

Proton pump inhibitor prescription abuse and sepsis in cirrhosis

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Abstract

Proton pump inhibitors (PPIs) represent one of the most extensively prescribed classes of drugs in general and in patients with liver cirrhosis. Many prescriptions are

made without a clear adherence to standard indications. As a class of ordinarily well tolerated drug, PPIs are not free of side-effects and concerns have been raised about a possible role for PPIs in predisposing patients to an increased risk of bacterial infections and sepsis. As evidences of different power are accumulating on this topic, prospective studies are needed to reach a more universal agreement, but definitely more attention is needed by prescribers in being more adherent to the few recognized indications for the use of PPIs, particularly in patients with liver cirrhosis. Otherwise, doctors could run the risk of being accused of "abused" prescription.

Key words: Proton pump inhibitors; Liver cirrhosis; Bacterial infection; Sepsis

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Core tip: Many prescriptions of proton pump inhibitors (PPIs) are made without adhering to standard recognized indications. PPIs are ordinarily well tolerated but are not free of side-effects, and, in patients with liver cirrhosis, concerns are accruing on a possible role for PPIs in increasing the risk of infections and sepsis. As evidences of different power are accumulating, prospective studies are needed. However, prescribers should put definitely more attention in adhering to the recognized indications for the use of PPIs, especially in patients with cirrhosis. Otherwise, doctors could be responsible for "abuse" of prescription.

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UPPER DIGESTIVE BLEEDING DISORDERS IN CIRRHOSIS

Portal hypertension changes the clinical picture of patients with liver cirrhosis causing the most untamable complications that set up the clinical syndrome of advanced liver cirrhosis, such as ascites, porto-systemic encephalopathy, *etc.* Among those, upper gastrointestinal bleeding (UGIB) from esophageal varices is one of the most fearsome acute complications of liver cirrhosis, and constitutes one of the genuine medical emergencies. This is the reason why UGIB entails a prompt and appropriate management and every effort is attempted by clinicians and investigators to predict and, possibly, prevent its occurrence^[1]. Mortality of UGIB can range from 2% to 15%, with re-bleeding rates as high as 10%-30% in the brief term^[2,3]. Indeed, the underlying hepatic dysfunction in liver cirrhosis is associated with an impaired coagulation capacity, that further increases morbidity. Recently, mortality at 90 d after UGIB in liver cirrhosis was shown to be significantly increased included when bleeding was not due to esophageal varices^[4].

PROTON PUMP INHIBITORS INDICATIONS AND SHORTCOMINGS

Incidentally, proton pump inhibitors (PPIs) are powerful agents for controlling gastric acid secretion and actually they changed the clinical scenario of peptic ulcer disease^[5-8]. Thus, assuming a causative role for gastric acid production in any UGIB, a very extensive use of PPIs is made worldwide in very different clinical settings, ranging from peptic ulcer disease to general medicine and the more so in liver cirrhosis. Actually, acid suppressant drugs and especially PPIs represent the most frequently prescribed drugs in chronic among patients with liver cirrhosis, ranging from 25% to more than 40% of cirrhotic patients in various series. They are often prescribed on discharge also from specialized tertiary centers to cirrhotic patients who were not assuming ulcer healing drugs on hospital admission and who lack any proper current indication^[9,10]. Indeed, the only recognized indications for the use of PPIs - at term or in chronic - include very few items, namely: Peptic ulcer disease, gastroesophageal reflux disease (GERD), non-variceal UGIB, and bleeding prophylaxis in selected users of nonsteroidal anti-inflammatory drugs (NSAIDs)^[11].

Even if usually well tolerated^[12], PPIs are not avoid of class specific systemic side effects- incidence on the order of 1% to 5% - that include headache, diarrhea, constipation, nausea, and rash. Recently, they also surged as culprit of important drug-drug interactions that could reduce the efficacy of life saving drugs^[8]. Secondary side effects after long term use of PPIs include osteoporosis, infections (as will be discussed

further on) and the formation of gastric polyps/ carcinoids^[8,12].

IS THERE A ROLE FOR PPI IN PREVENTING UPPER DIGESTIVE BLEEDING ACCORDING TO GUIDELINES?

If we look at the case of patients with liver cirrhosis, few and scant specific indications exist for the use of PPIs. Benefits are documented only for their use in active bleeding from varices - starting before and continuing after endoscopic band ligation or sclerotherapy - and merely if associated with the mainstay of medical treatment of bleeding in cirrhosis with vasoconstrictors and antibiotics^[13-15]. The efficacy of PPIs after endoscopic treatment for the prevention of re-bleeding seems to be linked with the reduction of the dimensions of post-ligation ulcers^[15], then with a use limited to a short period of time (2-3 wk after band ligation). Conversely, manifestations of portal hypertension like congestive gastropathy and not actively bleeding esophageal or gastric varices are at risk for an inappropriate use of PPIs^[16]. Definitely, PPIs have been shown recently to be not effective in the primary prevention of UGIB in cirrhotic patients^[17]. Whatsoever, more than 60% of patients with liver cirrhosis have been found to have no documented indications for the use of a PPI in different published series^[10,14,16-18], in contrast with the low overall prevalence of peptic disease in patients with cirrhosis that ranges from 5% to 20% in different populations, and reaches a maximum of 28% in the most severe patients with decompensated cirrhosis^[14].

CONCERNS AND WARNINGS: DO PPIs INCREASE THE RISK OF INFECTION/ SEPSIS?

Starting from the early 80's, evidences are accumulating on an increased risk of infections in patients who are persistently assuming acid suppressant drugs in different clinical settings in the general population^[19-23], but also in the more definite population of patients with liver cirrhosis. In these patients any intercurrent infection is at higher risk of evolution into sepsis or severe sepsis, by the addition of any other organ dysfunction (mainly the kidney), the deterioration of the same liver function and of the overall prognosis^[24-26]. Pneumonia, *Clostridium difficile* (*C. difficile*) and other infectious gastroenteritis or cholangitis have been extensively studied, where the administration of PPIs also changed the pattern of etiologic agents over time^[23,27]. The mechanisms involved in shaping such predisposition to infection and sepsis are supposed to be related, on the one hand, to the loss of the modulating effect of the acidic gastric secretion on the gut microbiota (favoring small intestinal bacterial overgrowth: SIBO). On the

other hand, to a possible direct immunosuppressive effect of PPIs making patients prone to bacterial colonization and translocation^[23,28,29]. Whatever the underlying mechanistic reason, with the exception of a recent metanalysis^[12], recent prospective papers have shown that PPIs render the cirrhotic patients prone to infections and sepsis^[18,23,30-35], with a class specific effect independent from acidic secretion control. In facts, anti-H2 agents had no influence on the risk of infection when compared to PPIs^[25].

Indeed, in another recent prospective paper, the use of a PPI was documented in a rough 80% of patients with cirrhosis, and in 50% of those patients the prescription was fixed merely to control generic abdominal symptoms. Finally, in this population the use of PPIs was associated with a trend toward more infections in PPI users compared to non-users, and resulted independently associated with increased overall mortality compared with cirrhotic patients who were not assuming PPIs^[36].

CONCLUSION

In conclusion, we need to keep in mind - and maybe re-discover - the few unquestionable and appropriate indications for the use of PPIs, especially when dealing with the very fragile population of patients with liver cirrhosis (mainly if advanced cirrhosis). This not only to reduce and control the pharmaceutical expenditure, whoever is the payer, but also in the respect of the rules of good medical practice regarding adherence to guidelines and recognized indications. Cirrhosis constitutively exposes patients to develop more severe infections with systemic involvement and other organ dysfunction, compared to other patients. Otherwise, patients with cirrhosis have a basally reduced gastric acid secretion and are exposed to many drug-drug interactions. Declining to adhere to the universally recognized indications for the use of such an extensively prescribed class of drugs could actually expose many doctors at the fault of "abuse" in drug prescription!

REFERENCES

- 1 **Pezzulo G**, Kruger D. Assessing upper gastrointestinal bleeding in adults. *JAAPA* 2014; **27**: 19-25 [PMID: 25102077 DOI: 10.1097/01.JAA.0000453234.32378.cb]
- 2 **Carbonell N**, Pauwels A, Serfaty L, Fourdan O, Lévy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. *Hepatology* 2004; **40**: 652-659 [PMID: 15349904 DOI: 10.1002/hep.20339]
- 3 **Cheng DW**, Lu YW, Teller T, Sekhon HK, Wu BU. A modified Glasgow Blatchford Score improves risk stratification in upper gastrointestinal bleed: a prospective comparison of scoring systems. *Aliment Pharmacol Ther* 2012; **36**: 782-789 [PMID: 22928529 DOI: 10.1111/apt.12029]
- 4 **Holland-Bill L**, Christiansen CF, Gammelager H, Mortensen RN, Pedersen L, Sørensen HT. Chronic liver disease and 90-day mortality in 21,359 patients following peptic ulcer bleeding--a Nationwide Cohort Study. *Aliment Pharmacol Ther* 2015; **41**: 564-572 [PMID: 25588862 DOI: 10.1111/apt.13073]
- 5 **Holt S**, Howden CW. Omeprazole. Overview and opinion. *Dig Dis Sci* 1991; **36**: 385-393 [PMID: 2007354]
- 6 **Leontiadis GI**, Sharma VK, Howden CW. WITHDRAWN: Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database Syst Rev* 2010; **(5)**: CD002094 [PMID: 20464720 DOI: 10.1002/14651858.CD002094.pub4]
- 7 **Ramakrishnan K**, Salinas RC. Peptic ulcer disease. *Am Fam Physician* 2007; **76**: 1005-1012 [PMID: 17956071]
- 8 **Chubineh S**, Birk J. Proton pump inhibitors: the good, the bad, and the unwanted. *South Med J* 2012; **105**: 613-618 [PMID: 23128806 DOI: 10.1097/SMJ.0b013e31826efbea]
- 9 **Lewis JH**, Stine JG. Review article: prescribing medications in patients with cirrhosis - a practical guide. *Aliment Pharmacol Ther* 2013; **37**: 1132-1156 [PMID: 23638982 DOI: 10.1111/apt.12324]
- 10 **Lucena MI**, Andrade RJ, Tognoni G, Hidalgo R, De La Cuesta FS. Multicenter hospital study on prescribing patterns for prophylaxis and treatment of complications of cirrhosis. *Eur J Clin Pharmacol* 2002; **58**: 435-440 [PMID: 12242604 DOI: 10.1007/s00228-002-0474-1]
- 11 **Barrison AF**, Jarboe LA, Weinberg BM, Nimmagadda K, Sullivan LM, Wolfe MM. Patterns of proton pump inhibitor use in clinical practice. *Am J Med* 2001; **111**: 469-473 [PMID: 11690573 DOI: 10.1016/S0002-9343(01)00901-9]
- 12 **Attwood SE**, Ell C, Galmiche JP, Fiocca R, Hatlebakk JG, Hasselgren B, Långström G, Jahreskog M, Eklund S, Lind T, Lundell L. Long-term safety of proton pump inhibitor therapy assessed under controlled, randomised clinical trial conditions: data from the SOPRAN and LOTUS studies. *Aliment Pharmacol Ther* 2015; **41**: 1162-1174 [PMID: 25858519 DOI: 10.1111/apt.13194]
- 13 **Garcia-Tsao G**, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. *N Engl J Med* 2010; **362**: 823-832 [PMID: 20200386 DOI: 10.1056/NEJMr0901512]
- 14 **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**: 2980-2985 [PMID: 18494046]
- 15 **Shaheen NJ**, Stuart E, Schmitz SM, Mitchell KL, Fried MW, Zacks S, Russo MW, Galanko J, Shrestha R. Pantoprazole reduces the size of postbanding ulcers after variceal band ligation: a randomized, controlled trial. *Hepatology* 2005; **41**: 588-594 [PMID: 15726658 DOI: 10.1002/hep.20593]
- 16 **Chavez-Tapia NC**, Tellez-Avila FI, Garcia-Leiva J, Valdovinos MA. Use and overuse of proton pump inhibitors in cirrhotic patients. *Med Sci Monit* 2008; **14**: CR468-CR472 [PMID: 18758417]
- 17 **Garcia-Saenz-de-Sicilia M**, Sanchez-Avila F, Chavez-Tapia NC, Lopez-Arce G, Garcia-Osogobio S, Ruiz-Cordero R, Tellez-Avila FI. PPIs are not associated with a lower incidence of portal-hypertension-related bleeding in cirrhosis. *World J Gastroenterol* 2010; **16**: 5869-5873 [PMID: 21155009 DOI: 10.3748/wjg.v16.i46.5869]
- 18 **Goel GA**, Deshpande A, Lopez R, Hall GS, van Duin D, Carey WD. Increased rate of spontaneous bacterial peritonitis among cirrhotic patients receiving pharmacologic acid suppression. *Clin Gastroenterol Hepatol* 2012; **10**: 422-427 [PMID: 22155557 DOI: 10.1016/j.cgh.2011.11.019]
- 19 **du Moulin GC**, Paterson DG, Hedley-Whyte J, Lisbon A. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. *Lancet* 1982; **1**: 242-245 [PMID: 6120273 DOI: 10.1016/S0140-6736(82)90974-6]
- 20 **Aseeri M**, Schroeder T, Kramer J, Zackula R. Gastric acid suppression by proton pump inhibitors as a risk factor for clostridium difficile-associated diarrhea in hospitalized patients. *Am J Gastroenterol* 2008; **103**: 2308-2313 [PMID: 18702653 DOI: 10.1111/j.1572-0241.2008.01975.x]
- 21 **Bavishi C**, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. *Aliment Pharmacol Ther* 2011; **34**: 1269-1281 [PMID: 21999643 DOI: 10.1111/j.1365-2036.2011.04874.x]
- 22 **Dalton BR**, Lye-Maccannell T, Henderson EA, Maccannell DR,

- Louie TJ. Proton pump inhibitors increase significantly the risk of *Clostridium difficile* infection in a low-endemicity, non-outbreak hospital setting. *Aliment Pharmacol Ther* 2009; **29**: 626-634 [PMID: 19183143 DOI: 10.1111/j.1365-2036.2008.03924.x]
- 23 **Wang YP**, Liu CJ, Chen TJ, Lin YT, Fung CP. Proton pump inhibitor use significantly increases the risk of cryptogenic liver abscess: a population-based study. *Aliment Pharmacol Ther* 2015; **41**: 1175-1181 [PMID: 25871643 DOI: 10.1111/apt.13203]
- 24 **Bajaj JS**, Zadornova Y, Heuman DM, Hafeezullah M, Hoffmann RG, Sanyal AJ, Saeian K. Association of proton pump inhibitor therapy with spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Am J Gastroenterol* 2009; **104**: 1130-1134 [PMID: 19337238 DOI: 10.1038/ajg.2009.80]
- 25 **Bajaj JS**, Ratliff SM, Heuman DM, Lapane KL. Proton pump inhibitors are associated with a high rate of serious infections in veterans with decompensated cirrhosis. *Aliment Pharmacol Ther* 2012; **36**: 866-874 [PMID: 22966967 DOI: 10.1111/apt.12045]
- 26 **Bajaj JS**, O'Leary JG, Reddy KR, Wong F, Biggins SW, Patton H, Fallon MB, Garcia-Tsao G, Maliakkal B, Malik R, Subramanian RM, Thacker LR, Kamath PS. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. *Hepatology* 2014; **60**: 250-256 [PMID: 24677131 DOI: 10.1002/hep.27077]
- 27 **Schneider J**, Weidner W, Hapfelmeier A, Wantia N, Feihl S, Schmid RM, Neu B, von Delius S, Algül H, Huber W, Weber A. The use of proton pump inhibitors and the spectrum and number of biliary pathogens in patients with acute cholangitis. *Aliment Pharmacol Ther* 2014; **39**: 1194-1203 [PMID: 24628434 DOI: 10.1111/apt.12694]
- 28 **Kedika RR**, Souza RF, Spechler SJ. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. *Dig Dis Sci* 2009; **54**: 2312-2317 [PMID: 19714466 DOI: 10.1007/s10620-009-0951-9]
- 29 **Lombardo L**, Foti M, Ruggia O, Chiecchio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. *Clin Gastroenterol Hepatol* 2010; **8**: 504-508 [PMID: 20060064 DOI: 10.1016/j.cgh.2009.12.022]
- 30 **Sargenti K**, Prytz H, Strand A, Nilsson E, Kalaitzakis E. Healthcare-associated and nosocomial bacterial infections in cirrhosis: predictors and impact on outcome. *Liver Int* 2015; **35**: 391-400 [PMID: 25039438 DOI: 10.1111/liv.12625]
- 31 **Merli M**, Lucidi C, Di Gregorio V, Giannelli V, Giusto M, Ceccarelli G, Riggio O, Venditti M. The chronic use of beta-blockers and proton pump inhibitors may affect the rate of bacterial infections in cirrhosis. *Liver Int* 2015; **35**: 362-369 [PMID: 24836902 DOI: 10.1111/liv.12593]
- 32 **Deshpande A**, Pasupuleti V, Thota P, Pant C, Mapara S, Hassan S, Rolston DD, Sfera TJ, Hernandez AV. Acid-suppressive therapy is associated with spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *J Gastroenterol Hepatol* 2013; **28**: 235-242 [PMID: 23190338 DOI: 10.1111/jgh.12065]
- 33 **Min YW**, Lim KS, Min BH, Gwak GY, Paik YH, Choi MS, Lee JH, Kim JJ, Koh KC, Paik SW, Yoo BC, Rhee PL. Proton pump inhibitor use significantly increases the risk of spontaneous bacterial peritonitis in 1965 patients with cirrhosis and ascites: a propensity score matched cohort study. *Aliment Pharmacol Ther* 2014; **40**: 695-704 [PMID: 25078671 DOI: 10.1111/apt.12875]
- 34 **Kwon JH**, Koh SJ, Kim W, Jung YJ, Kim JW, Kim BG, Lee KL, Im JP, Kim YJ, Kim JS, Yoon JH, Lee HS, Jung HC. Mortality associated with proton pump inhibitors in cirrhotic patients with spontaneous bacterial peritonitis. *J Gastroenterol Hepatol* 2014; **29**: 775-781 [PMID: 24219827 DOI: 10.1111/jgh.12426]
- 35 **de Vos M**, De Vroey B, Garcia BG, Roy C, Kidd F, Henrion J, Deltenre P. Role of proton pump inhibitors in the occurrence and the prognosis of spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Liver Int* 2013; **33**: 1316-1323 [PMID: 23730823 DOI: 10.1111/liv.12210]
- 36 **Dultz G**, Piiper A, Zeuzem S, Kronenberger B, Waidmann O. Proton pump inhibitor treatment is associated with the severity of liver disease and increased mortality in patients with cirrhosis. *Aliment Pharmacol Ther* 2015; **41**: 459-466 [PMID: 25523381 DOI: 10.1111/apt.13061]

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