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Eradication of *Helicobacter pylori* Prevents Recurrence of Ulcer After Simple Closure of Duodenal Ulcer Perforation

Randomized Controlled Trial

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Objective
In this randomized trial, the authors sought to determine whether eradication of *Helicobacter pylori* could reduce the risk of ulcer recurrence after simple closure of perforated duodenal ulcer.

Background Data
Immediate acid-reduction surgery has been strongly advocated for perforated duodenal ulcers because of the high incidence of ulcer relapse after simple patch repair. Although *H. pylori* eradication is now the standard treatment of uncomplicated and bleeding peptic ulcers, its role in perforation remains controversial. Recently a high prevalence of *H. pylori* infection has been reported in patients with perforations of duodenal ulcer. It is unclear whether eradication of the bacterium confers prolonged ulcer remission after simple repair and hence obviates the need for an immediate definitive operation.

Methods
Of 129 patients with perforated duodenal ulcers, 104 (81%) were shown to be infected by *H. pylori*. Ninety-nine *H. pylori*-positive patients were randomized to receive either a course of quadruple anti-helicobacter therapy or a 4-week course of omeprazole alone. Follow-up endoscopy was performed 8 weeks, 16 weeks (if the ulcer did not heal at 8 weeks), and 1 year after hospital discharge for surveillance of ulcer healing and determination of *H. pylori* status. The endpoints were initial ulcer healing and ulcer relapse rate after 1 year.

Results
Fifty-one patients were assigned to the anti-*Helicobacter* therapy and 48 to omeprazole alone. Nine patients did not undergo the first follow-up endoscopy. Of the 90 patients who did undergo follow-up endoscopy, 43 of the 44 patients in the anti-*Helicobacter* group and 8 of the 46 in the omeprazole alone group had *H. pylori* eradicated; initial ulcer healing rates were similar in the two groups (82% vs. 87%). After 1 year, ulcer relapse was significantly less common in patients treated with anti-*Helicobacter* therapy than in those who received omeprazole alone (4.8% vs. 38.1%).

Conclusions
Eradication of *H. pylori* prevents ulcer recurrence in patients with *H. pylori*-associated perforated duodenal ulcers. Immediate acid-reduction surgery in the presence of generalized peritonitis is unnecessary.

The long-term results of omental patch repair for perforated duodenal ulcer are unsatisfactory; a high incidence of ulcer recurrence has been repeatedly reported.[1–4] Some advocate immediate acid-reduction procedures in addition to repair of the ulcer as a preventive measure against subsequent ulcer relapse.[5,6] Immediate definitive surgery in selected patients is safe, without increasing the rate of perioperative complications or death.[7] However, with recent advances in antiulcer medical therapy, fewer surgeons have acquired sufficient expertise in performing the definitive operation. Moreover, because perforated peptic ulcer is often an "out of hours" emergency, a simpler life-saving procedure such as omental patch repair is an attractive option in many centers.

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The recent rediscovery of *Helicobacter pylori* has revolutionized the therapeutic approach to peptic ulcer disease. Eradication of *H. pylori* heals most uncomplicated peptic ulcers and prevents relapse.[8–10] In the case of bleeding peptic ulcers, a short course of antibiotics eradicating *H. pylori* is as efficacious as maintenance acid-reduction medication in preventing recurrent ulcer hemorrhage.[11] Both the National Institute of Health Consensus Meeting and the Maastricht Meeting of the European *Helicobacter pylori* Study Group have recommended eradication of *H. pylori* as the standard treatment for uncomplicated and bleeding peptic ulcers.[12,13]

However, the association between *H. pylori* and perforated duodenal ulcer is less well defined. The reported infection rates range widely, from 47% by serologic testing[14] to more than 80% in two recent biopsy-based studies.[15,16] Whether there is a causal relation between the bacterium and duodenal ulcer perforation is controversial. We therefore performed a prospective randomized trial to determine whether eradication of *H. pylori* could lead to sustained ulcer remission in patients who underwent only simple repair for duodenal ulcer perforation.

METHODS

Patients

Patients with clinical or radiologic signs of perforated peptic ulcers were considered for inclusion in the study. The study was approved by the Ethics Committee of the Faculty of Medicine, The Chinese University of Hong Kong. Informed consent was obtained for surgical exploration, intraoperative per oral gastroscopy, and possible enrollment into the study if infected with *H. pylori*. Exclusion criteria were age younger than 16 or older than 75 years, use of antibiotics or acid-suppressing medications within 4 weeks before admission, previous gastrectomy or vagotomy, pregnancy, sealed-off perforation, and inpatients in whom ulcer perforation developed while receiving treatment for other medical conditions.

Procedures

All patients received fluid resuscitation. Parenteral analgesics were prescribed for pain relief after the decision for surgical intervention was made. Informed consent was obtained for surgical exploration and possible enrollment into the study. Intravenous cefuroxime (1.5 g) was administered during induction of anesthesia. No other antibiotics or acid-suppressing medications were prescribed before surgery.

When duodenal ulcer perforation was confirmed by laparoscopy or laparotomy, intraoperative flexible gastroscopy (Q20, Olympus, Tokyo, Japan) was performed to obtain biopsy samples of the gastric antrum. Seven samples were obtained: one for rapid urease test (*Campylobacter*-Like Organism test [CLOtest], Delta West, West Australia), three in brain–heart–infusion medium for subsequent Gram stain and culture, and three in 10% buffered formalin for histologic examination.

Definition of *H. pylori* Status

Patients were considered to be *H. pylori* positive if any one of the following criteria was fulfilled: a positive culture, a positive CLOtest result plus gram-negative helical bacteria in the smear, or a positive CLOtest result plus helical microorganisms in histologic section of the gastric biopsy samples.

Surgery

Perforations less than 1 cm in diameter were repaired using the conventional open method or the laparoscopic technique, based on the surgeon's discretion. Gastrectomy or other definitive acid-reduction procedures were considered only if patients had a large perforation (>1 cm in diameter) not amenable to simple omental patch repair or a perforation concomitant with hemorrhage or obstruction. After closure of the perforation, thorough peritoneal lavage with warm normal saline was performed before closure of the abdominal incision. After surgery, patients were cared for in designated surgical wards. Intravenous cefuroxime (750 mg) was continued every 8 hours for 3 days, and intravenous omeprazole (40 mg/day) was given until the patient resumed eating an oral diet.

Random Assignment to Treatment Groups

Only *H. pylori*-positive patients who had undergone patch repair were eligible for the randomization trial. After resuming an oral diet, patients were randomly assigned to one of the two treatment options by opening sealed envelopes that contained treatment options previously determined from a list of computer-generated random numbers. For the eradication group, a 1-week course of oral antibacterial treatment (bismuth subcitrate 120 mg, tetracycline 500 mg, and metronidazole 400 mg four times daily) plus 4 weeks of omeprazole (20 mg twice daily) was prescribed. Patients assigned to the control group were given a 4-week course of omeprazole alone. Compliance with treatment was monitored by phone inquiry and tablet count on follow-up by research nurses.

Follow-Up and Endoscopy

Endoscopy was scheduled 8 weeks after randomization and was performed by an endoscopist masked to the assigned treatment. Biopsy samples were again obtained from the gastric antrum to determine the patient's *H. pylori* status. Additional biopsy samples were collected from body of the stomach to avoid false-negative results secondary to

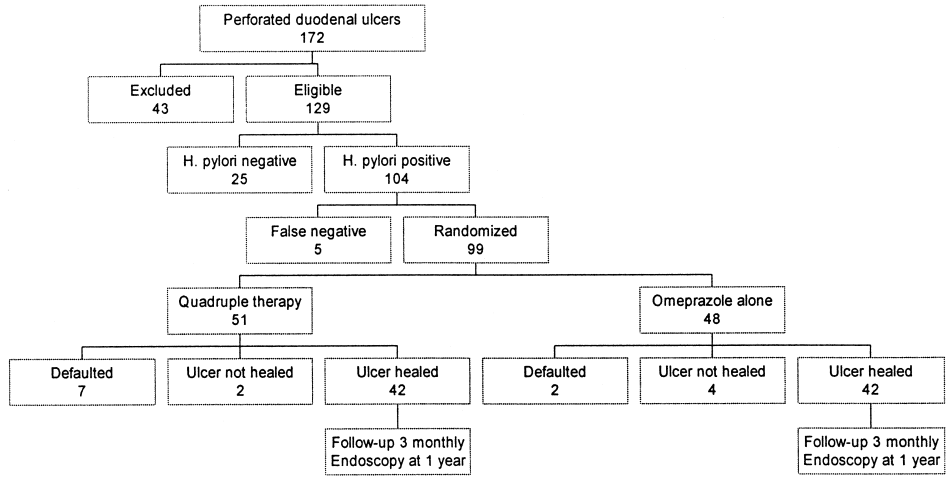

Figure 1. Trial profile.

proximal migration of the bacterium after therapy. All patients with complete ulcer healing confirmed on scheduled endoscopy were then interviewed every 3 months by research nurses. Maintenance acid-suppression agents were not prescribed during the follow-up period. Repeat endoscopic examination was performed whenever patients were symptomatic. All patients were invited for a follow-up endoscopy at 1 year for ulcer surveillance and determination of *H. pylori* status.

For patients whose ulcers had not healed at 8 weeks, another 4-week course of omeprazole (20 mg twice daily) was prescribed, and a second endoscopy was scheduled at 16 weeks. Primary treatment failure was considered to be present if patients had persistent nonhealing ulcers at that point.

Sample Size and Statistical Analysis

There are few data regarding the effect of *H. pylori* eradication in perforated ulcer disease. Based on studies of uncomplicated ulcers, we estimated that ulcers would relapse in fewer than 5% of the patients with perforated duodenal ulcers after eradication of *H. pylori*.[8–10] Studies before the era of *H. pylori* revealed a median ulcer recurrence rate of 40% if only simple repair was performed for duodenal ulcer perforation.[2–4] To show a 35% difference of ulcer recurrence with a 5% type I error risk and a power of 0.8 in a two-sided model, a minimum of 43 patients in each arm was required. Anticipating a default rate of 10%, we decided to recruit at least 48 patients into each treatment group. The differences in initial ulcer healing and ulcer recurrence between the two groups of patients were studied by intention-to-treat analyses. Patients who did not appear for follow-up were contacted by phone to ask about symptoms. Those who were symptomatic but refused to undergo endoscopy and those who could not be contacted were considered as treatment failures. All statistical analyses were performed with GraphPad Prism version 2 (GraphPad Software, Inc., San Diego, CA). Chi-square with Yates correction and Fisher's exact test were used to compare proportions when appropriate; continuous normally distributed numeric data were compared using the Student *t* test.

RESULTS

From September 1994 to January 1997, 172 patients (138 men and 34 women) with a mean age of 52.2 years (S.D. = 18.1) were confirmed to have duodenal ulcer perforation by laparoscopy or laparotomy (Fig. 1). Forty-three patients were not eligible for the study: 17 were older than 75 years, 10 required definitive operation, 7 failed endoscopic examination (equipment failure occurred with 5 patients, and the endoscopist could not pass the flexible endoscope through the cricopharyngeus when the other 2 patients were intubated), 4 refused to undergo intraoperative endoscopy, 3 did not live in Hong Kong (so long-term follow-up was not possible), 1 had disseminated malignancy, and 1 had a previous vagotomy (Table 1). Of the remaining 129 patients, 104 (80.6%) were infected with *H. pylori*. Five patients were not enrolled into the randomization study because the initial urease test and histology results were falsely negative. These five patients were prescribed a full course of eradication therapy on follow-up and were not included in the trial.

Of the remaining 99 patients, 51 were assigned to anti-*Helicobacter* therapy and 48 to omeprazole alone (see Fig. 1). The two groups were comparable in age, sex ratio, smoking habit, use of nonsteroidal antiinflammatory drugs (NSAIDs), previous ulcer history, size of perforation, severity of peritoneal contamination, and method of repair (Table 2). Ninety patients returned for follow-up endoscopy at 8 weeks. The dropout rate of the anti-*Helicobacter* group (seven patients: three had major side effects from the medication and four could not be contacted) exceeded that of the omeprazole group (two patients lost to follow-up), but the difference did not reach statistical significance ($P = .16$).

Table 1. CHARACTERISTICS OF EXCLUDED PATIENTS

Reason for Exclusion	Number of Patients	No. With HP Status Determined	No. With Positive HP Status	No. With Use of NSAID
Age >75	17	12	4	7
Failure in obtaining biopsy sample	11	—	—	1
Definitive surgery indicated				
Vagotomy and drainage	4	1	1	0
Partial gastrectomy	6	5	1	3
Non-Hong Kong residents	3	2	2	0
Previous gastric surgery	1	1	1	1
Concurrent malignancy	1	0	0	0

HP, *Helicobacter pylori;* NSAID, nonsteroidal antiinflammatory drug.

As expected, the *H. pylori* eradication rate of the anti-*Helicobacter* treatment group was significantly higher than that of the omeprazole alone group (84.3% vs. 16.7%, $P < .001$). Eight patients in the omeprazole alone group had inadvertent eradication of *H. pylori* (Table 3). When case records were reviewed, seven of these eight patients had received extra antibiotics, including ampicillin or metronidazole (both are effective antibiotics for eradication of *H. pylori*) in the early postoperative period because of persistent fever or other septic conditions.

Table 2. CHARACTERISTICS OF PATIENTS

	Quadruple Therapy (n = 51)	Omeprazole Therapy (n = 48)	*P* Value
Age (years)	44 ± 14	45 ± 15	.73*
Sex			
Female	8	7	.90†
Male	43	41	
Cigarette smoking			
Not smoke or ex-smoker	17	14	.08†
4–8 packs/week	23	30	
>8 packs/week	11	4	
NSAID intake	10	9	.88†
Dyspepsia > 3 months	34	31	.43†
Previous ulcer	15	10	
Previous ulcer complications	7	6	
Severity of peritonitis			
Mild	6	5	.50†
Moderate	37	39	
Severe	8	4	
Size of perforation (mm)	4.2 ± 1.3	4.6 ± 1.5	.72*
Type of repair			
Open method	40	39	.92†
Laparoscopic method	11	9	

NSAID, non-steroidal antiinflammatory drugs.
"Previous ulcer" signifies a history of peptic ulcer disease confirmed by either barium meal or endoscopy.
* Student *t* test.
† Chi-square analysis with Yates correction.

Initial healing of ulcers was comparable between the two groups (see Table 3). There were six nonhealing ulcers despite repeated courses of omeprazole, two in the anti-*Helicobacter* group and four in the omeprazole group. Complete ulcer healing was documented in 42 patients in each arm ($P = .58$). Patients with documented ulcer healing were scheduled for follow-up according to the study protocol.

After 1 year, two patients in the anti-*Helicobacter* group and four in the omeprazole group were lost to follow-up (Table 4). They reported no significant dyspeptic symptoms and refused to undergo further endoscopic examination when contacted by phone. Of the remaining 78 patients who followed the study protocol strictly, 18 had ulcer recurrence (see Table 4).

Two patients in the anti-*Helicobacter* group had ulcer relapse: one patient had profound duodenal ulcer bleeding 7 months after the index perforation and was subsequently found to have recurrent *H. pylori* infection; the other one was asymptomatic and had recurrent ulcer diagnosed at the scheduled 1-year endoscopy. Of the 16 patients with ulcer recurrence in the omeprazole alone group, 9 were symptomatic. Four patients returned before the scheduled endoscopy at 1 year: two with severe ulcer pain, one with bleeding, and one with gastric outlet obstruction. The difference in ulcer recurrence between the anti-*Helicobacter* group and the control group was statistically significant (4.8% vs. 38.1%, $P = .0001$, intention-to-treat) with a relative risk of 0.18 (95% confidence interval 0.04–0.69). Fifteen of these

Table 3. EARLY OUTCOMES

	Quadruple Therapy (n = 51)	Omeprazole Therapy (n = 48)	*P* Value*
Patients who underwent initial follow-up endoscopy	44 (86.3%)	46 (95.8%)	.16
H. pylori eradicated	43 (84.3%)	8 (16.7%)	<.001
Complete ulcer healing	42 (82.4%)	42 (87.5%)	.58

* Chi-square analysis with Yates correction (intention-to-treat).

Table 4. OUTCOMES OF PATIENTS AT 1-YEAR FOLLOW-UP

	Quadruple Therapy	Omeprazole Alone	*P* Value*	Relative Risk (95% CI)
Patients with complete ulcer healing on initial endoscopy	42	42	—	—
All ulcer recurrence	2 (4.8%)	16 (38.1%)	<.001	0.18 (0.04–0.69)
Duodenal	2	13		
Gastric	0	2		
Gastric + duodenal	0	1		
Symptomatic ulcer recurrence	1 (2.4%)	9 (21.4%)	.02	0.18 (0.03–1.17)
Pain	1	7		
Bleeding	0	1		
Obstruction	0	1		

* Two-tailed Fisher exact test, intention-to-treat.

18 ulcer recurrences were associated with persistent *H. pylori* infection: 14 in the omeprazole group and 1 in the anti-*Helicobacter* group (see Fig. 1).

DISCUSSION

The optimal surgical treatment for perforated duodenal ulcer has been controversial. Simple repair has been the most commonly performed procedure since its popularization by Graham in 1937.[17] However, long-term follow-up of patients who underwent simple repair reveals a high incidence of ulcer relapse.[1–4] In a prospective series by Bornman et al,[18] 48 of 131 patients (42.5%) had recurrent ulcer disease after simple closure of duodenal perforation over a median follow-up of 42 months; 30% of them required further surgery for intractable symptoms or recurrent ulcer complications. Because of the unsatisfactory result of simple repair, immediate acid-reduction procedures have been strongly advocated. In the 1980s, several prospective randomized studies reported significantly fewer ulcer recurrences by adding immediate proximal gastric vagotomy to patch repair of ulcer perforation.[7,19–21] Although the procedure has been shown to be safe, without increasing the rate of perioperative complications, it is technically demanding and requires prolonged operation time. With the recent rapid decline in the number of elective peptic ulcer operations, immediate proximal gastric vagotomy is unlikely to be a practical procedure for most surgical residents, the front-line personnel managing patients with duodenal ulcer perforation.

The recent rapid development in laparoscopic surgery has complicated the issue. Since the first successful laparoscopic repair performed by Mouret et al[22] in 1990, several minimal-access techniques have been described for repair of perforated peptic ulcers.[23–25] Nevertheless, reservations about the use of laparoscopic repair still exist. The inability to perform a concomitant acid-reduction procedure must be weighed against the analgesic and cosmetic advantages of laparoscopic repair. Although laparoscopic vagotomy has been reported as an elective procedure for chronic duodenal ulcer,[26] the procedure is likely to be time-consuming, and its use in patients with peritonitis from a perforated duodenal ulcer is probably limited.

Our study was designed to determine whether perforated duodenal ulcer is causally related to *H. pylori* infection. Anti-*Helicobacter* therapy would be a more desirable option than definitive surgery if eradication of the bacterium confers prolonged ulcer remission after simple closure of the perforation. In our early[27] and the present series of consecutive patients with perforated duodenal ulcers, *H. pylori* infection rates exceeded 80%. This figure is much higher than that reported by Reinbach et al[14] but is consistent with that of Sebastian et al[15] and Matsukura et al,[16] suggesting an association between *H. pylori* infection and duodenal ulcer perforation.

In contrast to the high consumption rate of NSAIDs in most Western series,[28,29] only 26 of 129 patients (20%) in the present series reported a history of use of these agents. This could partly be attributed to the younger age of the patients in our study. Although perforated peptic ulcers have been related to the use of NSAIDs, the association was shown mainly in the elderly patients who took these drugs on a long-term basis.[30] *H. pylori* infection, as a risk factor, appears to be more relevant in younger patients, in whom acid-reduction surgery with its attendant complications is most undesirable.

To the best of our knowledge, this is the first randomized study examining the effect of *H. pylori* eradication in patients with perforated duodenal ulcers. After *H. pylori* eradication and without maintenance acid-suppression agents, 95% of patients remained ulcer-free at 1-year follow-up. The remission rate is similar to those previously reported in uncomplicated ulcers after *H. pylori* eradication[8,9] and is comparable to that achieved by immediate proximal gastric vagotomy during emergency laparotomy.[5–7] In light of the high prevalence of *H. pylori* infection and the few recurrences after eradication, the bacterium is likely to be causally related to the strong ulcer diathesis in patients with duodenal ulcer perforation. Simple repair, either conventional or laparoscopic, is the procedure of choice for duo-

denal ulcer perforation, especially in younger patients. *H. pylori* status should be determined when the patients recover from the acute episode, by either endoscopic biopsy or serology, and the bacterium should be eradicated in those who were infected. Immediate acid-reduction surgery is unnecessary unless there are other concurrent ulcer complications, such as hemorrhage or obstruction.

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