Discovery of *Helicobacter pylori* in gallbladder

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Helicobacter pylori, a gramnegative and microaerophilic organism, is transmitted from person-to-person through the feco-oral route and colonizes the stomach. The organism persists in the healthy host in equilibrium, which is disturbed at times, leading to formation of peptic ulcer and gastric cancer. Presence of *H. pylori* in the biliary tree of a small proportion of individuals has led to the conjecture that it is a potential cause of gallbladder disease. The exact pathway of how the organism reaches the gallbladder is unclear. It could reach the gallbladder directly from the stomach or through the portal blood circulation. In contrast to the stomach, colonization of the gallbladder is unlikely due to the alkaline pH of bile, *H. pylori* being known to thrive at the low pH of gastric juice.

There are several tests to confirm presence of *H. pylori* in the stomach. These include rapid urease test, and demonstration of the bacterium on histology and culture of gastric biopsy, and positive urea breath (^{13}C or ^{14}C) test. Molecular tests identify the genes of *H. pylori* in the tissue. Immunological evidence of *H. pylori* infection is provided by presence of *H. pylori*-specific IgG and IgM antibodies in the blood. Similar tests can be used to demonstrate *H. pylori* in gallbladder and bile.

Demonstration of *H. pylori* in gallbladder has been attempted directly by culture of gallbladder, bile or gallbladder mucosal scrappings or demonstration of the bacillus on histology of gallbladder. Demonstration of *Helicobacter* in

gallbladder tissue histology varies 40 from 0 % to 28 % [1–6]. BostanoAylu et al. [1] could not culture *Helicobacter* in any of their 47 patients with gallstone disease and 30 controls. However, Mishra et al. [2] recently demonstrated positive culture in 30 % patients of gallstone disease and 44 % gallbladder cancer specimens.

Indirect evidence of *H. pylori* in gallbladder by demonstration of DNA of different components of bacillus is found in 7 % to 61.5 % tissue examined [2–10].

Evidence of immunological response to *Helicobacter* is often positive in patients with gallbladder disease. Antibodies to *Helicobacter* have been reported in 18 % to 80 % of patients with gallstone disease [2, 11–13], 32 % to 38.8 % of cancer gallbladder [2, 11] and 13.1 % to 47.5 % of controls [11, 13]. However, serology is not specific for *Helicobacter* infection of the gallbladder. It is a systemic effect of *Helicobacter* infection anywhere in the body.

In this issue of the *Journal*, Bansal et al. [12] demonstrate the presence of *H. pylori* DNA in 32.6 % of 49 gallbladders surgically removed for benign biliary disease. None of these gallbladders showed *H. pylori* organisms on histology, even when special stains were used. DNA detection by PCR is very sensitive. *Helicobacter* genus (total 32 species) in general and *H. pylori* specifically are detected by an array of PCR tests using 26KDA, HSP60, Flagellin gene and other primers with varying sensitivities. The accuracy of the 26KDa primer is 9.3 % compared to that of 11.6 % using the Ure A gene on the same samples. Mishra and others [2] recently reported that 42.5 % of gallbladder carcinoma tissues were positive for the HSP60 gene. Bansal et al. [12] based the PCR on the UreA gene of *H. pylori*. However, it has been shown that this gene shares homology

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with urease genes of other species including *Bacillus* species [14]. There was a strong association between *H. pylori* DNA positivity in gallbladder tissue and a positive urea breath test signifying presence of *H. pylori* in the stomach. Bulajic et al. [15] reported significant correlation of presence of *H. pylori* on PCR in stomach and gallbladder. But there is paucity of literature on correlation of gastric *H. pylori* with that of biliary *H. pylori*.

Biliary *H. pylori* is positively associated with, presence of gallstones, gallbladder cancer, and age, but not with gender. Yet presence of live *H. pylori* in bile is very rare. Bile with high pH is a toxic growth medium for *H. pylori* whose natural habitat is low pH gastric juice. This is a feasible hypothesis that due to some, hitherto not understood factor gastric *H. pylori* are sucked in the gallbladder where they perish. This may explain why live bacteria are rarely found in the gallbladder, and PCR detects the remains of the *H. pylori* ‘the straggler’ rather than *H. pylori* ‘the invader’ in the gallbladder. Alternatively, the genetic residue of *H. pylori* in the stomach, finds its way to gallbladder by hitherto not understood route.

Presence of *Helicobacter* in the gallbladder indicates that it is in fact invading the gallbladder. In general, *Helicobacter* is demonstrated by at least one of the methods of examination in one-third of cases of gallstone disease and about one half of those with gallbladder cancer. Moreover many of the 32 known species of *Helicobacter* are being isolated from the gallbladder such as: *H. aurati*, *H. pullorum*, *H. bizzozeronii*, *H. canis*, *H. felis*, *H. cholecystus*, *H. ganmani*, *H. hepaticus* and *H. bilis*.

Two-thirds of the world population is infected with *H. pylori*. The main arena of activity of *H. pylori* is the stomach but the biliary tract forms an important alleyway where *H. pylori*, rarely, or its component DNA, more commonly, is discovered on close scrutiny. *H. pylori* is found 3.5 times more frequently in presence of gallstones and 9.9 times more frequently in presence of gallbladder cancer in comparison to normal control [15] but it is uncertain if *H. pylori* has a role, in any form, to cause pathogenesis of gallbladder disease. The work of Bansal and colleagues [12] is silent on this aspect of *Helicobacter* culpability in causing gallbladder disease.

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