

## LACK OF REINFECTION AFTER *HELICOBACTER PYLORI* ERADICATION IN DUODENAL ULCER DISEASE: A PROSPECTIVE STUDY FROM TURIN, ITALY

Rinaldo Pellicano, MD; Franco Palmas, MD; Vincenzo Arena, MD; Brunello Demarchi, MD;  
Nicola Leone, MD; Mario Rizzetto, MD; Antonio Ponzetto, MD

*Helicobacter pylori* (*H. pylori*) infection plays an important role in the cause of duodenal ulcer (DU). Successful cure of the infection modifies the natural history of the disease, leading to a dramatic reduction of recurrence.<sup>1</sup> In the event of a recurrence, DU can be due to reinfection or recrudescence by *H. pylori*, therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), or rare and less clear pathogenetic mechanisms. Differences in *H. pylori* reinfection rates have been reported in several studies,<sup>2-4</sup> and a comparison of strains obtained prior to and after therapy by fingerprint analysis was rarely possible. Therefore, it remains speculative whether true reinfection occurred, or whether it was simply a recrudescence of the previous bacterial infection.<sup>5</sup> The objective of our study was to assess the incidence of reinfection and new ulceration events after demonstrated *Helicobacter pylori* eradication, in a cohort of patients with recurrent duodenal ulcers.

### Materials and Methods

We followed up the natural history of duodenal ulcer disease in 115 patients (83 males, mean age 54.8 years). All of them had a previous diagnosis of recurrent duodenal ulcer documented by endoscopy, and associated *H. pylori* infection as shown by histology and serology.

The starting point of the study was considered the confirmed eradication of the bacterium and DU absence at three months after the end of antibiotic treatment. Each patient underwent the monitoring scheme at 6, 12 and 24 months after the starting point.

The presence of *Helicobacter pylori* infection was judged: 1) by histology (Giemsa staining) on biopsies obtained during endoscopy from the antrum and the fundus; and 2) by measuring specific IgG antibodies against *H. pylori* by a commercial enzyme-linked immunosorbent assay (ELISA).

The infection was considered eradicated when: 1) histology did not demonstrate the bacterium either in the antrum or in the fundus; and 2) the level of circulating anti-*Helicobacter pylori* antibodies decreased in titer by at least 50% of the initial value. The patients whose levels of specific antibodies did not decrease were offered, independent of the histologic result, a <sup>13</sup>C urea breath test (<sup>13</sup>C-UBT), using the European Standard Protocol.<sup>6</sup>

The <sup>13</sup>C-UBT was administered to every patient in case of an ulcer recurrence. We defined reinfection, the positivity for *H. pylori* infection, as a significant increase of specific IgG antibodies, confirmed by evidence on histology and/or positivity on <sup>13</sup>C-UBT at 12 or 24 months after a demonstrated eradication at six months. Patients were excluded from the study if they were on ulcerogenic drugs, or were taking long-term maintenance anti-secretory therapy with proton pump inhibitors or H<sub>2</sub>-receptor blocker drugs.

### Results

Seven of the initial 115 patients were lost to follow-up. None of the 108 patients followed up during the average period of 24 months (range 20-27) had a reinfection. Five patients (4.6%) had a duodenal ulcer recurrence, and their mean age was 57.3 years. Four out of five were male, and none had taken nonsteroidal anti-inflammatory drugs during the follow-up period. Two of the five (both males) were cigarette smokers. No complications of ulcer disease were observed.

### Discussion

Although the main route of *H. pylori* infection remains controversial, previous studies have demonstrated that the infection is apparently acquired in early childhood,<sup>7</sup> thereby causing a lifelong infection of the gastric mucosa, with a wide spectrum of clearly and less clearly demonstrated consequences.<sup>8</sup>

It is well known that "peptic" ulcer disease has a strong relationship with the *H. pylori* infection, probably by a stimulus of excess gastric acid secretion.<sup>9</sup> Perhaps the best evidence of the pathogenic role of *H. pylori* in duodenal

From the Department of Gastroenterology, Molinette Hospital, Turin, Italy.  
Address reprint requests and correspondence to Dr. Pellicano:  
Ambulatorio di Gastroenterologia, via Chiabrera 34, III Piano, 10126 Turin,  
Italy.

Accepted for publication 12 April 1999. Received 28 September 1998.

TABLE 1. Demography of the population studied. Patients with recurrent duodenal ulcer and *Helicobacter pylori* infection.

Patients included (n)	115
Sex (M/F)	83/32
Mean age (yr)	54.8
Follow-up (mn) after <i>H. pylori</i> eradication	24 (range 20-27)

ulcer disease arises from the successes of antibacterial therapy. Previous research<sup>1</sup> on this issue has demonstrated that the effective eradication of the bacterium leads to a significant decrease of both DU, its complications and its recurrences, as compared with controls receiving no antibiotic therapy. In the case of DU recurrence, the cause might be attributed to the failure of bacterial eradication, to a reinfection, or to the use of ulcerogenic drugs.<sup>10</sup> However, a number of patients (5%-10%) have been reported to suffer from DU in the absence of any of these. It seems clear that the pathogenesis of "peptic" ulcer has not yet been fully clarified.

Contrasting reinfection rates have been shown in different studies. Data from developed countries are in accord with a recent study from China,<sup>3</sup> showing that after the eradication of DU, the average annual reinfection rate was 1.08%, while recurrence occurred in 6/184 (3.2%). In two of three patients reinfected, the fingerprint analysis demonstrated nonidentical strains before and after treatment, a clear indication of a newly acquired infection. However, previous studies conducted in South America<sup>11</sup> and Africa<sup>4</sup> suggested higher rates of reinfection.

Our findings in Turin demonstrated that *H. pylori* reinfection appears to be rare in adults (0% in the present paper) after a successful treatment. In support of these results, we were able to confirm our data by a third test,<sup>12</sup> the urea breath test that is considered even more accurate than biopsy-based methods, because it is not as prone to sampling errors.<sup>13</sup> The mean follow-up of two years enabled us to avoid biases linked to a temporary clearance of the bacteria and not to the eradication. Seven of 115 patients (6%) originally included denied consent to the follow-up endoscopies because their symptoms had cleared. Indeed, the compliance of our patients to invasive tests diminished after therapy cleared their symptoms. Hence, even if we were unable to establish a precise diagnosis in these seven patients lost to follow-up, they were symptom-free, and the likelihood of a DU recurrence became extremely remote.

Our experience in Turin confirmed that there is a need for routine eradication in patients with DU and *H. pylori* infection. The cost of antibiotic therapy is far lower when compared with long-term management by antisecretory drugs.<sup>14</sup> The patients in this cohort will be followed-up long-term, to ascertain the benefits of the treatment against *H. pylori*. The main objective will be the reduction of the number of upper GI endoscopies and the overall costs of

management of DU disease by the use of noninvasive techniques, such as specific IgG antibodies titer in serum or the <sup>13</sup>C urea breath test.

In future, the focus on the pathogenesis of ulcers might move on from *H. pylori* infection or NSAIDs, to new multiple risk factors, such as the *a* defect in the production of growth factors and their receptors, and of polyamines.<sup>15</sup> Our findings provide further evidence that the cure of *Helicobacter pylori* infection allows for a dramatic reduction in the frequency of DU recurrences, and that the reinfection in adults is unlikely in our population.

### Acknowledgement

The authors wish to thank Debora Pellicano for her help in recording the data.

### References

- 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.
- Cayla R, Zerbib F, de Mascarel A, Mégraud F, Lamouliatte H. Long-term follow-up of duodenal ulcer patients: recurrence of *H. pylori* infection after eradication (abstract). *Am J Gastroenterol* 1994;89:A257.
- Mitchell HM, Hu P, Chi Y, Chen MH, Li YY, Hazell SL. A low rate of reinfection following effective therapy against *Helicobacter pylori* in a developing nation (China). *Gastroenterology* 1998;114:256-61.
- Louw JA, Lucke W, Jaskiewicz K, Lastovica AJ, Winter TA, Marks IN. *Helicobacter pylori* eradication in the African setting, with special reference to reinfection and duodenal ulcer recurrence. *Gut* 1995;36:544-7.
- Van der Ende A, Van der Hulst RWM, Dankert J, Tytgat GNJ. Reinfection versus recrudescence in *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 1997;11:55-61.
- Logan RPH, Dill S, Bauer FE, Walker MM, Hirschl AM, Gummett PA, et al. The European <sup>13</sup>C-Urea Breath Test for the detection of *Helicobacter pylori*. *Eur J Gastroenterol Hepatol* 1991;3:915-21.
- Cullen DJE, Collins BJ, Christiansen KJ, Epis J, Warren JR, Surveyor I, et al. When is *Helicobacter pylori* infection acquired? *Gut* 1993;34:1681-2.
- Gasbarrini A, Franceschi F, Gasbarrini G, Pola P. Extraintestinal pathology associated with *Helicobacter* infection. *Eur J Gastroenterol Hepatol* 1997;9:231-3.
- McColl KEL, El-Omar EM, Gillen D. The role of *H. pylori* infection in the pathophysiology of duodenal ulcer disease. *J Physiol Pharmacol* 1997;48:287-95.
- Wang GM, Yang KC, Chen TJ, Lee SC. Causative factors of recurrent ulcers after *Helicobacter pylori* eradication: a long-term survey (abstract). *Gut* 1998;43:A100.
- Figuerola G, Acuna R, Troncoso M, Portell DP, Toledo MS, Alborno V, et al. Low *H. pylori* reinfection rate after triple therapy in Chilean duodenal ulcer patients. *Am J Gastroenterol* 1996;91:1395-9.
- Mégraud F. Diagnosis and candidates for treatment of *Helicobacter pylori* infection. How should *Helicobacter pylori* infection be diagnosed? *Gastroenterology* 1997;113:593-8.
- Bayerdörffer E, Oertel H, Lehn N, Kasper G, Mannes GA, Sauerbruch T, et al. Topographic association between active gastritis and *Campylobacter pylori* colonisation. *J Clin Pathol* 1989;42:834-9.
- Jönsson B. Cost-effectiveness of *Helicobacter pylori* eradication therapy in duodenal ulcer disease. *Scand J Gastroenterol* 1996;31:90-5.
- Brzozowski T, Konturek SJ, Majka J, Dembinski A, Drozdowicz D. Epidermal growth factor, polyamines and prostaglandins in the healing of stress-induced gastric lesions in rats. *Dig Dis Sci* 1993;38:276-83.