

Helicobacter pylori infection among patients with liver cirrhosis

Joanna Pogorzelska^a, Magda Łapińska^b, Alicja Kalinowska^a, Tadeusz W. Łapiński^a and Robert Flisiak^a

Background and aim Inflammatory changes in the stomach caused by *Helicobacter pylori* indirectly and directly affect liver function. Moreover, the bacteria may worsen the course of the liver cirrhosis. The study aimed at evaluating the incidence of *H. pylori* infection among patients with liver cirrhosis, depending on the etiology and injury stage, scored according to Child–Pugh classification. Stage of esophageal varices and endoscopic inflammatory lesions in the stomach were evaluated, depending on the presence of *H. pylori* infection.

Patients and methods The study included 147 patients with liver cirrhosis: 42 were infected with hepatitis C virus, 31 were infected with hepatitis B virus, 56 had alcoholic liver cirrhosis, and 18 had primary biliary cirrhosis. Diagnosis of *H. pylori* infection was performed based on the presence of immunoglobulin G antibodies in serum.

Results *H. pylori* infection was found in 46.9% of patients. The incidence of *H. pylori* infection among patients with postinflammatory liver cirrhosis was significantly higher ($P=0.001$), as compared with patients with alcoholic liver cirrhosis. Ammonia concentration was significantly higher in patients infected with *H. pylori*, compared with noninfected individuals (129 vs. 112 $\mu\text{mol/l}$; $P=0.002$). Incidence of *H. pylori* infection in patients without esophageal varices was significantly lower compared with patients with esophageal varices (14 vs. 60%; $P<0.001$).

Conclusion *H. pylori* infection is significantly more frequent among patients with postinflammatory liver cirrhosis (infected with hepatitis C virus or hepatitis B virus) than in patients with alcoholic liver cirrhosis or primary biliary cirrhosis. *H. pylori* infection correlates with elevated concentration of blood ammonia and the incidence of esophageal varices. Eur J Gastroenterol Hepatol 29:1161–1165

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Introduction

Helicobacter pylori is a microaerophile, a Gram-negative bacillus, resistant to the activity of gastric juice. The bacteria may take the vegetative form (spiral shape) or sporulation form. *H. pylori* lives mainly on the surface of epithelial cells of mucous membranes of the prepyloric part of the stomach. The cilia present on the bacteria allow it to move into intercellular spaces and adhere to the surface of cells. Infection with these bacteria is one of the most common in the world. In highly developed countries, 50% of the population is infected, whereas in the developing countries the proportion reaches as much as 90% [1].

H. pylori infection causes local (limited to the gastric mucous membrane) and general increase of proinflammatory cytokines interleukin (IL)-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17,

interferon- β , and tumor necrosis factor- α [2]. This phenomenon not only leads to stimulation of local inflammatory reaction but also exacerbates different inflammatory reactions in the organism. *H. pylori* underlies chronic atrophic gastritis, metaplasia, and dysplasia, leading to the development of gastric cancer. According to the WHO, the bacteria is a class I carcinogenic factor. It may influence extragastric organ disturbances, exacerbating cardiovascular diseases, metabolic diseases, disturbing normal liver function, especially in patients with liver cirrhosis [3].

In the group of patients infected with *H. pylori*, morphologic studies on liver of patients infected with hepatitis B virus (HBV), hepatitis C virus (HCV), and patients with chronic noninfectious liver diseases have demonstrated the presence of *H. pylori* DNA in the perihepatic tissues. Such an infection is caused by disturbances of immunologic functions in this group of patients [4]. *H. pylori* infection influences the disturbances of lipid metabolism, manifesting with hypertriglyceridemia and hypercholesterolemia, with concurrent fall in high-density lipoprotein. This is especially important in the metabolism of hepatocytes, their steatosis, and liver fibrosis [5].

In the course of liver cirrhosis, pathological lesions often appear in the mucous membranes of the stomach. Portal gastropathy is a chronic inflammatory state that occurs most frequently. *H. pylori* infection in the group of patients with liver cirrhosis may influence exacerbation of inflammatory lesions in the stomach, which could directly and indirectly lead to impairment of liver function. This is

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Departments of ^aInfectious Diseases and Hepatology and ^bPopulation Medicine and Civilization Diseases Prevention, Medical University of Białystok, Białystok, Poland

Correspondence to Tadeusz W. Łapiński, MD, Zurawia str.14, 15-550 Białystok, Poland

Tel: +48 604 651 709; fax: +48 85 7416 921; e-mail: twlapinski@wp.pl

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especially dangerous in patients with advanced liver injury. Studies on this group of patients point to high importance of cytopathological effect of *H. pylori* on hepatocytes [4].

Aim

The study aimed at determining the incidence of *H. pylori* infection among patients with liver cirrhosis. The presence of this infection was analyzed depending on the cause of liver cirrhosis and failure stage. Incidence of *H. pylori* infection was evaluated depending on the stage of esophageal varices and endoscopic changes of gastric mucous membranes. The effect of *H. pylori* infection on ammonia concentration was determined.

Patients and methods

The study was conducted to assess patients with liver cirrhosis in the North-East of Poland. The study included patients with postinflammatory liver cirrhosis, connected with HCV or HBV infection, primary biliary cirrhosis (PBC), and alcoholic liver cirrhosis. The severity of liver cirrhosis was estimated based on Child–Pugh score. An ultrasound examination was performed in all patients, determining liver parenchyma and signs of portal hypertension, using USG Power Doppler technique. Liver cirrhosis was estimated on the basis of clinical evaluation, liver biopsy, or elastography as a noninvasive method for liver fibrosis evaluation.

Endoscopy of the upper part of the gastrointestinal tract was performed in all patients. Stage of esophageal varices was established based on three-stage OMED classification, as varices bulging only slightly above the surface of mucous membrane; medium ones, bulging up to one-third of the lumen; and large ones, bulging over one-third of the esophageal lumen [6].

Gastric mucous membrane inflammation was estimated on the basis of endoscopic image, with the use of Sydney classification, updated in Houston [7].

H. pylori infection diagnosis was performed on the basis of the presence of specific immunoglobulin G antibodies in the serum, with the use of the qualitative and quantitative test Enzygnost anti-*H. pylori* II/IgG (Siemens, Siemens company, Germany; in population of adults: sensitivity is 96.8%, and overall specificity is 98.8%).

In some patients, without significant abnormal blood coagulation measures and low platelet count, measurement of bacterial urease activity was performed in the biopsy specimen of gastric mucous membrane excised during endoscopic procedure.

Ammonia blood concentration was estimated with immunochemical tests, using COBAS C501 machine, Roche company, USA.

Statistical analysis was performed using χ^2 and Mann–Whitney *U*-tests. Statistical significance was established as *P* value less than 0.05.

After approval of the study by the Bioethical Committee at the Medical University of Bialystok, the patients provided informed consent to participate in the research.

Results

Among 147 patients with liver cirrhosis included in the study, there were 44 women and 103 men aged 58 years on average (from 23 to 86 years). Liver cirrhosis was caused by HCV infection (42 patients), HBV infection (31 patients), alcohol abuse (56 patients), and PBC (18 patients) (Table 1).

Irrespective of the cause of cirrhosis, 27% patients were graded as Child–Pugh class A, 47% as Child–Pugh class B, and 26% as Child–Pugh class C. Class C included mostly patients with alcoholic liver cirrhosis (41%) (Table 1).

H. pylori infection was diagnosed in 69 (46.9%) patients, usually among those chronically infected with HBV or HCV.

The incidence of *H. pylori* infection among patients with postinflammatory liver cirrhosis was significantly higher ($P=0.001$), as compared with patients with alcoholic liver cirrhosis (Fig. 1).

H. pylori infection among all the patients with liver cirrhosis with respect to Child–Pugh classification was comparable, irrespective of the stage of liver failure. However, in relation to patients with alcoholic liver failure and those infected with HBV or HCV, increase of *H. pylori* incidence and worsening of liver function was observed (the increase of incidence was not statistically significant).

Among the patients without esophageal varices, *H. pylori* infection was found in 14% cases, which was a significantly lower number than in the case of patients with esophageal varices (60%; $P<0.005$) (Tables 2 and 3).

In the performed analysis of the incidence of *H. pylori* infection versus advancement stage of esophageal varices, a statistically significant correlation was found between the stage of varices and incidence of *H. pylori* infection (Fig. 2).

Reflux, erythematous, or atrophic gastropathy was most often diagnosed in the studied patients. No statistically significant differences of incidence of gastric mucous lesions were found between different ethiological factors of cirrhosis (Fig. 3).

H. pylori infection was significantly more frequent among patients with postinflammatory liver cirrhosis, compared with alcoholic liver cirrhosis, with respect to diagnosed reflux (this did not apply to HBV infection), erythematous, or atrophic gastropathy.

Table 1. Characteristics of patients with liver cirrhosis

Cause of liver cirrhosis	<i>n</i>	Women/men	Age (mean±SD)	Child–Pugh classification [<i>n</i> (%)]		
				A	B	C
Alcohol abuse	56	12/44	57.4±10.6	10 (18)	23 (41)	23 (41)
HBV infection	31	5/26	58.5±15.4	14 (45)	14 (45)	3 (10)
HCV infection	42	12/30	58.5±12.4	20 (48)	17 (36)	5 (16)
PBC	18	15/3	58.2±11.6	4 (22)	10 (56)	4 (22)
All	147	35/84	58.6±11.4	48 (33)	64 (43)	35 (24)

HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis.

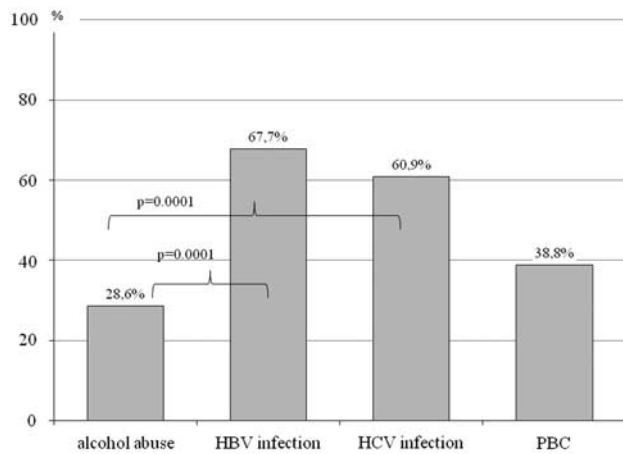


Fig. 1. *Helicobacter pylori* infection in different groups of patients. HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis.

Table 2. The presence of esophageal varices in relation to the severity of liver failure, and the cause of cirrhosis

The severity of esophageal varices	Child–Pugh classification [n (%)]			
	All (n = 147)	A (n = 48)	B (n = 64)	C (n = 35)
0	42 (29)	14 (29)	19 (30)	9 (26)
Hp +	6 (14)*	0 (0)	5 (26)	1 (11)
1	40 (27)	19 (40)	17 (27)	4 (11)
Hp +	18 (45)	10 (25)	8 (47)	0 (0)
2	54 (37)	12 (25)	22 (34)	20 (57)
Hp +	38 (70)	10 (83)	15 (68)	13 (65)
3	11 (29)	3 (6)	6 (9)	2 (6)
Hp +	7 (78)	2 (67)	3 (50)	2 (100)
Patients with esophageal varices	105 (71)	34 (71)	45 (70)	26 (74)
Hp +	63 (60)*	22 (65)	26 (58)	15 (58)

Hp +, *Helicobacter pylori* positive.

*P < 0.05, statistically significant.

Significantly higher ammonia concentration was found in patients with *H. pylori* infection (Table 4). There were no statistically significant differences in ammonia concentration related to the stage of liver injury or the cause of liver cirrhosis. The only exception was significant difference between the patients with alcoholic liver cirrhosis and PBC (Fig. 4).

Discussion

One of the first studies performed on mice and rats infected with *H. pylori* have shown the effect of this infection on the degree of fibrosis and development of liver cirrhosis [8]. Stalke et al. [9] who studied patients with chronic liver injury, have demonstrated the presence of bacteria from the genus *Helicobacter* spp. in liver tissue of 26% of patients. Both experimental and clinical studies show detrimental effect of *H. pylori* infection on the progression of liver injury, especially on the stage of fibrosis. The impact of infection on metabolic changes connected with carbohydrates, synthesis of high-energy molecules (mainly ATP), and increased concentration of proinflammatory cytokines may be one of the reasons for this effect. *H. pylori*

infection may contribute to different organ injuries. Irrespectively from the effect onto the gastric mucosa, *H. pylori* infection causes multiorgan injuries, including chronic injury of the pancreas, which indirectly influences the function of the liver [10]. Research by Sumida et al. [11] clearly points to high significance of *H. pylori* infection in patients with nonalcoholic fatty liver for the development of nonalcoholic steatohepatitis. Eradication of this bacteria significantly simplifies the therapy of fatty liver.

Meta-analysis of 21 studies evaluating *H. pylori* infection among patients with liver cirrhosis did not find higher incidence of infection in this group versus people without liver cirrhosis [12]. It is, however, worth mentioning that the analysis included mainly patients with alcoholic liver cirrhosis. Also in our own research, the presence of *H. pylori* infection was found in 46.9% of patients, which is proportional to the incidence of this infection in the general population (up to 50%). In our observations, incidence of *H. pylori* infection among people infected with HCV or HBV was significantly higher (60.9–67.7%). These observations comply with the research by Hanafy et al. [13], who have demonstrated *H. pylori* infection in 70% (281/400) of patients chronically infected with HCV. A meta-analysis of 20 studies, performed by Wang et al. [14], clearly shows higher incidence of *H. pylori* infection among HCV-positive patients versus people not infected with the virus. El-Masry et al. [15] argue that the incidence of *H. pylori* infection among patients with liver cirrhosis and those infected with HCV increases with more pronounced liver failure. Moreover, Wang et al. [14] demonstrate that the highest proportion of patients with *H. pylori* infection in the group of those who are HCV-positive can be detected in the case of hepatocellular carcinoma (HCC) development. It seems that very frequent coinfection with *H. pylori* and HCV among people with HCC may contribute to increased incidence of this tumor, because HCV and *H. pylori* are deemed to be carcinogenic. Unfavorable effect of *H. pylori* infection among patients with HCV may be diverse. In the past, eradication of this bacteria led to increased platelet number, which allowed administration of antiviral treatment (with interferon). Moreover, the efficacy of antiviral therapies was better among people previously subjected to eradication of *H. pylori* [13,16]. At the moment, during the time of broad use of direct-acting antivirals, this probably does not seem so important; however, such studies have not been performed.

Wang et al. [17] analyzed 15 studies evaluating the effect of *H. pylori* infection on the progress of chronic HBV infection. In the analyzed groups, the incidence of infection was from 30 to over 80%. Results of studies pointed to a correlation between the progression of inflammatory changes in the liver, development of liver cirrhosis and occurrence of HCC, and infection with the bacteria [17]. In the study by Zhang et al. [18] performed in 225 patients chronically infected with HBV and compensated liver cirrhosis with thrombocytopenia, eradication of *H. pylori* irrespectively of the antiviral therapy positively impacted the progression of the disease and increased platelet count.

H. pylori synthesizes urease, catalyzing urea decomposition to ammonia and carbon dioxide. However,

Table 3. Endoscopic gastric changes in relation to causative agents of liver cirrhosis

Type of change	All (n = 147)	HBV infection (n = 31)	Cause of liver cirrhosis		
			HCV infection (n = 42)	Alcohol abuse (n = 56)	PBC (n = 18)
Erythematous gastropathy	33 (22)	7 (23)	9 (21)	14 (25)	3 (17)
Hp+	15 (45)	5 (71)	6 (67)	3 (21)	1 (33)
Reflux gastropathy	58 (39)	9 (29)	16 (38)	25 (45)	8 (44)
Hp+	23 (40)	2 (22)	9 (56)	10 (40)	2 (25)
Atrophic gastropathy	30 (20)	12 (39)	9 (21)	8 (14)	1 (6)
Hp+	19 (63)	11 (92)	6 (67)	1 (13)	1 (100)
Gastropathy (aphthous)	6 (4)	2 (0)	0 (0)	3 (50)	1 (6)
Hp+	4 (71)	2 (0)	0 (0)	1 (25)	1 (100)
Gastropathy (papular)	11 (23)	0 (0)	5 (12)	4 (7)	2 (11)
Hp+	6 (67)	0 (0)	4 (80)	1 (25)	1 (50)
Hemorrhagic gastropathy	3 (2)	0 (0)	0 (0)	1 (2)	2 (11)
Hp+	1 (33)	0 (0)	0 (0)	0 (0)	1 (50)
Gastric ulcer	3 (2)	1 (3)	1 (2)	1 (2)	0 (0)
Hp+	1 (33)	1 (100)	0 (0)	0 (0)	0 (0)
No change	3 (2)	0 (0)	2 (5)	0 (0)	1 (6)
Hp+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

HBV, hepatitis B virus; HCV, hepatitis C virus; Hp+, *Helicobacter pylori* positive; PBC, primary biliary cirrhosis.

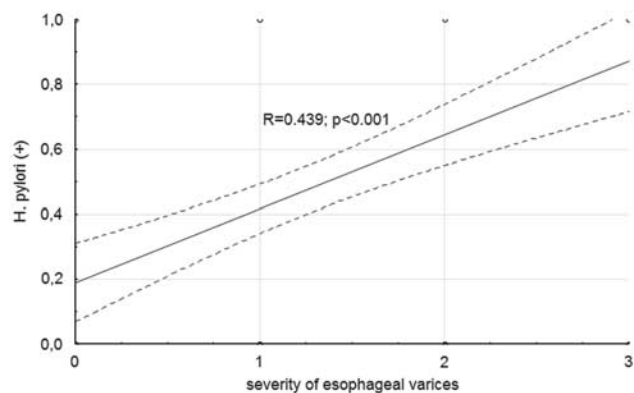


Fig. 2. The occurrence of *Helicobacter pylori* infection in respect to the advancement of esophageal varices.

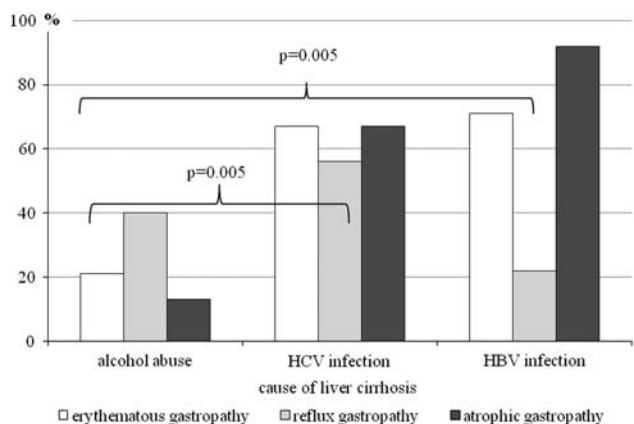


Fig. 3. Infection with *Helicobacter pylori* in respect to changes of the gastric mucosa and liver cirrhosis agent. HBV, hepatitis B virus; HCV, hepatitis C virus.

among patients with subclinical hepatic encephalopathy, *H. pylori* infection does not result in higher concentration of ammonia in the blood [19]. Observation of patients with liver cirrhosis, especially caused by inflammatory reaction, points to a higher incidence of symptomatic hepatic encephalopathy among people infected with

Table 4. The ammonia concentration according to the degree of liver damage and infection with *Helicobacter pylori*

Child–Pugh classification	n	Ammonia concentration (μmol/l)				P
		<i>Helicobacter pylori</i> (+)		<i>Helicobacter pylori</i> (–)		
		Mean ± SD	n	Mean ± SD	n	
A	22	132 ± 33	26	83 ± 20	0.0002*	
B	31	124 ± 39	33	118 ± 44	0.228	
C	16	133 ± 51	19	141 ± 52	0.667	
All	69	129 ± 40	78	112 ± 46	0.002*	

*P < 0.05, statistically significant.

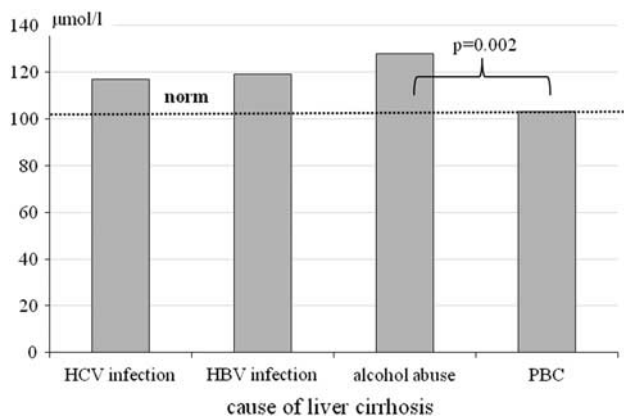


Fig. 4. The ammonia concentration according to the cause of cirrhosis. HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis.

H. pylori, compared with people without this infection [20]. On the basis of our own observations, we did not find higher ammonia concentration among patients infected with *H. pylori*, as compared with uninfected individuals. Chen *et al.* [21] indicate the potential for *H. pylori* infection to increase serum ammonia levels, which may be responsible for the mental disorders associated with hepatic encephalopathy. This may be a direct effect on hepatocytes or on intestinal flora and increased intestinal permeability for ammonia produced in bacteria [21].

The research of Sathar *et al.* [22] demonstrated much more frequent severe inflammatory reaction of gastric mucosa among patients with liver cirrhosis infected with *H. pylori*. However, these observations seem to be obvious. Infection with this bacteria often accompanies inflammatory lesions in the stomach, leading to gastric ulcer development. In our own patient population we also found high incidence of *H. pylori* infection among patients with severe inflammatory lesions of the gastric mucosa [22]. Interestingly, according to our observations, esophageal varices occur more often in the group of patients infected with *H. pylori*. Moreover, the correlation between the stage of varices and incidence of *H. pylori* infection may point to significant, direct effect of this bacteria on liver function [3]. Licinio *et al.* [23] argue for high probability of the influence of *H. pylori* infection on increase of portal hypertension, which is one of the most important causes of the development of esophageal varices.

Conclusion

H. pylori infection is significantly more frequent among patients with postinflammatory liver cirrhosis related to HCV or HBV infection than in patients with alcoholic liver cirrhosis or PBC. The type of inflammatory lesions in the stomach is not dependent on the causative factor of liver cirrhosis. The incidence of esophageal varices correlates with the incidence of *H. pylori* infection.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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