EXTRAGASTRIC GASTROINTESTINAL MANIFESTATIONS OF *HELICOBACTER PYLORI*: FRIEND OR FOE?

Ade Omodele-Lucien,[1,2] *Idan Goren[1,3,4]

1. Internal Medicine T, Sheba Medical Center, Ramat Gan, Israel
2. St George's University of London Medical School, London, UK
3. Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
4. Division of Gastroenterology, Rabin Medical Center, Petah Tikva, Israel
*Correspondence to idango1@clalit.org.il

ABSTRACT

Since it was first identified in 1982, *Helicobacter pylori* has continued to draw attention far beyond its role in peptic ulcer disease and is now associated with a myriad of immune-mediated diseases, both inside the gastrointestinal tract (GIT), such as mucosa-associated lymphoid tissue lymphoma, and systemic diseases, such as *H. pylori*-associated immune thrombocytopenia. This association has ignited research into the mechanisms of *H. pylori* pathogenicity, especially regarding its role within a multitude of diseases outside the GIT. Despite controversies, a growing body of evidence has begun to establish potential associations between *H. pylori* and extragastric GIT pathologies; *H. pylori* has recently been associated with luminal diseases, such as inflammatory bowel diseases and coeliac disease, as well as pancreatic, hepatobiliary, and malignant diseases of the GIT. Despite the lack of conclusive evidence regarding the mechanisms of these relationships, studies have found strong associations, like the case of *H. pylori* and coeliac disease, while others have not discovered such connections. In addition, while studies have established positive associations between *H. pylori* and various extragastric diseases, other studies have found the pathogen to play a protective role in disease development. This review comments on the latest evidence that addresses the role of *H. pylori* in non-gastric gastrointestinal diseases, and establishes the nature of these relationships and the implications of *H. pylori* eradication from a clinical perspective.

Keywords: Associations, gastrointestinal, *Helicobacter pylori,* manifestations.

INTRODUCTION

Helicobacter pylori is a curved, Gram-negative bacillus that colonises the gastric mucosa, usually during childhood, and can persist throughout the host's life without requiring intervention.[1,2] The prevalence of *H. pylori* in the adult population of north Europe and the USA is approximately 30%, compared to a higher range of 40–80% reported in adults living in or immigrating from south and east Europe, South America, and Asia.[3] Moving away from its most well-known role in gastritis and peptic ulcer diseases,[4,5] increasing evidence focusses on *H. pylori*-associated extragastric manifestations within the gastrointestinal tract (GIT).

HELICOBACTER PYLORI AND INFLAMMATORY BOWEL DISEASES

Cases of inflammatory bowel disease (IBD), consisting mostly of ulcerative colitis and Crohn's disease (CD), are immune-mediated chronic inflammatory diseases of the bowel. The exact pathogenesis of IBD is unknown; however, it is theorised to result from a dysregulated immune response to host intestinal microflora among genetically susceptible individuals.[6]

Recent data focussing on *H. pylori* involvement in the pathogenesis of IBD is gaining attention.[6-9] Various mechanisms have been proposed that link *H. pylori* to IBD, including induction of alterations in gastric and intestinal permeability via various immunological pathways, or via induction of

antigenic material absorption with subsequent loss of self-tolerance.[10] In the context of gastritis, the histopathology of the gastric mucosa infected with *H. pylori* is understood to strongly stimulate mucosal inflammation, thereby causing an inflammatory response characterised by an influx of neutrophils, mononuclear cells, and T helper 1 (Th1) cells that destroy intracellular pathogens.[4,11,12] Furthermore, *H. pylori* interaction with the gastric epithelium induces a proinflammatory response, including the recruitment and upregulation of chemokines and cytokines. However, as *H. pylori* does not exist intracellularly, the Th1 response results in endothelial damage to the host's gastric mucosa and is incapable of pathogen clearance.[13]

Several studies have reported that the prevalence of *H. pylori* infection is lower in patients with IBD compared to controls,[7,8,10,14,15] and this inverse relationship prompted investigations and shifted the focus of research to the potential protective role of *H. pylori* in the development of IBD. By colonising the gastric mucosa, *H. pylori* has acquired a series of attributes, primarily a downregulation of the host's immune system to evade both the innate and acquired immune system and prevent pathogen clearance.[4,12] While the mechanisms of proinflammatory states are linked to the development of gastritis and other inflammatory diseases, the long-term, sustained relationship between *H. pylori* and the human host raises the possibility of an existing symbiotic relationship, in which its persistence in the GIT may be beneficial to some individuals. Through these proposed mechanisms, it has been suggested that *H. pylori* plays a protective role in some immune-mediated and allergic diseases.[11,12,16-18]

A meta-analysis of the prevalence of *H. pylori* among IBD patients compared to their control subjects showed a lower prevalence of *H. pylori* infection among IBD patients.[10] Another meta-analysis, including 4,400 IBD patients and 4,763 controls, resulted in a prevalence of 26.0% versus 44.7% of *H. pylori* positivity in the IBD versus control group, respectively.[19] This inverse relationship may have some alternative explanations; firstly, it has been suggested that treatment with sulfasalazine, or the long-term and wide-spectrum antibiotic therapy among IBD patients, could be responsible for the eradication of *H. pylori*.[6,20] Notwithstanding this, a recent meta-analysis found that the protective effect of *H. pylori* was not influenced by previous use of amino salicylates or corticosteroids; however,

antibiotics amplified this negative association.[7] Secondly, it is possible that immunological alterations of the gut mucosa induced by IBD could prevent *H. pylori* colonisation.[8] Lastly, it has been proposed that *H. pylori* infection shifts the equilibrium between Th1 and Th2 immune responses to a Th2-dominant pattern.

In addition, since the eradication of *H. pylori* increases the levels of Th1 proinflammatory cytokines, genetically susceptible individuals are predisposed to CD.[14] With respect to Th1 and Th2 immune responses, data are limited on the prevalence of virulent *H. pylori* strains among IBD patients; however, one study showed that both CD patients and controls were equally infected by *H. pylori* seropositive for cytotoxin-associated antigen A (Cag A), demonstrating no correlation between virulent *H. pylori* strains and the risk of IBD.[6] Furthermore, Engler et al.[20] investigated the possible protective effects of *H. pylori* by administering regular doses of *H. pylori* extract into dextran sodium-sulfate-induced chronic colitis mouse models. The results demonstrated that this experimental infection with *H. pylori* in mouse models alleviated clinical and histopathological features of chronic colitis and T cell transfer-induced colitis, and proposed that *H. pylori* can be exploited for the prevention and/or treatment of IBD through its immunomodulatory activity.[18,20] Taken together, this evidence indicates that there is a relatively strong negative association between the presence of *H. pylori* and IBD, whereas direct inhibition of IBD by *H. pylori* remains to be determined in humans.

HELICOBACTER PYLORI AND MICROSCOPIC COLITIS

Microscopic colitis is an umbrella term consisting of chronic colonic inflammation characterised by a normal macroscopic appearance of the colonic mucosa, contrasted by the presence of intraepithelial lymphocytic infiltrate or subepithelial collagen bands on biopsy. The primary cause of microscopic colitis is not fully understood, but it has been suggested to be a result of an immunological reaction to luminal antigens of ileal origin.[21,22]

Current data support an inverse relationship between *H. pylori* and microscopic colitis, similar to that seen in IBD. While Sonnenberg et al.[23,24] also established a negative correlation between microscopic colitis and *H. pylori*, another potential factor was exposed. The prevalence of *H. pylori* was shown to vary among ethnic groups, which in

turn directly affected the prevalence of microscopic colitis among patients. For example, where *H. pylori* was prevalent within the Hispanic populations, there was a notable reduction in the incidence of microscopic colitis, whereas there was an increased prevalence among Caucasians and African-American populations. This inverse relationship established between *H. pylori* and microscopic colitis may shed light on the ethnic variations in *H. pylori* gastric colonisation and may be partly responsible for the observed ethnic distribution of microscopic colitis.[23,25] Research addressing the associations between *H. pylori* and microscopic colitis remains limited; to gain further insight into the precise role of *H. pylori* in microscopic colitis pathophysiology, additional research is warranted.

HELICOBACTER PYLORI AND COELIAC DISEASE

Coeliac disease, also known as gluten-sensitive enteropathy, is an autoimmune disease involving interactions between environmental, genetic, and immunologic factors; specifically, it is defined as a T cell-mediated immune disorder that is induced by gluten ingestion in genetically predisposed individuals.[26,27] There has been a significant increase in the incidence of coeliac disease in recent decades,[28] rather than those cases recorded solely as a by-product of improved and increased detection. This trend is not well understood; however, environmental factors, specifically a reduced exposure to bacteria, also known as the 'hygiene hypothesis', have been proposed to be reponsible.[29] As part of an analysis of a nationwide pathology database, Lebwhol et al.[29] found a strong inverse relationship between the presence of *H. pylori* and coeliac disease, independent of confounding factors. Although the potential protective mechanism is uncertain, this study is consistent with other studies attributing the role of *H. pylori* with a decreased risk of allergic and inflammatory conditions.[18]

In 2015, Robinson et al.[5] conducted a systematic review on the protective role of *H. pylori* against the risk of acquired autoimmune disorders. Where some studies showed that the prevalence of *H. pylori* was reduced in coeliac disease, other reports found no differences. While these controversies could be explained by research methodologies, biases, or confounders, the mechanisms by which *H. pylori* might protect against CD remain unknown. Shortly after this review, Rostami-Nejad et al.[30] reviewed a series of reports addressing pathological and clinical correlations between coeliac disease and *H. pylori* infection. A comprehensive review of research articles from 1985–2015 concluded that examinations of the correlation between *H. pylori* and CD have once again yielded discordant outcomes.[30]

More recently, Basyigit et al.[31] failed to confirm a significant relationship between coeliac disease and *H. pylori*. Serum levels of coeliac disease-specific autoantibodies or immunoglobulin A were analysed among both *H. pylori* and non-*H. pylori*-infected individuals and no significant differences in serum level antibodies were found. Conversely, Narang et al.[32] concluded that the prevalence of *H. pylori* in children with confirmed coeliac disease was lower in comparison to *H. pylori* infection rates in children without coeliac disease, signifying an inverse relationship. While protectivity has still not been confirmed, the potentiality now merits further longitudinal investigations to ascertain whether *H. pylori* infection confers protection or a reduced risk of developing coeliac disease.

HELICOBACTER PYLORI AND HEPATOBILIARY DISEASES

Early research suggests the *Helicobacter* species is implicated in hepatobiliary diseases, ranging from chronic cholecystitis and primary sclerosing cholangitis (PSC), to gallbladder and primary hepatic carcinomas (Table 1).[17,69,70] The *Helicobacter* species, including *H. pylori*, has been implicated as a potential inducer of hepatocyte and biliary autoimmunity, primarily based on their tolerance to, and ability to survive in, bile.[71]

However, *H. pylori* primarily affects the GIT and is not commonly present in the liver and bile ducts of *H. pylori*-infected individuals. Contamination of the hepatobiliary system is most likely due to contamination from potentially damaged gastrointestinal epithelium, or to the dysfunctional sphincter of the common bile duct; however, the entry of *H. pylori* through this mechanism, and the susceptibility of biliary tract contamination, is not limited to *H. pylori*. This presents challenges in the assessment and controlled research concerning the role of *H. pylori* in the development of hepatobiliary pathologies.

There is minimal evidence of association pertaining to the role of *H. pylori* in autoimmune biliary diseases, including primary biliary cirrhosis (PBC) and PSC.[33,71]

Table 1: Extragastric gastrointestinal associations of *Helicobacter pylori*.

Disease	Conclusion
Inflammatory bowel diseases[7,8,10,14,15]	Epidemiological data and meta-analysis show a negative association.
Microscopic colitis[23-25]	Epidemiological data and cohort studies indicate a positive association.
Coeliac disease[5,29,30,32]	Conflicting evidence is present.
Primary biliary cirrhosis[33-36]	No statistically significant associations found.
Primary sclerosing cholangitis[37-40]	Cohort and prospective analysis shows a positive association.
Gallstone disease[36,40-46]	Epidemiological and cohort data show a positive association.
Autoimmune hepatitis[47]	Currently lacks conclusive evidence due to limited research.
NAFLD[48-53]	Majority of data (case-control, cross-sectional, and systematic reviews) confirm a positive association of *H. pylori* infectivity and insulin resistance, predisposing patients to NAFLD.
Pancreatitis[54,55]	Majority of data confirm a positive association, including cross-sectional and cohort analysis.
Pancreatic cancer[56-62]	Majority of data suggest a positive association, including a meta-analysis, but two case-control studies found no association.
Colorectal cancer[63-68]	Systematic review and meta-analysis support the positive association.

NAFLD: non-alcoholic fatty liver disease.

As both conditions are caused by an immune-mediated cellular destruction within the biliary system, research into the implication of *H. pylori* infectivity within the pathophysiology of these diseases has recently gained attention.

Primary Biliary Cirrhosis

While certain attempts have failed to detect *H. pylori* in the livers of patients with PBC,[33] others have detected *H. pylori* in a very limited number of samples.[34] Studies, such as that by Boomkens et al.,[70] could only find the presence of *Helicobacter* species in approximately one-third of all samples tested, which suggested that PBC is unlikely to be caused or influenced by *Helicobacter* infection. Additionally, research specifically assessing Cag A seropositivity of *H. pylori* in PBC patients compared to control groups also found conflicting evidence.[33,34,71] Research on molecular mimicry between *H. pylori* and PBC-specific autoantigens identified a significant amino acid sequence similarity between the mitochondrial autoepitope region of pyruvate dehydrogenase complex E2 subunit and urease beta of *H. pylori*, without any evidence of immunological cross-reactivity. Other studies involving cross-reactive antibodies against *H. pylori* also demonstrated that *H. pylori* antigens are unlikely candidates of cross-reactive targets in molecular mimicry mechanisms in PBC, contributing further to the evidence against *H. pylori* association with PBC.[35]

Primary Sclerosing Cholangitis

In comparison to PBC cases, there was some evidence identifying a positive association between PSC and *H. pylori*. A study on *H. pylori* DNA in liver samples from PSC patients detected *H. pylori* DNA in micro-dissected hilar biliary epithelium in a higher number of PSC patients compared to controls.[35] This supports the hypothesis that bile reflux, or translocation from the duodenum into the biliary tract, might transport *H. pylori* organisms into the biliary system, contributing to PSC development. Gut translocation of pathogens has been suggested among several studies as a plausible mechanism for the induction of hepatobiliary autoimmunity within the context of *H. pylori* involvement in hepatobiliary pathology.[37,39,71] Although several studies assessing the prevalence of anti-*H. pylori* antibodies in PSC patients found that titres did not differ significantly between PSC patients and control groups, it has been hypothesised that, since many PSC patients suffer from ulcerative colitis, *H. pylori* could account for any documented associations.[36-38] Thus far, a positive association between *H. pylori* and PSC has been elucidated; however, the attempts made to uncover any potential association between *H. pylori* and PSC have been limited, thereby requiring further clarification.

Gallstone Diseases

H. pylori is positively associated with cholestatic conditions, albeit with limited evidence.[34,38]

It has been proposed that *H. pylori* plays a role in the formation of cholesterol gallstones, and consequentially chronic cholecystitis.[39] For example, Attaallah et al.[41] found 37% of patients with symptomatic gallstone disease were locally infected with *H. pylori*. Other studies also found *H. pylori* to be a predisposing factor and showed that it may have a pertinent role within the aetiology and pathophysiology of gallstone formation;[40,42-44] no evidence was found for any negative or non-association in our literature review. Although causality is uncertain at this point, *H. pylori* plays a role in gallstone pathogenesis, either directly or as a potential cofactor.[45]

Autoimmune Hepatitis

Although a high prevalence of *H. pylori* infection was demonstrated in patients with viral-related cirrhosis, it was not studied in cases of autoimmune hepatitis. Durazzo et al.,[46] in their attempts to establish a relationship between autoimmune hepatitis and *H. pylori*, found no association. Current data on the role of *H. pylori* in autoimmune hepatitis are limited and inconclusive.

Helicobacter Pylori and Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is regarded as a hepatic manifestation of metabolic syndrome. It is a concerning disease, not only because of its high prevalence, but also due to its potential risk of progressing to cirrhosis and hepatocellular carcinoma. The literature focussing on the association between *H. pylori* and NAFLD is conflicting; as we have established, *H. pylori* is a pathogen reported to be well associated with metabolic syndrome,[48] but whether there is a direct association with regard to NAFLD still remains unclear.[49,50]

Okushin et al.,[49] in a cross-sectional study, aimed to clarify the nature of association between NAFLD with causative background factors, including *H. pylori* infection. While BMI, serum alanine aminotransferase, and platelet count were significantly associated with NAFLD, *H. pylori* infection was not.[49] However, others have found *H. pylori* to be an independent risk factor for the development of NAFLD.[50,51] Cheng et al.,[50] in a systematic review of *H. pylori* involvement in the pathogenicity of NAFLD, revealed the possible contributory mechanisms of *H. pylori* to the disease: *H. pylori* infection causes chronic low-grade systemic inflammation, which increases the levels of inflammatory cytokines, and, through a series of pathways ultimately leading to insulin resistance, acts as a leading contributor to NAFLD.[48,50] Lastly, Tang and Kumar[53] stated that small trials examining the effect of *H. pylori* eradication have shown improvement in markers of NAFLD activity. Not only does this support a link between the two conditions, but it substantiates the potential clinical implications beyond *H. pylori* eradication in patients with NAFLD.

HELICOBACTER PYLORI AND PANCREATITIS

Pancreatitis can be of acute, chronic, and autoimmune nature, each displaying differences in pathophysiology. Acute pancreatitis is defined as an acute inflammation of the pancreas, consequentially causing a dysregulation of pancreatic enzyme activity, and the pathogenesis ranges from hereditary and behavioural, to environmental aetiologies.[16] In contrast, chronic pancreatitis is a more progressive fibro-inflammatory disease, characterised by irreversible fibrosis of the pancreatic gland,[47] and autoimmune pancreatitis (AIP) is characterised by fibrotic, lymphoplasmacytic inflammatory processes accompanied by T cell apoptosis, which contribute to pancreatic tissue destruction.[17]

The implication of *H. pylori* in the pathogenesis of AIP via an induction of autoimmunity has been a recent topic of investigation. The role of *H. pylori* in AIP has also been investigated within the context of a high prevalence of peptic ulcer disease (PUD) in patients with AIP.[16,72] Lee et al.[72] found PUD to be positively associated with severe acute pancreatitis, thereby concluding that there are implications beyond the treatment of PUD, and the condition should be considered in the management of acute pancreatitis. Another study found that *H. pylori* increases the severity of ischaemia-induced pancreatitis, as well as inducing production of proinflammatory interleukin-1β, further aggravating disturbances in the pancreatic microcirculation in acute pancreatitis.[54] Lastly, *H. pylori* may potentiate the onset of AIP due to molecular mimicry; research investigating this molecular mimicry found *H. pylori* alpha carbonic anhydrase and human carbonic anhydrase II, among other enzymes, were highly expressed in the pancreatic ductal and acinar cells, exposing the immune system to the potential of cross-reactivity.[55] While the exact mechanisms are still unknown,

molecular mimicry, proinflammatory response, and the development of *H. pylori*-induced PUD may be involved in the development of AIP.

There is a positive association between pancreatitis and *H. pylori*; the evidence against any association between the two was not found to be statistically significant. Whether this relationship is incidental, causative, or a risk factor remains to be understood. The question concerning the implications of eradication of *H. pylori* to patients with AIP, in terms of the potential benefits, is now becoming more relevant and, therefore, as we consider the increased burden of pancreatic cancer and its association with AIP, the development of an underlying link motivates further research.

HELICOBACTER PYLORI AND PANCREATIC CANCER

Pancreatic cancer is currently the fourth leading cause of cancer-related deaths worldwide and the risk factors include tobacco, smoking, diabetes, chronic pancreatitis, alcohol, and specific genetic conditions.[73] Recently, research focussing on the associations between *H. pylori* and autoimmune diseases has found conflicting evidence for *H. pylori* involvement in pancreatic cancer. Several studies have established a positive association between *H. pylori* and pancreatic cancer.[56-58] For example, Risch et al.[57] found that there is evidence for the involvement of *H. pylori*-modulated gastric acidity in the risk of pancreatic carcinoma. Additionally, the interaction of the ABO genotype and phenotype status of an individual influences the behaviour of *H. pylori* infectivity, which in turn affects gastric and pancreatic secretory function. This ultimately influences the pancreatic carcinogenicity of dietary and smoking-related N-nitrosamine exposures.[56,59] The association of ABO-product antigen and *H. pylori* is now understood to be strongly implicated in the disease aetiology of pancreatic cancer. Furthermore, a meta-analysis including 1,003 pancreatic cancer patients and 1,754 healthy controls evaluated the presence of *H. pylori* and the risk of developing pancreatic cancer. The results indicated a significant correlation between *H. pylori* and pancreatic cancer, and showed that *H. pylori* infection can increase the risk of developing pancreatic cancer.[59] With regard to Cag A seropositivity, Stolzenberg-Solomon et al.[69] found that, compared with seronegative subjects, those with *H. pylori* or Cag A+ strains were at an elevated risk of developing pancreatic cancer.

However, several other studies found no association between *H. pylori* and the development of pancreatic cancer.[60,61] Both a case-control study by de Martel et al.[61] and a meta-analysis by Xiao et al.[74] found no associations between the presence of *H. pylori* or the Cag A protein and pancreatic cancer, whereas smoking and education were associated. Due to the limited number of studies, suspected publication bias, relatively small sample size, as well as statistical heterogeneity, the need for high-quality studies to further clarify the role of *H. pylori* in pancreatic cancer still stands.

HELICOBACTER PYLORI AND COLON CANCER

Colorectal cancer is the third most common cancer worldwide, accounting for >9% of all cancer incidences.[75] Although colonic carcinogenesis is considered a multifactorial process, including a combination of environmental factors, Western dietary and social practices, as well as genetic susceptibility, the precise mechanisms of its initiation remain unknown. Given the increased incidence of colon cancer worldwide, as well as a growing interest in the involvement of *H. pylori* in gastrointestinal diseases, studies have begun to examine the relationship, or potential association, between *H. pylori* and colonic carcinogenesis.[63]

Until now, the role of *H. pylori* in the development of colorectal neoplasm remains controversial. A study that involved mice infected with *H. pylori* exhibited oncogenic properties within the colon epithelia, including an increased expression of mutations.[64] Selgrad et al.[65] found an upregulation of Cag A expression to be associated with an increased risk of colon cancer, also associating infectivity with *H. pylori* to the development of colorectal cancer. A broader and more recent study in China, based on a retrospective analysis of intestinal biopsies, revealed that interstitial metaplasia accompanied by *H. pylori* infection was significantly associated with an increased risk of adenomas, suggesting a plausible carcinogenic effect of *H. pylori*.[66] Several large-scale studies, which included data from several case-control studies, cross-sectional studies, and meta-analyses, found a similar statistically significant association between *H. pylori* and the risk of colorectal adenoma and colorectal neoplasm.[66-68] However, it still remains to be elucidated whether the induction and perpetuation of inflammatory responses, alteration of gut microflora, and release of toxins mediated by *H. pylori* can

claim causality to colorectal tumourigenesis.[76] While the evidence thus far indicates an association, rather than a proof of causality, it calls for further large-scale studies to confirm *H. pylori* as a contributor in the pathogenesis of colorectal cancer.

CONCLUSION

H. pylori is a pathogen that has continued to draw attention for decades. Thus far, despite the increasing evidence of both positive and negative associations of *H. pylori* and extragastric diseases, specifically within gastrointestinal and hepatobiliary systems, the direct role of the pathogen in the pathophysiology of the aforementioned diseases remains elusive. The main protective effect is postulated to result from the long-term interaction of *H. pylori* with the immune system, acquired in early childhood. Evidence suggesting whether *H. pylori* eradication truly reverses the immunological benefits is lacking; however, evidence regarding the benefits of eradication exists. The lack of a concise and comprehensive understanding makes the implications of *H. pylori* infectivity unclear from a clinical standpoint. Lastly, although *H. pylori* is both a friend and a foe, currently there is no evidence against treating a patient with *H. pylori* when there is a strong clinical indication for therapy.

REFERENCES

1. Tytgat GN, Rauws EA. Significance of Campylobacter pylori. Aliment Pharmacol Ther. 1987;1(S1):527S-39S.

2. Lee SK, Josenhans C. *Helicobacter pylori* and the innate immune system. Int J Med Microbiol. 2005;295(5):325-34.

3. Eusebi LH et al. Epidemiology of *Helicobacter pylori* infection. Helicobacter. 2014;19(S1):1-5.

4. Kusters JG et al. Pathogenesis of *Helicobacter pylori* infection. Clin Microbiol Rev. 2006;19(3):449-90.

5. Robinson K et al. The inflammatory and immune response to *Helicobacter pylori* infection. Best Pract Res Clin Gastroenterol. 2007;21(2):237-59.

6. Papamichael K et al. Helicobacter pylori infection and inflammatory bowel disease: Is there a link? World J Gastroenterol. 2014;20(21):6374-85.

7. Castaño-Rodríguez N et al. Dual role of Helicobacter and Campylobacter species in IBD: A systematic review and meta-analysis. Gut. 2017;66(2):235-49.

8. Lahat A et al. *Helicobacter pylori* prevalence and clinical significance in patients with quiescent Crohn's disease. BMC Gastroenterol. 2017;17(1):27.

9. Sonnenberg A, Genta RM. Low prevalence of *Helicobacter pylori* infection among patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2012;35(4):469-76.

10. Rokkas T et al. The association between *Helicobacter pylori* infection and inflammatory bowel disease based on meta-analysis. United European Gastroenterol J. 2015;3(6):539-50.

11. White JR et al. Differential inflammatory response to *Helicobacter pylori* infection: Etiology and clinical outcomes. J Inflamm Res. 2015;8:137-47.

12. Lina TT et al. Immune evasion strategies used by *Helicobacter pylori*. World J Gastroenterol. 2014;20(36): 12753-66.

13. Meyer F et al. Modulation of innate cytokine responses by products of *Helicobacter pylori*. Infect Immun. 2000; 68(11):6265-72.

14. Murad HA. Does *Helicobacter pylori* eradication therapy trigger or protect against Crohn's disease? Acta Gastroenterol Belg. 2016;79(3):349-54.

15. Kyburz A, Müller A. *Helicobacter pylori* and extragastric diseases. Current Top in Microbiol Immunol. 2017;400:325-47.

16. Kountouras J et al. A concept on the role of *Helicobacter pylori* infection in autoimmune pancreatitis. J Cell Mol Med. 2005;9(1):196-207.

17. Rabelo-Gonçalves EM et al. Extragastric manifestations of *Helicobacter pylori* infection: Possible role of bacterium in liver and pancreas diseases. World J Hepatol. 2015;7(30): 2968-79.

18. Arnold IC et al. The immunomodulatory properties of *Helicobacter pylori* confer protection against allergic and chronic inflammatory disorders. Front Cell Infect Microbiol. 2012;2:10.

19. Luther J et al. Association between *Helicobacter pylori* infection and inflammatory bowel disease: A meta-analysis and systematic review of the literature. Inflamm Bowel Dis. 2010; 16(6):1077-84.

20. Engler DB et al. *Helicobacter pylori*-specific protection against inflammatory bowel disease requires the NLRP3 inflammasome and IL-18. Inflamm Bowel Dis. 2015;21(4):854-61.

21. Williams JJ et al. Microscopic colitis-defining incidence rates and risk factors: a population-based study. Clin Gastroenterol Hepatol. 2008;6(1):35-40.

22. Pardi DS, Kelly CP. Microscopic colitis. Gastroenterology. 2011;140(4): 1155-65.

23. Sonnenberg A et al. Interaction of ethnicity and H. pylori infection in the occurrence of microscopic colitis. Dig Dis Sci. 2017;62(4):1009-15.

24. Sonnenberg A, Genta RM. Inverse association between *Helicobacter pylori* gastritis and microscopic colitis. Inflamm Bowel Dis. 2016;22(1):182-6.

25. Halme L et al. Inverse correlation between *Helicobacter pylori* infection and inflammatory bowel disease. J Clin Pathol. 1996;49(1):65-7.

26. Kagnoff MF. Overview and pathogenesis of celiac disease. Gastroenterology. 2005;128(4S1):210-8.

27. Plenge RM. Unlocking the pathogenesis of celiac disease. Nat Genet. 2010;42(4):281-2.

28. Rubio-Tapia A et al. Increased prevalence and mortality in undiagnosed celiac disease. Gastroenterology. 2009; 137(1):88-93.

29. Lebwohl B et al. Decreased risk of celiac disease in patients with helicobacter pylori colonization. Am J Epidemiol. 2013;178(12):1721-30.

30. Rostami-Nejad M et al. Pathological and clinical correlation between celiac disease and *Helicobacter pylori* infection; A review of controversial reports. Middle East J Dig Dis. 2016;8(2):85-92.

31. Basyigit S et al. Relationship between *Helicobacter pylori* infection and celiac disease: A cross-sectional study and a brief review of the literature. Prz Gastroenterol. 2017;12(1):49-54.

32. Narang M et al. Celiac disease and *Helicobacter pylori* infection in children: Is there any association? J Gastroenterol Hepatol. 2017;32(6):1178-82.

33. Tanaka A et al. Are infectious agents involved in primary biliary cirrhosis? A PCR approach. J Hepatol. 1999; 31(4):664-71.

34. Ram M et al. *Helicobacter pylori* serology in autoimmune diseases - Fact or fiction? Clin Chem Lab Med. 2013; 51(5):1075-82.

35. Bogdanos DP et al. Extensive homology between the major immunodominant mitochondrial antigen in primary biliary cirrhosis and *Helicobacter pylori* does not lead to immunological cross-reactivity. Scand J Gastroenterol. 2004;39(10):981-7.

36. Krasinskas AM et al. *Helicobacter pylori* may play a contributory role in the pathogenesis of primary sclerosing cholangitis. Dig Dis Sci. 2007;52(9): 2265-70.

37. Casswall TH et al. Helicobacter species DNA in liver and gastric tissues in children and adolescents with chronic liver disease. Scand J Gastroenterol. 2010;45(2):160-7.

38. Eksteen B et al. Hepatic endothelial CCL25 mediates the recruitment of CCR9+ gut-homing lymphocytes to the liver in primary sclerosing cholangitis. J Exp Med. 2004;200(11):1511-7.

39. Leong RWL, Sung JJY. Review article: Helicobacter species and hepatobiliary diseases. Aliment Pharmacol Ther. 2002; 16(6):1037-45.

40. Apostolov E et al. *Helicobacter pylori* and other Helicobacter species in gallbladder and liver of patients with chronic cholecystitis detected by immunological and molecular methods. Scand J Gastroenterol. 2005;40(1): 96-102.

41. Attaallah W et al. Gallstones and concomitant gastric *Helicobacter pylori* infection. Gastroenterol Res Pract. 2013; 2013.

42. Abayli B et al. *Helicobacter pylori* in the etiology of cholesterol gallstones. J Clin Gastroenterol. 2005;39(2):134-7.

43. Monstein HJ et al. Identification of *Helicobacter pylori* DNA in human cholesterol gallstones. Scand J Gastroenterol. 2002;37:112-9.

44. Lee JW et al. Identification of *Helicobacter pylori* in gallstone, bile, and other hepatobiliary tissues of patients with cholecystitis. Gut Liver. 2010;4(1): 60-7.

45. Chen W et al. Common presence of Helicobacter DNA in the gallbladder of patients with gallstone diseases and controls. Dig Liver Dis. 2003;35(4): 237-43.

46. Durazzo M et al. *Helicobacter pylori* seroprevalence in patients with autoimmune hepatitis. Dig Dis Sci. 2002; 47(2):380-3.

47. Czul F et al. [Update on chronic pancreatitis: Review article]. Rev Gastroenterol Peru. 2017;37(2):146-55. (In Spanish).

48. Li M et al. Potential role of *Helicobacter pylori* infection in nonalcoholic fatty liver disease. World J Gastroenterol. 2013;19(41):7024-31.

49. Okushin K 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 Gastroenterol. 2015;15(25):1-11.

50. Cheng D et al. The possible role of *Helicobacter pylori* infection in non-alcoholic fatty liver disease. Front Microbiol. 2017;8:743.

51. Takuma Y. [*Helicobacter pylori* infection and liver diseases]. Gan To Kagaku Ryoho. 2011;38(3):362-4. (In Japanese).

52. Polyzos SA et al. *Helicobacter pylori* infection in patients with nonalcoholic fatty liver disease. Metabolism. 2013; 62(1):121-6.

53. Tang DM, Kumar S. The association between *Helicobacter pylori* infection and nonalcoholic fatty liver disease. Curr Gastroenterol Rep. 2017;19(2):5.

54. Warzecha Z et al. Deleterious effect of *Helicobacter pylori* infection on the course of acute pancreatitis in rats. Pancreatology. 2002;2(4):386-95.

55. Bulajic M et al. *Helicobacter pylori* and pancreatic diseases. World J Gastrointest Pathophysiol. 2014;5(4): 380-3.

56. Risch HA et al. ABO blood group, helicobacter pylori seropositivity, and risk of pancreatic cancer: A case-control study. J Natl Cancer Inst. 2010;102(7): 502-5.

57. Risch H et al. *Helicobacter pylori* seropositivities and risk of pancreatic carcinoma. Cancer Epidemiol Biomarkers Prev. 2014;23(1):172-8.

58. Takayama S et al. Effects of *Helicobacter pylori* infection on human pancreatic cancer cell line. Hepatogastroenterology. 2007;54(80): 2387-91.

59. Risch HA. Pancreatic cancer: *Helicobacter pylori* colonization, N-Nitrosamine exposures, and ABO blood group. Mol Carcinog. 2012;51(1): 109-18.

60. Trikudanathan G et al. Association between *Helicobacter pylori* infection and pancreatic cancer. A cumulative meta-analysis. JOP. 2011;12(1):26-31.

61. De Martel C et al. *Helicobacter pylori* infection and development of pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2008;17(5):1188-94.

62. Lindkvist B et al. A prospective study of *Helicobacter pylori* in relation to the risk for pancreatic cancer. BMC Cancer. 2008;8(1):321.

63. Kim TJ et al. *Helicobacter pylori* infection is an independent risk factor of early and advanced colorectal neoplasm. Helicobacter. 2017;22(3):e12377.

64. Kim BG et al. H. pylori infection promotes intestinal inflammation and colitis-associated colon cancer in mice with a lineage-restricted deletion of the Smad4 gene in T cells. J Immunol. 2016; 196(s1):208.

65. Selgrad M et al. *Helicobacter pylori* but not gastrin is associated with the development of colonic neoplasms. Int J Cancer. 2014;135(5):1127-31.

66. Yan Y et al. *Helicobacter pylori* infection with intestinal metaplasia: An independent risk factor for colorectal adenomas. World J Gastroenterol. 2017; 23(8):1443-9.

67. Wu Q et al. Association between *Helicobacter pylori* infection and the risk of colorectal neoplasia: A systematic review and meta-analysis. Colorectal Dis. 2013;15(7):e352-64.

68. Nam JH et al. *Helicobacter pylori* infection is an independent risk factor for colonic adenomatous neoplasms. Cancer Causes Control. 2017;28(2):107-15.

69. Stolzenberg-Solomon RZ et al. *Helicobacter pylori* seropositivity as a risk factor for pancreatic cancer. J Natl Cancer Inst. 2001;93(12):937-41.

70. Boomkens SY et al. The role of Helicobacter spp. in the pathogenesis of primary biliary cirrhosis and primary sclerosing cholangitis. FEMS Immunol Med Microbiol. 2005;44(2):221-5.

71. Smyk DS et al. *Helicobacter pylori* and autoimmune disease: Cause or bystander. World J Gastroenterol. 2014; 20(3):613-29.

72. Lee KM et al. Association between acute pancreatitis and peptic ulcer disease. World J Gastroenterol. 2011; 17(8):1058-62.

73. Zhang Q et al. Pancreatic cancer epidemiology, detection, and management. Gastroenterol Res Pract. 2016;2016.

74. Xiao M et al. Association between Helicobacter pylori infection and pancreatic cancer development: A meta-analysis. PLoS One. 2013;8(9):e75559.

75. Haggar FA, Boushey RP. Colorectal cancer epidemiology: Incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg. 2009;22(4):191-7.

76. Papastergiou V et al. *Helicobacter pylori* and colorectal neoplasia: Is there a causal link? World J Gastroenterol. 2016; 22(2):649-58.