

Screening and Treatment for *Helicobacter pylori* Infection in Teenagers in Japan

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Abstract

To elucidate the prevalence and effect of *H. pylori* infection in Japanese teenagers, we underwent an examination and treatment of it in one high school health screening between 2007 and 2015. The study subjects were students ages 16 to 17. Students who tested positive on this screening using urine-based rapid test kits (RUPIRAN®) examination visited Shinshu University Hospital and underwent esophagogastroduodenoscopy (EGD) and were taken biopsy samples to determine their *H. pylori* status using culture and histology. Cure of *H. pylori* infections was determined by urea breath test. For 9 years, 4,297 of 4,312 students (99.7%) received a screening examination for *H. pylori* infection. One hundred and sixty-two of 4,297 students (3.8%) were positive for *H. pylori*. Ninety-three of these 162 with *H. pylori*-positive students visited our hospital, and 91 underwent EGD and 78 (85.7%) were confirmed to be *H. pylori* infected. The most common endoscopic findings for *H. pylori* infection were nodular gastritis (80.8%) and closed-type atrophic gastritis (61.5%). A scar from duodenal ulcer was recognized in 6 of them (7.7%), and intestinal metaplasia was histologically present in two. All 78 students with *H. pylori* infection and their parents agreed to receive eradication therapy using regimens according to the susceptibility of *H. pylori*. Finally, all except 3 were successfully cured of *H. pylori* infection. Remaining 3 students have not yet been assessed the decision of *H. pylori* infection. If this procedure were to be introduced into nationwide health screening at Japanese high schools, we calculated that the cost of the prevention of a gastric cancer would be 495,958 yen (4,508.71 dollars) for each person. The low rate of prevalence of *H. pylori* infection in present Japanese teenagers would make it possible to perform the screening examination and treatment for this infection in nationwide health screening of high school students in the way that is practical and feasible.

Keywords: *Helicobacter pylori*; Gastric cancer; Teenager; Screening; Eradication; Cost-effectiveness

Introduction

Helicobacter pylori (*H. pylori*) infection is etiologically related to several gastric diseases, such as gastritis, gastroduodenal ulcer, gastric cancer, and gastric MALT lymphoma. Recently, it has been confirmed that *H. pylori* infection is a significant risk factor for gastric cancer, epidemiologically, experimentally, and clinically. This has been proved by experiments using animals [1] and also by randomized clinical studies [2,3] showing that eradication of *H. pylori* reduces the occurrence of gastric cancer. In 2003, Nozaki et al [4] reported that early stage eradication of *H. pylori* was more effective in reducing the late occurrence of gastric cancer compared with late-stage eradication in animal experimentation. From these data, eradication of *H. pylori* is thought to be beneficial for the prevention of human gastric cancer, and it is more effective to treat *H. pylori* infection in young people compared with old people.

The purpose of this study is to collect data regarding the screening for *H. pylori* infection in health screenings in school, and to identify the actual effects of *H. pylori* infection in Japanese teenagers.

Screening and Treatment for *H. pylori* Infection in high school students

We have proposed that a screening for *H. pylori* infection should be introduced into health screenings in school, and have performed this procedure in one Japanese high school every year since 2007 [5,6]. All students of the second year in high school were annually examined about the status of *H. pylori* infection using urine-based rapid test kit (RUPIRAN®, Otsuka Pharmaceutical Co. Tokyo, Japan) [7]. Students were between ages 16 and 17. The study was approved by the Ethics Committee of Shinshu University School of Medicine.

First examination of *H. pylori* infection

Participation rate of high school students in the first screening examination of *H. pylori* infection was showed in Table 1. Between 2007 and 2015, 4,297 of 4,312 students (99.7%) received a first screening examination. Positive rate of high school students in the first screening examination of *H. pylori* infection was showed in Table 2. One hundred and sixty-two of 4,297 students (3.8%) were positive for *H. pylori*.

Year	No of Participating students	Participating rate of high school students
2007	409/414	98.80%
2008	370/373	99.20%
2009	445/445	100%
2010	478/480	99.60%
2011	400/401	99.80%
2012	539/539	100%
2013	610/611	99.80%
2014	516/518	99.60%
2015	530/531	99.80%
Total	4297/4312	99.70%

Table 1: Participation rate of high school students in the first screening examination of *H. pylori* infection.

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Further examination for *H. pylori* infection

The first screening-positive students and their parents were recommended to receive further examination of the status of *H. pylori* in medical institutions by a school doctor. Ninety-three of 162 students visited Shinshu University Hospital. Ninety-one of them underwent further examination using EGD, but the remaining 2 students declined to undergo EGD. Other 10 students consulted other medical institutions, and the remaining 59 students were no response (Figure 1).

The students who visited to Shinshu University Hospital were performed EGD and taken biopsies (total 8 points) to examine the status of *H. pylori* infection using culture and immunohistological test with anti-*H. pylori* polyclonal antibody (DAKO, Carpinteria, CA, USA) after written informed consent. *H. pylori* infection was deemed to be present if either or both tests were positive, and absent if both tests were negative. Further, results of a urea breath test and a test for serum anti-*H. pylori* antibody if necessary to confirm the infection.

Positive rate of further examination of *H. pylori* infection

Positive rate of further examination of *H. pylori* infection was showed in Table 3. Seventy-eight of 91 students (85.7%) who underwent EGD were infected by *H. pylori*, and the remaining 13 students were not infected. However, serum anti-*H. pylori* antibody showed positive in 3 of the 13 students without *H. pylori* infection.

Year	No of <i>H. pylori</i> positive students	<i>H. pylori</i> positive rates of High school students
2007	14/409	3.40%
2008	28/370	7.60%
2009	22/445	4.9%
2010	23/478	4.80%
2011	12/400	3.00%
2012	17/539	3.20%
2013	20/610	3.30%
2014	12/516	2.30%
2015	14/530	2.60%
Total (Male=77, Female=85)	162/4297	3.80%

Table 2: Positive rate of high school students in the first screening examination of *H. pylori* infection.

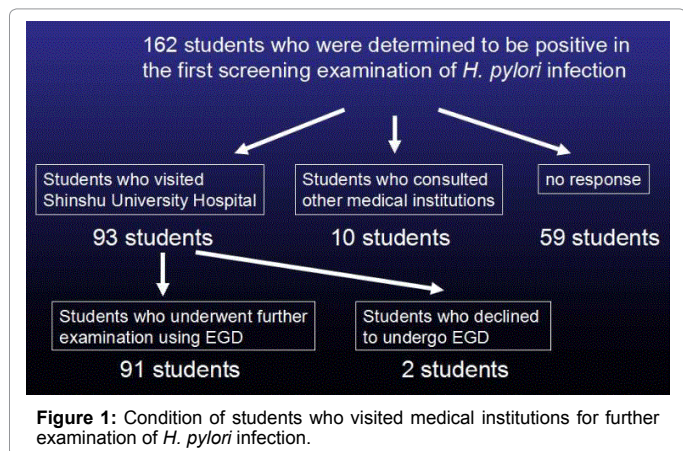


Figure 1: Condition of students who visited medical institutions for further examination of *H. pylori* infection.

<i>H. pylori</i> positive students	78/91 (85.7%)
<i>H. pylori</i> negative students	13*/91 (14.3%)

*Serum and anti-*H. pylori* antibody showed positive in 3 of 13 students without *H. pylori* infection

Table 3: Positive rate of further examination of *H. pylori* infection (n=91).

Symptoms of the students with *H. pylori* infection

Symptoms of 78 students with *H. pylori* infection were showed in Table 4. Abdominal pain was most common symptom (28.2%), however 65.4% of students had no symptom.

Endoscopic findings of the students with and without *H. pylori* infection

Endoscopic findings of 91 students with and without *H. pylori* infection were showed in Table 5.

The most common endoscopic appearance was nodular gastritis recognized in 63 of 78 students (80.8%) with *H. pylori* infection. Endoscopic findings of atrophic gastritis were found in 48 of them (61.5%). The endoscopic degree of atrophic gastritis according to Kimura-Takemoto classification [8] was the closed type in all 48 students. None had the open type atrophic gastritis which is thought to be advanced atrophic change compared with closed type. A scar from duodenal ulcer was present in 7.7% of the students with *H. pylori* infection, and duodenal erosion was observed in 5.1%.

On the other hand, normal endoscopic findings were present in 10 of 13 students without *H. pylori* infection. However, endoscopic findings of open type severe atrophic gastritis were identified in two of the remaining 3 who are also positive for serum anti-*H. pylori* antibody despite no active *H. pylori* infection. Type A gastritis was ruled out because these students showed negative results for anti-parietal cell antibody and did not have hypergastrinemia. These 3 students were thought to have had *H. pylori* infection in the past and have rapidly developed atrophic changes caused by *H. pylori* infection.

Histological findings of biopsy specimen

Inflammatory cell infiltration and focal atrophic changes were recognized in all 78 students with *H. pylori* infection. Only two students had intestinal metaplasia.

Susceptibility of *H. pylori* to antibiotics

H. pylori was cultured in 74 of 78 students with *H. pylori* infection,

abdominal pain	22 students (28.2%)
anemia	5 students (6.4%)
abdominal discomfort	2 students (2.6%)
appetite loss	1 student (1.3%)
heart burn	1 student (1.3%)
no symptom	51 students (65.4%)

Table 4: Symptoms of students with *H. pylori* infection (n=78).

		<i>H. pylori</i> positive n=78	<i>H. pylori</i> negative n=13
Nodular gastritis	positive	63 (80.8%)	0
	negative	15 (19.2%)	13
Atrophic gastritis	non	30 (38.5%)	10
	C-1	10	1
	C-2	30	0
	C-3	8	0
	O-1	0	1
	O-2	0	0
	O-3	0	1
Total		48 (61.5%)	
Duodenal ulcer (Scar)		6 (7.7%)	0
Duodenal erosion		4 (5.1%)	0
Gastric ulcer (Scar)		1 (1.1%)	0

Table 5: Endoscopic findings (n=91). C: Closed type; O: Open type (Kimura-Takemoto classification).

and not cultured in the remaining 4. The susceptibility of *H. pylori* to clarithromycin, metronidazole, and amoxicillin was assessed by a modified agar plate dilution method. Clarithromycin resistance was present in 28 of 74 students (37.8%) with *H. pylori* infection. Metronidazole resistance was present in 27 of them (36.5%), and 22 of them (29.7%) had dual clarithromycin-metronidazole resistance. No amoxicillin resistance was present in any students (Table 6).

Outcomes of *H. pylori* eradication therapy

After informed consent, eradication therapy was performed. Students with *H. pylori* that were sensitive to clarithromycin received clarithromycin based triple therapy for 7 days. On the other hand, if *H. pylori* had resistance to clarithromycin, using metronidazole based triple therapy was performed whether or not *H. pylori* had resistance to metronidazole. The decision of *H. pylori* was assessed more than 8 weeks after treatment by a urea breath test (UBT).

All 75 students except 3 (96.0%) with *H. pylori* infection were successfully cured by the first eradication therapy. Other 3 students were cured by the second eradication therapy. Remaining 3 students have not yet been assessed the decision of *H. pylori* infection.

Adverse events

No remarkable complications related EGD, including taking biopsy specimens, was recognized in any of the 91 students who received EGD.

On the other hand, skin rash was observed in 6 of 78 students (7.7%) who received eradication therapy for *H. pylori*. Three of them (3.8%) complicated of slightly diarrhea (Table 7). No student was suspended to take medicine of eradication therapy due to adverse events.

Discussion

We calculated cost of the procedure of *H. pylori* infection in the nationwide health screening of high school students in Japan. Cost of the examination and treatment of *H. pylori* infection for each person was shown in Table 8. Cost of the first screening, further examination,

	Sensitive	Resistant
Clarithromycin	46	28 (37.8%) ^a
Metronidazole	47	27 (36.5%) ^a
Amoxicillin	74	0 (0%) ^{***}

Table 6: Susceptibility of *H. pylori* to antibiotics (n=74^a). *MIC ≥ 1 µg/ml, **MIC ≥ 16 µg/ml, ***MIC ≥ 1 µg/ml. MIC: Minimal Inhibitory concentration. a: *H. pylori* were not cultured in other 4 cases.

Skin rash	6 students (7.7%)
Diarrhea	3 students (3.8%)
Vomiting	1 student (1.3%)

Table 7: Adverse events (n=78).

1	The first screening examination	
	Cost of a urine-based rapid test kit of <i>H. pylori</i> infection (RUPIRAN®)	700 yen (\$6.36) ^c
2	Further examination and treatment for <i>H. pylori</i> infection	
	Costs of endoscopy and taking biopsy samples	14,500 yen (\$131.82) ^c
	Costs of histopathological examination	10,300 yen (\$93.64) ^c
	Cost of culture and sensitivity testing	4,100 yen (\$37.27) ^c
	Charge of medicines	6,000 yen (\$54.55) ^c
	Cost of urea breath test	5,400 yen (\$49.09) ^c
	Total	40,300 yen (\$366.36) ^c

Table 8: Cost of the examination and treatment of *H. pylori* infection for each person. ^cUS dollar is calculated at the rate of 110 yen to the US dollar.

and treatment of *H. pylori* infection was shown in Table 9, and total cost of it was calculated 2,699,994,000 yen (\$24,545,400). Expected cost-effectiveness of the prevention of gastric cancer by curing *H. pylori* infection in teenagers was shown Table 10. The rate of persons with *H. pylori* infection who will suffer from gastric cancer in their lifetime is 14.8%. This data was calculated using Uemura's cohort study [9]. The rate of persons who will be prevented against suffering from gastric cancer by curing *H. pylori* infection in teenagers is 80%. This percentage estimated based on the results of an experiment using an animal model, which have been reported by Nozaki et al [4]. Cost of prevention of gastric cancer for each person was 495,958 yen (\$4,508.71). Treating patients with gastric cancer, especially those with advanced disease, is very costly. Furthermore, the curing of *H. pylori* infection would also prevent other *H. pylori* related diseases such as gastroduodenal ulcer, gastric MALT lymphoma, and idiopathic thrombocytopenic purpura etc. Therefore, the screening and treatment for *H. pylori* infection in young people is thought to be useful from the view point of medical economy [5]. If further examination for *H. pylori* infection were to be performed not by using endoscopy but using UBT or the stool antigen of *H. pylori*, the total cost of this attempt would be more reduced [6], especially the cost of further examination of *H. pylori* infection would become about one fifth.

Problems about children are different in each country. In Japan, the most serious problem is decreasing childbirth and reducing a population of children. Our country will become a super-aging society in the near future. Furthermore, total Japanese population is suspected to decrease. Gastric cancer is the most common malignant neoplasms in Japan, and about 50,000 persons die of this disease in per year. It is well known that a significant relationship is recognized between

1	Population of a 1-year generation in the present Japanese teenagers	1,210,000 persons
2	Cost of the first screening examination for <i>H. pylori</i> infection	700 yen (\$6.36) ^a × 1,210,000=847,000,000 yen (\$7,700,000) ^a (A)
3	Positive rate in the first screening examination for <i>H. pylori</i> infection	3.8% ^b
4	The number of students who required the further examination for <i>H. pylori</i> infection	1,210,000 persons × 0.038=45,980 persons
5	Cost of further examination and treatment of <i>H. pylori</i> infection	40,300 yen × 45,980 = 1,852,994,000 yen (\$16,845,400) ^a (B)
Total cost (A+B)		2,699,994,000 yen (\$ 24,545,400) ^a per year

Table 9: Cost of the first screening, further examination and treatment of *H. pylori* infection in the nationwide health screening of high school standards. ^aUS dollar is calculated at the rate of 110 yen to the dollar. a. Current data of the Statistics Bureau in the Ministry of Public Management, Home Affairs, Posts and Telecommunications. b. Our data in the present study.

1	The rate of persons with <i>H. pylori</i> infection who will suffer from gastric cancer in their lifetime	14.8% ^a
2	The number of persons with <i>H. pylori</i> infection who will suffer from gastric cancer in their lifetime	45,980 persons × 0.148=6,805 persons
3	The rate of persons who will be prevented against suffering from gastric cancer by curing <i>H. pylori</i> infection in teenagers	80% ^b
4	The number of persons who will be prevented against suffering from gastric cancer by curing <i>H. pylori</i> infection in teenagers	6,805 persons × 0.8=5,444 persons
5	Cost of prevention of gastric cancer for each person	Total cost (A+B) ^c /5,444=495,958 yen (\$4,508.71) ^c

Table 10: Expected cost-effectiveness of the prevention of gastric cancer by curing *H. pylori* infection in teenagers. ^cUS dollar is calculated at the rate of 110 yen to the dollar. a. See the test. b. See the test. c. See the Table 9.

gastric cancer and *H. pylori* infection in East Asia. We believe that eradication therapy for *H. pylori* in young people is very effective to prevent the occurrence of gastric cancer, and to reduce the decreasing tendency of Japanese population. On the other hand, *H. pylori* infection is not so significant risk of gastric cancer in many countries except East Asia. However, gastroduodenal ulcer related *H. pylori* infection is an important problem in the worldwide, especially children in the developing countries sometimes die of a perforation and massive bleeding due to gastroduodenal ulcer.

From these reasons, we think that screening to identify and eradicate *H. pylori* infection in young people in worldwide is useful to prevent several diseases, and can reduce the number of death due to them such as gastric cancer and gastroduodenal ulcer.

Limitation

This study has been performed in only one Japanese high school. We should expand this attempt in more other schools in the future. Furthermore, the cost of this attempt is not calculated including personnel expenses.

Conclusion

The low rate of prevalence of *H. pylori* infection in present Japanese teenagers would make it possible to perform the screening examination and treatment for this infection in nationwide health screening of high school students in the way that is practical and feasible.

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