

# The Effect of Eradication of *Helicobacter pylori* upon the Duodenal Ulcer Recurrence

—A 24 month follow-up study—

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**Objectives:** To evaluate the effect of eradication of *Helicobacter pylori* (*H. pylori*) in the patients with duodenal ulcer (DU) upon the DU recurrence.

**Methods:** This study was performed for 190 patients with DU. Four different methods—microscopy of Gram stained mucosal smear, specific culture, biopsy urease test, histology of H & E staining—were taken for identifying colonization of *H. pylori* before treatment, and for finding the eradication of *H. pylori* 4 weeks after completion of therapy in each treatment group (cimetidine, omeprazole, colloidal bismuth subcitrate (CBS), CBS and metronidazole double therapy, CBS, metronidazole and amoxicillin triple therapy). To detect DU recurrence, the gastroscopy was performed at 6, 12, 18, and 24 months after therapy.

**Results:** The eradication rate of the cimetidine group, the omeprazole group, and the CBS group were 0%, 7.7%, 0%, respectively, and that of the double therapy group and the triple therapy group were 44.4% and 89.3%, respectively. Seventy three patients who were followed up for 2 years were categorized into two groups according to the eradication of *H. pylori*. The recurrence rate was 3.2% both in 1 year and 2 years later in the former group—one consisting of 31 patients with *H. pylori* eradicated, while the recurrence rate was 57.1% in 1 year and 78.6% in 2 years later, in the latter group—the other of 42 patients with *H. pylori* not eradicated.

**Conclusion:** The eradication of *H. pylori* in patients with DU reduces the recurrence of DU.

**Key Words :** *Helicobacter pylori*, Eradication, Duodenal ulcer, Recurrence

## INTRODUCTION

Although antacids, H<sub>2</sub>-antagonist and proton pump inhibitor can promote ulcer healing within 4–8 weeks in most patients with duodenal ulcer (DU)<sup>1)</sup>, approximately 70% to 90% of DU recurs within 12 months<sup>2,3)</sup>. Maintenance therapy can be used for the prevention of DU recurrence. However, DU recurrence, sometimes with com-

plication which needs surgical intervention occurs frequently during or just after maintenance therapy<sup>4)</sup>.

Since *Helicobacter pylori* (*H. pylori*) was first cultured in 1983<sup>5,6)</sup>, many studies confirmed that *H. pylori* is the major causal agent of chronic antral gastritis<sup>7–11)</sup>, today classified as *H. pylori*-associated chronic gastritis of the antrum<sup>12,13)</sup>. The close linkage between diffuse antral gastritis infected with *H. pylori* and DU<sup>14)</sup>, and the presence of *H. pylori* in the stomach of more than 90% of patients with DU<sup>7,8,15)</sup> have stimulated studies on the use of anti-*H. pylori* antimicrobial agents in DU<sup>16–21)</sup>. However, the definition of eradication, particularly regarding when to make an assess-

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ment for identifying eradication after the completion of therapy, has not been unified among studies and, moreover, eradication of *H. pylori* is no easy matter.

This study was performed, first, to find when the assessment should be made in order to identify the eradication of *H. pylori*, second, to evaluate the eradication rate of *H. pylori* via each DU treatment regimen and, ultimately, to evaluate whether the DU recurrence rate is reduced by eradication of *H. pylori*.

## METHODS

This study was performed for 190 patients with active DU. Patients with pregnancy or lactation, treatment with colloidal bismuth subcitrate(CBS) or antibiotics within 3 weeks of gastroscopy, severe concomitant diseases, a history of stomach resection, and lack of consent to participate in the study were excluded.

Six biopsy specimens were taken within 5cm of pyloric ring before beginning, immediately after, and 4 weeks after completion of ulcer therapy. The biopsy specimens were analyzed with urease test(CLO test), microscopy of Gram stained mucosal smear, specific culture, and histology after H&E staining as described in detail elsewhere<sup>22,23</sup>. 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.

*H. pylori*-positive patients were randomized to five ulcer treatment groups: cimetidine group (300mg thrice a day), omeprazole group(20mg once a day), CBS group(240mg twice a day), double therapy group(CBS 240mg twice and metronidazole 250mg thrice a day), and triple therapy group(CBS 240mg twice with metronidazole 250mg thrice and amoxicillin 500mg thrice a day), and all of these treatments consisted of 6 weeks course. Four patients of triple therapy group complained of aggravation of epigastric soreness, and another patient of the same group of pruritus with urticaria, respectively, which led to termination of therapy, so these patients were excluded. One patient and another patient of triple therapy group complained of nausea and pruritus, respectively, but these symptoms could be controlled with supportive care and so managed to end the triple therapy. In the other treatment groups, there were no specific complaints during treatment. Some of the patients who

showed *H. pylori*-negative just after therapy became *H. pylori*-positive 4 weeks after completion of therapy, and this indicates that such *H. pylori* negatives are nothing but temporary. Hence all *H. pylori* negatives, detected immediately after therapy, were defined to be negative conversion. On the other hand, we regarded *H. pylori* as eradicated only when the four follow-up *H. pylori* tests, which were carried out 4 weeks after completion of therapy, were all negative.

Follow-up gastroscopy was performed 6, 12, 18, and 24 months after treatment or whenever ulcer symptom recurred for evaluation of ulcer recurrence. To determine what clinical factor affects DU recurrence, gender, smoking, prior recurrence of DU, and eradication of *H. pylori* were evaluated for each group of patients who were followed up for 2 years.

For statistical analysis, first any two treatment groups were selected and chi-square test or, when appropriate, Fisher's exact test was used to compare the treatment rate, eradication rate of *H. pylori* and recurrence rate of DU in one group with that in the other. Chi-square test was also used to evaluate the recurrence rate of DU versus eradication of *H. pylori*, and *p* value for significance was set to be 0.05. The factors such as gender, smoking, prior recurrence of DU, and eradication of *H. pylori*, were incorporated into a stepwise logistic regression model to identify the best fitting model(EGRET, version 0.19.6).

## RESULTS

The study group included 114 men and 76 women(190 patients) with a mean age of  $41.0 \pm 11.7$ yr(range 14-70 years). *H. pylori* was identified in 94.2%(179 of 190 patients) of the patients with DU. The repeated gastroscopy for *H. pylori* tests were taken for 82 of the 179 patients after completion of each treatment to find the *H. pylori* negative conversion and eradication after treatment. Cimetidine group, omeprazole group and CBS group consisted of 12 patients, 13 patients and 11 patients, respectively. Double therapy group and triple therapy group consisted of 18 patients and 28 patients, respectively. Of the 12 patients in the cimetidine group, none showed *H. pylori* negative conversion, so the eradication rate was 0%. Of the 13 patients in the omeprazole group, 2 patients(15.4%) show-

ed *H. pylori* negative conversion but one of two negative converted patients was converted to be positive 4 weeks after completion of therapy, so the eradication rate was 7.7%. Of the 11 patients in the CBS group, 3 patients(27.3%) showed *H. pylori* negative conversion but all of these patients were converted to be positive 4 weeks after completion of therapy, so the eradication rate was 0%. Of the 18 patients in the double therapy group, 13 patients(72.2%) showed *H. pylori* negative conversion but 8 patients persisted to be negative 4 weeks after completion of therapy, so the eradication rate was 44.4%. This eradication rate of the double therapy group was higher than that of the cimetidine, the omeprazole and the CBS group( $p < 0.05$ ). Of the 28 patients of the triple therapy group, 27 patients showed *H. pylori* negative conversion (96.4%) and 25 patients persisted to be negative 4 weeks after completion of therapy, so the eradication rate was 89.3%(Fig. 1). This eradication rate of the triple therapy group was significantly higher than that of the double therapy group( $p < 0.001$ ).

Treatment rate of the cimetidine group, the omeprazole group and the CBS group were 91.7% (11 of 12 patients), 100%(13 of 13 patients) and 72.7%(8 of 11 patients), respectively. That of the double therapy group and the omeprazole group and one patient of the triple therapy group were 88.9%(16 of 18 patients) and 96.4%(27 of

28 patients). There was no statistical significance in the treatment rate between any two groups.

Of the 82 patients analyzed for eradication of *H. pylori*, one patient in the cimetidine group, 3 patients in the CBS group, 2 patients in the double therapy group and one patient in the triple therapy group were excluded in the analysis of DU recurrence rate due to treatment failure. One patient of the omeprazole group and one patient of the triple therapy group in both of whom *H. pylori* was eradicated were excluded due to loss of follow-up. So 73 patients remained for the analysis of DU recurrence rate(Table 1). The DU recurrence rate of the 11 patients in the cimetidine group was 36.4%(4 patients) in 6 months, 63.6%(7 patients) in 1 year, 81.8%(9 patients) in 18 months and 90.9%(10 patients) in 2 years later, respectively. For the 12 patients in the omeprazole group, that was 33.3%(4 patients) in 6 months, 75.0%(9 patients) in 1 year, and 83.3%(10 patients) both in 18 months and 2 years later. All of the recurrence cases in the omeprazole group were patients with the *H. pylori* not eradicated. For the 8 patients in CBS group, that was 37.5%(3 patients) both in 6 months and 1 year, 50.0%(4 patients) in 18 months, and 75.0%(6 patients) in 2 years later. There was no statistical significance between any two groups of the cimetidine group, the omeprazole group and the CBS group. For the 16

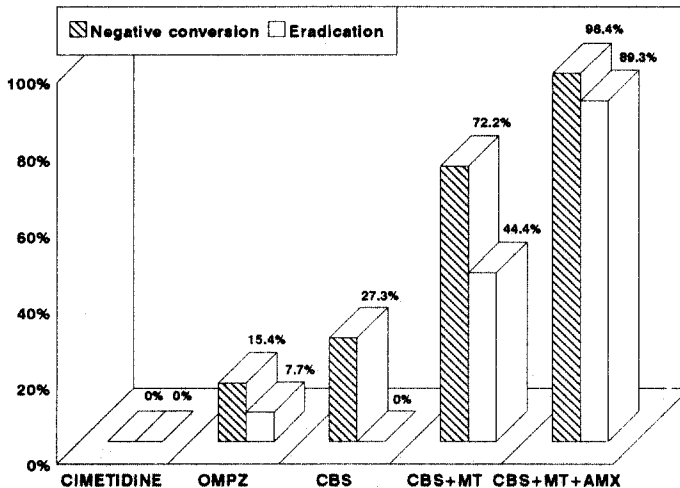


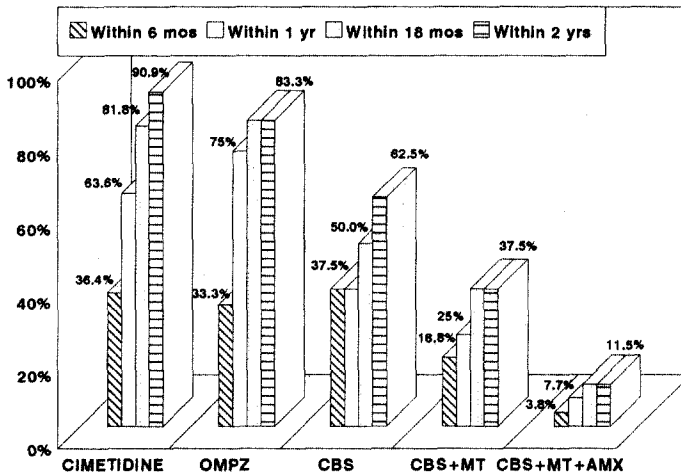
Fig. 1. Negative conversion rate immediately after treatment and eradication rate of *H. pylori* in each treatment group. OMPZ:omeprazole, CBS:colloidal bismth subcitrate, MT; metronidazole, AMX:amoxicillin

**Table 1. Characteristics of each Treatment Group Patients Who were Followed-up for 2 Years**

	Cimetidine	Omeprazole	CBS	CBS+MT	CBS+MT+AMX
No. of patients	11	12	8	16	26
Age(yr)	40.9±11.7	48.7±10.6	34.4±15.0	34.4±12.5	43.6±13.2
Male : Female	7 : 4	7 : 5	7 : 1	13 : 3	19 : 7
Smoker	5(45.5%)	6(50.0%)	5(62.5%)	8(50.0%)	18(69.2%)
Prior recurrence fo DU	7(63.6%)	10(83.3%)	5(62.5%)	7(43.8%)	18(69.2%)
Eradication of <i>H. pylori</i>	0(0%)	0(0%)*	0(0%)	8(50.0)*	23(88.5%)*
DU recurrence 2yrs later	10(90.9%)	10(83.3%)	5(62.5%)	6(37.5%)	3(11.5%)

CBS : Colloidal bismuth subcitrate, MT : metronidazole, AMX : amoxicillin

\* Because 9 patients were excluded in the analysis of DU recurrence due to treatment failure or loss of follow-up of the 82 patients analyzed for eradication of *H. pylori*, there was slight difference between the eradication rate of *H. pylori* in this table and that of Fig. 1.



**Fig. 2.** Recurrence rate of duodenal ulcer in each treatment group. OMPZ;omeprazole, CBS;colloidal bismuth subcitrate, MT; metronidazole, AMX;amoxicillin

patients in the double therapy group, that was 18.8%(3 patients) in 6 months later, 25.0% (4 patients) in 1 year later, and 37.5%(6 patients) both in 18 months and 2 years later. The rate of 1 year of the double therapy group was significantly lower than that of the omeprazole group, and the rates of 18 months and 2 years than those of the cimetidine group and the omeprazole group(Fig. 2). All of the recurrence cases in the double therapy group were patients with *H. pylori* not eradicated. For the 26 patients in the triple therapy group, that was 3.8%(one patient) in 6 months, 7.7%(2 patients) in 1 year, and 11.5%(3 patients) both in 18 months and 2

years later. These rates of triple therapy group were significantly lower than those of the cimetidine group, the omeprazole group and the CBS group, and the rates of 18 months and 2 years than those of the double therapy group, respectively(Fig. 2). One of the 3 recurring patients in the triple therapy group was *H. pylori* eradicated case, and *H. pylori* test, taken when DU recurred 9 months later in this patient, was positive.

In univariate analysis, treatment group, gender, smoking and prior recurrence of DU were not statistically significant and only the eradication of *H. pylori* had significant odds ratio of 0.008( $p <$

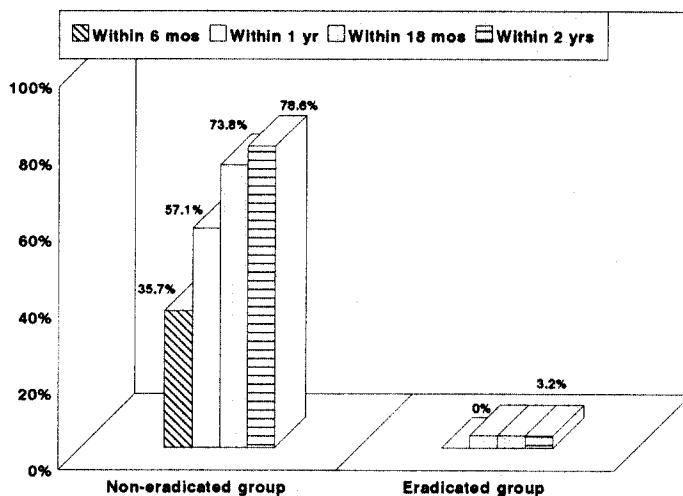


Fig. 3. Recurrence rate of duodenal ulcer according to the eradication of *H. pylori*.

0.001, Table 1). In multivariate analysis, the model including prior recurrence of DU and eradication of *H. pylori* has the highest fitness, and the odds ratio of eradication of *H. pylori* was 0.005 ( $p < 0.001$ , 95% C.I.: 0.0005–0.049). When the 73 patients were categorized into two groups according to the eradication of *H. pylori*, 31 patients were *H. pylori* eradicated and 42 patients were not eradicated. In the 31 *H. pylori* eradicated patients, the DU recurrence rate was 0% in 6 months, 3.2% (one patient) in 1 year, 18 months and 2 years later. In the 42 patients with *H. pylori* not eradicated, that was 35.7% (15 patients) in 6 months, 57.1% (24 patients) in 1 year, 73.8% (31 patients) in 18 months and 78.6% (33 patients) in 2 years later (Fig. 3). In relation to the *H. pylori* eradication, there was found statistical significance in the recurrence rate for the 6 months, the 1 year, the 18 months and the 2 years ( $p < 0.005$ ).

## DISCUSSION

Recurrence of DU after healing is a major problem. It has been reported that recurrence 12 months after initial healing with CBS is significantly less than with  $H_2$ -antagonist, with overall recurrence rates of 54% or 55% and 78% or 85%, respectively<sup>24,31</sup>, and that CBS had anti-*H. pylori* activity both in vivo<sup>10,25</sup> and in vitro<sup>26</sup>. This suggests some relationship between the DU and *H. pylori*. Moreover, *H. pylori* was identified in

about 90% of patients with DU<sup>7,8,15</sup> compared with the fact that it was identified below 10% under the age of 30 years old and about 60% over the age of 60 years old in the asymptomatic subjects of the developed country<sup>27–29</sup>. In the present study, the rate of *H. pylori* identification in patients with DU was 94.2%, compared with the fact that it was identified 21.2% under the age of 20 years old and 69.4% above the age of 20 years old in the asymptomatic Korean subjects<sup>30</sup>. Because of its almost universal prevalence in patients with DU, it has been suggested that *H. pylori* might be the predisposing factor in DU<sup>31,32</sup>, though there is no consensus on how it causes ulcer yet. Because only a minority of those with *H. pylori* have DU, *H. pylori* may be, like acid and pepsin, a permissive factor without which DU seldom occurs but with which an ulcer is far from inevitable. The reports that the eradication of the organism, like the suppression of gastric acidity, resulted in markedly lower rates of recurrence<sup>16–21,33</sup> supported this association of *H. pylori* with DU. However, the definition of eradication has differed among studies, some considered the absence of *H. pylori* immediately after therapy to be evidence of eradication<sup>16,34</sup>, whereas others insist on waiting at least a month<sup>19,35,36</sup>. From the result of this study (Fig. 1), that the negative conversion rate immediately after therapy is higher than that tested 4 weeks after completion of therapy, it is evident that the test to find eradication of *H. pylori* should be done at

least 4 weeks after completion of therapy to exclude subjects in whom the organism is only temporarily suppressed.

Comparing with the cimetidine group whose negative conversion rate was 0%, *H. pylori* in one patient of the omeprazole group was found to be eradicated. In this patient, the *H. pylori* was diagnosed to be positive only by microscopy of Gram stained mucosal smear with mild degree, and this method was reported to be more sensitive than the other tests<sup>37)</sup>, and when we compared the four tests for *H. pylori* used in this study with one another, the microscopy of Gram stained mucosal smear was the most sensitive one and the next was biopsy urease test<sup>38)</sup>. Because the multiplication of *H. pylori* at a high pH is difficult<sup>39, 40)</sup> and the acid suppression of omeprazole is more powerful than H<sub>2</sub>-antagonist<sup>41)</sup>, it is thought that in the case of weak colonization state of *H. pylori*, omeprazole might suppress or eradicate *H. pylori*. Moreover, it was reported that omeprazole eradicated *H. pylori* in individual cases<sup>42)</sup>. In our study the eradication rate of *H. pylori* by CBS alone was 0% and in other reports it was 9.1%<sup>43)</sup> or 10%<sup>19)</sup>. This fact shows that it is difficult to eradicate *H. pylori* by CBS alone. Moreover, Gorbach<sup>44)</sup> reported that bismuth acts as an antimicrobial agent, suppressing the organism but not eliminating it. However, when metronidazole was added to this CBS, the eradication rate was 44.4%, and when amoxicillin was added to double therapy, it became 89.3%, significantly higher than that of the double therapy. Some wonder whether combining a third agent (amoxicillin or tetracyclin) with bismuth and metronidazole adds to the effectiveness of the regimen<sup>32)</sup>, and Weil et al<sup>45)</sup> reported that the eradication rate of *H. pylori* by 4 weeks double therapy was 75%, but we found from our result that the triple therapy is superior to the double therapy for eradicating *H. pylori* in patients with DU.

The DU recurrence rate in each treatment group in 2 years follow-up study, was 90.9% in the cimetidine group, 83.3% in the omeprazole group, and 75.0% in the CBS group. That was 37.5% in the double therapy group which was significantly lower than the cimetidine group and the omeprazole group, and that was 11.5% in triple therapy group which was significantly lower than any single group and the double therapy group (Fig. 2). When we investigated the influence of gender, smoking, prior recurrence of

DU, and eradication of *H. pylori* to determine which clinical factor affects difference of DU recurrence among treatment groups, the factor of eradication of *H. pylori* and prior recurrence influenced the recurrence rate of DU. There was prominent difference in the DU recurrence rate in relation to the eradication of *H. pylori* even when we adjusted for the prior recurrence—the recurrence rate was 3.2% both in 1 year and 2 years later in the 31 patients with *H. pylori* eradicated, and that was 57.1% in 1 year and 78.6% in 2 years later, in the 42 patients with *H. pylori* not eradicated (Fig. 3). This result suggests that, though there is no consensus whether *H. pylori* causes ulcer or not, or how—even if that is true—and though there is no general agreement on how *H. pylori* could be eradicated, it seems to be reasonable for the patients with recurrent DU or DU complication, that can become problems such as in old age, the ulcer treatment including eradication of *H. pylori* should be used than H<sub>2</sub>-antagonist which has not an effect upon the eradication of *H. pylori*.

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