

Screening to Identify and Eradicate *Helicobacter pylori* Infection in Teenagers in Japan

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I have no financial relationships to disclose.

Background 1

Helicobacter pylori infection is etiologically related to several gastric diseases, such as gastritis, gastroduodenal ulcer, gastric cancer, and MALT lymphoma. Gastric cancer is one of the common malignant neoplasms in East Asia, and about 50,000 persons die of gastric cancer each year in Japan.

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 and also by randomized clinical studies showing that eradication of *H. pylori* reduces the occurrence of gastric cancer.

Background 2

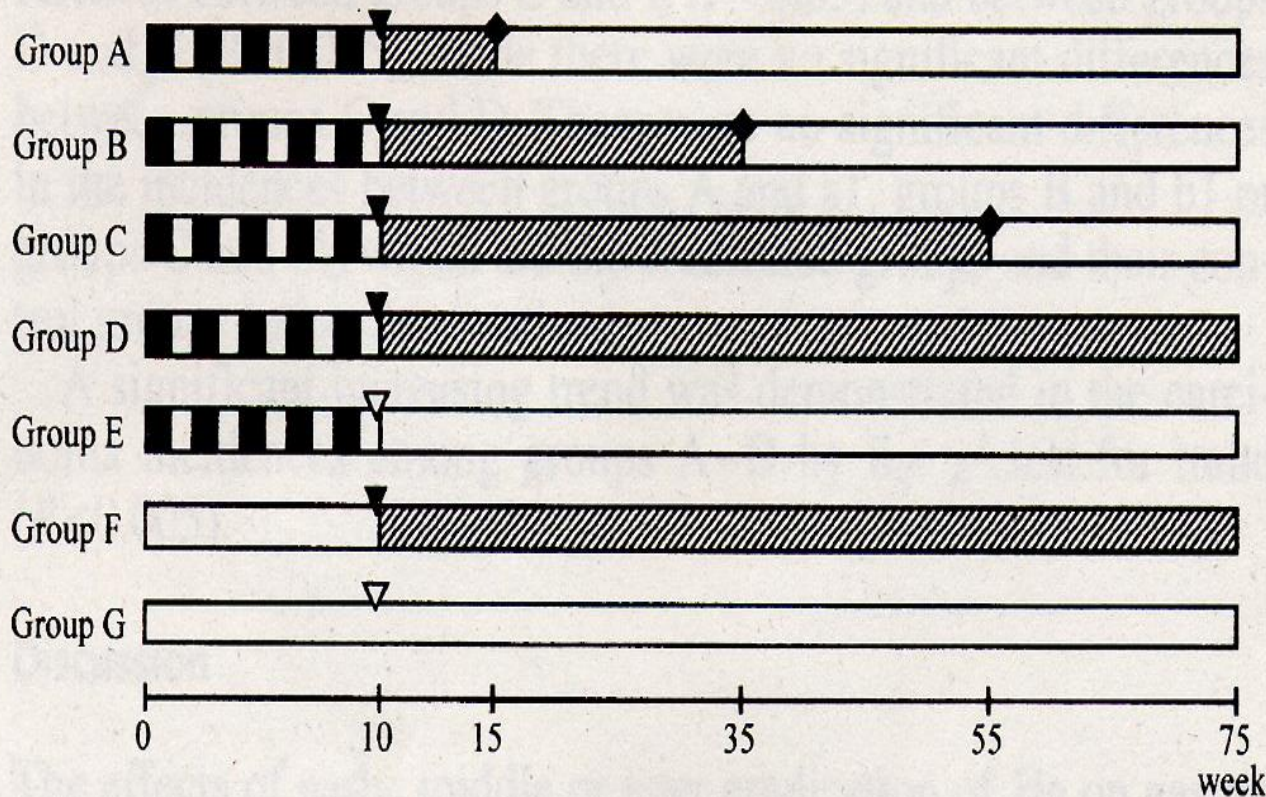
In 2003, Nozaki et al reported that early stage eradication of *H. pylori* was more effective in reducing the late occurrence of gastric cancer compared with late-stage eradication in animal experimentation.

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. Furthermore, *H. pylori*-related diseases, especially complicated gastroduodenal ulcer, which can cause death and emergency operation because of perforation or bleeding, can be prevented by cure of *H. pylori*

Effect of early eradication on *Helicobacter pylori*-related gastric carcinogenesis in Mongolian gerbils

Nozaki K et al. Cancer Sci 94; 235-239: 2003

occurrence rate
of gastric cancer



A: 1/15 (6.7%)

B: 3/11 (27.3%)

C: 13/34 (38.2%)

D: 9/16 (56.3%)

E: 1/16 (6.3%)

F: 0/8 (0.0%)

G: 0/9 (0.0%)

Purpose

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.

Methods

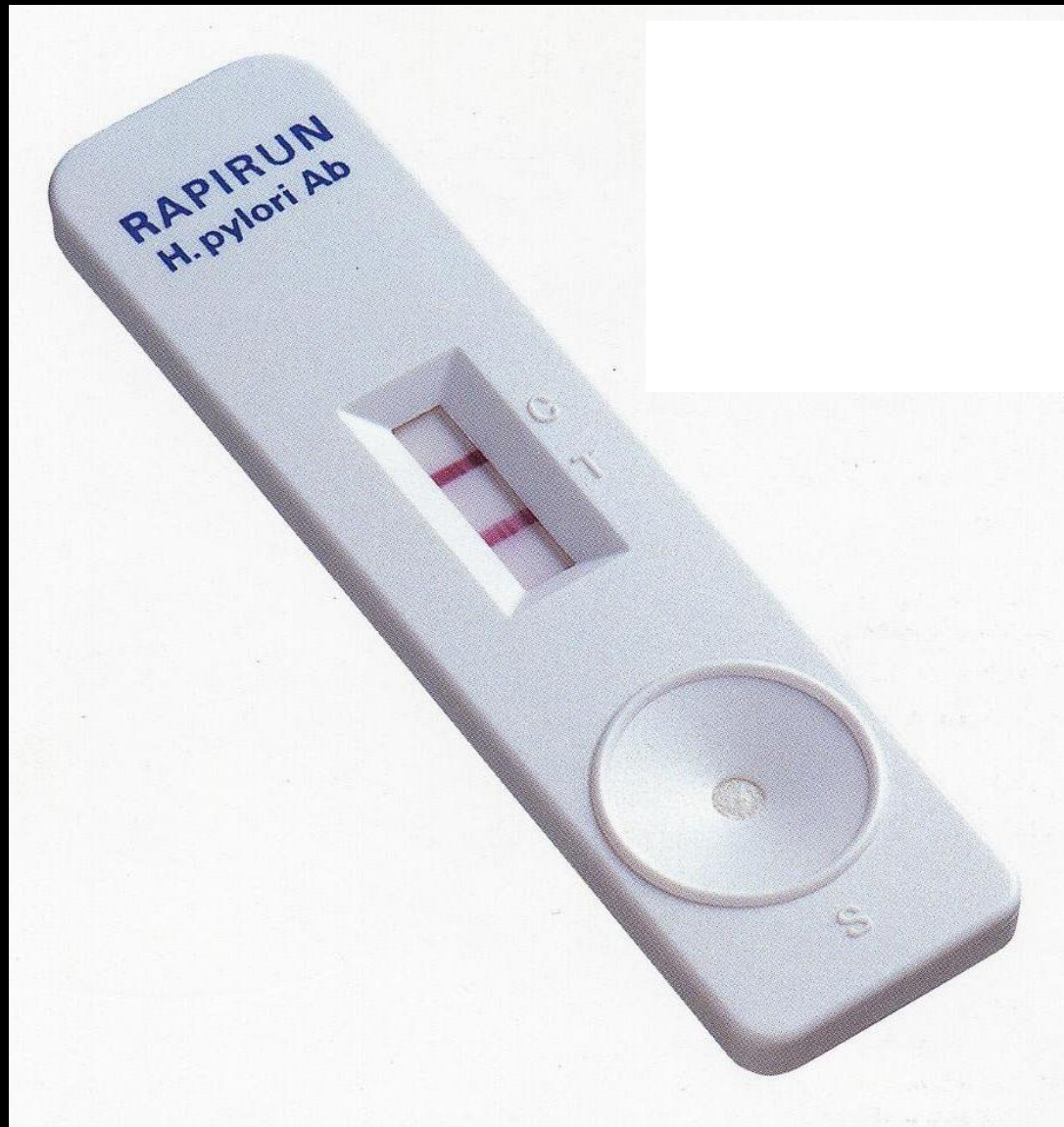
We have proposed that a screening for *H. pylori* infection should be introduced into health screenings in school, and have performed this procedure in one Japanese high school every year since 2007.

The study was approved by the Ethics Committee of Shinshu University School of Medicine.

First screening examination for *H. pylori* infection

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 (RUPIRUN[®], Otsuka Pharmaceutical Co. Tokyo, Japan). Students were between ages 16 and 17.

RUPIRAN®



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

year	The number of participating students	Participating rate of high school students
2007	409/414	98.8%
2008	370/373	99.2%
2009	445/445	100%
2010	478/480	99.6%
2011	400/401	99.8%
2012	539/539	100%
2013	610/611	99.8%
2014	516/518	99.6%
2015	530/531	99.8%
Total	4,297/4,312	99.7%

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

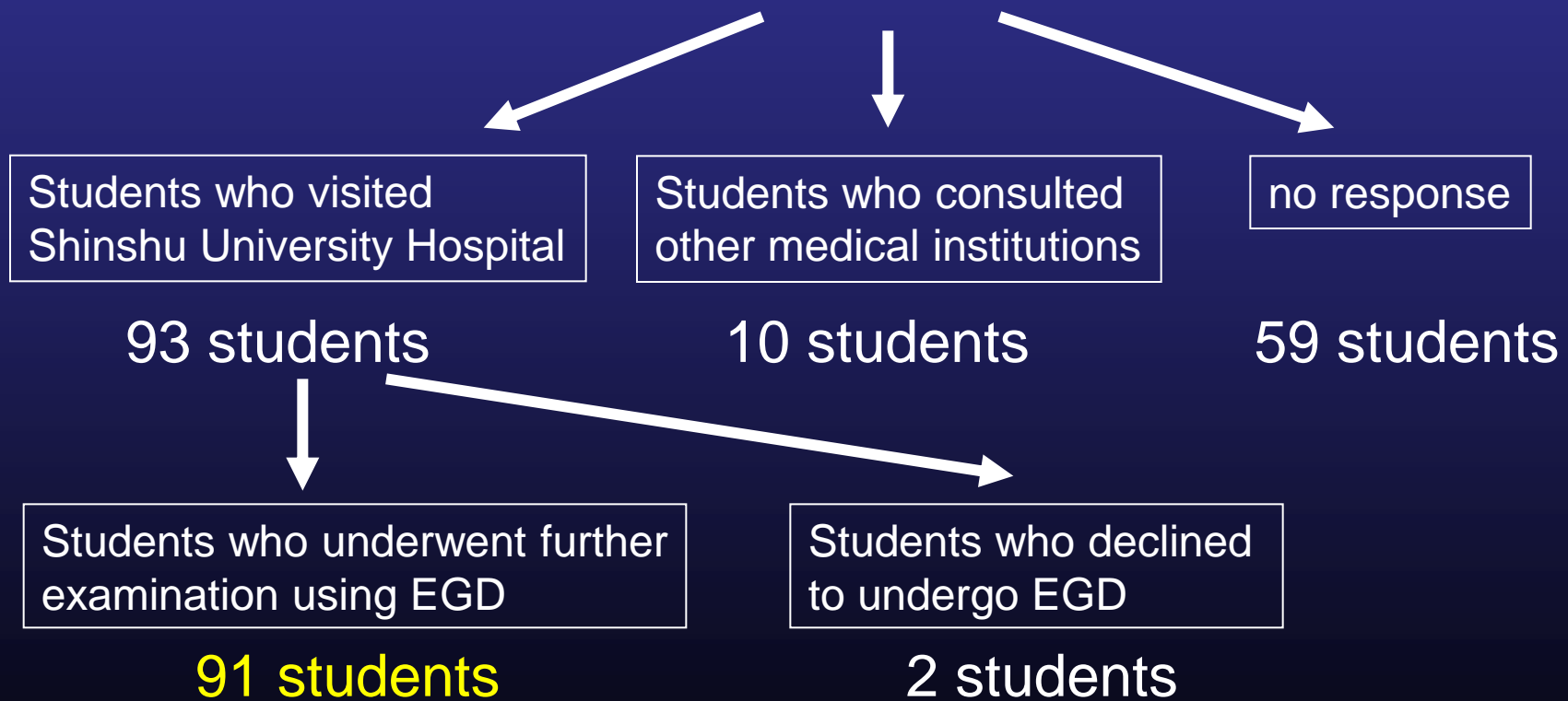
year	The number of <i>H. pylori</i> -positive students	<i>H. pylori</i> -positive rates of high school students
2007	14/409	3.4%
2008	28/370	7.6%
2009	22/445	4.9%
2010	23/478	4.8%
2011	12/400	3.0%
2012	17/539	3.2%
2013	20/610	3.3%
2014	12/516	2.3%
2015	14/530	2.6%
Total	162/4,297 (Male:77, Female:85)	3.8%

Further examination for *H. pylori* infection

1. 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.
2. The students who visited to Shinshu University Hospital were performed esophagogastroduodenoscopy and taken biopsies 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.
3. *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 (Eiken Chemical, Tochigi, Japan) if necessary to confirm the infection.

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

162 students who were determined to be positive in the first screening examination of *H. pylori* infection



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

H. pylori-positive students 78/91 (85.7%)

H. pylori-negative students 13*/91 (14.3%)

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

Symptoms (n=78)

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

Endoscopic findings (n=91)

H. pylori-positive
n=78

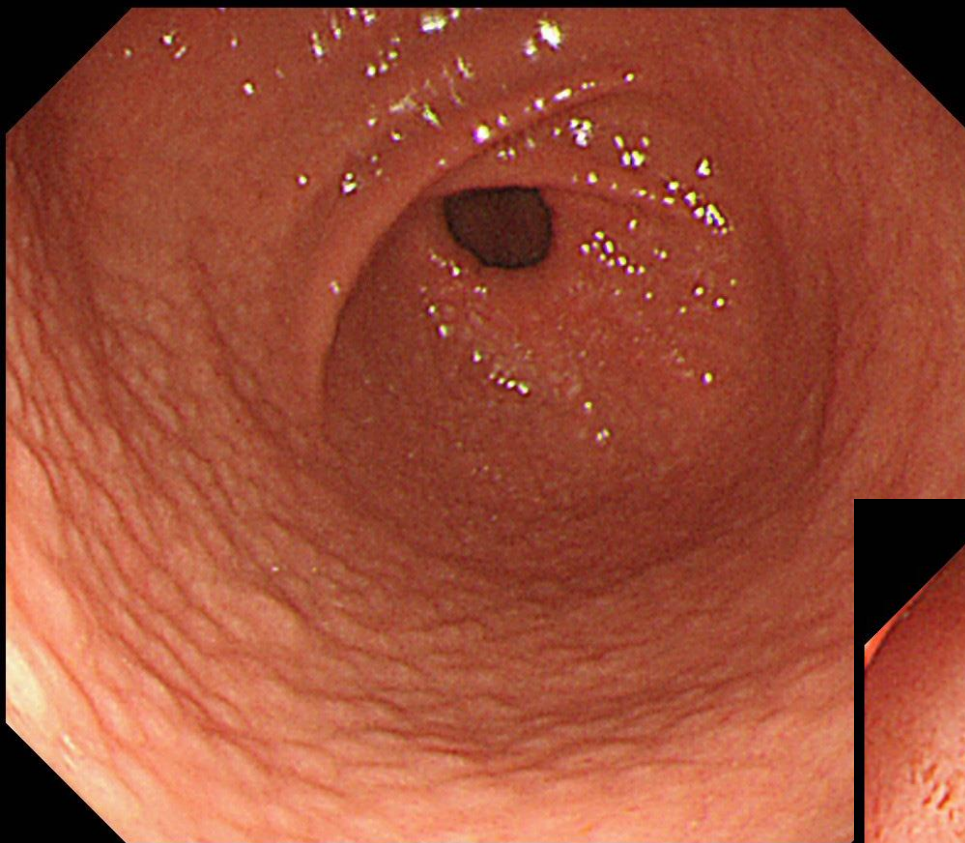
H. pylori-negative
n=13

		<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- I	10	1
	C- II	30	0
	C- III	8	0
	O- I	0	1
	O- II	0	0
	O- III	0	1
		48(61.5%)	
Duodenal ulcer (scar)		6(7.7%)	0
Duodenal erosion		4(5.1%)	0
Gastric ulcer(scar)		1(1.1%)	0

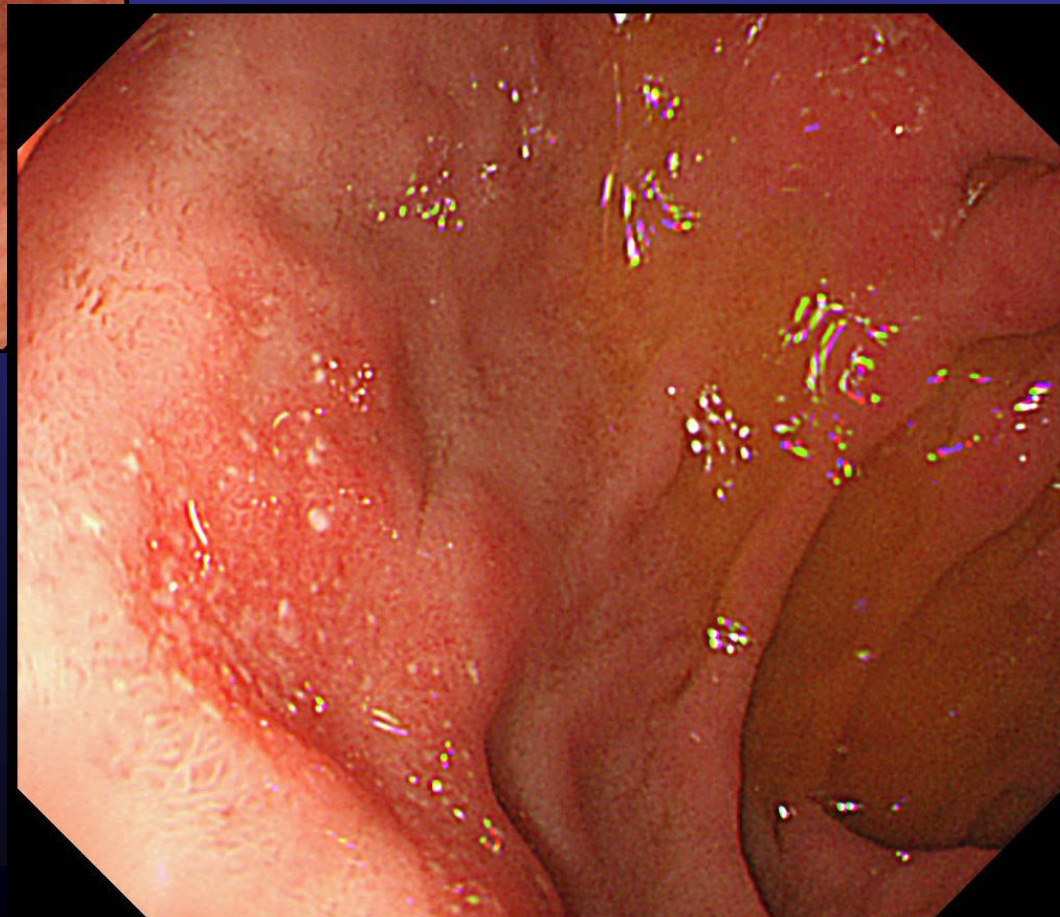
C: closed type O: open type (Kimura-Takemoto classification)

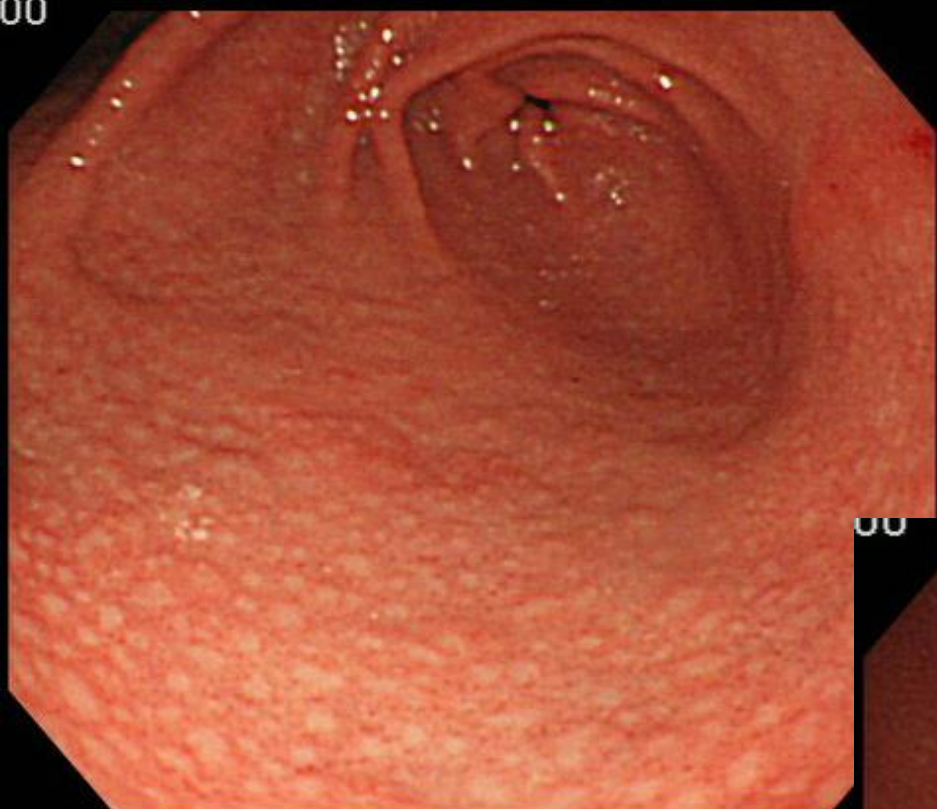
Case 1

Duodenal erosion



Nodular gastritis





Nodular gastritis

C: closed type

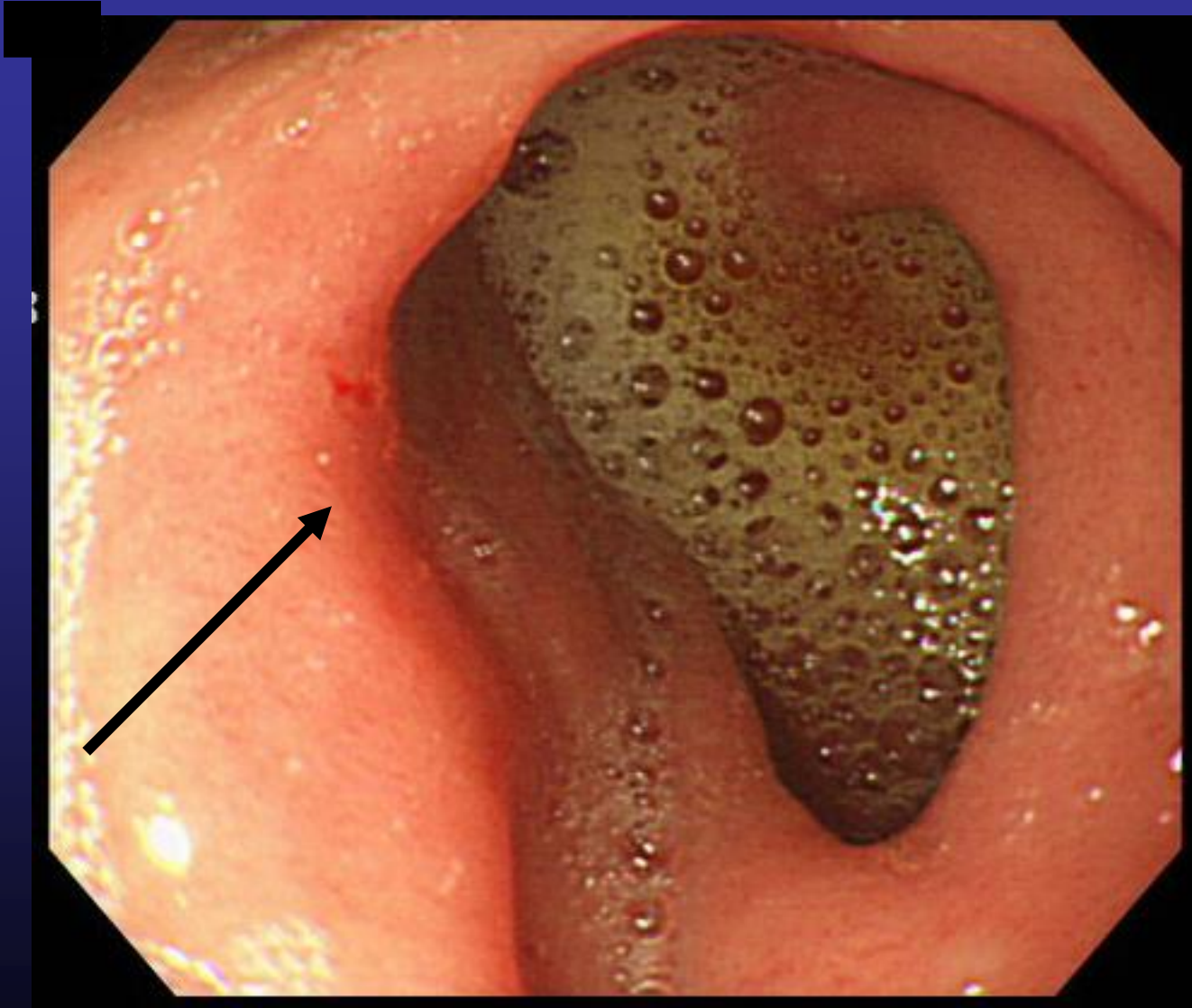
Case 2

Atrophic gastritis (C- II)

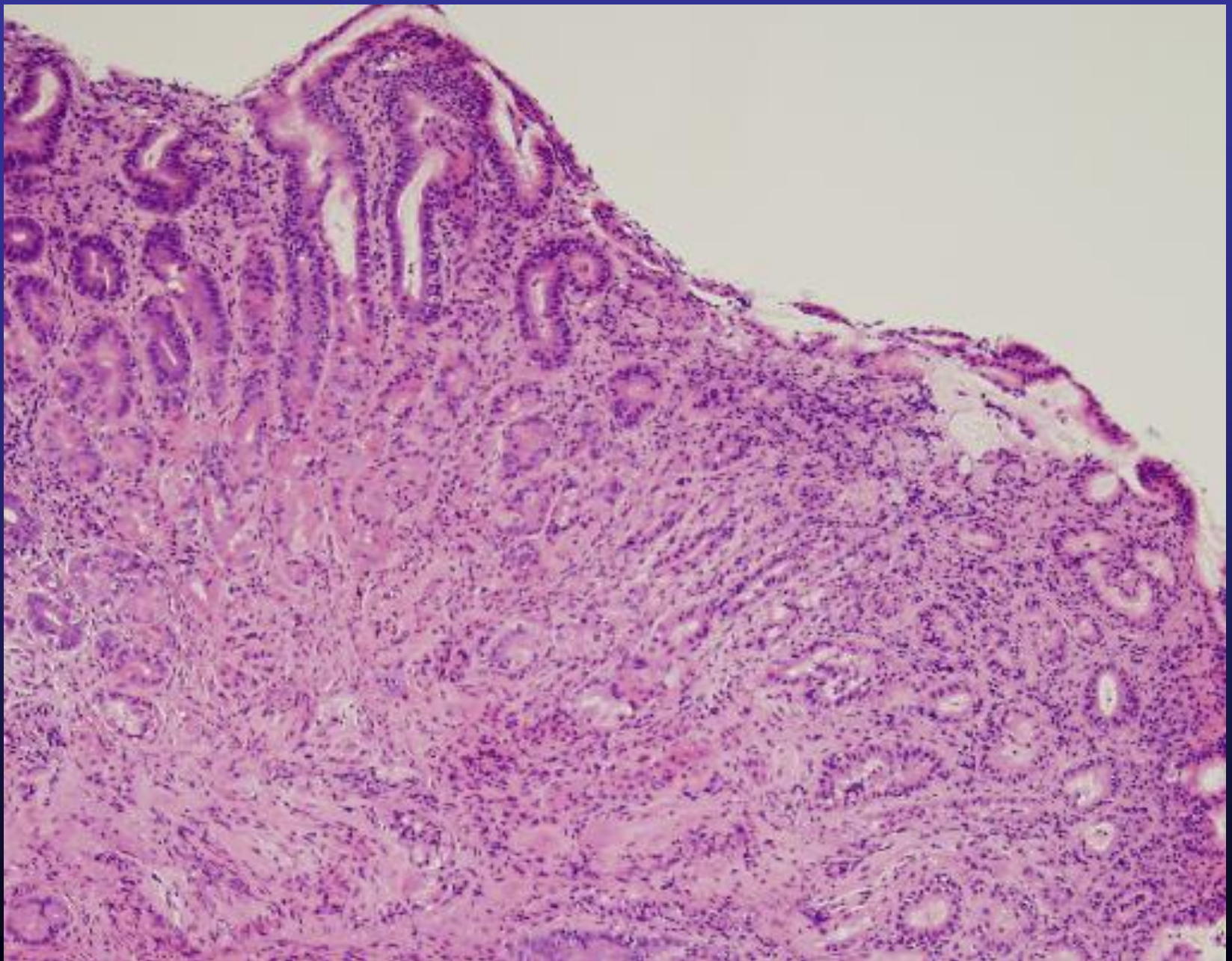


Case 3

A scar from duodenal ulcer



Histological findings of biopsy specimen



Susceptibility of *H. pylori* to antibiotics (n=74)

H. pylori were not cultured in other 4 cases

	sensitive	resistant
clarithromycin	46	28 (37.8%)*
metronidazole	47	27 (36.5%)**
amoxicillin	78	0 (0%)***

* MIC \geq 1 μ g/ml **MIC \geq 16 μ g/ml ***MIC \geq 1 μ g/ml

Eradication therapy and resolution of *H. pylori*

1. Regimens of eradication therapy

1) Clarithromycin sensitive

rabeprazole	20 mg/day		
amoxicillin	1500 mg/day	2 ×	7 days
clarithromycin	800mg/day		

2) Clarithromycin resistance

rabeprazole	20 mg/day		
amoxicillin	1500 mg/day	2 ×	7 days
metronidazole	500 mg/day		

2. The decision of *H. pylori* after eradication therapy

The decision of *H. pylori* was assessed more than 8 weeks after treatment by urea breath test.

Outcomes of *H. pylori* eradication therapy (n=78)

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 resolution of *H. pylori* infection.

Adverse events (n=78)

Skin rash 6 students (7.7%)

Diarrhea 3 students (3.8%)

Vomiting 1 students (1.3%)

Cost of the examination and treatment of *H. pylori* infection for each person

1. The first screening examination

Cost of a urine-based rapid test kit of <i>H.pylori</i> infection (RUPIRAN®)	700 yen (\$6.36)
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2. Further examination and treatment for *H. pylori* infection

Costs of endoscopy and taking biopsy samples	14,500 yen (\$131.82)
Cost of histological examination	10,300 yen (\$93.64)
Cost of culture and sensitivity testing	4,100 yen (\$37.27)
Charge for medicines	6,000 yen (\$54.55)
Cost of urea breath test	5,400 yen (\$49.09)

Total	40,300 yen (\$366.36) *
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*US dollar is calculated at the rate of 110 yen to the US dollar

Cost of the first screening, further examination, and treatment of *H. pylori* infection in the nationwide health screening of high school students

1. Population of a 1-year generation in the present Japanese teenagers 1,210,000 persons
2. Cost of the first screening examination for *H. pylori* infection
 $700 \text{ yen } (\$ 6.36) \times 1,210,000 = \underline{847,000,000 \text{ yen } (\$ 7,700,000)}$ (A)
3. Positive rate in the first screening examination for *H. pylori* infection 3.8%
4. The number of students who required the further examination for *H. pylori* infection
 $1,210,000 \text{ persons} \times 0.038 = 45,980 \text{ persons}$
5. Cost of further examination and treatment of *H. pylori* infection
 $40,300 \text{ yen} \times 45,980 = \underline{1,852,994,000 \text{ yen } (\$ 16,845,400)}$ (B)

Total cost (A+B) $269,999,4000 \text{ yen } (\$ 24,545,400)$ per year

*US dollar is calculated at the rate of 110 yen to the US dollar

Expected cost-effectiveness of the prevention of gastric cancer by curing *H. pylori* infection in teenagers

1. The rate of persons with *H. pylori* infection who will contract gastric cancer in their lifetimes 14.8%

2. The number of persons with *H. pylori* infection who will contract gastric cancer in their lifetimes

$$45,980 \text{ persons} \times 0.148 = 6,805 \text{ persons}$$

3. The rate of persons who will be prevented from contracting gastric cancer by curing *H. pylori* infection in teenagers 80%

4. The number of persons who will be prevented from contracting gastric cancer by cure of *H. pylori* infection in teenagers

$$6,805 \text{ persons} \times 0.8 = 5,444 \text{ persons}$$

5. Cost of prevention of gastric cancer for each person

$$\text{Total cost (A+B)} \div 5,444 = 495,958 \text{ yen } (\$4508.71)$$

Simulation of cost-effective calculation on the assumption that the urea breath test would be used for further examination of *H. pylori* infection and that the eradication therapy would be performed using a metronidazole-based regimen as the first-line therapy

1. The first screening examination

Cost of a urine-based rapid test kit of <i>H.pylori</i> infection (RUPIRAN®)	700 yen (\$6.36)
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2. Further examination and treatment for *H. pylori* infection

Cost of urea breath test (further examination and assessment after eradication therapy)	5,400 yen (\$49.09) × 2 = 10,800 yen (\$98.18)
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Charge for medicines	438.6yen (\$3.99) × 7 = 3,070 yen (\$27.91)
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Total	13,870 yen (\$126.09)
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*US dollar is calculated at the rate of 110 yen to the US dollar

Simulation of cost-effective calculation on the assumption that the urea breath test would be used for further examination of *H. pylori* infection and that the eradication therapy would be performed using a metronidazole-based regimen as the first-line therapy

1. Cost of further examination and treatment of *H. pylori* infection in the nationwide health screening of high school students

$$13,870 \text{ yen } (\$126.09) \times 1,210,000 \times 0.038 = 637,742,600 \text{ yen } \quad (\text{C})$$

(\$5,797,660)

2. Total cost of adding the first screening examination of *H. pylori* per year

$$700 \text{ yen } (\$6.36) \times 1,210,000 + \text{C} = 1,484,742,600 \text{ yen } \quad (\text{D})$$

(\$13,497,660)

3. Cost of prevention of gastric cancer for each person

$$\text{Total cost (D)} \div 5,444 = 272,730 \text{ yen } (\$2479.36)$$

*US dollar is calculated at the rate of 110 yen to the US dollar

Key points

1. The rate of prevalence of *H. pylori* infection in Japanese teenagers is about 4% at present.
2. A very high participation rate of screening examination for *H. pylori* infection using urine-based rapid test kit was achieved in high school health screening.
3. Most common endoscopic findings for students with *H. pylori* infection are nodular gastritis and closed-type atrophic gastritis.
4. Clarithromycin and metronidazole resistance were present in 37.8 % and 36.5% of 74 students with *H. pylori* infection, respectively. No amoxicillin resistance was present.
5. If this procedure was introduced nationwide, the cost of the prevention of a gastric cancer would be 330,683 yen (3,006 dollars) per person.

Conclusions

The low rate of prevalence of *H. pylori* infection in present Japanese teenagers makes it possible to perform this nationwide plan from a view point of medical economy.

Furthermore, the occurrence of *H. pylori*-related diseases, such as gastritis, gastroduodenal ulcer, and gastric MALT lymphoma, will be reduced in their lifetimes simultaneously.

Thank you for your attention

