Active peptic ulcer disease in patients with hepatitis C virus-related cirrhosis: The role of *Helicobacter pylori* infection and portal hypertensive gastropathy

Maria Pina Dore MD PhD, Daniela Mura MD, Stefania Deledda MD, Emmanouil Maragkoudakis MD, Antonella Pironti MD, Giuseppe Realdi MD

MP Dore, D Mura, S Deledda, E Maragkoudakis, A Pironti, G Realdi. Active peptic ulcer disease in patients with hepatitis C virus-related cirrhosis: The role of Helicobacter pylori infection and portal hypertensive gastropathy. Can J Gastroenterol 2004;18(8):521-524.

BACKGROUND & AIM: The relationship between *Helicobacter pylori* infection and peptic ulcer disease in cirrhosis remains controversial. The purpose of the present study was to investigate the role of *H pylori* infection and portal hypertension gastropathy in the prevalence of active peptic ulcer among dyspeptic patients with compensated hepatitis C virus (HCV)-related cirrhosis.

METHODS: Patients undergoing upper endoscopy with compensated HCV-related cirrhosis were enrolled. Child-Pugh's score was determined at the entry. Variceal size was measured endoscopically and the severity of portal hypertensive gastropathy was graded. *H pylori* infection status was determined by urea breath testing and/or histology.

RESULTS: A total of 178 patients positive for HCV (A and B Child-Pugh's score) were prospectively included. The prevalence of *H pylori* infection was 43%. An active peptic ulcer was found in 14 patients (8%) and was significantly more common among those with *H pylori* infection (16% versus 2% in *H pylori* uninfected patients, odds ratio: 8.0). No association was observed between *H pylori* infection and variceal size, or hypertensive gastropathy.

CONCLUSIONS: Patients with compensated cirrhosis and *H pylori* infection showed higher risk of developing a peptic ulcer. Clinical relevance of this result would be that dyspeptic patients with HCV-related cirrhosis may benefit from preventive screening and eradication of *H pylori*, especially those with features of insufficient hemostasis.

Key Words: *Cirrhosis; Congestive gastropathy;* Helicobacter pylori *infection; Portal hypertension*

Ulcère gastroduodénal évolutif chez les patients atteints de cirrhose liée au HCV : Le rôle de l'infection à *Helicobacter pylori* et de la gastropathie liée à l'hypertension portale

HISTORIQUE ET BUT : Le lien entre l'infection à *Helicobacter pylori* et l'ulcère gastroduodénal dans la cirrhose reste controversé. Le but de la présente étude est de vérifier le rôle de l'infection à *H. pylori* et de la gastropathie liée à l'hypertension portale dans la prévalence de l'ulcère gastroduodénal évolutif chez les patients dyspeptiques souffrant d'une cirrhose à HCV compensée.

MÉTHODES : Les patients devant subir une endoscopie des voies digestives supérieures et souffrant d'une cirrhose à HCV compensée ont été inscrits à l'étude. Le score de Child-Pugh a été calculé au moment de l'inscription. Les sites variqueux ont été mesurés par endoscopie et la gravité de la gastropathie liée à l'hypertension portale a été évaluée. L'infection à *H. pylori* a été déterminée par test respiratoire et/ou histologique.

RÉSULTATS : En tout, 178 patients HCV-positifs (score de Child-Pugh A et B) ont été inclus de façon prospective. La prévalence de l'infection à *H. pylori* a été de 43 %. L'ulcère gastroduodénal évolutif a été observé chez 14 patients (8 %) et s'est révélé plus commun chez les sujets porteurs d'une infection à *H. pylori* (16 % versus 2 % chez les patients indemnes de *H. pylori*, risque relatif : 8,0). Aucun lien n'a été observé entre l'infection à *H. pylori* et la taille des varices ou la gastropathie hypertensive.

CONCLUSION : Les patients qui souffrent de cirrhose compensée et d'une infection à *H. pylori* ont semblé exposés à un risque plus élevé à l'égard de l'ulcère gastroduodénal. La portée clinique de ce résultat serait que les patients dyspeptiques souffrant d'une cirrhose à HCV gagneraient à subir un dépistage préventif et un traitement d'éradication de *H. pylori*, surtout s'ils présentent des signes de dysfonction hémostatique.

The prevalence of peptic ulcer in patients with liver cirrhosis is increased compared with that in the general population, suggesting that factors such as congestive gastropathy associated with portal hypertension, impaired mucus and bicarbonate secretion and reduced mucosal prostaglandin levels may increase the risk to develop a gastric lesion (1,2). Although *Helicobacter pylori* is the major cause of peptic ulcers, the pathogenesis of ulcer disease in cirrhosis is unclear. Several studies have reported a relationship between *H pylori* and peptic ulcer in this population (3-5). Calvet et al (6) observed that male sex and *H pylori* seropositivity are significantly related to peptic ulcer disease in cirrhotic patients. Multivariate analysis showed that these factors were independently related to lifetime prevalence of peptic ulcer: male sex (OR 1.56, 95% CI 1.03 to 2.36), and seropositivity for *H pylori* (OR 1.65, 95% CI 1.15 to 2.37) (6). In a meta-analysis of 679 cirrhotic patients, Gisbert et al (7) reported higher prevalence of *H pylori* in patients with peptic ulcer disease

Istituto di Clinica Medica, Università degli Studi di Sassari, Italy
Correspondence and reprints: Professor Maria Pina Dore, Istituto di Clinica Medica, Università di Sassari, Viale San Pietro, 8, Sassari 07100, Italy. Telephone +39-079-229886, fax +39-079-228207, e-mail mpdore@ssmain.uniss.it
Received for publication November 24, 2003. Accepted June 18, 2004

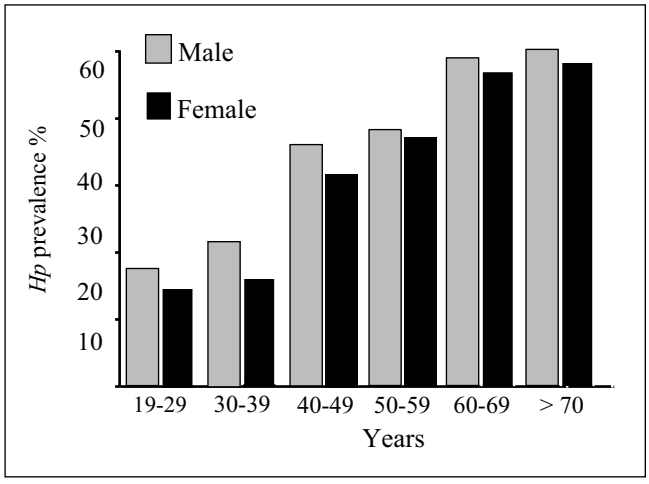

Figure 1) *Prevalence of* Helicobacter pylori (Hp) *infection by age decades in patients with hepatitis* C *virus-related compensated cirrhosis*

(75%; 95% CI 68% to 81%) compared with cirrhotic patients without peptic ulcer (57%; 95% CI 53% to 62%). The OR for the difference was 2.36 (95% CI 1.29 to 4.33). Interestingly, they found that cirrhotic patients with gastric ulcer were more likely to be positive for *H pylori* infection (69% versus 47%), than cirrhotic patients with duodenal ulcer (69% versus 63%) (7). This observation was not confirmed in another meta-analysis by Vergara et al (8) where the risk of developing peptic ulcer disease in cirrhotic *H pylori*-infected patient was almost equal for gastric and duodenal ulcers (OR 2.51; 95% CI 1.38 to 3.40 versus OR 2.17; 95% CI 1.56 to 4.07, respectively) (8).

The present study investigated the role of *H pylori* infection and portal hypertension gastropathy in the prevalence of active peptic ulcer among dyspeptic patients with compensated hepatitis C virus (HCV)-related cirrhosis.

METHODS

Dyspeptic patients with compensated HCV-related cirrhosis enrolled in an interferon treatment trial were recruited for the present study. The diagnosis of cirrhosis was confirmed by a combination of clinical, biochemical and virological markers, ultrasound imaging and histopathological parameters. The clinical severity of liver disease was determined in each patient using the Child-Pugh's classification. Patients with confirmed liver cirrhosis but without ascites, jaundice and encephalopathy were classified as having compensated liver cirrhosis. Patients with uncompensated cirrhosis were excluded from the study because of increased risks of bleeding associated with biopsies of the liver and gastric mucosa. The etiology of cirrhosis was determined by serum hepatitis markers and histopathology features in liver tissue specimens obtained by needle biopsies.

Each patient was interviewed by a physician, and demographic and medical history were recorded. Patients who received bismuth compounds, antisecretory drugs or antibiotics four weeks before upper endoscopy were excluded. Other exclusion criteria included gastrointestinal surgery, regular use of nonsteroidal anti-inflammatory drugs including acetylsalicylic acid, malignancy, severe heart, kidney and lung disease, or prior treatment for *H pylori* infection.

The diagnosis of peptic ulcer was based on the endoscopic detection of a typical ulcer crater in the stomach or duodenum of 0.5 cm or larger in diameter. *H pylori* active infection was defined by ^{13}C-urea breath testing according to a standard protocol (9), and/or identification of the organisms on histological examination of gastric mucosal biopsies obtained at the endoscopy. Two biopsies were taken from the antrum, one from the angulus, and one from the gastric corpus for histological examination. Biopsy specimens were immediately fixed in 10% buffered formalin and subsequently stained with hematoxylin and eosin and giemsa to assess for the presence of *H pylori*.

Variceal size was measured endoscopically by using Beppu's classification subsequently modified by the North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices (NIEC) (10), and the severity of portal hypertensive gastropathy was graded as mild to severe as described by McCormack et al (11):

- none: normal endoscopic appearance of the gastric mucosa;
- mild: mosaic or snake-skin appearance;
- moderate: presence of erythema; or
- severe: erosive or hemorrhagic gastritis.

Informed consent was obtained from all patients included in the study and the protocol was approved by the Ethics Committee of the Faculty of Medicine, University of Sassari, Italy.

Statistical analysis

The Fishers Exact test or χ^2 was used for analysis of categorical data. The T test was used for continuous data. $P<0.05$ was considered to be statistically significant.

RESULTS

A total of 178 consecutive patients with compensated cirrhosis who met the inclusion criteria were prospectively enrolled in the study (104 men; mean age 60.5±10.5 years). All patients had HCV-related cirrhosis based on the presence of anti-HCV immunoglobulin G and HCV-RNA positivity in the serum. The prevalence of Child-Pugh's class A cirrhosis was 46% (81 of 178). In the remaining patients, a compensated functional class B cirrhosis was observed.

The overall prevalence for *H pylori* infection was 43% (76 of 178 patients) (Figure 1). There was no significant difference in the prevalence of *H pylori* infection between men and women (41% versus 44%, respectively). A clear trend of higher prevalence in older patients was observed (Figure 1). The prevalence of *H pylori* infection was numerically greater among patients with Child's B (45%; 44 of 97) than in patients with Child's A cirrhosis (37%; 30 of 81), although the difference was not statistically significant (P=0.3). No significant association was observed between *H pylori* infection and the presence or size of esophageal varices.

The frequency of peptic ulcer disease was 8% in the total population and was statistically more prevalent in *H pylori*-infected cirrhotic patients (eg, 16% [five patients with gastric ulcers, six with duodenal ulcers, and one with both] versus 2% among *H pylori* uninfected patients [two patients with gastric ulcers] [OR 8; 95% CI 53.6 to 45.4]). Peptic ulcer was more prevalent in patients with severe portal hypertensive gastropathy (four of 13) compared with patients with mild gastropathy (six of 89) (31% versus 7%) (Table 1). Eighty-six per cent of all patients with peptic ulcers were positive for *H pylori* infection (Table 1). Gastric mucosal erosions were detected endoscopically in 36% of the population, with a similar prevalence in patients with and without *H pylori* infection (39% versus 33%). Erosions were significantly more common in patients

with severe (92%) than in patients with mild (47%) portal hypertensive gastropathy (12 of 13 versus 42 of 89, respectively; P=0.006) (Table 1). There was no association between severity of portal hypertension gastropathy and *H pylori* infection.

TABLE 1
***Helicobacter pylori* prevalence in peptic ulcer disease and erosions according to the congestive gastropathy grade in patients with liver compensated cirrhosis**

	Mild gastropathy (n=89) Hp^+ ratio (%)		Severe gastropathy (n=13) Hp^+ ratio (%)		No gastropathy (n=76) Hp^+ ratio (%)	
Erosions	23:42	(55)	4:12	(33)	3:10	(30)
Gastric ulcer (GU)	3:3	(100)	2:3	(67)	0:1	(0)
Duodenal ulcers (DU)	2:2	(100)	1:1	(100)	3:3	(100)
GU + DU	1:1	(100)	–	–	–	–

Hp+ H pylori-*positive*

DISCUSSION

Cirrhosis represents a late stage of progressive hepatic fibrosis. Generally, cirrhosis is considered to be irreversible in its advanced stages. At this point, the only option may be liver transplantation. Patients with cirrhosis are susceptible to a variety of complications and their life expectancy is markedly reduced. Once a patient develops complications of cirrhosis, they are considered to have decompensated disease. The high morbidity and mortality of cirrhosis is secondary to these devastating complications. The quality of life and survival of cirrhotic patients can be improved by the prevention and treatment of these complications.

Peptic ulcer prevalence has been reported to be higher in patients with cirrhosis than in controls, with an incidence 10-fold greater than the normal population (12), and has been recognized as the cause of 16% of overall upper intestinal hemorrhages in those patients (13). More importantly, bleeding from a peptic lesion is associated with an increased risk of death in cirrhotic patients of fivefold (14); therefore, prevention of bleeding has to be considered in these patients.

The present study endoscopically evaluated the presence of an active peptic ulcer in a large population of dyspeptic patients with cirrhosis. Overall, the point prevalence of peptic ulcer observed in our study was in agreement with that reported in previous studies, conducted in the same geographical area, among dyspeptic patients positive for *H pylori* infection but negative for HCV infection and cirrhosis (15,16). Importantly, in the present study, peptic ulcer was associated more often with *H pylori* infection (16% versus 2%; OR 8.0). Although peptic ulcer was numerically greater among *H pylori*-infected patients with congestive gastropathy than in patients without gastropathy (9% versus 4%, respectively), the difference was not statistically significant. Available data on the prevalence of *H pylori* infection in cirrhotic patients with peptic ulcer, established using serology, range widely from 44% to 95% and from 50% to 87% for duodenal and gastric ulcer, respectively (17). Siringo et al (18) reported a highly significant difference in the prevalence of *H pylori* infection between cirrhotic patients with and without peptic ulcer disease (95% versus 70%, P=0.0004). In the study by Wu et al (4), the prevalence of *H pylori* infection was higher in cirrhotic patients with peptic ulcer (79%) than in those without (65%), although the difference did not reach the statistical significance. Moreover, the presence of immunoglobulin G anti-*H pylori* was found to be a significant independent risk factor for peptic ulcer development in patients with cirrhosis (6). More specifically, when invasive methods such as histology, rapid urease test and culture were used simultaneously to detect the bacteria, the prevalence of *H pylori* infection was 94% in patients with peptic ulcer disease (19). In our study, *H pylori* infection was not detected in only one patient with gastric ulcer, using histology and ^{13}C-urea breath testing (Table 1).

Congestive gastropathy is a clinically relevant entity because of its significant risk for both chronic occult and overt bleeding in cirrhotic patients. This gastric manifestation of portal hypertension is present in up to 50% of cirrhotic patients (20), and accounts for one-third of bleeding events in these patients (21). In the present study, the prevalence of *H pylori* infection was similar in patients with congestive gastropathy compared with patients without (42% versus 46%), as previously demonstrated (22,23), and peptic ulcer disease was slightly more prevalent among *H pylori*-infected patients with congestive gastropathy than in infected patients without congestive gastropathy. Overall, observations from the literature seem to indicate that congestive gastropathy and *H pylori* infection are independent factors that may affect the gastric mucosa. A possible synergism between *H pylori* infection and portal hypertensive gastropathy leading to peptic ulcer disease may be present (17). Factors such as a reduced production of bile salts and the impairment of gastric mucosal defense due to the portal hypertensive gastropathy in cirrhotic patients may allow *H pylori* to be more aggressive in the stomach and duodenal bulb than in subjects without cirrhosis.

CONCLUSIONS

The clinical relevance of these results would be that dyspeptic patients with HCV-related cirrhosis might benefit from preventive screening and eradication of *H pylori*, especially those with congestive gastropathy and stigmata of insufficient hemostasis.

It has been evaluated that treatment of *H pylori* infection is more effective than antisecretory noneradicating therapy (with or without long-term maintenance antisecretory therapy) in preventing recurrent bleeding from peptic ulcer (24). The eradication of *H pylori* may have several theoretical advantages among this population group, including prevention of *H pylori*-related peptic ulcers and ulcer complications as well as decreasing the burden of dyspeptic symptoms.

REFERENCES

1. Zullo A, Rinaldi V, Meddi P, et al. *Helicobacter pylori* infection in dyspeptic cirrhotic patients. Hepatogastroenterology 1999;46:395-400.
2. Kitano S, Dolgor B. Does portal hypertension contribute to the pathogenesis of gastric ulcer associated with liver cirrhosis? J Gastroenterol 2000;35:79-86.
3. Chen JJ, Changchien CS, Tai DI, Chiou SS, Lee CM, Kuo CH. Role of *Helicobacter pylori* in cirrhotic patients with peptic ulcer. A serological study. Dig Dis Sci 1994;39:1565-8.
4. Wu CS, Lin CY, Liaw YF. *Helicobacter pylori* in cirrhotic patients with peptic ulcer disease: A prospective, case controlled study. Gastrointest Endosc 1995;42:424-7.
5. Tsai CJ. *Helicobacter pylori* infection and peptic ulcer disease in cirrhosis. Dig Dis Sci 1998;43:1219-25.
6. Calvet X, Navarro M, Gil M, et al. Epidemiology of peptic ulcer disease in cirrhotic patients: Role of *Helicobacter pylori* infection. Am J Gastroenterol 1998;93:2501-7.

7. Gisbert JP, Moreno-Otero R, Pajares JM. [Prevalence of *Helicobacter pylori* infection in chronic liver disease and relationship with its complications: Systematic review and meta-analysis.] Med Clin (Barc) 2002;119:464-74. Spanish
8. Vergara M, Calvet X, Roque M. *Helicobacter pylori* is a risk factor for peptic ulcer disease in cirrhotic patients. A meta-analysis. Eur J Gastroenterol Hepatol 2002;14:717-22.
9. Dore MP, Negrini R, Tadeu V, et al. Novel monoclonal antibody-based *Helicobacter pylori* stool antigen test. Helicobacter 2004;9:228-32.
10. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices: Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med 1988;319:983-9.
11. McCormack TT, Sims J, Eyre-Brook I, et al. Gastric lesions in portal hypertension: Inflammatory gastritis or congestive gastropathy? Gut 1985;26:1226-32.
12. Soll A. Gastric, duodenal and stress ulcer. In: Sleisenger MH, Fordtran JS, eds. Gastrointestinal Disease. Philadelphia: Saunders, 1993:580-679.
13. Dagradi AE, Mehler R, Tan DT, Stempien SJ. Sources of upper gastrointestinal bleeding in patients with liver cirrhosis and large esophagogastric varices. Am J Gastroenterol 1970;54:458-63.
14. Bonnevie O. Causes of death in duodenal and gastric ulcer. Gastroenterology 1977;73:1000-4.
15. Dore MP, Piana A, Carta M, et al. Amoxycillin resistance is one reason for failure of amoxycillin-omeprazole treatment of *Helicobacter pylori* infection. Aliment Pharmacol Ther 1998;12:635-9.
16. Realdi G, Dore MP, Piana A, et al. Pretreatment antibiotic resistance in *Helicobacter pylori* infection: Results of three randomized controlled studies. Helicobacter 1999;4:106-12.
17. Zullo A, Hassan C, Morini S. *Helicobacter pylori* infection in patients with liver cirrhosis: Facts and fictions. Dig Liver Dis 2003;35:197-205.
18. Siringo S, Vaira D, Menegatti M, et al. High prevalence of *Helicobacter pylori* in liver cirrhosis: Relationship with clinical and endoscopic features and the risk of peptic ulcer. Dig Dis Sci 1997;42:2024-30.
19. Kirchner GI, Wagner S, Schmidt H, et al. Pathogenetic role of *Helicobacter pylori* infection in chronic liver disease. Gastroenterology 1996;110:A157. (Abst)
20. Parikh SS, Desai SB, Prabhu SR, et al. Congestive gastropathy: factors influencing development, endoscopic features, *Helicobacter pylori* infection, and microvessel changes. Am J Gastroenterol 1994;89:1036-42.
21. D'Amico G, Montalbano L, Traina M, et al. Natural history of congestive gastropathy in cirrhosis. The Liver Study Group of V. Cervello Hospital. Gastroenterology 1990;99:1558-64.
22. Bahnacy A, Kupcsulik P, Eles Z, Jaray B, Flautner L. *Helicobacter pylori* infection in congestive gastropathy. Helicobacter 1996;1:168-71.
23. Balan KK, Jones AT, Roberts NB, Pearson JP, Critchley M, Jenkins SA. The effects of *Helicobacter pylori* colonization on gastric function and the incidence of portal hypertensive gastropathy in patients with cirrhosis of the liver. Am J Gastroenterol 1996;91:1400-6.
24. Gisbert J, Khorrami S, Carballo F, Calvet X, Gene E, Dominguez-Munoz J. *H pylori* eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer. Cochrane Database Syst Rev 2004;2:CD004062.