Proton pump inhibitors in cirrhosis: Tradition or evidence based practice?

Francesca Lodato, Francesco Azzaroli, Maria Di Girolamo, Valentina Feletti, Paolo Cecinato, Andrea Lisotti, Davide Festi, Enrico Roda, Giuseppe Mazzella

Francesca Lodato, Francesco Azzaroli, Maria Di Girolamo, Valentina Feletti, Paolo Cecinato, Andrea Lisotti, Davide Festi, Enrico Roda, Giuseppe Mazzella, Department of Internal Medicine and Gastroenterology, Gastroenterology Unit, University of Bologna, Bologna 40138, Italy
Author contributions: Lodato F, Azzaroli F and Mazzella G wrote the paper; Di Girolamo M, Feletti V, Cecinato P, Lisotti A did the bibliographic research; Festi D and Roda E contributed in writing and reviewing the paper.
Correspondence to: Francesca Lodato, Dr, Dipartimento di Medicina Interna e Gastroenterologia, U.O. di Gastroenterologia, Via Massarenti 9, Bologna 40138, Italy. francesca.lodato@unibo.it

Abstract
Proton Pump Inhibitors (PPI) are very effective in inhibiting acid secretion and are extensively used in many acid related diseases. They are also often used in patients with cirrhosis sometimes in the absence of a specific acid related disease, with the aim of preventing peptic complications in patients with variceal or hypertensive gastropathic bleeding receiving multidrug treatment. Contradicting reports support their use in cirrhosis and evidence of their efficacy in this condition is poor. Moreover there are convincing papers suggesting that acid secretion is reduced in patients with liver cirrhosis. With regard to Helicobacter pylori (H pylori) infection, its prevalence in patients with cirrhosis is largely variable among different studies, and it seems that H pylori eradication does not prevent gastro-duodenal ulcer formation and bleeding. With regard to the prevention and treatment of oesophageal complications after banding or sclerotherapy of oesophageal varices, there is little evidence for a protective role of PPI. Moreover, due to liver metabolism of PPI, the dose of most available PPIs should be reduced in cirrhotics. In conclusion, the use of this class of drugs seems more habit related than evidence-based eventually leading to an increase in health costs.

Key words: Proton pump inhibitors; Cirrhosis; Helicobacter pylori; Peptic ulcer; CYP P450

Peer reviewer: Katja Breitkopf, Dr, Department of Medicine II, University Hospital Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, Mannheim 68167, Germany
Lodato F, Azzaroli F, Di Girolamo M, Feletti V, Cecinato P, Lisotti A, Festi D, Roda E, Mazzella G. Proton pump inhibitors in cirrhosis: Tradition or evidence based practice? World J Gastroenterol 2008; 14(19): 2980-2985 Available from: URL: http://www.wjgnet.com/1007-9327/14/2980.asp DOI: http://dx.doi.org/10.3748/wjg.14.2980

INTRODUCTION
Proton Pump Inhibitors (PPI) are extensively used in different acid related diseases. Their efficacy in inhibiting acid secretion is well known[1-4], and the use of this class of drugs has increased worldwide. They act through inhibition of the H⁺/K⁺ ATPase of parietal cells producing the so called “inhibitory complex” and blocking HCl secretion[5]. They are metabolized in the liver by the CYP450 cytochrome[6].

PPI are also often used in patients with liver cirrhosis sometimes in the absence of a specific acid related disease, with the aim of preventing peptic complications in patients with variceal or hypertensive gastropathic bleeding receiving multidrug treatment.

The aim of this editorial is to revise the efficacy and safety profile of PPI in patients with liver cirrhosis.

GASTRIC ACID SECRETION AND LIVER CIRRHOSIS
The role of gastric secretion in cirrhosis is controversial. Some studies report reduced acid production[7-10] while others reported normal production[11,12]. The evaluation of 24-h acidity by gastric ph-metry in 49 patients with cirrhosis showed a marked hypoaclidity in patients with cirrhosis compared to controls, mainly during the night hours[10]. This may depend on hemodynamic alterations consequent to portal hypertension and is supported by experimental studies showing reduced gastric acid secretion in animals with portal hypertension[13,14]. These observations rule out the relevance of gastric acid in the pathogenesis of ulcers in cirrhotics.

Gastrin, the gastric hormone whose secretion is regulated by intragastric pH, and that regulates the production of HCl and pepsin, is partially metabolized...
by the liver and mainly by the kidneys. Gastrin is elevated in serum of patients with Helicobacter pylori (H pylori) infection or atrophic gastritis. Few studies have evaluated gastrin levels in cirrhosis, and their contribution towards understanding the pathophysiology of gastric acid secretion is very limited. Avgeronos et al\(^\text{[30]}\) evaluated the urinary gastrin output in patients with cirrhosis with and without hepatorenal syndrome. Serum gastrin levels were higher in cirrhotics compared to controls; and in cirrhotics with hepatorenal syndrome the difference was greater suggesting that impaired urinary gastrin secretion may contribute to their hypergastrinemia. The same results were found by Lo et al\(^\text{[31]}\) who also showed a significantly lower maximal pepsin output in cirrhotics compared to controls.

Pregastrin and gastrin serum levels have been reported to be significantly higher in patients with cirrhosis of any Child-Pugh class compared to controls while there are no differences between controls and patients with chronic hepatitis B or C\(^\text{[24]}\). Indeed, it is important to note that in this study, the prevalence of H pylori infection in cirrhotic patients was 83% versus 50% in controls. Therefore, it is not clear whether the difference in progastrin and gastrin level was due to reduced liver metabolism, to H pylori infection, or both. In summary, gastrin increase in patients with liver cirrhosis could be related to: (1) impaired hepatic gastrin catabolism; (2) impaired renal function, at least in those with HRS; (3) gastric mucosal alteration due to gastropathy-related cirrhosis.

### PEPTIC ULCERS AND LIVER CIRRHOSIS

Many authors reported an increased prevalence of peptic ulcers in patients with cirrhosis\(^\text{[21,22]}\) and it was shown that cirrhotics have an increased risk of developing gastric or duodenal ulcers during an interval of one year compared to non cirrhotics\(^\text{[31]}\). The prevalence of peptic ulcers ranges between 4.6% and 21% in patients with cirrhosis\(^\text{[21,22,24,30-39]}\) (Table 1). However, the pathogenesis of this finding is far from being elucidated and different factors have been proposed in relation to increased ulcer prevalence in patients with cirrhosis. Furthermore the prevalence of duodenal and gastric ulcers in patients with liver cirrhosis increases with disease progression\(^\text{[27]}\) (Table 2). Several theories have been postulated. It has been demonstrated that the gastric mucosa in rats with portal hypertension is more susceptible to aggressive agents such as bile acids, aspirin and alcohol\(^\text{[29]}\). Some investigators have attributed to portal hypertension itself the increased risk of peptic ulcer\(^\text{[29]}\), nevertheless no study has clarified the pathogenesis of peptic ulceration in cirrhosis.

### H PYLORI IN PATIENTS WITH LIVER CIRRHOSIS

The prevalence of H pylori in patients with cirrhosis has been investigated in many epidemiological studies with values ranging from 27% to 89%\(^\text{[24,27,30-33]}\). This large variability may be due to the test used to evaluate H pylori infection. In the study with the largest prevalence of H pylori infection, values were obtained by titration of serum IgG, against H pylori. The tests usually used for evaluating the presence of H pylori should be revised since haemodynamic alterations in cirrhosis could impair the results of urea 13C BT, and hypergammaglobulinemia typical of cirrhosis, might produce a false positive test\(^\text{[24-28]}\). Italian studies generally and sometimes significantly showed a higher prevalence than in non cirrhotic patients, while studies from Taiwan failed to show a similar trend. When evaluating the prevalence of H pylori infection in cirrhotics there seems to be no relationship between the aetiology of cirrhosis and the prevalence of H pylori evaluated by determination of serum IgG\(^\text{[24]}\). The role of H pylori in determining peptic ulceration in cirrhosis is controversial: some authors conclude that the increased risk of gastroduodenal ulcer is not related to H pylori infection, whilst others conclude that peptic disease and non-ulcer dyspepsia are firmly linked to H pylori infection\(^\text{[32,39-41]}\). A meta-analysis showed an increased risk of ulcers developing in patients with H pylori infection and cirrhosis\(^\text{[42]}\).

If H pylori infection were an etiopathological factor implicated in digestive bleeding in cirrhosis, eradication of infection would decrease the risk of ulcer recurrence. However a study aiming to investigate the role of H pylori eradication in cirrhotics demonstrated a similar recurrence rate between cirrhotics with successful H pylori eradication and those with active H pylori infection\(^\text{[43]}\). In conclusion, the role of H pylori infection in the occurrence of gastric or duodenal ulcers or in determining digestive bleeding in the setting of liver cirrhosis is still unclear.

### ESOPHAGEAL DISORDERS AND LIVER CIRRHOSIS

It has been postulated in the past, that gastro-esophageal reflux may contribute to oesophagitis and variceal

---

### Table 1 Prevalence of peptic ulcer in patients with liver cirrhosis

| Investigator | Number of patients | Gastric ulcer prevalence (%) |
|-------------|--------------------|-----------------------------|
| Stringo, 1995 | 324 | 4.6 |
| Chen, 1996    | 245 | 20.8 |
| Tsai, 1998    | 130 | 16.1 |
| Kirk, 1980    | 163 | 14.7 |
| Rabinovitz, 1990 | 216 | 7.8 |

### Table 2 Gastric and duodenal ulcer in patients with liver cirrhosis according to the severity of portal hypertension (from Wu et al 1995)

|                     | Controls (n = 60) | Compensated cirrhosis (n = 60) | Decompensated cirrhosis (n = 60) | P |
|---------------------|------------------|-------------------------------|---------------------------------|---|
|                     | n     | %     | n     | %     | n     | %     |         |
| Duodenal ulcer      | 2     | 3.3   | 10    | 16.7  | 8     | 13.3  | 0.046   |
| Gastric ulcer       | 1     | 1.7   | 2     | 3.3   | 9     | 15.0  | 0.006   |
| All ulcers          | 3     | 5.0   | 12    | 20.0  | 17    | 28.3  | 0.003   |
bleeding in cirrhotic patients\cite{49}, and acid reflux could be exacerbated by the presence of ascites and water retention\cite{50}. More recent papers do not confirm these hypotheses\cite{46,47} and report a high incidence of gastro-esophageal reflux only in patients with alcoholic cirrhosis, though the presence of reflux did not correlate with disease severity or bleeding episodes\cite{48}. Functional studies showed decreased lower esophageal sphincter function with low amplitude of primary peristalsis and acid clearance in patients with large varices\cite{49-53}. These phenomena could also be due to a mechanical effect of the presence of varices. In conclusion, it is unclear whether the presence of cirrhosis itself could predispose to the onset of gastro-esophageal reflux. It seems that the presence of varices is related to reflux episodes, although it is not clear whether these might contribute to bleeding from varices.

Another more studied point is the fact that endoscopic treatment for variceal bleeding or prevention of bleeding varices, may produce oesophageal motility dysfunction. Several studies evaluated the effect of endoscopic variceal sclerosis therapy (EVS) on gastro-esophageal reflux. Some authors suggest that endoscopic treatment produces an acute impairment of oesophageal motility which is partially restored after days or weeks\cite{52-54}, others suggest that sclerosis therapy produce a chemical esophagitis that impairs oesophageal motility and in turn may favour acid related reflux esophagitis\cite{55}. It seems that endoscopic variceal ligation (EVL) is safer in terms of oesophageal dysmotility induction when compared to EVS\cite{56,59}. The reason for this finding is unclear. Autopsy studies after EVS show the presence of obliteration of the submucosal vascular channels, fibrosis and oesophagitis\cite{50} reflecting the necrosis induced by the sclerosing agent. The inflammation caused by EVS may justify motor dysfunctions and acid reflux. Agerinos et al\cite{61} showed that EVL produces a higher early increase in lower oesophageal sphincter pressure, and this might prevent gastro-esophageal reflux.

Apart from the pathogenesis of motor dysfunction following EVS and EVL, these procedures are related to local complications such as oesophageal ulcerations, strictures and perforations\cite{62,63}, although from this point of view, EVL seem to be safer than EVS\cite{59,50}. Uncontrolled non randomized studies, showed that PPI may have a role in the prevention and healing of post-EVS ulcerations\cite{56,59} although this was not confirmed by other authors\cite{70}. With regard to post EVL ulcers, the incidence is between 2% to 5%\cite{71,72}. Pantoprazole has been shown to reduce the size of ulcers in patients undergoing elective band ligation, but not the rate of occurrence or the symptoms\cite{73}. Given the relatively benign nature of the intervention, the authors conclude that PPI treatment is advisable in patients undergoing elective EVL.

In summary, expert opinion based on evidence of scarce value, advise PPI use in cirrhotic patients undergoing endoscopic treatment for varices, especially when treatment is performed by EVS, to prevent gastro-esophageal reflux which may worsen the procedure related inflammation or ulceration.

**PPI SAFETY IN CIRRHOTIC PATIENTS**

Acute hepatitis due to PPI use is described in the literature for most PPIs available on the market\cite{74-77}. All PPIs are metabolized in the liver by cytochrome CYP450; two isoenzymes are involved in PPI metabolism (CYP2C19 and CYP3A4)\cite{40}. CYP2C19 is the main metabolic pathway while CYP3A4 is activated only when the other enzyme is saturated\cite{80}. Nevertheless, the affinity of each isoenzyme for different PPIs is different and rabeprazole is metabolized mainly by a non enzymatic pathway. There are two CYP2C19 phenotypes: extensive and poor metabolisers\cite{81-83}. The poor phenotype is present in 2%-6% of Caucasians and 20% of the Asian population. Poor metabolisers have higher plasma levels of PPI, which could lead to higher efficacy but also to potential adverse events. The effects of these genotypes varies according to the specific PPI used and in general is greater when using omeprazole decreasing progressively to lansoprazole, esomeprazole, pantoprazole and finally rabeprazole\cite{84}.

PPI are metabolized in the liver and secreted by the kidney. Renal impairment has minimal effect on PPI clearance, and therefore there is no need to reduce PPI dosage in patients with renal diseases\cite{80,84}. This is not the case for liver impairment in which the Area under the Curve (AUC) of PPIs increases and their half-life becomes 4 h to 8 h greater\cite{86} with increasing risk of accumulation. This effect was also seen with rabeprazole\cite{85} although a dose reduction seems to be unnecessary with a 20 mg, once daily dose in patients with mild to moderate liver cirrhosis. When using other PPIs or rabeprazole at 40 mg/d dose, dose reduction in patients with cirrhosis is advisable.

**CONCLUSION**

PPI drugs are extensively used in clinical practice in cirrhotic patients. Besides habit, the evidence that PPI are necessary in most indications is very weak. First of all, there is convincing evidence that acid secretion is reduced in patients with liver cirrhosis. This is mainly due to the presence of hypertensive gastropathy for which there is no evidence of any efficacy of PPI. With regard to *H pylori* infection, its prevalence in patients with cirrhosis is largely variable among different studies, probably as a result of different diagnostic tests used. We believe that the condition of hypochloridemia of cirrhotics makes it more probable that its prevalence is lower than in the general population. Nevertheless, it seems that *H pylori* eradication does not prevent from gastro-duodenal ulcer formation and bleeding.

It is probable that the main reason for PPI use in cirrhosis might be the prevention and treatment of oesophageal complications after banding or sclerotherapy of oesophageal varices. However even in this case evidence for a protective role of PPI are scarce. When using PPI in cirrhotic patients, the dose should be reduced in consideration of the increased half-life of these drugs in this group of patients. Dose adjustment does not seem necessary when using rabeprazole at a 20 mg, once daily
REFERENCES

1. Bamberg P, Caswell CM, Frame MH, Lam SK, Wong EC. A meta-analysis comparing the efficacy of omeprazole with H2-receptor antagonists for acute treatment of duodenal ulcer in Asian patients. J Gastroenterol Hepatol 1992; 7: 577-585
2. Eriksson S, Langstrom G, Rikner L, Carlsson R, Naesdal J. Omeprazole and H2-receptor antagonists in the acute treatment of duodenal ulcer, gastric ulcer and reflux oesophagitis: a meta-analysis. Eur J Gastroenterol Hepatol 1995; 7: 467-475
3. Gisbert JP, Gonzalez L, Calvet X, Roque M, Gabriel R, Pajares JM. Proton pump inhibitors versus H2-antagonists: a meta-analysis of their efficacy in treating bleeding peptic ulcer. Aliment Pharmacol Ther 2001; 15: 917-926
4. Gisbert JP, Khorrami S, Calvet X, Gabriel R, Carballo F, Pajares JM. Meta-analysis: proton pump inhibitors vs. H2-receptor antagonists--their efficacy with antibiotics in Helicobacter pylori eradication. Aliment Pharmacol Ther 2003; 18: 757-766
5. Sachs G, Shin JM, Briving C, Wallmark B, Hersey S. The pharmacology of the gastric acid pump: the H+-, K+-ATPase. Annu Rev Pharmacol Toxicol 1995; 35: 277-305
6. Andersson T, Cederberg C, Edvardsson G, Heggelund A, Lundborg P. Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. Clin Pharmacol Ther 1990; 47: 79-85
7. Fraser AG, Pounder RE, Burroughs AK. Gastric secretion and peptic ulceration in cirrhosis. J Hepatol 1993; 19: 171-182
8. Scobie BA, Summerskill WH. Reduced Gastric Acid Output in Cirrhosis: Quantitation and Relationships. Gut 1964; 5: 422-428
9. Lam SK. Hypergastrinaemia in cirrhosis of the liver. Gut 1976; 17: 700-708
10. Gaur SK, Vaira D, Menegatti F, Piscaglia F, Calvet X, Gabriel R, Pajares JM. Gastric secretion and peptic ulcer following portacaval shunt. J Gastroenterol Hepatol 1990; 5: 232-239
11. Tabaqchali S, Dawson AM. Peptic Ulcer and Gastric Secretion in Patients with Liver Disease. Gut 1964; 5: 417-421
12. Orloff MJ, Chandler JG, Alderman SJ, Keiter JE, Rosen H. Gastric secretion and peptic ulcer following portacaval shunt in man. Ann Surg 1989; 170: 515-527
13. Lenz HJ, Struck T, Goret H, Koss MA, Eysselein VE, Walsh JH, Isenberg J. Increased sensitivity of gastric acid secretion to gastrin in cirrhotic patients with portacaval shunt. J Clin Invest 1987; 79: 1120-1124
14. Savarino V, Mela GS, Zentilin P, Mansi C, Mele MR, Vigneri S, Cutela P, Vassallo A, Dallorto E, Celle G. Evaluation of 24-hour gastric acidity in patients with hepatic cirrhosis. J Hepatol 1996; 25: 152-157
15. Kaur S, Kaur U, Agnihotri N, Tandon CD, Majumdar S. Modulation of acid secretion in common bile duct ligated-related gastropathy in Wistar rats. J Gastroenterol Hepatol 2001; 16: 755-762
16. Agnihotri N, Kaur U, Dhawan V, Dilawari JB. Extrahepatic portal hypertensive gastropathy in Wistar rats: modulation of acid secretion in isolated parenial cells. Dig Dis Sci 1998; 43: 56-66
17. Avgserinos A, Dimitriou-Voudri Y, Adamopoulos A, Papadimitriou N, Voudris B, Rekoumis G, Raptis S. Urinary gastrin output and serum gastrin in patients with liver cirrhosis.

Urinary gastrin output in cirrhosis. Hepatogastroenterology 1994; 41: 445-448
18. Konturek SJ, Gonciarz M, Gonciarz Z, Bielanski W, Mazar W, Mularczyk A, Konturek PC, Goette JP, Rehfeld JF. Posastram and its products from patients with chronic viral hepatitis and liver cirrhosis. Sand J Gastroenterol 2003; 38: 643-647
19. Kirk AP, Dooley JS, Hunt RH. Peptic ulceration in patients with chronic liver disease. Dig Dis Sci 1980; 25: 756-760
20. Rabinovitz M, Schade RR, Dindzans V, Van Thiel DH, Gavalier JS. Prevalence of duodenal ulcer in cirrhotic males referred for liver transplantation. Does the etiology of cirrhosis make a difference? Dig Dis Sci 1990; 35: 321-326
21. Siringo S, Burroughs AK, Bolondi L, Muia A, Di Febo G, Miglioli M, Cavalli G, Barbara L. Peptic ulcer and its course in cirrhosis: an endoscopic and clinical prospective study. J Hepatol 1995; 22: 633-641
22. Siringo S, Vaira D, Menegatti F, Piscaglia F, Calvet X, Gabriel R, Pajares M, Miglioli M, Corinaldesi R, Bolondi L. 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: 204-210
23. Chen LS, Lin HC, Lee FY, Hou MC, Lee SD. Prevalence of duodenal ulcer in cirrhotic patients and its relation to Helicobacter pylori and portal hypertension. Zhonghua Yi Xue Za Zhi (Taipei) 1995; 56: 226-231
24. Sacchetti C, Capello M, Rebenci P, Roncucci L, Zanghiere G, Tripodi A, Ponz de Leon M. Frequency of upper gastrointestinal lesions in patients with liver cirrhosis. Dig Dis Sci 1988; 33: 1218-1222
25. Wu CS, Lin CY, Liaw YF. Helicobacter pylori in cirrhotic patients with peptic ulcer disease: a prospective, case controlled study. Gastrointest Endosc 1995; 42: 424-427
26. Sarfieh IJ, Tarnawski A, Malik A, Mason GR, Mach T, Ivey KJ. Portal hypertension and gastric mucosal injury in rats. Effects of alcohol. Gastroenterology 1983; 84: 987-993
27. Chen LS, Lin HC, Hwang SJ, Lee FY, Hou MC, Lee SD. Prevalence of gastric ulcer in cirrhotic patients and its relation to portal hypertension. J Gastroenterol Hepatol 1996; 11: 59-64
28. Nam YJ, Kim SJ, Shin WC, Lee JH, Choi WC, Kim KY, Han TH. [Gastric pH and Helicobacter pylori infection in patients with liver cirrhosis] Korean J Hepatol 2004; 10: 216-222
29. Pellicano R, Leone N, Ferrutti M, Cutufia MA, Fiorentino M, Rizzato M, Ponzetto A. Helicobacter pylori seroprevalence in hepatitis C virus positive patients with cirrhosis. J Hepatol 2000; 33: 648-650
30. Zullo A, Rinaldi V, Meddi P, Fonillo S, Lauria V, Diana F, Winn S, Attili AF. Helicobacter pylori infection in dyspeptic cirrhotic patients. Hepatogastroenterology 1999; 46: 395-400
31. Chen JJ, Changchien CS, Tai DI, Chio SS, Lee CM, Kuo CH. Role of Helicobacter pylori in cirrhotic patients with peptic ulcer. A serological study. Dig Dis Sci 1994; 39: 1565-1568
32. Nishiguchi S, Kuroki T, Ueda T, Fukuda K, Takeda T, Nakajima S, Shiomi S, Kobayashi K, Otani S, Hayashi N. Detection of hepatitis C virus antibody in the absence of viral RNA in patients with autoimmune hepatitis. Ann Intern Med 1992; 116: 21-25
33. Theilmann L, Blazeck M, Goeser T, Gmelin K, Kommerell B, Fiehn W. False-positive anti-HCV tests in rheumatoid arthritis. Lancet 1990; 335: 1346
34. Rivera J, Garcia-Monforte A, Pineda A Millan Nunez-Cortes J. Arthritis in patients with chronic hepatitis C virus infection. J Rheumatol 1999; 26: 420-424
35. Maillefert JF, Muller G, Falgarone G, Bour JB, Ratovohery D, Dougdos M, Tavernier G, Cervenak C. Prevalence of hepatitis C virus infection in patients with rheumatoid arthritis. Ann Rheum Dis 2002; 61: 635-637
36. Borque L, Elena A, Maside C, Rus A, Del Cura J. Rheumatoid arthritis and hepatitis C virus antibodies. Clin Exp Rheumatol 1991; 9: 617-619
37. Tsai CJ. Helicobacter pylori infection and peptic ulcer disease in cirrhosis. Dig Dis Sci 1998; 43: 1219-1225
38. Calvet X, Navarro M, Gil M, Lafont A, Sanfeliu I, Bruillet E,
Campo R, Dalmau B, Rivero E, Mas P. Epidemiology of peptic ulcer disease in cirrhotic patients: role of Helicobacter pylori infection. Am J Gastroenterol 1998; 93: 2501-2507.

Dore MP, Sura D, Deleda S, Maragkoudakis E, Pironti A, Realdi G. Active peptic ulcer disease in patients with hepatitis C virus-related cirrhosis: the role of Helicobacter pylori infection and portal hypertension gastropathy. Can J Gastroenterol 2004; 18: 521-524.

Verghera 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: 717-722.

Lo GH, Yu HC, Chan YC, Chen WC, Hsu PI, Lin CK, Lai KH. The effects of eradication of Helicobacter pylori on the recurrence of duodenal ulcers in patients with cirrhosis. Gastrointest Endosc 2005; 62: 350-356.

Ahmed AM, al Karawi MA, Shariq S, Mohamed AE. Frequency of gastroesophageal reflux in patients with liver cirrhosis. Hepatogastroenterology 1993; 40: 478-480.

Simpson JA, Conn HO. Role of ascites in gastroesophageal reflux with comments on the pathogenesis of bleeding esophageal varices. Gastroenterology 1986; 85: 17-25.

Van Thiel DH, Stremple JF. Lower esophageal sphincter pressure in cirrhotic men with ascites: before and after diuresis. Gastroenterology 1977; 72: 842-844.

Eckardt VF, Grace ND, Kantrowitz PA. Does lower esophageal sphincter incompetency contribute to esophageal bleeding? Gastroenterology 1976; 71: 185-189.

Arsene D, Bruley des Varannes S, Galimiche JP, Denis P, Chavyvialle JA, Hellot MF, Ducrotte P, Colin R. Gastro-oesophageal reflux and alcoholic cirrhosis. A reappraisal. J Hepatol 1987; 4: 250-258.

Iwakiri K, Kobayashi M, Sosoko M, Nomura T. Gastroesophageal reflux and esophageal motility in patients with esophageal varies. Gastroenterol Jpn 1993; 28: 477-482.

Flores PP, Lemme EM, Coelho HS. [Esophageal motor disorders in cirrhotic patients with esophageal varices non-submitted to endoscopic treatment] Arq Gastroenterol 2005; 42: 213-220.

Passaretti S, Mazzotti G, de Franchis R, Cipolla M, Testoni PA, Tittobello A. Esophageal motility in cirrhosis with and without esophageal varices. Scand J Gastroenterol 1989; 24: 334-338.

Grande L, Planas R, Lacima G, Boix J, Ros E, Esteve M, Morillas R, Gasull MA. Sequential esophageal motility studies after endoscopic injection sclerotherapy: a prospective investigation. Am J Gastroenterol 1991; 86: 36-40.

Snady H, Korsten MA. Esophageal acid-clearance and motility after endoscopic sclerotherapy of esophageal varices. Am J Gastroenterol 1986; 81: 419-422.

Sauerbruch T, Wirsching R, Leinsr B, Weinzierl M, Pfalsher M, Panaigter M. Esophageal function after sclerotherapy of bleeding varices. Scand J Gastroenterol 1982; 17: 745-751.

Reilly JJ Jr, Schade RR, Van Thiel DS. Esophageal function after injection sclerotherapy: pathogenesis of esophageal stricture. Am J Surg 1984; 147: 85-88.

Viazis N, Armonis A, Vlachogiannakos J, Rekoumias G, Stefanidis G, Papadimitriou N, Manolakopoulos S, Avgieris A. Effects of esophageal variceal treatment on oesophageal function: a prospective, randomized study. Eur J Gastroenterol Hepatol 2002; 14: 263-269.

Goff JS, Reveille RM, Van Stiegmann G. Endoscopic sclerotherapy: effects of eradication of Helicobacter pylori on the incidence of esophageal varices. Endosc 1986; 28: 477-482.

Berner JS, Gaing AA, Sharma R, Almenoff PL, Muhlfelder T, Korsten MA. Sequelae after esophageal variceal ligation and sclerotherapy: a prospective randomized study. Am J Gastroenterol 1994; 89: 852-858.

Hou MC, Yen TC, Lin HC, Kuo BI, Chen CH, Lee FY, Liu RS, Chang FY, Lee SD. Sequential changes of esophageal motility after endoscopic injection sclerotherapy or variceal ligation for esophageal varical bleeding: a scintigraphic study. Am J Gastroenterol 1997; 92: 1875-1878.

Papadimos D, Kerlin P, Harris OD. Endoscopic sclerotherapy: lessons from a necropsy study. Gastrointest Endosc 1986; 32: 260-269.

Averyinos A, Viazis N, Armonis A, Vlachogiannakos J, Rekoumias G, Stefanidis G, Papadimitriou N, Manolakopoulos S, Raptis SA. Early increase of lower oesophageal sphincter pressure after band ligation of oesophageal varices in cirrhotics: an intriguing phenomenon. Eur J Gastroenterol Hepatol 2002; 14: 1319-1323.

Stieggmann GV. Evolution of endoscopic therapy for esophageal varices. Surg Endosc 2006; 20 Suppl 2:S467-S470.

Krige JE, Bornmann PC, Shaw JM, Apostolou C. Complications of endoscopic variceal therapy. S Afr J Surg 2005; 43: 177-188, 190-194.

Schmitz RJ, Sharma P, Badr AS, Qamar MT, Weston AP. Incidence and management of esophageal stricture formation, ulcer bleeding, perforation, and massive hematoma formation from sclerotherapy versus band ligation. Am J Gastroenterol 2001; 96: 437-441.

Jaspersen K, Korner T, Schorr W, Hammar CH. Omeprazole in the management of sclerotherapy-induced esophageal ulcers resistant to H2 blocker treatment. J Gastroenterol 1995; 30: 128-130.

Gimson A, Polson R, Westaby D, Williams R. Omeprazole in the management of intractable esophageal ulcercation following injection sclerotherapy. Gastroenterology 1990; 99: 1829-1831.

Shephard H, Barkin JS. Omeprazole heals mucosal ulcers associated with endoscopic injection sclerotherapy. Gastrointest Endosc 1993; 39: 474-475.

Johlin FC, Labrecque DR, Neil GA. Omeprazole heals mucosal ulcers associated with endoscopic injection sclerotherapy. Dig Dis Sci 1992; 37: 1375-1376.

Garg PK, Sidhu SS, Bhargava DK. Role of omeprazole in prevention and treatment of postendoscopic varical esophageal variceal escharation complications. Double-blind randomized study. Dig Dis Sci 1995; 40: 1569-1574.

Laine L, el-Newihi HM, Migikovsky B, Sloane R, Garcia F. Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices. Ann Intern Med 1993; 119: 1-7.

Gimson AE, Ramage JK, Panos MZ, Hayllar K, Harrison PM, Williams R, Westaby D. Randomised trial of varical banding ligation versus injection sclerotherapy for bleeding oesophageal varices. Lancet 1993; 342: 391-394.

Shaheen NJ, Sturt E, Schmitz SM, Mitchell KL, Fried MW, Zacks S, Russo MW, Galanko J, Shrestha R. Pantoprazole reduces the size of postbanding ulcers after varical band ligation: a randomized, controlled trial. Hepatology 2005; 41: 588-594.

Koury SI, Stone CK, La Charite DD. Omeprazole and the development of acute hepatitis. Eur J Emerg Med 1998; 5: 467-469.

Romero-Gomez M, Otero MA, Suarez-Caricia E, Garcia Diaz E, Fobelo MJ, Castro-Fernandez M. Acute hepatitis related to omeprazole. Am J Gastroenterol 1999; 94: 1119-1120.

Viana de Miguel C, Alvaro Garcia M, Sanchez Sanchez A, Carvajal Garcia-Pando A. [Lansoprazole-induced hepatitis] Med Clin (Barc) 1997; 108: 599.

Cordes A, Vogt W, Maiher KP. [Pantoprazole-induced hepatitis] Dtsch Med Wochenschr 2003; 128: 611-614.

Garcia-Cortes M, Lucena MI, Andrade RJ, Romero-Gomez M, Fernandez MC. Lansoprazole-induced hepatic dysfunction. Ann Pharmacother 2003; 37: 173.

Darabi K. Proton-pump-inhibitor-induced hepatitis. South Med J 2005; 98: 844-845.
80 Thjodleifsson B. Treatment of acid-related diseases in the elderly with emphasis on the use of proton pump inhibitors. *Drugs Aging* 2002; 19: 911-927

81 Horai Y, Ishizaki T. Pharmacogenetics and its clinical implications. Part II. Oxidation polymorphism. *Ration Drug Ther* 1988; 22: 1-8

82 Kupfer A, Preisig R. Pharmacogenetics of mephenytoin: a new drug hydroxylation polymorphism in man. *Eur J Clin Pharmacol* 1984; 26: 753-759

83 Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors—emphasis on rabeprazole. *Aliment Pharmacol Ther* 1999; 13 Suppl 3: 27-36

84 Keane WF, Swan SK, Grimes I, Humphries TJ. Rabeprazole: pharmacokinetics and tolerability in patients with stable, end-stage renal failure. *J Clin Pharmacol* 1999; 39: 927-933

85 Hoyumpa AM, Trevino-Alanis H, Grimes I, Humphries TJ. Rabeprazole: pharmacokinetics in patients with stable, compensated cirrhosis. *Clin Ther* 1999; 21: 691-701

S- Editor Zhong XY  L- Editor Lalor PF  E- Editor Lu W