ORIGINAL INVESTIGATION

Maintenance Treatment Is Not Necessary After *Helicobacter pylori* Eradication and Healing of Bleeding Peptic Ulcer

A 5-Year Prospective, Randomized, Controlled Study

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Background: It is well accepted that in patients with uncomplicated peptic ulcers, *Helicobacter pylori* eradication therapy does not need to be followed by further antisecretory treatment. However, it is uncertain whether patients with bleeding peptic ulcers should receive maintenance antiulcer therapy after successful *H pylori* eradication and ulcer healing. The aim of this 5-year, prospective, randomized, controlled study was to investigate the role of long-term maintenance therapy after successful *H pylori* eradication and healing of bleeding ulcers.

Methods: A total of 82 consecutive patients with *H pylori*–associated bleeding peptic ulcers were enrolled in the study. After successful *H pylori* eradication with the 1-week proton pump inhibitor–based triple therapy and an additional 3-week treatment with 20 mg of omeprazole daily for ulcer healing, the patients were assigned to one of four 16-week maintenance treatment groups as follows: group A received 15 mL of an antacid suspension 4 times daily; group B received 300 mg of colloidal bismuth subcitrate 4 times daily; group C received 20 mg of famotidine twice daily; and group D, the control group, received placebo twice daily. Follow-up included an urea breath test labeled with carbon 13, biopsy-based tests, and repeated endoscopic examination.

Results: An analysis of variance revealed no difference in mean age and mean follow-up time among the groups. During a mean follow-up of 56 months, there was no peptic ulcer recurrence among the 3 treatment groups, and all of the patients remained free of *H pylori* infection during the study period.

Conclusions: In patients with bleeding peptic ulcers, antiulcer maintenance treatment was not necessary to prevent ulcer recurrence after successful *H pylori* eradication and ulcer healing. In addition, the 1-week proton pump inhibitor–based triple therapy had the efficacy to ensure long-term eradication of *H pylori* in a region of high prevalence.

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GASTROINTESTINAL hemorrhage, one of the most frequent complications of peptic ulcer disease, is associated with substantial morbidity, mortality, and health care costs.[1] Despite advances in diagnosis and treatment in the past decade, the mortality rate from upper gastrointestinal hemorrhage still remains around 6% to 14% and bleeding reoccurs after initial hemostasis in about 10% to 30% of patients with bleeding peptic ulcers.[1-4] To prevent recurrent ulcer bleeding is therefore a highly desirable clinical goal.

The importance of *Helicobacter pylori* in the pathogenesis of peptic ulcers and in ulcer recurrence is well established. At present, ingestion of nonsteroidal antiinflammatory drugs (NSAIDs) and *H pylori* infection are recognized as the 2 major factors predisposing to bleeding peptic ulcers.[1] Previous studies have shown that eradication of *H pylori* infection is associated with a significant decrease in the rate of ulcer recurrence.[5-7] In a long-term study of patients with uncomplicated ulcer disease who did not use NSAIDs or maintenance antisecretory therapy, the recurrence of duodenal or gastric ulcers was completely prevented during a median follow-up of 2.5 years after successful *H pylori* eradication therapy.[8] However, whether patients with bleeding peptic ulcers should receive the same treatment as patients with uncomplicated ulcers, with no antiulcer maintenance therapy after successful *H pylori* eradication and ulcer healing, is uncertain.

The main purpose of our 5-year, prospective, randomized, controlled study was to investigate the need for maintenance therapy in the long-term management of patients after successful *H pylori* eradica-

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tion therapy and subsequent healing of a bleeding ulcer. In addition, we assessed the long-term success rate of *H pylori* eradication after the 1-week proton pump inhibitor (PPI)–based triple therapy in Taiwanese patients with complicated ulcers.

METHODS

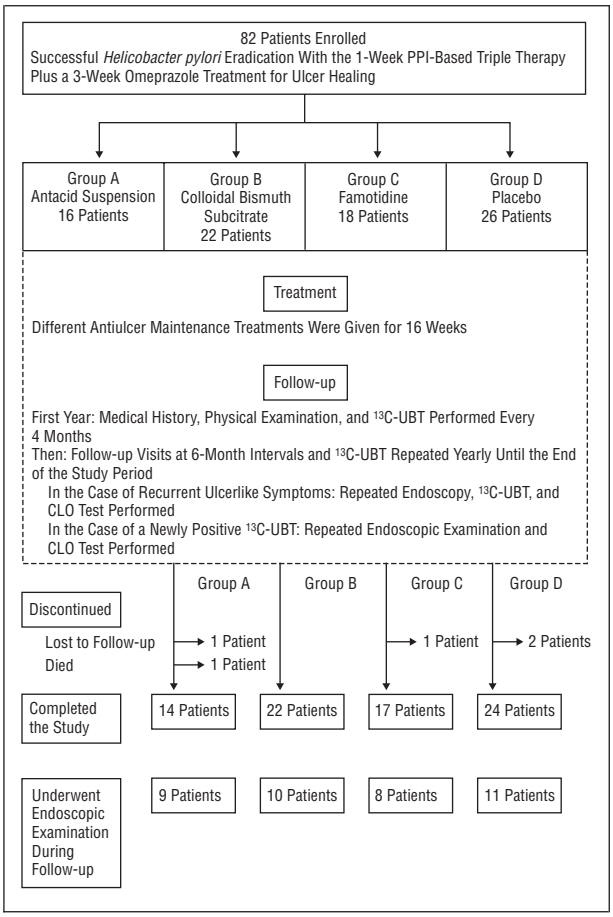
This study was conducted at Cathay General Hospital, Taipei, Taiwan. Patients presenting with upper gastrointestinal tract bleeding from June 1996 to March 1998 were considered for enrollment. The inclusion criteria were diagnosis of *H pylori* infection, plus endoscopic evidence of active peptic ulcer bleeding or any one of the following stigmata of recent ulcer hemorrhage: red or black spots in the ulcer base, blood clot adherent to the ulcer base, or visible vessel end. Peptic ulcers were identified as disruptions in the mucosa measuring no less than 5 mm in diameter, with an apparent depth.[9] Patients with a history of gastric surgery or specific antiulcer treatment, or who used antibiotics or NSAID within 2 weeks prior to admission, were excluded. Informed consent was obtained from each patient before the procedures were performed.

ASSESSMENT OF *H PYLORI* STATUS

The diagnosis of *H pylori* infection was based on the results of invasive and noninvasive tests. A total of 4 biopsy specimens were taken from the gastric mucosa for each patient: 1 antral specimen for a rapid urease test (CLO test; Delta West Pty Ltd, Bently, Australia); 1 antral specimen and 1 specimen from the corpus for histologic evaluation; and 1 antral specimen for bacterial culture (ground in blood agar in a 5% microaerobic environment). Noninvasive methods included the 15-minute urea breath test labeled with 100 mg of carbon 13 (^{13}C-UBT) (INER-HP ^{13}U-Tester; Lungtan, Taiwan), and an enzyme-linked immunosorbent assay. The ^{13}C-UBT was considered positive when the value gradient of the $^{13}C/^{12}C$ ratio between baseline and test gas sample was greater than 0.3%; and the enzyme-linked immunosorbent assay (AMRAD Operations Pty Ltd, Melbourne, Australia) for blood IgG antibodies was considered positive when the titer was greater than 30 U/mL. A positive diagnosis of *H pylori* infection required a positive culture, a positive histologic finding, or a positive result for 2 of the following tests: CLO test, ^{13}C-UBT, and enzyme-linked immunosorbent assay.

STUDY DESIGN

Most patients were hospitalized and underwent nasogastric tube drainage of stomach contents. During hospitalization, treatment with intravenous administration of H_2-blockers and oral antacid suspensions, but without PPIs, was allowed. Once patients could be discharged or eat normally, a PPI-based triple therapy was initiated. Each patient received 20 mg of omeprazole, 250 mg of clarithromycin, and 500 mg of metronidazole orally twice daily (bid) for 1 week, followed by a 3-week treatment of 20 mg of omeprazole once daily to heal the ulcer. Endoscopic examination was repeated at least 4 weeks after treatment completion for the assessment of ulcer healing. The ^{13}C-UBT and 2 biopsy-based tests (an histologic examination and the CLO test) were performed again to determine whether the patient was free of *H pylori* infection. *Helicobacter pylori* infection was considered to be eradicated when a negative histologic finding and a negative result for either of the other tests (the CLO test and the ^{13}C-UBT) were obtained. Otherwise, the eradication was considered unsuccessful. If *H pylori* had not been successfully eradicated, the patient was excluded from the study and another regimen was given. It was a quadruple therapy consisting of 150 mg of ranitidine bid, 500 mg of tinidazole bid, 250 mg of amoxicillin 4 times daily (qid), and 300 mg of colloidal bismuth subcitrate qid for 2 weeks. After confirmation of *H pylori* eradication, patients were divided into 4 groups by a computer-generated table of random numbers and received different maintenance treatment regimens for 16 weeks. The treatment regimens were as follows: group A received 15 mL of an antacid suspension (aluminum-magnesium-hydrate and dimethyl polysiloxane) qid; group B received 300 mg of colloidal bismuth subcitrate qid; group C received 20 mg of famotidine bid; and group D, the control group, received placebo bid.



Summary of the study design and flow diagram of the progress of participants. PPI indicates proton pump inhibitor; ^{13}C-UBT, urea breath test labeled with 100 mg of carbon 13.

FOLLOW-UP SCHEDULE AND STATISTICAL ANALYSIS

After receiving the 16-week maintenance treatment, all patients were asked to report to the outpatient clinics every 4 months in the first year, and then at 6-month intervals until the end of the study in 2002. The ^{13}C-UBT was performed at 4-month intervals during the first year and at 1-year intervals thereafter for the assessment of *H pylori* status (**Figure**). If a ^{13}C-UBT result was newly positive, the patient underwent a follow-up endoscopic examination followed by a CLO test to confirm the presence of *H pylori* infection. All patients were instructed to contact the responsible physician if ulcerlike symptoms occurred, and endoscopic evaluation was repeated for possible peptic ulcer recurrence. A ^{13}C-UBT and a CLO test were performed to assess *H pylori* status during the same visit. If patients missed a follow-up visit, they were contacted by tele-

Table 1. General Characteristics of 99 Patients With Bleeding Peptic Ulcers

Characteristic	Ulcer Type		
	Duodenal (n = 78)	Gastric (n = 11)	Combination (n = 10)
Age, mean ± SD, y	47 ± 1.4	57.9 ± 3.3	49.4 ± 4.1
Sex, M/F, No.	56/22	8/3	9/1
Transfusion requirement, mean ± SD, U	0.87 ± 0.18	1.33 ± 0.75	0.89 ± 0.59

phone. If they refused to return, they were interviewed by phone about the recurrence of gastrointestinal bleeding and ulcer symptoms.

The different rates of recurrent peptic ulcer in the 4 groups were compared using an analysis of variance. A *P* value of less than .05 was considered statistically significant.

RESULTS

The study was completed in February 2002. A total of 99 patients (78 patients with bleeding duodenal ulcers, 11 patients with bleeding gastric ulcers, and 10 patients with bleeding duodenal and gastric ulcers) were recruited for participation in the study. Their characteristics are shown in the following tabulation:

Endoscopic Finding	No. of Patients
Fresh blood in stomach or duodenum	12
Blood oozing from the ulcer	16
Red or black spots in ulcer base	24
Blood clot adherent to ulcer base	19
Nonbleeding visible vessel end	28

A blood transfusion was required in some patients to maintain their hemodynamic status (**Table 1**). A follow-up endoscopic examination, performed after the 1-week PPI-based triple therapy and an additional 3 weeks of omeprazole therapy, showed that ulcer healing had occurred in all of the recruited patients (100%). However, *H pylori* eradication had failed in 7 patients who were thus excluded. The *H pylori* eradication rate for our 1-week PPI-based triple therapy was 92.9% (92/99).

Of the 92 patients with bleeding peptic ulcers whose *H pylori* infections had been eradicated and ulcers had healed, 82 agreed to receive 16 weeks of maintenance therapy and were randomized to receive 1 of 4 treatment regimens. The other 10 patients refused further management but agreed to be followed up, and were therefore designated as the contrast group. An analysis of variance revealed no statistically significant differences among the 4 treatment groups regarding mean age and mean follow-up time. One patient died of myocardial infarction during the second year and 4 patients were lost to follow-up. Their mean age was 61 years (range, 55-73 years) and their mean follow-up time was 18 months (range, 12-28 months). Therefore, only 77 patients adhered to the protocol until the end of the follow-up period (**Table 2**). The mean age of these 77 patients was 49 years (range, 20-76 years), and their mean follow-up time was 56 months (range, 44-66 months).

During the 56-month follow-up, 38 patients underwent endoscopic examination because of recurrent ulcerlike symptoms. No evidence of ulcer relapse or bleeding recurrence was found, however, and all of these patients remained free of *H pylori* infection (**Table 3**). One male patient in group C reported hematemesis after 45 months of follow-up. Emergency endoscopic examination revealed Mallory-Weiss syndrome but no recurrent gastric or duodenal ulcer was detected. The other patients who did not choose to undergo repeated endoscopic evaluations reported no symptoms or signs of recurrent peptic ulcer during the entire follow-up period. An analysis of variance showed no differences among the 4 groups regarding the absence of ulcer recurrence.

The ^{13}C-UBT was performed every year to evaluate *H pylori* status after successful eradication therapy (Figure). No newly positive ^{13}C-UBT result was found in any of the 82 patients during the follow-up period. There was no reappearance of infection during a mean follow-up of 54 months after successful eradication of *H pylori*. An analysis of variance showed no statistically significant differences among the 4 treatment groups regarding the absence of *H pylori* reinfection.

The mean age of the 10 patients in the contrast group was 43 years (range, 17-74 years). All of them completed their scheduled follow-up visits. Recurrence of peptic ulcer and reappearance of *H pylori* infection were also absent in this group.

COMMENT

Gastrointestinal hemorrhage is the most frequent complication of peptic ulcer disease, and 20% of all patients with duodenal ulcers and 15% of all patients with gastric ulcers experience ulcer bleeding at least once in their lifetimes.[10] Despite major advances in the treatment of upper gastrointestinal hemorrhage in recent years, mortality from peptic ulcer bleeding has remained significantly high[2,11-14] but the correct approach to prevent ulcer recurrence and further bleeding in the long term is still debated.

Before the recognition of the role of *H pylori* in the pathogenesis of peptic ulcer disease, maintenance therapy with H_2-receptor antagonists was commonly used to prevent recurrent ulceration; high ulcer relapse rates were noted, however, ranging from 13% to 62%.[15] Some studies indicated that treatment with compounds containing bismuth decreased the 1-year relapse rate compared with H_2-antagonists.[16,17] This may be related to suppressing effect of bismuth compounds on *H pylori*.[18]

It is now well accepted that *H pylori* is a major etiological factor in peptic ulcer disease.[19,20] Several randomized controlled trials have shown that eradication of the organism remarkably reduces the possibility of recurrence and further bleeding in peptic ulcer disease.[5-7,21-23] The European *Helicobacter pylori* Study Group[24] and, in the United States, the National Institutes of Health,[25] advise eradication of *H pylori* in all cases of peptic ulcer disease, complicated or uncomplicated.

In patients with uncomplicated peptic ulcer, it is strongly recommended that *H pylori* eradication therapy not be followed by maintenance antiulcer treatment.[24] In

Table 2. Medications and Clinical Characteristics of Patients Who Completed the Study*

Characteristic	Group A: Antacid Suspension	Group B: Colloidal Bismuth Subcitrate	Group C: Famotidine	Group D: Placebo	Contrast Group: No Medication
Patients, No.	14	22	17	24	10
DU/GU/DU + GU, No.	13/0/1	16/3/3	13/2/2	19/3/2	9/0/1
Sex, M/F, No.	10/4	13/9	10/7	18/6	9/1
Age, mean ± SD, y	47.1 ± 14.6	49.6 ± 12.0	50.9 ± 8.5	48.4 ± 14.9	43.1 ± 16.6
Follow-up, mean ± SD, mo	55.2 ± 6.9	57.3 ± 6.5	55.0 ± 6.7	56.7 ± 6.6	57.1 ± 7.9

Abbreviations: DU, duodenal ulcer, GU, gastric ulcer.
*An analysis of variance revealed no differences in mean age and mean follow-up time among the 4 groups.

Table 3. Medications and Clinical Characteristics of Patients Who Underwent Endoscopic Examination During Follow-up*

Characteristic	Group A: Antacid Suspension	Group B: Colloidal Bismuth Subcitrate	Group C: Famotidine	Group D: Placebo	Contrast Group: No Medication
Patients, No.	9	10	8	11	4
Sex, M/F, No.	6/3	6/4	5/3	7/4	4/0
Age, mean ± SD, y	44.8 ± 13.5	45.4 ± 12.4	54.8 ± 7.3	47.3 ± 17.2	55.5 ± 17.8

*The urea breath test labeled with carbon 13 and the CLO test were performed. None of the patients experienced peptic ulcer recurrence or *Helicobacter pylori* reinfection (patients were considered infected with *H pylori* if the result of 1 test was positive and they were considered uninfected if the results of both tests were negative).

Table 4. Peptic Ulcer Reappearance and Bleeding Recurrence After *Helicobacter pylori* Eradication

Source	Patients, No.	Maintenance Treatment	Mean Follow-up, mo	Patients With Ulcer Reappearance		Patients With Bleeding Recurrence	
				HP+	*HP–*	*HP+*	*HP–*
Lai et al[26]	96	No	53	17/55	0/41	16/55	2/41
Macri et al[23]	32	No	48	0/11	0/21	9/11	0/21
Labenz et al[27]	66	No	17	6/24	1/42	9/24	0/42
Present study, groups A, B, and C	53	Yes	56	NA	0/53	NA	0/53
Present study, group D, and contrast group	34	No	57	NA	0/34	NA	0/34

Abbreviations: *HP+*, *H pylori* was present; *HP–*, *H pylori* was absent; NA, not applicable.

a long-term follow-up study, Van der Hulst et al[8] found that, for up to 9.8 years after true *H pylori* eradication, there were no relapses of peptic ulcers in patients who had uncomplicated peptic ulcers and no maintenance therapy. However, the optimal treatment for patients with bleeding ulcers remains to be established. Limited research data are available for evaluating the long-term outcome of patients with bleeding ulcers after successful *H pylori* eradication (**Table 4**).[23,26,27] No study has investigated the role of maintenance antiulcer treatment in the long-term management of patients with complicated ulcer after a successful *H pylori* eradication therapy. This study evaluated 3 different maintenance treatments in patients with bleeding peptic ulcers after successful eradication therapy and ulcer healing. The relapse rates of peptic ulcers and the reinfection rates of *H pylori* were compared among these 3 maintenance treatment groups. There were no recurrences of peptic ulcers during a mean follow-up of 56 months among the patients who received maintenance therapy after successful *H pylori* eradication and ulcer healing, and *H pylori* infection did not recur among them. However, there were also no recurrences of peptic ulcers or reinfection by *H pylori* among the patients who received placebo or among the patients who did not receive any maintenance treatment during the same mean follow-up of 56 months. Our results demonstrate that for patients with bleeding peptic ulcer who do not use NSAIDs, antiulcer maintenance treatment is not necessary after successful *H pylori* eradication and ulcer healing. *Helicobacter pylori* seems to be the major factor in the recurrence of peptic ulcers. Successful eradication of *H pylori* drastically changes the natural history of bleeding peptic ulcers.

Proton pump inhibitor–based or ranitidine bismuth citrate–based triple therapy with clarithromycin plus amoxycillin or metronidazole for 1 week is the standard treatment for *H pylori* eradication. In our previous study, we found that the standard 1-week PPI-based triple therapy is effective to eradicate *H pylori* infection in patients with bleeding peptic ulcers.[28] However, no study

has reported the long-term efficacy of the 1-week PPI-based triple therapy for the eradication of *H pylori* in patients with complicated peptic ulcers. In this study, a newly positive ^{13}C-UBT result was not found in any of the patients during follow-up. Reappearance of *H pylori* infection was not documented for up to 66 months. These findings highlight the efficacy of the 1-week PPI-based triple therapy in providing long-term *H pylori* eradication in patients with bleeding peptic ulcers. The reappearance of *H pylori* infection could be completely prevented in patients with complicated ulcers after a successful eradication therapy, even in a country with a high prevalence rate (the overall seropositive rate was 54.4% in Taiwan).[29]

In conclusion, the results of 5 years of follow-up observation in this randomized controlled study have shown that in patients with bleeding peptic ulcers who do not use NSAIDs, antiulcer maintenance treatment is not necessary if *H pylori* has been successfully eradicated and the ulcer has healed. Successful *H pylori* eradication therapy can change the natural course of peptic ulcers and completely prevent ulcer recurrence in patients with or without peptic ulcer complications. Finally, the 1-week PPI-based triple therapy has the efficacy to provide long-term eradication of *H pylori* in patients with bleeding peptic ulcers, even in a region of high prevalence.

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