REVIEW

doi.org/10.1590/S0004-2803.202302023-15

Helicobacter and hepatobiliary diseases: update 2023

Tatyana **KUGLER** and Gennady **TARADIN***

*Donetsk National Medical University, Faculty of postgraduate education, Department of Therapy, Donetsk Oblast, Ucrânia.

HIGLIGHTS

- Clinical studies have shown that hepatobiliary diseases of inflammatory and neoplastic origin are associated with *Helicobacter* infection.
- Translocation and the ascending pathway are putative mechanisms for Helicobacter spp to enter the hepatobiliary system.
- *H. pylori* infection has a systemic effect through the activity of pro-inflammatory cytokines, TNF-α, leukotrienes, interferon-β, interferon-γ, and acute phase proteins.
- Histopathological confirmation is needed to present that *H. pylori* eradication prevents or improves hepatobiliary disease progression.

ABSTRACT – *Helicobacter Pylori (H. pylori)* is one of the main infectious causes of gastroduodenal diseases, however, its role in developing different extragastric diseases has been proven. The possible involvement of *H. pylori* in the pathogenesis of cardiovascular, metabolic, neurodegenerative, skin, and hepatobiliary diseases is suggested. The bacterium has been found in tissue samples from the liver, biliary tract, and gallstones of animals and humans. However, the role of *H. pylori* infection in the pathogenesis of liver and biliary diseases has not been finally established. The histopathological confirmation of the positive effect of *H. pylori* eradication is needed. In addition, there are discussions on the clinical significance of other *Helicobacter species*. The review presents the data available for and against the involvement of *H. pylori* in hepatobiliary disease development and progression.

Keywords – *Helicobacter Pylori*; nonalcoholic fatty liver disease; autoimmune liver diseases; viral hepatitis; cirrhosis; cholelithiasis; cancer.

INTRODUCTION

Helicobacter Pylori (H. pylori) infection is a major cause of gastroduodenal diseases, including distal cancer and gastric lymphoma. As shown by many studies over the past two decades, *H. pylori* infection is likely to be a risk factor for several extragastric diseases. Its role in developing idiopathic iron deficiency anemia, B12 deficiency anemia, and idiopathic thrombocytopenic purpura has been proven. The European Working Group on the study of *H. pylori* and microbiota included these diseases in the indications for eradicating *H. pylori* infection (Maastricht VI, 2022)[1]. The involvement in the pathogenesis of cardiovascular, metabolic, neurodegenerative, skin, and other diseases is assumed. Many authors note the connection between *H. pylori* infection and chronic hepatobiliary diseases[2-4]. In patients with hepatobiliary diseases living in different geographic regions, the presence of the bacterium was found in tissue samples of the liver, biliary tract,

Received: 26 January 2023
Accepted: 28 April 2023

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
Corresponding author: Tatyana Kugler. E-mail: kugler2@mail.ru

and gallstones[2]. Progression of inflammation in the liver of any nature was also noted in the presence of *H. pylori* infection[4]. However, some researchers consider that there is no such correlation[5,6]. The role of the bacterium in the development of liver and biliary tract diseases has not been proven. This review presents the data available on the possibility of involvement of *H. pylori* in the pathogenesis of hepatobiliary diseases.

HELICOBACTER SPP AND THE LIVER

Animal studies

The successful treatment of many diseases has been based on the study of animal models. Clinical studies have shown that diseases of the hepatobiliary system of inflammatory and neoplastic origin are associated with *Helicobacter* infection[7,8]. In 1982, *H. pylori* was recognized as the cause of chronic gastritis, and later its role in developing a peptic ulcer and gastric cancer was established[9]. Since then, the *Helicobacter* has expanded to include over 30 officially named species, including the enterohepatic *Helicobacter* spp (EHS), which causes inflammation and cancer of the liver, gallbladder, and intestines in susceptible hosts[10].

The results of studies on animals infected experimentally or naturally has shown that *H. bilis* and *H. hepaticus* are able to cause chronic active hepatitis, hepatocellular carcinoma and biliary tract carcinoma, typhlocolitis, and cancer of the lower intestine, although some individuals were recorded only asymptomatic carriage. EHS may cause cholesterol gallstone formation and intrahepatic cholelithiasis, as presented by recent studies in vivo[11].

In a study by Takemura et al.[7], whose goal was to identify *Helicobacter* spp in the hepatobiliary tract of dogs and elucidate the possible association of these bacteria with liver diseases, *Helicobacter* was found in 21.2% of hepatobiliary system samples (15.2% in the liver and 9.1% in the gallbladder). The main defeat observed in infected animals was chronic hepatitis, associated or not associated with degenerative or proliferative changes. The analysis of the sequence of seven amplicons of the 16S rRNA gene of the *Helicobacter* genus from hepatobiliary samples has shown from 97.8 to 100% nucleotide identity with gastric *Helicobacter*, which confirms the hypothesis of the transfer of bacteria from the stomach to the liver by the biliary route. One amplicon of the ureA and ureB genes of the stomach *Helicobacter* showed nucleotide identity from 89.1 to 90.7% with *H. heilmannii*.

According to other studies, *Helicobacter* DNA fragments have been found in cats[12,13], dogs[7,14], ferrets[15], rodents[16], and monkeys[17]. These data are presented in TABLE 1.

Chronic active hepatitis has been detected in radiation experiments on male C3H/HeNrs mice in a study by Nam et al.[18]. Histopathologically, more than 10% of mice had liver lesions regardless of irradiation. Mild lesions have only shown focal necrosis and focal inflammation in the liver. Severe cases have been associated with hepatocytomegaly, bile duct hyperplasia, Kupffer cell hypertrophy and activation, cholangitis, pleomorphic hepatocytes, and/or tumor.

TABLE 1. *Helicobacter* spp isolated from different animals.

Author	Year	Helicobacter spp	Animals	Diseases
Fox et al.[17]	2001	*Helicobacter cinaedi*	Monkey	Chronic colitis and hepatitis
Garcia et al.[15]	2002	*Helicobacter cholecystus, Helicobacter spp. 266-1*	Ferrets	Chronic cholangiohepatitis, carcinoma
Shen et al.[16]	2005	*Helicobacter mastomyrinus*	Rodents	Chronic hepatitis
Greiter-Wilke et al.[12]	2008	*Helicobacter pylori, Helicobacter fenelliae/ cinaedii, Helicobacter nemistrineae*	Cats	Cholangiohepatitis
Beisele et al.[14]	2011	*Helicobacter marmotae*	Dogs	Chronic hepatitis, hepatocellular carcinoma
Takemura et al.[8]	2019	*Helicobacter pylori, Helicobacter heilmannii*	Dogs	Chronic hepatitis,
Elyasi et al.[13]	2020	Helicobacter *pylori,* Helicobacter *bilis, Helicobacter canis*	Cats	Chronic hepatitis, enterocolitis

Translocation and the ascending pathway are putative mechanisms for *Helicobacter* spp to enter the hepatobiliary system[7]. These data are consistent with the results of a Brazilian study where *Helicobacter* has been found in 43.3% of cats in the liver[13]. In addition, *H. pylori* infection in both the liver and intestines in most of the cats has been found, demonstrating the ability for bacterial migration. These results prove the hypothesis that the bacterium can move from the intestine to the liver via the biliary tract.

Molecular methods such as polymerase chain reaction (PCR) and sequencing are used to identify *Helicobacter* in clinical specimens[19]. The whole genome sequencing has rapidly improved the characterization of *Helicobacter* spp. In 1997, the first *H. pylori* genome was published[20], and today the genomes of more than 1000 different strains are available. Bioinformatics analysis has provided invaluable insight into the physiology and mechanisms of *H. pylori* virulence. Later, in 2003, the genome sequence of the EHS prototype, *H. hepaticus*, was published. The genomic comparison of *H. pylori* and *H. hepaticus* revealed significant differences in gene structure and content, suggesting that essential differences underlie the contrasting colonization niches and pathogenic potentials of the stomach compared to EHS[21]. However, there are also common properties, *H. hepaticus* can cause persistent infection in its host, leading to chronic inflammation, which is a prerequisite for the progression of carcinogenesis. Inflammation has been related to the Th-1-associated cytokine profile, including increased expression of IFN-γ and interleukin (IL)-17 mRNA in the colon. The pro-inflammatory cytokine tumor necrosis factor (TNF)-α is also one of the oncogenic risk factors[11]. Later, a whole genome sequencing report was published on seven EHSs, including *H. bilis* ATCC 43879, *H. canis* NCTC 12740, *H. canadensis* NCTC 13241, *H. cinaedi* CCUG 18818, *H. macacae* CCUG 55313^T, *H. pullorum* MIT 98-5489 and *H. winghamensis* ATCC BAA-430[16].

EHSs have a larger additional gene pool than gastric *Helicobacter* spp, which may be due to their larger genome size (average genome length about 2 Mb compared to gastric ones: average genome length 1.63 Mb)[22]. It should also be taken into account that the intra-intestinal environment is less aggressive than the acidic environment in the stomach due to the hydrochloric acid and, thus, is inhabited by a more diverse microbiome, which suggests the possibility of genetic exchange. These adaptive mechanisms are a consequence of the evolution of pathogens. A study by Smet et al. examined the genetic features of *H. pylori* and EHS, as in recent studies, but by more than a 3-fold increase in the genomic sequences of gastric NHPH and EHS[22]. EHS-specific genes are associated with macrolide resistance and the ability to synthesize L-arginine from L-ornithine. Arginine and ornithine play an important role in intestinal permeability and adaptive responses. These results can probably help in the development of new therapeutic strategies for the eradication of *Helicobacter*, taking into account the knowledge of its protective methods.

CURRENT DATA FROM HUMAN BEINGS

Nonalcoholic fatty liver disease (NAFLD)

NAFLD is characterized by a fatty liver in the early stage that can progress to steatohepatitis, cirrhosis, liver cancer, and liver failure[23]. The incidence of NAFLD increases annually and reaches 20–30% today, seriously affecting patient's quality of life. Data from clinical and experimental studies on the involvement of the microbiota of the gastrointestinal tract in the pathogenesis of NAFLD, including *H. pylori* infection[2,24], have become known. However, there are still disagreements[25-27].

An important finding was that Cindoruk et al.[28] detected the presence of *H. pylori* 16S rDNA in a liver sample from a 44-year-old woman with NAFLD. In 2009, another study added credibility to this finding. Pirouz et al.[29] observed that patients with various chronic liver diseases were more likely to be positive for *H. pylori* 16S rDNA compared to controls. They found *H. pylori* DNA in 5 of 11 samples taken from patients with NAFLD. Genetic analysis has shown that *H. pylori* and NAFLD share common genetic bases (95 genes, *P*-value = 2.5E-72). Genetic network analysis has shown that there may be mutual regulation between *H. pylori* and NAFLD through 21 of 95 genes[30]. There have been six systematic reviews with meta-analysis, all of which found a positive relation between *H. pylori* and NAFLD[23,30-35]. A recent

meta-analysis by Wei et al.(n=91,958) has also confirmed that *H. pylori* infection was associated with an elevated risk of NAFLD (Odds ratio (OR) = 1.38, 95% confidence interval (CI) 1.23–1.55, *P*<0.001)[36]. The researchers point out the strengths and weaknesses of their study, and conclude that subsequent prospective studies are needed to confirm the association between *H. pylori* and NAFLD. If these data are verified, eradication of *H. pylori* may become a new promising point in the treatment of NAFLD.

Autoimmune liver diseases

Autoimmune liver diseases (ALD) are chronic inflammatory diseases of the hepatobiliary system that are common in clinical practice[37]. ALD includes primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis (AIH)[38]. Nilson et al.[39] have studied 36 blood samples of patients with PSC, 21 patients with PBC, 19 patients with AIH, and 80 blood donors by immunoblotting using *Helicobacter pullorum*, *Helicobacter bilis*, and *Helicobacter hepaticus* cell surface proteins as antigens. They have shown that the incidence of antibodies to non-gastric *Helicobacter* spp in patients with ALD was higher than in healthy volunteers (*P*<0.001).

PBC is an autoimmune liver disease whose pathognomonic manifestations are chronic progressive non-suppurative cholangitis or granulomatous cholangitis involving the small bile ducts. The disease can proceed in an asymptomatic form, but laboratory testing reveals an elevated alkaline phosphatase level, and antimitochondrial antibodies are found in 80–95% of patients with PBC[40].

Goo et al.[41] reported a case of PBC in which a mouse was infected with *H. pylori*. Abenavoli et al.[42] diagnosed PBC and celiac disease in *H. pylori*-positive woman. Their experience confirmed the pathogenic role of increased intestinal permeability in the induction of PBC in celiac disease and *Helicobacter* infection. Specific interactions of infections may increase the risk of PBC. There is a much higher prevalence *of H. pylori* antibodies in PBC patients than in controls (54% vs 31 %, *P*<0.01)[43]. The mitochondrial auto-epitopic region of the pyruvate dehydrogenase complex E2 (PDC-E2) resembles *H. pylori* urease β, which may be related to the incidence of PBC[4]. Researchers have added *H. pylori* to the list of PBC etiopathogenetic factors due to presence of its DNA in the liver tissue and antibodies to *H. pylori* in the bile and serum of PBC patients[40].

PSC is an idiopathic progressive chronic intrahepatic cholestasis most commonly caused by fibrostenosis of the extrahepatic bile ducts. This can lead to biliary cirrhosis, which entails liver failure[40]. An early study of PSC patients showed the detection of *H. pylori* DNA in the liver of patients with PSC and other liver diseases. This contributed to a series of subsequent studies investigating the role of *Helicobacter* species in PSC and other ALD[44]. Krasinskas et al.[45] studied 25 end-stage PSC patients and 31 controls and found that 7 of 25 PSC patients (28%) and 3 of 31 controls (9.7%) were *H. pylori* positive (*P*=0.087). As shown by the results of the microdissection of the epithelium of the hilar bile ducts, patients with PSC are more often infected with *H. pylori* than the control group, presumably indicating bile reflux from the duodenum to the biliary tract. The development or progression of PSC may be associated with the entry of *H. pylori* into the proximal biliary system. These patients with PSC are more likely to develop ulcerative colitis, as increased intestinal permeability will stimulate *H. pylori* transport, triggering autoimmune mechanisms[40].

AIH is a rare syndrome that occurs without an established cause and is characterized by the destruction of liver cells by the immune system, mainly caused by autoantibodies[46]. The inability to tolerate hepatic antigens is hypothesized to be due to environmental factors, which include xenobiotics and pathogens in genetically predisposed patients[47]. *H. pylori* may be one of the triggers for this process. According to studies, the intestinal microbiota, which contains more genes than the human genome, has become a key factor in understanding the pathogenesis of liver diseases along the gut-liver axis[48]. The inflammatory process caused by *H. pylori* alters the microbiota of the gastrointestinal tract, therefore, *H. pylori* can also promote the movement of pathogens and lead to the triggering of autoimmune processes in the liver, affecting the intestinal flora[49]. *H. pylori* DNA has been detected in the liver tissues of a small number of patients with AIH, no significant differences have been found between these patients and controls[44]. Durazzo et al.[50] showed that patients

and controls had similar rates of *H. pylori* infection (*P*=0.3, OR=1.60, 95%CI 0.60–4.28). Peng et al.[39] reported that 61.67% of the 60 AIH patients were positive for *H. pylori* infection. Hepatic autoantibody profile rates in *H. pylori*-positive patients were significantly higher than in the negative group. But levels of liver function tests did not show any significant difference between *H. pylori*-positive or negative cases. Such pro-inflammatory cytokines as IFN-γ, IL-6, IL-10, and TNF-α were significantly higher in a blood sample of infected patients.

Viral hepatitis (HBV, HCV)

Hepatitis B and C viruses (HBV and HCV) are well-studied causative agents of liver cirrhosis. They are classified as type I liver carcinogens by the International Agency for Research on Cancer (IARC). Given that there are about 296 million people worldwide living with chronic hepatitis B according to WHO estimates[51], and more than half of the population is affected by *H. pylori*, more and more studies are being conducted to demonstrate an association between *H. pylori* infection and HBV. The social significance of the proposed association is because 25–30% of patients with chronic HBV develop liver cirrhosis, hepatocellular carcinoma (HCC), or death. A large study (n=4645) conducted by Wang et al.[52] aimed to demonstrate the role of *H. pylori* in the evolution of HBV and led to the recommendation to screen and treat *H. pylori*. This study showed some associations: a much higher prevalence of *H. pylori* among patients with HBV than in the healthy group (OR=3.17, 95%CI 2.38–4.22; *P*<0.01); the role of *H. pylori* as a risk factor in the development of HBV and the progression of chronic HBV to liver fibrosis; the prevalence of *H. pylori* infection in a group with B-viral cirrhosis (OR=4.28, 95%CI 2.99–6.13; *P*<0.01) is higher than in the healthy population.

A study by Segura-López et al.[11] has confirmed that the prevalence of *H. pylori* infection in patients with HBV-associated liver cirrhosis and HBV-associated cancer was significantly higher than in controls. Another study has demonstrated that the HBV-associated cirrhosis group had the highest incidence of *H. pylori* infection (79.3%) compared with chronic HBV, HBV-negative liver carcinoma, and the control group, indicating an increase in the incidence of *H. pylori* as the disease progressed in patients with HBV. The occurrence of *H. pylori* infection in patients with ≥10^3 copies/mL HBV DNA was significantly higher than in patients with <10^3 copies/mL HBV DNA (*P*<0.05), but there was no further correlation between *H. pylori* infection rate and viral load[53].

The Chinese multicenter observational study of 255 patients with HBV-induced cirrhosis treated with nucleoside analogues has demonstrated the effect of *H. pylori* infection on platelet levels in these patients. It was found that in individuals with *H. pylori,* the platelet count was significantly lower than in non-infected patients with compensated cirrhosis. During 2 years of follow-up, the platelet count has increased significantly in the presence of triple eradication therapy[54]. It was suggested that *H. pylori* infection might be linked to the clinical manifestations and progression of HBV. Therefore, eradication of *H. pylori* in this category of patients might be beneficial, especially among those who had developed thrombocytopenia.

A growing body of evidence suggests that *H. pylori* may be a risk factor for liver cirrhosis and HCC in patients with HCV. According to the meta-analysis by Wang et al.[55], the prevalence of *H. pylori* is almost three times higher among patients with HCV than in the healthy population (OR=2.93, 95%CI 2.30–3.75, *P*=0.05). The main factor influencing the rate of positive *H. pylori* results among patients with HCV is the stage of the disease. Esmat et al.[56] has found correlation between HCV and *H. pylori* infection. It was performed on 85 patients, divided into five groups, where liver tissue samples have been taken and tested by PCR for the *H. pylori* Cag A DNA gene. The presence of the Cag A gene is the highest in the group with HCV-associated liver cirrhosis and HCC (75%), 52.9% in the group of patients with HCV--associated liver cirrhosis; and 32% in the group of patients with chronic HCV compared with controls, where the PCR positivity of the Cag A gene is significantly lower. In a study by Mahmoud et al.[57], antibodies to *H. pylori* IgG have been detected in the plasma of 59.6% of patients. *Helicobacter* DNA has been present in 11.5% of liver biopsies taken from HCV patients using *Helicobacter* genus-specific 16S rRNA gene primers. All cases positive for *H. pylori* DNA in tissue samples are positive for *H. pylori* IgG in plas-

ma and negative for anti-schistosomal antibodies. *H. pylori* DNA-positive cases tend to be higher in HCV patients with high-stage liver fibrosis (33.3%) than those with low-stage liver fibrosis (2.7%) (P=0.0057). Thus, a strong association has been presented between *H. pylori* DNA in the liver and the fibrosis stage. However, no correlation has been found between *H. pylori* DNA in the liver and age, gender, liver function tests, alpha-fetoprotein levels, or HCV viral load. This discovery confirms the involvement of this bacterium in the progression of chronic HCV to HCC. Similar results have been obtained in a later study[58]. Immunohistochemical detection of *H. pylori* has shown positive reactivity in 62 biopsies out of 100 biopsies (38% of HCV patients and 62% of HCV patients co-infected with *H. pylori*). The histological examination of the liver of HCV patients revealed microvesicular and macrovesicular steatosis, lymphocytic infiltration, fibrosis, and cirrhosis. Cirrhotic nodules and hepatic parenchymal involvement are common in HCV patients co-infected with *H. pylori.* HCV patients with *H. pylori* have higher NIC scores and advanced fibrosis stages than HCV patients. Glycogen and total protein decrease in hepatocytes and cirrhotic nodes in patients with HCV. This decrease has been noted in the liver of HCV patients co-infected with *H. pylori.* A recent study, which assesses the potential role of *H. pylori* in the progression of chronic liver disease associated with HCV is of interest[59]. As a method of laboratory screening of *H. pylori,* the authors have used quantitative determination of the *H. pylori* antigen with a molecular weight of 58 kDa. The results have shown that *H. pylori* positivity increases significantly (P=0.021) with the progression of liver fibrosis, as it has been found in 44.45% of patients with fibrosis and 71.88% with cirrhosis. They have demonstrated that patients with F4 have been accompanied by a significant (P<0.05) increase in the concentration of *H. pylori* antigen with a 16.52-fold and 1.34-fold increase in its level compared with F0 and F1-F3, respectively. Patients co-infected with *H. pylori* and HCV are 3.19 times (219%) more likely to suffer from liver cirrhosis than patients with HCV mono-infection. This may prove that *H. pylori* infection may potentially affect liver disease progression. This highlights the importance of *H. pylori* screening in patients with HCV, as well as HBV, to select the correct treatment and prevent the further development of existing disease and the occurrence of cancer.

However, not all studies support the idea of correlation between HCV and *H. pylori* infection. In a study by Gutwerk et al.[60], seropositivity has been higher in the non-cirrhotic group than in the cirrhotic group (45.4% vs 20.0%, P<0.05). The IL28B SNP is well known to influence the spontaneous and treatment-induced clearance of HCV infection. For the first time, scientists have evaluated a possible link between the IL28B SNP and *H. pylori*. Still, no differences in IL28B genotypes among *H. pylori*-positive and *H. pylori*-negative groups have been found.

Cirrhosis

Several studies have shown that the prevalence of gastric and/or duodenal ulcers caused by *H. pylori* is much more often in patients with liver cirrhosis[4]. A meta-analysis by Feng et al.[61] has shown that among groups of patients with cirrhosis, the rate of *H. pylori* infection is significantly higher than in controls (OR=2.05, 95%CI 1.33–3.18, P<0.0001). According to another study[62], the number of patients with *H. pylori* and post-inflammatory liver cirrhosis is significantly higher (P=0.001) than those with alcoholic cirrhosis. Ammonia concentrations is significantly higher in *H. pylori*-infected patients compared to non-infected patients (129 vs 112 µmol/L; P=0.002). *Helicobacter* contributes to the development of hepatic encephalopathy and hyperammonemia. In a meta-analysis of six cohort studies involving 632 *H. pylori*-positive and 396 negative patients with cirrhosis, infection was associated with elevated blood ammonia levels. The effectiveness of *H. pylori* eradication in treating hepatic encephalopathy has not been thoroughly studied[4].

Abdel-Razik et al. have succeeded to demonstrate a correlation between liver cirrhosis and HCC in patients infected with *H. pylori*[63]. *H. pylori* is an independent risk variable for portal vein thrombosis and HCC (P=0.043, P=0.037). The study has also shown an increase levels of inflammatory factors such as serum C-reactive protein, TNF-α, IL-6, nitric oxide, and vascular endothelial growth factor in patients infected with *H. pylori*. A decrease in markers of inflammation and cirrhotic complications has been noted one year after *H. pylori* eradication.

Hepatobiliary cancer

Hepatobiliary cancer is a highly lethal cancer that includes a variety of invasive carcinomas developing in the liver (HCC), bile duct, intrahepatic and extrahepatic cholangiocarcinoma, gallbladder, and biliary tract cancer. These malignancies account for approximately 13% of all annual cancer deaths worldwide and 10–20% of deaths from hepatobiliary oncology[11]. Since *Helicobacter* spp have been successfully isolated from the biliary system, a hypothetical question is raised about the role of these organisms in the development of biliary tract cancer.

HCC is the most common primary liver cancer, accounting for about 75–85% of liver cancers[64]. *H. pylori* and similar species have been found in liver samples from patients with HCC[65]. Pellicano et al. have demonstrated earlier that *H. pylori* infection is about 85% among patients who has developed HCC secondary to HCV-related cirrhosis[66]. The incidence of *H. pylori* infection among patients with HBV-associated liver carcinoma (68.9%) and HBV-negative liver carcinoma (33.3%) is higher compared with controls (P<0.001)[53]. In addition, a meta-analysis reports a positive relation between *H. pylori* and the risk of developing HCC[67]. The incidence of *H. pylori* infection is 53.3% in HCC patients and 10.4% in controls, and the OR is 13.63 (95%CI 7.90–23.49) between *H. pylori* and the developing HCC. A recent large-scale meta-analysis by Madala et al.[64] including 26 studies has shown a significant difference in *H. pylori* infection in patients with HCC compared with controls. *H. pylori* infection is significantly higher in patients with HCC (OR= 4.75, 3.06–7.37). The results have shown an increased risk of developing HCC in the presence of *Helicobacter* infection, and the risk is significantly higher with HCV and *H. pylori* co-infection. Further prospective cohort studies are needed to prove a causal relationship, especially in cases of HBV and HCV coinfection and in patients with liver cirrhosis.

However, the studies of *Helicobacter* spp can enhance chronic parenchyma inflammation and lead to the development of HCC and other malignant neoplasms of the hepatobiliary system. Clinical studies using metagenomic analysis have shown that *Methylophilaceae, Fusobacterium, Prevotella, Actinomyces, Novosphingobium,* and *H. pylori* are increased in cholangiocarcinoma tissue samples compared with non-tumor tissue samples[68]. A meta-analysis has examined the association between *Helicobacter* spp and biliary tract cancer. *Helicobacter* spp are detected by PCR or immunohistochemical analysis of bile samples and tissues. A significantly higher cumulative incidence of *H. pylori* and *H. bilis* is traced in the biliary tract of the malignancy group (P=0.0001) and benign biliary disease group (P=0.0001) than in the healthy controls[8]. In recent studies, there is increasing evidence that the East Asian liver fluke *Opisthorchis viverrini* may serve as a reservoir of *Helicobacter,* implicating *Helicobacter* in the pathogenesis of Opisthorchis's-associated cholangiocarcinoma. Cholangiocytes affected by opisthorchiasis lining the intrahepatic biliary tract are considered to be the cell of origin of this malignant neoplasm. The authors investigate *in vitro* interactions between human cholangiocytes, *H. pylori* strain NCTC 11637, and the related bacillus *H. bilis.* Real-time quantification of cell proliferation, migration, and invasion by both H69 cholangiocytes and the CC-LP-1 cholangiocarcinoma cell line has shown that cell exposure to ≥10 *H. pylori* bacilli stimulates migration and invasion of cholangiocytes. In addition, 10 *H. pylori* bacilli stimulates contact-independent colony formation on soft agar[69]. These data support the hypothesis that *H. pylori* infection promotes malignant transformation of the biliary epithelium. A meta-analysis of 10 case-control studies confirms a possible correlation between *Helicobacter* spp and cholangiocarcinoma (OR=8.88, 95%CI 3.67–21.49). When analyzing subgroups by geographic location, it has been found that *H. pylori* infection can be a risk factor not only in the Asian region with a high incidence of cholangiocarcinoma but also in Europe, where the incidence rate is much lower[70].

Cholelithiasis

Recent studies have investigated a possible risk affiliation between *Helicobacter* and the development of gallstones and cholecystitis. Studies have shown that *H. pylori* in bile may be a risk factor for its development[71]. For example, according to Zhang et al.[72], age, aspartate aminotransferase, total cholesterol, *H. pylori* infection, HCV, and fatty liver are significantly associated with gallstones (P<0.05). The collated analysis has detected that gallstones among

H. pylori-eradicated subjects are significantly lower compared to *H. pylori*-positive subjects (P<0.05). Moreover, a meta-analysis has demonstrated a positive correlation between *H. pylori* infection and chronic cholecystitis and cholelithiasis (OR=3.022; 95%CI 1.897–4.815; I^2=20.1%)[73]. Among the possible explanations for this phenomenon, it is believed that *H. pylori* can infect the biliary system, causing chronic inflammation of its mucosa and, as a result, leading to impaired acid secretion and a decrease in the solubility of calcium salts in bile, which predisposes to the formation of gallstones.

Mechanisms by which *Helicobacter* could generate damage

Inflammation and fibrosis are key factors in the progression of chronic liver diseases (FIGURE 1). Several theories explain how *H. pylori* infection can influence the development of hepatobiliary diseases[74]. One of them is the violation of the epithelium of the gastrointestinal tract, the translocation of the microbiota and its metabolites into the portal system and the stimulation of inflammation through toll-like receptors (TLR) that transmit signals in hepatocytes. *H. pylori* induces human β-defensin-1, which may be a biomarker for bacterial translocation[26]. *H. pylori* also induces the release of vasoactive and pro-inflammatory molecules such as IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, TNF-α, leukotrienes, prostaglandins, interferon-β, interferon-γ and acute phase proteins[24,63,66]. It has been suggested that *H. pylori* infection has a systemic effect through the activity of these cytokines and the exacerbation of various inflammatory responses[63].

A possible mechanism for the interaction between *H. pylori* infection and NAFLD involves Fetuin A or alpha-2-HS glycoprotein synthesized by hepatocytes and acting as a free fatty acid carrier. Higher serum levels of Fetuin A in *H. pylori*-positive patients correlate with insulin resistance. Fetuin A also acts as an endogenous adapter protein for free fatty acid-mediated TLR4 activation and triggers the release of inflammatory mediators. In addition to increasing Fetuin A levels, *H. pylori* infection may increase the permeability of the intestinal barrier, leading to the translocation of lipopolysaccharides and pathogen-associated molecular fragments (PAMPs) to the liver, which are known to be activators of Kupffer cells and stellate cells, promoting the development of fibrosis[75].

Recent work has suggested that *H. pylori* may lead to chronic vasculitis, thus causing endothelial dysfunction. Systemic inflammatory conditions caused by *H. pylori* increase NO production. Studies have shown that NO concentration was increased in cirrhotic patients infected with H. pylori. It is also known that excess NO generation can initiate neoplastic transformation[63]. *H. pylori* is thought to increase vascular endothelial growth factor (VEGF) expression through a signaling pathway involving the MEK-ERK and NF-kB cascade. An increased concentration of VEGF has been associated with a significant increase in neoangiogenesis, as assessed by the definition of CD34-positive microvessels[76]. VEGF is the main regulator of angiogenesis in malignant and normal tissues. It is vital in playing an important role in enhancing endothelial cell proliferation thereby and promoting neovascularization in and around malignant cells. It is involved in many

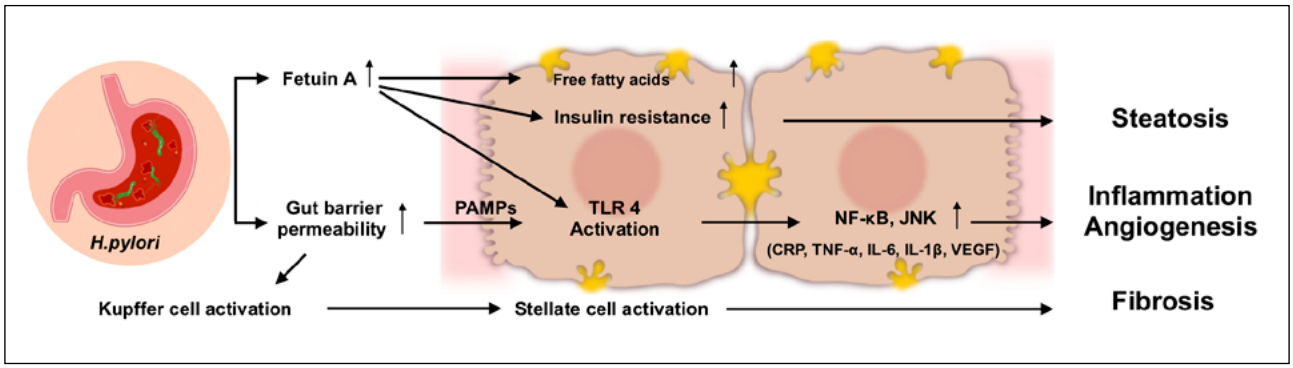

FIGURE 1. Mechanisms mediated by *H. pylori* infection leading to hepatic injury.
CRP: C-reactive protein; IL: interleukin; JNK: c-Jun N-terminal kinase; PAMPs: pathogen-associated molecular patterns; TLR: toll-like receptors; TNF: tumor necrosis factor, VEGF: vascular endothelial growth factor.

other conditions such as receptor activation associated with tumor cell proliferation and endothelial cell recruitment[63]. It has been declared that the bacterium enhances the secretion of adhesion molecules, which can improve the induction of neutrophils through the endothelium, which is a key crucial moment in the etiopathogenesis of endothelial dysfunction. The pro-oncogenic role of *H. pylori* infection is partly explained by the activation of the transforming growth factor β1-dependent oncogenic pathway, which affects the balance between hepatocyte proliferation and apoptosis *in vitro* models[63]. Activation of a proto-oncogene may represent a crucial step in the mechanism of *H. pylori*-induced neoplasia[66]. *H. pylori* has a pathological effect on HepG2 hepatoma cells, increasing the expression of some proteins associated with gene transcription and signal transduction[6]. The virulent type of *H. pylori* causes cell cycle arrest and apoptosis in Huh7 cells, another hepatoma cell line. According to Liu et al.[77], histidine-rich protein, a small histidine-rich *H. pylori* cytoplasmic protein, induces apoptosis by downregulating ubiquitin-specific peptidase 5 expressions and activating the P14-P53 signaling pathway. However, these data are only indirect findings from *in vitro* cancer cell line studies.

CONCLUSION

H. pylori, a known gastric carcinogen, is likely involved in developing many other extragastroduodenal diseases. Many studies show that *H. pylori* infection contributes to the etiopathogenesis of fatty liver disease. In addition, only a few studies have investigated the effect of *H. pylori* eradication on the development of NAFLD. Histopathological confirmation is needed to present that *H. pylori* eradication prevents or improves disease progression. The significance of *H. pylori* in the exacerbation of autoinflammatory processes of various origins should also be considered. The role of infectious agents in the development of HCC provides new insights into the pathogenesis of this disease and may influence future screening recommendations. In addition, the significance of other *Helicobacter* spp in hepatobiliary diseases is discussed. However, many conflicting results indicate that some evidence is inconclusive and further research is needed. Since access to the biliary pathways is only possible through invasive procedures or surgery, it is necessary to develop PCR protocols, more suitable antigens for immunohistochemistry, and simple and effective serological methods for the early detection of *Helicobacter* spp, which will help reduce morbidity and mortality associated with hepatobiliary diseases.

Authors' contribution

Kugler T: data collection, analysis and interpretation, formulation of conclusions, final approval for the publication of the manuscript; consent of the author to be responsible for all aspects of the work. Taradin G: data collection, analysis and interpretation.

Orcid

Tatyana Kugler: 0000-0001-5547-6741.
Gennady Taradin: 0000-0003-3984-8482.

Kugler T, Taradin G. *Helicobacter pylori* e as doenças hepatobiliares: atualização 2023. Arq Gastroenterol. 2023;60(2):271-81.

RESUMO – *Helicobacter pylori* (*H. pylori*) é uma das principais causas infecciosas de doenças gastroduodenais, no entanto, seu papel no desenvolvimento de diferentes doenças extragástricas tem sido comprovado. Sugere-se o possível envolvimento do *H. pylori* na patogênese de doenças cardiovasculares, metabólicas, neurodegenerativas, cutâneas e hepatobiliares. A bactéria tem sido encontrada em amostras de tecido do fígado, trato biliar e cálculos biliares de animais e humanos. No entanto, o papel da infecção por *H. pylori* na patogênese de doenças do fígado e das vias biliares ainda não foi estabelecido definitivamente. A confirmação histopatológica do efeito positivo da erradicação do *H. pylori* é necessária. Além disso, existem discussões sobre a importância clínica de outras espécies de *Helicobacter*. A revisão apresenta os dados disponíveis a favor e contra o envolvimento do *H. pylori* no desenvolvimento e progressão das doenças hepatobiliares.

Palavras-chave – *Helicobacter pylori*; doença hepática gordurosa não alcoólica; doenças hepáticas autoimunes; hepatite viral; cirrose; colelitíase; câncer.

REFERENCES

1. Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou JM, Schulz C, et al. European Helicobacter and Microbiota Study group. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. Gut. 2022:gutjnl-2022-327745. doi:10.1136/gutjnl-2022-327745.
2. German SV, Bobrovnitsky IP. Helicobacter pylori Infection and Hepatobiliary Pathology. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2018;28:15-22. doi:10.22416/1382-4376-2018-28-4-15-22.
3. Kugler TE, Taradin GG, Pellicano R. The role of Helicobacter pylori in metabolic and cardiovascular diseases. Experimental and Clinical Gastroenterology. 2021;193:86-95. doi: 10.31146/1682-8658-ecg-193-9-86-95.
4. Waluga M, Kukla M, Żorniak M, Bacik A, Kotulski R. From the stomach to other organs: Helicobacter pylori and the liver. World J Gastroenterol. 2015;7:2136-46. doi: 10.4254vjh.v7.i18.2136.
5. Baeg MK, Yoon SK, Ko SH, Noh YS, Lee IS, Choi MG. Helicobacter pylori infection is not associated with nonalcoholic fatty liver disease. World J Gastroenterol. 2016;22:2592-600. doi:10.3748/wjg.v22.i8.2592.
6. Okushin K, Takahashi Y, Yamamichi N, Shimamoto T, Enooku T, Fujinaga H, et al. Helicobacter pylori infection is not associated with fatty liver disease including non-alcoholic fatty liver disease: a large-scale cross-sectional study in Japan. BMC Gastronterol. 2015;15:25.
7. Takemura LS, Marcasso RA, Lorenzetti E, Alfieri AA, Bracarense APL. Helicobacter infection in the hepatobiliary system and hepatic lesions: a possible association in dogs. Braz J Microbiol. 2019;50:297-305. doi: 10.1007/s42770-018-0003-8.
8. Zhou D, Wang JD, Weng MZ, Zhang Y, Wang XF, Gong W, Quan ZW. Infections of Helicobacter spp. in the biliary system are associated with biliary tract cancer: a meta-analysis. Eur J Gastroenterol Hepatol. 2013;25:447-54. doi: 10.1097/MEG.0b013e32835c0362.
9. Marshall BJ. Helicobacter pylori in peptic ulcer: have Koch's postulates been fulfilled? Ann Med. 1995;27:565-8. doi: 10.3109/07853899509002470.
10. Mannion A, Shen Z, Fox JG. Comparative genomics analysis to differentiate metabolic and virulence gene potential in gastric versus enterohepatic Helicobacter species. BMC genomics. 2018;19:830. https://doi.org/10.1186/s12864-018-5171-2.
11. Segura-López FK, Güitrón-Cantú A, Torres J. Association between Helicobacter spp. infections and hepatobiliary malignancies: a review. World J Gastroenterol. 2015;21:1414-23. doi: 10.3748/wjg.v21.i5.1414.
12. Greiter-Wilke A, Scanziani E, Soldati S, McDonough SP, McDonough PL, Center SA, et al. Association of Helicobacter with cholangiohepatitis in cats. J Vet Int Med. 2006;20:822-7. doi: 10.1111/j.1939-1676.2006.tb01792.x.
13. Elyasi B, Rezaie A, Moori Bakhtiari N, Mosallanejad B. Helicobacter genus in the intestine and liver of stray cats: the molecular, histopathological, and immunohistochemical study. Braz J Microbiol. 2020;51:2123-32. doi: 10.1007/s42770-020-00359-1.
14. Beisele M, Shen Z, Parry N, Mobley M, Taylor NS, Buckley E, et al. Helicobacter marmotae and novel Helicobacter and Campylobacter species isolated from the livers and intestines of prairie dogs. J Med Microbiol. 2011;60:1366-74. doi:10.1099/jmm.0.032144-0.
15. Garcia A, Erdman SE, Xu S, Feng Y, Rogers AB, Schrenzel MD, et al. Hepatobiliary inflammation, neoplasia, and argyrophilic bacteria in a ferret colony. Vet Pathol. 2002;39:173-9. doi:10.1354/vp.39-2-173.
16. Shen Z, Sheh A, Young SK, Abouelliel A, Ward DV, Earl AM, et al. Draft genome sequences of six enterohepatic helicobacter species isolated from humans and one from rhesus macaques. Genome Announc. 2014;2:e00857-14. doi:10.1128/genomeA.00857-14.
17. Fox JG, Handt L, Sheppard BJ, Xu S, Dewhirst FE, Motzel S, et al. Isolation of Helicobacter cinaedi from the colon, liver, and mesenteric lymph node of a rhesus monkey with chronic colitis and hepatitis. J Clin Microbiol. 2001;39:1580-85.
18. Nam C, Ohmachi Y, Kokubo T, Nishikawa T, Uchida K, Nakayama H. Histopathological studies on cases of chronic mouse hepatitis by natural Helicobacter infections. J Vet Med Sci. 2013;75:1231-5. doi:10.1292/jvms.12-0304.
19. Ménard A, Péré-Védrenne C, Haesebrouck F, Flahou B. Gastric and Enterohepatic Helicobacters other than Helicobacter pylori. Helicobacter. 2014;19:59-67. doi:10.1111/hel.12162.
20. Tomb JF, White O, Kerlavage AR, Clayton RA, Sutton GG, Fleischmann RD, et al. The complete genome sequence of the gastric pathogen helicobacter pylori. Nature. 1997;388:539-47. doi:10.1038/41483.
21. Suerbaum S, Josenhans C, Sterzenbach T, Drescher B, Brandt P, Bell M, et al. The complete genome sequence of the carcinogenic bacterium helicobacter hepaticus. Proc Natl Acad Sci U S A. 2003;100:7901-6. doi:10.1073/pnas.1332093100.
22. Smet A, Yahara K, Rossi M, Tay A, Backert S, Armin E, et al. Macroevolution of gastric Helicobacter species unveils interspecies admixture and time of divergence. ISME J. 2018;12:2518-31. doi: 10.1038/s41396-018-0199-5.
23. Liu R, Liu Q, He Y, Shi W, Xu Q, Yuan Q, et al. Association between Helicobacter pylori infection and nonalcoholic fatty liver: A meta-analysis. Medicine (Baltimore). 2019;98: e17781.
24. Doulberis M, Srivastava S, Polyzos SA, Kountouras J, Papaefthymiou A, Klukowska-Rötzler J, et al. Active Helicobacter Pylori infection is independently associated with nonalcoholic steatohepatitis in morbidly obese patients. J Clin Med. 2020;9:933. doi:10.3390/jcm9040933
25. Lecube A, Valladares S, López-Cano C, Gutiérrez L, Ciudin A, Fort JM, et al. The role of morbid obesity in the promotion of metabolic disruptions and non-alcoholic steatohepatitis by Helicobacter Pylori. PLoS One. 2016;11:e0166741. doi:10.1371/journal.pone.0166741.
26. Lu LJ, Hao NB, Liu JJ, Li X, Wang RL. Correlation between Helicobacter Pylori infection and metabolic abnormality in general population: A Cross-Sectional Study. Gastroenterol Res Pract. 2018;7410801. doi:10.1155/2018/7410801.
27. Fan N, Peng L, Xia Z, Zhang L, Wang Y, Peng Y. Helicobacter pylori infection is not associated with non-alcoholic fatty liver disease: a cross-sectional study in China. Front. Microbiol. 2018;9:73. doi:10.3389/fmicb.2018.00073.
28. Cindoruk M, Cirak MY, Unal S, Karakan T, Erkan G, Engin D, et al. Identification of Helicobacter species by 16S rDNA PCR and sequence analysis in human liver samples from patients with various etiologies of benign liver diseases. Eur J Gastroenterol Hepatol. 2008;20:33-6.
29. Pirouz T, Zounubi L, Keivani H, Rakhshani N, Hormazdi M. Detection of Helicobacter pylori in paraffin-embedded specimens from patients with chronic liver diseases, using the amplification method. Dig Dis Sci. 2009;54:1456-9.
30. Chen CX, Mao YS, Foster P, Zhu ZW, Du J, Guo CY. Possible association between Helicobacter pylori infection and nonalcoholic fatty liver disease. Appl Physiol Nutr Metab. 2017;42:295-301. doi: 10.1139/apnm-2016-0499.
31. Mantovani A, Turino T, Altomari A, Lonardo A, Zoppini G, Valenti L, et al. Association between Helicobacter pylori infection and risk of nonalcoholic fatty liver disease: An updated meta-analysis. Metabolism. 2019;96:56-65. doi:10.1016/j.metabol.2019.04.012.
32. Ning L, Liu R, Lou X, Du H, Chen W, Zhang F, et al. Association between Helicobacter pylori infection and nonalcoholic fatty liver disease: A systemic review and meta-analysis. Eur J Gastroenterol Hepatol. 2019;31:735-42. doi:10.1097/MEG.0000000000001398.
33. Zhou BG, Yang HJ, Xu W, Wang K, Guo P, Ai YW. Association between Helicobacter pylori infection and nonalcoholic fatty liver disease: A systematic review and meta-analysis of observational studies. Helicobacter. 2019;24:e12576. doi:10.1111/hel.12576.
34. Wijarnpreecha K, Thongprayoon C, Panjawatanan P, Manatsathit W, Jaruvongvanich V, Ungprasert P. Helicobacter pylori and Risk of Nonalcoholic Fatty Liver Disease. J Clin Gastroenterol. 2018;52:386-91. doi:10.1097/MCG.0000000000000784.
35. Ma Z, Chu X, Yan X, Wang W. Association between Helicobacter pylori infection and non-alcoholic fatty liver disease for Asian and non-Asian population: A systematic review and meta-analysis. Front Public Health. 2022;10:1062942. doi: 10.3389/fpubh.2022.1062942.
36. Wei L, Ding HG. Relationship between Helicobacter pylori infection and nonalcoholic fatty liver disease: What should we expect from a meta-analysis? Medicine (Baltimore). 2021;100:e26706. doi:10.1097/MD.0000000000026706.
37. Trivedi PJ, Hirschfield GM. Recent Advances in Clinical Practice: Epidemiology of Autoimmune Liver Diseases. Gut. 2021;70:1989-2003. doi:10.1136/gutjnl-2020-322362.
38. Peng XG, Li YY, Chen HT, Zhou Y, Ma JG, Yin HM. Evolution of correlation between Helicobacter pylori infection and autoimmune liver disease. Exp Ther Med. 2017;14:1487-90. doi:10.3892/etm.2017.4696.

39. Nilsson I, Kornilovs'ka I, Lindgren S, Ljungh Å, Wadström T. Increased prevalence of seropositivity for non-gastric helicobacter species in patients with autoimmune liver disease. J Med Microbiol. 2003;52:949-53. doi:10.1099/jmm.0.05344-0.
40. Wang L, Cao ZM, Zhang LL, Dai XC, Liu ZJ, Zeng YX, et al. Helicobacter Pylori and Autoimmune Diseases: Involving Multiple Systems. Front Immunol. 2022;13:833424. doi:10.3389/fimmu.2022.833424.
41. Goo MJ, Ki MR, Lee HR, Hong IH, Park JK, Yang HJ, et al. Primary biliary cirrhosis, similar to that in human beings, in a male c57bl/6 mouse infected with Helicobacter Pylori. Eur J Gastroenterol Hepatol. 2008;20:1045-8. doi:10.1097/MEG.0b013e3282f5e9db.
42. Abenavoli L, Arena V, Giancotti F, Vecchio FM, Abenavoli S. Celiac Disease, Primary Biliary Cirrhosis and Helicobacter Pylori Infection: One Link for Three Diseases. Int J Immunopath PH. 2010;23:1261-5. doi: 10.1177/039463201002300431.
43. Shapira Y, Agmon-Levin N, Renaudineau Y, Porat-Katz BS, Barzilai O, Ram M, et al. Serum Markers of Infections in Patients with Primary Biliary Cirrhosis: Evidence of Infection Burden. Exp Mol Pathol. 2012;93:386-90. doi:10.1016/j.yexmp.2012.09.012.
44. Smyk DS, Koutsoumpas AL, Mytilinaiou MG, Rigopoulou EI, Sakkas LI, Bogdanos DP. Helicobacter pylori and autoimmune disease: cause or bystander. World J Gastroenterol. 2014;20:613-29. doi:10.3748/wjg.v20.i3.613.
45. Krasinskas AM, Yao Y, Randhawa P, Dore MP, Sepulveda AR. Helicobacter Pylori may play a contributory role in the pathogenesis of primary sclerosing cholangitis. Dig Dis Sci. 2007;52:2265-70. doi: 10.1007/s10620-007-9803-7.
46. Webb GJ, Hirschfield GM, Krawitt EL, Gershwin ME. Cellular and Molecular Mechanisms of Autoimmune Hepatitis. Annu Rev Pathol. 2018;13:247-92. doi: 10.1146/annurev-pathol-020117-043534.
47. Mieli-Vergani G, Vergani D, Czaja AJ, Manns MP, Krawitt EL, Vierling JM, et al. Autoimmune Hepatitis. Nat Rev Dis Primers. 2018;4:18017. doi: 10.1038/nrdp.2018.17.
48. Tang R, Wei Y, Li Y, Chen W, Chen H, Wang Q, et al. Gut Microbial Profile is Altered in Primary Biliary Cholangitis and Partially Restored After UDCA Therapy. Gut. 2018;67:534-41. doi: 10.1136/gutjnl-2016-313332.
49. Wei Y, Li Y, Yan L, Sun C, Miao Q, Wang Q, et al. Alterations of gut microbiome in autoimmune hepatitis. Gut. 2020;69:569-77. doi: 10.1136/gutjnl-2018-317836.
50. Durazzo M, Pellicano R, Premoli A, Berrutti M, Leone N, Ponzetto A, et al. Helicobacter Pylori seroprevalence in patients with autoimmune hepatitis. Dig Dis Sci. 2002;47:380-3. doi: 10.1023/A:1013782408510.
51. [Electronic resource]. [Internet]. Available from: https://www.who.int/ru/news-room/fact-sheets/detail/hepatitis-b
52. Wang J, Chen RC, Zheng YX, Zhao SS, Li N, Zhou RR, et al. Helicobacter pylori infection may increase the risk of progression of chronic hepatitis B disease among the Chinese population: a meta-analysis. Int J Infect Dis. 2016;50:30-7.
53. Huang J, Cui J. Evaluation of Helicobacter pylori Infection in Patients with Chronic Hepatic Disease. Chin Med J (Engl). 2017;130:149-54. doi:10.4103/0366-6999.197980
54. Zhang XH, He Y, Feng R, Xu LP, et al. Helicobacter pylori infection influences the severity of thrombocytopenia and its treatment response in chronic hepatitis B patients with compensatory cirrhosis: A multicenter, observational study. Platelets. 2016;27(3):223–229.
55. Wang J, Li WT, Zheng YX, Zhao SS, Li N, Huang Y, et al. The Association between Helicobacter Pylori Infection and Chronic Hepatitis C: A Meta-Analysis and Trial Sequential Analysis. Gastroenterol Res Pract. 2016;2016:8780695. doi:10.1155/2016/8780695.
56. Esmat G, El-Bendary M, Zakarya S, Ela MA, Zalata K. Role of Helicobacter pylori in patients with HCV-related chronic hepatitis and cirrhosis with or without hepatocellular carcinoma: possible association with disease progression. J Viral Hepat. 2012;19:473-9. doi: 10.1111/j.1365-2893.2011.01567.x.
57. Mahmoud MA, Elden LA, Awad MM, Haile HA. Helicobacter Pylori DNA in Liver Tissues From Chronic Hepatitis C Egyptian Patients. Gastroenterology Res. 2011;4:262-7. doi:10.4021/gr356w
58. Sakr SA, Badrah GA, Sheir RA. Histological and histochemical alterations in liver of chronic hepatitis C patients with Helicobacter pylori infection. Biomed Pharmacother. 2013;67:367-74. doi: 10.1016/j.biopha.2013.03.004.
59. Attallah AM, Albannan MS, Ghaly MF, Sallam SE, Amer MM, Attia AA.Prevalence of Helicobacter pylori infection in patients with chronic hepatitis C. J Genet Eng Biotechnol. 2022;20:13. doi:10.1186/s43141-021-00293-1
60. Gutwerk A, Wex T, Stein K, Langner C, Canbay A, Malfertheiner P, et al. Helicobacter Pylori Serology in Relation to Hepatitis C Virus Infection and IL28B Single Nucleotide Polymorphism. J Clin Med. 2018;7:44. doi:10.3390/jcm7030044
61. Feng H, Zhou X, Zhang G. Association between cirrhosis and Helicobacter pylori infection: a meta-analysis. Eur J Gastroenterol Hepatol. 2014;26:1309-19.
62. Pogorzelska J, Łapiżka M, Kalinowska A, Łapiżki TW, Flisiak R. Helicobacter pylori infection among patients with liver cirrhosis. Eur J Gastroenterol Hepatol. 2017;29:1161-5. doi:10.1097/MEG.0000000000000928.
63. Abdel-Razik A, Mousa N, Elhelaly R, Elzehery R, Hasan AS, Abdelsalam M, et al. Helicobacter pylori as an initiating factor of complications in patients with cirrhosis: a single-center observational study. Front Med (Lausanne). 2020;7:96. doi:10.3389/fmed.2020.00096.
64. Madala S, MacDougall K, Surapaneni BK, Park R, Girotra M, Kasi A. Coinfection of Helicobacter pylori and Hepatitis C Virus in the Development of Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. J Clin Med Res. 2021;13:530-40. doi: 10.14740/jocmr4637.
65. Okushin K, Tsutsumi T, Ikeuchi K, Kado A, Enooku K, Fujinaga H, et al. Helicobacter pylori infection and liver diseases: Epidemiology and insights into pathogenesis. World J Gastroenterol. 2018;24:3617-25. doi:10.3748/wjg.v24.i32.3617
66. Pellicano R, Mazzaferro V, Grigioni WF, Cutufia MA, Fagoonee S, Silengo L, et al. Helicobacter species sequences in liver samples from patients with and without hepatocellular carcinoma. World J Gastroenterol. 2004;10:598-601. doi:10.3748/wjg.v10.i4.598.
67. Xuan SY, Xin YN, Chen AJ, Dong QJ, Qiang X, Li N, et al. Association between the presence of H pylori in the liver and hepatocellular carcinoma: a meta-analysis. World J Gastroenterol. 2008;14:307-12.
68. Avilés-Jiménez F, Guitron A, Segura-López F, Méndez-Tenorio A, Iwai S, Hernández-Guerrero A, et al. Microbiota studies in the bile duct strongly suggest a role for Helicobacter pylori in extrahepatic cholangiocarcinoma. Clin Microbiol Infect. 2016;22:178e11-22. doi: 10.1016/j.cmi.2015.10.008.
69. Thanaphongdecha P, Karinshak SE, Ittiprasert W, Mann VH, Chamgramol Y, Pairojkul C, et al. Infection with Helicobacter pylori Induces Epithelial to Mesenchymal Transition in Human Cholangiocytes. Pathogens. 2020;9:971. doi:10.3390/pathogens9110971
70. Xiao M, Gao Y, Wang Y. Helicobacter species infection may be associated with cholangiocarcinoma: a meta-analysis. Int J Clin Pract. 2014;68:262-70.
71. Santos MLC, de Brito BB, da Silva FAF, Sampaio MM, Marques HS, Oliveira E Silva N, et al. Helicobacter pylori infection: Beyond gastric manifestations. World J Gastroenterol. 2020;26:4076-93. doi:10.3748/wjg.v26.i28.4076
72. Zhang FM, Yu CH, Chen HT, Shen Z, Hu FL, Yuan XP, et al. Helicobacter pylori infection is associated with gallstones: Epidemiological survey in China. World J Gastroenterol. 2015;21:8912-9. doi:10.3748/wjg.v21.i29.8912
73. Cen L, Pan J, Zhou B, Yu C, Li Y, Chen W, et al. Helicobacter Pylori infection of the gallbladder and the risk of chronic cholecystitis and cholelithiasis: A systematic review and meta-analysis. Helicobacter. 2018;23:1. doi: 10.1111/hel.12457.
74. Sharndama HC, Mba IE. Helicobacter pylori: an up-to-date overview on the virulence and pathogenesis mechanisms. Braz J Microbiol. 2022;53:33-50. doi: 10.1007/s42770-021-00675-0.
75. Boeckmans J, Rombaut M, Demuyser T, Declerck B, Piérard D, Rogiers V, et al. Infections at the nexus of metabolic-associated fatty liver disease. Arch Toxicol. 2021;95:2235-53. doi:10.1007/s00204-021-03069-1
76. Kang MJ, Song EJ, Kim BY, Kim DJ, Park JH. Helicobacter pylori induce vascular endothelial growth factor production in gastric epithelial cells through hypoxia-inducible factor-1a-dependent pathway. Helicobacter. 2014;19:476-83. doi: 10.1111/hel.12169.
77. Liu Y, Wang WM, Zou LY, Li L, Feng L, Pan MZ, et al. Ubiquitin specific peptidase 5 mediates Histidine-rich protein Hpn induced cell apoptosis in hepatocellular carcinoma through P14-P53 signaling. Proteomics. 2017;17. doi: 10.1002/pmic.201600350.