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Clinical Manifestations of the *Epsilonproteobacteria* (*Helicobacter pylori*)

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Abstract

Epsilonproteobacteria is a large group of Gram-negative curved or spiral microaerophilic rods, of which many are difficult to culture. Because this group of bacteria is not very well investigated, our knowledge about them is limited, and a great amount of research is still needed. At least two species are well-established human pathogens: *Campylobacter jejuni/coli* causing gastroenteritis and *Helicobacter pylori* causing gastric and extra-gastric manifestations. It is well accepted that *H. pylori* causes a chronic inflammation in the stomach and thereby causes *H. pylori*-associated gastritis, which may or may not be symptomatic. The association between *H. pylori* and peptic ulcers, MALT lymphomas, gastric cancer, idiopathic thrombocytopenic purpura, and unexplained iron-deficiency anemia (IDA) is strongly evidence based. On the other hand, pernicious (vitamin B12 deficiency) anemia, neuromyelitis optica, asthma, and Graves' disease are less evidence based. *H. pylori* may also be associated with cardiovascular disease, pancreatitis, pancreatic cancer, obesity, diabetes mellitus type 2, Parkinson's disease, liver diseases, and preeclampsia. *H. pylori* is thus involved in many gastric and extra-gastric manifestations either directly or indirectly by several proposed mechanisms including antigenic mimicry.

Keywords: *Helicobacter pylori*, infection, mimicry, gastritis, anemia, thrombocytopenic purpura, gastric cancer

1. Introduction

Epsilonproteobacteria is a large group of Gram-negative curved or spiral rods which include the genera *Campylobacter* spp., *Helicobacter* spp., *Arcobacter* spp., and *Wolinella* spp. (Table 1) [1]. The bacteria have microaerobic or anaerobic growth requirements, and many of these are difficult to culture from clinical samples [2]. Recent studies with identification of *Epsilonproteobacteria* by PCR have shown that these bacteria cause infections in humans more commonly than previously thought [3, 4]. The most well-known species are *Campylobacter jejuni/coli* causing gastroenteritis [2] and *Helicobacter pylori* causing gastric and extra-gastric manifestations [5].

This chapter will focus on *Helicobacter* spp. and mainly on *H. pylori*. *Helicobacter* spp. can be divided into three groups: (1) gastric *Helicobacter* spp., (2) intestinal *Helicobacter* spp., and (3) hepatobiliary *Helicobacter* spp. [6]. The knowledge about intestinal *Helicobacter* spp. in human diseases is very limited mainly because they are very difficult to culture. In contrast to the intestinal and hepatobiliary *Helicobacter* spp., the gastric *Helicobacter* spp. produce a great amount of urease, which is important for its survival in the stomach by neutralizing acid, thereby creating a neutral microenvironment [7]. Urease is also crucial for the bacteria's survival through antigenic shedding where urease captures human antibodies [8]. The human gastric *Helicobacter* sp., *H. pylori*, is the most intensively investigated *Helicobacter* sp., but gastric *Helicobacter* spp. from animals (*Helicobacter heilmannii*, *Helicobacter bizzozeronii*, *Helicobacter suis*, etc.) have also been found in the human stomach [9]. These bacteria colonize the stomach in very different ways. *H. pylori* colonizes the antrum part of the stomach on the surface between epithelial cells and can actively move down between the epithelial cells [10]. On the other hand, *Helicobacter* sp. from animals colonizes the parietal cell glands in the corpus/fundus part of the stomach which may contribute to other manifestations than those caused by *H. pylori* [11]. Usually, a stronger cellular immune response is seen in *H. pylori* in comparison to the animal-associated *Helicobacter* spp. [11].

Genus	Species
<i>Arcobacter</i>	<i>anaerophilus</i> , <i>aquimarinus</i> , <i>bivalviorum</i> , <i>butzleri</i> , <i>cibarius</i> , <i>cloacae</i> , <i>cryaerophilus</i> , <i>defluvii</i> , <i>ebronensis</i> , <i>ellisii</i> , <i>haliotis</i> , <i>halophilus</i> , <i>lanthieri</i> , <i>lekithochrous</i> , <i>marinus</i> , <i>molluscorum</i> , <i>mythili</i> , <i>nitrofigilis</i> , <i>pacificus</i> , <i>suis</i> , <i>thereius</i> , <i>trophiarum</i> , <i>venerupis</i>
<i>Campylobacter</i>	<i>avium</i> , <i>canadensis</i> , <i>coli</i> , <i>concisus</i> , <i>corcagiensis</i> , <i>cuniculorum</i> , <i>curvus</i> , <i>fetus</i> subsp. <i>fetus</i> , <i>fetus</i> subsp. <i>testudinum</i> , <i>fetus</i> subsp. <i>venerealis</i> , <i>geochelonis</i> , <i>helveticus</i> , <i>hepaticus</i> , <i>hominis</i> , <i>hyoilei</i> , <i>hyointestinalis</i> subsp. <i>hyointestinalis</i> , <i>hyointestinalis</i> subsp. <i>lawsonii</i> , <i>iguanorium</i> , <i>insulaenigrae</i> , <i>jejuni</i> subsp. <i>doylei</i> , <i>jejuni</i> subsp. <i>jejuni</i> , <i>lanienae</i> , <i>lari</i> subsp. <i>concheus</i> , <i>lari</i> subsp. <i>lari</i> , <i>mucosalis</i> , <i>ornithocola</i> , <i>pyloridis</i> , <i>pinnipediorum</i> , <i>pinnipediorum</i> subsp. <i>caledonicus</i> , <i>pinnipediorum</i> subsp. <i>pinnipediorum</i> , <i>rectus</i> , <i>showae</i> , <i>sputorum</i> , <i>subantarcticus</i> , <i>upsaliensis</i> , <i>ureolyticus</i> , <i>volucris</i>
<i>Helicobacter</i>	<i>acinonychis</i> , <i>ailurogastricus</i> , <i>anseris</i> , <i>apri</i> , <i>aurati</i> , <i>baculiformis</i> , <i>bilis</i> , <i>bizzozeronii</i> , <i>brantae</i> , <i>canadensis</i> , <i>canicola</i> , <i>canis</i> , <i>cetorum</i> , <i>cholecystus</i> , <i>cinaedi</i> , <i>cynogastricus</i> , <i>equorum</i> , <i>felis</i> , <i>fennelliae</i> , <i>ganmani</i> , <i>heilmannii</i> , <i>hepaticus</i> , <i>himalayensis</i> , <i>jaachi</i> , <i>japonicus</i> , <i>macacae</i> , <i>marmotae</i> , <i>mastomyrinus</i> , <i>mesocricetorum</i> , <i>muridarum</i> , <i>mustelae</i> , <i>pamatensis</i> , <i>pullorum</i> , <i>pylori</i> , <i>rodentium</i> , <i>salomonis</i> , <i>saguini</i> , <i>suis</i> , <i>trogontum</i> , <i>typhlonius</i> , <i>valdiviensis</i>
<i>Wolinella</i>	<i>succinogenes</i>

Table 1. The species belonging to the four largest groups of *Epsilonproteobacteria* [102].

H. pylori may either cause direct or indirect damage to the stomach: direct damage where *H. pylori* infections disintegrate gastric mucosa and cause apoptosis through cytotoxin-associated gene A (CagA) and vacuolating toxin (VacA) or indirect damage where *H. pylori* induces a strong and chronic immune response by activating B and T lymphocytes, macrophages, neutrophilic lymphocytes, and probably also eosinophil leukocytes. T cell-activated B lymphocytes, regulatory T cells (Treg), and T helper 17 cells (Th17) are some of the B and T lymphocytes that are important in *H. pylori* infections. T cell-activated B lymphocytes are responsible for a strong humoral immune response primarily toward *H. pylori* urease, flagella, CagA, and VacA. These activated B and T lymphocytes release a large range of cytokines of which IL1- β , TNF- α , INF- γ , IL6, IL-8, IL-10, IL-17, and cyclooxygenase-2 (COX-2) are the most important cytokines in severe *H. pylori* infections [12, 13].

Many microorganisms can cause autoimmune diseases. The mechanisms involved include molecular mimicry (when bacterial antigens cross-react with human tissue), epitope spreading, bystander effect, microbial superantigens, immune complex formation, MHC class II expression on nonimmune cells, and high levels of pro-inflammatory cytokines [14–17]. *H. pylori* has been implicated in both organ-specific and non-organ-specific autoimmune diseases and has been investigated sporadically or systematically in 95 autoimmune-related diseases [18]. Many mechanisms underlying the antigenic mimicry between *H. pylori* and the host have been proposed. Efforts have been made to identify homologous sequences between *H. pylori* and host polypeptides. H⁺/K⁺ –adenosine triphosphatase, Lewis antigens, and lipopolysaccharide seem to be autoantigens in autoimmune gastritis. Glycoproteins and Lewis antigens may be autoantigens directed against platelets in idiopathic thrombocytopenic purpura (ITP). Lewis antigens, heat shock protein 60 (HSP60), and 160/180 kDa antigens appear to be autoantigens to the endothelium, while alpha-carbon anhydrase and plasminogen-binding proteins could to be autoantigens in the pancreas [13].

All in all, *H. pylori* can cause both gastric and extra-gastric diseases through a complex mechanism involving both host and bacterial factors.

2. Gastritis and peptic ulcer

Whenever *H. pylori* is found in the human stomach, there is never just a simple colonization. Instead, there is always a cellular and humoral immune response confirming that *H. pylori* causes infection [10, 19, 20]. Thus, patients with gastritis and *H. pylori* have *H. pylori*-related gastritis. However, if there is no *H. pylori* infection, patients may have functional gastritis but no inflammation. *H. pylori*-related gastritis may benefit from antibiotic treatment, whereas there is no indication for antibiotic treatment for functional gastritis [21].

Peptic ulcers occur in about 10% of patients infected with *H. pylori* where most (80%) are duodenal ulcers [19]. More than 90% of duodenal ulcers are caused by *H. pylori* [19]. The pathogenesis of these ulcers is not clear, but they often occur in the part of the duodenum where the flow from the stomach content is the highest. Duodenal ulcers may be caused by a combination of physical, physiological, and immunologic effects as well as *H. pylori*. Patients with duodenal ulcers almost always benefit from antibiotic treatment. More than 60% of gastric

ulcers are caused by *H. pylori*, while the remaining 40% may be caused by different sources such as medication (NSAID, etc.) [21, 22]. Gastric ulcers are often found in the isthmus area of the stomach where the amount of blood flow of the stomach is the lowest. *H. pylori* stimulates the production of platelet-activating factor (PAF) which acts on angiogenesis by contracting blood vessels [23]. *H. pylori* has a direct damaging effect on the epithelium and interferes with the immune system in many ways [24]. However, the mechanisms are very complex, and the pathogenesis is still not completely understood.

3. Mucosa-associated lymphoid tissue (MALT) lymphomas

MALT lymphomas are a group of lymphomas which arise in the tissue normally devoid of lymphoid tissue, such as the stomach. These tissues accumulate lymphoid tissue during chronic antigenic stimulation such as chronic infections and autoimmune diseases. *H. pylori* causes about 80% of low-grade MALT lymphomas and 60% of high-grade MALT lymphomas [19]. Eradication of *H. pylori* stops the progression in most cases, and 60–80% of early-state low-grade MALT lymphomas will regress [25]. The mechanism by which *H. pylori* induces MALT lymphomas is unclear, and there is no evident correlation between MALT lymphomas and *H. pylori* virulence factors [26]. One theory is that the development of gastric MALT lymphomas in patients with *H. pylori* could be secondary to chronic antigenic stimulation of the immune system by the pathogen [27]. However, as in many other diseases, antigenic mimicry may also play a role [27]. Finally, it is possible that MALT lymphomas are correlated to non-*pylori Helicobacter* spp. instead of *H. pylori* [28, 29].

4. Gastric cancer

H. pylori causes approximately 80% of all gastric cancer cases, and in 1994 *H. pylori* became categorized as a Group 1 carcinogen meaning that *H. pylori* is a definite carcinogen to humans [30].

The development of gastric cancer is a complex process that depends on *H. pylori* virulence factors, host mucosa properties, immunological reactions to infections, as well as environmental factors in the stomach. In *H. pylori*, virulence factors like CagA and VacA have been suggested to influence cancer development. CagA gene and the type IV secretion system (T4SS) are encoded by a 40-kb DNA fragment called *cag* pathogenicity island (*cagPAI*) [19, 31]. CagA protein infects host gastric epithelial cells via the T4SS, where it is tyrosine-phosphorylated by host kinases at specific glutamate-proline-isoleucine-tyrosine-alanine (EPIYA) motifs [31, 32]. CagA thereafter interferes with different host cell-signaling pathways causing changes in cell growth, polarity, and motility, thereby increasing the risk for gastric cancer [19, 32]. VacA toxin affects gastric epithelial cells in a similar manner by affecting the host's inflammatory response as well as cellular apoptosis among other ways [19]. Other host factors could be high-salt diets and iron deficiency, which have been proven to increase the risk for gastric cancer [33, 34].

If *H. pylori* is treated in the early premalignant stages (atrophic gastritis), further cancer development can be prevented [35]. If intestinal metaplasia has developed, it is believed that antibiotic treatment has no effect [21]. As with gastritis and peptic ulcers, the relationship between *H. pylori* and gastric cancer has many loose ends that need to be explained before we can completely understand the process.

5. Idiopathic thrombocytopenic purpura (ITP)

Idiopathic thrombocytopenic purpura or immune thrombocytopenic purpura (ITP) is an acquired autoimmune disease resulting in the destruction of antibody-covered platelets and decreased platelet production. This results in an increased risk for bruising and bleeding. ITP is defined as a platelet count $<100 \times 10^9 /L$, may be either primary or secondary, and is classified as acute, persistent, or chronic [36].

The mechanism that leads to ITP in *H. pylori*-infected patients is not entirely established. It is proposed that molecular mimicry may be involved [13]. Cross-reactivity between platelet-associated immunoglobulin G and CagA has been found, which suggests that mimicry through CagA may play a role in the development of ITP [37].

It is well established that *H. pylori* screening may be warranted in patients with ITP. A systematic review from 2009 with 696 evaluable patients found that in patients with *H. pylori* infection, eradication of the bacteria led to a complete treatment response in 43% of the patients and an overall response (platelet count $\geq 30 \times 10^9/L$ and at least a doubling of initial platelet count) of 50%. The treatment tended to be more effective in milder forms of thrombocytopenia. The authors found that the predictors of treatment response were quite heterogeneous from study to study. Shorter duration of ITP was consistently found, and response rates tended to be higher in countries with a higher prevalence of *H. pylori* [38]. In the highly *H. pylori* prevalent country of South Korea, a more recent prospective study with 26 patients with persistent or chronic ITP investigated the efficacy of *H. pylori* eradication as a first-line treatment in patients with moderate thrombocytopenia [39]. The study found an eradication rate of 80% and a maximal complete response rate of 65% [39].

The most recent ITP guidelines from the American Society of Hematology (ASH) recommend eradication therapy in adult ITP patients with *H. pylori* infection. They do not define which patients should be screened or at what point in the course of the illness patients should receive treatment [36]. ASH recommends against routine testing in children because of diverging results but rather argues for the consultation with a pediatric gastroenterologist beforehand. Since the publication of the ASH guidelines, a randomized-controlled trial (RCT) with 85 ITP-affected children has been published. Twenty-two children were *H. pylori* infected, and they were randomized to receive either eradication therapy or no therapy. Complete response was achieved in 60% of the treated children compared to 18% of the children who were not treated. The authors suggested that *H. pylori* infection may play a bigger role in the pediatric ITP population than the earlier notions. It is also noted that 86% of the patients had CagA

antibodies and 82% harbored VacA antibodies [40]. The recently updated joint European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN/NASPGHAN) guidelines recommend testing for *H. pylori* in children with chronic ITP [41].

6. Iron-deficiency anemia

H. pylori infection has also been linked to iron-deficiency anemia (IDA) [42–44]. Mechanisms that cause IDA may increase iron loss due to hemorrhagic gastritis, gastric cancer, peptic ulcers, iron utilization for bacterial growth, achlorhydria resulting in reduced iron uptake, and reduced secretion of ascorbic acid [45].

A meta-analysis comprising 15,183 patients from 20 studies found an association between *H. pylori* infection and IDA (odds ratio (OR) 2.22) [46]. They also found a greater effect of eradication therapy plus iron than iron supplements alone but with heterogeneous results. Adult IDA patients reacted more strongly to eradication than children and adolescents, and bismuth triple therapy seemed to be more effective than proton pump inhibitor (PPI) triple therapy. The authors do not recommend a population-based screening for *H. pylori* to prevent IDA [46].

On the other hand, Herschko et al. studied 160 patients with autoimmune gastritis, of whom 83 presented with IDA [47]. When stratifying by age, they found a decreasing prevalence of coexistent *H. pylori* infection with increasing age: 88% at age <20 years, 47% at 20–40 years, 38% at 41–60 years, and 13% at age >60 years. A possible explanation, which other authors also have mentioned, is that *H. pylori* demands an acidic environment to survive, which no longer exists in advanced atrophic anemia. This might suggest that *H. pylori* infection in autoimmune gastritis may represent an early phase of the disease in which an infectious process is gradually replaced by an autoimmune disease terminating in a burned-out infection and the irreversible destruction of gastric mucosa. This might explain why younger patients with IDA have a high prevalence of *H. pylori* infection [47].

The British Society of Gastroenterology recommends noninvasive testing and antibiotic treatment for *H. pylori* in patients with IDA and normal esophagogastroduodenoscopy and colonoscopy [48]. The American College of Gastroenterology also recommends testing for *H. pylori* in patients with unexplained IDA [49]. The association between IDA and *H. pylori* infection in the pediatric population is less studied and with heterogeneous results. ESPGHAN/NASPGHAN guidelines propose that in children with refractory IDA where there is an indication for upper endoscopy, it might be considered taking biopsies to test for *H. pylori* [41].

7. Vitamin B₁₂ deficiency anemia

Vitamin B₁₂ (cobalamin) deficiency is estimated to affect approximately 10–15% of the population older than 60 years. There are several causes where pernicious anemia and food-cobalamin malabsorption are the most common reasons. Cobalamin is obtained primarily from food through a complicated process where an acidic environment releases cobalamin from food

and thereafter binds to intrinsic factors secreted from parietal cells and finally is absorbed by specific receptors in the terminal ileum. Pernicious anemia is an autoimmune disorder consisting of chronic atrophic gastritis, decreased acid secretion, and antibodies directed against parietal cells and/or intrinsic factors, thereby leading to decreased cobalamin absorption. *H. pylori* possibly stimulates these antibodies directed against parietal cells/intrinsic factors, thereby inducing pernicious anemia. In food-cobalamin malabsorption, there is an inability to absorb food-bound or protein-bound cobalamin in a person that normally can absorb free cobalamin. *H. pylori* infection predisposes to a more severe form of food-cobalamin malabsorption [50].

As mentioned above, it has been proposed that B₁₂ deficiency can arise as the result of a late phase of *H. pylori*-induced atrophic gastritis [47]. This theory has been mentioned already in the early 1990s [51]. In a prospective case series with 138 patients with megaloblastic anemia and low cobalamin, it was found that 56% had *H. pylori* infection. Eradication therapy was successful in 40% of the infected patients, and the hematological parameters and B₁₂ levels improved in all these patients without complementary cobalamin therapy [52].

The literature regarding the association between *H. pylori* and pernicious anemia shows more heterogeneous results than for ITP and IDA [52]. Therefore, treatment guidelines do not yet recommend screening for *H. pylori* in pernicious anemia. However, the Maastricht V/Florence Consensus Report does recommend that in all three of the abovementioned disorders *H. pylori* should be screened for and eradicated [21].

8. Cardiovascular disease

Studies indicate an association between *H. pylori* and cardiovascular disease (CVD) [53, 54]. However, the stratification of patient groups and methods are very heterogeneous which may be the reason for the very diverging results in the studies [53]. *H. pylori* seems to mostly be associated with coronary atherosclerosis [55, 56]. This is in accordance with an unpublished study where we found increased antibodies to *H. pylori*, but not to *Chlamydomphila pneumoniae* and *Cytomegalovirus* in patients undergoing surgery for coronary atherosclerosis. *H. pylori* can survive in monocytes, and it might be speculated whether the bacteria could be transferred from the stomach to the coronary vessels. Here, *H. pylori* may stimulate PAF and other factors that may act on angiogenesis [23, 56]. *H. pylori* may also stimulate the atherogenesis through molecular mimicry or vitamin B12 and folate malabsorption [13, 53, 54]. In addition, *H. pylori* may change the lipid profile by increasing LDL levels and decreasing HDL levels as seen in many other infections, which leads to atherogenesis [53, 54, 57–59].

9. Pancreatitis and pancreatic cancer

Studies have shown a correlation between increased antibody levels to *H. pylori* in patients with pancreatitis and pancreatic cancer [60–63]. In an unpublished study, we showed that in more than 50% of patients with pancreatitis *H. pylori* was cultured from the antral part of the

stomach. The interaction leading to pancreatic cancer is unknown, but *H. pylori* infection in the antral part of the stomach decreases the production of somatostatin. This increases pancreatic bicarbonate and secretin which stimulates ductal epithelial cell proliferation [64]. In addition, studies indicate that *H. pylori* increases the risk of autoimmune pancreatitis through molecular mimicry and thereby increases the risk for pancreatic cancer [13, 60, 63–65]. These findings are of great interest and need further intensive research.

10. Obesity and diabetes mellitus type 2

Obesity is becoming a worldwide problem, and population studies have shown that in the same areas where the prevalence of *H. pylori* is decreasing, the prevalence of obesity is increasing [21, 66]. An implication of obesity could be diabetes mellitus type 2. A possible mechanism in which *H. pylori* affects obesity and thereby also affects type 2 diabetes is persistent damage of gastric mucosa, e.g., chronic gastritis. This might affect ghrelin production, thereby changing food intake and increasing body weight [67, 68].

Ghrelin is a hormone mainly produced by endocrine cells in the gastrointestinal mucosa and is released to the surroundings. This molecule is important for stimulating food intake and weight gain [69]. The damages that *H. pylori* introduce on gastric mucosa reduce the number of ghrelin-producing cells and decrease plasma ghrelin concentrations significantly, thereby reducing the feeling of satiety which can lead to obesity [67, 68, 70].

Ghrelin also seems to play a role in fat metabolism and glucose homeostasis, which can lead to a cross-reaction between lipid and glucose metabolisms that may result in insulin resistance [71]. However, one thing is clear, diabetes mellitus type 2 is a multifactorial disease, and *H. pylori* is only one of the many risk factors. *H. pylori* may also act on leptin or by activating cytokines that together can have an effect on insulin secretion [72, 73].

Although many studies have shown that there could be a correlation between *H. pylori* and obesity and diabetes mellitus type 2, other studies have shown that there are none and the correlation is still uncertain [66, 74].

11. Parkinson's and Alzheimer's diseases

Numerous studies indicate that *H. pylori* infection is associated with a more rapid development of cognitive and functional deterioration. Furthermore, eradication of *H. pylori* could give an improved disease severity [75–78]. Also, a study by Weller et al. showed that the presence of CagA antibodies is associated with a poorer Parkinson's prognosis [79]. It is proposed that *H. pylori* initiates the destruction of mitochondria and together with antigenic mimicry stimulates Parkinson's disease [72]. Only few studies focus on *H. pylori* and Alzheimer's disease, and they are too preliminary to show a causal or therapeutic association [72, 75].

12. Neuromyelitis optica

Several studies have shown a correlation between *H. pylori* and neuromyelitis optica (NMO) [18]. NMO is a disease where antibodies attack aquaporin-4 on astrocytes in the central nervous system [80]. There is a close relationship between *H. pylori* and antibodies to aquaporin-4, and thus molecular mimicry could play a role [18].

13. Asthma

The prevalence of asthma is increasing in areas where the prevalence of *H. pylori* is decreasing [81]. Meta-analyses have found an inverse correlation between *H. pylori* and asthma, but the mechanism is unclear [72, 82, 83]. CagA-positive *H. pylori* strains especially have been found to have a greater inverse relationship with asthma than those without *H. pylori* [81]. The long-established hygiene hypothesis, where a lack of exposure to infectious agents leads to an increased risk for allergens, has been proposed as one way in which an absence of *H. pylori* causes asthma [82]. Th2-mediated immune responses drive allergies, while Th1-mediated immune responses inhibit these reactions. *H. pylori* appears to stimulate Th1-mediated immune responses but inhibit Th2-mediated immune responses through neutrophil-activating protein (HP-NAP), thereby inhibiting asthma development [84]. Another possible mechanism of *H. pylori* is upregulation of Treg cells which can control Th2-mediated immune responses [82]. A mouse study by Arnold et al. proved that *H. pylori* infection protected mice against asthma and an upregulation of Treg cells was found in mice infected with *H. pylori* [85]. Thus, *H. pylori* could inhibit asthma in a multitude of ways.

14. Hepatobiliary diseases

Non-*pylori Helicobacter* species have been isolated from the liver of a variety of animals. *H. hepaticus*, *H. bilis*, and *H. cholecystus* are involved in the pathogenesis of chronic liver diseases and liver carcinomas [86–88]. *H. pylori*, *H. hepaticus*, *H. bilis*, and *H. cholecystus* have been detected in the human hepatobiliary tissue mainly by PCR [89–91]. Several studies have shown an increased prevalence of *H. pylori* in patients with hepatocellular carcinomas (HCC), liver encephalopathy (HE), liver fibrosis, cholangiocarcinoma (CCA), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis [92]. Much interest has been linked to HCC and CCA which histologically is characterized as adenocarcinomas. The pathogenesis has been proposed to follow the same pattern as in stomach cancer: hyperplasia, metaplasia, dysplasia, and lastly cancer [92]. Inflammatory cytokines and chemokines may play an important role in the pathogenesis. HE is a frequent complication to liver cirrhosis with a wide variety of neuropsychiatric symptoms, and high levels of ammonia play an important role in the pathogenesis [93]. *H. pylori* produces urease which reacts to ammonium, which might explain a possible mechanism in HE development. Liver fibrosis, among other ways, may be caused by *H. pylori* stimulating

hepatocytes and results in accumulation of collagen, thereby causing fibrosis [63]. Some of the risk factors for these cancers are population genetics, geographical and environmental factors, cholelithiasis, obesity, chronic inflammation, and obstruction of the bile duct [92, 94].

15. Autoimmune thyroid diseases

Both Graves' disease and Hashimoto's thyroiditis are autoimmune diseases in the thyroid. Graves' disease is characterized by hyperthyroidism and an enlarged gland, while Hashimoto's thyroiditis is characterized by hypothyroidism and the destruction of thyroid tissue. There is an association between Graves' disease and *H. pylori*, where CagA is most likely an important virulence factor [95]. A study by Bassi et al. showed that 82% (43/52) of patients with Graves' disease were positive for *H. pylori*, where 84% (36/43) of *H. pylori*-positive Graves' disease patients were positive for CagA antigens. Also, a different study by Bertalot et al. showed a reduction in thyroid autoantibodies following *H. pylori* eradication [96]. Amino acid sequences of thyroid peroxidase and CagA are very similar, and cross-reactivity is a possible mechanism by which *H. pylori* increases the risk of developing Graves' disease [18, 95]. In addition, Graves' disease is often found with other autoimmune diseases which may reflect the ability of *H. pylori* to induce multiple autoimmune diseases simultaneously [97]. However, the same cannot be said about Hashimoto's thyroiditis where a significant association between Hashimoto's thyroiditis and *H. pylori* was not found by Bassi et al. [95].

16. Preeclampsia

The first study investigating the association between *H. pylori* infection and preeclampsia (PE) was conducted in Italy and published in 2006 [98]. It was found that 32% of women with a normal pregnancy harbored anti-*H. pylori* antibodies compared to 51% of preeclamptic women. The difference was even bigger when looking at the presence of anti-CagA antibodies: 15 vs. 81% in women with a normal pregnancy vs. preeclamptic women. The authors concluded that the increased inflammatory activity in *H. pylori*-infected patients may contribute to the development of PE, especially in CagA strains. Interestingly, no *H. pylori* DNA was present in the placentas that were studied, and therefore the inflammation is probably not locally induced.

A review from 2014 concluded that there is evidence indicating that *H. pylori* negatively influences human reproductivity, including PE [99]. This is probably due to both increased inflammatory activity and antigenic mimicry with CagA-positive strains appearing to be the most important culprits [99]. A recent meta-analysis of observational studies with 9787 women (879 preeclamptic) confirmed these theories, with an OR of 2.32 for anti-*H. pylori* antibodies in cases compared to controls and an OR of 3.97 for having anti-CagA antibodies in preeclamptic patients [100]. A review on the topic of infections and the risk of PE mentions *H. pylori* as a possible cause of PE and recommends that screening (and treatment) of known infectious organisms causing PE should be included in antenatal programs [101]. However, as mentioned by Bellos et al., it is yet unknown if *H. pylori* predisposes to mild or severe PE, at which gestational age optimal screening should be conducted, and most importantly how effective eradication is in terms of reducing the incidence and severity of PE [100].

17. Discussion

H. pylori can induce many pathogenic reactions in infected individuals. There are mainly three different ways *H. pylori* acts. (1) The bacteria have several virulence factors (Cag PAI, Vac A, etc.) that can cause direct damage and apoptosis of epithelial cells in the stomach and can stimulate mast cells to liberate PAF which affects the angiogenesis in the stomach. This may be some of the main actions on gastric diseases such as peptic ulcers and gastric cancer (**Figure 1**). (2) There is a strong cellular and humoral immune response to *H. pylori* with the release of different cytokines and chemokines. Cytokines and chemokines subsequently react both in the stomach and in extra-gastric organs (**Figure 2**). In addition, several *H. pylori* antigens are structurally like antigens of the human body and therefore may cause cross-reactions (antigenic mimicry) (**Figure 3**). All these pathogenic mechanisms of *H. pylori* may result in different diseases both in the stomach and in extra-gastric organs.

The role of *H. pylori* in relation to gastritis, peptic ulcers, MALT lymphomas, and gastric cancer is well known and established. However, there is confusion about the difference between

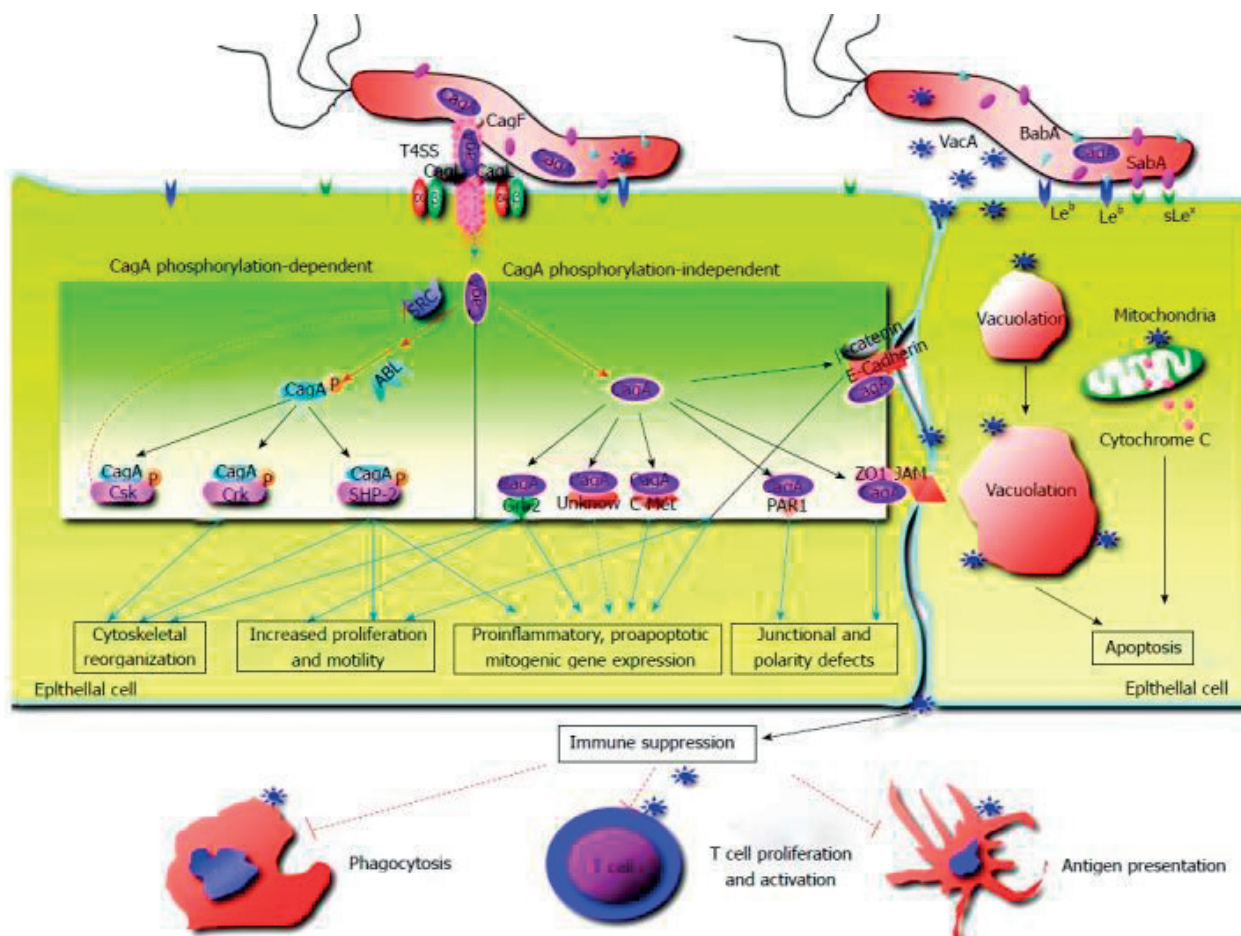


Figure 1. The roles of the main virulence factors in pathogenesis of *Helicobacter pylori* infection [6]. Adherence of *Helicobacter pylori* to gastric epithelial cells is mediated by BabA and SabA binding Le^b and Lewis x/a, respectively. CagA is translocated into epithelial cells through T4SS and then tyrosine-phosphorylated at EPIYA sites by Src and Abl kinases. CagA contributes to alteration of myriad signaling transduction, which affects host cell physiology with disruption of intercellular junctions, loss of cell polarity, promotion of inflammation, dysregulation of cellular apoptosis, and proliferation. VacA induces cytoplasmic vacuolation, apoptosis, and immune suppression [6, 103].

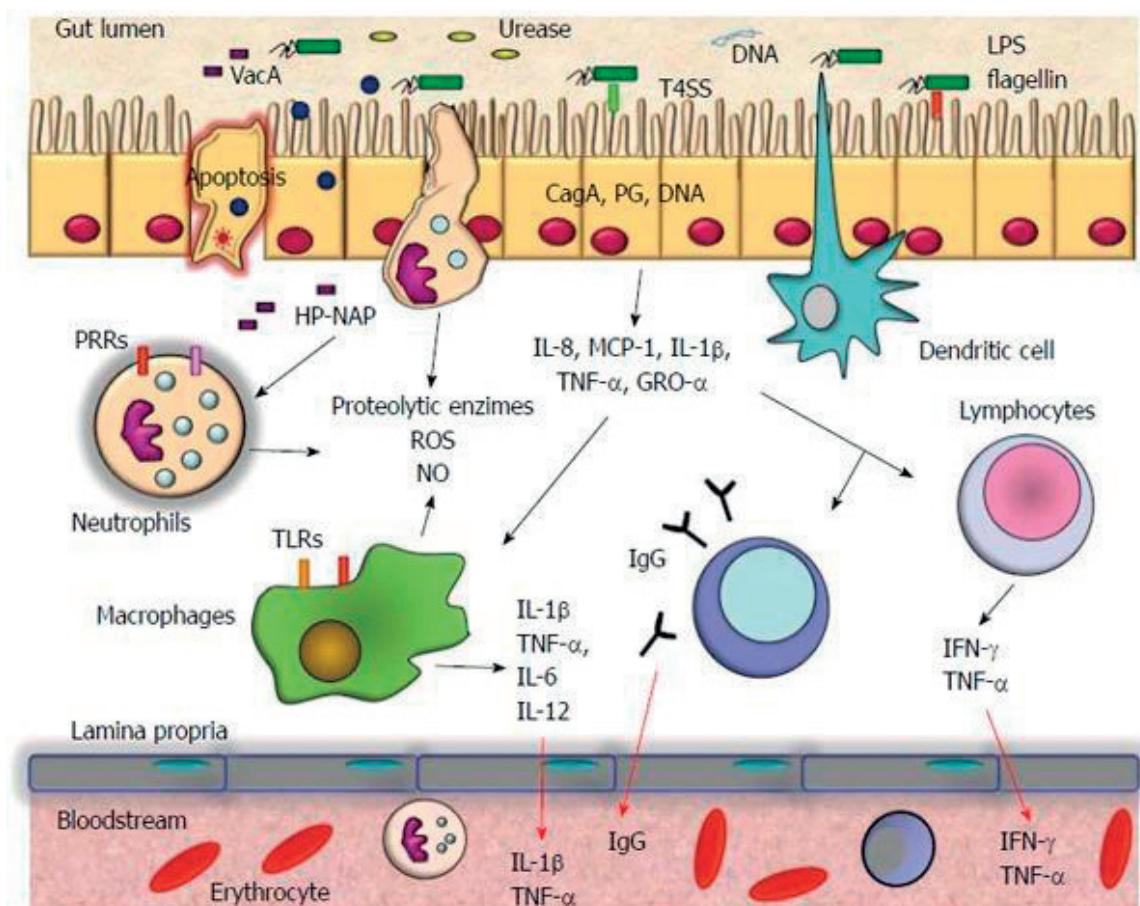


Figure 2. The inflammatory response in *Helicobacter pylori* infection. Immune cells are recruited to the lamina propria of the gastric epithelium by chemokines and cytokines (IL-8, MCP-1, GRO- α , IL-1 β , TNF- α) produced by epithelial cells or directly by bacterial products including *H. pylori* neutrophil-activating protein, VacA, and urease. At the site of infection, the immune cells are activated and exert their effector functions, including the production of cytokines (IL-1 β , TNF- α , IL-6, IL-12, IFN- γ), chemokines (IL-8, MCP-1), proteolytic enzymes, oxide nitric (NO), and reactive oxygen species (ROS). PG, peptidoglycan; T4SS, type IV secretion system; IL, interleukin; TNF, tumor necrosis factor; MCP, macrophage chemotactic protein; GRO, growth-regulated oncogene [104].

functional dyspepsia and *H. pylori*-induced gastritis even though *H. pylori* is always followed by a strong cellular and humoral immune response and fulfills the criteria for a true infection.

As with many other infections, *H. pylori* infection does not always cause symptoms. The evidence-based associations between *H. pylori* and ITP and unexplained IDA are less well known. Patients with these diseases should be tested for *H. pylori*. There are slightly weaker associations found between *H. pylori* and B₁₂ deficiency anemia, neuromyelitis optica, and Graves' disease, and patients with these diseases should also be tested for *H. pylori* [21].

Weaker associations between *H. pylori* and cardiovascular disease, pancreatic cancer, pancreatitis, obesity and type 2 diabetes, Parkinson's disease, asthma, liver diseases, and preeclampsia have been found. *H. pylori* possibly causes these diseases through antigenic mimicry, and affected patients should be considered for *H. pylori* testing.

In conclusion, a variety of diseases may be caused by *H. pylori*, and affected patients should be tested for *H. pylori*. However, further larger and more well-designed studies with better stratification of patients and better diagnostics of *H. pylori* are needed.

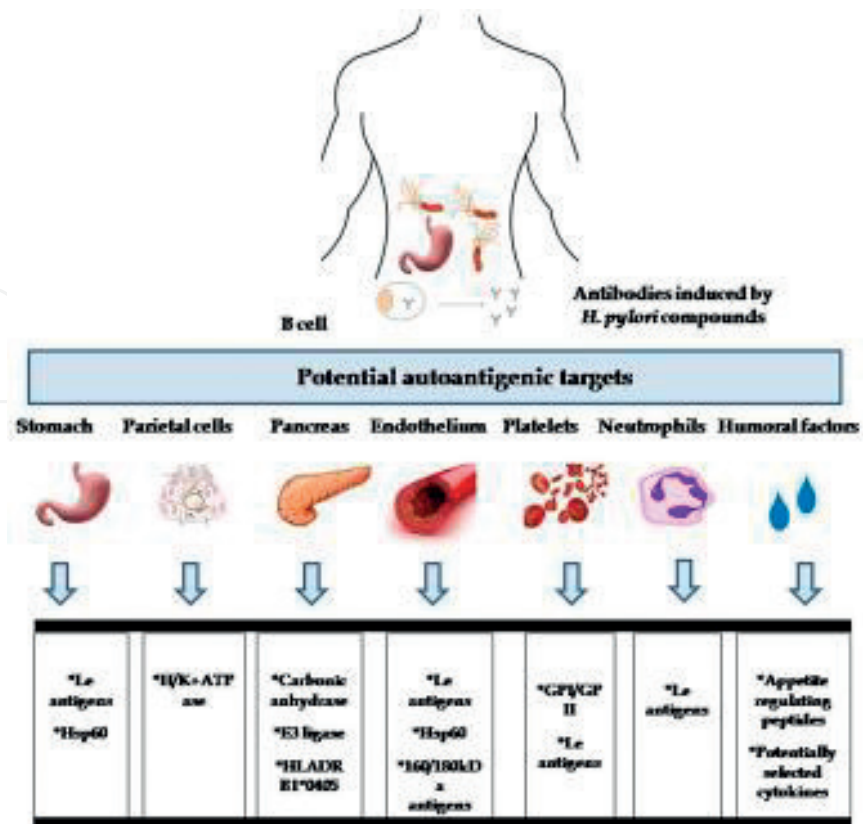


Figure 3. Hypothesis of autoimmune disorders due to molecular mimicry between *Helicobacter pylori* and the host components. Chronic exposure of the host immune system to *Helicobacter pylori* (*H. pylori*) components that have homologous sequences with the host cellular or soluble compounds may initiate the production of autoantibodies. However, how often the autoantibodies arising during *H. pylori* infection are involved in various post-infectious pathologies should be elucidated. The graph shows the examples of host targets for the antibodies induced by *H. pylori* components. GP, glycoproteins; HSP, heat shock protein; H+/K+ ATPase, H+/K+ -adenosine triphosphatase; HLA, human leukocyte antigens; CCRL1, CC chemokine receptor-like 1; Le, Lewis antigens [105].

18. Conclusion

A variety of diseases are may be caused by *H. pylori*; some such as peptic ulcer and gastric cancer by a direct effect on the gastric epithelial cells cause cell damage and apoptosis. The complex immune response to *H. pylori* contributes to the pathogenesis such as mast cells liberating PAF which affect the angiogenesis in the stomach. The complex immune response to *H. pylori* is also involved in the pathogenesis of extra-gastric manifestations of *H. pylori* infection. In addition to the immune response to *H. pylori*, *H. pylori* also contains a lot of antigens which cross-react with human antigens (antigenic mimicry) that is responsible for many autoimmune diseases such as thrombocytopenia purpura, B12 deficiency anemia, neuromyelitis optica, Graves' disease, etc. Thus, *H. pylori* causes or may cause a lot of well-known and less well-investigated diseases, and these patients should be tested for *H. pylori*. However, many of these diseases are rather rare especially in children that need larger, and more well-designed multicenter studies with better stratification of patients and better diagnostics of *H. pylori* for prober studies are needed. In addition, little is known about the exact virulence and pathogenic mechanisms of *H. pylori*, and basic research in these diseases is urgently needed.

Conflict of interest

The authors declare that they have no conflict of interest.

Abbreviations

CVD	cardiovascular disease
CagA	cytotoxin-associated gene A
<i>H. pylori</i>	<i>Helicobacter pylori</i>
IDA	iron-deficiency anemia
ITP	idiopathic thrombocytopenic purpura
MALT	mucosa-associated lymphoid tissue
NMO	neuromyelitis optica
OR	odds ratio
PAF	platelet-activating factor
PE	preeclampsia
Treg	regulatory T cells
VacA	vacuolating toxin

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