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Effect of Eradication of *Helicobacter pylori* on the Benign Gastric Ulcer Recurrence -A 24 month follow-up study-

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Objectives : *To evaluate the effect of eradication of Helicobacter pylori(H.pylori) on the recurrence of benign gastric ulcer(BGU) in the patients with BGU*

Methods : *This study was performed for 40 H.pylori-positive BGU patients cured of BGU and H.pylori eradicated, and for 25 H.pylori-positive patients(non-eradicated group) who were not treated with H.pylori eradication regimen or H.pylori was not eradicated. Four different methods - CLOtest, microscopy of Gram stained mucosal smear, culture and histology of modified Giemsa staining - were taken for identifying colonization of H.pylori before treatment, and 4 weeks after completion of triple therapy. For the control group in which triple therapy was not tried, follow-up gastroscopy was done to confirm the healing of the ulcer. To detect BGU recurrence, the gastroscopy was performed at 6, 12, 18, and 24 months after therapy.*

Results : *In the non-eradicated group, the BGU recurrence rate was 16% within 6 months, 40% within 1 year, 56% within 18 months and 60% within 2 years. The respective recurrence rates in the 40 patients in whom the bacteria had been eradicated were 0%, 7.5%, 10% and 10%(4 patients), respectively. Among the four BGU-recurred patients in whom H.pylori had been eradicated, one patient was found to have BGU recurring with H.pylori positive again in one year, and another two patients had NSAIDs ingestion history.*

Conclusion : *The eradication of H. pylori in patients with BGU reduces the recurrence of BGU. In addition, the major causes of BGU recurrence look like NSAIDs ingestion and reinfection of H.pylori.*

Key Words : *Helicobacter pylori, Eradication, Benign gastric ulcer, Recurrence*

INTRODUCTION

The pathogenic role of *H.pylori* in chronic gastritis and its association with duodenal ulcer (DU) are well established[1-3]. Therefore, the 1994 NIH Consensus Development Conference recommended eradication of *H.pylori* in all patients with documented peptic ulcer disease[4]. The dramatic effect of *H.pylori*-eradication on the natural course of DU disease has been sufficiently well reported by now[5-9]. However, published studies on BGU relapse are scarce, and its follow-up periods do not exceed 12 months[10-14].

There are a few differences between DU and BGU: positivity rates of *H.pylori* in BGU patients have been reported at 70-90%[15], lower than that of DU, 95%-99%[1-3]. The reason for this difference may

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originate from the fact that nonsteroidal anti-inflammatory drugs (NSAIDs) are another major cause of BGU. These facts may play a role in the pattern of recurrence in BGU and DU. However, there is still a considerable lack of knowledge on the post-therapeutic course of BGU disease. We conducted this study to investigate how the BGU recurrence rate is reduced by eradication of *H.pylori* in a 2 year follow-up.

MATERIALS AND METHODS

This study was performed for *H. pylori*-positive 65 patients with active BGU, who were enrolled between October 1995 and September 1996, and followed up for 2 years. In forty patients, *H. pylori* was eradicated by triple therapy: omeprazole 20mg once a day, clarithromycin 500mg twice a day and amoxicillin 1.0g twice a day. The non-eradicated group consisted of 19 patients in whom the triple therapy was not conducted and 6 patients in whom *H. pylori* was not eradicated with the triple therapy. Patients with pregnancy or lactation, treatment with colloidal bismuth subcitrate or antibiotics within 3 weeks of gastroscopy, severe concomitant diseases and a history of previous gastric surgery were excluded. In addition, patients were excluded if they were under maintenance acid-suppressive therapy.

Six biopsy specimens were taken within 3cm of the pyloric ring before beginning, and 4 weeks after completion of triple therapy. The biopsy specimens were analyzed with CLOtest, microscopy of Gram stained mucosal smear, culture and histology after H&E staining as described in detail elsewhere[16, 17]. A patient was regarded as *H. pylori*-positive if one or more of the four aforementioned test methods demonstrated *H.pylori* colonization of the gastric mucosa.

Follow-up gastroscopy was performed 6, 12, 18 and 24 months after treatment, or whenever the ulcer symptom recurred, for evaluation of ulcer recurrence. BGU recurrence was defined as endoscopically confirmed recurrent ulcer after endoscopically proven healing of the initial ulcer. By definition, superficial erosions were not considered to be ulcers. Four *H. pylori* tests were conducted in the eradicated group whenever follow-up gastroscopy was taken. Clinical factors, such as age, gender, smoking, alcohol, past history of BGU and ingestion history of NSAIDs were evaluated.

For statistical analysis, continuous variables were analyzed by Student's *t* test, and categorical variables by Chi-square test and Fisher's exact test. A p value of <0.05 was considered to be significant.

RESULTS

The mean age of the non-eradicated group was 51.6 ± 13.0 years and that of the eradicated group 50.6 ± 12.0 years (Table 1). The number of males was 22 (sex ratio, 7.3:1) in 25 patients of the non-eradicated group, and 33 (sex ratio, 4.7:1) in the 40 patients of the eradicated group. Smoking history was found in 16 patients (64%) of the non-eradicated group, and in 20 patients (50%) of the eradicated group. Alcohol history was found in 11 patients (44%) of the non-eradicated group and in 26 patients (65%) of the eradicated group. Past BGU history was found in 17 patients (68%) of the non-eradicated group and in 18 patients (45%) of the eradicated group. Ingestion

Table 1. Clinical characteristics

	Non-eradicated group	Eradicated group
No.	25	40
Age(year)	51.6 ± 13.0	50.6 ± 12.0
M:F (ratio)	22:3 (7.3:1)	33:7 (4.7:1)
Smoking(%)	16 (64%)	20 (50%)
Alcohol(%)	11 (44%)	26 (65%)
Past BGU history(%)	17 (68%)	18 (45%)
NSAIDs history(%)	6 (24%)	6 (15%)
BGU recurrence(%)*	15 (60%)	4 (10%)

* $p < 0.001$

BGU, benign gastric ulcer; NSAIDs, nonsteroidal anti-inflammatory drugs

history of NSAIDs was found in 6 patients (24%) of the non-eradicated group and in 6 patients (15%) of the eradicated group. There was no statistical difference between these two groups in age, gender, smoking, alcohol, past history of BGU and ingestion history of NSAIDs. BGU recurrence was found in 15 patients (60%) of the non-eradicated group: 12 of 19 patients (63.2%) in whom triple therapy was not conducted and 3 of 6 patients (50%) in whom *H. pylori* was not eradicated with triple therapy. In comparison, BGU recurrence was found in 4 patients (10%) of the eradicated group, which was significantly lower than that of the non-eradicated group ($p<0.0001$, Table 1). In the 25 non-eradicated patients, the BGU recurrence rate was 16% (4 patients) within 6 months, 40% (10 patients) within 1 year, 56% (14 patients) within 18 months and 60% (15 patients) within 2 years (Fig. 1). The respective recurrence rates in the 40 eradicated patients were 0%, 7.5% (3 patients). 10% (4 patients) and 10%, respectively (Fig. 1). The recurrent ulcer sites in the 15 BGU patients of the non-eradicated group were the same as the ulcer sites of the initial diagnosis. In two patients, the number of ulcers increased to 3 and 5, including the initial one. The recurrent ulcer sites in the 4 recurred patients of the eradicated group were the same as those of the initial ulcer.

The mean age of the recurred group was 65.3 ± 15.2 years, which is significantly older than that of the non-recurred group, 49.1 ± 10.9 years ($p<0.05$, Table 2). The two female patients who had BGU recurrence

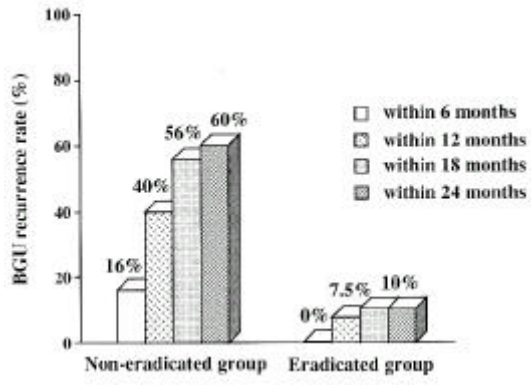

Fig. 1. Recurrence rate of benign gastric ulcer according to the eradication of *H. pylori*.

and NSAIDs history were very old (67 and 83 years old), and this brought about a significant increase of the mean age for the recurrence group. Two patients were male (sex ratio, 1:1) in the recurred group, and 31 patients (sex ratio, 6.2:1) in the non-recurred group. Smoking history was found in 3 patients (75%) of the recurred group and 17 patients (47.2%) of the non-recurred group. Alcohol history was found in 1 patient (25%) of the recurred group and 25 patients (69.4%) of the non-recurred group. Past BGU history was found in 3 patients (75%) of the recurred group and 15 patients (41.7%) of the non-recurred group. Ingestion history of NSAIDs was found in 3 patients (75%) of the recurred group and 3 patients (8.3%) of the non-recurred group. There was no statistical

Table 2. Comparison according to benign gastric ulcer recurrence for the eradicated group

	Recurred group	Non-Recurred group
No.	4	36
Age(year)*	65.3 ± 15.2	49.1 ± 10.9
M:F (ratio)	2:2 (1:1)	31:5 (6.2:1)
Smoking(%)	3 (75%)	17 (47.2%)
Alcohol(%)	1 (25%)	25 (69.4%)
Past BGU history(%)	3 (75%)	15 (41.7%)
NSAIDs history(%)	3 (75%)	3 (8.3%)
H. pylori reappearance(%)	1 (25%)	1 (2.8%)
NSAIDs ingestion history before BGU recurring(%)	2 (50%)	

* $p < 0.05$

BGU, benign gastric ulcer; NSAIDs, nonsteroidal anti-inflammatory drugs

difference between these two groups in gender, smoking, alcohol, past history of BGU and ingestion history of NSAIDs. When BGU recurrence was found in the 4 patients of the eradicated group, one patient (25%) was found to be *H. pylori* positive and two patients (50%) irregularly took NSAIDs due to arthritis before BGU recurring. The BGU recurrence in these 3 patients occurred within 1 year. In the remaining one patient, *H. pylori* was still negative and he denied ingestion history of NSAIDs when BGU recurred within 18 months. In the 36 non-recurred patients, only one patient (2.8%) was found to be *H. pylori* positive again in 1 year.

DISCUSSION

H. pylori infection and NSAIDs are very important risk factors for peptic ulcer[18]. The positivity rates of *H. pylori* in patients with DU and BGU were somewhat different: that is, they have been reported to be 95-99% in DU[1-3], but 70-90% in BGU[15], which is lower than in DU and shows a wider variation than in DU. These results suggest that NSAIDs as the cause of BGU might be more significant than DU[19]. We have previously shown that the *H. pylori* infection rate and the rate of NSAIDs history were 82.8% and 26.1% of BGU patients, respectively, and 91.1% of the BGU patients had either *H. pylori* infection or NSAIDs history[20]. In contrast, *H. pylori* infection rate of patients with DU was 94.2%[9], higher than that of BGU patients. In addition, even though the major cause of DU and BGU is *H. pylori*, their pathogenensis is thought to be different. That is, if the *H. pylori* infection occurs when the gastric acid secretion from parietal cell is high, *H. pylori* resides and multiplies in the antrum, avoiding the body, causing chronic antral gastritis and DU[21]. However, if *H. pylori* infection occurs in the low acid secretory state, such as malnutrition, immaturity, and intercurrent infection, pangastritis and multifocal gastric atrophy occur, and BGU or stomach cancer can develop[22, 23]. Actually, *H. pylori* density was higher in the antrum than in the body for DU patients, but it was somewhat reversed for BGU patients[24]. In addition, the body is more adequate for *H. pylori* detection in BGU and stomach cancer patients, but it was reversed in DU patients[25]. These differences between DU and BGU may cause a difference in their pattern of recurrence.

Combined data from 30 pilot and controlled studies show an overall DU relapse rate of 61% (range, 20-100%) in patients who remain *H. pylori*-positive, compared with 3% (range, 0-22%) in patients free of *H. pylori*[10, 26-32]. This wide variance in the study results may be caused by several factors: absence of documented initial ulcer disease and ulcer healing; unknown *H. pylori* status at the time of ulcer relapse or at the conclusion of the study[10, 27-29] and the assessment for cure of the infection by *H. pylori* clearance instead of *H. pylori* eradication, leading to high rates of *H. pylori* recrudescence and ulcer relapse rates[10, 29-32]. Only a few studies have reported gastric ulcer relapse rate in relation to *H. pylori* status with a follow-up period of 1 year[10-14]. Gastric ulcer relapsed in 47-55.6% of patients who remained *H. pylori*-positive compared with 3-7% of the cured patients[10-14]. Because *H. pylori* infection is associated with ulcer disease, ulcer relapses will also be related to recurrent infection[1, 33]. It is therefore crucial that *H. pylori* eradication is documented accurately. Nevertheless, studies performed with appropriate diagnostic accuracy still report *H. pylori*-negative ulcer relapses[10, 12, 14, 29, 32]. In these cases, the (occult) use of aspirin or NSAIDs may account for recurrent ulcers in the absence of *H. pylori* infection[12, 34]. In one study where patients taking aspirin or NSAIDs were excluded, recurrence of DU or BGU was completely prevented by successful *H. pylori* eradication for up to 9.8 years (mean follow-up: 2.5 years)[26]. In the present study, the BGU recurrence rates in the 25 non-eradicated group were 16% within 6 months, 40% within 1 year, 56% within 18 months and 60% within 2 years (Fig. 1). The respective recurrence rates in the 40 eradicated patients were 0%, 7.5% (3 patients), 10% (4 patients) and 10%, respectively (Fig. 1), which were significantly lower than those of the non-eradicated group ($p<0.001$).

We also investigated the similar study in DU patients with a 4 year follow-up[35]. When BGU recurrence pattern is compared with that of DU, there were two kinds of difference between BGU and DU. One is that the recurrence rate of BGU patients in the non-eradicated group looked lower than that of DU patients. That is, in a control group, comprising 31 patients with DU who were not treated with *H.pylori* eradication regimen, the DU recurrence rate was 61% within 1 year, 81% within 2 years, 84% within 3 years and 90% within 4 years[35]. The recurrence rate of BGU

in the non-eradicated group in the present study shows 40% within 1 year and 60% within 2 years, and these rates are lower than those of the DU group. The other is that the main cause of recurrence looks different in DU and BGU. In the 45 patients with DU in whom bacteria had been eradicated, DU recurrences were 0% within 1 year, 4% within 2 years, 13% within 3 years and 18% within 4 years, and all of them were found to be *H.pylori* positive again[35]. Moreover, no DU recurrence was found in the patients who remained *H.pylori* negative. In BGU patients, the recurrence rate of the eradicated group was 7.5% (3 patients) within 1 year and 10% (4 patients) within 2 years, which looks like slightly higher than that of the DU group. Among these 4 recurred BGU patients, only one patient was found to be *H.pylori* positive again within 1 year, and two patients had NSAIDs ingestion history. In the remaining one patient in whom BGU was found to recur within 18 months after eradication, *H. pylori* was still negative and there was no history of NSAIDs ingestion. These results suggest that BGU recurrence is caused by NSAIDs or *H. pylori* reinfection, although DU recurrence after eradication of *H. pylori* nearly depends on *H. pylori* reinfection. In the present study, most of the recurrent ulcer sites in the 19 recurred BGU patients were the same as the ulcer sites of the initial diagnosis, regardless of eradicated (4 patients) or not (15 patients). In two cases of BGU-recurred patients of the non-eradicated group, the number of ulcers increased to 3 and 5, including the initial one. These results suggest that the original weak mucosal point, which had already appeared as an ulcer, is the persistent weak site where BGU can easily recur even after healing, regardless of whether the reattacking cause is *H. pylori* or NSAIDs.

In conclusion, the eradication of *H.pylori* in patients with BGU reduces the recurrence of BGU similar to DU. However, the major causes of BGU recurrence appear to be NSAIDs ingestion and reinfection of *H.pylori*, which is different from DU in which *H.pylori* reinfection is the main cause.

REFERENCES

1. Rauws EAJ, Langenberg W, Houthoff HJ, Zanen HC, Tytgat GNJ. *Campylobacter pylori associated chronic antral gastritis. Gastroenterology 1988; 94:33-40.*
2. Van der Hulst RWM, Tytgat GNJ. *Helicobacter pylori and peptic ulcer disease. Scand J Gastroenterol 1996; 31(Suppl 220); 10-18.*
3. Hopkins RJ, Girardi LS, Turney EA. *Relationship between Helicobacter pylori eradication and reduced duodenal and gastric ulcer recurrence: a review. Gastroenterology 1996; 110:1244-1252.*
4. National Institutes of Health Consensus Development Conference: *Helicobacter pylori in peptic ulcer disease. JAMA 1994; 272:65-69.*
5. Bayerdorffer E, Mannes GA, Sommer A, Hochter W, Weingart J, Hatz R. *High dose omeprazole treatment combined with amoxicillin eradicates Helicobacter pylori. Eur J Gastroenterol Hepatol 1992; 4:697-702.*
6. Graham DY, Lew GM, Klein PD, Evans DG, Evans DJ, Saeed ZA, Malaty HM. *Effect of treatment of Helicobacter pylori infection on the long-term recurrence of gastric or duodenal ulcer. Ann Intern Med 1992; 116:705-708.*
7. Marshall BJ, Goodwin CS, Warren JR, Murray R, Blincow D, Blackbourn SJ, Phillips M, Waters TE, Sanderson CR. *Prospective double-blind trial of duodenal ulcer relapse after eradication of Campylobacter pylori. Lancet 1988; ii:1437-1442.*
8. Rauws EAJ, Tytgat GNJ: *Cure of duodenal ulcer associated with eradication of Helicobacter pylori. Lancet 1990; ii:1233-1235.*
9. Kim NY, Oh HS, Jung HM, Wee SH, Choi JH, Lee KH: *The effect of eradication of Helicobacter pylori upon the duodenal ulcer recurrence. -A 24 month follow-up study- Kor J Int Med 1994; 9:72-78.*
10. Sung JJ, Chung SC, Ling TKW, Yung MY, Leung VK, Ng EK, Li MK, Cheng AF, Li AK. *Antibacterial treatment of gastric ulcers associated with Helicobacter pylori. N Engl J Med 1995; 332:139-142.*
11. Axon ATR, O'Morain CA, Bardhan KD, Crowe JP, Beattie AD, Thompson RPH, Smith PM, Hollanders FD, Baron JH, Lynch DAF, Dixon MF, Tompkins DS, Birrell H, Gilon KRW. *Randomised double blind controlled study of recurrence of gastric ulcer after treatment for eradication of Helicobacter pylori infection. BMJ 1997; 314:565-568.*
12. Seppala K, Pikkarainen P, Sipponen P, Kivilaakso E, Gormsen MH, Finnish Gastric Ulcer Study Group. *Cure of peptic gastric ulcer associated with eradication of Helicobacter pylori. Gut 1995; 36:834-837.*
13. Bayerdorffer E, Mannes GA, Hochter W, Weingart J, Sommer A, Klann H, Heldwein W, Hatz R, Simon T, Eimiller A, Bolle F, Miehlke S, Bastlein E, Ruckdeschel G, Lehn N, Stolte M: *Antibacterial treatment of gastric ulcers. German gastric ulcer study [Abstract]. Gastroenterology 1993; 104:40.*
14. Labenz J, Borsch G: *Evidence for the essential role of Helicobacter pylori in gastric ulcer disease. Gut 1994; 35:19-22.*
15. Isenberg J, McQuaid KR, Laine L, Walsh JH.

Acid-peptic disorders. *In: Yamada T, ed. Textbook of gastroenterology. Vol. 1. 2nd ed. Philadelphia:JB Lippincott, 1995;1356.*

16. Satoh K, Kimura K, Yoshida Y, Kasano T, Kihira K, Taniguchi Y. *A topographical relationship between Helicobacter pylori in the gastric mucosa. Am J Gastroenterol 1991; 86:285-291.*
17. Madsen JE, Vetvik K, Aase S. *Helicobacter pylori and chronic active inflammation of the duodenum and stomach in duodenal ulcer patients treated with ranitidine, misoprostol or an acid-neutralizing agent. Scand J Gastroenterol 1991; 26:465-470.*
18. Soll AH. Peptic ulcer. *In: Bennet JC, Plum F, ed. Cecil textbook of medicine. 20th ed. Philadelphia:WB Saunder Co, 1996:662.*
19. Laine L. *Helicobacter pylori, gastric ulcer and agents noxious to the gastric mucosa. Gastroenterol Clin Nor Am 1993; 22:117-125.*
20. Kim NY, Park YJ, Ahn KJ, Lee GH, Lim BC, Koh YH, Ko JJ, Lim SH, Lee KH, Jung HC, Song IS, Kim CY. *The role of Helicobacter pylori and NSAID in patients with benign gastric ulcer. Kor J Int Med 1998; 54:502-513.*
21. Dixon MF. *Helicobacter pylori and peptic ulceration: histopathological aspects. J Gastroenterol Hepatol 1991; 6:125-130.*
22. Sipponen P, Seppala K, Aarynen M, Helske T, Kettunen P. *Chronic gastritis and gastroduodenal ulcer: a case control study on risk of coexisting duodenal or gastric ulcer in patients with gastritis. Gut 1989; 30:922-929.*
23. Miehlke S, Bayerdorffer E, Meining A, Stolte M, Malfertheiner P. *Identifying persons at risk for gastric cancer? Helicobacter 1997; 2(Suppl 1):S61-S66.*
24. Kim N, Ko JJ, Lim SH, Lee KH. *Difference in expression of H. pylori and gastritis in antrum and corpus and the effect of eradication upon chronic gastritis and intestinal metaplasia [Abstract]. Gastroenterology 1988; 114:176.*
25. Kim N, Ko JJ, Ko YH, Oh JH, Lee CG, Lim SH, Lee KH, Choi SE. *The detection rate of H. pylori and intestinal metaplasia in the antrum and in the body. Kor J Gastroendoscopy (Accepted for publication).*
26. Van der Hulst RWM, Rauws EAJ, Koycu B, Keller JJ, Bruno MJ, Tijssen JGP, Tytgat GNJ. *Prevention of ulcer recurrence after eradication of Helicobacter pylori: a prospective long-term follow-up study. Gastroenterology 1997; 113:1082-1086.*
27. Flocca R, Solcia E, Santoro B. *Duodenal ulcer relapse after eradication of Helicobacter pylori (letter). Lancet 1991; 337:1614.*
28. Unge P, Gad A, Erikkson K, Bergman B, Carling L, Ekstrom P, Glise H, Gnarpe H, Junhadd D, Lindholmer C, Sandzen B, Strandberg L, Stuccerod H, Weywadt L. *Amoxicillin added to omeprazole prevents relapse in the treatment of duodenal ulcer patients. Eur J Gastroenterol Hepatol 1993; 5:325-331.*
29. Sung JJ, Chung SCS, Ling TKW, Yung MY, Cheng AF, Hosking SW, Li AK. *One-year follow-up of duodenal ulcers after 1-week triple therapy of Helicobacter pylori. Am J Gastroenterol 1994; 89: 199-202.*
30. Marshall BJ, Goodwin CS, Warren JR, Murray R, Blincow ED, Blackbourn SJ, Phillips M, Waters TE, Sanderson CR. *Prospective double-blind trial of duodenal ulcer relapse after eradication of Campylobacter pylori. Lancet 1988; 2:1437-1442.*
31. Coghlan JG, Humphries H, Dooley C, Keane C, Gilligan D, McKenna D, Sweeney E, O'Morain C. *Campylobacter pylori and recurrence of duodenal ulcers: a 12-month follow-up study. Lancet 1987; 2:1109-1111.*
32. Blum AL, Armstrong D, Dammann H, Fischer M, Greiner L, Haase W, Hogeboom-Verdegal A, Liszkay M, Stolte M, Sulser H, Simon B. *The effect of Helicobacter pylori on the healing and relapse of duodenal ulcer [Abstract]. Gastroenterology 1990; 98:22.*
33. Borody TJ, Cole P, Noonan S, Morgan A, Lenne J, Hyland L, Brandl S, Borody EG, George LL. *Recurrence of duodenal ulcer and Campylobacter pylori infection after eradication. Med J Aust 1989; 151:431-435.*
34. Bell GD, Powell KU. *Helicobacter pylori reinfection after apparent eradication: the Ipswich experience. Scand J Gastroenterol 1996; 215(Suppl):96-104.*
35. Kim N, Lim SH, Lee KH, Jung HC, Song IS, Kim JY. *Helicobacter pylori reinfection rate and duodenal ulcer recurrence. Clin J Gastroenterol (Accepted for publication).*