Available online www.worldscientificnews.com

World Scientific News

An International Scientific Journal

WSN 209 (2025) 33-48 EISSN 2392-2192

Immune-Evasion Strategies and Immune Escape Mechanisms of Multi-Drug-Resistant *H. pylori* with Probable Immunotherapeutic Approaches

Tista Das[1], Kaustav Chakraborty[1*]

[1]PG Department of Zoology, Barasat Government College, 10 K.N.C. Road, Barasat, North 24 Parganas, Kolkata – 700124, West Bengal, India.

Email ID: tistadas03@gmail.com, kaustavc17@gmail.com

*Corresponding Author's Details: Dr. Kaustav Chakraborty,

Assistant Professor, PG Department of Zoology, Barasat Government College, 10 K.N.C. Road, Barasat, North 24 Parganas, Kolkata – 700124, West Bengal, India. kaustavc17@gmail.com

ABSTRACT

Helicobacter pylori is a spiral-shaped, gram-negative bacterium that lives within the human stomach and is responsible for persistent gastritis, peptic ulcers, and gastric cancers, along with adenocarcinoma and MALT lymphoma. Over the years, the increasing incidence of multi-drug resistant (MDR) nature of *H. pylori* has made treatment difficult, lowering the success of traditional antibiotic treatment options. The bacterium's unique potential to escape the host immune system facilitates it to survive within the harsh acidic environment of the stomach and establish long-term inflammation. It modifies its surface antigens to avoid recognition by using Pathogen Recognition Receptors (PRRs) and manipulates host's innate and adaptive immune responses. Virulence factors, including VacA, CagA, and γ-glutamyl transpeptidase, suppress T-cell activation, inhibit Th1 and Th17 immune responses, and enhance regulatory T-cell (T_{reg}) development, which together make contributions to persistent infection and long-term persistence.

(Received 24 September 2025; Accepted 15 October 2025; Date of Publication 9 November 2025)

Increasing resistance to generally used antibiotics like clarithromycin, metronidazole, and levofloxacin, etc. have significantly reduced treatment efficiency, depending on alternative therapeutic strategies. Recent research have highlighted the promising value of immunotherapy in controlling MDR *H. pylori* as therapeutic vaccines, monoclonal antibodies in against to bacterial virulence elements, cytokine-based modulation, and immune checkpoint inhibitors to restore host immunity and overcome bacterial persistence. Other modern approaches, which include IgY antibody immunotherapy extracted from egg yolks, bovine immunoglobulin, vonoprazan-primarily based triple therapy, and bismuth-containing regimens etc. have additionally proven significant outcomes. Understanding how *H. pylori* escapes immune detection and develops multi-drug resistance is essential for developing new innovative, efficient solutions. Combining rational antibiotic use with proper immunotherapeutic and preventive strategies ought to appreciably enhance treatment success. Such these integrated method will efficiently encounter MDR *H. pylori* infections and stopping their progression to lifestyle disrupting gastric sicknesses and life-threatening cancer.

Keywords: Helicobacter pylori, multi-drug resistance, immunotherapeutic approaches, Regulatory T-cell (T_{reg}), immune evasion strategies.

1. INTRODUCTION

Helicobacter pylori is a gram-negative bacterium which colonizes in the human stomach, developing severe and dangerous life-threatening diseases like peptic ulcer and gastritis, and cancer like adenocarcinoma and stomach cancer etc. *Helicobacter pylori* formerly known as *Campylobacter pylori.* In *H. pylori*, **"helical"** refers to **its helical nature,** and **"*pylori*"** refers to **the pylorus, which is the exit from the stomach**. In recent decades, the emergence and rapid spread of antimicrobial drug resistance among *H. pylori* strains have posed a major obstacle to effective treatment, resulting in declining eradication rates and prompting significant concern within the global medical community. *H. pylori*'s unique immune evasion strategy helps it to escape human host's immune system and facilitates the persistency in the host stomach.

The bacterium escape host Immunity at various levels-from modulation of innate immune recognition via altered PAMP (Pathogen associated molecular pattern) which is recognized by PRR (Pattern Recognition Pattern) signaling. It also suppresses adaptive immune responses through virulence factors such as VacA, Cag A, γ-glutamyl transpeptidase etc. *H. pylori* also establish its persistence inside host stomach by neutralizing acidic *p*H environment. The bacterium shows growing resistance to some commonly used antibiotics (Metronidazole, Clarithromycin, Levofloxacin**)** leading to decreased treatment success. Co-operation between *H. pylori*'s immune evasion mechanism and multidrug resistance nature of this bacterium should be understood for developing alternative control strategies. Immunotherapeutic approaches—such as therapeutic vaccines, monoclonal antibodies, immune checkpoint modulation, and cytokine-based interventions—offer promising strategies to failed antibiotic regimens. A deeper observation into these mechanisms could facilitate the development of targeted therapies aimed at restoring effective immune responses while overcoming multi-drug resistance.

Recent research has emphasized immunotherapeutic approaches as a promising frontier in combating MDR *H. pylori*. Strategies such as therapeutic vaccination, monoclonal antibodies targeting virulence factors, modulation of T-cell responses, and immune checkpoint inhibition are being explored to restore effective immunity and overcome bacterial persistence.

Thus, a deeper insight into the interplay between bacterial virulence, immune evasion, and resistance mechanisms may pave the way for innovative immunotherapy-driven interventions to control *H. pylori*-associated diseases. This review on *H. pylori* emphasizes the need for rational antibiotic use, personal treatment strategies, and better public health initiatives to effectively control infections, causing by *Helicobacter pylori* [1].

2. SYMPTOMS & PATHILOGICAL INFESTATIONS

Pathological infestation refers to the presence of various no. of parasites present on or within a host, causing serious suffering or disease to the host, heading to significant pathological changes in the host's tissues or bodily functions, often leading to noticeable medical symptoms.

a) Acute gastritis
b) Chronic gastritis
c) Peptic ulcer disease
d) Non-ulcer dyspepsia
e) Gastric MALT lymphoma
f) Extragastroduodenal disorders

a) **Acute gastritis:** Colonization of *H. pylori* associated with acute gastritis results in fullness, nausea, and vomiting with inflammation of both proximal and distal stomach mucosa. This acute phase is often followed by hypochlorhydria, lasts for months.

b) **Chronic gastritis:** When uninterrupted colonization occurs, a close correlation between the level of acid secretion and the distribution of gastritis is gas-lighted. In individual with normal acid output, *H. pylori* colonize the gastric antrum, which is full with few numbered acid-secreting cells. While *H. pylori* infection is the most common cause of gastritis, other factors can also lead to inflammation of the stomach lining. These include viral infections like cytomegalovirus, chronic inflammatory or autoimmune conditions such as Cohn's disease and pernicious anemia, as well as chemical irritation from excessive alcohol consumption or prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs).

c) **Peptic ulcer disease:** Peptic ulcers are defined as mucosal breaks measuring at least 0.5 cm in diameter that extend through the muscularis mucosa layer. Gastric ulcers typically form along the lesser curvature of the stomach, especially at the junction between the corpus and antrum. Duodenal ulcers are most frequently found in the duodenal bulb, the part of the intestine most exposed to stomach acid. The development of both gastric and duodenal ulcers is closely linked to *Helicobacter pylori* infection. Potential complications of peptic ulcer disease include bleeding, perforation, and narrowing of the gastrointestinal tract (stricture formation). Among these, bleeding is the most frequent, occurring in roughly 15 to 20% of ulcer cases. Almost 40% of individuals with upper gastrointestinal bleeding are leading to bleeding ulcers.

d) **Non-ulcer dyspepsia:** Functional or non-ulcer dyspepsia refers to upper gastrointestinal discomfort that occurs without any sensible structural abnormalities upon individual evaluation, including upper gastrointestinal endoscopy. The symptoms may vary in nature; some may resemble reflux, characterized by heartburn and regurgitation; others may present as dysmotility, such like, with early fullness and nausea; while some cases may mimic ulcer symptoms, featuring abdominal pain and vomiting.

e) **Gastric MALT lymphoma:** Under normal conditions, lymphoid tissue is absent in the gastric mucosa; however, mucosa-associated lymphoid tissue (MALT) generally develops following *Helicobacter pylori* colonization. Nearly all individualities who are diagnosed with the severe MALT lymphoma test positive for *H. pylori* infection because this two are interrelated.

f) **Extragastroduodenal disorders:** *H. pylori* infection has been associated with several diseases outside the stomach. These include coronary artery disease, skin conditions like rosacea and chronic urticaria, autoimmune thyroid disorders, immune thrombocytopenic purpura, iron deficiency anemia, Raynaud's phenomenon, scleroderma, migraines, and Guillain-Barré syndrome. Proposed mechanisms behind these associations involve persistent, low-level activation of the blood clotting system, advancement of atherosclerosis, and molecular mimicry between *H. pylori* antigens and human tissues, potentially driving autoimmune reactions [2].

Table 1. List of antibiotics against which *H. pylori* show resistance.

Antimicrobial	Commonly used compound	Resistance rates*	Mode of action	Mechanism of resistance
Nitroimidazoles	Metronidazole, Tinidazole	20–95%	Reduction of prodrug by nitroreductases leads to formation of nitro-anion radicals and imidazole intermediates and subsequent DNA damage	Absence of imidazole reduction caused by reduced or abolished activity of electron transport proteins (e.g., RdxA, FrxA, FdxB)
Macrolides	Clarithromycin, Erythromycin	0–50%*	Binds 23S rRNA ribosomal subunit, resulting in inhibition of protein synthesis	Point mutations in 23S rRNA genes

Penicillins	**Amoxicillin**	**0–30%**	**Binding of beta-lactam antibiotic to penicillin-binding proteins (PBP) inhibits cell division**	**Decreased binding of amoxicillin to PBP D (tolerance) or PBP1A (resistance caused by point mutation in the pbp1A gene), and reduced membrane permeability (resistance)**
Tetracyclines	Tetracycline	0–10%	Binding to ribosome prevents association with aminoacyl-tRNA and subsequent protein synthesis	Point mutations in 16S rRNA genes and reduced membrane permeability
Fluoroquinolones	Ciprofloxacin, Moxifloxacin, Levofloxacin	0–20%	Inhibition of DNA gyrase and topoisomerases, interfering with DNA replication	Point mutations in the DNA gyrase gene, gyrA
Rifamycins	Rifabutin	0–2%	Binding to RNA polymerase, resulting in transcription inhibition	Point mutations in the RNA polymerase gene, rpoB
Nitrofurans	Furazolidone	0–5%	Reduction of prodrug by nitroreductases, leads to formation of nitro anion radicals and subsequent DNA damage	Unknown
Proton pump inhibitor	Omeprazole, Lansoprazole, Pantoprazole	Not reported	Inhibits the proton motive force of the bacterium, and destabilizes its site of colonization in the stomach	Unknown

Bismuth	**Bismuth subcitrate, Bismuth subsalicylate, Ranitidine bismuth citrate**	**Not reported**	**Inhibits protein, ATP, and cell membrane synthesis**	**Unknown**

[Reference: Gerrits Monique M *et al,* 2006][3]

3. IMMUNE EVASION STRATEGY OF HELICOBACTER PYLORI

H. pylori is a gram-negative bacterium and the first officially classified bacterial carcinogen [21]. The process of colonization by *H. pylori* involves several adaptive mechanisms, uch as the production of urease to neutralize stomach pH, the presence of polar flagella for easing motility, and modifications in bacterial morphology that help to access the mucosal barrier to reach the epithelial surface. The effectiveness of colonization and the threat of related diseases are even enhanced by bacterial virulence factors like cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA), γ –glutamyl transpeptidase, etc. [4]. A major contributor is the persistence of *H. pylori* which is the capability to evade and manipulate the host's immune defenses. *H. pylori* interfere innate immunity by forming inflammasome and adaptive immunity by regulating T cell responses, helping the bacterium persist within the host's stomach [5].

—

3.1. Innate Immunity Evasion Strategies

Evasion from recognition by TLRs

TLR is toll-like receptors, which is an example of PRR, which helps to identify the foreign particle and facilitates the immune mechanism. Among the different TLRs, TLR2, TLR3, TLR4, TLR5, and TLR9 are incorporated in the context of *H. pylori* infection and are recognized by lipoteichoic acid /or lipoprotein, double-stranded RNA (dsRNA), LPS, flagellin, and un-methylated CpG motifs, respectively [6-9].

Evasion from RLR recognition

TLR8 on Dendritic cell recognizes the RNA of *H. pylori*'s RNA with the help of RIG-1, MDA5, and LGP2. But the frequently changing nature of mRNA dampens RLR recognition [9-11].

Evasion from CLR recognition

Fucosylated ligand of *H. pylori* is recognized by DS- SIGN facilitates the suppression of pro inflammatory cytokine production. Acetylation of p56 subunit of NF-κB enhances anti-inflammatory response through IL-10 transcription [12].

New players of innate immunity: NLRs and inflammasome

NOD (Nucleotide-binding and oligomerization domain)-like cytoplasmic receptors (NLR) is an important member of PRR family. NLRs detect a wide range of damage-associated molecular patterns (DAMPs) that are creating disturbance in tissue homeostasis. NLRs are divided into two groups, including NOD1 and NOD2. The NOD1 recognizes *H. pylori* peptidoglycan in the cytoplasm of epithelial cells and activates NF-kB signaling and its translocation to the nucleus. The NOD1 signaling causes *H. pylori* killing in the activated epithelial cell through β-defencin 2 as an antimicrobial peptide. Overall, *H. pylori* were reported to be recognized via NOD1 in epithelial cells and via NOD2 in bone marrow–derived DCs [13,14].

The second category in NLRs strengthens the formation of a complex containing several proteins called inflammasome, which activates the cysteine protease of caspase-1 that control the processing of pro-IL1β and IL-18 [15]. The inflammasome involves a cytoplasmic sensor protein (NLRP1 (NLR family, pyrin domain–containing 1), NLRP3, or NLR family, CARD domain–containing 4 (NLRC4) of the NLR family), the adaptor protein apoptosis-associated speck-like domain containing CARD (Caspase recruitment domain) (ASC) and procaspase-1 [15-17]. Recently, following *H. pylori* infection, has shown that potassium efflux, reactive oxygen species (ROS) and lysosomal destabilization are the crucial cellular targets responsible for activation of NOD and NLRP3 inflammasome. In addition, VacA and CagPAI were introduced as the bacterial virulence factors that are involved in inflammasome complex.

Consequently, recognition of *H. pylori* with NLRs, activation of inflammasome complex, and the downstream signaling pathways are essential for controlling *H. pylori* infection. Yet, these signaling pathways will limit the immunopathological tissue damages with effector T cell responses. Therefore, these observations suggest a dual role for the inflammasome during *H. pylori* infection [18-21].

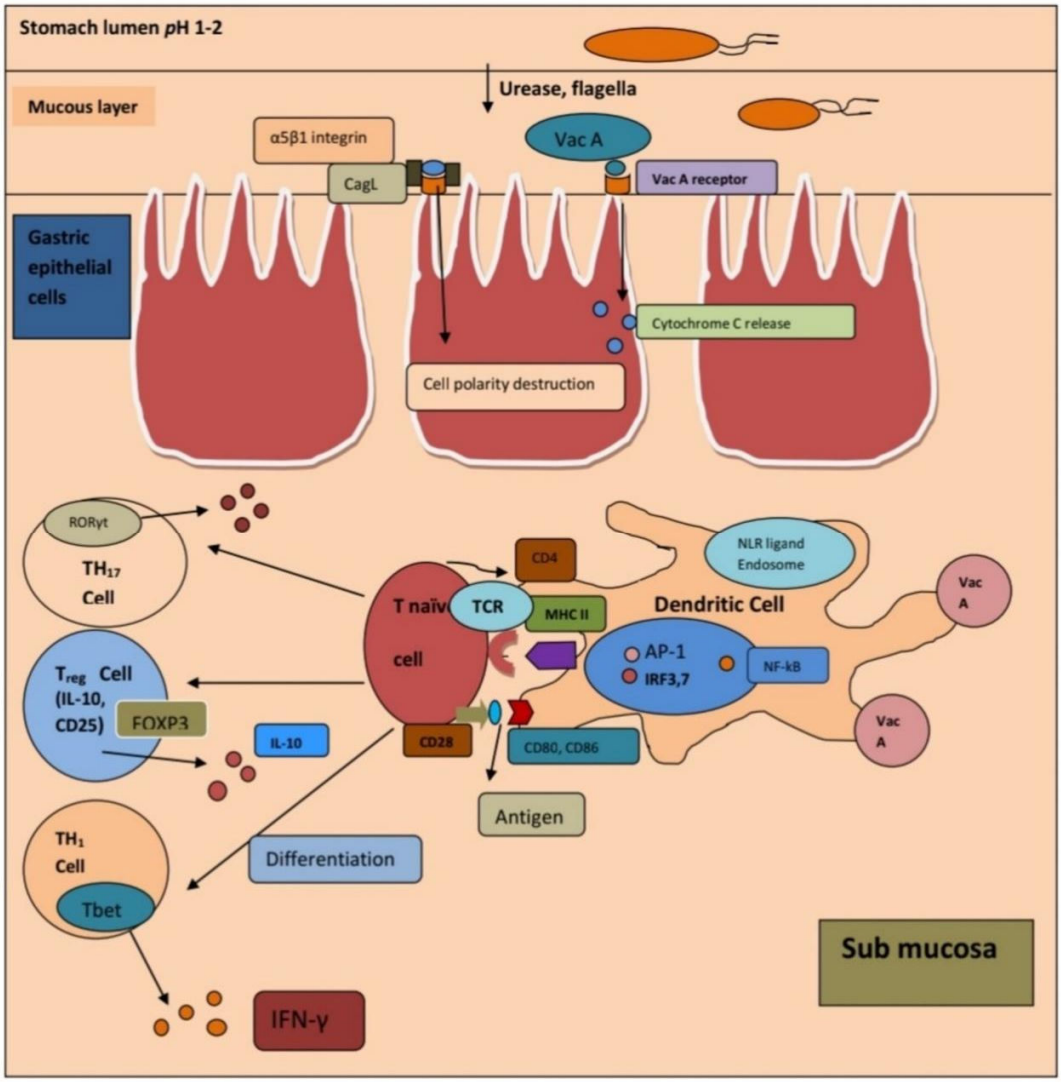

Figure 1. Immune Evasion Strategy of *H. **pylori*** (Source: Karkhah *et al.,* 2019)

3.2. Adaptive Immunity Evasion Strategies

Effector T cell response to *H. pylori*

CD4+ T cells are the key effector cells of adaptive immunity in the immune response to *H. pylori* compared to the relatively inactive role of CD8 T cells. The immune response was originally considered as a Th1 response, but other CD4+ T cell subsets, including Th17 and Tregs, have been introduced in *H. pylori* infection. Generally, activation of Th1 and Th17 cells follows with consequent production of IFN-γ, IL-17, and TNF-α [22]. Neutrophils and monocytes, in response to the neutrophil activating protein of *H. pylori* (HP-NAP) produce IL-12 that promotes Th1 responses. Furthermore, Th1 cells, in response to HP-NAP producing IFN-γ in the gastric mucosa cause chronic gastric inflammation.

Th17 cells appear to be essential in the clearance of *H. pylori*. IL-17 facilitates the release of IL-8 that promotes gastric inflammation. On the other hand, IL-8 recruits neutrophils that are critical for the clearance of the bacteria.

In the distal gastric adenocarcinoma, a part of Th cells shows significant proliferation to the peptidyl-prolyl cis-trans isomerase of *H. pylori* (HP0175). HP0175 induces high level of IL-17 and IL-21 production by lymphocytes, therefore promoting Th17 responses. IL-21 is a complicated cytokine that modulates the differentiation of CD4+ and CD8+ T cells in context dependent manner. Although IL-21 promotes Th17 differentiation and IL-10 production, but inhibits the generation of potentially pathogenic Th1 and Th17 effector cells. These Th17 cells had reduced cytolytic activity while helping to monocyte matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), and vascular endothelial growth factor (VEGF) production. Hence, HP0175 provides a link between *H. pylori* related inflammation and gastric cancer. Th1 and Th17 cells are involved in enhancing the immunopathological and histopathologic changes of the gastric mucosa that outcome in gastric inflammation, atrophic gastritis, epithelial hyperplasia, and intestinal metaplasia in chronic infections. T_{regs} that produced during *H. pylori* infection contribute to bacterial persistence. Tregs protect the host cells infected with *H. pylori* against excessive gastric inflammation and may also promote bacterial colonization, which may lead to gastric tumor progression [22-26].

Evasion of Th1 and Th17 cells

A prominent feature of *H. pylori* infection is that effector T cell responses are mostly impaired during infection, leading to hyporesponsivity or anergy of T cells. *H. pylori* virulence factors contributing in interfering with T cell responses are VacA, γ-glutamyl transpeptidase (GGT), and Arginase. VacA inhibits the proliferation of T cells. First, VacA binds to an unknown receptor on T cells which inhibits cell proliferation through actin rearrangement. Secondly, VacA binds to the mitochondria and leading to apoptosis. This mechanism is able to induce inhibition of T cell proliferation [28]. Likewise, VacA inhibits the proliferation of T cells via interfering with the signaling pathway of TCR-IL-2 and upstream molecules such as calcium/calmodulin-dependent phosphatase calcineurin. VacA also prevents nuclear translocation of the nuclear factor of activated T cells (NFAT) transcription factor and consequently inhibits transcription of specific T cell genes. Further studies identified integrin β2 (CD18) on T cells act as VacA receptor. The integrin β2 along with CD11a creates lymphocyte function-associated antigen-1 (LFA-1) on the surface of the T cell.

GGT is able to inhibit T cell proliferation. The GGT mediates the extracellular cleavage of glutathione and, through ROS production leading to cell cycle arrest in lymphocytes. GGT disrupts Ras signaling pathway that result in G1 cell cycle arrest and then inhibits T cell proliferation. B7-H2 (ICOS-L) is a new member of the B7-family receptors that have the co-stimulatory function on T cell activity upon binding to inducible co-stimulator (ICOS). Recently, the B7-H2/ICOS interaction in Th17 cell development, maintenance, and function has been identified. The virulence factor CagA also shows a key role in the modulation of Th17 cell response indirectly through restricting expression of B7-H2 on gastric epithelial cells. Th17 suppression leads to the persistence of *H. pylori* infection in stomach [27-32].

Deviation in T cell response

Unusual activation of T_{regs} by microbial antigens may provide a mechanism of *H. pylori* evasion from immune response. The GGT and VacA from *H. pylori* molecules indirectly affect the activity of T lymphocytes and promote the differentiation of effector CD4+ T cells to T_{regs}. The gastric mucosal inflammatory response to *H. pylori* could be modulated by Tregs, which is characterized with the expression of transcription factor FOXP3, CD25, and production of IL-10. T_{regs} can suppress cytokine proliferation and production of other T cells. The interaction between the naïve CD4+ T cell and tolerogenic dendritic cells exposed to *H. pylori* is crucial for Tregs differentiation. In addition, gastric epithelial cells exposed to *H. pylori* induced T_{regs}. This interaction mostly happens in the gastric mucosa or the mesenteric lymph nodes. It seems that the induction of T_{regs} is dependent on the age when the host gets the infection. Hence, the level of T_{regs} in children with *H. pylori* infection has increased, and gastric pathology has reduced in comparison with adults. A study showed that outer inflammatory protein A (OipA) of *H. pylori* is a DC maturation suppression factor. In fact, *H. pylori* OipA helps the establishment of chronic infection through decreasing IL-10 levels and suppressing DC maturation. Hence, tolerogenic programming in DCs by *H. pylori leads* to persistent gastric colonization [33-36, 37].

4. IMMUNOTHERAPEUTIC APPROACHES

While traditional *H. pylori* treatment focuses on antibiotics and proton pump inhibitors, ongoing research explores immunotherapy as a potential alternative, particularly for patients who don't respond to conventional therapies or have developed antibiotic resistance. Immunotherapy aims to stimulate the patient's own immune system to fight the infection or to enhance the effectiveness of other treatments. The standard approach to treat *H. pylori* infection involves using a combination of antibiotics, along with a proton pump inhibitor (PPI), as a part of triple and quadruple therapy. Despite decades of research, no *H. pylori* vaccine has been approved for use. *H. pylori*'s ability to evade immune responses, difficulty in targeting, and the choice of adjuvants and delivery systems are some of the challenges in vaccine development.

4.1. Some Current Immunotherapeutic Approaches

Cancer Immunotherapy

Studies indicate that *H. pylori* infection can influence the tumor microenvironment and affect the response to immunotherapy.

Personalized Approaches

Immunotherapy strategies are becoming more personalized, with research focusing on identifying biomarkers like PD-L1 expression and *H. pylori* status to predict treatment response and guide therapeutic decisions.

Family-Based *H. pylori* eradication strategies

In comparison to population- or community-based approaches, there are advantages of a whole-family approach which identifies and continues to treat people infected with *H. pylori* [38]. When there is a high rate of infection in a population, as well as in a family, there is strong possibility that the members will be infected. Taking advantage of this method improves the management and monitoring of infected patients so that pre-cancerous lesions can be detected earlier. The preliminary practice findings of a whole family-based approach suggest that patients and family members are highly satisfied with the treatment they receive and are highly compliant; therefore, this approach deserves further research and improvement.

A concern with this approach is that it can lead to an over screening of involved family members, which can lead to over diagnosis. Noninvasive serological tests, urease breath tests, and stool antigen tests are all more cost effective, accessible, and effective than invasive serological tests, so these approaches are viable alternatives for testing and treating entire families whose members are at high risk of developing *H. pylori* infection. Generally, it is not recommended that individuals with asymptomatic infections of *H. pylori* be tested for infections, but in some cases, such as patients who require long-term nonsteroidal anti-inflammatory drug therapy or individuals with a family history of stomach cancer, this may be important [38].

Vonoprazan-Based Therapy

Vonoprazan-based dual and triple therapy regimens are non-inferior to lansoprazole-based triple therapy in patients infected with *H. pylori* strains not resistant to clarithromycin or amoxicillin, based on eradication of *H. pylori* infection. Vonoprazan is a potent inhibitor of the gastric proton pump H+/K+-ATPase. It binds to H+/K+-ATPase in a non-covalent and reversible manner, blocking potassium binding through competitive inhibition. Through this action, Vonoprazan causes rapid, profound, and sustained suppression of gastric acid secretion, resulting in an elevation in intragastric pH. The increase in intragastric pH improves the stability of antibacterial used in the treatment of *H. pylori* infection. Following oral administration, Vonoprazan is rapidly absorbed, reaching maximum plasma concentrations approximately 1–3 h. post dosing. Based on clinical trials with once-daily dosing in healthy subjects, Vonoprazan exposure is approximately dose-proportional over the dose range of 10–40 mg, with steady-state concentrations reached by day 3–4. This triadic therapy consists of Vonoprazan, Amoxicillin, and Clarithromycin [39].

Lansoprazole Triple Therapy

Lansoprazole triple therapy is consisted with proton pump inhibitor, Clarithromycin, Metronidazole. Five-day lansoprazole triple therapy is an effective regimen for *H. pylori* infection which combines a high cure rate and ulcer healing efficacy with the advantages of excellent patient acceptability and compliance.

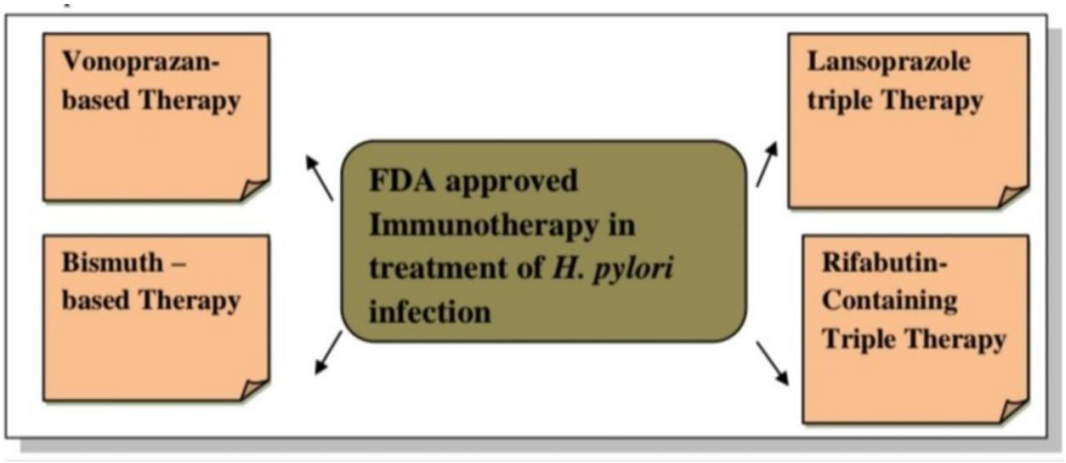

Figure 2. FDA approved Immunotherapeutic Strategies in Treatment of *H. pylori* Infection.

Bismuth–based Therapy

In the mid-20th century, peptic ulcer and its complications was a major medical problem in Western countries. The initial trials of bismuth as an antimicrobial therapy for *H. pylori* eradication reported *H. pylori* eradication rates ranging from 10% to 30%. When a single antibiotic proved ineffective, dual and triple drug therapies were tried, and eventually, an effective regimen consisting of bismuth subcitrate, tetracycline, and metronidazole was identified by Tom Borody in Australia. The regimen, often called bismuth quadruple therapy, consists of a PPI, bismuth, metronidazole, and tetracycline [40].

Rifabutin-containing Talicia

Rifabutin-Containing Triple Therapy contains Esomeprazole, Amoxicillin, and Rifabutin. Due to increasing resistance to commonly used antibiotics, the World Health Organization and Food and Drug Administration have advocated the development of new therapeutic regimens for *Helicobacter pylori* [41].

IgY-Technology

One form of immunotherapy being investigated is the use of immunoglobulin Y (IgY), which are antibodies found in egg yolks. Studies have shown that oral administration of IgY against *H. pylori* can be effective.

5. CONCLUSION

The persistence of multi-drug-resistant *Helicobacter pylori* underscores the combined challenge of antimicrobial resistance and immune evasion. This pathogen deploys a wide spectrum of strategies, including modulation of antigen presentation, suppression of effector T-cell responses, induction of regulatory T cells, and interference with innate immune recognition to establish chronic infection despite robust host defenses. The growing inefficacy of standard antibiotic regimens due to rising resistance further complicates eradication and calls for alternative approaches.

Immunotherapeutic strategies hold significant promise in this context. Therapeutic vaccines, monoclonal antibodies targeting key virulence factors, modulation of host immune checkpoints, and strategies aimed at rebalancing Th1/Th17 versus Treg responses represent innovative avenues to restore protective immunity. Future research must integrate a deeper understanding of the molecular mechanisms of immune escape with the development of safe and effective immunomodulators. Ultimately, a combined approach—incorporating rational antibiotic use, resistance surveillance, and immunotherapy—offers the most effective path forward in combating MDR *H. pylori*. Such integrative strategies not only provide hope for overcoming treatment failures but also open possibilities for preventing the long-term squeal of chronic infection, including gastric cancer.

Acknowledgement:

Authors are grateful to their Head of the Department, Dr. Sumana Saha, and the Principal of the institute, Dr. Santanu Chakrabarti, for support and encouragement.

References

[1] Ahmed Sirwan K. *et al,* Antimicrobial resistance: Impacts, challenges, and future prospects. *Journal of Medicine, Surgery and Public Health* **2** (2024)

[2] Kusters JG, van Vliet AH, and Kuipers EJ, Pathogenesis of *Helicobacter pylori* Infection. *Clinical Microbiology Reviews* 19 (2006) 449-490.

[3] Gerrits Monique M, Vliet Arnoud H M van, Kuipers Ernst J, Kusters Johannes G, *Helicobacter pylori* and antimicrobial resistance: molecular mechanisms and clinical implications. *Lancet Infect Dis* 6 (2006) 699-709.

[4] Hooi, J.K.Y., Lai, W.Y., Ng, W.K., Suen, M.M.Y., Underwood, F.E., Tanyingoh, D., Malfertheiner, P., Graham, D.Y., Wong, V.W.S., Wu, J.C.Y., Chan, F.K.L., Sung, J.J.Y., Kaplan, G.G., Ng, S.C., Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. *Gastroenterology* 153 (2017) 420–429.

[5] Dunne, C., Dolan, B., Clyne, M., Factors that mediate colonization of the human stomach by *Helicobacter pylori*. *World J. Gastroenterol.* 20 (2014) 5610–5624.

[6] Peek Jr., R.M., Fiske, C., Wilson, K.T., Role of innate immunity in *Helicobacter pylori*-induced gastric malignancy. *Physiol. Rev.* 90 (2010) 831–858.

[7] Satoh, T., Akira, S., 2016. Toll-like receptor signaling and its inducible proteins. *Microbiol. Spectrum* 4 (2016)

[8] Akira, S., Takeda, K., 2004. Toll-like receptor signalling. *Nat. Rev. Immunol.* 4 (2004) 499–511.

[9] Rad, R., Ballhorn, W., Voland, P., Eisenacher, K., Mages, J., Rad, L., Ferstl, R., Lang, R., Wagner, H., Schmid, R.M., Bauer, S., Prinz, C., Kirschning, C.J., Krug, A., Extracellular and intracellular pattern recognition receptors cooperate in the recognition of Helicobacter pylori. *Gastroenterology* 136 (2009) 2247–2257.

[10] Matsumiya, T., Stafforini, D.M., Function and regulation of retinoic acid-inducible gene-I. Crit. Rev. *Immunol.* 30 (2010) 489–513.

[11] Tatsuta, T., Imaizumi, T., Shimoyama, T., Sawaya, M., Kunikazu, T., Matsumiya, T., Yoshida, H., Satoh, K., Fukuda, S., Expression of melanoma differentiation associated gene 5 is increased in human gastric mucosa infected with *Helicobacter pylori*. *J. clin. Pathol.* 65 (2012) 839–843.

[12] Wu, J., Lin, K., Zeng, J., Liu, W., Yang, F., Wang, X., Xiao, Y., Guo, X., Nie, H., Zhou, T., Xu, C., Role of DC-SIGN in *Helicobacter pylori* infection of gastrointestinal cells. *Front. Biosci.* 19 (2014) 825–834

[13] Land, W.G., The role of damage-associated molecular patterns (DAMPs) in human diseases: part II: DAMPs as diagnostics, prognostics and therapeutics in clinical medicine. *Sultan Qaboos Univ. Med. J.* 15 (2015) e157–e170.

[14] Minaga, K., Watanabe, T., Kamata, K., Asano, N., Kudo, M., Nucleotide-binding oligomerization domain 1 and *Helicobacter pylori* infection: a review. *World J. Gastroenterol.* 24 (2018) 1725–1733.

[15] Tourani, M., Habibzadeh, M., Karkhah, A., Shokri-Shirvani, J., Barari, L., Nouri, H.R.,Association of TNF-alpha but not IL-1beta levels with the presence of *Helicobacter pylori* infection increased the risk of peptic ulcer development. *Cytokine* 110 (2018) 232–236

[16] Guo, H., Callaway, J.B., Ting, J.P., Inflammasomes: mechanism of action, role in disease, and therapeutics. *Nat. Med.* 21 (2015) 677–687.

[17] Hitzler, I., Sayi, A., Kohler, E., Engler, D.B., Koch, K.N., Hardt, W.D., Muller, A., Caspase-1 has both proinflammatory and regulatory properties in *Helicobacter* infections, which are differentially mediated by its substrates IL-1beta and IL-18. *J. Immunol.* 188 (2012) 3594–3602.

[18] Hitzler, I., Sayi, A., Kohler, E., Engler, D.B., Koch, K.N., Hardt, W.D., Muller, A., Caspase-1 has both proinflammatory and regulatory properties in *Helicobacter* infections, which are differentially mediated by its substrates IL-1beta and IL-18. *J. Immunol.* 188 (2012) 3594–3602.

[19] Semper, R.P., Mejias-Luque, R., Gross, C., Anderl, F., Muller, A., Vieth, M., Busch, D.H., Prazeres da Costa, C., Ruland, J., Gross, O., Gerhard, M., *Helicobacter pylori*-induced IL-1beta secretion in innate immune cells is regulated by the NLRP3 inflammasome and requires the cag pathogenicity island. *J. Immunol.* 193 (2014) 3566–3576.

[20] Huang, F.Y., Chan, A.O., Lo, R.C., Rashid, A., Wong, D.K., Cho, C.H., Lai, C.L., Yuen, M.F., Characterization of interleukin-1beta in *Helicobacter pylori*-induced gastric inflammation and DNA methylation in interleukin-1 receptor type 1 knockout (IL-1R1(-/-)) mice. *Eur. J. Cancer* 49 (2013) 2760–2770.

[21] Mak'Anyengo, R., Duewell, P., Reichl, C., Horth, C., Lehr, H.A., Fischer, S., Clavel, T., Denk, G., Hohenester, S., Kobold, S., Endres, S., Schnurr, M., Bauer, C., Nlrp3-dependent IL-1beta inhibits CD103+ dendritic cell differentiation in the gut. *JCI Insight* 3 (2018) 96322.

[22] Bagheri, N., Salimzadeh, L., Shirzad, H, The Role of T Helper 1-Cell Response in *Helicobacter Pylori*-Infection. *Microbial Pathogenesis* (2018) 1-8

[23] Amedei, A., Cappon, A., Codolo, G., Cabrelle, A., Polenghi, A., Benagiano, M., Tasca, E., Azzurri, A., D'Elios, M.M., Del Prete, G., de Bernard, M., The neutrophil-activating protein of *Helicobacter pylori* promotes Th1 immune responses. *J. Clin. Investig* 116, (2006) 1092–1101.

[24] Amedei, A., Munari, F., Bella, C.D., Niccolai, E., Benagiano, M., Bencini, L., Cianchi, F., Farsi, M., Emmi, G., Zanotti, G., de Bernard, M., Kundu, M., D'Elios, M.M., *Helicobacter pylori* secreted peptidyl prolyl cis, trans-isomerase drives Th17 inflammation in gastric adenocarcinoma. *Intern. Emerg. Med.* 9 (2014) 303–309.

[25] Luzza, F., Parrello, T., Monteleone, G., Sebkova, L., Romano, M., Zarrilli, R., Imeneo, M., Pallone, F., Up-regulation of IL-17 is associated with bioactive IL-8 expression in *Helicobacter pylori*-infected human gastric mucosa. *J. Immunol.* 165 (2000) 5332–5337.

[26] Tian, Y., Zajac, A.J., IL-21 and T Cell differentiation: consider the context. *Trends Immunol.* 37 (2016) 557–568.

[27] Rimbara, E., Mori, S., Kim, H., Shibayama, K., Role of gamma-glutamyl-transpeptidase in the pathogenesis of *Helicobacter pylori* infection. *Microbiol. Immunol.* 57 (2013) 665–673.

[28] Abadi, A.T.B., Strategies used by *Helicobacter pylori* to establish persistent infection. *World J. Gastroenterol.* 23 (2017) 2870–2882.

[29] Gebert, B., Fischer, W., Weiss, E., Hoffmann, R., Haas, R., *Helicobacter pylori* vacuolating cytotoxin inhibits T lymphocyte activation. *Science* 301 (2003) 1099–1102.

[30] Sewald, X., Gebert-Vogl, B., Prassl, S., Barwig, I., Weiss, E., Fabbri, M., Osicka, R., Schiemann, M., Busch, D.H., Semmrich, M., Holzmann, B., Sebo, P., Haas, R. Integrin subunit CD18 Is the T-lymphocyte receptor for the *Helicobacter pylori* vacuolating cytotoxin. *Cell Host Microbe*. 3 (2008) 20–29.

[31] Lina, T.T., Alzahrani, S., Gonzalez, J., Pinchuk, I.V., Beswick, E.J., Reyes, V.E., Immune evasion strategies used by *Helicobacter pylori*. *World J. Gastroenterol.* 20 (2014) 12753–12766.

[32] Lina, T.T., Pinchuk, I.V., House, J., Yamaoka, Y., Graham, D.Y., Beswick, E.J., Reyes, V.E., CagA-dependent downregulation of B7-H2 expression on gastric mucosa and inhibition of Th17 responses during *Helicobacter pylori* infection. *J. Immunol.* 191 (2013) 3838–3846.

[33] Oertli, M., Muller, A., *Helicobacter pylori* targets dendritic cells to induce immune tolerance, promote persistence and confer protection against allergic asthma. *Gut Microbes* 3 (2012) 566–571.

[34] Lundgren, A., Suri-Payer, E., Enarsson, K., Svennerholm, A.M., Lundin, B.S., *Helicobacter pylori*-specific CD4+ CD25high regulatory T cells suppress memory T-cell responses to *H. pylori* in infected individuals. *Infect. Immun.* 71 (2003) 1755–1762.

[35] Salama, N.R., Hartung, M.L., Muller, A., Life in the human stomach: persistence strategies of the bacterial pathogen *Helicobacter pylori*. *Nat. Rev. Microbiol.* 11 (2013) 385–399.

[36] Teymournejad, O., Mobarez, A.M., Hassan, Z.M., Moazzeni, S.M., Ahmadabad, H.N., In vitro suppression of dendritic cells by *Helicobacter pylori* OipA. *Helicobacter* 19 (2014) 136–143.

[37] Karkhah A, Ebrahimpour S, Rostamtabar M, Koppolu V, Darvish S, Vasigala VKR, Validi M, Nouri HR, *Helicobacter pylori* evasion strategies of the host innate and adaptive immune responses to survive and develop gastrointestinal diseases. *Microbial Res.* 218 (2019) 49-57.

[38] Elbehiry A., Marzouk E., Aldubaib M., Abalkhail A, Anagreyyah S., Anajirih N., Almuzaini AM., Rawway M., Alfadhel A., Draz A., Abu-Okail A., *Helicobacter pylori* Infection: Current Status and Future Prospects on Diagnostic, Therapeutic and Control Challenges. *Antibiotics (Basel).* 12 (2023) 191.

[39] Shirley M., Vonoprazan: A Review in *Helicobacter pylori* Infection. *Drugs* 84 (2024) 319-327.

[40] Graham DY., Lee SY., How to Effectively Use Bismuth Quadruple Therapy: The Good, the Bad, and the Ugly. *Gastroenterol Clin North Am.* 44 (2015) 537-563.

[41] Kalfus IN., Graham DY., Riff DS., Panas RM., Rifabutin-Containing Triple Therapy (RHB-105) for Eradication of *Helicobacter pylori*: Randomized ERADICATE Hp Trial. *Antibiotics (Basel).* 9 (2020) 685