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Letter: *Helicobacter pylori* in proton pump inhibitor-associated biliary disease

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EDITORS,

Min et al.¹ in their cohort study, proposed the role of proton pump inhibitors (PPI) as a risk factor of cholangitis, especially during the period of their use. This observational result could include unrecognized confounders, one of which to consider being the overlap between *Helicobacter pylori* infection (*Hp-I*) and the conditions treated using a PPI; dyspepsia, peptic ulcer disease and, at least in some populations, gastro-oesophageal reflux disease—Barrett's oesophagus—oesophageal cancer sequence are associated with *Hp-I* and represent the most frequent indications for PPI prescription.² Moreover *Hp-I* is involved in PPI-related disorders discussed by the authors.¹⁻³

The impact of *Hp-I* with biliary tree diseases has been described. Bile stasis has primarily been connected with hepatobiliary *Hp* contamination, thus leading to a threefold risk of chronic lithiasis and cholecystitis, triggered by a perpetual inflammation of the gallbladder.^{4,5} In this respect, our data indicated *Hp* presence in gallbladder tissue in 19.33% of patients who were submitted to cholecystectomy due to lithiasis,⁶ while chronic biliary *Hp-I* has been identified in 75% of patients with gallbladder cancer.⁷

The proposed routes of contamination, although unproved, include ascending migration through the sphincter of Oddi and hematogenous spread to the liver and then excretion into bile. In this respect, the potential influx of activated monocytes infected with *Hp* (due to defective autophagy) from the circulation into the gallbladder might relate to gallbladder-related pathologies ("Trojan horse" pathway); biliary excretion of *Hp* invaded macrophages might trigger proinflammatory cytokine release, oxidative stress and inflammation, thus promoting gallstone formation and its

complications (cholecystitis/cholangitis/pancreatitis). Additionally, biliary *Hp-I* could provoke an imbalance of apoptotic cellular processes and contribute to biliary carcinogenesis. In vitro data support this, indicating that *Hp* promotes cell proliferation and suppresses apoptosis of human intrahepatic biliary epithelial cells by increasing reactive oxygen species release.⁸ Finally, the authors suggested as a possible pathogenetic mechanism of PPI-related cholangitis, the imbalance between the normal small intestine microbiota and the bacterial overgrowth due to gastric acid suppression.¹ Nevertheless, *Hp-I* seems to cause more significant alterations in gut microbiota than PPI use, thus contributing to biofilm formation.⁹

Hp-I has also been associated with a plethora of extragastric conditions, such as cardiovascular and neurodegenerative diseases, glaucoma, gastrointestinal tract oncogenesis, non-alcoholic fatty liver disease and hepatic encephalopathy.¹⁰ Therefore, it seems reasonable to consider adjusting for the presence of *Hp-I* as a potential cofounder in PPI-related disorders, as it is perhaps potentially relevant to a wide range of conditions necessitating their use.

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LINKED CONTENT

This article is linked to Min et al paper. To view this article, visit <https://doi.org/10.1111/apt.15466>.

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