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Pathophysiology of *H. pylori*

Karam Dawood and Israa Mamdooh

Abstract

Helicobacter species were known for long as a causative agent of gastritis. *H. pylori* associated gastritis is characterized by the presence of acute and chronic inflammation. Previously, it was believed that in *H. pylori* gastritis, fundic inflammation was less important than that of the antral mucosa. However, *H. pylori* and gastroesophageal reflux disease create, or arise concurrently, may also be caused by the anatomical role of the inflammatory cell infiltrate. The source of *H. pylori* is mostly unknown. *H. pylori* has a small host range and is present in people and some non-human primates nearly exclusively. In rare cases, the presence of pets may be a concern for *H. pylori* infection; hence, pets should be isolated. There is also no definitive proof for zoonotic *H. pylori* transmission. The direct transmission from person to person, either oral or fecal-oral route or both, is expected to lead to new infections. *H. pylori* colonization is not an infection itself, but it impacts the relative likelihood that multiple pathological conditions of the upper gastrointestinal tract and even the hepatobiliary tract will grow. Therefore, *H. pylori* examination alone is not relevant but can be done in order to ascertain the cause of a basic disorder, such as peptic ulcer disease or to avoid disease, for example in subjects with family gastric carcinoma. A positive test result will validate the procedure, and a negative test result can suggest that other etiological causes or prevention steps needs to be examined. Gastritis is divided into acute and chronic. Several virulence factors play a role in the disease such as *cag* PAI (Pathogenicity Island) and VacA vacuolating cytotoxin. Different adhesins and their receptors aid in *H. pylori* colonization and invasion. Based on analogy with other mucosal infections, it was initially assumed that a protective immune response against *H. pylori* would predominantly be mediated by antibodies. Subsequent experiments have indicated that the relevance of the humoral system for protective immunity is only marginal. Antibodies can effectively prevent infection and reduce colonization in animal models.

Keywords: *Helicobacter*, Gastritis, CAG pathogenicity island, Vac A vacuolating cytotoxin, Autoantibodies

1. Introduction

1.1 History of gastritis

Warren and Marshall in 1983 first recorded *H. pylori*'s relationship of gastric mucosa in adults with antral gastritis [1]. Shortly thereafter, Hill *et al.*, four children who were afflicted with *H. pylori* had identified chronic mononuclear cell gastritis [2]. That same year, Cadranel and colleagues described organisms present in eight children with chronic, lymphocytic gastritis [3]. Subsequently, Drumm *et al.* observed *Helicobacter-like* organisms in 70% of 67 pediatric patients with a chronic-active

Gastritis [4]. Related findings have been made of spiral-shaped species colonizing the mucosa and the overlying gastric-epithelium mucus layer. Infiltrate gastric inflammatory cells Czinn and Carrl in 25 children. More studies indicate that *H. pylori* colonization in the gastritis of a primarily chronic inflammatory cell infiltrate is almost always linked to gastritis in children [5, 6]. Reports of *H. pylori* eradication from gastric mucus suggest that the antral gastritis is resolved in combination with a single core case sequence. However, *H. pylori*-infected children have not undergone multicenter randomized controlled eradication trials and are important [6].

Studies in adults established the presence of the organism in nearly all cases of chronic gastritis [7]. At first, *H. pylori* was proposed to colonize inflamed tissue, rather than to induce inflammation, since gastritis is widespread in adults [7]. However, the prevalence of gastritis is less frequent in children thereby enabling the investigation of *H. pylori* as a cause for gastritis rather than an opportunistic colonizer of inflamed tissue [8]. Studies have observed that colonization of *H. pylori* in children with secondary causes, such as NSAID, eosinophilic gastroenteritis and Crohn's disease is not normal in the gastric mucosa [8]. These findings together show clearly the pathogenic role of *H. pylori* in the development of chronic antral gastritis in infants.

For over a century, bacteria have been known to be found in the human body [9]. These bacteria, however, were thought to be contaminants from digested food rather than true gastric colonizers. Around 20 years ago, the isolation and culture of a bacterial spiral species known later as *Helicobacter pylori* was announced successfully by Barry and Robin Warren [10], from the human stomach. Self-ingestion experiments by Marshall [11] and Morris [12] and later experiments with volunteers [13] demonstrated that these bacteria can colonize the human stomach, thereby inducing inflammation of the gastric mucosa. After ingestion of *H. pylori*, Marshall produced intermittent gastritis; Morris' condition progressed into more persistent gastritis, which cleared doxycycline and sub-salicylate bismuth after sequential care. These initial data were closely used as a stimulus in further studies, demonstrating that gastrointestinal disorders such as chronic gastric gastritis, peptic ulcer, lymphoma associated with gastric mucous membrane and stomach cancer can lead to a variety of upper gastrointestinal disorders. This knowledge has a direct therapeutic influence on disease control. In addition, insights into the pathogenesis of chronic disease are provided by the persistence of a pathogen in an area long believed to be sterile. This discovery has resulted in Robin Warren and Barry Marshall's "discovery of the bacterium *Helicobacter pylori* and his role in gastritis and peptic ulcer diseases" won the 2005 Nobel Prize in physiology or medicine.

The genus *Helicobacter* belongs to the subdivision of the *Proteobacteria*, order *Campylobacterales*, family *Helicobacteraceae*. This family also includes the genera *Wolinella*, *Flexispira*, *Sulfurimonas*, *Thiomicrospira*, and *Thiovulum*. The *Helicobacter* genus consists of more than 20 species, all of which have been recognized officially. Members of the *Helicobacter* family are all microaerophile organisms and most of them are positive for catalase and oxidase and many but not all species also are positive for urease [14].

It is possible to separate *Helicobacter* species into two main lines, the gastric *Helicobacter* species and the enterohepatic (nongastric) species of *Helicobacter*. They have a strong degree of organ specificity, which in general indicates gastric *Helicobacter* cannot colonize the intestine or liver, and vice versa.

2. Gastric *Helicobacter* species

Gastric *Helicobacter* organisms have evolved to the unfriendly environments at the stomach surface and are currently suspected to colonize the stomachs of all

mammals through *Helicobacter* members. The urease is positive and extremely mobile by flagella are all recognized gastric *Helicobacter* species [15, 16]. Urease is believed to enable brief survival in a very acidic gastric lumen, but motility has been thought to allow quick travel into the more neutral pH of gastric mucosa; this may explain why the colonization of gastric mucosa is conditional upon both factors [17]. When joining, the *Helicobacter* gastric species display a chemical motility of urea and bicarbonate to the mucus layer [16]. The spiral morphology and flagellate motility help the viscous mucus layer penetrate, where the more pH-neutral conditions allow the genital *Helicobacter* species to grow.

i. *Helicobacter felis*

ii. *Helicobacter mustelae*

iii. *Helicobacter acinonychis*

iv. *Helicobacter heilmannii*.

H. pylori is a demanding micro-organism that needs complex media for development. Sometimes, blood or serum was applied to these medias. These supplements are additional food sources and can also be used for defending against long-chain fatty acid toxic effects [18].

H. pylori associated gastritis is characterized by the presence of acute and chronic inflammation, with immature surface epithelial cells [19]. Mucus degeneration is also found by successful cell renewal of epithelial cells. The degree of mucosal infection ranges from the lowest inflammatory infiltration in lamina propria to the extreme gastritis with thick mucoal inflammation with retained architecture. In extreme cases, all surface epithelium and gastric wells can be used as micro-abscesses for intraepithelial neutrophils [20].

Previously, it was believed that in *H. pylori* gastritis, fundic inflammation was less important than that of the antral mucosa [21]. However, *H. pylori* and gastroesophageal reflux disease create, or arise concurrently, may also be caused by the anatomical role of the inflammatory cell infiltrate [22]. Moreover, patients who have been receiving a proton pump inhibitor for acid suppression frequently have colonization of fundic and cardia mucosa by *H. pylori*. Carditis, of both a chronic and active phenotype, is frequent in *H. pylori*-infected adults [23]. Children require research to help establish the association between *H. pylori* infection, gastric inflammation sites and sequelae of long-term diseases.

H. pylori-associated gastritis in children is commonly not apparent at endoscopy, thereby making biopsy essential for definitive diagnosis [24]. Nodularity of the antral mucosa has been described in association with *H. pylori* gastritis in children [25]. Its value has not yet been identified. However, antral nodularity was found in *H. pylori* infected adults and less common in children [26].

Columbia or Brucella agar, (lysed) horse or sheep blood agar, or fetal calf serum as substitute, is widely used as a solid medium for regular isolation and *H. pylori* culture.

3. Transmission and sources of infection

Most unknown are the precise processes by which *H. pylori* is obtained. *H. pylori* has a small host range and is present in people and some non-human primates nearly exclusively.

In rare cases, the presence of pets may be a concern for *H. pylori* infection; hence, pets should be isolated [27]. There is also no definitive proof for zoonotic *H. pylori* transmission [28]. The direct transmission from person to person, either oral or fecal-oral route or both, is expected to lead to new infections. In saliva, vomit, gastric refluxate and diarrhea, *H. pylori* has been detected [29]. Yet there is no definitive proof that either of these products had the predominant transmission. This may be because most transmission research has concentrated on adults.

It indicates that for dentists, gastroenterologist, nurses, spousal partners or physicians with sexually transmitted diseases there was no clear rise in risk of carrying *H. pylori* [30]. As a result of these and other investigations, it is generally believed that acquisition mostly occurs in early childhood, most likely from close family members [31].

Crowding inside and outside families with children are both linked to the occurrence of *H. pylori* [32], Although the adult crowd seems less significant, except for some situations, for example amongst military recruits [33]. Several experiments have shown that *H. pylori* DNA is found in environmental bodies of water [34].

Spread via fecal contaminants is supported by the occurrence of *H. pylori* infections among institutionalized young people during outbreaks of gastroenteritis [35]. Additional sources are infected food, as *H. pylori* can briefly live on cooled food [36]. In tandem with *H. pylori*'s intense exposure to oxygen demand, nutrient exclusion and temperatures outside 34–40°C [37]. The most likely path of direct person-to-person transmission.

The incidence of gastric cancer is higher in poor areas and in developing and advanced countries in lower socioeconomic groups [38]. Gastric cancer remains the most prevalent malignancy among men and the second most commonly identified among women in many countries of Latin America and Asia. Colombia and Japan recorded incidence rates of up to 80 per 100,000 populations. The gastric cancer in the United States and Western Europe, by comparison, affects less than 10 per 100,000 individuals per year [39]. However, ethnic groups with elevated risk remain in low-risk nations. For instance, in the US, gastric cancer is nearly double that prevalent among Blacks, Asians and Hispanics. It is noteworthy that *H. pylori* prevalence rates are 2-10 times higher in all of these populations than in the total population [40].

4. Clinical aspects of *H. pylori*-associated diseases

H. pylori colonization is not an infection itself, but it impacts the relative likelihood that multiple pathological conditions of the upper gastrointestinal tract and even the hepatobiliary tract will grow. Therefore, *H. pylori* examination alone is not relevant but can be done in order to ascertain the cause of a basic disorder, such as peptic ulcer disease or to avoid disease, for example in subjects with family gastric carcinoma. A positive test result will validate the procedure, and a negative test result can suggest that other etiological causes or prevention steps needs to be examined.

4.1 Types of Disease

Although gastric *H. pylori* colonization causes histologic gastritis in all infected persons, only a minority experience any apparent clinical symptoms. *H. pylori*-positive patients are estimated to have a 10–20 percent life-cycle risk for ulcer and a 1–2 percent risk for distal gastric cancer [41]. The probability of developing *H. pylori* disorders depends on a range of bacterial, host, and environmental factors, most of which are related to gastritis pattern and severity (**Figure 1**).

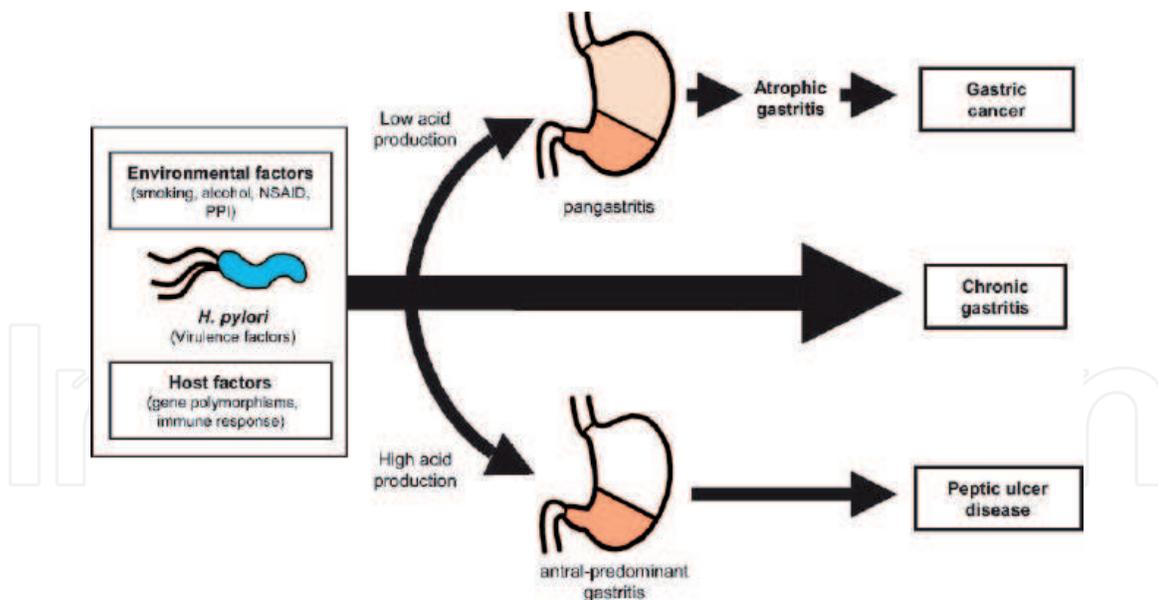


Figure 1.
Schematic representation of the factors contributing to gastric pathology and disease outcome in *H. pylori* infection [42].

4.2 Acute and chronic gastritis

The scale of *H. pylori* colonization nearly always contributes to gastric mucosa invasion of neutrophilic and mononuclear cells in the antrum and corpus. The principal condition of this chronic active gastritis is *H. pylori* colonization, in particular as consequence of this chronic inflammation phase, and other *H. pylori*-related conditions [42].

4.2.1 Acute gastritis

Acute infection results are uncommon and come mostly from accounts of subjects who knowingly or accidentally took *H. pylori* or were exposed to hazardous substance procedures [43]. Recently, an *H. pylori* infection human challenge model was introduced, which permitted managed acute infection analysis with deliberate safe volunteer infection by a well-characterized *H. pylori* laboratory strain [44]. Along with these findings, these reports have shown that the acute process of *H. pylori* colonization can include temporary non-specific dyspeptic symptoms, including completeness, nausea, vomiting, and severe inflammation of the proximal, and distal stomach mucus or pangastritis. This process is also related to the period of months of hypochlorhydria. It is uncertain whether spontaneous clearing and resolution of gastritis can be accompanied by this initial colonization and, if so, how often that happens. Further trials in young children with serology or breathing tests have shown that certain patients in this age group might spontaneously lose the infection [45]; This was not found in the development of atrophic gastritis other than under particular circumstances.

Studies of homozygotic twins however demonstrated a concordance with their classification as *H. pylori* regardless of their cohabitation or break [46]. This consensus between heterozygous twins has not been observed. This indicates that some people are likely to be colonized with *H. pylori* while others may avoid or eradicate a proven infection. This theory is also backed by the finding that *H. pylori* sensitivity in many developing countries is very strong in young age and yet chronic *H. pylori* infections are never acquired by any individuals.

4.2.2 Chronic gastritis

When colonization becomes persistent, the acid secretion level and the gastritis distribution interact closely (**Figure 2**). The association between acid and bacterial growth arises from the counteractive effects of acid against bacterial growth and subsequent mutation inflammation on the acid separation and regulation. The effect of *H. pylori* infection is important in this relationship. *H. pylori* particularly colonizes the gastric antrum in subjects with intact acid secretion, where there are only a few parietal acid secretory cells present [42].

This pattern of colonization is linked to gastritis which prevails. Histological examination of the gastric corpus specimens shows that the amount of superficially colonized *H. pylori* bacteria is reduced by chronically dormant inflammation and that. Those of which the secretion of acid is affected by some process have a more equal distribution of bacteria in the antrum and corpus and are in closer proximity of the mucosa bacteria, inducing pangastritis, which are predominate [47].

The acid secretion may be diminished by loss of parietal cells due to atrophic gastritis, but it can also happen when acid's secretive potential is intact, although the work of parietal cells is inhibited by vagotomy or acid-suppressive drugs, particularly proton pump inhibitors (PPIs) [47]. The subsequent active inflammation of the corpses raises hypochlorhydra parallel to an acute period of infection with a strong suppressive effect on the celestial function, since local inflammatory factors, including cytokines, like interleukin-1 beta (IL-1 β) are strongly suppressive. Different findings illustrate that. The first argument is that *H. pylori*-corpus gastritis frequently is related to hypochlorhydrate, and eradication treatment leads to greater secretion of acid [48].

Secondly, *H. pylori* corpus gastritis augments the acid-suppressive effects of PPIs [49]. As a result, *H. pylori*-positive patients with gastroesophageal reflux disease (GERD) may respond somewhat faster to PPI treatment both with respect to symptom resolution and with healing of esophagitis [50], However, this effect of everyday clinical practice is marginal and essentially negligible. This means that the status of *H. pylori* is not general in decision-making regarding GERD dose of PPI medication. A third observation in favor of the acid repression effects of active corpus gastritis has been made in more recent significant research that indicates the risk of corpus predominant pangastritis from subject with proinflammatory genotype predisposing people to atrophic gastritis, intestinal metaplasia and gastric cancer [51].

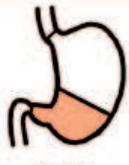
| Pattern of gastritis | Gastric histology | Duodenal histology | Acid secretion | Clinical condition |
|---|--|---|---|---|
|  Pan-gastritis | <ul style="list-style-type: none"> Chronic inflammation Atrophy Intestinal metaplasia | <ul style="list-style-type: none"> Normal | <ul style="list-style-type: none"> Reduced | <ul style="list-style-type: none"> Gastric ulcer Gastric cancer |
|  Antral-predominant | <ul style="list-style-type: none"> Chronic inflammation Polymorph activity | <ul style="list-style-type: none"> Gastric metaplasia Active chronic inflammation | <ul style="list-style-type: none"> Increased | <ul style="list-style-type: none"> Duodenal ulcer |

Figure 2. Acid secretion and the associated pattern of gastritis play an important role in disease outcome in *H. pylori* infection. The figure displays the correlations between the pattern of *H. pylori* colonization, inflammation, acid secretion, gastric and duodenal histology, and clinical outcome [42].

Although colonization by *H. pylori* is almost invariably associated with gastritis, and gastritis is mainly attributed to colonization by *H. pylori*, gastritis is due to other causes of gastritis, such as cytomegalovirus, chronic inflammatory idiopathic diseases, and auto-immune disease such as Crohn's disease and pernicious anemia.

5. Role of *H. pylori* virulence factors

5.1 *cag* PAI (Pathogenicity Island)

Although the *H. pylori* infection nearly always triggers chronic active gastritis, most affected patients are free of apparent health signs and have no other complications [52]. This led to the belief that some strains could be more virulent than others. Early studies of variations of *H. pylori* strains demonstrated the capacity of such virulent strains to cause morphological changes, vacuolizations and successive degeneration from in vitro-cultivated cells. This pathogenicity is linked [53]. This activity was then linked to the presence of a protein with a molecular mass of approximately 140 kDa that was named CagA (for "cytotoxin-associated gene A").

The CagA protein is a highly immunogenic protein encoded by the *cagA* gene [54]. About 50–70 percent of *H. pylori* strains have this gene [55] and is a marker for the presence of a genomic PAI of about 40 kb that, depending on the strain analyzed, encodes between 27 and 31 proteins [54]. Strains carrying the Cag PAI are called CagA+ strains, as their ability to cause major antibody titers against the CagA marker protein is widely recognized in patients. In CagA patients, inflammation is typically higher and the probability of developing a sign (peptic ulcer or gastric cancer) in western populations is considerably higher [56], though not in Asian populations [57]. While CagA+ strains are associated with a higher risk of ulceration, gastritis and gastric cancer, *cag* PAI strains are also associated with a higher risk of peptic ulcer or gastrointestinal cancer, even though at a smaller frequency.

Eighteen *cag* PAI-coded proteins are used to form a type IV secretive unit that forms a structure like a syringe that is able to penetrate gastric epithelial cells and to promote the translocation of CagA, peptidoglycan, and probably other bacterial components into host cells [58] (**Figure 3**). Once delivered inside the cell, the CagA protein is phosphorylated at tyrosine residues in EPIYA motifs [59] by Src family kinases [60]. Phosphorylated CagA interacted then with a number of host signaling molecules, including tyrosine phosphate SHP-2, which results in morphological changes in the epithelial cells [61].

Apoptosis of T cells is impaired by the *cag* PAI since the immune response is also affected [62]. The association of type IV formation with the host cell also results in pro-inflammatory cytokines in epithelial cell induction [63].

It was originally believed that this proinflammatory cytokines are caused by a CagA protein itself, but nowadays CagA only plays, if any, a minor role in triggering them [63]. It is possible that the intimate contact with the IV-type form contributes to peptidoglycan leak into the eukaryotic cell [64] (**Figure 3**), although it cannot be ruled out completely that the activation of the IL-8 signaling cascade results from the translocation of a thus-far-unknown bacterial factor [63].

Tyrosine Phosphorylation is necessary for binding CagA to SHP-2 within the CagA EPIYA motif. [65]. The number of EPIYA tyrosine phosphorylation motives within the CagA proteins of various *H. pylori* isolates varies considerably. CagA is specifically correlated with the amount of repetitions of tyrosine phosphorylation. [66]. Strains with a larger number of CagA repetitions cause more marked morphological changes in cultivated epithelial cells [67] and an increased risk of gastric carcinogenesis being correlated. CagA also interacts through SH2 domains with the

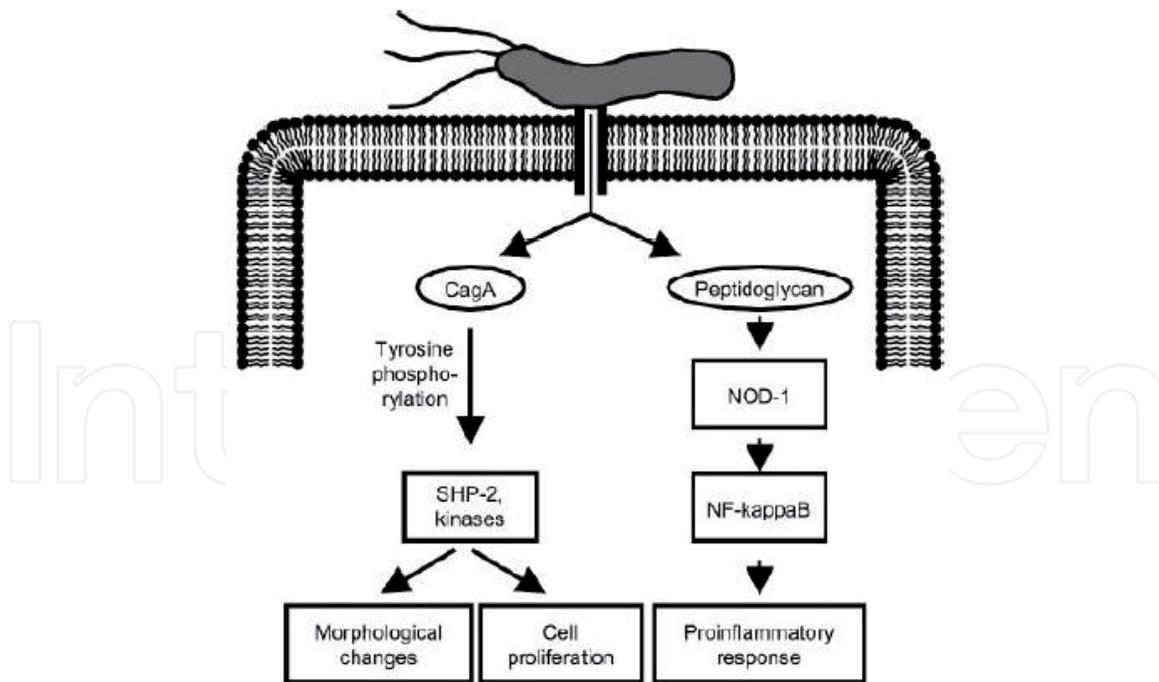


Figure 3. Schematic representation of the different roles of the Cag type IV secretion system in immune modulation, cell proliferation, and morphological changes [42].

c-terminal Src kinase, which contributes to c-tyrosine Src's kinase inactivation. This inactivation, since it mediates CagA tyrosine phosphorylation, leads to a decrease in CagA phosphorylation, thereby creating a feedback loop to control CagA behavior [65]. This cross talk of host-pathogen results in tested virulence and can thus serve to colonize the host for a lifetime.

5.2 VacA vacuolating cytotoxin

Around 50% of all strains of *H. pylori* secrete VacA, a highly immunogenic 95 kDa protein that is causing massive vacuolisation of epithel cells in vitro [68]. VacA is a key factor in both peptic ulceration and gastric cancer pathogenesis. Though VacA is not necessary for in vitro growth of *H. pylori* the murine gastric colonization by *H. pylori* has been shown to make a substantial contribution [69].

The activities of VacA include development of the membrane channel, endosomal and lysosomal disorders, incorporate cell receptor signaling effects and cytoskeleton-related interference with cell-dependent functions, apoptosis induction and immune regulation (**Figure 4**). Although vacuolization is readily observed in vitro, it does not seem to occur *in vivo* [42]. The VacA protein is formed with a protoxin of 140 kDa and is broken into the shape of 95 kDa as it is secreted.

While all strains have a functional vacA gene, the vacuolating activities among strains differ considerably [69]. This is due to the sequence heterogeneity within the *vacA* gene at the signal region (s) and the middle region (m). The s region of the gene, which encodes the signal peptide, occurs as either an s1 or s2 type, whereas the m region, which contains the p58 cell binding domain, exists as an m1 or m2 type [70].

In the cell epithelial membrane, VacA forms pores that cause urea and anions to be released from the host cells. It also enhances transcellular penetration, resulting in nutrient and cation releases [71]. Interestingly, a major portion of the secreted toxin does not go to the environment, but is bound to the outer membrane of *H. pylori*. These toxin clusters are passed to the host cell surface following bacterial

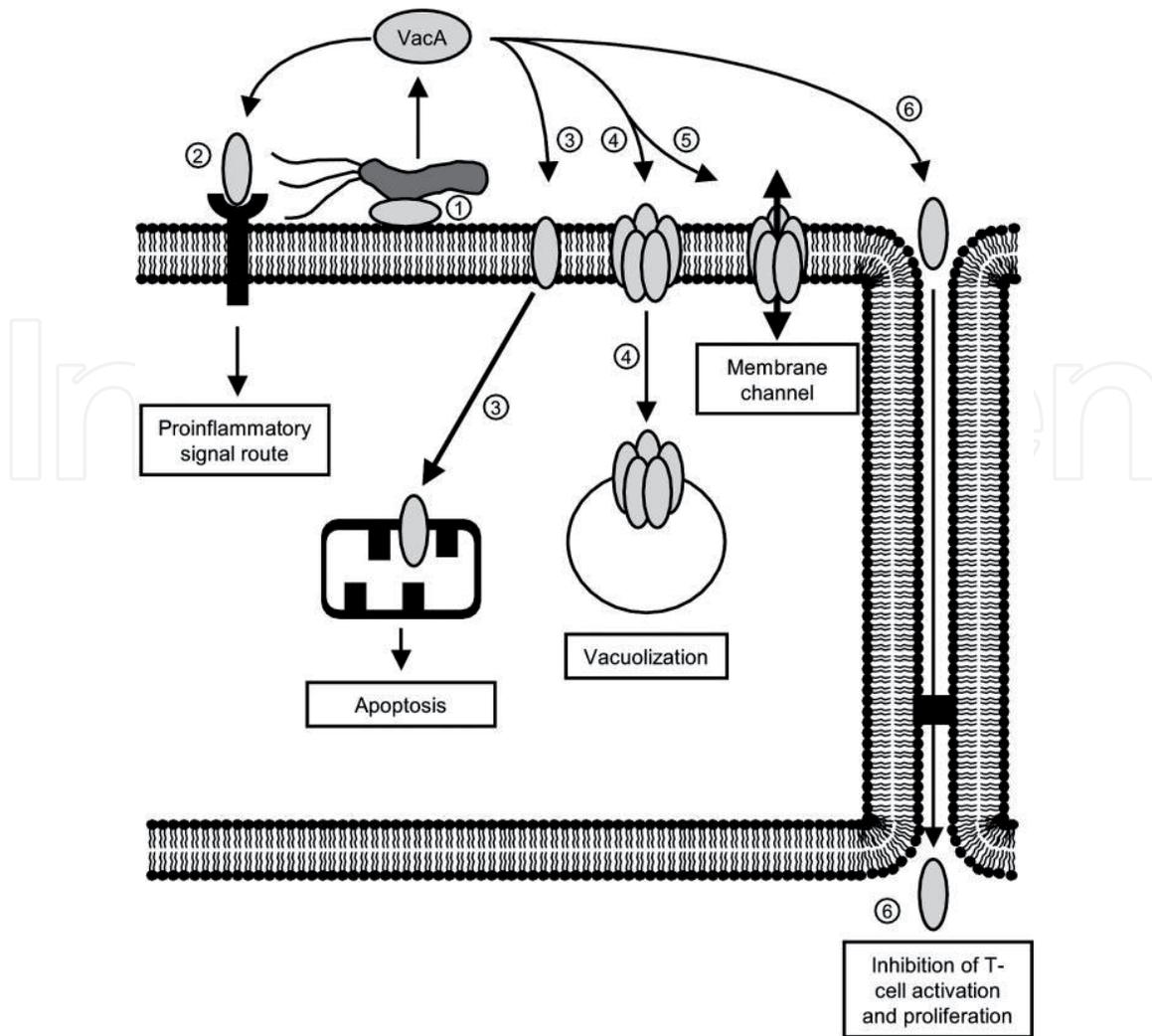


Figure 4.

The VacA protein influences cellular processes via different routes, thus assisting in chronic colonization of the gastric mucosa by *H. pylori*. (1) Surface-bound VacA may be directly delivered to the cell membrane. Secreted VacA may either (2) bind to a cell membrane receptor and initiate a proinflammatory response, (3) be taken up directly by the cell and be trafficked to the mitochondria and induce apoptosis, (4) be taken up by pinocytosis and induce vacuolization, (5) form a membrane channel, resulting in leakage of nutrients to the extracellular space, or (6) pass through the tight junctions and inhibit T-cell activation and proliferation. (Modified with permission from Nature Reviews Microbiology [23].)

interaction with their host cells and have their toxic effects. This touch-dependent mechanism for direct delivery proposes the inclusion in bacterial-cell contact of particular receptors. However, such a receptor has not yet been identified [72].

Secreted VacA can be further processed into a 33-kDa N-terminal fragment and a 55-kDa C-terminal fragment through proteolytic cleavage. In the development of anion channels, the N-terminal protein plays an important role while C-terminal proteins mediate cell binding [73].

In spite of the proteolytic cleavage, these fragments remain noncovalently associated with each other [74]. Spontaneously purified VacA forms oligomeric aggregates and disassembles in the active monomers of pores in the cell membrane after exposed to acidic pH. Spontaneously purified VacA forms oligomeric aggregates and disassembles in the active monomers of pores in the cell membrane after exposed to acidic pH but are likely to be an *in vitro* artifact [75].

While several VacA-mediated effects are induced by membrane binding and pore formation, VacA also reaches the cytosol, then accumulates in the mitochondrial inner membrane and causes apoptosis, activating endogenous mitochondrial channels [76]. The proapoptotic influence of VacA is based on the cell type and may

be restricted to gastric epithelial cells like parietal cells. This may result in reduced acid secretion, thereby predisposing for development of gastric cancer [77].

6. Pathogenesis of infection

6.1 *H. pylori*-associated pathogenesis

Chronic active gastritis is the principal disease after *H. pylori* colonization. In all *H. pylori*-positive subjects this syndrome can be found. Various different factors such as colonizing stress characteristics, host physiology, immune response, diet, and development rate depend on the intragastric distribution and intensity of the chronic inflammatory process. Many of the complications of this chronic inflammation include *H. pylori*-induced ulcers, gastric cancer and lymphoma; in particular, ulcerative and gastric cancers arise in these people and in the areas of the most serious inflammation. Therefore, recognizing these factors is important in order to consider *H. pylori*'s role in the etiology of the upper gastrointestinal disorder [42].

H. pylori colonizes the membrane in the stomach antrum of the gastric epithelia. *H. pylori* adhere to the stomach epithelia is a prime and significant step towards colonization of gastric mucosa and gastritis [78].

In duodenum, *H. pylori* only infects gastric mucosa and gastric metaplasia [79]. In comparison, on intestinal epithelium *H. pylori* is never seen. Dunn *et al.*, stated in vitro, that *H. pylori* was more effective than human intestine (Int-407) cells, and sac cells with yolk bags, on human gastric epithelial cells [80]. Similarly, the adherence rate of *H. pylori* to gastric cell lines (KatoIII, MKN45) was shown to be significantly higher than that to Int-407 cells. These results indicate that *H. pylori* has specific binding activity to human gastric epithelial cells [81].

In a logarithmic point, *H. pylori* has strong nourishment with a spiral morphology. But spiral to coccoid conversion may be inducted by alkaline pH, rise in temperature, antibiotic therapy, aerobics or anaerobics, or prolonged incubation. The type of coccoid *H. pylori* is known as viable but not cultivable. *H. pylori* coccoid bind to both the stomach epithelial MKN45 cells and the spiral form. Although it is unknown whether the coccoid form has any role in the infection pathogenesis., Cole *et al.*” The type of coccoid has been reported to bind badly to gastric epithelial cells. In contrast to spiral shape the form induces a short interleukin 8 (IL-8) chain. The coccoid shape, by comparison, was more frequent than the spiral of *H. pylori* induces cellular changes of pedestal formation [82].

6.2 Gastric environment at the site of infection

The human stomach has a medium luminal pH, with elevations until around pH 4 during meals due to nutrient buffering, when set to natural physiological acid secretion [83]. *H. pylori* originally occupied a more neutral niche at the gastric region with gastric acidity defense offered by the secretion of bicarbonate from epithelial cells and mucus. Studies with glass microelectrodes indicated a pH gradient in the stomach mucus and an epithelial pH virtually neutral [84]. The measuring technique may have delayed these studies as open tip microelectrodes may have stopped proton diffusion. Later microelectrode experiments using a similar method of calculation in mice found that all obstacles to the proton diffusion were eliminated and acidic pH was indicated in the bacterial niche [85]. Fluorescent dyeing tests in the anesthetic mice's externalized stomachs showed an acidic gastral pH surface regardless of the mucus layer [86]. The pH of the gastric surface is a

combination between the regulation of acid and alkaline secretion at a certain stage instead of the trapping of mucus-layer buffers or protons [87].

Analysis of *H. pylori* transcriptome provides additional evidence of acidic pH on gastric surfaces. Several in Vitro experiments have reported improvements in acidic pH expression of the gene using varying duration and conditions of incubation [87–89]. The unifying finding of these research studies is that there are a variety of genes that alter expression depending on environmental pH and indicate adaptation in order to permit gastric colonization.

The well-documented movements of *H. pylori* from its usual gastric niche to the fundus in human or gerbil acid inhibitory Therapy are proof that the bacteria need to remain in a particular pH setting [90–92]. The *H. pylori* transcriptome has been studied in the gerbil's stomach to correlate with in vitro pH changes [93]. Gerbil is a suitable model system since the gastric pH profile of *H. pylori* and its advanced sequelae are close to the ones found in humans [94–96]. The pattern of *H. pylori* gene changes in the gerbil stomach were comparable to gene changes seen in vitro at acidic pH, providing additional evidence for an acidic environment at the site of infection [97].

6.3 Attaching and effacement by adherence of *H. pylori*

Attaching and effacement is characterized by microvilli effacement, actin rearrangement and pedestal formation following bacterial adhesion to cells as described for enteropathogenic *Escherichia coli* (EPEC) [7]. The attachment and effacement of *H. pylori* in the gastric cells have been documented [97].

The tyrosine Phosphorylation of two host cell proteins (145 kDa and 105 kDa) has been shown to be inducted after *H. pylori* binding to gastric pathologic cells. Although it is hypothesized that tyrosine Phosphorylation of host cell proteins is implicated in pathogenesis of gastric diseases related to *H. pylori* infection However, other researchers found that an attachment of *H. pylori* does not contribute to pedestal formation or actin rearrangement [98].

6.4 Adhesin of *H. pylori* and its receptor

H. pylori adhesively adheres to a receptor on the gastric cell surface by its adhesives. The adhesins and their receivers have been recorded in several respects. As the adhesion of *H. pylori* to cells is not entirely hindered by the human antibody to an adhesin, adherence by the use of many adhesins and their receptors is known to be the outcome.

6.5 HpaA (Sialyllactose-Binding Adhesin)

Evans *et al.* purified 20 kDa protein as an adhesin of *H. pylori* recognizing N-acetylneuraminylactose, and cloned its gene, *hpaA*. The protein HpaA functions as hemagglutinin and aggregates the fibrillary structure together. HpaA is stated to be a lipoprotein intracellular and the inactivation of the HpaA did not affect *H. pylori*'s adherence to gastric cells. Consequently, the value of HpaA as *H. pylori* adhesin is contentious [99].

6.6 Adhesin recognizing phosphatidylethanolamine

Specific binding of *H. pylori* to a glycerophospholipid species in the antrum of the human stomach was reported. The thin-layer chromatogram overlay technique showed this species to be a type of phosphatidylethanolamine. Since the exoenzyme from *Pseudomonas aeruginosa* displays similar binding specificity,

the binding of *H. pylori* to its lipid receptor was expected to be induced by an exoenzyme S-like adhesive [100].

6.7 BabA protein recognizing Lewisb antigen

The Lewis antigens (Lewis, Lewisb, Lewisx, and LewisY) are one of the blood-group antigens that is glycosylated and expressed in human epithelial cells and erythrocytes. Lewis antigen that recognizes non-secretory blood groups (O) has been reported to be mediating adhesion of *H. pylori* to human gastric epithelial cells. Preferential relation between *H. pylori* and Lewisb antigen suggests that certain patients are more vulnerable to the development of peptic ulcers [101].

6.8 Adhesin recognizing extracellular matrix components

Many researchers have reported that *H. pylori* has been bound to different extracellular matrix components such as vitronectin, heparin sulfate, collagen, fibronectin, lactoferrin, plasminogen and laminin. There are about 20 Specific attachment of *H. pylori* to extracellular matrix components promotes bacterial colonization [102].

6.9 Induction of secretion of various cytokines from gastric cells

In vivo, *H. pylori* gastric infection induces several cytokines, including IL-1 beta, IL-6, IL-7 and alpha tumor necrosis, to develop mucous membranes. IL-8 particularly consists of a small peptide (chemokine), secreted by a range of cell types, which helps to attract and activate neutrophils as a powerful inflammatory mediator. IL-8 development stimulation in gastric epithelial cells was recorded by *H. pylori*. The positive CagA strains displayed a significant increase in IL-8 relative to cag negative strains. Transposon inactivation of several genes in *cagA* pathogenicity island (PAI) showed that various genes (*cagB* C) D) E) G) H, ~ L) A1) were responsible for the induction of IL-8 from gastric epithelial cells [29]. Recently, Li et al., [30] reported that multiple genes encoding HP0521, 0525, 0527, 0528 and 0529 ORF in the left half of the *cag* PAI of *H. pylori* are required for tyrosine-kinase dependent transcription of IL-8 in gastric epithelial cells. In addition, Yamaguchi et al., [31] reported the induction of IL-8 by HSP60 of *H. pylori* from gastric epithelial KatoIII cells [103].

7. *H. pylori* gastritis and the possible pathogenic

7.1 Role of anti-gastric autoimmune reactions

The serological study in *H. pylori* gastritis provided more indications on the relation between anti gastric autoimmunity and *H. pylori* gastritis. In older patients, *H. pylori* infection is linked to developing anti-parietal cell antibodies [55]. In addition, some *H. pylori*-infected patients, observed 32 years, produce both chronic atrophic gastritis and anti-parietal cell antibodies [104]. These patients eventually become *H. pylori* negative. Also Negrini *et al.*, reported on autoantibodies against gastric epithelial cells in up to 84% of *H. pylori* infected subjects [105].

When sera of *H. pylori*-infected subjects were screened for autoantibodies reacting against human gastric tissue by immunohistochemistry, for these autoantibodies two separate binding sites could be seen; The luminal membranes in the antral and corpus mucosa foveolar epithelial cells first and the channel membranes in the gastric corpus mucosa, second in the parietal cells. Antichannel autoantibodies were called the latter type [106].

7.2 Motility

In early childhood, *H. pylori* infection is obtained through oral-oral or oral-fecal infection. The microbe has to enter its chosen location of colonization, the mucosa of the gastric antrum in the first phase towards colonization. *H. pylori* has formed a spiral mode and unipolar scourge to enter the gastric niche to transit the mucus membrane that overlays the gastric epithelial surface. Host factors steer the migration of *H. pylori* towards the gastric mucosa by means of the chemical reaction of bacteria.

The transcription from intracellular localized components to extracellular flagellar filaments is transient regulated by the expression of the flagellar gene. *H. pylori* is primarily present on the usual acid-secreting stomach, with about one-third of the mucus layer next to the epithelial cells (0–5 μm) in a predominant 15–30 μm mucus above the antrum [107]. About 2 percent of bacteria bind to the gastric epithelium. In order to colonize this niche, the bacteria find that the host attractants or repellents and travel toward or away from them, respectively.

Urea, bicarbonate, pH, zinc, nickel, arginine, glutamine, histidine, and other amino acids elicit chemotactic responses by *H. pylori* [108–112]. These chemotactic factors are sensed by methylaccepting chemotaxis proteins (MCPs) that transduce the signal and alter flagellar rotation. *H. pylori* has at least four MCPs, the membrane proteins TlpA, TlpB, and TlpC and the cytoplasm located TlpD. TlpA senses arginine, other amino acids, and bicarbonate [108]; TlpB is required for pH and urea taxis and also senses the quorum sensing molecule autoinducer-2 (AI-2) [113]; TlpC regulates whether acid is sensed as an attractant or repellent [111]; and TlpD senses the internal energy state of the bacterium [114].

7.3 Acid acclimation

Colonization is prevented by gastric acid. *H. pylori* is a neutrophil that rises from pH 6.0 to 8.0 and lives from pH 4.0 to 8.0. Since the median pH of the stomach is less than 2.0 and *H. pylori* not only lives in this high acidity, but also prospers, the single acid acclimation process has evolved. The ability of *H. pylori* to retain a near-neutral periplasmic pH in an acidic environment is accurate [115]. This is different from the acid resistance mechanism which enables a cytoplasmic pH near 5 to allow bacteria to transit the stomach [116]. Examples of proteins involved with acid resistance include the glutamate decarboxylase- glutamate aminobutyrate antiporter and the arginine decarboxylase-arginine agmatine antiporter, which consume protons and produce carbon dioxide, and the proton transporters including the F₁F₀ ATPase and the Na⁺/2H⁺ antiporter [117, 118]. These systems are designed to control the cytoplasm but do not monitor the pH of periplasm.

Gastric colonization is not possible if cytoplasmic pH cannot be elevated to a level that allows critical metabolic processes such as protein synthesis, a level of buffering that requires periplasmic pH regulation [116]. While *H. pylori* expresses some of the known acid resistance or tolerance genes [119], these proteins complement rather than explain gastric colonization. The principle component of acid acclimation is the neutral pH optimum, highly expressed cytoplasmic urease enzyme. The *H. pylori* urease gene cluster is made up of seven genes under the control of two promoters. *ureA* and *ureB*, under the control of the first promoter, encode the structural subunits of the urease enzyme [120].

Urease is a hexameric heterodimer that requires nickel incorporation for activation. Downstream from the second promoter are *ureI*, *ureE*, *ureF*, *ureG*, and *ureH* [121]. *ureI* encodes in an operon the only integral membrane protein. The Cytoplasmic proteins *UreE*, *UreF*, *UreG*, and *UreH* help to integrate nickel in apourease.

Urease is required for acid survival and gastric colonization [122, 123]. *H. pylori* urease production is constitutive, contributing about 10 percent of the total cell protein [124, 125]. A neutral pH-based cytoplasmic enzyme catalyzes the degradation of urea into carbonic acid and, eventually, with a low pH activity and inactivation, the pH-reduced into the region contained inside the intestines, the activity curve of the free urease is optimum near neutral. The activity of urease in intact bacteria is marginal at neutral pH and increases to no more than pH 6 to roughly pH 2.5 [126]. This curve of activity indicates a limit to urea entry to the enzyme. The only membrane protein of the urease gene cluster, UreI, was seen as a proton gated urea channel, which enables urea into cytoplasm at acidic pH [127]. Deletion of *ureI* leads to loss of acid activation of urease [125]. *ureI* deletion mutants cannot live in acid at physiologic urea concentrations. Periplasmic pH sinks as well as the medium pH drops. This leads to opening of UreI, movement of urea into the cytoplasm, and breakdown to the eventual end products of carbon dioxide and ammonia, catalyzed by the urease enzyme. The two gasses then buffer the periplasm to the pH range that is consistent with neutrophil survival without having to adjust the atmosphere with bulk pH.

Ni²⁺ per active site are required for activation of urease, and a large fraction of urease can be inactive, especially at neutral pH [128, 129]. This will likely avoid the over-alkalization of this neutrophil in situations where the pH increases, and would thus create a urease pool that is primed and ready to go into action in setting a decrease in pH [130]. UreE forms a heterodimer with UreG and UreF with UreH, as evidenced by yeast two hybrid and homology analysis, and these protein pairs bind urease most likely via UreB to aid with nickel incorporation and enzyme activation [131, 132]. Each accessory protein has a specific role in urease activation. UreE aids directly with incorporation of nickel into the active site [132]. UreF prevents premature nickel binding [133]. UreG provides energy for assembly of urease. UreH provides stability for apourease [134]. A broad number of regulatory mechanisms, many of which are involved in acid survival, can be controlled directly and indirectly by the nickel regulation protein NikR [135]. For example, NikR has been shown both in vitro and in vivo to positively regulate expression of *ureA* [136–139].

7.4 pH alteration and treatment efficacy

H. pylori is unique for survival in an acidic gastric environment, but bacteria are separated and formed at neutral pH as a neutrophil. Transcription of growth-dependent genes in higher medium pH is increased [140]. Most antibiotics used in treating *H. pylori* infection are bacterial-dependent for optimum effectiveness. Ampicillin is slightly more effective at near-neutral pH against *H. pylori* in vitro [140]. Adding bismuth to the treatment regimens also has a pH effect, at least in part, because the compound impairs the proton entry and reduces the decrease in cytoplasmic pH with medium acidification, which improves bacterial metabolism and increased antibiotic effectiveness [141]. With this in mind, The more bacteria are separated in the therapeutic cycle, the more successful conventional treatment, a proton pump inhibitor and a triple or quadruple therapy regimen of antibiotics are used. This concept is likely homologous to the concept of persisters seen across bacterial species.

Persisters are members of a bacterial population that survive exposure to bactericidal antibiotics yet, when re-cultured, display the same antibiotic sensitivity as the population as a whole [142, 143]. *H. pylori* that are not dividing at administered antibiotic time will not be eliminated, leaving a limited population

of viable bacteria that can restore stomach colonization when antibiotics are stopped. At recommended doses, drugs currently available in acid blockade will not achieve the required sustained pH shift to imitate the bactericidal effect seen in in vitro studies [140, 144].

The current treatment effectiveness challenges can be solved by introducing non antibiotic treatment schemes, using the colonization mechanisms mentioned here, by prevention, intervention or acclimatization of motility, adhesion or acidity. The in vitro efficacy of the carbonic anhydrase inhibitor acetazolamide against *H. pylori* is one example of a potential treatment targeting acid acclimation and periplasmic pH regulation [123]. In the creation of new and better treatment regimes, a continuous research and understanding of the molecular processes of *H. pylori* gastric colonization are crucial.

8. Immune response role of antibodies in protective immunity

Analogy with other mucosal pathogens was originally thought to be primarily antibodies to mediate a defensive immune reaction against *H. pylori*. Subsequent studies found that the importance of the humoral immunity mechanism is negligible. Antibodies can prevent infection successfully and decrease the colonization in animal models studies [145]. *H. pylori* infection results in an induction of a Th1-polarized response that does not result, however, in clearance of the infection. This is striking, because the primary function in sterilizing Immunity is stated to be cellular rather than humoral immunity [146], Although it is now widely agreed that *H. pylori*-induced gastritis and/or pathology primarily rely on Th1 cells and Th1 cytokines [147]. While a polarized Th2 reaction defends against this pathology, it doesn't generally include the defense of Th2 cells after immunization. In fact, Th1-polarized T cells recruit mononuclear cells to the infection site instead of Th2-polarized, thereby removing bacteria [148].

9. Conclusion

From various studies it is concluded that gastritis still pose world -wide burden and requires extensive studies on the pathogenesis of the disease. *H. pylori* remains the most causative agent and it possess the virulence factors such as cag pathogenicity island and vacA vacuolating cytotoxin. These factors influence cellular processes via different routes, thus assisting in chronic colonization of the gastric mucosa by *H. pylori*. Gastritis infection highly results in induction of the protective immune response. Further studies should focus on the immunity to gastritis and the role of cytokines should be ruled out.

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