

# The Long-Term Reinfection Rate and the Course of Duodenal Ulcer Disease After Eradication of *Helicobacter pylori* in a Developing Country

Antonio Rollan, M.D., Rossana Giancaspero, Francisco Fuster, M.D., Claudia Acevedo, Cecilia Figueroa, Karen Hola, M.D., Marcela Schulz, M.D., and Ignacio Duarte, M.D.

Department of Gastroenterology and Pathology, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile; and Department of Gastroenterology, Hospital Naval "Almirante Nef," Viña del Mar, Chile

**OBJECTIVE:** The aim of this study was to evaluate the effect of *Helicobacter pylori* (*H. pylori*) eradication on the natural history of duodenal ulcer disease and the reinfection rate after treatment in a developing country.

**METHODS:** A total of 111 *H. pylori*-infected patients with duodenal ulcer were treated with either omeprazole or famotidine plus two antibiotics for 2 wk. Those failed to respond to treatment were retreated with bismuth-based triple therapy.

**RESULTS:** The eradication rate was 76% (95% CI: 67–83%). Eventually, *H. pylori* was eradicated in 96 of the 111 patients (86%), who were followed-up clinically and endoscopically for a mean of 37.2 months. The cumulative reinfection rate after eradication (Kaplan-Meier) was 8%  $\pm$  3% in yr 1, 11%  $\pm$  4% in yr 2, and 13%  $\pm$  4% in yr 3. Nine of the 12 reinfections occurred during yr 1. Recurrence of duodenal ulcer was detected in five patients (5.2%), all of them during yr 1 of follow-up. Histologically, gastritis scores (according to the Sydney system) improved significantly after eradication.

**CONCLUSIONS:** In a high prevalence setting, *H. pylori* eradication and early reinfection rates after treatment are similar to rates observed in a low prevalence environment, whereas the late reinfection rate seems to be higher. However, up to 3 yr after treatment, most treated patients are free of *H. pylori* infection and/or ulcer activity. Even longer follow-up studies are necessary to determine whether specific retreatment policies are necessary to maintain long term eradication in developing countries. (Am J Gastroenterol 2000;95: 50–56. © 2000 by Am. Coll. of Gastroenterology)

## INTRODUCTION

The epidemiology of *Helicobacter pylori* (*H. pylori*) infection differs greatly between the developed and developing worlds. In industrialized countries, infection is acquired at a fairly constant rate of 0.5–2%/yr, reaching a prevalence of 20–40% in the adult population. In developing countries, *H. pylori* is acquired mainly during early childhood at a very

fast rate. By the age of 20 yr, 70–90% of the population is already infected (1–3). These epidemiological differences may influence the outcome of *H. pylori* infection. Early childhood infection seems to be associated with a higher risk for gastric ulcer and gastric cancer, whereas infection in the young adult years may be associated with a relatively increased risk for the development of duodenal ulcer (4, 5). It is not clear whether differences between developed and developing countries, with respect to *H. pylori* infection, may also include the effectiveness of treatment and the long term reinfection rate.

Information about the response to antibiotic treatment, reinfection rate, and long term course of peptic ulcer disease after *H. pylori* eradication has come almost exclusively from studies performed in developed countries. Current regimens in use in those countries eradicate *H. pylori* in >90% of patients (6–8). The reinfection rate is lower than the primary infection rate, reaching 0.2–1%/yr (1) and clearly declines after the first 1 yr (9, 10). Because reinfection is so rare in this low prevalence setting, little is known about its effect on the late clinical course of peptic ulcer disease. The overwhelming reduction in ulcer recurrence rate after treatment has led to the recommendation of *H. pylori* eradication as the standard treatment for peptic ulcer disease (11, 12). However, the epidemiological differences between developed and developing countries may restrict the simple extrapolation of these data as universally representative.

Data on the response to *H. pylori* eradication treatments in developing countries are sparse and fragmentary. Some reports suggest that *H. pylori* eradication rate after treatment is lower in developing compared to developed countries (13–15), whereas others suggest that treatment efficacy is similar (16, 17). Because of the high frequency of infection, overcrowding and lower standards of hygiene, it has been generally assumed that the reinfection rate after treatment is higher in developing countries, reaching as much as 100% according to some authors (18, 19). Few data exist to confirm or refute this assertion (1, 20–22). If proven, the combination of lower eradication and higher reinfection rates may have an important influence

on the long term effects of *H. pylori* eradication in developing countries.

The main purpose of this study was to determine the long term reinfection rate after eradication of *H. pylori* in a country with a high prevalence of *H. pylori* infection (3, 23, 24). In addition, we assessed the impact of this therapeutic strategy on the course of duodenal ulcer disease. Finally, we gathered information about the histological evolution of gastritis after *H. pylori* eradication in Chile, a country with a high prevalence of gastric cancer (25).

## PATIENTS AND METHODS

### *Patient Selection and Treatment*

This study was approved by the ethical committee of the Faculty of Medicine of the Pontificia Universidad Católica de Chile. Two hospitals were involved in this study: the Clinical Hospital of the Pontificia Universidad Católica de Chile, in Santiago, and the Navy hospital "Almirante Nef," in Valparaíso. Both serve mainly a medium income population. Between January and December 1994, patients with endoscopically confirmed active duodenal ulcer (circumscribed break in the duodenal mucosa that measured  $\geq 5$  mm in diameter and had apparent depth) and a positive rapid urease test on gastric antral mucosa were invited to enter the study. Patients with previous gastric surgery, concomitant gastric ulcer, known bleeding diathesis, penicillin allergy, age  $< 16$  yr or  $> 75$  yr, or taking oral anticoagulants were excluded. Socioeconomic status was assessed by means of Graffar's index (26).

Patients were consecutively assigned to two treatment groups. One group (FAM) received famotidine 40 mg once a day for 6 wk. During the first 2 wk, 750 mg of amoxicillin *t.i.d.* and 500 mg of metronidazole *t.i.d.* were added (11). The other group (OAT) received 20 mg omeprazole *b.i.d.* for 4 wk. After the first 2 wk, 750 mg of amoxicillin *b.i.d.* and 500 mg of tinidazole *b.i.d.* were added for the last 14 days. Compliance was evaluated by the pill count method at the middle and at the end of treatment. Those who failed to respond to treatment were crossed-over for a new course of treatment, or received bismuth-based triple therapy (240 mg of bismuth subsalicylate *q.i.d.*, 500 mg of tetracycline *q.i.d.*, and 500 mg of metronidazole *t.i.d.* for 2 wk). After a second failure to respond to treatment, the patient was retired from the study.

The assessment of *H. pylori* status after treatment was done 4–6 wk after the end of treatment. At this time, patients were submitted to a  $^{14}\text{C}$ -urea breath test (UBT) (only those studied in Santiago, where UBT was available), and an endoscopy was performed. To maximize the performance of biopsy-based tests, three sets of three biopsies each, from the greater curve, anterior wall, and posterior wall of gastric antrum were obtained for rapid urease test (RUT), polymerase chain reaction (PCR) detecting *H. pylori* 16S rRNA sequences (27), and histology (Warthin-Starry stain), respectively. A full explanation of the diagnostic

assays employed in this study has been published previously (28). To determine a patient's infection status after treatment, no single test was used as the gold standard (28–30). *H. pylori* infection was considered to be eradicated when a concordant negative result was obtained in at least three of four direct detection tests (rapid urease test,  $^{14}\text{C}$ -UBT, Warthin-Starry stain, and PCR), or in two of three (RUT, histology, and PCR) when UBT was not available. Otherwise the patient was considered to be infected.

### *Follow-up*

*H. pylori*-negative patients were followed-up clinically and endoscopically at 4, 8, and 12 months after eradication to determine ulcer disease activity and *H. pylori* infection status by means of RUT, PCR, Warthin-Starry stain of antral biopsies, and UBT (when available), as described previously. Histological evaluation of serial biopsies was performed blindly according to the Sydney system (31). Inflammation was graded as 0 (absent) when only edema or isolated lymphocytes were observed (32). At the 8- or 12-month control, additional biopsies of the gastric corpus and fundus were also studied histologically. In a previous study we showed that UBT, RUT, and histology have a high (93–98%) and comparable diagnostic accuracy for determining *H. pylori* infection status after treatment (28). Accordingly, a patient was considered reinfected by *H. pylori* if he or she tested positive by any one of these three assays. After 1 yr of follow-up, patients were followed-up yearly, both clinically and by UBT. Endoscopy was performed only if clinically indicated. During the follow-up period patients were advised to avoid self-medication with antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), or proton-pump inhibitors, but antacids or H<sub>2</sub>-blockers were allowed.

### *Statistical Analysis*

The chance of remaining eradicated was calculated by the Kaplan-Meier method. Comparability between groups of patients was tested by  $\chi^2$  analysis, Fisher's exact test, or Student's *t* test, as required. The differences were considered to be significant at  $p < 0.05$ . Data analysis was done by means of EpiInfo 6 (Epidemiology Program Office, CDC, Atlanta, GA) and SAS (SAS Institute, Cary, NC) computer programs.

## RESULTS

### *Patients and Ulcer Disease Characteristics*

A total of 134 eligible patients accepted the invitation to participate in the study and received the indicated treatment. Eighteen patients did not return to the scheduled control, and five patients did not take the medication as indicated, one of them because of a cutaneous reaction. Demographic and clinical data for these 23 noncompliant patients were similar to those of the included patients. A total of 111 patients (83%) who completed the first course of treatment and returned to the eradication control, 4–6 wk

**Table 1.** Characteristics of Patients Studied (n = 111)

Sex (male/female)	80/31
Mean age yr (range)	38 (16–67)
Socioeconomic status (Graffar index)	
Low, n (%)	41 (37)
Medium–low, n (%)	67 (60)
Medium, n (%)	3 (3)
Previous episodes of ulcer disease, n (%)	73 (66)
Previous episodes of ulcer bleeding, n (%)	23 (21)
Current ulcer bleeding, n (%)	27 (24)
Previous treatment	
None, n (%)	37 (33)
Omeprazole, n (%)	8 (7)
H2-blockers, n (%)	66 (60)
Antibiotic use during previous year, n (%)	22 (20)
NSAIDs use during previous month, n (%)	25 (23)
Eradication regimen	
FAM, n (%)	63 (57)
OAT, n (%)	48 (43)
Pooled eradication rate, % (95% CI)*	76 (67–83%)

FAM = famotidine, amoxicillin, and metronidazole; OAT = omeprazole, amoxicillin, and tinidazole (see Materials and Methods for dosage).

\* Eradication rate was similar for both regimens (see Results).

after concluding the treatment with antibiotics or omeprazole, were finally included; 59 were recruited in Santiago and 52 in Valparaíso. Table 1 shows clinical and demographic characteristics of the group. In all, 25 patients (23%) had taken NSAIDs (aspirin ten patients, piroxicam seven, other NSAIDs eight) in the previous month before entrance to the study, 10 of them at least daily for  $\geq 1$  wk. In addition, 22 patients (20%) had taken antibiotics (amoxicillin eight patients, penicillin eight, unidentified four) during the previous 1 yr. All patients with bleeding ulcer were initially hospitalized. Recruitment and sampling of these patients was performed after complete clinical and endoscopic stabilization of the ulcer bleeding.

### Effects of Antibiotic Treatment

As shown in Table 1, 63 patients were treated with famotidine-amoxicillin-metronidazole (FAM) and 48 with omeprazole-amoxicillin-tinidazole (OAT). Both groups were comparable concerning age, gender, socioeconomic level, NSAID ingestion, smoking habits, and previous antibiotic use. Except for amoxicillin allergy in one excluded patient, there were no serious side effects of treatment.

According to the previous definition, at 4–6 wk after treatment, 84 patients (76%; 95% confidence interval [CI]: 67–83%) had *H. pylori* eradicated (*per protocol* result). Eradication rate was not significantly different when comparing either treatment (79% for FAM and 73% for OAT;  $p = 0.43$ ) or residence. Also, no evidence of significant interaction between treatment and city of residence was detected. Neither demographic characteristics nor previous use of NSAIDs or antibiotics were associated with treatment failure.

Of the 27 patients who failed to respond to treatment, 22 were retreated, either with the alternative regimen (n = 7) or with bismuth-based triple therapy (n = 14). The other five

patients refused further treatment and were retired from the study. *H. pylori* was eradicated in 12 of the retreated patients (55%), and they were added to the eradicated group.

### Reinfection Rate During Follow-up

In 96 patients, *H. pylori* infection was considered eradicated after one (n = 84) or two (n = 12) courses of antibiotic treatment. These patients have been followed for a mean of 37.2 months (range 4–46 months). At the time of analysis, 69 patients were re-examined after 1 yr, 53 patients after 2 yr, and 28 patients after 3 yr, giving a total of 260 patient-years of follow-up. The median value of follow-up was 26 months. Another 47 patients (49%) were lost to follow-up over the study period, mainly because of a change of address, 16 during yr 1, 16 during yr 2, and 15 during yr 3.

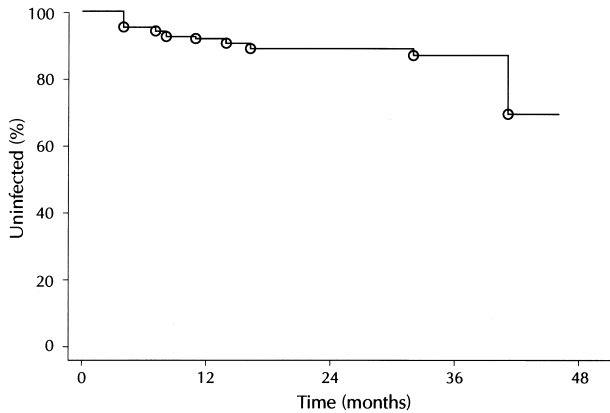
Recurrence of *H. pylori* infection has been documented in 12 patients (12.5%), nine of them during yr 1 (five of them detected at the first posteradication control, which took place 4 months after eradication), one patient during yr 3, and 2 patients during yr 4 of follow-up. Recurrence of *H. pylori* infection was more frequent in those patients who required two courses of treatment to eradicate the infection, compared to those who required only one course of antibiotic therapy (four of 12 and eight of 84 respectively;  $p < 0.05$ ). All reinfections of the first group were detected during yr 1 of follow-up.

Recurrence of infection was not associated with any demographic characteristic, city of residence, or treatment employed. At some time during follow-up, 12 (12.5%) and 16 (17%) of the 96 eradicated patients acknowledged consumption of uncooked vegetables or raw shellfish, respectively; however, in contrast to a previous report (3), this was not associated with the risk of reinfection. The PCR assay, although very sensitive in detecting persistent *H. pylori* infection after treatment (28), was not able to predict those patients in which *H. pylori* reappeared during follow-up. At the eradication control, a positive PCR result was obtained in four of the 12 patients (33%) who later became reinfected, but also in 18 of the 84 patients (21%) who did not show evidence of *H. pylori* infection during the follow-up period ( $p = \text{NS}$ ). At the same control point, active gastritis was detected in six of seven (86%) of the later reinfected patients and in 25 of 45 (56%) of the eradicated patients, for which analyses of biopsies were available ( $p = \text{NS}$ ).

Figure 1 shows the Kaplan-Meier analysis of the risk for *H. pylori* recurrence in this sample, plotted as the probability of remaining free of infection over time. The cumulative risk of recurrence of *H. pylori* infection (value  $\pm$  SE of proportion) was 8%  $\pm$  3% in yr 1, 11%  $\pm$  4% in yr 2, and 13%  $\pm$  4% in yr 3.

### Effect of *H. pylori* Eradication on Ulcer Disease Activity

The ulcer healing rate was the same for the two treatment groups: at the eradication control point, 94% of patients had healed ulcers in the FAM group, as did 92% in the OAT



**Figure 1.** Kaplan-Meier analysis of the risk for *H. pylori* recurrence after eradication, plotted as the probability of remaining free of infection over time.

group ( $p = 0.72$ ). During yr 1 of follow-up, 20 patients were recognized to have taken NSAIDs and six patients PPIs, all of them occasionally (1–2 pills/wk). This occasional NSAID ingestion was not associated with the risk of ulcer recurrence. Five patients received antibiotics because of a respiratory infection. Endoscopic recurrence of duodenal ulcer was demonstrated in five patients (5.2%) during the same period. Two of them acknowledged NSAID ingestion during the previous month, and three referred symptoms suggestive of ulcer syndrome (detected before the endoscopy). Table 2 shows the relationship between ulcer activity and *H. pylori* infection. At the eradication control point, *H. pylori*-positive patients showed a higher frequency of active ulcer compared to *H. pylori*-negative patients (19% and 3.6%, respectively;  $p < 0.05$ ). During the follow-up, the number of reinfected patients was too small to demonstrate statistical significance, but the risk of ulcer recurrence seems clearly to be higher in those patients who became *H. pylori*-positive compared to those who remain eradicated. During the yr 2 and 3 of follow-up, no clinical recurrence of duodenal ulcer has been detected. Endoscopy has been per-

**Table 2.** Relationship Between Ulcer Activity and *H. pylori* (HP) Infection in Patients With Duodenal Ulcer (DU) Treated With Antibiotics

	N With Active DU†/Total n (%)	
	HP-Positive	HP-Negative
Pretreatment‡ (n = 111)	111/111 (100%)	
Posttreatment§ (n = 111)	5/27 (19%)*	3/84 (3.6%)*
4 Months   (n = 91)	1#/5** (20%)	1#/87 (1.1%)
8 Months   (n = 80)	1/2** (50%)	1/78 (1.3%)
12 Months   (n = 74)	0/2** (0%)	1/72 (1.4%)

\*  $p < 0.05$  comparing HP-positive versus HP-negative.

† As determined by upper GI endoscopy.

‡ Before antibiotic treatment.

§ Eradication control, 4–6 wk after antibiotic treatment.

|| Four, 8 and 12 months after HP eradication.

#Patients with NSAID ingestion during this period.

\*\* Patients HP-negative after treatment, who became HP-positive during the follow-up period.

formed in a few patients, mainly because of symptoms suggesting gastroesophageal reflux disease.

**Evolution of Gastritis After Eradication**

Serial histological analysis of gastric biopsies up to 1 yr after treatment was available only for those patients recruited in Santiago (n = 58). Time-course evolution of the histological variables evaluated by the Sydney system is shown in Table 3. Initially, all patients showed chronic inflammation, and 95% of them showed acute inflammation (activity) in antral biopsies. Compared to the initial and immediately posttreatment biopsies, the proportion of patients with activity and/or inflammation on gastric biopsies at 4, 8, and 12 months after eradication showed a highly significant reduction ( $p < 0.0001$ ). Symptomatic status and the risk of subsequent *H. pylori* infection were not different in the small proportion of eradicated patients who persisted with some evidence of chronic or acute inflammation on gastric biopsies after treatment. Atrophy and intestinal metaplasia were initially almost absent in this group of duodenal ulcer patients, and no significant progression was observed over time. As stated before, histological findings at the first posttreatment control point were not different in those patients that got reinfected compared to those that remain eradicated during the follow-up period.

**DISCUSSION**

The eradication of *H. pylori* infection changes dramatically the natural history of peptic ulcer disease and results in a marked reduction or abolition of ulcer relapse (33, 34). The availability of effective eradication treatments and the low reinfection rates observed in developed countries are probably critical factors for obtaining this goal (35). If the eradication rate is low after treatment and/or the reinfection rate is high, and if ulcer recurs after reinfection, the long term effects of *H. pylori* eradication on the natural history of peptic ulcer disease could be nullified (36). The epidemiological situation of *H. pylori* infection in developing countries may be compatible with such a scenario.

The scarce reports about reinfection rates in developing countries are mostly based on short term follow-up of a limited number of patients. Reported reinfection rates range from 0 (22) to 100% (18). Coelho *et al.*, from Brazil, reported that six of 29 eradicated patients (20%) became reinfected after 18 months of follow-up (20). From a subsequent report of 147 patients, reported only in abstract form, Parsonnet estimated a reinfection rate of 8.8%/yr (1). Another report showed a reinfection rate of 4.2% in 47 Chilean patients after 1 yr of follow-up (21), whereas, in Africa, two of 27 patients (3.7%) were shown to be reinfected during a 2-yr period (37). In contrast, Goh *et al.* reported no reinfections in 38 eradicated Southeast Asian patients during a 2-yr period (22). A recent, well-designed study from Guangzhou, China, reported only four reinfections among 184 patients followed up for 2 yr, three of them

**Table 3.** Serial Histological Findings on Gastric Biopsies During Follow-up According to Sidney Classification (31)

Variable	Score	Pretreatment*	Posttreatment†	4 Months‡	8 Months‡	12 Months‡
		(%) n = 56	(%) n = 58	(%) n = 50	(%) n = 46	(%) n = 42
Inflammation	None	0	37	72	76	83
	Mild	100	64	26	22	17
	Moderate	0	0	2	2	0
	Severe	0	0	0	0	0
Activity	None	5	41	92	85	88
	Mild	75	57	6	11	12
	Moderate	18	2	2	4	0
	Severe	2	0	0	0	0
Atrophy	None	93	97	90	87	98
	Mild	7	3	10	11	2
	Moderate	0	0	0	2	0
	Severe	0	0	0	0	0
Intestinal metaplasia	None	100	97	96	98	93
	Mild	0	3	2	2	7
	Moderate	0	0	2	0	0
	Severe	0	0	0	0	0
<i>H. pylori</i>	None	9	77	100	100	100
	Mild	37	9	0	0	0
	Moderate	34	12	0	0	0
	Severe	20	2	0	0	0

\* In two patients initial biopsy was not available.

† At least 1 month after stopping antibiotics or omeprazole.

‡ Includes only eradicated patients.

occurring during the first 6 months, giving an average annual recurrence rate of 1.08%. The authors conclude that reinfection with *H. pylori* is rare also in developing countries where treatment is effective (17). However, the prevalence of *H. pylori* infection in this Chinese population is reported to be 56%, a figure considered as intermediate between that of developed and developing countries (38), and follow-up was only 2 yr. Our results were obtained in a country where *H. pylori* infection is detected in up to 80% of the general population (3, 23, 24), and the mean follow-up period after eradication was >3 yr. To our knowledge, this represents the longest follow-up study reported from a developing country until now, and may be more representative to the epidemiological situation observed in a high prevalence setting.

Our results show that the cumulative risk of reinfection in a group of duodenal ulcer patients from a developing country reached 13% ± 4% after 3 yr of apparent eradication, giving an average annual recurrence rate of 4.3%, which is clearly higher than the 0–1.2%/yr reported from several studies from developed countries (1, 39). Moreover, our data suggest a bimodal distribution for the risk of reinfection. As shown in Figure 1, there is an early component, comprising most of the cases and detected within the first 1 yr after treatment, and a late component, occurring >2 yr after treatment. Most of the reinfected patients were detected at the first control point after therapy, and the reinfection risk was significantly higher for those patients who required two courses of treatment. This suggests that recrudescence, and not true reinfection, explains most of these early reappearances of *H. pylori* infection, although we

followed current recommendations for posttreatment assessment (33, 40). As convincingly shown by Bell and Powell (16), the magnitude of this early component of the reinfection curve is inversely related to the eradication rate after treatment, so any study about reinfection must consider the result of treatment. Some reports suggest that *H. pylori* eradication rate is lower in developing compared to developed countries (13–15). The comparatively higher short term reinfection rate reported in some studies from developing countries may be related to an ineffective therapy (17). The eradication rate we obtained with two nonbismuth-based triple regimens was somewhat lower, although not significantly, than results obtained in developed countries with similar regimens (11). According to the predictions of Bell and Powell (16), our eradication rate of 76% should be associated to a reinfection rate of about 5% at 6 months, very close to the actual 5.2% detected at 4 months. We conclude that, as in developed countries (1, 16, 41), inadequate primary therapy and recrudescence of infection probably accounts for the majority of early reappearances of *H. pylori* infection.

Although our early reinfection rate was as predicted by the eradication rate, our late reinfection rate seems higher than rates observed in developed countries. If, to exclude recrudescence, we accept as eradicated only those patients that were *H. pylori*-negative 1 yr after the end of antimicrobial therapy (9, 42), three of the 69 patients at risk became *H. pylori*-positive at some point during the follow-up. The Kaplan-Meier analysis gives a cumulative reinfection rate of 3.5% ± 3% after 2 yr, or 1.8%/yr. A significant loss to follow-up was noted during the study period. This

should be considered as an independent competing event, because most subjects dropped out for reasons unrelated to the condition under study (emigration) (43). In this situation, the Kaplan-Meier method is adequate to estimate the survival function (44)

A similar study in the United States, also defining reinfection as those cases occurring 1 yr after treatment, showed a reinfection of 5.1% over 5 yr since treatment (three of 59 patients) or a 1.0% *H. pylori* recurrence per year posttreatment (45). Our results suggest that living in a high prevalence setting may be associated with a higher risk of true (late) reinfection. Moreover, within the first 1 yr after treatment, the risk of reinfection is clearly declining over time, but this tendency has not been established for the late component of the reinfection curve. Even after an effective therapy, the "cured once, cured forever" statement (46) may not hold true for *H. pylori*-infected patients living in developing countries.

What is the effect of this higher reinfection risk on the natural history of duodenal ulcer disease after *H. pylori* eradication? Its magnitude seems too low to compromise the overall clinical benefits of *H. pylori* eradication, at least within the 3-yr period considered in our study. In this population of 96 duodenal ulcer patients with a rather aggressive course of disease (66% with previous ulcer episodes, 21% with previous bleeding, and 23% with current bleeding), only five patients had an endoscopic recurrence of duodenal ulcer. No complications were documented during the first 1 yr after eradication, and no clinical ulcer recurrence or complications have been detected after that time. The number of late-reinfected patients is still too small to ascertain the actual long term effect of *H. pylori* reinfection on the clinical course of ulcer disease, although, as shown in Table 2, reinfection seems to be associated with a higher risk of ulcer reactivation. If a significant proportion of eradicated patients become eventually reinfected and experience reactivation of the ulcer disease, then specific policies for *H. pylori* detection and retreatment should be considered in term of cost-benefit analyses in developing countries. Only long enough follow-up studies will elucidate this important question.

Serial histological analysis of gastric biopsies was available only for the first 1 yr after treatment, as no routine endoscopies were scheduled after that time. The marked improvement in gastritis scores is a well described, but not immediate, effect of *H. pylori* eradication (48-50). We (28) and others (50) have previously shown that 4 wk after treatment, a significant proportion of eradicated patients still have evidence of antral gastritis, and in a country with a high prevalence of gastric cancer, it is interesting to follow the evolution of this histological abnormality. However, duodenal ulcer patients are probably not representative of *H. pylori*-infected populations from developing countries, where gastric cancer is more frequent than duodenal ulcer (51). As confirmed by our observations during the follow-up period, duodenal ulcer patients do not develop atrophic

gastritis (25), which probably explains their lower risk of gastric cancer compared to that of the general population or that of gastric ulcer patients (52).

In summary, this long term follow-up study, conducted in a country with a prevalence of *H. pylori* infection that is probably representative of the epidemiological situation observed in the developing world, shows that long term eradication of *H. pylori*, and cure of ulcer disease, can be achieved in most patients if treated with an effective regimen. This supports the recommendation of *H. pylori* eradication as the standard treatment for peptic ulcer disease in developing countries as well. However, it also suggests that late reinfection is a particular problem in this high prevalence setting. Even longer follow-up studies are needed to determine its actual magnitude and final epidemiological significance.

#### ACKNOWLEDGMENT

This study was partially supported by grant 1960780 from Fondo para el Desarrollo de la Ciencia y Tecnología (Fondecyt), Chile.

**Reprint requests and correspondence:** Antonio Rollan, M.D., Department of Gastroenterology, Faculty of Medicine, Pontificia Universidad Católica de Chile, Av. B. O'Higgins 340 Casilla 114-D, Santiago, Chile.

Received Dec. 31, 1998; accepted Sep. 7, 1999.

#### REFERENCES

1. Parsonnet J. The incidence of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 1995;9:45-51.
2. Marshall BJ. *Helicobacter pylori*. *Am J Gastroenterol* 1994; 89:S116-28.
3. Hopkins RJ, Vial PA, Ferreccio C, et al. Seroprevalence of *Helicobacter pylori* in Chile: Vegetables may serve as one route of transmission. *J Infect Dis* 1993;168:222-6.
4. Hansson L-E, Nyrén O, Hsing AW, et al. The risk of stomach cancer in patients with gastric or duodenal ulcer disease. *N Engl J Med* 1996;335:242-9.
5. Parsonnet J. *Helicobacter pylori* in the stomach—A paradox unmasked. *N Engl J Med* 1996;335:278-80.
6. Bazzoli F, Zagari RM, Fossi S, et al. Short-term low dose triple therapy for the eradication of *Helicobacter pylori*. *Eur J Gastroenterol, Hepatol* 1994;6:773-7.
7. Damianos AJ, McGarrity TJ. Treatment strategies for *Helicobacter pylori* infection. *Am Fam Physician* 1997;55:2765-74,2784-6.
8. Chiba N, Matisko A, Sinclair P, et al. *Helicobacter pylori* from bench to bedside. *Can J Gastroenterol* 1997;11:589-96.
9. Borody TJ, Andrews P, Mancuso N, et al. *Helicobacter pylori* reinfection rate, in patients with cured duodenal ulcer. *Am J Gastroenterol* 1994;89:529-32.
10. Cutler AF, Schubert TT. Long-term *Helicobacter pylori* recurrence after successful eradication with triple therapy. *Am J Gastroenterol* 1993;88:1359-61.
11. Hentschel E, Brandstätter G, Dragosics B, et al. Effect of ranitidine, and amoxicillin plus metronidazole on the eradication of *Helicobacter pylori* and the recurrence of duodenal ulcer. *N Engl J Med* 1993;328:408-12.

12. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. *Helicobacter pylori* in Peptic Ulcer Disease. JAMA 1994;272:65-9.
13. Muñoz N, Vivas J, Buiatti E, et al. Chemoprevention trial on precancerous lesions of the stomach in Venezuela: Summary of study design and baseline data. IARC Sci Publ 1996;125-33.
14. Simsek H, Kadayifci A, Tatar G. Low eradication rates of *Helicobacter pylori* with omeprazole plus amoxicillin Combination in a Turkish population. Am J Gastroenterol 1996; 91:1062 (letter).
15. Buiatti E, Muñoz N, Vivas J, et al. Difficulty in eradicating *Helicobacter pylori* in a population at high risk for stomach cancer in Venezuela. Cancer Causes Control 1994;5:249-54.
16. Bell GD, Powell KU. *Helicobacter pylori* reinfection after apparent eradication—the Ipswich experience. Scand J Gastroenterol 1996;215(suppl):96-104.
17. Mitchell HM, Hu P, Chi Y, et al. A low rate of reinfection following effective therapy against *Helicobacter pylori* in a developing nation (China). Gastroenterology 1998;114:256-61.
18. Sack RB, Gyr K. *Helicobacter pylori* in developing world. Lancet 1993;341:1274-5.
19. Guisset M, Coton T, Rey P, et al. *Helicobacter pylori* infection in developing countries. Med Trop 1997;57:77-82.
20. Coelho LG, Passos MC, Chausson Y, et al. Duodenal ulcer and eradication of *Helicobacter pylori* in a developing country. An 18-month follow-up study. Scand J Gastroenterol 1992;27:362-6.
21. Figueroa G, Acuña R, Troncoso M, et al. Low *H. pylori* reinfection rate after triple therapy in Chilean duodenal ulcer patients. Am J Gastroenterol 1996;91:1395-9.
22. Goh KL, Navaratnam P, Peh SC. Reinfection and duodenal ulcer relapse in south-east Asian patients following successful *Helicobacter pylori* eradication: Results of a 2-year follow-up. Eur J Gastroenterol Hepatol 1996;8:1157-60.
23. Figueroa G, Acuna R, Troncoso M, et al. *Helicobacter pylori* infection in Chile. Clin Infect Dis 1997;25:983-9.
24. Russell RG, Wasserman SS, O'Donnoghue M, et al. Serological response to *Helicobacter pylori* among children, and teenagers in northern Chile. Am J Trop Med Hyg 1993;49:189-91.
25. Correa P, Schmidt BA. The relationship between gastric cancer and the ratio of gastric to duodenal ulcer. Aliment Pharmacol Ther 1995;9:13-9.
26. Graffar M. Une méthode de classification sociale d'échantillons de population. Courier 1956;6:445-9.
27. Ho SA, Hoyle JA, Lewis FA, et al. Direct polymerase chain reaction test for detection of *Helicobacter pylori* in humans and animals. J Clin Microbiol 1991;29:2543-9.
28. Rollan A, Giancaspero R, Arrese M, et al. Accuracy of invasive and noninvasive tests to diagnose *Helicobacter pylori* infection after antibiotic treatment. Am J Gastroenterol 1997; 92:1268-74.
29. Cutler AF, Havstad S, Ma CK, et al. Accuracy of invasive and noninvasive tests to diagnose *Helicobacter pylori* infection. Gastroenterology 1995;109:136-41.
30. Fabre R, Sobhani I, Laurent-Puig P, et al. Polymerase chain reaction assay for the detection of *Helicobacter pylori* in gastric biopsy specimens: comparison with culture, rapid urease test, and histopathological tests. Gut 1994;35:905-8.
31. Price AB. The Sydney system: Histological division. J Gastroenterol Hepatol 1991;6:209-22.
32. Zaitoun AM. Histological study of chronic gastritis from the United Arab Emirates using the Sydney system of classification. J Clin Pathol 1994;47:810-5.
33. Hopkins RJ, Girardi LS, Turney EA. Relationship between *Helicobacter pylori* eradication and reduced duodenal and gastric ulcer recurrence: A review. Gastroenterology 1996; 110:1244-52.
34. Forbes GM. *Helicobacter pylori*. Current issues and new directions. J Gastroenterol Hepatol 1997;12:419-24.
35. Blum AL. *Helicobacter pylori* and peptic ulcer disease. Scand J Gastroenterol 1996;214(suppl):24-7.
36. Miehke S, Lehn N, Meining A, et al. *Helicobacter pylori* reinfection is rare in peptic ulcer patients cured by antimicrobial therapy. Eur J Gastroenterol Hepatol 1996;8:1161-3.
37. Louw JA, Lucke W, Jaskiewicz K, et al. *Helicobacter pylori* eradication in the African setting, with special reference to reinfection and duodenal ulcer recurrence. Gut 1995;36: 544-7.
38. Rodrigo Saez L, Riestra Menendez S, Fernandez Rodriguez E, et al. Epidemiological study of the prevalence of *Helicobacter pylori* infection in the general population in Asturias, Spain. Rev Esp Enferm Dig 1997;89:511-22.
39. Miehke S, Bayerdörffer E, Lehn N, et al. Recurrence of duodenal ulcers during five years of follow-up after cure of *Helicobacter pylori* infection. Eur J Gastroenterol Hepatol 1995;7:975-8.
40. Megraud F. How should *Helicobacter pylori* infection be diagnosed? Gastroenterology 1997;113:S93-8.
41. Xia HX, Gilvarry J, Beattie S, et al. Recrudescence of *Helicobacter pylori* infection in patients with healed duodenal ulcer after treatment with different regimens. Am J Gastroenterol 1995;90:1221-5.
42. Forbes GM, Glaser ME, Cullen DJE, et al. Duodenal ulcer treated with *Helicobacter pylori* eradication: Seven-year follow-up. Lancet 1994;343:258-60.
43. Bland JM, Altman DG. Survival probabilities (the Kaplan-Meier method). Br Med J 1998;317:1572.
44. Moeschberger ML, Klein JP. Statistical methods for dependent competing risks. Lifetime Data Anal 1995;1:195-204.
45. Abu-Mahfouz MZ, Prasad VM, Santogade P, et al. *Helicobacter pylori* recurrence after successful eradication. 5-year follow-up in the United States. Am J Gastroenterol 1997;92: 2025-8.
46. van der Ende A, van der Hulst RW, Dankert J, et al. Reinfection versus recrudescence in *Helicobacter pylori* infection. Aliment Pharmacol Ther 1997;11(suppl 1):55-61.
47. Gisbert JP, Mur M, Boixeda D, et al. One-week treatment with omeprazole, clarithromycin, and amoxicillin. High efficacy in the eradication of *Helicobacter pylori* and cicatrization of duodenal ulcer. Med Clin (Barc) 1997;108:524-9.
48. Kuipers EJ. *Helicobacter pylori* and the risk and management of associated diseases: Gastritis, ulcer disease, atrophic gastritis and gastric cancer. Aliment Pharmacol Ther 1997; 11(suppl 1):71-88.
49. van der Hulst RW, van der Ende A, Dekker FW, et al. Effect of *Helicobacter pylori* eradication on gastritis in relation to cagA: A prospective 1-year follow-up study. Gastroenterology 1997;113:25-30.
50. Gisbert JP, Boixeda D, Vila T, et al. Verification of decreased basal, and stimulated serum pepsinogen-I levels is a useful non-invasive method for determining the success of eradication therapy for *Helicobacter pylori*. Scand J Gastroenterol 1996;31:103-10.
51. Burstein M, Monge E, Leon-Barua R, et al. Low peptic ulcer and high gastric cancer prevalence in a developing country with a high prevalence of infection by *Helicobacter pylori*. J Clin Gastroenterol 1991;13:154-6.
52. Blaser MJ, Chyou PH, Nomura A. Age at establishment of *Helicobacter pylori* infection and gastric carcinoma, gastric ulcer, and duodenal ulcer risk. Cancer Res 1995;55:562-5.