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Current Understanding of the Transmission, Diagnosis, and Treatment of *H. pylori* Infection: A Comprehensive Review

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Abstract

H. pylori infection is a prevalent bacterial infection that affects the gastric mucosa of humans, with a prevalence ranging from 30% to 90%, depending on the region. The infection is a significant cause of gastritis, peptic ulcer disease, and gastric cancer. In this comprehensive review, we discuss the current understanding of the transmission, diagnosis, and treatment of H. pylori infection. We describe the risk factors and epidemiology of the infection, along with its pathogenesis, which involves multiple virulence factors that contribute to the colonization and survival of the bacteria in the acidic stomach environment. Diagnostic tests for H. pylori infection include invasive and non-invasive methods, with the choice of test depending on several factors. Treatment of H. pylori infection is aimed at eradicating the bacteria and preventing complications. Antibiotic-based triple or quadruple therapy, in combination with acid-suppressing agents, is the standard treatment, but antibiotic resistance is an emerging problem that needs to be addressed. This comprehensive review provides a useful resource for clinicians, researchers, and public health officials involved in managing H. pylori infection and its associated complications.

***Keywords*— Diagnostic, and Treatment, Epidemiology of H. pylori, H. pylori, Risk factors, Pathogenesis.**

I. OVERVIEW

H. pylori is a helical-shaped, microaerophilic, and Gram-negative bacterium with a unipolar flagella bundle (Figure 1) [1].which was first diagnosed in gastric mucosa of patients suffering from gastritis and peptic ulcer, it was then successfully cultured by the two Australian doctors; Barry J Marshall and Robin Warren, [2]. Noticeably, this discovery contradicted the previously held scientific belief that the stomach is a germ-free organ, and this discovery resulted in the award. of the Noble prize 2005 to Marshall and Warren in Physiology and Medicine. Chronic infection of *H. pylori* in humans is prevalent in more than half of the world's population [3]. Furthermore, *H. pylor*i may also be associated with gastric mucosa-associated lymphoid tissue lymphoma, one of the most prevalent extranidal non-Hodgkin lymphomas [4]. There is evidence that this neoplasm is caused by chronic gastritis caused by *H. pylori*. There is no specific clinical presentation of this disease, which can range from dyspepsia to the classic B-symptoms associated with other lymphomas.

Acute complications may also occur, including intestinal obstruction, perforation, and hemorrhaging [5]. However, only a few infected people are prone to develop serious clinical symptoms of *H. pylori* infection, which in turn is determined by several factors which particularly depend on the host's immune status, such as the presence of particular receptors and the efficiency of inflammatory responses. Clinical outcome of *H. pylori* infection also depends on factors in the environment and strain specificity that influence the pathogenicity of the strains (strain diversity) [6].

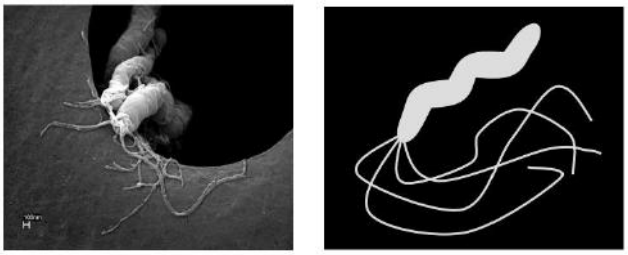

Fig.1 H. pylori; Under a scanning electron microscope (left), with its unipolar flagella is shown in a schematic (right).[1]

1.1 Taxonomy of *H. pylori*

H. pylori has a helix-shaped shape (hence its name) and to colonize the stomach, it can physically screw itself into the lining. Scientific classification of the bacteria is:

Kingdom: Bacteria

Phylum: Proteobacteria

Class: Epsilon Proteobacteria

Order: Campylobacterales

Family: Helicobacteraceae

Genus: Helicobacter

Species*: H. pylori* [7]

1.2 Gastric helicobacter species

To present, nine Helicobacter species capable of hydrolyzing urea have been cultured from the stomachs of humans and land animals (Table 1). **[8]**. The Lockard classification system divides these into three types: Type 1 has a tapered end and a fusiform to slightly spiral shape; Type 2 has sparsely distributed periplasmic fibers and can be seen singly or in groups of two to four, and has a spiral shape; and Type 3 has a tightly coiled structure and lacks periplasmic fibers.

Generally, stomach Helicobacter species isolated from animals other than cats and dogs exhibit distinct and sometimes similar morphology to *H. pylori*. On the basis of 16s rRNA similarity, a phylogenetic analysis of contemporary gastric, enteric, and hepatobiliary *Helicobacter* species has been conducted. [8].

Table 1 Human and land animal gastric Helicobacter [8]

TAXONOMY	NATURAL HOST
H. acinonychis	Cheetah
H. bizzeroni	Dog
Candidatus Helicobacter bovis	Cattle
H. felis	Cat
H. heilmannii	Human, non-human primate, pigs
Candidatus Helicobacter suis	Pig
H. mustelae	Ferret
H. nemestrinae	Macaque
H. pylori	Human, monkey,sheep
H. salomonis	Dog
H. suncus	Shrew

II. TRANSMISSION OF H. PYLORI INFECTION

The precise mode of route of *H. pylori* infection transmission unproven. The *H. pylori* can spread either directly from person to another or indirectly from an infected person to the environment, according to studies [9]. The human stomach is the most significant reservoir of *H. pylori*, and it is possible for pass from the stomach to the external environment via feces, vomitus, or gastric regurgitation [10].Currently, interpersonal transmission is more likely than environmental transmission. Transmission from person to person can be primarily fecal-oral or oral-oral. In the last 30 years, it has been reported in numerous articles that there are several potential sources and vectors of *H. pylori* infections, as well as risk factors related to both fecal-oral and oral-oral transmission routes, and

exposure to contaminated food, water, and animals. They tried isolating *H. pylori* from feces, saliva, and dental plaque [9].

2.1 Gastro-oral routes

H. pylori is acquired during infancy and transmission may occur through the vomiting of achlorhydric mucus. Transmission may occur through the gastric juices, particularly as a result of vomiting in childhood [11]. Studies reported percentages of *H. pylori* isolated from the gastric juice of symptomatic patients: A high concentration of the microorganism is frequently found in vomit, where it appears to survive outside of the human body in unbuffered gastric juice. The results of these studies support the hypothesis that gastro-oral transmission occurs in unsanitary conditions, particularly during childhood [12].

2.2 Oral-oral route

Despite the possibility that the human oral cavity may serve as a source of *H. pylori* infection, It is not certain whether the oral cavity can function as a lasting reservoir for the microorganism, or if it is only occasionally detected due to gastroesophageal reflux or vomiting in the saliva or on the oral mucosa [13]. One might be first address if oral and gastric *H. pylori* carriage are associated. A number of studies have reported a relation between oral and gastric *H. pylori* [14]. Saliva has been found to directly culture *H. pylori,* and the DNA from both subgingival biofilm and dental plaque has been amplified on numerous occasions [15]. Oral-oral transmission involves infants can be infected with *H. pylori* directly from their mothers through their oral secretions. Discordance of strain types between mother and child is one of the negative arguments against oral-oral transmission [16], Although this is debatable, other reports indicate the presence of common strains that infect couples [17].

2.3 Fecal-Oral Transmission

DNA of *H .pylori* has been frequently detected in human feces, but there has been limited success in cultivating *H. pylori* from feces because this organism persists in a non-cultivable form (coccoid) [10]. Many studies have established the relation between the seroprevalence of hepatitis A virus and *H. pylori*, suggesting similar (fecal-oral) mode of transmission for both pathogens [18]. In addition, *H. pylori* has been detected and cultured in samples of drinking water. Consequently, the public water system has been identified as a potential source of *H. pylori* infection [19].

2.4 Contaminated water sources and food

Based on the analysis of the genome, it has been determined that *H. pylori* is unlikely to multiply in the environment. When kept refrigerated, *H. pylori* can remain viable in water, milk, and a range of foods for several days. This suggests that water or food that is contaminated with *H. pylori* could pose a risk of infection for humans [10]. In water, at 20–23^0 C, *H. pylori* could be cultured for up to 24 hours, while at 16^0 C, it might to 3 days [20]. Among Lima children living in low and high socioeconomic status families, municipal water supply appears to be a significant source of infection [21]. A mode of transmission of *H. pylori* has also been described through the consumption of raw vegetables [22], also reported that the infection was more prevalent in children who regularly consumed raw vegetables and who swam in rivers and pools or used streams as a source of drinking water [23]. Milk, meat, and vegetables are among the food products analyzed. Milk products have been the subject of the most research, likely due to the fact that the infection is typically acquired during childhood, when milk consumption is prevalent [24].

2.5 Animal reservoirs

There is a possibility of zoonotic transmission of *H. pylori* from non-primate reservoirs, but this transmission has not been demonstrated [25]. In1990.strain of the bacteria was isolated from the stomach of a pig, suggesting that pigs could serve as a reservoir for this bacterium [26]. The hypothesis was supported by other studies; by successfully infecting pigs, specimens that subsequently developed gastroenteritis were obtained [27].

A second study identified *H .pylori* in six cats using 16S rDNA sequencing [28]. However, no other studies confirm these results. Further studies are needed to determine whether cats are an important route of transmission for *H. pylori*. According to the available data, owners of cats are not at risk of contracting *H. pylori* from their pets.

2.6 Interfamilial transmission

There is a higher prevalence of *H. pylori* infection among children whose parents are infected than among children whose parents are uninfected. Molecular studies have demonstrated that family members frequently share the same *H. pylori* strain.[10]. It is likely that the infection transmitted from one member of the family to another within the family or contracted from an environmental source within the family.

The spread of the infection appears to be facilitated by close intrapersonal contact: childhood overcrowding has been repeatedly identified as a significant risk factor for the development of *H. pylori* infection. Infection in both children and adults, supporting the person-to-person transmission theory [29]. In developing countries, with large families and numerous siblings, sibling-sibling transmission may be more significant [30], whereas in developed countries, the average number of children per family is low, mothers may play a crucial role [31]. The majority of studies have not found fathers who are positive for *H. pylori* to be significant risk factors for their children's infection [32]. Child-to-adult transmission appears to be improbable. A nine-year follow-up study of 46 families in Japan revealed no cases of transmission from an infected child to an uninfected parent [33]. There was no higher likelihood of *H. pylori* infection observed among children who attended day care centers in Sweden, compared to those who received care exclusively at home [10].

III. RISK FACTORS FOR INFECTION

Exposure to the bacterium is a necessary condition for the development of infection. It is dependent on the characteristics of the infectious source and the contact that results in exposure, but the infection and persistence are also influenced by the host and the bacterium. The successful establishment of an infection in a new individual, the bacterium must overcome numerous obstacles [34].

Exit from an infected individual,

Surviving outside the gastric niche,

New host introduction,

Gastric mucosa colonization, and;

Colonization maintenance.

Predominant person-to-person transmission is hypothesized. This theory is based on the fact that the infection tends to cluster within families [32] and in institutionalized individuals in the absence of consistent and verifiable environmental reservoirs [35].

3.1 The family

Transmission of *H. pylori* primarily occurs within the family context, with a child's likelihood of infection being linked to the presence of infected family members [32]. It is often suggested that family size and residential crowding (persons per room or m2) are risk factors for *H .pylori* infection and may be considered indicators of the number of infected members in a family [36]. Similarly, children living in low-prevalence regions are more likely to become infected if their families are connected to high-prevalence areas, and these effects diminish with each successive generation [37]. Infection in adulthood can be predicted by the living conditions during childhood in relation to acquiring *H. pylori* from household members during childhood [38]. The prevalence of mother-to-child transmission suggests that having an infected mother is a more significant risk factor for childhood infection than having an infected father. The clustering of the infection on sib ships has also been interpreted as evidence of transmission among siblings. [32]. Although *H. pylori* infection is usually contracted during early childhood, certain epidemiological evidence suggests that it could be transmitted within families during adulthood as well. Having a spouse who is infected has been identified as a risk factor for infection [39]. In addition, the risk of infection in adults has been associated with having a greater number of children, indicating that children may play a role as transmission mediators within families [40].

3.2 Environmental and behavioral factors

Environmental and behavioral factors related to low socioeconomic status have been investigated in relation to *H. pylori* infection. Theoretically, the observed clustering of *H. pylori* infection within families may be due to a common environmental source of the infection. Since the use of certain water sources, like wells, has been correlated with the

infection, it has been suggested that contaminated water may be the source [41].

However, other studies have not found an association between the water source and infection [23]. Furthermore, it has been suggested that *H. pylori* have zoonotic potential, with reservoirs including houseflies, cats, , and sheep, but these theories have been contested [34]. Behavior factors may influence *H. pylori* acquisition and persistence. Living in a high-prevalence nation can facilitate infection, as increasing bacterial exposure is possible due to regular and close interaction with individuals who are infected, as well as inadequate hygiene practices [41]. Intimate contact has also been proposed as an explanation for other observed risk factors, including bedsharing and breastfeeding. It has also been hypothesized that breastfeeding may provide protection against early infection through passive immunization. These results suggest that such protection, if present, is of limited importance after weaning [30]. Moreover, consumption of antibiotics has been shown to negatively correlate with *H. pylori* infection [34]. In a different study, a comparable negative correlation was no longer observed once the country of origin was taken into account, potentially because low-prevalence countries have a higher rate of antibiotic usage [38]. Several behavioral factors have been identified as factors that influence the likelihood of *H. pylori* infection in adults. Among the examples are possible negative associations with alcohol consumption [42], and possibly a positive relationship with smoking, although data are contradictory [38].

3.3 Host and bacterial factors

The ability of *H. pylori* strains to initiate and maintain an infection in a specific host can be influenced by various factors, including both the host and bacterial characteristics, as well as their compatibility with one another [43]. During childhood, transient infections may occur when the bacteria are not optimally suited for the new host and adaptation is not feasible or quick enough, resulting in the infection being cleared by the host [44]. Based on the fact that there is a higher agreement of infection between monozygotic twins (81%) compared to dizygotic twins (63%), it has been proposed that a person's genetic makeup plays a role in their susceptibility to *H. pylori* infection. However, there are certain host factors that may be linked to an increased susceptibility to infection, though the particular genetic elements of this predisposition remain unknown. It has been suggested that the expression of blood group antigens that mediate bacterial adhesion to the gastric mucosa is crucial for susceptibility to *H. pylori* infection [34].

The binding affinities of *H. pylori* strains have been shown to be adapted according to the expression of blood group antigens in various human populations, according to some research [45]. Moreover, individuals who release receptors into their bodily fluids, which can act as detachable binding sites that compete with tissue-bound receptors, have been found to have a reduced risk of infection [46]. However, studies have raised questions about the hypothesis that adhesion mediated by blood group antigens plays a role in determining susceptibility to infection [47]. The susceptibility to *H. pylori* infection may also be influenced by the immune system. This notion is supported by studies demonstrating that alleles within the HLA-DQA1 human leukocyte antigen locus are associated with infection. [48]. The infection has also been correlated with a polymorphism in the interleukin (IL)-1 receptor of unknown functional significance [49].

Furthermore, low gastric acid secretion may promote the spread of the bacterium, this may be particularly important in young children and in cases of infectious gastroenteritis [50]. Some studies have found slightly higher in infection among males [38]. This tendency's causes are unknown, and other studies have been unable to confirm this correlation [44]. *H.* pylori has evolved a range of mechanisms for survival in harsh gastric niches, which include the ability to tolerate acid, to move, to adhere, to evade immune system detection, and to adapt to the environment. These traits play a role in the interplay between the host and the bacteria and can affect the acquisition and longevity of infection in animal models. The first factors implicated in colonization were acid tolerance and motility of bacteria [34]. These findings have been validated by global mutagenesis techniques, which have also increased the number of putative essential genes [51]. However, it is unclear how relevant these findings are to human populations. In a Finnish population, it has been shown that strains with the cag

pathogenicity island (PAI), a virulence factor, disappear more rapidly than strains without the cag PA [52]. The reduction in transmissibility or persistence of cag PAI strains in this population might explain this phenomenon. however, the majority of infection in worldwide is cag PAI+ [53].

IV. EPIDEMIOLOGY OF H. PYLORI INFECTION

4.1 Prevalence and geographical distribution

H. pylori is the most prevalent human infection worldwide, colonizing over fifty percent of the world's population with a wide variation in its geographical distribution. Africa has the highest prevalence of *H. pylori* at approximately 79.1%, while Northern America and Oceania have the lowest at 24.4%. [3] (Figure 3). Rural areas have a higher prevalence of the disease than urban areas reflects differences in sanitation, socioeconomic status, urbanization, and access to clean water [54]. Interestingly, the prevalence of *H. pylori* varies between populations even in the same country. Moreover, *H. pylori* prevalence varies between different ethnic groups residing in the same country. For instance, The prevalence of *H. pylori* infection varies between non-white and non-Hispanic white populations in the United States, with a range of 34.5% to 61.6% among non-whites and 18.4% to 26.6% among non-Hispanic whites[55]. Similarly, Malaysian population comprise of Malay, Chinese and Indians ethnic groups, the *H. pylori* prevalence in Malay is (19.9%), Indians (50.7%) and Chinese (40%) [56]. WHO has identified *H. pylori* as a Group I carcinogen responsible for the development of gastric adenocarcinoma. Infection with *H. pylori* is responsible for nearly 89 % of gastric cancer cases [57]. Previously, in China, complete eradication of *H. pylori* infection has been shown to reduce gastric cancer incidences from 25% to 16.67%. [58]. In developed countries such as Canada, the United States, and Northern Europe, the prevalence of *H. pylori* is low and infection rates remain constant compared to Africa, Latin America, India, and Eastern Europe. This may be a result of enhanced hygiene, sanitation, and the active elimination of carrier state by antimicrobial therapies [59]. Furthermore, *H. pylori* shows high prevalence rates of 58 to 62% in India in patients with dyspeptic symptoms [60].

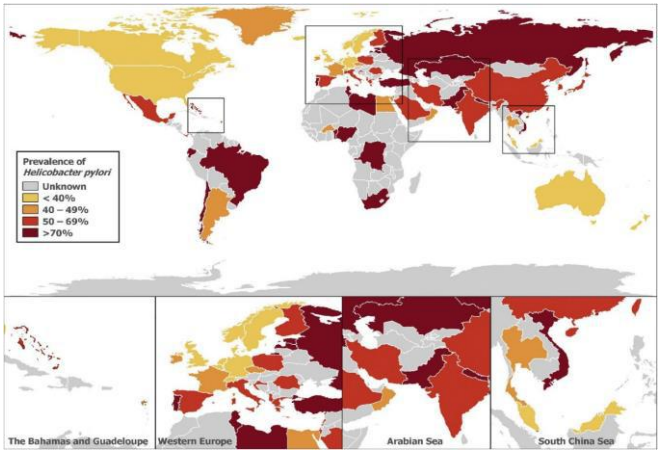

Fig.2 Map represents the global prevalence of H. pylori. To display smaller countries, certain regions magnified [3].

4.2 Incidence of *H. pylori* infection

Comparatively, the annual incidence of *H. pylori* infection in industrialized countries is approximately 0.5%, compared to 4%–15% in developing countries [61]. Living in an underdeveloped nation and possessing a low economic status are well-documented factors that increase the likelihood of being at risk [62]. Retrospective longitudinal sero surveys conducted primarily in industrialized countries are the main source for incidence rates in adults. Seroconversion (i.e., change in serostatus from seronegative to seropositive) generally occurs at a rate of less than 1% per year of follow-up, indicating that adult infection appears to be a rare occurrence. Seroreversion appears to occur at a similar or higher frequency than seroconversion [10]. Few data exist regarding the prevalence of infection between adults in developing countries. During 56 months of follow-up in Brazil, every year, a 1.1% rate of seroconversion and a 0.2% rate of seroreversion were observed [63]. In low-income countries, early childhood incidence rates above 20% per year have been reported [34].

V. CLINICAL MANIFESTATIONS OF H. PYLORI INFECTION

Over 50% of the population of the world is infected with *H. pylori* and causes histologic gastritis in all patients; however, only 10 to 20 percent of infected individuals develop ulcer disease and 1 to 2 percent

are likely to develop gastric cancer. Furthermore, the severity and frequency of disease caused by *H. pylori* are governed by various host and environmental factors [64-66] (Figure 4).

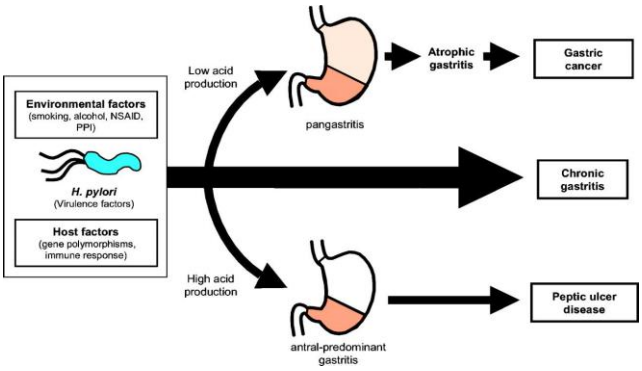

Fig.3 Schematic graph illustrating the factors that are responsible for gastric pathology and the subsequent disease consequences [67].

The ability of *H. pylori* to maintain long-term colonization is an important factor in the development of diseases [34]. The symptoms of acute *H. pylori* infection in adults usually include mild to moderate dyspepsia and occasional vomiting, which can begin a few days after infection, reach their maximum intensity during the second week, and then gradually decrease. The clinical course of chronic *H. pylori* infection can vary greatly and is influenced by factors such as the microbe itself, the host, and the environment. In almost all infected individuals, *H. pylori* causes chronic gastric mucosal inflammation [10]. Gastritis develops rapidly and persists following *H. pylori* infection. Along with its persistence, chronic gastritis may gradually transform into atrophic gastritis after several years of infection. To *H. pylori*-positive adults, atrophic gastritis is known to occur at a rate of 1-3% per year [68]. Minorities of individuals infected with *H .pylori* develop severe gastroduodenal disease, such as Duodenal Ulcers (DU), gastric ulcers, and rarely gastric adenocarcinomas or mucosa-associated lymphomas (MALTs) [10]. To individuals who are not infected with H. pylori, those who are infected have a 4-6 times higher chance of developing peptic ulcer disease. They also have a roughly 6 times higher chance of developing non-cardia gastric adenocarcinoma and gastric MALT lymphoma. In people who are infected with *H. pylori*, the chances of developing peptic ulcers during their lifetime are roughly 6-20%. In western societies, the likelihood of developing gastric cancer during one's lifetime is around 1%-2%, while in Japan, it is 11%-12% or even higher. A hypothesis suggests that being infected with *H. pylori* during childhood could raise the likelihood of developing stomach cancer at a later stage of life. The study of Mongolian gerbils indicated that early infection with *H. pylori* was associated with a significant increase in susceptibility to gastric chemical carcinogenesis compared to late infection [10].

5.1 Anemia

Among the most important micronutrients for animals and microorganisms, iron serves as a cofactor for enzymes involved in oxygen and electron transport, as well as DNA synthesis. During infection, an iron retention mechanism reduces the redistribution of iron from the cell cytosol to the cell surface, as well as circulating transferrin and the growth of invading pathogens [69]. Kato *et al.* demonstrate bacterial isolates from iron deficiency anemia patients, the SabA gene was highly expressed, suggesting that this virulence factor may contribute to anemia development [70]. Additionally, *H. pylori* cause hypochlorhydria and atrophic gastritis, as well as peptic ulcer disease and an increased risk of gastric cancers. In this instance, diminished iron absorption can result in iron deficiency anemia [71]. In patients with atrophic corpus gastroenteritis, intrinsic factor secretion is impaired, hypochlorhydria may occur, and iron and B12 may not be absorbed in the intestines as a result [72].

5.1 Gastric cancer

Despite a decline in incidence in high-income countries, gastric cancer is the second leading cause of cancer-related death globally [73]. In 1994, the World Health Organization categorized *H. pylori* as a class 1 carcinogen due to its potential to cause cancer in humans [34] . Subsequent studies have confirmed the link between *H. pylori* infection and gastric cancer, attributing approximately 70% of 35 non-cardia adenocarcinomas to *H. pylori* infection [74]. However, a Few percentages of infected people develop stomach cancer [75]. Individuals who have low levels of gastric acid secretion and corpus-predominant gastritis, a condition that results in

atrophic gastritis, loss of parietal cells, and subsequent hypochlorhydria, are more likely to develop gastric cancer [76]. There are several postulated carcinogenic mechanisms, including inflammation-induced epithelial turnover. In addition, hypertrophy and hypochlorhydria of the stomach can lead to impaired antioxidant absorption, infection with carcinogenic microbes, and the accumulation of carcinogenic compounds in the body [75]. Infection with *H. pylori* upregulates the proinflammatory cytokine IL-1, which is also a potent acid secretion inhibitor. Hypochlorhydria and cancer have been linked to polymorphisms believed to increase IL-1 activity, evidence supporting the role of gastric acidity in the development of cancer [77].

5.2 Gastritis

5.2.1 Acute gastritis

Significant inflammation of the distal and proximal stomach mucosa, momentary nonspecific dyspeptic symptoms, nausea, vomiting, and stomach fullness characterize an acute infection with *H. pylori*. On the basis of reports from patients who accidentally or deliberately consumed *H. pylori* or acquired infections through contaminated food or water, these symptoms were identified. [78, 79].

5.2.2 Chronic gastritis

Persistent infection of *H. pylori* in the human Gut correlates with the distribution of gastritis and the level of acid secretion (Figure 4). The acid secretion level has antagonistic effects on *H. pylori.* In particular, *H. pylori* infects the gastric antrum, where a low acid-secretory layer of parietal cells exists. This infection is identified by a predominant antrum-based gastric inflammation. In patients with deficient acid secretion, bacteria are uniformly distributed within the corpus and antrum, as well as in close proximity to the gastric mucosa [80]. Persistent inflammation of the corpus mucosa promotes hypochlorhydria, in conjunction with local inflammatory factor responses such as interleukin-1(IL-1), which then produces suppressive responses on parietal cell function, as evidenced by reports indicating that eradication therapy increases acid secretion in patients [81] Furthermore, patients with a proinflammatory genotype are more likely to develop chronic gastritis, making them prone to intestinal metaplasia, atrophic gastritis, and ultimately gastric cancers [77].

5.3 Peptic ulcer disease

The revelation that *H. pylori* is the cause of peptic ulcer disease has resulted in a change in the treatment approach for patients with ulcers [82]. Infected individuals face a lifetime risk of peptic ulcer ranging from 3% in the United States to 25% in Japan [83]. *H. pylori* is believed to be the cause of 95% of DUs and 70% of gastric ulcers [84]. *H. pylori*-induced gastritis, diminished somatostatin levels, and increased gastrin and acid secretion are associated with duodenal ulcers [83]. As a result of gastric metaplasia in the duodenum, additional bacterial colonization may occur, resulting in duodenitis and epithelial damage. Gastric ulcers are linked to corpus gastritis, which is believed to harm the epithelial lining [75].

5.4 MALT Lymphoma

Among digestive system marginal zone lymphomas, gastric MALT lymphoma (GML) is the most prevalent. In accordance with epidemiological, pathological, clinical, and bacteriological evidence, the association between *H. pylori* and this lymphoma is now well established [85]. *H. pylori* eradication therapy is now regarded as the primary treatment for low-grade GML [86, 87]. After eradicating the bacteria with antibiotics, additional research has indeed revealed a regression of GML lesions. 60% to 90% of patients can experience lymphoma regression after *H. pylori* eradication [88]. The neoplastic cells of GML are already sensitized to the antigens of *H. pylori* if a reinfection occurs [89]. *H. pylori* infection was the first bacterial infection to be categorized as a type 1 carcinogen, the highest level, due to its link with gastric adenocarcinoma. It has been extensively studied since its discovery in order to identify virulence factors or genetic markers. but *H. pylori* strains associated with GML have received little attention. [88].

5.5 Non-ulcer dyspepsia

Non-ulcer dyspepsia (NUD) or functional dyspepsia refers to pain or discomfort in the upper gastrointestinal tract without any observable structural irregularities. The relationship between *H. pylori* infection and non-ulcer dyspepsia has been intensively studied. 30–60% of patients with

dyspepsia will be infected with *H. pylori*. However, the rate of symptoms in the non-infected control group is also comparable [90]. Therefore, there has been considerable debate regarding the anticipated outcome of *H. pylori* eradication in dyspepsia patients. In a meta-analysis of non-ulcer dyspepsia (NUD), according to a study, eradicating *H. pylori* decreased the chance of experiencing dyspeptic symptoms by 8% when compared to a placebo. The study also found that eradicating *H. pylori* in 18 patients would be necessary to alleviate dyspeptic symptoms in one patient [91]. Nonetheless, in patients with functional dyspepsia, Maastricht IV guidelines now recommend eradication, particularly in regions with a high prevalence [87].

5.6 Insulin Resistance

The immune system is activated by H. pylori infection, resulting in the production of inflammatory cytokines such as tumor necrosis factor (TNF-) as well as leptin and adipokines, which mount an immune response against the inflammation. Studies have shown that low levels of leptin can cause insulin resistance (IR) due to elevated levels of TNF- and IL-6 [92]. Inflammatory cytokines can have a substantial impact on insulin function by phosphorylating serine residues on insulin receptor substrates, which interferes with their interaction with insulin receptors. Thus, diabetes can result from a breakdown in blood glucose regulation [92].

VI. PATHOGENESIS OF H. PYLORI INFECTION

In the past, it was believed that the gastric environment was sterile due to its high acidity before Warren and Marshall discovered that *H .pylori* [93]. To achieve in challenging conditions, the bacterium employs several mechanisms to enhance its mobility, robust adhesion to epithelial cells, and use enzymes to establish an optimal microenvironment to sustain infection [94].

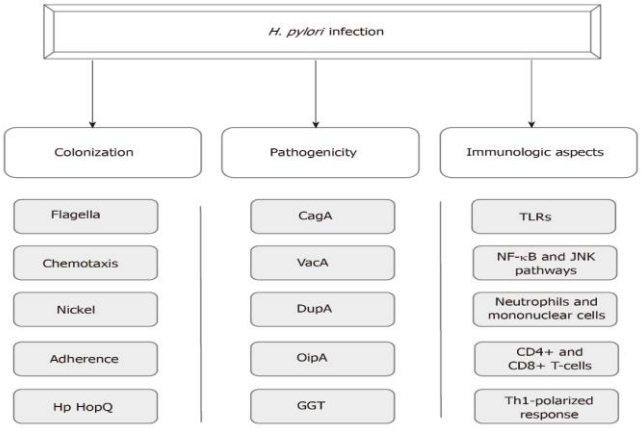

Figure 4 Aspects of *H. pylori* infection. CagA: Cytotoxin associated antigen A; VacA: Vacuolating cytotoxin; DupA: Duodenal ulcer promoting gene A protein; OipA: Outer inflammatory protein; GGT: Gamma-glutamyl transpeptidase; TLRs: Toll-like receptors [95].

In addition, the pathogenicity of this infection (GGT) can be attributed to various virulence factors, such as cytotoxin associated antigen A (CagA), vacuolating cytotoxin (VacA), duodenal ulcer-promoting gene A protein (DUPA protein), outer inflammatory protein (OipA), and gamma-glutamyl transpeptidase [96]. Moreover, probably through a Th1-polarized response against the pathogen, the host immune system plays a crucial role in the infection's progression (Figure 5) [95].

While most individuals with *H. pylori* infection do not exhibit any symptoms, such infections raise the likelihood of developing diseases like peptic ulcers and gastric adenocarcinomas [97]. In this way, proper clinical management precedes an accurate diagnosis and is followed by effective treatment in order to improve a patient's clinical outcome [98]. *H .pylori* has been detected using a variety of invasive and noninvasive diagnostic methods, and bacterial resistance is a significant obstacle to eradicating infection [99]. In this sense, in an effort to improve treatment outcomes, new therapy regimens and probiotic administration have been tried [100]. Moreover, several researchers have focused their efforts on the development of vaccines against *H. pylori* infection.

6.1 Colonization

There are different factors that are critical during *H. pylori* colonization in the mucosa tissue of the stomach (Figure 6)

6.1.1 Production of Urease

H. pylori is not an organism that prefers an acidic environment, and the production of urease enzyme is one of its signature strategies to neutralize the acidic environment of the gastric lumen. For successful colonization of the gastric mucosa, *H. pylori* requires the presence of urease and its activation [78]. It has been shown in the presence of urea, *H. pylori* can tolerate a pH as low as 2.5, whereas in its absence, it can tolerate a pH range between 8.0 and 4.0 [101]. It contains a cluster of seven genes that control and regulate the urease enzyme biosynthesis process [102], and it has a complex structure composed of twelve subunits of UreA and UreB.. [103].

H. pylori urease is a hydrolase enzyme that hydrolyses urea to CO_2 and NH3. In contrast to ureases produced by other bacterial species, *H. pylori* urease has a Km value of 0.8 Mmol/L, which enables it to act on even minute amounts of urea (as low as 5 Mmol/L). Utilization of urea and production of NH3 generate acid-neutralizing capacity, which enables *H. pylori* to maintain the proper pH in its periplasm and microenvironment. Thus, regulation of the proton motive force [104] . This strategy of *H. pylori* to maintain a neutral pH intracellularly while the pH of the surrounding environment remains low is a peculiar characteristic of *H. pylori*. This is necessary for the survival of H. pylori in acidic gastric juice. Moreover, the generation of NH3 by the urease enzyme in non-acidic environments may raise the native pH above pH 7.0, which may explain why *H. pylori* does not colonize niches other than the Gut. Furthermore, it has been demonstrated *H. pylori* is intolerant to alkaline conditions [105].

6.1.2 Response to the harsh environment in the stomach

Jones and Zamble conducted an experiment in which they simulated the acidic conditions of the human stomach by exposing *H. pylori* to an external pH of 2.0 and observed the impact of a decrease in cytosolic pH on the bacteria. As a result, nickel-responsive transcription factors (HpNikR) activated transcription of the ureA gene, demonstrating how these bacteria adapt to harsh acidic conditions [106]. The data obtained allows for the correlation between the acid adaptation of *H. pylori* and nickel homeostasis to be made. The reduction in mucosal bicarbonate secretion caused by *H. pylori* may protect the gastric barrier from acid-induced damage to the mucosa, plays a role in the development of duodenal ulcers [107]. Through the transforming growth factor beta (TGF)-mediated p38 mitogen-activated protein kinase (MAPK) signaling pathway, *H. pylori* downregulate the expression of two transporters of cellular bicarbonate in the duodenal epithelium: (a) the cystic fibrosis transmembrane conductance regulator (CFTR) and (b) the solute linked carrier 26 gene family A6 (ALC26A6) [107]. In a comparative transcriptomic analysis, Hathroubi et al discovered that 8% of the genes examined exhibited differences between *H. pylori* biofilm cells and planktonic cells. The biofilm-downregulated genes were involved in metabolism and translation, while Biofilm-upregulated genes encode proteins involved in stress response and flagellum formation [108]. Potentially promoting the persistence of *H. pylori* in the stomach, this biofilm formation.

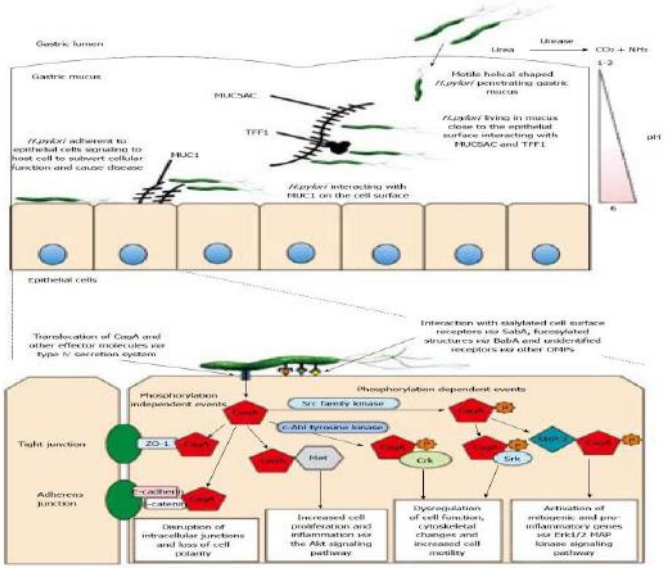

Fig.5 Colonization strategies and establishment of gastric mucosal infection by H. pylori [109].

6.2 Virulence factors

6.2.1 Outer membrane vesicles

virulence factors of *H. pylori* can be present in a soluble form, attached to the cell surface, or delivered into host cells through the host's type IV secretion system (T4SS). Recently, there is a proposed significant function of outer membrane vesicles (OMVs) produced by *H. pylori* in the dissemination of bacterial antigens. OMVs contain a variety of

biologically active compounds produced by *H. pylori*, are capable of being internalized into host cells, and as a consequence, in addition to influencing signaling pathways, they can promote the apoptosis of gastric epithelial cells as well as immune cells. This can have the effect of either enhancing or suppressing immune responses, resulting in the eventual onset of a disease [110]. Through the utilization of protonography and mass spectrometry, Ronci et al. confirmed the existence of -carbonic anhydrase (CA) in OMVs produced by *H. pylori* strains with planktonic and biofilm characteristics. This work suggested that CA, along with urease, may have a crucial role in reducing the acidity of gastric juice caused by *H pylori* [111]. The protein composition, immunogenicity, and method of entry into host cells of OMVs are influenced by their size. OMVs with sizes ranging from 20-100 nm can enter host cells via caveolin-dependent endocytosis, while OMVs with sizes of 90-150 nm can enter through macropinocytosis and endocytosis. These results indicate the importance of OMVs in the pathogenesis of *H pylori* and the possible use of OMVs in the development of vaccines [112].

6.2.2 CagA

It is a bacterial protein called CagA, which induces changes in morphology, alters their polarity, and causes hummingbird-like phenotypes in epithelial cells. This virulence factor can also trigger changes in the cytoskeleton associated with gastric adenocarcinoma development [113]. In addition to the CagA gene, the cag pathogenicity island also contains the code for a type IV secretion system (T4SS) [114]. CagA and peptidoglycans are translocated into host cells by this bacterial structure [115]. In the host cell, CagA is tyrosine phosphorylated at the Glu-Pro-Ile-Tyr-Ala (EPIYA) motif, which consists of different EPIYA segments (EPIYA-A, EPIYA-B, EPIYA-C, and EPIYA-D) in the variable C-terminal region of the protein [116]. While EPIYA-A and EPIYA-B segments are found in most cagA-positive *H. pylori* strains, the EPIYA-C and EPIYA-D segments are linked to Western and Eastern strains, respectively [117] . Strains of *H. pylori* with EPIYA-D or at least two EPIYA-C segments in their cagA gene are related with an increased risk of cancer [118]. Moreover, research on a Brazilian population has revealed that relatives of individuals with gastric cancer are more likely to be infected with H. pylori strains containing two or more EPIYA-C segments [119]. CagA is activated by phosphorylation, resulting in the activation of SHP-2 (SH2-containing protein-tyrosine phosphatase), which promotes the changes described above in the cell [120].

6.2.3 Non-CagA virulence factors

Several virulence factors have been associated with an increased ability of *H. pylori* to impair gastric homeostasis. Among them, VacA gene is present in almost all strains of bacteria, including *H. Pylori*, and is a determinant of the pathogenicity of this bacterium. VacA induces the creation of acidic vacuoles within the cytoplasm of gastric epithelial cells. This results in the destabilization of mitochondria, cytoplasmic membranes, and endomembranous structures, leading to the collapse of cells [121]. Additionally, this protein may also be responsible for activating and suppressing the immune response, resulting in immunity tolerance and persistent infection with *H. pylori* through interactions with T-cells and antigen-presenting cells [122]. This virulence factor is responsible for a series of alterations that contribute to increased gastritis, as well as the development of ulcers and cancer [123]. Another bacterial protein known as DupA appears to give the bacterium with a higher level of acid tolerance. It also has the potential to stimulate an increase in the synthesis of IL-8 in the mucosa of the antral gastric region. Elevated levels of IL-8 result in mucosal inflammation and the influx of polymorphonuclear leukocytes, potentially causing gastritis and duodenal ulcers [124]. Notably, a link between dupA-positive *H. pylori* strains and duodenal ulcers has been established in Asian countries, but not in Western countries [125]. Furthermore, the research has shown that the presence of functional dupA in *H. pylori* strains should be considered a protective factor against the development of gastric cancer. [126]. The gene products of dupA show similarity to the VirB4 ATPase, which plays a role in the construction of the secretion machinery. Nonetheless, the precise connection between dupA and *H. pylori* T4SS remains to be elucidated [124]. OipA, an outer membrane protein contributes to adhesion and inflammation by stimulating the production of IL-8. The increased

number of investigations on this *H. pylori* virulence factor stemmed from the identification of the link between OipA and the increased incidence of peptic ulcers and gastric cancer [127]. Since the expression of the oipA gene is regulated by a repair process called "slipped strand mispairing," which depends on the quantity of CT dinucleotide repeats in the oipA 5' region, the functional status of OipA has been described as an important factor in the outcome of the infection. This is because the expression of the oipA gene is regulated by a repair process called "slipped strand mispairing.". This process determines whether oipA in a specific bacterial strain is nonfunctional or functional, and the latter condition is associated with higher stomach pathogenicity [128]. Furthermore, it is plausible that OipA is linked to modifications in -catenin signaling, reduction in cell-cell junctions, and enhanced cell proliferation [129]. *H. pylori* produces GGT, which is an enzyme with N-terminal nucleophile hydrolase activity. GGT can facilitate the conversion of glutamine into glutamate and ammonia, and also catalyzes the hydrolysis of glutathione into glutamate and cysteinylglycine [96]. As a result of its activity, reactive oxygen species (ROS) are produced, which, like ammonia, cause cell cycle arrest, apoptosis, and necrosis [130]. In addition, according to scientific investigations, this enzyme inhibit T cell proliferation and dendritic cell differentiation. [131]. Patients with peptic ulcers have been found to have a greater GGT activity than those with other gastroduodenal disorders [132].

6.3 Immunologic aspects

H. pylori infection induces complex immune responses, including innate and adaptive responses [133]. Considering the initial exposure to the pathogen, various *H. pylori* antigens such as lipoteichoic acid, lipoproteins, lipopolysaccharide, HSP-60, NapA, DNA, and RNA bind to gastric cell receptors, including toll-like receptor (TLR) 1, TLR2, TLR4, TLR5, TLR6, and TLR10 located on epithelial cell membranes, and TLR9, found in intracellular vesicles [134]. This connection stimulates, among other signaling pathways, the activation of NF-B and c-jun N-terminal kinase, followed by the release of proinflammatory cytokines [135]. The injection of CagA through T4SS does not only activate receptors by pathogen-associated molecular patterns, but also induces the production of cytokines, a process that is dependent on the NF-B pathway [136]. Subsequently Neutrophils and mononuclear cells infiltrate the stomach mucosa, leading in the generation of nitric oxide and reactive oxygen species [137]. In addition, adaptive immunity's components, namely CD4+ and CD8+ T cells, are also brought in. There may be a preferential activation of CD4+ cells over CD8+ cells, and a particular response is focused toward the bacterium [138]. Studies suggest that in H. pylori-positive patients, there is a Th1-polarized response in terms of cytokine profiles, characterized by decreased levels of the Th2 cytokine IL-4 and increased levels of gamma interferon, tumor necrosis factor, IL-1, IL-6, IL-7, IL-8, IL-10, and IL-18 [139]. Apart from IL-10, which appears to have a function in controlling the inflammatory response, the other cytokines that are elevated may contribute to the proinflammatory effects that occur during infection with *H. pylori*. Additionally, it is shown that an increase in IL-17 is associated with *H. pylori* infection, especially in adults [140]. The presence of *H. pylori*-specific serum IgM antibodies in patient serum can be detected 4 weeks after infection when it comes to the production of immunoglobulins [141]. During chronic infection, a variety of bacterial antigens are targeted by IgA and IgG immunoglobulins in the bloodstream [95] . The majority of *H. pylori*-positive individuals do not experience symptoms of this inflammation, however, it increases their risk of developing duodenal and gastric ulcers as well as stomach cancer in the long run [83].

VII. DIAGNOSTIC TESTS FOR DETECTION OF H. PYLORI INFECTION

Infection with *H. pylori* is detectable by both invasive and non-invasive diagnostics. The technique chosen depends on the patient's requirements. Several factors need to be taken into account, such as the existence of warning signs, the application of non-steroidal anti-inflammatory drugs (NSAIDs), and being elderly (either over 45-50 years old or over 60 years old)[142], history of premalignant symptoms or surveillance for a past malignancy mandates an upper endoscopic assessment. Doctors can utilize esophagogastric-duodenoscopy to visually inspect the mucosa, take biopsy samples for histological analysis, urease testing, bacterial culture, and,

potentially, molecular testing. In the absence of an endoscopic suggestion, non-invasive diagnostics, such as urea breath testing or stool antigen assay, can be used to confirm the presence of an active infection. In certain circumstances, a physician may employ serology as a diagnostic tool to assist in the identification of bacterial infections [143]. However, the diagnostic approach can't be independent of the availability of the test in the patient's area, how much it will cost, or what the patient wants. Wang et al. briefly review the current options and advances of diagnostic tests and their associated clinical applications, as well as the selection of diagnostic tests for various clinical situations (Table 3) [144].

Table 2 Diagnostic options for H. pylori infection in various clinical settings and specific diagnostic test applications [144]. Although serology is unaffected by local changes in the stomach, it should be evaluated with caution prior to further management.*

Methods	Gastroduodenal bleeding	Post gastrectomy	Post eradication therapy	Special applications
Rapid urease test		√		
Histology		√		
Culture				Antibiotic sensitivity
Polymerase chain reaction	√		√	Antibiotic sensitivity, Virulence factors, Environmental/oral sample
Urea breath test	√		√	
Stool antigen test			√	
Serology*	√	√	√	Virulence factors

7.1 Non-Invasive Tests:

Non-invasive test can detect the active infection or provide with information a previous infection.

7.1.1 Urea breath test

The diagnosis of *H. pylori* can be done non-invasively through UBT. Based on a basic premise, to perform UBT, patients ingest urea that has been tagged with ^{13} C or ^{14} C. H. pylori produces the enzyme urease, which breaks down the urea into ammonia and ^{13} C-labeled carbon dioxides. This ^{13} C carbon dioxide then enters the bloodstream, travels to the lungs, and is eliminated through exhalation [145]. Typically, it is administered in combination with citrus juices, such as lemon or orange, to postpone the process of gastric emptying and enhance the duration of contact with the mucosal lining. After drinking the test solution, the exhaled air is collected in a sealed plastic bag 30 minutes later. Air sample analysis can be performed using either a mass spectrometer or infrared spectroscopy. The latter is considered a more straightforward and cost-efficient alternative to mass spectrometry. Infrared spectroscopy is the method of choice for determining the $^{13}C/^{12}C$ isotope ratio. The increase in labeled CO2 is expressed as a delta value compared to the baseline (DOB). The DOB measurement is directly associated with the bacterial load of *H. pylori*, meaning a higher DOB value indicates a higher bacterial load. Thus, based on the presence of 13C in exhaled air, we can detect with great accuracy whether a patient is infected with *H. pylori*, and based on the value of the $^{13}C/^{12}C$ ratio, we can evaluate the severity of infection. It is similar to the ^{14}C urea breath test, except that ^{13}C is not a radioactive isotope. The typical urea breath test contains 75 mg of ^{13}C. ^{13}C-UBT has a sensitivity of 96–100% and a specificity of 93–100% [145, 146]. The BREATH QUALITY UBT could be decreased to 15 minutes, according to one study, without compromising the method's accuracy [147]. The meta-analysis conducted showed that the test is highly accurate in children of any age. For children older than 6 years old, sensitivity was 96.6% and

specificity was 97.7%, respectively; for children younger than 6 years old, sensitivity was 95% and specificity was 93.5%. [148]. Recently, a new UBT approach employing a tablet formulation of ^{13}C-urea has been proposed. This technique provides for highly accurate breath sampling within 10 minutes after ingesting a tablet. Using tablets has a benefit of preventing the interaction between the urease-producing bacteria in the oropharynx and the formulation, which could cause inaccurate positive results. This is one of the benefits of taking the medication in this form [149, 150]. Although rare, false-positive outcomes can occur in patients who have undergone gastric resection or have experienced a significant reduction in stomach output, especially when endoscopy with biopsy has been performed shortly before the test. The primary cause of false-positive results is typically the breakdown of urea by bacteria that possess urease in the oral cavity or the stomach [151]. This is especially common when achlorhydria or hypochlorhydria is present. A few instances of false-negative outcomes could be due to errors in the method of collecting and storing exhaled air samples, or from physical exertion before or during the test. As with most other tests, a reliable UBT result may be obtained after discontinuing PPIs for a period of two weeks, and no earlier than four weeks after stopping antibiotics and bismuth [145].

7.1.2 Stool Antigen Test

Tests that are easy to perform and designed to identify *H. pylori* antigen in stool samples have been shown to have a high level of accuracy in extensive comparisons with identical tests [152]. In general, stool monoclonal antibody tests are more precise than stool polyclonal antibody tests, with a combined sensitivity of 93% and specificity of 96% [153]. They also demonstrated a high level of diagnostic accuracy in pediatric settings, particularly when tests were based on ELISA rather than immunochromatography [154]. In a Houston Consensus Conference, a group of 11 experts recommended using stool antigen testing (or UBT) for the initial diagnosis of *H. pylori* infection and post-treatment (when endoscopy is not required) [142]. The UBT and the stool antigen test both have the advantage of being able to evaluate the entirety of the stomach's contents, in contrast to the histology and RUT, which can only evaluate a small portion of a biopsy specimen. Both stool antigen tests and UBT are the most reliable methods of diagnosing an active infection with H pylori, both theoretically and practically. Nevertheless, any drug that lowers *H. pylori* numbers below the threshold of detection may result in false negative results, especially when used in conjunction with a proton pump inhibitor, bismuth-containing compound, or antibiotic [155].

7.1.3 Serology

A systemic immune response is brought on by *H. pylori* infection of the stomach. Antibodies to *H. pylori* can be detected in the blood anywhere from three to four weeks after infection. The presence of these antibodies can be ascertained using any one of the following three techniques: an enzyme-linked immunosorbent assay (ELISA), a latex agglutination test, or a Western blotting analysis. Among these, the ELISA test is the one that is used most frequently [156] . Detection of IgG, IgA, and IgM antibodies in the bloodstream is the basis of this technique. Since *H .pylori* is a chronic infection, only a validated IgG test can be used to detect it [157]. There are a number of serologic tests available for the diagnosis of *H. pylori*; they can be performed non-invasively, and quickly, no special equipment is required, and can be used to screen large populations for the presence of the infection. However, Serology may be positive as a result of a current infection at the time of the test, a past infection, or cross-reacting non-specific antibodies [158]. The production of immunoglobulins (antibodies) against antigens is triggered by active infection, previously acquired infection, or non-specific cross-reacting antibodies [156]. Serological tests are therefore able to be used for both the initial diagnosis and confirmation of *H. pylori* infection. Serological tests should not be used for therapeutic follow-up after successful eradication because the level of quantitative antibodies after successful eradication, the population does not decline significantly for a long time. Moreover, false-positive serologic results are common in populations with a low prevalence (40%) of *H .pylori* infection, since the positive predictive value of serology is dependent on the prevalence of *H .pylori* infection in the population [159]. Serology is not recommended in such populations, and if a serological test of *H. pylori* is positive, further confirmation is necessary, such as a biopsy culture, urea breath test, or stool antigen test.

Recent The use of proton-pump inhibitors, antibiotics, bismuth preparations, gastrointestinal hemorrhaging, or atrophy of the gastric mucosa does not affect the serological results [157]. Serological tests vary in their specificity and sensitivity. The test's sensitivity and specificity were 85% and 79%, respectively, according to a meta-analysis. According to another study, the range of sensitivity was 76% to 84% and the range of specificity was 79% to 90% [159]. Several investigations have shown that elevated levels of anti-*H. Pylori* IgG antibodies are linked to the severity of histological gastritis, the density of bacteria in the mucosal lining, and the presence of blood biomarkers for stomach function, such as PGI, PGII, PGI/II ratio, and gastrin-17. However, there have been other studies with contradictory findings, making the results inconclusive [160].

7.2 Invasive Tests:

7.2.1 Histology

By analyzing biopsy samples of stomach mucosa, it is possible to detect *H. pylori* with a sensitivity of 95% and a specificity of 98%. In addition, it makes it possible to visualize the morphology of the stomach at any time. To achieve a precise diagnosis, two antral biopsies must be performed, one from the gastric angulus and two from the corpus [161]. For example, when biopsy samples were not obtained from the angulus in 213 patients, 8% and 3% of cases of atrophic gastritis and intestinal metaplasia were missed, respectively [162]. There is some concern that the widespread use of proton pump inhibitors (PPIs) may lead to the development of an atypical gastritis or bacterial density changes at several sites in the body as a result of the use of these medications [163]. *H. pylori* infections can be accurately diagnosed histologically by utilizing unique staining techniques, immune stains, or digital pathology [164, 165]. However, according to a recent study, standard hematoxylin-eosin staining was able to detect 94% of *H pylori,* while special staining did not show the same level of detection. [166].

7.2.2 Rapid Urease test

Upper endoscopy enables the collection of biopsy specimens for urease testing. The approach takes advantage of the organism's pre-formed urease; in solutions containing urea, the enzyme releases ammonia, resulting in an increase in pH and a color change in the medium. The rapid urease test (RUT) is a quick, simple, cost-effective, and very specific method of diagnosing *H. pylori* infection. However, in order to perform RUT, a high density of bacteria is necessary. For instance, in the normal commercial kits at least 104 bacteria must be present in the stomach specimen [167]. It is possible to obtain false negatives if you have recently taken antibiotics, bismuth-containing compounds, or PPIs, especially omeprazole and lansoprazole, or if your child is younger than five years of age [168]. It has been demonstrated that obtaining biopsies from the corpus, as opposed to the antrum, or mixing antral and corpus samples, increases RUT sensitivity [169, 170]. In contrast, Dechant et al. found that the rapid urease test (RUT) is more effective than histology in detecting H. pylori infection in patients who have undergone treatment with PPIs or antibiotics [171].

7.2.3 Culture

As well as performing histological examinations and RUTs, upper endoscopy can be employed to collect gastric specimens in order to conduct bacterial culture, susceptibility testing, and, ultimately, organism genotyping. Although culture has a high specificity, low sensitivity, because *H. pylori* are difficult to grow, and requires the expertise of a laboratory. Using a preheated 35Co blood agar and transporting the material to the laboratory within 30 minutes of collection can improve sensitivity (BD Diagnostics, Sparks, MD, USA) and a *helicobacter* selective agar, containing polymyxin (Hy-Laboratories, Rehovot, Israel) and the antibiotics colistin. An alternative strategy to consider is to culture the specimens under microaerophilic conditions (using CampyGenTM, Oxoid, Hampshire, UK) at 35°C for an extended period of 14 days, or to modify the atmosphere by adding hydrogen, or by treating the specimens with trypsin [172, 173].

7.2.4 Endoscopy

The development of high-resolution endoscopic technology has made it possible to increase diagnostic accuracy in the process of identifying *H. pylori* infection and the lesions that are associated with it. Advanced imaging methods with the highest resolution include high-resolution microendoscopy, optical coherence tomography, endocytoscopy, and

confocal laser endoscopy [174, 175]. At present, none of these techniques allow for "optical biopsies" to be widely available or specific enough to allow for a real-time diagnosis of *H. pylori* infection. A study involving 300 patients in Japan showed that the conventional narrow-band imaging (NBI) technique is strongly associated with the histopathologic severity of *H. pylori* gastritis. The NBI mucosal patterns showed five different degrees of *H. pylori* gastritis (gastric atrophy, inflammatory infiltration, and H. pylori density) [176] . Kawamura et al [177] indicated endoscopic magnifying technique using NBI demonstrated micromorphological differences that correlated with histological findings among individuals with distinct *H.pylori*-related diseases. Confocal laser endomicroscopy is a functional imaging method that can be used to identify abnormalities in the mucosal barrier in patients with *H. pylori* infection and IM [178]. Moreover, a new endoscopic imaging technique called endocytoscopy, in vivo histology and guided biopsies can be obtained accurately and safely using this approach. Endocytoscopy permits microscopic imaging at a 1,400-fold magnification, it allows for cellular examination of mucosal structures and detection of *H .pylori* in vivo [179].The current development of functional and molecular-targeted imaging technologies may be useful in diagnosing *H. pylori* infections in real-time [180].

7.3 Molecular test

Molecular methods, such as polymerase chain reaction (PCR), have increasingly been used to detect and type *H. pylori* and related species, as well as determine how susceptible these bacteria are to antibiotics in recent years. Kalach et al [181], as a result of the study, they concluded that quantitative real-time PCR (qPCR) in detecting *H. pylori* infections in gastric biopsies of French children, it is more precise than routine culture, histology, or RUT alone. It permits the detection of low bacterial loads. It has been demonstrated that quantitative PCRs and nested PCR techniques can detect *H. pylori* in specimens such as inflammatory tooth pulp, saliva, and dental plaque in the oral cavity [182, 183]. Comparatively to conventional methods, a novel method for detecting 16S rRNA and ureC genes of *H .pylori* using the GenomeLabTM Genetic Analysis System (Beckman Coulter) has demonstrated high performance [184]. Paraffin and formaldehyde used for tissue preservation may reduce the efficiency of subsequent molecular amplification of microbial DNA. Rabelo-Goncalves et al [185] A study compared the efficacy of five different commercial DNA extraction methods and the phenol-chloroform method for detecting *H. pylori* using PCR amplification of the 16S rRNA gene in liver tissue that had been formalin-fixed and paraffin-embedded. Although samples extracted with phenol–chloroform included the highest proportion of positive cases (70%), there was no statistically significant difference between the techniques. Infections caused by *H. pylori* are being treated with omics-based methods. Kim et al [186] through pyrosequencing 16S rDNA amplicons of gastric biopsy specimens, *H. pylori* was detected in all samples suspected to be positive for *H. pylori*, as well as, shockingly, in sixty percent of the samples that were thought to be negative for *H. pylori*. In one work, SOLiD sequencing was done on two H. suis genomes in order to generate appropriate PCR primers. The researchers were successful in finding H. suis DNA in gastric biopsy specimens taken from mice that had been experimentally infected [187]. Electrophoresis was performed using two-dimensional (2D) gels [188] to compare the cellular proteomes of *H. pylori* with non-pylori *Helicobacter species, including Helicobacter mustelae, Helicobacter felis, Helicobacter cinaedi, Helicobacter hepaticus, Helicobacter fennelliae, Helicobacter bilis, and Helicobacter cholecystus.* It was feasible to differentiate between stomach and enterohepatic *Helicobacter* species on the basis of their characteristic 2D protein profiles. In order to detect the presence of levofloxacin resistance directly in gastric biopsy samples, Trespalacios et al. developed novel primers for the identification of the N87I mutation in the gyrA gene of *H. pylori*. The application of the new primers resulted in an increase in the sensitivity of the approach for predicting levofloxacin resistance from 52 to 100 [189]. The efficacy of the GenoType HelicoDR kit for the rapid detection of the A2143G mutation in the 23S rRNA gene associated with clarithromycin resistance and the N87K mutation linked to fluoroquinolone resistance was evaluated in 42 *H. pylori* isolates. Compared to sequencing, the test demonstrated a sensitivity and specificity of over 80% for the identification of clarithromycin and fluoroquinolone resistance.; however, compared to

MIC results, it demonstrated a sensitivity of 55% for detecting clarithromycin resistance [190].

VIII. TREATMENT OF H. PYLORI INFECTION

The Maastricht V/Florence Consensus Report, a brand-new European standard for treating *H. pylori* infection, suggests the following treatment plan (Figure 7) [191]. At first, when there is less than 15% of a region's population that is resistant to clarithromycin, the conventional triple regimen of proton pump inhibitors (PPI), amoxicillin, and clarithromycin is advised. According to Murakami et al., the standard triple regimen (Lansoprazole 30 mg bi-day, 750 mg bi-day amoxicillin, and 400 or 800 mg bi-day clarithromycin for 7 days) obtained a 97.3% success rate in the elimination of the strains that are sensitive to clarithromycin [192]. As a first-line treatment for clarithromycin-resistant infections, bismuth-containing quadruple therapy is recommended for areas with a high level of resistance (> 15%) to clarithromycin. An alternative treatment option is non-bismuth quadruple concomitant therapy (metronidazole , amoxicillin, clarithromycin, and PPI) in regions in which clarithromycin resistance is high, but metronidazole resistance is low to intermediate [191, 193]. When clarithromycin and metronidazole face significant resistance in a particular region, the recommended primary treatment option is bismuth-containing quadruple therapy. In China, patients diagnosed with *H. pylori*-induced chronic gastritis have a higher success rate with first-line therapy consisting of ten days of bismuth quadruple therapy as opposed to ten days of normal triple therapy (86.1% vs. 58.4%, ITT analysis) [194]. If both the initial treatment (triple or non-bismuth quadruple therapy) and the second treatment (quinolone-containing therapy) fail, then the appropriate course of action is to use quadruple therapy that includes bismuth. In France, 83% of individuals treated with bismuth-containing triple therapy were successfully eradicated [195].

It is recommended that after the failure of first-line therapy with bismuth quadruple and second-line therapy with quinolones, triple or quadruple therapy with quinolones be used [191]. In areas where clarithromycin resistance is high but metronidazole resistance is low or moderate, the triple therapy (which includes amoxicillin, metronidazole, and PPI) may be a useful alternative if metronidazole was not initially used as a treatment [196] . The third- and fourth-line therapy reports are detailed in Tables 1, 2, and 3. Quinolone-based treatment is one of the most prevalent third-line regimens. Levofloxacin has been frequently utilized as an *H. pylori* rescue medication [197-199]. However, the efficiency of levofloxacin-based therapy against gyrA mutation-positive bacteria is insufficient; approximately 40% eradication rates are seen [200]. As a result of using a sitafloxacin-containing treatment, up to 70% of gyrA mutation-positive strains were able to be eradicated successfully [201, 202]. A randomized trial demonstrated that the eradication rate of triple regimens including sitafloxacin was superior to that of triple regimens containing levofloxacin [203]. Therefore, currently, if available, sitafloxacin is the most effective fluoroquinolone. However, quinolone resistance is easily acquired, and some strains acquire double mutations in gyrA that confer a high level of resistance [204]. In contrast, it has been reported that rifabutin-containing medication is a third-line treatment [205]. Due to the rarity of rifabutin resistance, *H. pylori* strains resistant to numerous antibiotics can be defeated by rifabutin-containing therapy. However, Rifabutin-containing therapy should be used with caution due to side effects such as leukopenia and thrombocytopenia, as well as the occurrence of multi-resistant strains of *Mycobacterium tuberculosis* [206]. In terms of the duration of rifabutin-containing therapy, 10-day or longer therapy was superior to 7-day therapy [206, 207]. An eradication rate of 83.3% was reported for 10-day regimens containing rifabutin and 94.1% for 14-day regimens [207]. In terms of PPI dosage, rifabutin therapies with high dose PPI achieved more effective eradication than standard PPI dosage [208]. The presence of bismuth had an additional effect on the metabolism of rifabutin-containing regimens. Contrary to what most people believe, the use of high-dose PPI and amoxicillin as a third-line treatment regimen can be a useful alternative [209-211]. Rabeprazole (10 mg qid) and amoxicillin (500 mg qid) for 14 days were previously reported to have an eradication rate of 63.0% [209]. There is no significant difference between the eradication rates achieved with quinolone- or rifabutin-containing

therapies; however, there are fewer worries about some problems and the development of new drug resistance with high-dose PPI and amoxicillin combination therapy. Vonoprazan, a the first-of-its-kind potassium-competitive acid blocker with a potent effect on inhibiting stomach acid secretion, is highlighted. There was a clear improvement in the efficacy of the vonoprazan, amoxicillin, and clarithromycin triple regimen when compared with the standard lansoprazole, amoxicillin, and clarithromycin triple regimen (82.0 vs. 40.0%) for eradicating clarithromycin-resistant strains [192]. There are only limited reports of vonoprazan-containing regimens that exclusively use a triple therapy approach [212]. Therefore, it is recommended to consider alternative regimens that include vonoprazan, such as bismuth-quadruple therapy or concomitant therapy.

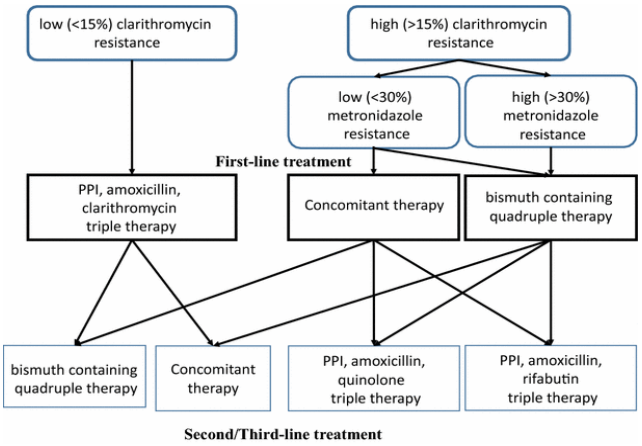

Fig.6 The Maastricht V/Florence Consensus Report-aligned treatment strategy for H. pylori infection is presented. [191].

IX. RECURRENCE OF INFECTION

Recrudescence and reinfection are thought to be the mechanisms behind the recurrence of *H. pylori*. Recrudescence is not a sign of successful eradication but rather the return of the original strain of *H. pylori* after a brief suppression. Instead, genuine reinfection happens when a patient contracts the original strain of *H. pylori* or a different strain after eradication is complete [213]. There has been evidence that late recurrence is responsible for the high recurrence rates during the first three to twelve months after cure. A verified absence of *H. pylori* for a year following therapy is a credible sign of eradication effectiveness without recrudescence. It appears that low-efficacy medication merely temporarily suppresses the *H. pylori* infection in the gastric mucosa rather than curing it or removing it entirely from the host [214, 215]. The recurrence of *H. Pylori* infection after successful eradication is one of the most challenging aspects of its management. Most recurring cases are presumably caused by recrudescence rather than reinfection because the frequency of recurrences declines over time, dropping off dramatically after the first year, and identified strains (before and after therapy) are typically genetically identical. In adults, reported "real" reinfection rates typically ranged from 0 to 23.4%. There were significantly lower annual "real" reinfection rates within the first year of eradication than reported annual recurrence rates within those first few years following eradication [213]. *H. pylori* reinfection may also be caused through intrafamilial transmission; the presence of this organism in asymptomatic family members may encourage transmission between households [216]. In developed countries like Europe and the USA, the rate of *H. pylori* reinfection following eradication medication is incredibly low. Zendehdel et al. reported an annual reinfection rate of approximately 1% [215] . Contrary to western populations, which have reported low rates of H pylori reinfection, developing countries have reported high rates of recurrence [217, 218]. Therefore, Due to the increased danger of re-exposure, it's possible that the high frequency of *H. pylori* infection is linked to a high rate of infection recurrence following eradication [12]. Genetic factors may also be at play; those who have successfully eradicated *H. pylori* may still be susceptible to reinfection when exposed to *H. pylori*-positive individuals [216]. There have been a number of publications written about the occupational risk of *H. pylori* infection. Matysiak-Budnik [219] demonstrated a link between work exposure and a higher risk of infection. Williams [220], too, said that endoscopic staff members have higher job risk.

X. CONCLUSION

H. pylori infection is a major public health concern with significant morbidity and mortality worldwide. In this comprehensive review, we have highlighted the current understanding of the transmission, diagnosis, and treatment of *H. pylori* infection. The risk factors and epidemiology of *H. pylori* infection

have been discussed, along with the clinical manifestations and pathogenesis of the infection. Diagnostic tests for detection of *H. pylori* infection have been described, along with the various treatment options available for *H. pylori* infection. Although significant progress has been made in our understanding of *H. pylori* infection, challenges remain, particularly in the areas of antibiotic resistance and the development of effective treatments. In addition, the role of *H. pylori* infection in the development of extra-gastric diseases, such as cardiovascular disease and diabetes, remains an active area of research. In conclusion, continued efforts are needed to improve the diagnosis, treatment, and prevention of *H. pylori* infection. These efforts will require collaboration among researchers, clinicians, public health officials, and policymakers. By working together, we can reduce the burden of *H. pylori* infection and its associated complications, and improve the health outcomes of individuals affected by this infection.

REFERENCES

[1] Kivi, M., *Aspects of Helicobacter pylori transmission*. 2005: Karolinska Institutet (Sweden).

[2] Marshall, B.J., et al., *Attempt to fulfil Koch's postulates for pyloric Campylobacter.* Medical Journal of Australia, 1985. **142**(8): p. 436-439.

[3] Hooi, J.K., et al., *Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis.* Gastroenterology, 2017. **153**(2): p. 420-429.

[4] Parsonnet, J., et al., *Helicobacter pylori infection and gastric lymphoma.* New England Journal of Medicine, 1994. **330**(18): p. 1267-1271.

[5] Fischbach, W., *Gastric mucosal-associated lymphoid tissue lymphoma.* Gastroenterology Clinics, 2013. **42**(2): p. 371-380.

[6] Backert, S. and M. Clyne, *Pathogenesis of Helicobacter pylori infection.* Helicobacter, 2011. **16**: p. 19-25.

[7] Marshall, B. and J.R. Warren, *Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration.* The lancet, 1984. **323**(8390): p. 1311-1315.

[8] Solnick, J.V. and D.B. Schauer, *Emergence of diverse Helicobacter species in the pathogenesis of gastric and enterohepatic diseases.* Clinical microbiology reviews, 2001. **14**(1): p. 59-97.

[9] Mladenova, I. and M. Durazzo, *Transmission of Helicobacter pylori.* Minerva gastroenterologica e dietologica, 2018. **64**(3): p. 251-254.

[10] Oona, M., et al., *Helicobacter pylori infection in children in Estonia: decreasing seroprevalence during the 11-year period of profound socioeconomic changes.* Helicobacter, 2004. **9**(3): p. 233-241.

[11] Bürgers, R., et al., *Helicobacter pylori in human oral cavity and stomach.* European journal of oral sciences, 2008. **116**(4): p. 297-304.

[12] Stefano, K., et al., *Helicobacter pylori, transmission routes and recurrence of infection: state of the art.* Acta Bio Medica: Atenei Parmensis, 2018. **89**(Suppl 8): p. 72.

[13] Song, Q., et al., *Helicobacter pylori in the Oral Cavity.* Digestive diseases and sciences, 2000. **45**(11): p. 2162-2167.

[14] Yee, J.K., *Are the view of Helicobacter pylori colonized in the oral cavity an illusion?* Experimental & Molecular Medicine, 2017. **49**(11): p. e397-e397.

[15] Gebara, E., et al., *Persistence of Helicobacter pylori in the oral cavity after systemic eradication therapy.* Journal of clinical periodontology, 2006. **33**(5): p. 329-333.

[16] Kivi, M.r., et al., *Concordance of Helicobacter pylori strains within families.* Journal of clinical microbiology, 2003. **41**(12): p. 5604-5608.

[17] Queralt, N., R. Bartolome, and R. Araujo, *Detection of Helicobacter pylori DNA in human faeces and water with different levels of faecal pollution in the north-east of Spain.* Journal of applied microbiology, 2005. **98**(4): p. 889-895.

[18] Bui, D., et al., *Serologic evidence for fecal–oral transmission of Helicobacter pylori.* The American journal of tropical medicine and hygiene, 2016. **94**(1): p. 82.

[19] Santiago, P., Y. Moreno, and M.A. Ferrús, *Identification of viable Helicobacter pylori in drinking water supplies by cultural and molecular techniques.* Helicobacter, 2015. **20**(4): p. 252-259.

[20] Adams, B., T. Bates, and J. Oliver, *Survival of Helicobacter pylori in a natural freshwater environment.* Applied and environmental microbiology, 2003. **69**(12): p. 7462-7466.

[21] Klein, P.D., et al., *Water source as risk factor for Helicobacter pylori infection in Peruvian children.* The Lancet, 1991. **337**(8756): p. 1503-1506.

[22] Salih, B.A., *Helicobacter pylori infection in developing countries: the burden for how long?* Saudi journal of gastroenterology: official journal of the Saudi Gastroenterology Association, 2009. **15**(3): p. 201.

[23] Goodman, K.J., et al., *Helicobacter pylori infection in the Colombian Andes: a population-based study of transmission pathways.* American journal of epidemiology, 1996. **144**(3): p. 290-299.

[24] ZHANG, Y.Y., et al., *'true're-infection of Helicobacter pylori after successful eradication–worldwide annual rates, risk factors and clinical implications.* Alimentary pharmacology & therapeutics, 2009. **29**(2): p. 145-160.

[25] Momtaz, H., et al., *Study of Helicobacter pylori genotype status in cows, sheep, goats and human beings.* BMC gastroenterology, 2014. **14**(1): p. 1-7.

[26] Payão, S.L.M. and L.T. Rasmussen, *Helicobacter pylori and its reservoirs: A correlation with the gastric infection.* World journal of gastrointestinal pharmacology and therapeutics, 2016. **7**(1): p. 126.

[27] Engstrand, L., et al., *Inoculation of barrier-born pigs with Helicobacter pylori: a useful animal model for gastritis type B.* Infection and Immunity, 1990. **58**(6): p. 1763-1768.

[28] Handt, L.K., et al., *Helicobacter pylori isolated from the domestic cat: public health implications.* Infection and immunity, 1994. **62**(6): p. 2367-2374.

[29] Rodrigues, M.N., et al., *Prevalence of Helicobacter pylori infection in children from an urban community in north-east Brazil and risk factors for infection.* European journal of gastroenterology & hepatology, 2004. **16**(2): p. 201-205.

[30] Glynn, M.K., et al., *Seroincidence of Helicobacter pylori infection in a cohort of rural Bolivian children: acquisition and analysis of possible risk factors.* Clinical Infectious Diseases, 2002. **35**(9): p. 1059-1065.

[31] Rothenbacher, D., et al., *Role of infected parents in transmission of Helicobacter pylori to their children.* The Pediatric infectious disease journal, 2002. **21**(7): p. 674-679.

[32] Rocha, G.A., et al., *Transmission of Helicobacter pylori infection in families of preschool-aged children from Minas Gerais, Brazil.* Tropical Medicine & International Health, 2003. **8**(11): p. 987-991.

[33] Malaty, H.M., et al., *Evidence from a nine-year birth cohort study in Japan of transmission pathways of Helicobacter pylori infection.* Journal of clinical microbiology, 2000. **38**(5): p. 1971-1973.

[34] Kivi, M., et al., *Helicobacter pylori status in family members as risk factors for infection in children.* Epidemiology & Infection, 2005. **133**(4): p. 645-652.

[35] Lambert, J.R., et al., *High Prevalence of Helicobacter pylori Antibodies in an Institutionalized Population: Evidence for Person--to--Person Transmission.* American Journal of Gastroenterology (Springer Nature), 1995. **90**(12).

[36] Tindberg, Y., et al., *Helicobacter pylori infection in Swedish school children: lack of evidence of child-to-child transmission outside the family.* Gastroenterology, 2001. **121**(2): p. 310-316.

[37] Tsai, C.J., et al., *Helicobacter pylori infection in different generations of Hispanics in the San Francisco Bay Area.* American journal of epidemiology, 2005. **162**(4): p. 351-357.

[38] Woodward, M., C. Morrison, and K. McColl, *An investigation into factors associated with Helicobacter pylori infection.* Journal of clinical epidemiology, 2000. **53**(2): p. 175-181.

[39] Brenner, H., et al., *Active infection with Helicobacter pylori in healthy couples.* Epidemiology & Infection, 1999. **122**(1): p. 91-95.

[40] Mendall, M., et al., *Childhood living conditions and Helicobacter pylori seropositivity in adult life.* The Lancet, 1992. **339**(8798): p. 896-897.

[41] Brown, L.M., et al., *Helicobacter pylori infection in rural China: demographic, lifestyle and environmental factors.* International journal of epidemiology, 2002. **31**(3): p. 638-645.

[42] Kuepper-Nybelen, J., et al., *Patterns of alcohol consumption and Helicobacter pylori infection: results of a population-based study from Germany among 6545 adults.* Alimentary pharmacology & therapeutics, 2005. **21**(1): p. 57-64.

[43] Salaün, L., S. Ayraud, and N.J. Saunders, *Phase variation mediated niche adaptation during prolonged experimental murine infection with Helicobacter pylori.* Microbiology, 2005. **151**(3): p. 917-923.

[44] Malaty, H.M., et al., *Age at acquisition of Helicobacter pylori infection: a follow-up study from infancy to adulthood.* The Lancet, 2002. **359**(9310): p. 931-935.

[45] Aspholm-Hurtig, M., et al., *Functional adaptation of BabA, the H. pylori ABO blood group antigen binding adhesin.* Science, 2004. **305**(5683): p. 519-522.

[46] Rothenbacher, D., et al., *Role of Lewis A and Lewis B blood group antigens in Helicobacter pylori infection.* Helicobacter, 2004. **9**(4): p. 324-329.

[47] Yamaoka, Y., et al., *Helicobacter pylori infection in mice: role of outer membrane proteins in colonization and inflammation.* Gastroenterology, 2002. **123**(6): p. 1992-2004.

[48] Magnusson, P.K., et al., *Gastric cancer and human leukocyte antigen: distinct DQ and DR alleles are associated with development of gastric cancer and infection by Helicobacter pylori.* Cancer research, 2001. **61**(6): p. 2684-2689.

[49] Hartland, S., et al., *A functional polymorphism in the interleukin-1 receptor-1 gene is associated with increased risk of Helicobacter pylori infection but not with gastric cancer.* Digestive diseases and sciences, 2004. **49**(9): p. 1545-1550.

[50] Björkholm, B., et al., *Gnotobiotic transgenic mice reveal that transmission of Helicobacter pylori is facilitated by loss of acid-producing parietal cells in donors and recipients.* Microbes and infection, 2004. **6**(2): p. 213-220.

[51] Salama, N.R., B. Shepherd, and S. Falkow, *Global transposon mutagenesis and essential gene analysis of Helicobacter pylori.* Journal of bacteriology, 2004. **186**(23): p. 7926-7935.

[52] Perez-Perez, G., et al., *Evidence that cagA+ Helicobacter pylori strains are disappearing more rapidly than cagA− strains.* Gut, 2002. **50**(3): p. 295-298.

[53] Nilsson, C., et al., *Correlation between cag pathogenicity island composition and Helicobacter pylori-associated gastroduodenal disease.* Infection and immunity, 2003. **71**(11): p. 6573-6581.

[54] Cardenas, V.M., et al., *Iron deficiency and Helicobacter pylori infection in the United States.* American journal of epidemiology, 2006. **163**(2): p. 127-134.

[55] Everhart, J.E., et al., *Seroprevalence and ethnic differences in Helicobacter pylori infection among adults in the United States.* The Journal of infectious diseases, 2000. **181**(4): p. 1359-1363.

[56] Goh, K.-L. and N. Parasakthi, *The racial cohort phenomenon: seroepidemiology of Helicobacter pylori infection in a multiracial South-East Asian country.* European journal of gastroenterology & hepatology, 2001. **13**(2): p. 177-183.

[57] Asaka, M., et al., *Gastric cancer.* Helicobacter pylori: physiology and genetics, 2001: p. 481-498.

[58] Yeh, J.M., et al., *Exploring the cost-effectiveness of Helicobacter pylori screening to prevent gastric cancer in China in anticipation of clinical trial results.* International journal of cancer, 2009. **124**(1): p. 157-166.

[59] Torres, J., et al., *A comprehensive review of the natural history of Helicobacter pylori infection in children.* Archives of medical research, 2000. **31**(5): p. 431-469.

[60] Agarwal, P.K., et al., *Prevalence of Helicobacter pylori infection in upper gastrointestinal tract disorders (dyspepsia) patients visiting outpatient department of a hospital of North India.* Journal of family medicine and primary care, 2018. **7**(3): p. 577.

[61] Lacy, B.E. and J. Rosemore, *Helicobacter pylori: ulcers and more: the beginning of an era.* The Journal of nutrition, 2001. **131**(10): p. 2789S-2793S.

[62] Gold, B.D., *Helicobacter pylori infection in children.* Current Problems in Pediatrics, 2001. **31**(8): p. 247-266.

[63] De Oliveira, A.M.R., et al., *Seroconversion for Helicobacter pylori in adults from Brazil.* Transactions of the Royal Society of Tropical Medicine and Hygiene, 1999. **93**(3): p. 261-263.

[64] Ernst, P.B. and B.D. Gold, *The disease spectrum of Helicobacter pylori: the immunopathogenesis of gastroduodenal ulcer and gastric cancer.* Annual review of microbiology, 2000. **54**: p. 615.

[65] Kuipers, E., *Exploring the link between Helicobacter pylori and gastric cancer.* Alimentary pharmacology & therapeutics, 1999. **13**: p. 3-11.

[66] Kuipers, E., J. Thijs, and H. Festen, *The prevalence of Helicobacter pylori in peptic ulcer disease.* Alimentary pharmacology & therapeutics, 1995. **9**: p. 59-69.

[67] Kusters, J.G., A.H. Van Vliet, and E.J. Kuipers, *Pathogenesis of Helicobacter pylori infection.* Clinical microbiology reviews, 2006. **19**(3): p. 449-490.

[68] Maaroos, H.-I., et al., *An 18-year follow-up study of chronic gastritis and Helicobacter pylori: association of CagA positivity with development of atrophy and activity of gastritis.* Scandinavian journal of gastroenterology, 1999. **34**(9): p. 864-869.

[69] Flores, S.E., et al., *Helicobacter pylori infection perturbs iron homeostasis in gastric epithelial cells.* PLoS One, 2017. **12**(9): p. e0184026.

[70] Kato, S., et al., *Helicobacter pylori sabA gene is associated with iron deficiency anemia in childhood and adolescence.* PloS one, 2017. **12**(8): p. e0184046.

[71] Rockey, D.C., et al., *AGA technical review on gastrointestinal evaluation of iron deficiency anemia.* Gastroenterology, 2020. **159**(3): p. 1097-1119.

[72] Sipponen, P., et al., *Prevalence of low vitamin B12 and high homocysteine in serum in an elderly male population: association with atrophic gastritis and Helicobacter pylori infection.* Scandinavian journal of gastroenterology, 2003. **38**(12): p. 1209-1216.

[73] Correa, P., M.B. Piazuelo, and M.C. Camargo, *The future of gastric cancer prevention.* Gastric cancer, 2004. **7**(1): p. 9-16.

[74] Uemura, N., et al., *Helicobacter pylori infection and the development of gastric cancer.* New England journal of medicine, 2001. **345**(11): p. 784-789.

[75] Blaser, M.J. and J.C. Atherton, *Helicobacter pylori persistence: biology and disease.* The Journal of clinical investigation, 2004. **113**(3): p. 321-333.

[76] Danesh, J., R. Collins, and R. Peto, *Chronic infections and coronary heart disease: is there a link?* The lancet, 1997. **350**(9075): p. 430-436.

[77] El-Omar, E.M., et al., *Interleukin-1 polymorphisms associated with increased risk of gastric cancer.* Nature, 2000. **404**(6776): p. 398-402.

[78] Eaton, K.A. and S. Krakowka, *Effect of gastric pH on urease-dependent colonization of gnotobiotic piglets by Helicobacter pylori.* Infection and immunity, 1994. **62**(9): p. 3604-3607.

[79] Sobala, G., et al., *Acute Helicobacter pylori infection: clinical features, local and systemic immune response, gastric mucosal histology, and gastric juice ascorbic acid concentrations.* Gut, 1991. **32**(11): p. 1415-1418.

[80] Kuipers, E.J., et al., *Increase of Helicobacter pylori--Associated Corpus Gastritis during Acid Suppressive Therapy: Implications for Long--Term Safety.* American Journal of Gastroenterology (Springer Nature), 1995. **90**(9).

[81] El-Omar, E.M., et al., *Helicobacter pylori infection and chronic gastric acid hyposecretion.* Gastroenterology, 1997. **113**(1): p. 15-24.

[82] Consensus, N., *Helicobacter pylori in peptic ulcer disease.* JAMA, 1994. **272**: p. 65-69.

[83] Suerbaum, S. and P. Michetti, *Helicobacter pylori infection.* New England Journal of Medicine, 2002. **347**(15): p. 1175-1186.

[84] Rothenbacher, D. and H. Brenner, *Burden of Helicobacter pylori and H. pylori-related diseases in developed countries: recent developments and future implications.* Microbes and Infection, 2003. **5**(8): p. 693-703.

[85] Pereira, M.-I. and J.A. Medeiros, *Role of Helicobacter pylori in gastric mucosa-associated lymphoid tissue lymphomas.* World journal of gastroenterology: WJG, 2014. **20**(3): p. 684.

[86] Zucca, E., et al., *Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Annals of Oncology, 2013. **24**: p. vi144-vi148.

[87] Malfertheiner, P., et al., *Management of Helicobacter pylori infection—the Maastricht IV/Florence consensus report.* Gut, 2012. **61**(5): p. 646-664.

[88] Floch, P., F. Mégraud, and P. Lehours, *Helicobacter pylori strains and gastric MALT lymphoma.* Toxins, 2017. **9**(4): p. 132.

[89] Cammarota, G., et al., *Helicobacter pylori reinfection and rapid relapse of low-grade B-cell gastric lymphoma.* The Lancet, 1995. **345**(8943): p. 192.

[90] Talley, N.J. and R.H. Hunt, *What role does Helicobacter pylori play in dyspepsia and nonulcer dyspepsia? Arguments for and against H. pylori being associated with dyspeptic symptoms.* Gastroenterology, 1997. **113**(6): p. S67-S77.

[91] Moayyedi, P., et al., *Eradication of Helicobacter pylori for non-ulcer dyspepsia.* Cochrane Database of Systematic Reviews, 2005(2).

[92] Öztekin, M., et al., *Overview of Helicobacter pylori Infection: Clinical Features, treatment, and nutritional aspects.* Diseases, 2021. **9**(4): p. 66.

[93] Wroblewski, L.E. and R.M. Peek, *Helicobacter pylori, cancer, and the gastric microbiota.* Stem Cells, Pre-neoplasia, and Early Cancer of the Upper Gastrointestinal Tract, 2016: p. 393-408.

[94] Eaton, K., D. Morgan, and S. Krakowka, *Motility as a factor in the colonisation of gnotobiotic piglets by Helicobacter pylori.* Journal of Medical Microbiology, 1992. **37**(2): p. 123-127.

[95] De Brito, B.B., et al., *Pathogenesis and clinical management of Helicobacter pylori gastric infection.* World journal of gastroenterology, 2019. **25**(37): p. 5578.

[96] Shibayama, K., et al., *Metabolism of glutamine and glutathione via γ-glutamyltranspeptidase and glutamate transport in Helicobacter pylori: possible significance in the pathophysiology of the organism.* Molecular microbiology, 2007. **64**(2): p. 396-406.

[97] Malfertheiner, P., M. Venerito, and C. Schulz, *Helicobacter pylori infection: new facts in clinical management.* Current treatment options in gastroenterology, 2018. **16**(4): p. 605-615.

[98] Abadi, A.T.B. and J.G. Kusters, *Management of Helicobacter pylori infections.* BMC gastroenterology, 2016. **16**(1): p. 1-4.

[99] Safavi, M., R. Sabourian, and A. Foroumadi, *Treatment of Helicobacter pylori infection: Current and future insights.* World journal of clinical cases, 2016. **4**(1): p. 5.

[100] Ayala, G., et al., *Exploring alternative treatments for Helicobacter pylori infection.* World journal of gastroenterology: WJG, 2014. **20**(6): p. 1450.

[101] Meyer-Rosberg, K., et al., *The effect of environmental pH on the proton motive force of Helicobacter pylori.* Gastroenterology, 1996. **111**(4): p. 886-900.

[102] Turbett, G.R., et al., *Purification and characterization of the urease enzymes of Helicobacter species from humans and animals.* Infection and immunity, 1992. **60**(12): p. 5259-5266.

[103] Ha, N.-C., et al., *Supramolecular assembly and acid resistance of Helicobacter pylori urease.* Nature structural biology, 2001. **8**(6): p. 505-509.

[104] Dunn, B.E., et al., *Purification and characterization of urease from Helicobacter pylori.* Journal of Biological Chemistry, 1990. **265**(16): p. 9464-9469.

[105] Clyne, M., A. Labigne, and B. Drumm, *Helicobacter pylori requires an acidic environment to survive in the presence of urea.* Infection and immunity, 1995. **63**(5): p. 1669-1673.

[106] Jones, M.D., Y. Li, and D.B. Zamble, *Acid-responsive activity of the Helicobacter pylori metalloregulator NikR.* Proceedings of the National Academy of Sciences, 2018. **115**(36): p. 8966-8971.

[107] Wen, G., et al., *Helicobacter pylori infection downregulates duodenal CFTR and SLC26A6 expressions through TGFβ signaling pathway.* BMC microbiology, 2018. **18**(1): p. 1-11.

[108] Hathroubi, S., J. Zerebinski, and K.M. Ottemann, *Helicobacter pylori biofilm involves a multigene stress-biased response, including a structural role for flagella.* MBio, 2018. **9**(5): p. e01973-18.

[109] Dunne, C., B. Dolan, and M. Clyne, *Factors that mediate colonization of the human stomach by Helicobacter pylori.* World journal of gastroenterology, 2014. **20**(19): p. 5610-5624.

[110] Chmiela, M., N. Walczak, and K. Rudnicka, *Helicobacter pylori outer membrane vesicles involvement in the infection development and Helicobacter pylori-related diseases.* Journal of biomedical science, 2018. **25**(1): p. 1-11.

[111] Ronci, M., et al., *Identification and characterization of the a-CA in the outer membrane vesicles produced by*

Helicobacter pylori. Journal of enzyme inhibition and medicinal chemistry, 2019. **34**(1): p. 189-195.

[112] Turner, L., et al., *Helicobacter pylori outer membrane vesicle size determines their mechanisms of host cell entry and protein content.* Frontiers in immunology, 2018. **9**: p. 1466.

[113] Tsutsumi, R., et al., *Attenuation of Helicobacter pylori CagA · SHP-2 signaling by interaction between CagA and C-terminal Src kinase.* Journal of Biological Chemistry, 2003. **278**(6): p. 3664-3670.

[114] Fischer, W., *Assembly and molecular mode of action of the Helicobacter pylori Cag type IV secretion apparatus.* The FEBS journal, 2011. **278**(8): p. 1203-1212.

[115] Suarez, G., et al., *Genetic Manipulation of Helicobacter pylori Virulence Function by Host Carcinogenic PhenotypesH. pylori, Gastric Cancer, CagY.* Cancer research, 2017. **77**(9): p. 2401-2412.

[116] Kanada, R., et al., *Genotyping of the cagA gene of Helicobacter pylori on immunohistochemistry with East Asian CagA-specific antibody.* Pathology International, 2008. **58**(4): p. 218-225.

[117] Yamaoka, Y., et al., *Molecular epidemiology of Helicobacter pylori: separation of H. pylori from East Asian and non-Asian countries.* Epidemiology & Infection, 2000. **124**(1): p. 91-96.

[118] Basso, D., et al., *Clinical relevance of Helicobacter pylori cagA and vacA gene polymorphisms.* Gastroenterology, 2008. **135**(1): p. 91-99.

[119] Queiroz, D.M., et al., *Higher frequency of cagA EPIYA-C phosphorylation sites in H. pylori strains from first-degree relatives of gastric cancer patients.* BMC gastroenterology, 2012. **12**(1): p. 1-7.

[120] Higashi, H., et al., *SHP-2 tyrosine phosphatase as an intracellular target of Helicobacter pylori CagA protein.* Science, 2002. **295**(5555): p. 683-686.

[121] Atherton, J., et al., *Clinical and pathological importance of heterogeneity in vacA, the vacuolating cytotoxin gene of Helicobacter pylori.* Gastroenterology, 1997. **112**(1): p. 92-99.

[122] Djekic, A. and A. Müller, *The immunomodulator VacA promotes immune tolerance and persistent Helicobacter pylori infection through its activities on T-cells and antigen-presenting cells.* Toxins, 2016. **8**(6): p. 187.

[123] Boquet, P. and V. Ricci, *Intoxication strategy of Helicobacter pylori VacA toxin.* Trends in microbiology, 2012. **20**(4): p. 165-174.

[124] Lu, H., et al., *Duodenal ulcer promoting gene of Helicobacter pylori.* Gastroenterology, 2005. **128**(4): p. 833-848.

[125] Yamaoka, Y., *Roles of the plasticity regions of Helicobacter pylori in gastroduodenal pathogenesis.* Journal of medical microbiology, 2008. **57**(Pt 5): p. 545.

[126] Queiroz, D.M., et al., *dupA polymorphisms and risk of Helicobacter pylori-associated diseases.* International Journal of Medical Microbiology, 2011. **301**(3): p. 225-228.

[127] Yamaoka, Y., D.H. Kwon, and D.Y. Graham, *AM r 34,000 proinflammatory outer membrane protein (oipA) of Helicobacter pylori.* Proceedings of the National Academy of Sciences, 2000. **97**(13): p. 7533-7538.

[128] Sallas, M.L., et al., *Status (on/off) of oipA gene: Their associations with gastritis and gastric cancer and geographic origins.* Archives of microbiology, 2019. **201**(1): p. 93-97.

[129] Franco, A.T., et al., *Regulation of gastric carcinogenesis by Helicobacter pylori virulence factors.* Cancer research, 2008. **68**(2): p. 379-387.

[130] Kim, K.-M., et al., *Helicobacter pylori γ-glutamyltranspeptidase induces cell cycle arrest at the G1-S phase transition.* The Journal of Microbiology, 2010. **48**(3): p. 372-377.

[131] Oertli, M., et al., *Helicobacter pylori γ-glutamyl transpeptidase and vacuolating cytotoxin promote gastric persistence and immune tolerance.* Proceedings of the National Academy of Sciences, 2013. **110**(8): p. 3047-3052.

[132] Gong, M., et al., *Helicobacter pylori γ-glutamyl transpeptidase is a pathogenic factor in the development of peptic ulcer disease.* Gastroenterology, 2010. **139**(2): p. 564-573.

[133] Crabtree, J., et al., *Immune responses to Helicobacter pylori in children with recurrent abdominal pain.* Journal of clinical pathology, 1991. **44**(9): p. 768-771.

[134] Smith, S.M., *Role of Toll-like receptors in Helicobacter pylori infection and immunity.* World journal of gastrointestinal pathophysiology, 2014. **5**(3): p. 133.

[135] Smith, M.F., et al., *Toll-like receptor (TLR) 2 and TLR5, but not TLR4, are required for Helicobacter pylori-induced NF-κB activation and chemokine expression by epithelial cells.* Journal of Biological Chemistry, 2003. **278**(35): p. 32552-32560.

[136] Alandiyjany, M.N., et al., *A role for the tfs3 ICE-encoded type IV secretion system in pro-inflammatory signalling by the Helicobacter pylori Ser/Thr kinase, CtkA.* PLoS One, 2017. **12**(7): p. e0182144.

[137] Wilson, K.T., et al., *Helicobacter pylori stimulates inducible nitric oxide synthase expression and activity in a murine macrophage cell line.* Gastroenterology, 1996. **111**(6): p. 1524-1533.

[138] Lundgren, A., et al., *Helicobacter pylori-specific CD4+ CD25high regulatory T cells suppress memory T-cell responses to H. pylori in infected individuals.* Infection and immunity, 2003. **71**(4): p. 1755-1762.

[139] Crabtree, J., et al., *Mucosal tumour necrosis factor alpha and interleukin-6 in patients with Helicobacter pylori associated gastritis.* Gut, 1991. **32**(12): p. 1473-1477.

[140] De Melo, F.F., et al., *A regulatory instead of an IL-17 T response predominates in Helicobacter pylori-associated gastritis in children.* Microbes and Infection, 2012. **14**(4): p. 341-347.

[141] Nurgalieva, Z.Z., et al., *B-cell and T-cell immune responses to experimental Helicobacter pylori infection in humans.* Infection and immunity, 2005. **73**(5): p. 2999-3006.

[142] El-Serag, H.B., et al., *Houston consensus conference on testing for Helicobacter pylori infection in the United States.* Clinical Gastroenterology and Hepatology, 2018. **16**(7): p. 992-1002. e6.

[143] Dore, M.P., et al., *Dyspepsia: when and how to test for Helicobacter pylori infection.* Gastroenterology research and practice, 2016. **2016**.

[144] Wang, Y.-K., et al., *Diagnosis of Helicobacter pylori infection: Current options and developments.* World Journal of Gastroenterology: WJG, 2015. **21**(40): p. 11221.

[145] Pichon, M., et al., *Diagnostic accuracy of a noninvasive test for detection of Helicobacter pylori and resistance to clarithromycin in stool by the Amplidiag H. pylori+ ClariR real-time PCR assay.* Journal of clinical microbiology, 2020. **58**(4): p. e01787-19.

[146] Ferwana, M., et al., *Accuracy of urea breath test in Helicobacter pylori infection: meta-analysis.* World journal of gastroenterology: WJG, 2015. **21**(4): p. 1305.

[147] Mezmale, L., et al., *Epidemiology of Helicobacter pylori.* Helicobacter, 2020. **25**: p. e12734.

[148] Leal, Y.A., et al., *13C-urea breath test for the diagnosis of Helicobacter pylori infection in children: a systematic review and meta-analysis.* Helicobacter, 2011. **16**(4): p. 327-337.

[149] Peng, N.-J., et al., *Clinical significance of oral urease in diagnosis of Helicobacter pylori infection by [13C] urea breath test.* Digestive diseases and sciences, 2001. **46**(8): p. 1772-1778.

[150] Ricci, C., J. Holton, and D. Vaira, *Diagnosis of Helicobacter pylori: invasive and non-invasive tests.* Best Practice & Research Clinical Gastroenterology, 2007. **21**(2): p. 299-313.

[151] Bordin, D.S., et al., *Current Helicobacter pylori diagnostics.* Diagnostics, 2021. **11**(8): p. 1458.

[152] Dore, M.P., et al., *Characterization of a culture method to recover Helicobacter pylori from the feces of infected patients.* Helicobacter, 2000. **5**(3): p. 165-168.

[153] Gisbert, J.P., F. De La Morena, and V. Abraira, *Accuracy of monoclonal stool antigen test for the diagnosis of H. pylori infection: a systematic review and meta-analysis.* Official journal of the American College of Gastroenterology | ACG, 2006. **101**(8): p. 1921-1930.

[154] Guarner, J., et al., *Helicobacter pylori diagnostic tests in children: review of the literature from 1999 to 2009.* European journal of pediatrics, 2010. **169**(1): p. 15-25.

[155] Dore, M.P. and G.M. Pes, *What is new in Helicobacter pylori diagnosis. An overview.* Journal of Clinical Medicine, 2021. **10**(10): p. 2091.

[156] Best, L.M., et al., *Non-invasive diagnostic tests for Helicobacter pylori infection.* Cochrane Database of Systematic Reviews, 2018(3).

[157] Malfertheiner, P., et al., *European helicobacter and microbiota study group and consensus panel. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report.* Gut, 2017. **66**(1): p. 6-30.

[158] Okubo, M., et al., *Changes in gastric mucosal patterns seen by magnifying NBI during H. pylori eradication.* Journal of gastroenterology, 2011. **46**(2): p. 175-182.

[159] Stefano, K., et al., *Non-invasive tests for the diagnosis of helicobacter pylori: state of the art.* Acta Bio Medica: Atenei Parmensis, 2018. **89**(Suppl 8): p. 58.

[160] Tu, H., et al., *Serum anti-Helicobacter pylori immunoglobulin G titer correlates with grade of histological gastritis, mucosal bacterial density, and levels of serum biomarkers.* Scandinavian journal of gastroenterology, 2014. **49**(3): p. 259-266.

[161] Dixon, M.F., et al., *Classification and grading of gastritis: the updated Sydney system.* The American journal of surgical pathology, 1996. **20**(10): p. 1161-1181.

[162] Varbanova, M., et al., *Impact of the angulus biopsy for the detection of gastric preneoplastic conditions and gastric cancer risk assessment.* Journal of clinical pathology, 2016. **69**(1): p. 19-25.

[163] Graham, D., et al., *Early events in proton pump inhibitor-associated exacerbation of corpus gastritis.* Alimentary pharmacology & therapeutics, 2003. **17**(2): p. 193-200.

[164] Glickman, J.N., et al., *Helicobacter infections with rare bacteria or minimal gastritis: expecting the unexpected.* Digestive and Liver Disease, 2015. **47**(7): p. 549-555.

[165] Snead, D.R., et al., *Validation of digital pathology imaging for primary histopathological diagnosis.* Histopathology, 2016. **68**(7): p. 1063-1072.

[166] Benoit, A., N. Hoyeau, and J.-F. Fléjou. *Diagnosis of Helicobacter pylori infection on gastric biopsies: Standard stain, special stain or immunohistochemistry?* in *Annales de Pathologie*. 2018.

[167] Godbole, G., F. Mégraud, and E. Bessède, *Diagnosis of Helicobacter pylori infection.* Helicobacter, 2020. **25**: p. e12735.

[168] Seo, J.-H., et al., *Limitations of urease test in diagnosis of pediatric Helicobacter pylori infection.* World Journal of Clinical Pediatrics, 2015. **4**(4): p. 143.

[169] Cho, J.-H., et al., *Factors for improving the diagnostic efficiency of the rapid urease test from the gastric corpus.* Scandinavian Journal of Gastroenterology, 2017. **52**(12): p. 1320-1325.

[170] Parihar, V., et al., *A combined antral and corpus rapid urease testing protocol can increase diagnostic accuracy*

despite a low prevalence of Helicobacter pylori infection in patients undergoing routine gastroscopy. United European Gastroenterology Journal, 2015. **3**(5): p. 432-436.

[171] Dechant, F.-X., et al., *Accuracy of different rapid urease tests in comparison with histopathology in patients with endoscopic signs of gastritis.* Digestion, 2020. **101**(2): p. 184-190.

[172] Kuhns, L.G., et al., *Carbon fixation driven by molecular hydrogen results in chemolithoautotrophically enhanced growth of Helicobacter pylori.* Journal of Bacteriology, 2016. **198**(9): p. 1423-1428.

[173] Pohl, D., et al., *Review of current diagnostic methods and advances in Helicobacter pylori diagnostics in the era of next generation sequencing.* World journal of gastroenterology, 2019. **25**(32): p. 4629.

[174] Omori, T., et al., *Correlation between magnifying narrow band imaging and histopathology in gastric protruding/or polypoid lesions: a pilot feasibility trial.* BMC gastroenterology, 2012. **12**(1): p. 1-7.

[175] Shukla, R., et al., *Endoscopic imaging: How far are we from real-time histology?* World Journal of Gastrointestinal Endoscopy, 2011. **3**(10): p. 183.

[176] Alaboudy, A.A., et al., *Conventional narrow-band imaging has good correlation with histopathological severity of Helicobacter pylori gastritis.* Digestive diseases and sciences, 2011. **56**(4): p. 1127-1130.

[177] Kawamura, M., et al., *Topographic differences in gastric micromucosal patterns observed by magnifying endoscopy with narrow band imaging.* Journal of gastroenterology and hepatology, 2011. **26**(3): p. 477-483.

[178] Ji, R., et al., *Mucosal barrier defects in gastric intestinal metaplasia: in vivo evaluation by confocal endomicroscopy.* Gastrointestinal endoscopy, 2012. **75**(5): p. 980-987.

[179] Neumann, H., et al., *in vivo imaging by endocytoscopy.* Alimentary pharmacology & therapeutics, 2011. **33**(11): p. 1183-1193.

[180] Zhang, J.-G. and H.-F. Liu, *Functional imaging and endoscopy.* World journal of gastroenterology: WJG, 2011. **17**(38): p. 4277.

[181] Kalach, N., et al., *Usefulness of gastric biopsy–based real-time polymerase chain reaction for the diagnosis of Helicobacter pylori infection in children.* Journal of Pediatric Gastroenterology and Nutrition, 2015. **61**(3): p. 307-312.

[182] Ogaya, Y., et al., *Detection of Helicobacter pylori DNA in inflamed dental pulp specimens from Japanese children and adolescents.* Journal of medical microbiology, 2015. **64**(1): p. 117-123.

[183] Ismail, H., et al., *A newly developed nested PCR assay for the detection of Helicobacter pylori in the oral cavity.* Journal of clinical gastroenterology, 2016. **50**(1): p. 17-22.

[184] Zhou, L., et al., *A creative Helicobacter pylori diagnosis scheme based on multiple genetic analysis system: qualification and quantitation.* Helicobacter, 2015. **20**(5): p. 343-352.

[185] Rabelo-Goncalves, E., et al., *Evaluation of five DNA extraction methods for detection of H. pylori in formalin-fixed paraffin-embedded (FFPE) liver tissue from patients with hepatocellular carcinoma.* Pathology-Research and Practice, 2014. **210**(3): p. 142-146.

[186] Kim, J., et al., *An appropriate cutoff value for determining the colonization of Helicobacter pylori by the pyrosequencing method: comparison with conventional methods.* Helicobacter, 2015. **20**(5): p. 370-380.

[187] Matsui, H., et al., *Development of New PCR Primers by Comparative Genomics for the Detection of H elicobacter suis in Gastric Biopsy Specimens.* Helicobacter, 2014. **19**(4): p. 260-271.

[188] Fowsantear, W., et al., *Comparative proteomics of Helicobacter species: the discrimination of gastric and enterohepatic Helicobacter species.* Journal of Proteomics, 2014. **97**: p. 245-255.

[189] Trespalacios, A.A., et al., *Improved allele-specific PCR assays for detection of clarithromycin and fluoroquinolone resistant of Helicobacter pylori in gastric biopsies: identification of N87I mutation in GyrA.* Diagnostic microbiology and infectious disease, 2015. **81**(4): p. 251-255.

[190] Lee, J.W., et al., *GenoType HelicoDR test in the determination of antimicrobial resistance of Helicobacter pylori in Korea.* Scandinavian journal of gastroenterology, 2014. **49**(9): p. 1058-1067.

[191] Malfertheiner, P., et al., *Management of Helicobacter pylori infection—the Maastricht V/Florence consensus report.* Gut, 2017. **66**(1): p. 6-30.

[192] Murakami, K., et al., *Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for Helicobacter pylori eradication: a phase III, randomised, double-blind study.* Gut, 2016. **65**(9): p. 1439-1446.

[193] Molina-Infante, J. and J.P. Gisbert, *Optimizing clarithromycin-containing therapy for Helicobacter pylori in the era of antibiotic resistance.* World Journal of Gastroenterology: WJG, 2014. **20**(30): p. 10338.

[194] Wang, L., et al., *Ten-day bismuth-containing quadruple therapy is effective as first-line therapy for Helicobacter pylori–related chronic gastritis: a prospective randomized study in China.* Clinical Microbiology and Infection, 2017. **23**(6): p. 391-395.

[195] Muller, N., et al., *Rescue therapy with bismuth-containing quadruple therapy in patients infected with metronidazole-resistant Helicobacter pylori strains.* Clinics and research in hepatology and gastroenterology, 2016. **40**(4): p. 517-524.

[196] Nishizawa, T., et al., *Clarithromycin versus metronidazole as first-line helicobacter pylori eradication.* Journal of clinical gastroenterology, 2015. **49**(6): p. 468-471.

[197] Zullo, A., et al., *Prevalence of lesions detected at upper endoscopy: an Italian survey.* European Journal of Internal Medicine, 2014. **25**(8): p. 772-776.

[198] Gisbert, J., et al., *Third-line rescue therapy with levofloxacin is more effective than rifabutin rescue regimen after two Helicobacter pylori treatment failures.* Alimentary pharmacology & therapeutics, 2006. **24**(10): p. 1469-1474.

[199] Paoluzi, O.A., et al., *Low efficacy of levofloxacin-doxycycline-based third-line triple therapy for Helicobacter pylori eradication in Italy.* World Journal of Gastroenterology: WJG, 2015. **21**(21): p. 6698.

[200] Liou, J.-M., et al., *Genotypic resistance in Helicobacter pylori strains correlates with susceptibility test and treatment outcomes after levofloxacin-and clarithromycin-based therapies.* Antimicrobial Agents and Chemotherapy, 2011. **55**(3): p. 1123-1129.

[201] Matsuzaki, J., et al., *Efficacy of sitafloxacin-based rescue therapy for Helicobacter pylori after failures of first-and second-line therapies.* Antimicrobial agents and chemotherapy, 2012. **56**(3): p. 1643-1645.

[202] Mori, H., et al., *Efficacy of 10-day sitafloxacin-containing third-line rescue therapies for Helicobacter pylori strains containing the gyrA mutation.* Helicobacter, 2016. **21**(4): p. 286-294.

[203] Murakami, K., et al., *Multi-center randomized controlled study to establish the standard third-line regimen for Helicobacter pylori eradication in Japan.* Journal of Gastroenterology, 2013. **48**(10): p. 1128-1135.

[204] Mori, H., et al., *Acquisition of double mutation in gyrA caused high resistance to sitafloxacin in Helicobacter pylori after unsuccessful eradication with sitafloxacin-containing regimens.* United European gastroenterology journal, 2018. **6**(3): p. 391-397.

[205] Ciccaglione, A.F., et al., *Rifabutin containing triple therapy and rifabutin with bismuth containing quadruple therapy for third-line treatment of Helicobacter pylori infection: two pilot studies.* Helicobacter, 2016. **21**(5): p. 375-381.

[206] Gisbert, J. and X. Calvet, *rifabutin in the treatment of refractory Helicobacter pylori infection.* Alimentary pharmacology & therapeutics, 2012. **35**(2): p. 209-221.

[207] Mori, H., et al., *Rifabutin-based 10-day and 14-day triple therapy as a third-line and fourth-line regimen for Helicobacter pylori eradication: a pilot study.* United European gastroenterology journal, 2016. **4**(3): p. 380-387.

[208] Lim, H.C., et al., *Rifabutin-based high-dose proton-pump inhibitor and amoxicillin triple regimen as the rescue treatment for Helicobacter pylori.* Helicobacter, 2014. **19**(6): p. 455-461.

[209] Nishizawa, T., et al., *Dual therapy for third-line Helicobacter pylori eradication and urea breath test prediction.* World Journal of Gastroenterology: WJG, 2012. **18**(21): p. 2735.

[210] Miehlke, S., et al., *Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin.* Alimentary pharmacology & therapeutics, 2006. **24**(2): p. 395-403.

[211] Okimoto, K., et al., *Efficacy of levofloxacin based triple and high-dose PPI-amoxicillin dual eradication therapy for Helicobacter pylori after failures of first-and second-line therapies.* International Scholarly Research Notices, 2014. **2014**.

[212] Nishizawa, T., et al., *Effects of patient age and choice of antisecretory agent on success of eradication therapy for Helicobacter pylori infection.* Journal of Clinical Biochemistry and Nutrition, 2017. **60**(3): p. 208-210.

[213] Sachs, G. and D.R. Scott, *Helicobacter pylori: eradication or preservation.* F1000 medicine reports, 2012. **4**.

[214] Adachi, M., et al., *Reinfection rate following effective therapy against Helicobacter pylori infection in Japan.* Journal of gastroenterology and hepatology, 2002. **17**(1): p. 27-31.

[215] Zendehdel, N., et al., *Helicobacter pylori reinfection rate 3 years after successful eradication.* Journal of gastroenterology and Hepatology, 2005. **20**(3): p. 401-404.

[216] Ryu, K.H., et al., *Reinfection rate and endoscopic changes after successful eradication of Helicobacter pylori.* World journal of gastroenterology: WJG, 2010. **16**(2): p. 251.

[217] Wheeldon, T.U., et al., *Long-term follow-up of Helicobacter pylori eradication therapy in Vietnam: reinfection and clinical outcome.* Alimentary pharmacology & therapeutics, 2005. **21**(8): p. 1047-1053.

[218] Seo, M., et al., *Recurrence of Helicobacter pylori infection and the long-term outcome of peptic ulcer after successful eradication in Japan.* Journal of clinical gastroenterology, 2002. **34**(2): p. 129-134.

[219] Matysiak-Budnik, T. and F. Megraud, *Epidemiology of Helicobacter pylori infection with special reference to professional risk.* Journal of physiology and pharmacology: an official journal of the Polish Physiological Society, 1997. **48**: p. 3-17.

[220] Williams, C., *Helicobacter pylori and endoscopy.* Journal of Hospital Infection, 1999. **41**(4): p. 263-268.