given of *L. reuteri* ATCC 55730 the side effects were reduced to some extent.²⁷ Armuzzi et al. found a similar result when given *L. rhamnosus* GG supplemented as an additional treatment.²⁸ A double-blind research using placebo-controlled conducted by Ahmad et al., found 66 *H. pylori*-infected children were given the combination probiotics that contain of *L. acidophilus*, *L. bulgaricus*, *L. casei*, *B. breve*, *L. rhamnosus*, *B. infantis* and *S. thermophilus*, with triple therapy with a total of 90.09% of the children supplemented with probiotics were successfully cured from *H. pylori* infection while in the control group, 69.69% of children were cured. The rising significant cure rate of approximately 20% in the treated group proves that the probiotics have their role as an additional to eradication *H. pylori* treatment.²⁹ In our study, after a comparative analysis of the results of *H. pylori* examination between pre and post treatment using the Mc Nemar test, it appears that the two groups showed significant differences in each group ($p < 0.001$).

Our study compared triple therapy's side effects with and without probiotic, and we found a significant difference in side effects for symptoms of nausea/vomiting and diarrhea between in the two groups ($p =$

0.015). This occurs because of the protective effect from damage on mucosal barrier using probiotics by different mechanisms, including modifying expression of mucus protein and epithelial junctions and stabilizing the barrier by releasing the bioactive molecules, thereby preventing its disruption by pathogens. Other studies have shown that increased production of IgA by probiotic strains will help in strengthening mucosal barriers against invading pathogens.^{21,22}

Conclusion

H. pylori is negative gram of bacteria, spiral-shaped and often found on the gastric epithelium surface. Clinically, all humans infected with this organism can have gastritis symptoms in the form of abdominal pain that can last for years and can develop into chronic inflammation. The diagnosis of *H. pylori* infection is by using *H. pylori* stool antigens (HpSA) test or urea breath tests (UBT) and endoscopy.

Probiotics are known to be living microorganisms that support beneficial effect for human health if given in proper amount. Probiotics will stabilize the intestinal microflora by inhibiting the pathogens by attributed to their competitiveness for food and binding sites, immunomodulation, and production of antimicrobial substances.

Probiotics is useful for *H. pylori* infections by releasing antimicrobials as a result of fermentation, such as lactic acid, acetic acid, and hydrogen peroxide. protective effect from damage on mucosal barrier using probiotics by different mechanisms, thereby preventing its disruption by pathogens. Increased production of IgA by probiotic strains will help in strengthening mucosal barriers against invading pathogens.

In our study, we found that there is no significant difference effectiveness between triple therapy plus probiotics with triple therapy only in *H. pylori* eradication in children. However, our study has a significant value in reducing antibiotic side effects. Nevertheless, the effectiveness of probiotics in eradication of *H. pylori* needs to be considered, especially as adjunct to triple therapy.

Acknowledgements

I would like to dedicate my gratitude to all the lecturers of Pediatric Department, Faculty of Medicine Universitas Sumatera Utara, my family, and my friends for their endless support.

Conflicts of interest

The author declares that there is no conflicts of interest.

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