Chapter

Helicobacter pylori Gastric Infection: Pathogenesis and Clinical Management

Neha Bisht and Amar P. Garg

Abstract

Helicobacter pylori (H. pylori) is a Gram-negative bacterium that infects approximately 50% of the world population, and currently, no treatment is satisfactory for its management. Understanding the pathophysiology and pathogenesis mechanisms of *H. pylori* has increased over the years. Proper adherence and colonization of *H. pylori* induce genetic alterations, express numerous virulence factors, and trigger diverse adaptive mechanisms, making possible the colonization of an organ with a highly acidic lumen. The mode for the transmission of infection can be oral-oral or fecal-oral. Various effector proteins or toxins are released by the organism for successful colonization and infection. For the virulence and pathogenicity of *H. pylori*, the virulence factors, host, and environmental factors interplay a very important role. Virulence factors for *H. pylori* enhanced the pathogenicity of cytotoxin-associated antigen A, vacuolating cytotoxin, duodenal ulcer promoting gene A protein, outer inflammatory proteins, and gamma-glutamyl transpeptidase. The host immune system through Th1-polarized response plays a crucial role in the course of infection. The most common symptoms in *H. pylori*-positive individuals are peptic ulcers, gastric adenocarcinomas, and mucosa-associated lymphoid tissue lymphomas, whereas some positive individuals remain asymptomatic. Detection of *H. pylori* infection can be through invasive and noninvasive diagnostic methods. We critically reflect on the infection of *H. pylori* and the virulence and pathogenesis mechanisms of *H. pylori.*

Keywords: pathogenesis, virulence factor, colonization, transmission, diagnosis

1. Introduction

Helicobacter pylori (*H. pylori*) is a gram-negative, motile, helical, and microaerophilic (5% O_2, 15% CO_2 & 80% N, required low concentration of O_2 than in the atmosphere) microorganism that is considered as one of the most successful pathogens due to its persistent infection in the human stomach, that inhabits the gastric environment of more than half of the world population of 4.4 billion people worldwide [1–3]. Various shreds of evidence suggest that *H. pylori* are the etiological

agent of both extra-gastric and gastric diseases (gastric malignancy, peptic ulcer, chronic gastritis) [4–6]. The main reason for the occurrence of infection among the members of the same family (parents and children) is the route of transmission of *H. pylori* through oral–oral transmission. In this way, during feeding sharing utensils seems to be important for the establishment of infection [7]. Another route for the transmission of infection is fecal-oral, due to the ingestion of contaminated water and unsatisfactory basic sanitation conditions [8]. Improvement of living conditions and socioeconomic status are the two factors that greatly influence the reduction in *H. pylori* infection [9]. It was believed that the gastric environment was sterile because of its high acidity until the discovery of *H. pylori* infection from gastric mucosa by Warren and Marshall's [10, 11]. The bacteria use various mechanisms that provide mobility improvement, robust adherence to epithelial cells, and an enzymatic apparatus that allows the establishment of an appropriate microenvironment for the perpetuation of infection [12–15]. Certain virulence factors are responsible for the potential pathogenicity of infection such as vacuolating cytotoxin (VacA), cytotoxin-associated antigen A (CagA), duodenal ulcer promoting gene A protein (DupA), outer inflammatory protein (OipA) and gamma-glutamyl transpeptidase (GGT) and genetic substrates of the host [*e.g.*, IL1B gene cluster and tumor necrosis factor-α (TNFα) gene polymorphism] play an important role [16–20] shown in **Figure 1**. During the course of infection host immune system play a very pivotal role shown in **Figure 1**. Flagella-mediated motility is used by *H. pylori* for movement toward the epithelial cells of stomachs and penetrating the mucus lining [21]. With all the suitable conditions, organism crosses the acidic environment. At the mucus layer, the coccoid form enabled its colonization [22, 23]. Attachment to the host epithelial cells is through the production of an adhesin [21, 24]. So far colonization of *H. pylori* could be negatively and positively associated with the induction and progression of several diseases [23, 25, 26]. It has been reported to be linked to gastric and duodenal ulcers, gastric carcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [6, 27, 28]. Several other studies are also directing a positive correlation between gastrointestinal diseases and *H. pylori*. Many research shows a positive association between *H. pylori*, duodenal ulcer and gastric ulcer [29], gastritis [30], and esophageal cancer [31]. Moreover, evidence shows a positive

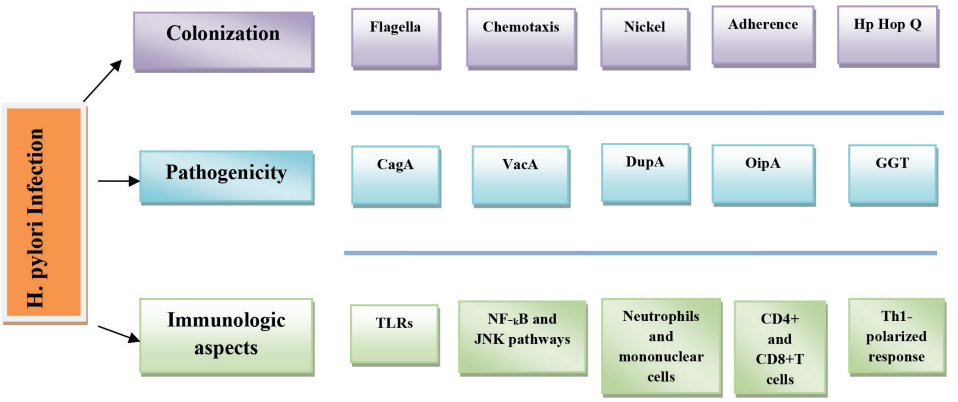

Figure 1.
Representation of characteristics of H. pylori *infection.*

association between *H. pylori* and non-gastrointestinal diseases such as diabetes mellitus [32], coronary artery disease [33], and anemia [34].

2. Clinical manifestations and diagnosis

The discovery of *H. pylori* in the early 1980s caused peptic ulcer diseases [35]. By International Agency for Research on Cancer in 1994 H. pylori was first classified as a carcinogen [36]. In 2001, an epidemiological study stated that patients with H. pylori were nearly six times more potent to develop gastric cancer compared with uninfected people [36]. In 2015, a community of gastroenterologists meticulously recognized *H. pylori* gastritis as an infectious disease and recommended its eradication [37]. This recommendation has repeatedly been confirmed by more recent consensus statements [35, 38, 39]. The most recent consensus conferences on the proactive testing and eradication of *H. pylori* infection [35, 38, 39]. Patients with uninvestigated dyspepsia, having a history of past or current gastric or duodenal ulcer, with a diagnosis of gastric mucosa-associated lymphoid tissue lymphoma, having a family history with peptic ulcer or gastric cancer, and a person with constant use of non-steroidal anti-inflammatory drugs should be recommended for *H. pylori* testing [35, 38]. The strengths and weaknesses of endoscopic and noninvasive tests are shown in **Table 1**.

First-generation immigrants from high-prevalence countries and potential high-risk populations were targeted for testing. Once the presence of the infection has been diagnosed and documented outreach to family members is suggested because transmission from person to person occurs within families [40]. Testing and treating of *H. pylori*-infected individuals can protect other members from infection as well as re-infection from its related diseases [41]. This approach may engage those who test positive to concur with the eradication treatment [41, 42]. To detect *H. pylori* infection a wide variety of methods is available [43]. Because the organism is trophic for gastric epithelium, *H. pylori* are primarily found in the stomach which causes an acute-on-chronic inflammation [44]. Using special stains, organisms can be detected the most accurate and popularly used is immunohistochemistry with *H. pylori*-specific antibodies [45, 46]. Wide range of other tests such as serologic tests for anti–*H. pylori* IgG antibodies and by using molecular testing such as next-generation sequencing [47]. Other tests are noninvasive while some require endoscopy to sample gastric contents, amongst them noninvasive testing is more preferred [48, 49].

The diagnostic strategy utilized clinical indication as well as the local availability and costs of the different tests followed by patient preferences [35]. The presence of the infection gives rise to a serum immune response. Recently, the most commonly used diagnostic test was serology [38]. By Medicare serology is generally neither recommended currently. Tests for the detection of *H. pylori* infection are shown in **Table 1**. IgA and IgM anti–*H. pylori* tests available in some laboratories are not recommended or trusted because of their low specificity and sensitivity generally not approved by the US Food and Drug Administration (FDA). Another important diagnostic method for *H. pylori* is the rapid urease test (RUT). RUT detects an increase in pH of the reagent after the addition of a biopsy specimen that contains *H. pylori* to the reagent [35, 38]. The sort of pH variation is caused by the transformation of the urea test reagent into ammonia. As compared to other tests, RUT is quick, cheap, easy, and specific and is a widely available test [50]. The urea

Tests	Mechanism	Strengths	Weaknesses
Endoscopic			
Culture	Can be kept in a transport medium, like Portagerm pylori or Stuart's transport medium up to 24 h at 4°C. The commonly used media include Pylori agar, Skirrow agar, Columbia blood agar, Brucella agar, Brain heart infusion or Trypticase soy agar, supplemented with sheep or horse blood.	Allows testing of antibiotic susceptibilities	Poor availability in some countries
Molecular-based	Several target genes like UreA, glmM, UreC, 16S rRNA, 23S rRNA, HSP60, and VacA genes detected for the detection of *H. pylori*	Detects infection and can assess susceptibility/ resistance for all six commonly used antibiotics. Stool can be used. It gives Rapid results (days)	not to be covered by insurance
Histology	Accuracy of histology, such as the site, size and number of biopsies, the staining methods, proton pump inhibitor (PPI), antibiotics of the examining pathologist.	Can be used for the testing of infection and evaluate for eradication. Provides additional information such as degree of inflammation and associated pathology	Accurate results require interested pathologist and use of special stain, preferably immunohistochemical
Rapid urease	Convert the urea test reagent to ammonia, resulting in increase of pH and color change during pH monitor	It is a Rapid, Inexpensive. Good sensitivity and specificity	Requires prior cessation of antibiotics, bismuth. products, or proton pump inhibitors to reduce risk of false negative results
Noninvasive			
Serology	Detection of Specific anti-*H. pylori* IgG antibodies in the patient's serum	Widely available, Least expensive. Does not require medication modifications prior to testing	Does not reliably delineate between active and previous infection. Cannot confirm eradication
Stool antigen	assesses the presence of bacterial antigens in stool.	High sensitivity and specificity. Can be used to test for active infection and evaluate for eradication	Stool sample needed, patient aversion. Requires prior cessation of antibiotics, bismuth products, or proton pump inhibitors to reduce risk of false negative results
Urea breath	Enzyme splits urea into ammonia and CO_2Patients ingest urea labeled with either 13C or 14C, and the labeled urea comes into contact with the mucosa and diffuses through the mucus towards the *H. pylori* and the mucosal blood supply	High sensitivity and specificity Can be used to test for active infection and evaluate for eradication	Resources and trained personnel needed to reliably reproduce test Requires prior cessation of antibiotics, bismuth products, or proton pump inhibitors to reduce risk of false negative results

Table 1.
Strengths and weakness of endoscopic and noninvasive tests for the detection of H. pylori *infection.*

breadth test (UBT) and the stool antigen test (SAT) are the main non-invasive tests for the diagnosis of active infection [51, 52]. UBT is based on the mechanism of degradation of 13C or 14C-labeled urea into CO_2 that can be measured by an infrared spectrometer [38, 52]. The false positive tests are commonly associated with serology but can occur in the UBT. For example presence of achlorhydria promotes excessive growth of non–*H. pylori* organisms that produce urease result in false positive UBTs. The apparent failure of repeated treatment is the main cause of false positive tests [38, 50, 51]. The apparent failure of repeated treatment results in False positive tests. When false positive tests are suspected, a less expensive option for UBT is with a stool antigen test or endoscopy for the diagnosis of *H. pylori* [51, 53]. For the diagnosis of *H. pylori* infection urine test has been a new promising non-invasive largely recommended as an alternative [51, 54].

A meta-analysis reported that testing for antibodies from urine samples might be a good diagnostic option [54, 55]. For the confirmation of the accuracy of this method, further studies are necessary. Through the discovery of specific serological markers for the diagnosis of *H. pylori*, the infection has been developed. A recent study confirmed the accuracy of the "hook-associated protein 2 homologs", FliD, as a marker of the diagnosis of *H. pylori* infection [54]. The use of Flid ELISA method for the detection of *H. pylori* infection provides up to 99% high specificity and 97% of sensibility at a low cost [35, 41, 51, 56].

3. Pathogenesis

3.1 Colonization

A special mechanism is required by *H. pylori* for successful colonization in the gastric environment. After entering the gastric environment *H. pylori* uses crucial flagellar motility for swimming in gastric content which allows the bacteria to get into the gastric mucus layer [38, 40, 51]. Flagella movements are differ in different media "spreading" in solid media and "swarming" movements, or "swimming motility" in liquid media [57]. Various mutations in genes that encode specific flagellar proteins such as fliD, FlaA, and FlaB disrupts the motility of *H. pylori* resulting in reduce colonization in the gastric mucosal layer [58]. Apart from flagella, the mobility of *H. pylori* lies in the chemotaxis actions of various molecules like mucin, urea, sodium bicarbonate, sodium chloride, and specific amino acids [59]. In recent years various colonization factors like urease, GGT, Flolitin-like protein (FLOT), and RhpA [60]. Several *H. pylori* chemoreceptors like T1pA, B, C, and D, CheA kinase, and various coupling proteins are all important for bacterium colonization [61].

Apart from them, various transition metals are crucial for living organisms, as they serve as cofactors for enzymatic reactions that enhanced the rate of reaction which carries out genetic material replication, transcription, attenuation of oxidative stress, and cellular energy production [54]. In bacteria for survival and successful infection, these metals are crucial [62]. Nickel is an essential metal for *H. pylori* and cofactors for two important enzymes like urease and hydrogenase, both enzymes play a vital role in the process of infection [14]. *H. pylori* urease catalyzes the hydrolysis of urea to ammonia and carbon dioxide which acts as a buffer medium that diminished the acidity of the stomach [63, 64]. Hydrogenase is a signaling cascade that allows Hydrogen as a source of energy for metabolism

to be used by *H. pylori* [65]. In the interaction between bacteria and host Adhesion molecules and surface receptors of gastric cells play a very important role [14, 65]. The well-characterized molecule is blood group antigen binding adhesin A (BabA) that carries specific binding to b and H-1 Lewis antigens from the surface of epithelial cells of gastric [66, 67]. The adhesion of the outer membrane Hp HopQ depicts the bacterial-host interaction. These adhesins bind to the cell adhesion molecules related to the carcinoembryonic antigen 1,3,5 and 6 (CEACAMs which give rise to cell signaling mediated by the HopQ-CEACAM interaction that allows the translocation of CagA which is the most crucial and virulence factor of *H. pylori* that increase pro-inflammatory mediators [63, 64, 68–70]. 64 outer membrane proteins (OMPs) of *H. pylori* are grouped into five gene families. *Hop* and *hor* genes are part of family 1, which encodes BabA/B/C, SabA/B, and AlpA/B [64]. In the virulence of *H. pylori,* various OMPs have been identified [64].

3.2 Cytotoxin-associated gene product (CagA)

Cytotoxin-associated gene product (CagA) is one of the most important and studied virulence factors of *H. pylori*. Expression of cagA is always induced whenever the pathogen adhered to the epithelial cells [71]. The cag-pathogenicity island (*cag*PAI) is approximately 40kb that encodes CagA [72], type (IV) secretion system (T4SS) [73], and oncoproteins [74]. CagPA1 is a 40kb chromosomal DNA region of which 31 genes form a type IV secretion system (T4SS) [65, 73]. Seven different secretion systems from I-VII are present, amongst them penetration in the plasma membrane and delivery of bacterial molecules directly to the cytoplasm of the target cells is done by Type III and IV. Flagellum-like tube to translocate effector proteins into eukaryotic host cells performed by type III secretion system (T3SS) whereas a pilus-based structure to mediate the delivery of DNA or proteins into target cells employed by type IV secretion system (T4SS). Cytotoxic effect on the host cell, induced by oncoprotein that is injected into the cell via a pilus formed by the T4SS [74, 75]. This results in the induction of cellular alterations like cellular proliferation, impairing cell motility, apoptosis, and change in the pattern of the cytoskeleton [76].

Transport of CagA protein from gastric mucosal surface to endothelial cells for the tyrosine phosphorylation, carried out by T4SS which directly induces an immune response [75, 77]. The specific interaction between the *H. pylori* HopQ adhesin and the CEACAM (a cellular adhesion molecule) is used for translocating CagA into gastric epithelial cells [77]. Some studies showed this interaction using CEACAM-humanized (hCEACAM) mouse PMNs and humans resulting that *H. pylori* Hop Q-dependent interaction greatly eases the translocation and phosphorylation of CagA. The PMNs positively enhanced the expression of pro-inflammatory chemokines MIP-1-alpha whereas chronic mouse model infection showed downregulation of hCEACAM and -6 receptors on neutrophils [38, 78, 79]. Once CagA, the effector protein of *H. pylori* outreach the host cell it interacts with a diversity of SH2 domains where tyrosine phosphorylation took place (**Table 2**). Site of phosphorylation in *H. pylori* coerce with Glu-Pro-Ile-Tyr-Ala (EPIYA) sequence simultaneously or with closely related sequence located at the N-terminal region and a C-terminal tail [87]. The classification of different subtypes of CagA such as CagA-AB, CagA-ABC, CagA-ABD, or CagA-BD totally based on the composition of the EPIYA-A, EPIYA-B, EPIYA-C, and EPIYA-D motifs [89]. Binding of the host SH2 domain with different EPIYA segments also differs, Among all, the D segment is more harmonious than the C segment and releases the maximum amount of IL-8. [77, 89]. The cytotoxin-associated gene A (*cagA*)-positive

Virulence factors	Functions	References
Arginase	Prevents bacterial killing & T-cell proliferation, Stimulate apoptosis, Impairing of immune responses, Help the *H. pylori* to withstand the acidic environment	[80]
Heat shock proteins	Enhancing adherence to epithelial surfaces, engaged in urease activation, apoptosis and autophagy Control, To maintain the structure and properties of the effector proteins, Protection of cell from reactive oxygen species (ROS),Promotes the production and release of IL-8, TNF-α, and COX-2	[81, 82]
Superoxide dismutase (SOD)	Protection of cell from reactive oxygen species (ROS), colonization enhancement, Inhibiting the production of cytokines, Stimulating the activation of macrophage	[83]
γ-glutamyl-transferase	Facilitating the apoptosis and necrosis, Inducing the release of pro-inflammatory proteins and release of ROS, Stimulate DNA damage	[84]
Lipopolysaccharide	Triggering of signaling pathways, Induction of several inflammatory responses, Induce immune responses, Disrupts the mucus secretion	[85]
Cholesteryl α-glucosyltransferase (αCgT)	Shield *H. pylori* from immunological attack, Stimulates the production of pro-inflammatory proteins (e.g. IL-8),Enhancing the bacterial growth and resistance to antibiotics	[86]
Phospholipase	Activating the signaling pathways (e.g. ERK1/2)and Trigger chronic inflammation, Enhancing the bacterial colonization, Involved in the degradation of lipids and damage to mucus layer	[87, 88]

Table 2.
Important virulence factors in H. pylori**.**

and *cagA*-negative are the two subclasses of *H. pylori* [88]. The *cagA*-positive is more motile as compared to *cagA* negative [88]. A more severe clinical outcome of *H. pylori* infection, associated with mucosal inflammation is due to the presence of two segments *cag* I and *cag* II [87]. The level of expression of *cagA* differs in *H. pylori* strains. Yeh *et al,* 2019 demonstrate that the *H. pylori* strains which possess Y58/E59 polymorphism in the *cagL* are at higher risk of facilitating gastric cancer [87, 88]. Mutations in genes present in the *cag*PAI totally influence virulence [87].

3.2.1 Non-CagA virulence factors

Impairing gastric homeostasis is the main capacity by other various virulence factors. Vacuolating cytotoxins (VacA) protein and its genes are presents in almost all the strains, promotes pathogenicity of *H. pylori* (**Table 2**). Vacuolation is known to be the creation of vacuoles on a host cell which promotes its pathogenicity by inducing cytotoxicity and apoptosis [90]. It promotes endocytic trafficking disruption, perturbations in mitochondrial, depolarization in plasma membrane potential and various ions like chloride, bicarbonate and urea efflux, and results in the activation of MAP kinases [91, 92]. The activation and suppression of the immune response is prompted by VacA that induce immune tolerance through T cells and antigen-presenting cells. Moreover, this protein also enhances the activation and suppression of the immune response resulting in immune tolerance and persistent infection through its activities

on T-cells and antigen-presenting cells [93]. The 140 kDa precursor is produced by VacA which undergoes proteolytic process to produce a toxin of 88 kDa in mass [90]. VacA bind to the epithelial cells with the help of receptor-like protein tyrosine phosphatase alpha and beta (RPTP-α, RPTP-β), sphingomyelin, and density lipoprotein receptor-related protein-1 (LRP-1) [90, 94] also binds to β2 integrin (CD18) receptors [90]. The VacA toxins in amino-terminal is 33KDa and carboxy-terminal 55 kDa that transport into extracellular space by type V secretion pathway, subsequently internalized into endosomal compartments [90, 93, 94]. Several clinical outcomes are due to the different polymorphic forms [94].

The virulence factor promotes gastritis, ulcer, and prolonged infection lead to the cancer development [17, 92]. Duodenal ulcer-promoting gene (DupA) gives a higher acid resistance to the bacterium which promote increase in the production of IL-8 in the gastric mucosa [95]. DupA belongs to the T4SS which integrate conjugative element (ICEHptfs4). VirB4 ATPase homolog is encoded by *dupA* ,linked with gastric ulceration [90, 93] .Pro-inflammatory cytokine secreted by mononuclear cells are induced by *dupA* [96]. The secretions of IL-8 and IL-12 are induced by DupA in the gastric mucosa by gastric epithelial cells in vitro [97]. The biomarkers for peptic ulcers disease is due to *dupA* [98]. Recently a study didn't show any positive correlation between *dupA* and peptic ulcer disease [99]. The increased development of peptic ulcers and gastric cancer totally correlated with the discovery of OipA [96]. OipA is one of the important factor in the outcome of the infection is regulated by "slipped strand mispairing", that depends on the quantity of CT dinucleotide repeats in the5' region of *oip*A [100]. This process determines the functionality and nonfunctionality of OipA that enhance the gastric pathogenicity [100]. OipA change the signaling of β-catenin, proliferation of the cell and decreased the cell-cell junctions [100, 101]. *H. pylori* produce the enzyme GGT which catalyzes the conversion of glutamine into glutamate and finally to ammonia; glutathione into glutamate and cysteinylglycine [102]. It lead to the production of reactive oxygen species (ROS) that induce apoptosis and necrosis [20, 21]. The enzyme inhibits T cell proliferation and dendritic cell differentiation [25, 51, 52]. Patients with peptic ulcers have high GGT activity as compared to the other gastroduodenal disease [90, 96]. Other important virulence factors in *H. pylori* shown in **Table 2**.

3.3 Treatment

No universal regimen for the treatment of *H. pylori* infection. Mostly target the regressing symptomatology and mucosa healing [102]. Since 1997 Maarstricht consensus, proton pump inhibitors (PPI) as standard triple therapy by using a standard dose of 500 mg of clarithromycin and 1g of amoxicillin twice for 7 days as a first-line regimen for the eradication of *H. pylori*. Triple therapy is still recommended as the first line of treatment for *H. pylori* infection in areas with a low rate of clarithromycin according to the European Helicobacter and Microbiota Study Group (EHMSG) [49]. A high dose of clarithromycin resistance lowers the rate for eradication rate of clarithromycin-containing triple therapy like 75% cure rate in Argentina is estimated [103]. A recent study showed that in type 2 diabetic patients the rate of infection eradication is up to 74% [103]. The PPIs, bismuth salt, tetracycline, and metronidazole are complex regimens of Bismuth quadruple therapy, recommended as the second-line or even first-line [104]. According to some previous studies it is stated that the multicenter randomized controlled trials (RCTs) rate of curing of bismuth quadruple therapy is notably high in the standard triple therapy from 90.4%

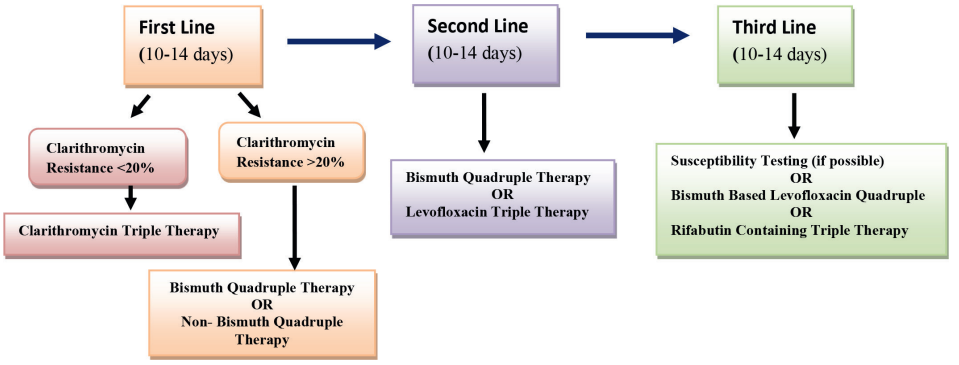

Figure 2.
Treatment regimens of H. pylori *infection.*

to 83.7% for 14 days [103, 104]. In a meta-analysis study, nine RCTs were evaluated and the eradication of infection by bismuth quadruple therapy was the same as those who had received clarithromycin triple therapy [104, 105]. The bismuth quadruple and Levofloxacin triple therapy are the two best therapeutic against infection of *H. pylori* [103]. Levofloxacin regime contains PPIs plus levofloxacin and amoxicillin [104]. Eradication rate of levofloxacin triple therapy (74.5%) and bismuth quadruple therapy (78%) [102, 105]. The third-line therapy is prescribed by using antibiotic susceptibility testing (AST) and prescribed only when the first and second lines of treatment failed [70]. Therapeutic protocols like bismuth-based levofloxacin quadruple therapy or rifabutin triple therapy are used [106]. All three treatment lines are summarized in **Figure 2**.

Probiotics are ——live microorganisms that, when administered in adequate amounts, confer health benefits on the host and they favorably alter the balance in intestinal microflora [107]. Probiotics prevent the adhesion of pathogens by competing for the binding site on intestinal epithelial cells, reducing the colonization of pathogens and thereby preventing the onset of infection. The probiotic's clinical benefits are widely accepted such as diarrhea, antibiotic-associated diarrhea, functional

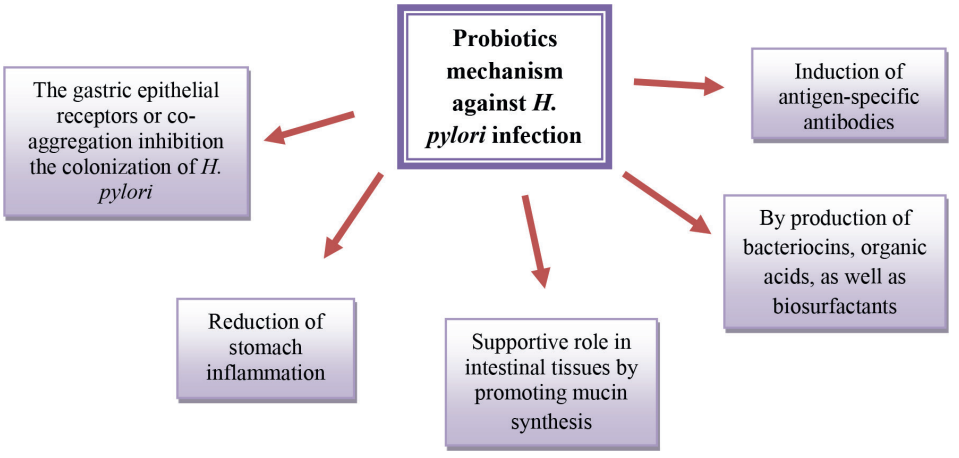

Figure 3.
Mechanism of probiotics against H. pylori infection.

digestive involvements, inflammatory bowel disease, cardiovascular diseases, allergic reactions, and cancer [104, 107]. Anti -*H. pylori* properties proved by spp. of *Lactobacillus* [108]. *Lactobacillus* strains prevent the colonization of *H. pylori* due to their specific adhesins [109] shown in **Figure 3**. The adjuvant therapies with probiotics cure infections caused by *H. pylori* according to the European Helicobacter Pylori Study Group (EHPSG) [104, 105]. *Lactobacillus* spp. and *Bifidobacterium* spp are used more in clinical trials than other probiotics [110]. Studies showed that the yogurt containing bacteria could improve the eradication rate of *H. pylori* infection in the fifth week of treatment [107, 110]. Probiotics act as antibiotic-producing bacteria as they produce antimicrobial substances that inhibit the growth of *H. pylori* [87]. Probiotics' short-chain fatty acids products such as acetic acid, propionic acid, and lactic acid lower the pH of the environment totally unfavorable conditions for the survival of *H. pylori* [111]. Bacteriocins produced by probiotics showed antagonistic activity against *H. pylori* [112]. *Lactobacillus acidophilus* significantly reduced the viability of *H. pylori* [112]. Inhibition of *H. pylori* is due to the antimicrobial Nisin A [113]. The heterogeneous group of antimicrobial proteins is mostly produced by all LAB lactic acid bacteria [114]. Inducing pores in the membrane, activating autolytic enzymes, and downregulating the expression of *vacA*, *cagA*, *luxS*, and *flaA* genes are several mechanisms by bacteriocin to inhibit the growth of *H. pylori* [112, 114].

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