Chapter

Helicobacter Pylori Infection Correlates with Lower Prevalence and Subsequent Incidence of Crohn's Disease

Chenxiao Hu, Ting Lei, Natalie Tai, Yan Li, Xiujing Feng, Zhi Huang and Yun Lu

Abstract

According to some researchs, Crohn's disease (CD) and Ulcerative colitis (UC), two chronic inflammatory bowel illnesses, may be protected against *Helicobacter pylori* infection. Many case–control studies have revealed that individuals with CD and UC had lower *H. pylori* prevalence than healthy controls. However, whether or not *H. pylori* plays a protective role in the development of Crohn's disease is debatable. CD was more common in *H. pylori*-negative individuals than in *H. pylori*-positive patients. After eradication of *H. pylori*, the CD was more common in the *H. pylori*-negative group than in the *H. pylori*-positive group over the previous research follow-up period. Although it has been strongly indicated in previous studies that *H. pylori* infection plays a significant role and triggers autoimmune reactions and may be implicated in the pathogenesis of autoimmune diseases, the role of *H. pylori* in inflammatory bowel disease, including Crohn's disease, is unclear.

Keywords: Helicobacter pylori, Crohn's disease, immune cells, cytokines

1. Introduction

Crohn's disease (CD) is an inflammatory disease that could cause chronic inflammation throughout the gastrointestinal tract without a definite etiology [1]. Even though the incidence of CD has been increasing for several decades worldwide, it is more common in northern Europe and the United States compared to other areas, including southern Europe [2]. In addition to the primary contributor to the disease, which is the genetic predisposition, there is a growing body of evidence to support the concept that environmental variables, in particular the gut flora and antigens, are also involved in the development of Crohn's disease (CD). Several different infections have been proposed as potential causes of CD without solid evidence supporting these hypotheses. There is an unmet need to investigate the role of bacteria during CD development. Helicobacter pylori (*H. pylori*) is a type of bacteria that could cause ulcers in the stomach. Although it has been strongly indicated in previous studies that *H. pylori* infection plays a significant role and triggers autoimmune reactions and may

be implicated in the pathogenesis of autoimmune diseases, the role of *H. pylori* in inflammatory bowel disease (IBD), including Crohn's disease, is unclear [3].

H. pylori is a stain of Gram-negative bacteria that is very infectious and found in the mucosa of the human stomach. Chronic *H. pylori* infection is quite common. It is estimated that roughly 20 percent of Danish patients diagnosed with dyspepsia are infected with *H. pylori* [4]. Most cases of *H. pylori* infection occur in children and young adults [5]. Inadequate sanitation and poor socioeconomic standards have been reported as factors that correlate the increased risk of *H. pylori* infection, which is prevalent in certain countries such as India, China, and Brazil, where the incidence of *H. pylori* infection is considered over 50 percent [6]. Living quality and sanity go hand in hand with the development of the economy, which may explain why the prevalence of *H. pylori* infection has significantly decreased as the western style civilization grown grow. A persistent *H. pylori* infection is a significant factor for the development of chronic gastritis, peptic ulcer disease, and stomach cancer. Oddly, while the incidence of *H. pylori* infection has been going down, the number of people developing chronic inflammatory conditions including Crohn's disease is going up for no apparent reason [7]. This observation has given rise to the hypothesis that *H. pylori* infection may have host-protective role.

2. Epidemiological correlation between CD and *H. pylori*

H. pylori caused active infection is responsible for the prolonged inflammation of the colon and cecum that are seen in immunocompromised rodents [8–11]. However, the findings from patients were difficult to interpret. The intestinal mucosa of the majority of patients did not contain Helicobacter, or the presence of *H. pylori* was only discovered in a minority of those individuals [12–16]. In addition, results from meta-analysis revealed that *H. pylori* infection plays a protective role CD from an etiology point of view [10, 17–19]; however, the heterogeneity among the studies that were included in the meta-analysis and the possibility of publication bias limit the confidence that could be placed in these findings. Furthermore, it is still controversial whether *H. pylori* serves a protective role in the development of CD, a persistent inflammatory condition of gastrointestinal tract [18, 20]. As shown by the results, having *H. pylori* infection was associated with a lower risk of Crohn's disease (CD), and this correlation remains even after potential confounding factors such as socio-economic status were taken into account (**Table 1**) [6, 10, 19, 21–30]. On the other hand, it was revealed in other studies that the presence of an *H. pylori* infection was associated with an increased frequency of CD [18, 31, 32].

H. pylori infection and the prevalence of Crohn's disease, ulcerative colitis, and celiac disease also been investigated in a cohort of more than 50,000 Danish citizens who successively underwent a first-time urea breath test [33]. Although the previous research has shown that there is a correlation between *H. pylori* infection and IBD, the results have been inconsistent [33, 34]. The occurrences of CD, UC were used as part of a follow-up checklist in order to determine whether or not the possible protective benefits of *H. pylori* lingered after the bacteria has probably been eradicated.

A number of hypotheses have been proposed to explain this discovery. For instance, if patients with Crohn's disease received antibiotics prior to an *H. pylori* eradicating *H. pylori*, the rate of *H. pylori* infections in Crohn's disease patients would be smaller [33, 35–37]. This would lead to a reduction in the prevalence of *H. pylori* infections in patients with CD. It is possible that *H. pylori* is just a proxy marker for

Author	Pooled RR/OR	95% CI	p-Value
Yue et al. [21]	0.63	0.49–0.81	< 0.001
Luther et al. [22]	0.6	0.40–0.72	NR
Wu et al. [10]	0.43	0.37–0.50	< 0.001
Wang et al. [23]	0.41	0.32–0.53	< 0.001
Hesamaddin et al. [24]	0.40	0.33–0.49	< 0.001
Rokkas et al. [19]	0.38	0.31–0.47	< 0.001
Castañorodríguez et al. [25]	0.38	0.31–0.47	< 0.001
Ding et al. [26]	0.236	0.14–0.39	< 0.001

Table 1.
Helicobacter pylori infection rates in patients with CD.

exposure to an environment that protects against Crohn's disease. Alternatively, it may be a case of selection biases where patients seeing doctor regularly get tested for *H. pylori* more often than those patients seeing doctors for a cause [38]. There are various potential sources of bias and confounding variables, including the fact that individuals with Crohn's disease may have received other medical treatments that have an effect on *H. pylori*, or the fact that publishing biases may have distorted the findings [35, 39].

Various researches included the ecological epidemiology studies in order to tackle the issue of overcoming biases and confounding in their researches. Information regarding the prevalence and incidence of CD was combined with geographically and temporally matched studies of the prevalence of *H. pylori* [2, 3, 16, 17, 30, 39]. Shah et al. also expanded that epidemiology study strategy and conduct an in-depth analysis of the published researches on the epidemiology of Crohn's disease from 1990 to 2016, comparing the findings of this research with findings on the incidence of *H. pylori* infection. A combined data set included 22 incidence and 19 prevalence data pairs for Crohn's disease and *H. pylori* derived from 13 different countries was included [35, 40]. However, there are still a number of possible risks associated with the research. There is a possibility that the presence of *H. pylori* is not the sole factor that differentiates the non-exposed group from the group that has been exposed to *H. pylori*. Nevertheless, antibiotics may have been administered in an inconsistent manner, which may had an impact on the outcomes [41, 42]. During the time period between 1990 and 2016, these nations may have seen the most significant shifts in both the incidence and prevalence of CD, as well as the prevalence of *H. pylori*. The incidence of Crohn's disease is reduced in proportion to the percentage of the population that is infected with *H. pylori* [7, 15, 32, 33, 35].

3. Molecular mechanisms

A few different immunological mechanisms that are responsible for the possible negative correlation between *H. pylori* infection and IBD have been proposed. First, it was demonstrated that immune cell activation was suppressed by *H. pylori* DNA, including dendritic cells, macrophages, and other types of immune cells, which in turn reduced the severity of the colitis [43–45]. Other possible mechanisms by which

gastric mucosa is protected by *H. pylori* infection from *S. typhimurium*-induced inflammation include the suppression of the inflammatory T helper 1/17 (Th1/17) response in the lower GI Tract. This has been found in mice, so was the increased production of the anti-inflammatory interleukin-10 (IL-10) in mesenteric lymph nodes [46, 47]. Infection with *H. pylori* may be associated with the presentation of microbiota in the gut. The presence of mutations in genes that are known to be associated with CD provided evidence that microbiota play a part in the pathogenesis of the illness. This might be accomplished by a change in the immune response, mucosal permeability, or the metabolic products of microbes [48–52]. Antibiotics and probiotics are two examples treatments targeting bacteria, and there has been a recent increase of the use of both approaches. Stomach mucosal infection caused by *H. pylori* has been shown to have an effect on the intestinal microbiota, resulting in a considerable decrease in gut inflammation. Treg cell activation is of the highest significance in this respect because Treg cells inhibit inflammatory and immunological responses to gut bacteria, perhaps by secreting anti-inflammatory and immunosuppressive cytokines [53–56]. This hypothesis helps to explain why the immune system tolerates a wide variety of "non-self" gut bacteria, despite their location on the mucosal surface of the digestive tract. It has been shown that infection with *H. pylori* increases the number of regulatory T cells in the mucosa of the stomach and in the peripheral circulation [54]. This infection also alters the actions of these cells, perhaps by affecting the expression of certain receptors. *H. pylori* modifies the host immune response to change the inflammatory Th1/17 pattern. This is accomplished by upregulating Foxp3, a marker of regulatory T cells, in the gastric mucosa. By inhibiting protective immunological response, regulatory T cells (also known as Treg cells) maintain a constant level of *H. pylori* colonization [57, 58]. Additionally, mucosal modifications that impede stomach colonization by *H. pylori* and/or its spontaneous elimination in response to CD therapy, particularly 5-aminosalicylic acid treatment, may account for the decreased incidence of *H. pylori* infection in CD patients [9, 59, 60].

Probiotics may be useful to reduce intestinal inflammation if they are administered to reestablish a healthy balance in the microbiota of the gut and/or to reset the immunological systems that have been dysregulated [19]. The anti-inflammatory and immune-modulatory effects of probiotics help decrease inflammation by inhibiting the production of pro-inflammatory cytokines and enhancing the production of anti-inflammatory cytokines. This is how probiotics work to reduce inflammation. There have been conflicting reports on using probiotics in terms of efficacy as part of a therapeutic strategy to eradicate *H. pylori*. In a number of clinical studies, the standard triple therapy for *H. pylori* was supplemented with adjuvant medications (such as lactoferrin and probiotics), trying to lower the risks of adverse side effects and raising the change of complete eradication [9, 35, 39, 50, 54]. The addition of lactoferrin or probiotics to the triple therapy did not result in an increase in the rate of *H. pylori* eradication; however, it did result in a reduction in epigastric pain, vomiting, and diarrhea, indicating a less degree of inflammation [53, 57]. This paradox may be caused antibiotic resistance, as well as the difference in treatment regimens used by different organizations.

The toxic strains of *H. pylori* are the most common cause of infection in people with CD. On the basis of the results of other studies demonstrating a higher incidence of Helicobacteraceae in patients with CD, it has been hypothesized that Helicobacteraceae may play a role in the etiology of CD, and that various strains of *H. pylori* may be able to adapt to colonize extra-gastric regions [61–64]. These hypotheses are based on the observation that CD patients have a higher prevalence of Helicobacteraceae.

Additionally, it was shown that CD patients who exhibited a UC-like phenotype had higher prevalence rates of *H. pylori* in their stomachs [61, 64]. Because of the *H. pylori*-induced immune activation, there is a good chance that interleukin-12 (IL-12) and the Th1 immune response will be elevated [65, 66]. CD is an example of a Th1-related sickness, and TNF and IL-2 are two examples of Th1 cytokines that contribute to the development of the disease [66]. Infection with *H. pylori* promotes inflammation of the gut epithelium, which then secretes IL-8, attracting neutrophils that are involved in the pathogenesis of IBD [67, 68].

The elimination of *H. pylori* with the use of clarithromycin and/or proton pump inhibitors (PPIs) has been related to a decrease in Th1 factors, which may provide some degree of protection against CD [69, 70]. Nevertheless, no epidemiological data is available so far to support this idea. It has been shown that the common antibiotic clarithromycin has anti-inflammatory and immunomodulatory effects. These effects include a large decrease in the release and gene expression of Th1 factors and a smaller reduction in the synthesis of Th2 factors [71]. However, in other studies, it was shown that clarithromycin, but not amoxicillin, is able to reduce the levels of immunological components indicative of Th1, Th2, and Th17 [72–74]. Patients with steroid-sensitive asthma showed a decrease in Th2 factors after taking clarithromycin, whereas those with "infection-induced" steroid-resistant asthma showed a decrease in Th1/Th17 factors [72, 75]. In a randomized clinical trial that was controlled with a placebo, researchers found that the antibiotic clarithromycin was effective in treating persons with active CD for 1 month [76], possibly due to bacterial resistance. Because of the potential of PPIs to lower the amount of acid produced by the stomach, microbial growth in the upper GI tract may considerably increase. PPIs, on the other hand, inhibit the membrane H^+/-ATPase of some gut microorganisms, which results in bacteriostatic and even bactericidal effects. Omeprazole has been shown to provide complete relief from UC symptoms in as little as 5 days. Lansoprazole may be beneficial in the treatment of IBD, including CD, by inhibiting the synthesis of specific proinflammatory cytokines in macrophages. *In vitro* research result revealed that the addition of lansoprazole to the culture media led to a decrease in the production of inflammatory cytokines (TNF- and IL-1) [77], which were produced by monocytes from peripheral blood. Because of their anti-inflammatory and immunomodulatory nature, clarithromycin and PPIs have been proposed as potential preventative approaches for CD; however, the epidemiological data to support this hypothesis is inadequate.

Putting aside any and all objections, the current research is a significant evidence that lends credence to the idea that the occurrences of *H. pylori* and CD have an negative association. More and more research results with consistent finding on the relationship between *H. pylori* infection and the CD development have been published. It has been suggested that *H. pylori* induce the development of regulatory T cells and impairs dendritic cell maturation, consequently resulting in a tolerogenic phenotype, which is a part of the mechanisms that *H. pylori* utilize to avoid host immune reactions.

Recent research results suggest that the processes that are responsible for the association may be more convoluted than previously thought. This is due to the fact that variables other than *H. pylori* infection influences the progression of CD. The findings of Shah et al. suggest that *H. pylori* may "serve as a signal for other gastrointestinal illnesses," which would provide some protection against CD [40]. It is noted in this study that the microbiota in the upper gastrointestinal tract differ among individuals who are positive for *H. pylori* from individuals who are negative for the infection.

Following the elimination of *H. pylori*, the changes of microbiota was found. Because it is considered that the gastrointestinal microbiota has a significant contribution to the development of CD, it is possible that a change in the components of the microbiota might change a person's vulnerability to CD. Since the relationship is clear, future research needs to focus more on the mechanisms that contribute to *H. pylori* infection, particularly in children. Another hotspot in the field would be the investigations focused on concomitant factors to *H. pylori* infection, such as alterations in the gut microbiota, which may potentially impact the etiology of Crohn's disease. A decision of the eradication of *H. pylori* in asymptomatic persons, in particular in patients with established Crohn's disease, should eventually be made based on the data collected from this type of researches.

4. Conclusion

Researchers have concluded that *H. pylori* should be classified as a suppress factor since patients with infections may have a reduced prevalence and subsequent incidence of CD. The Kyoto global agreement recommends eradicating *H. pylori* of each afflicted unless there are compelling reasons not to. This is because *H. pylori* may be associated with gastritis, which has been linked to an increased risk of developing stomach cancer. Despite the high infection incidence and the enormous amounts of antibiotics used, eradication of H. pylori has not been proven by various country recommendations. Unfortunately, epidemiologists specializing in *H. pylori control* paid little attention to the total impacts except for increased CD. *H. pylori* has an immunological tolerance mechanism, which allows it to stay in the mucosa while also the induced tolerogenic Th cells, immunosuppressive Tregs and cytokines are maintaining the critical systemic immune homeostasis. Consequently, the eradication of *H. pylori* with antibiotics is known to have greatly altered the microenvironment of gut bacteria. From the current review, this strategy has an indirect dramatic effect on immunological homeostasis, which may provide the potential risk of CD. The risk of gastric cancer in H. pylori-infected may not be calculated precisely, also the precise assessment of the risk of CD after *H. pylori* eradication is hard to be predicted and evaluated either. Therefore, the decreased prevalence and subsequent incidence of CD demonstrated the critical need for improved and individualized treatments for *H. pylori* infection.

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References

[1] Wang TC. Yamada's Textbook of Gastroenterology. Hoboken, NJ: Wiley; 2022 p. 1 online resource

[2] Sylla P, Kaiser AM, Popowich D. The SAGES Manual of Colorectal Surgery. Cham: Springer; 2020 p. 1 online resource

[3] Tersigni R, Prantera C. Crohn's Disease: A Multidisciplinary Approach. Dordrecht: Springer; 2010 xviii, p. 303

[4] Buratovich MA. Principles of Microbiology. Principles of Science. Amenia, NY, USA: Salem Press, a division of EBSCO Information Services; 2022 xxix, 697 pages

[5] Guandalini S, Dhawan A. Textbook of Pediatric Gastroenterology, Hepatology and Nutrition: A Comprehensive Guide to Practice. Cham: Springer; 2022 p. 1 online resource

[6] Shiotani A. Gastric cancer: With Special Focus on Studies from Japan. Singapore: Springer; 2019 p. viii, 201 pages

[7] Kamiya S, Backert S. *Helicobacter pylori* in Human Diseases, in Advances in Microbiology, Infectious Diseases and Public Health. Cham, Switzerland: Springer; 2019 p. xix, 284 pages

[8] Chichlowski M, Hale LP. Effects of Helicobacter infection on research: The case for eradication of Helicobacter from rodent research colonies. Comparative Medicine. 2009;**59**(1):10-17

[9] Yu Y et al. *Helicobacter pylori* infection and inflammatory bowel disease: A crosstalk between upper and lower digestive tract. Cell Death & Disease. 2018;**9**(10):961

[10] Wu XW et al. *Helicobacter pylori* infection and inflammatory bowel disease in Asians: A meta-analysis. World Journal of Gastroenterology. 2015;**21**(15):4750-4756

[11] Papamichael K, Konstantopoulos P, Mantzaris GJ. *Helicobacter pylori* infection and inflammatory bowel disease: Is there a link? World Journal of Gastroenterology. 2014;**20**(21):6374-6385

[12] Sun J. Inflammation, Infection, and Microbiome in Cancers: Evidence, Mechanisms, and Implications, in Physiology in Health and Disease. Cham, Switzerland: Springer; 2021 p. xii, 509 pages

[13] Kanoun O, Derbel N. Advanced Sensors for Biomedical Applications, in Smart Sensors, Measurement and Instrumentation. Cham: Springer; 2021 p. 1 online resource

[14] Nordenfelt P, Otto MW. Bacterial Pathogenesis: Methods and Protocols, in Springer Protocols. New York: Humana Press: Springer; 2017 p. xi, 357 pages

[15] Gracia-sancho J, Salvadó MJ. Gastrointestinal Tissue: Oxidative Stress and Dietary Antioxidants. London: Academic Press; 2017 xvii, 376 pages

[16] Suzuki H, Warren JR, Marshall BJ. *Helicobacter pylori*. Japan: Springer; 2016 p. x, 267 pages

[17] Lanas A. NSAIDs and Aspirin: Recent Advances and Implications for Clinical Management. Switzerland: Springer; 2016 p. 1 online resource

[18] Wang WL, Xu XJ. Correlation between Helicobacter pylori infection and Crohn's disease: A meta-analysis.

European Review for Medical and Pharmacological Sciences. 2019;**23**(23):10509-10516

[19] Rokkas T et al. The association between *Helicobacter pylori* infection and inflammatory bowel disease based on meta-analysis. United European Gastroenterology Journal. 2015;**3**(6):539-550

[20] Jones K. Cancer sourcebook: Basic consumer health information about major forms and stages of cancer, featuring facts about head and neck cancers, lung cancers, gastrointestinal cancers, genitourinary cancers, lymphomas, blood cell cancers, endocrine cancers, skin cancers, bone cancers, metastatic cancers, and more; along with facts about cancer treatments, cancer risks and prevention. In: Health Reference Series. Detroit, MI, USA: Omnigraphics; p. 2015 77 entries

[21] Yue M et al. Is *Helicobacter pylori* infection associated with celiac disease? A Meta-analysis. The Turkish Journal of Gastroenterology. 2022;**33**(3):205-212

[22] Luther J et al. Association between *Helicobacter pylori* infection and inflammatory bowel disease: A meta-analysis and systematic review of the literature. Inflammatory Bowel Diseases. 2010;**16**(6):1077-1084

[23] Wang WL, Xu XJ. Correlation between *Helicobacter pylori* infection and Crohn's disease: A meta-analysis. European Review for Medical and Pharmacological Sciences. Dec 2019;**23**(23):10509-10516. DOI: 10.26355/eurrev_201912_19691. PMID: 31841206

[24] Shirzad-Aski H et al. Association between *Helicobacter pylori* colonization and inflammatory bowel disease: A systematic review and Meta-analysis. Journal of Clinical Gastroenterology. 2021;**55**(5):380-392

[25] Castano-Rodriguez N et al. Dual role of Helicobacter and Campylobacter species in IBD: A systematic review and meta-analysis. Gut. 2017;**66**(2):235-249

[26] Ding ZH et al. The prevalence of *Helicobacter pylori* infection in inflammatory bowel disease in China: A case-control study. PLoS One. 2021;**16**(3):e0248427

[27] Chun HJ et al. Small Intestine Disease: A Comprehensive Guide to Diagnosis and Management. Singapore: Springer; 2022 p. 1 online resource

[28] Hohenberger W, Parker M. Lower Gastrointestinal Tract Surgery. Vol. 2, Open Procedures, in Springer Surgery Atlas Series. Cham: Springer; 2021 p. xvii, 614 pages

[29] Hyman N, Fleshner P, Strong S. Mastery of IBD Surgery. Cham: Springer; 2019 p. xi, 409 pages, color illustrations

[30] Kohlstadt I. Food and Nutrients in Disease Management. Boca Raton: CRC Press; 2009 xxii, 717 pages

[31] Wyllie R, Hyams JS, Kay M. Pediatric Gastrointestinal and Liver Disease. Sixth edition ed. Philadelphia, PA: Elsevier; 2021 xx, 1091 pages

[32] Zhong Y et al. The relationship between *Helicobacter pylori* and inflammatory bowel disease. Archives of Iranian Medicine. 2021;**24**(4):317-325

[33] Bartels LE et al. Diagnosis of *Helicobacter pylori* infection is associated with lower prevalence and subsequent incidence of Crohn's disease. Journal of Crohn's & Colitis. 2016;**10**(4):443-448

[34] Engstrand L, Graham DY. Microbiome and gastric Cancer. Digestive Diseases and Sciences. 2020;**65**(3):865-873

[35] Bartels LE, Dahlerup JF. Association of *Helicobacter pylori* and Crohn's disease incidence: An inversion reaction? Digestive Diseases and Sciences. 2017;**62**(9):2217-2219

[36] Xiang Z et al. *Helicobacter pylori* and Crohn's disease: A retrospective single-center study from China. World Journal of Gastroenterology. 2013;**19**(28):4576-4581

[37] Roka K et al. The prevalence of *Helicobacter pylori* gastritis in newly diagnosed children with inflammatory bowel disease. Helicobacter. 2014;**19**(5):400-405

[38] Lender N et al. Review article: Associations between *Helicobacter pylori* and obesity--an ecological study. Alimentary Pharmacology & Therapeutics. 2014;**40**(1):24-31

[39] Toscano EP et al. Epidemiological and clinical-pathological aspects of *Helicobacter pylori* infection in Brazilian children and adults. Gastroenterology Research and Practice. 2018;**2018**:8454125

[40] Shah A et al. Is there a link between *H. pylori* and the epidemiology of Crohn's disease? Digestive Diseases and Sciences. 2017;**62**(9):2472-2480

[41] Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nature Reviews. Gastroenterology & Hepatology. 2015;**12**(4):205-217

[42] Singh S et al. Epidemiology, risk factors and management of cardiovascular diseases in IBD. Nature Reviews. Gastroenterology & Hepatology. 2015;**12**(1):26-35

[43] Luther J et al. *Helicobacter pylori* DNA decreases pro-inflammatory cytokine production by dendritic cells and attenuates dextran sodium sulphate-induced colitis. Gut. 2011;**60**(11):1479-1486

[44] Owyang SY et al. *Helicobacter pylori* DNA's anti-inflammatory effect on experimental colitis. Gut Microbes. 2012;**3**(2):168-171

[45] Kim JM et al. *Helicobacter pylori* vacuolating cytotoxin induces apoptosis via activation of endoplasmic reticulum stress in dendritic cells. Journal of Gastroenterology and Hepatology. 2015;**30**(1):99-108

[46] Dixon BREA, Hossain R, Patel RV, Algood HMS. Th17 cells in *Helicobacter pylori* infection: A dichotomy of help and harm. Infection and Immunity. 18 Oct 2019;**87**(11):e00363-19. DOI: 10.1128/IAI.00363-19. PMID: 31427446; PMCID: PMC6803329

[47] Bhuiyan TR et al. Th1 and Th17 responses to *Helicobacter pylori* in Bangladeshi infants, children and adults. PLoS One. 2014;**9**(4):e93943

[48] Ansari S, Yamaoka Y. Animal models and *Helicobacter pylori* infection. Journal of Clinical Medicine. 31 May 2022;**11**(11):3141. DOI: 10.3390/jcm11113141. PMID: 35683528; PMCID: PMC9181647

[49] Vital JS, Tanoeiro L, Lopes-Oliveira R, Vale FF. Biomarker characterization and prediction of virulence and antibiotic resistance from *Helicobacter pylori* next generation sequencing data. Biomolecules. 11 May 2022;**12**(5):691. DOI: 10.3390/biom12050691. PMID: 35625618; PMCID: PMC9138241

[50] Suzuki R et al. Genome-wide mutation analysis of Helicobacter pylori after inoculation to Mongolian gerbils. Gut Pathog. 2019;**11**:45

[51] Cooper TK et al. Research-relevant conditions and pathology of laboratory

mice, rats, gerbils, Guinea pigs, hamsters, naked mole rats, and rabbits. ILAR Journal. 2021;**62**(1-2):77-132

[52] Israel DA et al. *Helicobacter pylori* strain-specific differences in genetic content, identified by microarray, influence host inflammatory responses. The Journal of Clinical Investigation. 2001;**107**(5):611-620

[53] Oster P et al. The efficacy of Cancer immunotherapies is compromised by *Helicobacter pylori* infection. Frontiers in Immunology. 2022;**13**:899161

[54] Reyes VE, Peniche AG. *Helicobacter pylori* deregulates T and B cell Signaling to trigger immune evasion. Current Topics in Microbiology and Immunology. 2019;**421**:229-265

[55] Baj J, Forma A, Sitarz M, Portincasa P, Garruti G, Krasowska D, et al. *Helicobacter pylori* virulence factors-mechanisms of bacterial pathogenicity in the gastric microenvironment. Cells. 25 Dec 2020;**10**(1):27. DOI: 10.3390/cells10010027. PMID: 33375694; PMCID: PMC7824444

[56] Gravina AG et al. *Helicobacter pylori* and extragastric diseases: A review. World Journal of Gastroenterology. 2018;**24**(29):3204-3221

[57] Wang L et al. *Helicobacter pylori* and autoimmune diseases: Involving multiple systems. Frontiers in Immunology. 2022;**13**:833424

[58] Bravo D et al. *Helicobacter pylori* in human health and disease: Mechanisms for local gastric and systemic effects. World Journal of Gastroenterology. 2018;**24**(28):3071-3089

[59] Arnold IC, Muller A. *Helicobacter pylori*: Does gastritis prevent colitis? Inflamm Intest Dis. 2016;**1**(3):102-112

[60] Fujita Y et al. Ulcerative colitis relapse after *Helicobacter pylori* eradication in a 12-year-old boy with duodenal ulcer. BMC Gastroenterology. 2021;**21**(1):424

[61] Axelrad JE et al. The role of gastrointestinal pathogens in inflammatory bowel disease: A systematic review. Therapeutic Advances in Gastroenterology. 2021;**14**:17562848211004493

[62] Sultan S et al. Metabolic influences of gut microbiota Dysbiosis on inflammatory bowel disease. Frontiers in Physiology. 2021;**12**:715506

[63] Raoul P, Cintoni M, Palombaro M, Basso L, Rinninella E, Gasbarrini A, et al. Food additives, a key environmental factor in the development of IBD through gut Dysbiosis. Microorganisms. 13 Jan 2022;**10**(1):167. DOI: 10.3390/microorganisms10010167. PMID: 35056616; PMCID: PMC8780106

[64] Zhang L et al. Bacterial species associated with human inflammatory bowel disease and their pathogenic mechanisms. Frontiers in Microbiology. 2022;**13**:801892

[65] Dann SM et al. Giardia infection of the small intestine induces chronic colitis in genetically susceptible hosts. Journal of Immunology. 2018;**201**(2):548-559

[66] Van Der Kraak LA et al. Genetic and commensal induction of IL-18 drive intestinal epithelial MHCII via IFNgamma. Mucosal Immunology. 2021;**14**(5):1100-1112

[67] Choi MS et al. *Helicobacter pylori*-derived outer membrane vesicles stimulate interleukin 8 secretion through nuclear factor kappa B activation. The Korean Journal of Internal Medicine. 2021;**36**(4):854-867

[68] Uotani T et al. Changes of tight junction and interleukin-8 expression

using a human gastroid monolayer model of *Helicobacter pylori* infection. Helicobacter. 2019;**24**(3):e12583

[69] Alexander SM et al. *Helicobacter pylori* in human stomach: The inconsistencies in clinical outcomes and the probable causes. Frontiers in Microbiology. 2021;**12**:713955

[70] Mladenova I. Clinical relevance of *Helicobacter pylori* infection. Journal of Clinical Medicine. 2021;**10**:3473. DOI: 10.3390/jcm10163473

[71] Taylor JM et al. Effects of a Th1- versus a Th2-biased immune response in protection against *Helicobacter pylori* challenge in mice. Microbial Pathogenesis. 2008;**44**(1):20-27

[72] Lindenberg M et al. Clarithromycin impairs tissue-resident memory and Th17 responses to macrolide-resistant *Streptococcus pneumoniae* infections. Journal of Molecular Medicine (Berlin, Germany). 2021;**99**(6):817-829

[73] Liu J et al. Erythromycin suppresses the cigarette smoke extract-exposed dendritic cell-mediated polarization of CD4(+) T cells into Th17 cells. Journal of Immunology Research. 2020;**2020**:1387952

[74] Takemori N et al. Possible mechanisms of action of clarithromycin and its clinical application as a repurposing drug for treating multiple myeloma. Ecancermedicalscience. 2020;**14**:1088

[75] Liu W et al. Mechanism of TH2/TH17-predominant and neutrophilic TH2/TH17-low subtypes of asthma. The Journal of Allergy and Clinical Immunology. 2017;**139**(5):1548-1558 e4

[76] Kim JJE et al. Efficacy of clarithromycin depends on the bacterial density in clarithromycin-Heteroresistant *Helicobacter pylori* infections: An In situ detected susceptibility and quantitative morphometry-based retrospective study. Pathology Oncology Research. 2021;**27**:1609863

[77] Mishima K et al. Lansoprazole upregulates Polyubiquitination of the TNF receptor-associated factor 6 and facilitates Runx2-mediated Osteoblastogenesis. eBioMedicine. 2015;**2**(12):2046-2061