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Chapter 4

The Importance of *H. pylori* Infection in Liver Diseases

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Abstract

The chapter is a review of current knowledge on the impact of *H. pylori* infection on the clinical course of patients with various forms of liver damage. *H. pylori* infection is found in 50–90% of the world population. The bacteria not only mainly contribute to occurrence of gastric mucosa inflammation but also to gastric ulcer and cancer. *H. pylori* contains an active antioxidative system, which not only neutralizes free radicals but also synthesizes specific VacA toxin, which leads to destruction and apoptosis of the cells. A specific system of bacterial CagA genes has a special role in carcinogenesis. There is an increasing number of reports describing lesions in the circulatory system, pancreas, or the skin, connected with *H. pylori* infection. Liver colonization by *H. pylori* happens after transmission of the bacteria from the stomach, with blood, through the portal vein or directly through the bile ducts. The bacteria promote liver function deterioration in the course of toxic injury, autoimmune inflammation, chronic HBV, and HCV infection. Infections among people with liver cirrhosis are especially dangerous. In this group of patients, *H. pylori* infection may significantly worsen liver function, leading to hyperammonemia, increased portal pressure, and development of esophageal varices. Thus, testing for and treating this infection among patients with liver cirrhosis is especially important.

Keywords: *H. pylori*, hepatitis, hepatic liver cirrhosis, liver and biliary tract cancer

1. Introduction

Helicobacter pylori (*H. pylori*) is a microaerophile described for the first time by Marshal and Warren in 1982. This Gram-negative bacillus is resistant to the activity of gastric acid. Active, vegetative form of the bacteria is spiral, while the sporulation form is granular [1]. The bacterium contains stable DNA and a system of very effective DNA repair.

In developed countries, infection by these bacteria is detected in about 50% of the population, while in developing countries, the percentage may even reach 90% [2]. Still, however, there are no definitive pointers as to risk factors of *H. pylori* infection.

H. pylori produces high amounts of ureases, enzymes catalyzing urea decomposition to ammonia. This is especially important for the neutralization of hydrochloric acid in the stomach, which contributes to the growth of the bacteria. Bacteria demonstrate also the ability to pump out H^+ ions from cells. This leads to changes in the pH in the stomach, which in turn causes destruction of gastric mucosa.

H. pylori has an active antioxidizing system, which neutralizes free radicals. The system contains catalase, superoxide dismutase, and specific proteins MdaB and NapA.

Bacterial DNA contains genes encoding cytotoxin synthesis system. VacA toxin (vacuolating toxin) is encoded by a changing system of genes in 40–60% of bacterial strains. This underlies different toxic properties. In epithelial cells, VacA promotes fusion of several lysosomes and formation of large vacuoles, which changes the construction of cytoskeleton. VacA toxin induces apoptosis of epithelial cells and shows highly immunogenic properties.

Specific system of CagA genes encodes synthesis of CagA toxin, demonstrating properties reorganizing cytoskeleton and cell shape. Moreover, the toxin controls transcription and proliferation of the cell, as well as inflammatory reaction. CagA toxin plays a very important role in carcinogenesis in the stomach and other organs, when CagA-synthesizing *H. pylori* is detected [3, 4].

H. pylori is mainly present on the surface of epithelial cells of the mucosa, in the prepyloric part of the stomach. It has cilia allowing transport into intercellular spaces, and thanks to produced adhesins, it adheres to cell surface [1].

H. pylori infection influences local (in the gastric mucosa) and systemic increase in proinflammatory cytokines IL-1, -2, -4, -6, -8, -10, -17, interferon-β, and TNF-α [5]. This leads not only to development of local inflammatory reaction, but also potentiates generalized inflammatory reactions in the organism. *H. pylori* causes chronic atrophic gastritis, metaplasia, and dysplasia, leading to the development of gastric cancer. According to World Health Organization (WHO), the bacteria are a class I carcinogen. *H. pylori* may also potentiate extragastric organ disturbances, exacerbating the diseases of cardiovascular system or metabolic diseases, deteriorating normal function of the liver, especially in patients with cirrhosis [6].

2. Organ pathologies connected with *H. pylori* infection

H. pylori infection, especially in the case of strains producing CagA toxin, promotes development of coronary sclerosis and increases the probability of angina pectoris and cardiac infarct [7]. Effect of CagA toxin on promotion of sclerotic changes in coronary arteries leads to exacerbation of coronary disease, which increases mortality caused by circulatory failure in the group of patients infected with these bacteria and not subjected to eradication [8, 9].

H. pylori infection among patients with type 2 diabetes presents more seriously compared to patients without diabetes [10]. Moreover, impact of this infection onto the development of chronic pancreatitis has been reported, which indirectly affects liver function [11].

H. pylori infection is associated with many skin conditions. Higher incidence of chronic urticaria, acne rosacea, idiopathic thrombocytopatic purpura, psoriasis, atopic dermatitis, and some other dermatological conditions among patients infected with *H. pylori* has been demonstrated [12].

3. Liver injury

Liver colonization by *H. pylori* happens after transmission of the bacteria from the stomach, with blood, through the portal vein or directly through the bile ducts [13].

Experimental studies performed on mice and rats infected with *H. pylori* have shown the effect of this infection onto up triggered fibrosis and development of liver cirrhosis [14]. One of the first studies performed in patients with chronic liver injury pointed to the presence of *Helicobacter* genus bacteria in the liver tissue in 26% of patients [15]. Current studies in patients infected with HBV, HCV, and patients with chronic noninfectious liver conditions point to much higher incidence of *H. pylori* or bacterial DNA in the liver tissue. Infections are thought to occur in effect of disturbances in patients' immune functions [16]. Both experimental and clinical studies demonstrate unfavorable effect of *H. pylori* infection onto the course of liver injury, especially exacerbated fibrosis. One of the reasons for this is the influence of infection onto metabolic changes connected with carbohydrate turnover, synthesis of high-energy compounds (mainly ATP), and increased concentration of proinflammatory cytokines.

4. Chronic HBV and HCV infections

The frequency of *H. pylori* infection among patients with chronic hepatitis B is around 30–80% [17]. *H. pylori* infection is confirmed in 79% of patients with postinflammatory liver cirrhosis connected with HBV infection [18]. Favorable effect of *H. pylori* eradication on the course of the disease, including increased platelet count, has been demonstrated in the studies on patients chronically infected with HBV, with compensated liver cirrhosis and thrombocytopenia [19].

Among people chronically infected with HBV with primary liver cancer, *H. pylori* infection is found in 69% of patients. In the group of patients with primary liver cancer, but without HBV infection, *H. pylori* infection is much less frequent, as it is found in 33% of patients. These observations consistently point to unfavorable effect of *H. pylori* infection among HBV-infected patients with liver cirrhosis onto the risk of occurrence of primary liver cancer. Frequency of *H. pylori* infection among patients with chronic hepatitis B correlates with the incidence of hepatocellular cancer, both in men and women [20]. Among this type of patients, fast progression of inflammatory changes in the liver is observed, as well as intensified fibrosis, which promotes occurrence of primary neoplastic lesions [17, 21].

Among patients infected with *H. pylori* and HBV, liver function is impaired (prothrombin time is extended, and AST activity and bilirubin concentration increased), and esophageal varices, ascites and hyperammonemia with hepatic encephalopathy occur much more frequently [18].

Evaluation of *H. pylori* infection among patients with chronic HCV infection is difficult. Some authors state that the frequency of *H. pylori* infection among the patients in this group is about 38%. Around 45% of those result from CagA-synthesizing bacteria. No significant differences are found in the morphological picture of HCV-infected liver, between patients with or without *H. pylori* infection. There is also no correlation between *H. pylori* infection and IL 28B polymorphism [22]. However, many other authors present other observations. *H. pylori* infection may be present in even 70% of patients chronically infected with HCV [23]. Meta-analysis of 20 studies demonstrated higher incidence of *H. pylori* infection among HCV-positive patients, compared to persons without viral infection [17, 24]. Much higher fibrosis, loss of cellular proteins, and glycogen was found in morphological studies of the liver from HCV-positive patients, if those were coinfected with *H. pylori*, compared to those without coinfection [25].

5. Autoimmune diseases and liver steatosis

Studies performed among patients with chronic viral autoimmune and toxic hepatitis and coexisting *H. pylori* infection demonstrated improvement in liver function, including decreased ALT and AST activity, after effective eradication of bacteria [26].

H. pylori infection is found in 20–50% of patients with AIH. Among patients with PBC, *H. pylori* infection is found more frequently than among people from the control group (54 vs. 31% $p = 0.01$). However, the effect of this infection on the course of PBC has not been elucidated [27].

Infection by these bacteria worsens the course of underlying disease; however, pathogenesis is not completely clear [28, 29]. In the group of patients with PBC and AIH, *H. pylori* infection may lead to precipitous, unfavorable progression of the disease [30].

Reports on the effect of *H. pylori* infection on lipid turnover disturbances, leading to hypertriglyceridemia and hypercholesterolemia with concomitant decrease of HDL level, are published more and more frequently. This is especially important for the metabolism of hepatocytes and their steatosis, as well as in the process of liver fibrosis [31]. Many reports point to the fact that *H. pylori* infection hastens the development of NAFLD [32]. It has been demonstrated that *H. pylori* infection among patients with NAFL results in the development of NASH. Eradication of the bacteria significantly facilitates the treatment of liver steatosis [33]. Moreover, it has been found that *H. pylori* infection and steatosis constitute the risk of more frequent occurrence of cholecystolithiasis and choledocholithiasis [34].

6. Liver cirrhosis, hepatocellular carcinoma (HCC), and cholangiocarcinoma (CCC)

Inflammation of gastric mucosa is a frequent complication of liver cirrhosis. Usually, occurrence of chronic inflammation is observed, described as portal gastropathy. *H. pylori* infection in the group of patients with liver cirrhosis impacts exacerbation of inflammatory changes

in the stomach, which in turn worsens liver function. This is especially dangerous among patients with advanced liver injury. Studies performed on this group of patients point to high significance of cytopathic effect of *H. pylori* onto hepatocytes [16, 35]. *H. pylori* infection affects increase of portal tension, which is one of the main etiologies of development of esophageal varices [6, 36]. In effect, correlation between the frequency of *H. pylori* infection and advancement of esophageal varices is observed [37].

Although in some studies more frequent *H. pylori* infection among patients with liver cirrhosis cannot be confirmed [38]; however, meta-analysis was performed that included mainly patients with alcoholic liver cirrhosis, which argues for much more frequent occurrence of these bacteria among such patients. *H. pylori* infection is much more frequent among patients with postinflammatory liver cirrhosis (connected with HBV or HCV infection) [37]. Incidence of *H. pylori* infection among patients with liver cirrhosis and concomitant HCV infection increases proportionally to progressing liver failure [39]. Moreover, it has been demonstrated that the highest percentage of people infected with *H. pylori* among those with HCV infection is observed in the case of patients in whom HCC developed [17, 24]. Many pieces of information argue that concomitant infection with *H. pylori* and HCV increases the incidence of HCC. Eradication of these bacteria in patients with cirrhotic liver leads to the increase of platelet count and improves efficacy of antiviral therapy [23, 40]. In the current setting, when direct-acting antivirals are commonly used, this is probably not so important; however, such studies have not been performed.

H. pylori catalyzes the reaction of urea decomposition to ammonia and carbon dioxide; however, among patients with subclinical hepatic encephalopathy, infection with these bacteria does not change the concentration of ammonia in the blood [41]. These observations are inconsistent, because among patients with liver cirrhosis, especially postinflammatory cirrhosis, more frequent occurrence of symptomatic hepatic encephalopathy with hyperammonemia is observed in the case of patients infected with *H. pylori*, compared to patients without this infection [37, 42]. In the studies performed in patients with liver cirrhosis, a correlation between increasing ammonia blood concentration and *H. pylori* infection has been demonstrated. Moreover, ammonia blood concentration was higher among patients with liver cirrhosis infected with *H. pylori*, compared to patients not infected with these bacteria [37].

In experimental studies performed on dogs, an association between *H. pylori* infection and occurrence of hepatocellular carcinoma (HCC) has been evidenced [43]. Evaluation of the effect of *H. pylori* infection on liver carcinogenesis in humans shows that in 58% of patients with HCC and in 62% of patients with CCC in the liver tissue surrounding focal lesion, DNA of these bacteria can be detected [44]. *H. pylori* may disturb the balance between hepatocyte proliferation and activity of apoptosis in the liver. In effect, there is a higher risk of occurrence of neoplastic cells in the liver [45].

In the pathogenesis of biliary duct carcinoma, *H. pylori* infection affects proliferation of biliary duct epithelium and development of inflammatory reaction in these cells. Activation of reactive oxygen species (oxidative stress) and reactive nitrogen species, mainly 8-nitroguanine, in the cells is detected. These reactions damage DNA of stem cells, playing a key role in carcinogenesis [46]. A special role in the development of bile duct carcinoma is attributed to *H. pylori* producing CagA toxin [47].

7. Conclusions

H. pylori infection is detected significantly more often among patients with chronic liver injury. This is especially dangerous in patients with liver cirrhosis. In this group of patients, *H. pylori* infection may significantly worsen liver function, affecting hyperammonemia, increase in portal pressure, and development of esophageal varices. Testing for and treating this infection is of paramount importance for these patients.

Current research on the impact of *H. pylori* infection in patients with chronic liver damage is inadequate. This points to the desirability of further research, particularly among patients with severe liver damage.

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Conflict of interest

No conflict of interest to be declared.

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