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REVIEW

Helicobacter Pylori-Induced Apoptosis in Gastric Diseases: Mechanisms, Implications, and Diagnostic Applications

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Abstract: *Helicobacter pylori (H. pylori)* is a spiral-shaped gram-negative bacterium that causes one of the most common infections worldwide, affecting a significant portion of the human population. It plays a crucial role in regulating cellular activities, such as apoptosis, through various virulence factors, thereby contributing to the development and progression of gastrointestinal diseases including gastritis, ulcers, and gastric cancer. Here, we explored the complex relationship between *H. pylori* infection and apoptosis, emphasizing how *H. pylori* induces apoptosis via virulence factors (such as cytotoxin-associated gene A and vacuolating cytotoxin A), death receptor pathways, and host cell responses. Additionally, we critically examine current diagnostic strategies used to detect *H. pylori* infection and apoptosis, including non-invasive tests, invasive histopathological methods, and emerging molecular techniques. We assess their diagnostic value, limitations, and applicability in clinical settings, with the aim of identifying more effective approaches for early detection and disease monitoring.

Keywords: *helicobacter pylori*, helicobacter infections, virulence factors, gastric diseases, diagnostic approaches

Introduction

Helicobacter pylori (*H. pylori*) is a microaerophilic gram-negative, helical bacterium[1] first identified in Australian scientists Barry Marshall and Robin Warren studied patients with gastric ulcers in 1983, revealing their pathogenic roles in gastrointestinal diseases.[2,3] The presence of this bacterium has profoundly altered the medical understanding of the etiology of gastritis and gastric ulcers.[4] *H. pylori* flourishes under highly acidic conditions by producing urease, an enzyme that converts urea into ammonia and carbon dioxide, thereby enabling survival.[5,6] Ammonia helps neutralize stomach acid, creating a slightly alkaline environment that is conducive to bacterial survival. Its spiral form and surface flagella allow it to navigate through thick gastric mucus, facilitating intricate biological interactions with host cells.[7]

Globally, the prevalence of *H. pylori* infection exhibits significant regional disparities influenced by economic development and public health conditions. Statistics indicate that the global average infection rate dropped from 58.2% in the 1980s to 43.1% now.[8] Which is primarily attributed to improved living standards, better hygiene practices, and the widespread use of antibiotics. In high-income countries, enhanced sanitary facilities and increased health awareness have significantly reduced the infection rates. Nevertheless, its prevalence continues to increase in low- and middle-income nations, especially across Africa, Russia, and South America.[9,10] *H. pylori* infection is not only widespread, but its associated clinical hazards are also of significant concern. According to the Global Burden of Disease Study in 2014,[9] peptic ulcer disease caused 3.5 deaths per 100,000 population in 2010. Furthermore, nearly 800,000 new cases of gastric cancer worldwide in 2018 were attributed to *H. pylori* infection.[11] The persistently high prevalence of

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H. pylori infection, along with its severe clinical consequences—particularly in endemic regions—underscores the urgent need for a deeper understanding of its pathogenic mechanisms, as well as the importance of early diagnosis and effective management.

Apoptosis, also known as programmed cell death,[12] is a tightly controlled mechanism of cellular self-destruction that is essential for maintaining homeostasis and health. In *H. Pylori* infection, apoptosis is complex and dual, serving as a defense mechanism and promoter of pathological processes. From a defensive standpoint,[13,14] apoptosis helps eliminate *H. pylori*-infected cells, thereby reducing bacterial persistence and spreading and limiting the progression of the infection.

Conversely, in promoting pathological processes,[14] *H. pylori* employs a series of virulence factors,[15] such as cytotoxin-associated gene product (CagA)[16,17] and vacuolating cytotoxin (VacA),[18] which directly disrupt host cell signaling pathways. This interference leads to significant alterations in cell structure and function, thereby triggering apoptosis. An increase in the apoptosis rate compromises the integrity of the gastric epithelial barrier, rendering the gastric mucosa more susceptible to invasion by *H. pylori* and other pathogens and exacerbating the severity of infection and inflammation.

Given the key role of apoptosis in *H. pylori* infection, understanding its underlying mechanisms and clinical implications is essential for advancing both scientific knowledge and clinical practice. This review explores the complex interactions between *H. pylori* and host cell apoptosis, focusing on bacterial virulence factors, host responses, and environmental influences that contribute to disease progression, including gastritis, ulcers, and gastric cancer. In addition, we summarize current diagnostic techniques for detecting both *H. pylori* infection and apoptosis and discuss the potential of integrated diagnostic approaches to improve early detection and guide personalized treatment strategies. Although each of these aspects has been studied individually, few reviews have systematically connected the molecular mechanisms, disease associations, and diagnostic technologies into a unified framework. By bridging these dimensions, this review aims to provide a comprehensive perspective on *H. pylori*-induced apoptosis and offer insights that support further research and the development of more effective diagnostic and therapeutic solutions.

Apoptosis and *H. Pylori*

The Biological Basis and Significant Pathways of Apoptosis

Apoptosis is essential for organism development, immune system regulation, and elimination of damaged or abnormal cells.[19,20] It involves distinct changes such as cell shrinkage, chromatin condensation, nuclear fragmentation, and apoptotic body formation.[21] These apoptotic cells and fragments are eventually engulfed and cleared by neighboring cells or macrophages, thereby maintaining tissue homeostasis and overall health. Dysregulated apoptosis is linked to various diseases including cancer, autoimmune disorders, and neurodegenerative conditions. Therefore, understanding the molecular mechanisms underlying apoptosis is crucial in disease research and therapeutic development.[22]

Apoptosis is primarily mediated through two main pathways: intrinsic and extrinsic.

Intrinsic Pathway

The intrinsic (or mitochondrial) pathway is initiated by internal damage such as DNA damage, lack of growth factors, or mitochondrial dysfunction.[23] Anoikis, a type of intrinsic apoptosis, occurs when cells lose their integrin-mediated attachment to the extracellular matrix. This pathway is controlled by the BCL-2 family, which includes pro-apoptotic (BAX, BAK, and BH3-only proteins, such as BIM, BID, BAD, NOXA, and PUMA) and anti-apoptotic proteins (BCL-2, BCL-xL, MCL-1, and BCL-W).[24,25]

In response to DNA damage or oxidative stress, pro-apoptotic BH3-specific proteins inhibit the anti-apoptotic BCL-2 proteins, thereby activating BAX and BAK. These proteins form pores in the mitochondrial outer membrane, facilitating the release of pro-apoptotic factors such as cytochrome c, activating caspase 9, and activating executioner caspases (caspase-3 and caspase-7), resulting in apoptosis.[26–28]

Extrinsic Pathway

Activation of death receptors such as Fas, TNFR1, TRAIL-R1, and TRAIL-R225 mediates the extrinsic pathway. These receptors have an intracellular interaction region called the death domain (DD). The Fas-FasL interaction is essential for the extrinsic pathway. Binding of FasL to Fas recruits the adaptor proteins FADD and caspase-8, forming the death-inducing signaling complex (DISC) and activating caspase-8, which subsequently triggers apoptosis.[29] The extrinsic pathway is associated with TNF-α-mediated TNFR1 activation. Upon activation, TNFR1 forms a transient intracellular signaling complex known as Complex I.[30] Activated TNFR1 recruits adaptor proteins such as TRADD and RIPK1 via its intracellular DD, further recruiting TRAF2, TRAF5, cIAP1, and cIAP2, which catalyze the polyubiquitination of Complex I. The LUBAC complex (comprising HOIP, HOIL1, and Sharpin) catalyzes the M1-linked ubiquitination of Complex I components, recruiting essential kinase complexes, such as TAK1-TAB and NEMO-IKK, thereby activating the NF-κB signaling pathway and promoting cell survival and inflammatory responses.

Specifically, TNFR1 activation can lead to RIPK1-dependent or RIPK1-independent apoptosis. Ubiquitination and phosphorylation of RIPK1 regulate its activity, and its dysregulation can promote RIPK1-dependent apoptosis (RDA). For instance, the loss of cIAP1, cIAP2, LUBAC, or NEMO or inhibition of TAK1, TBK1, or IKK can activate RIPK1, forming Complex IIa (comprising RIPK1, FADD, and caspase-8), thereby mediating caspase-8 activation and RDA.[31]

Mechanism of Apoptosis Induced by *H. Pylori*

H. pylori infection can colonize the gastric mucosal epithelium and glands. Various adhesion and virulence factors activate the host immune response, disrupt gastric homeostasis, and induce apoptosis, leading to gastrointestinal diseases. Understanding these mechanisms will elucidate the pathogenicity of *H. pylori* and aid in the development of new diagnostic and therapeutic strategies. This review summarizes the primary mechanisms by which *H. pylori* induces apoptosis, including bacterial virulence factors, death receptor pathways, and responses of the environment and host cells (Figure 1).

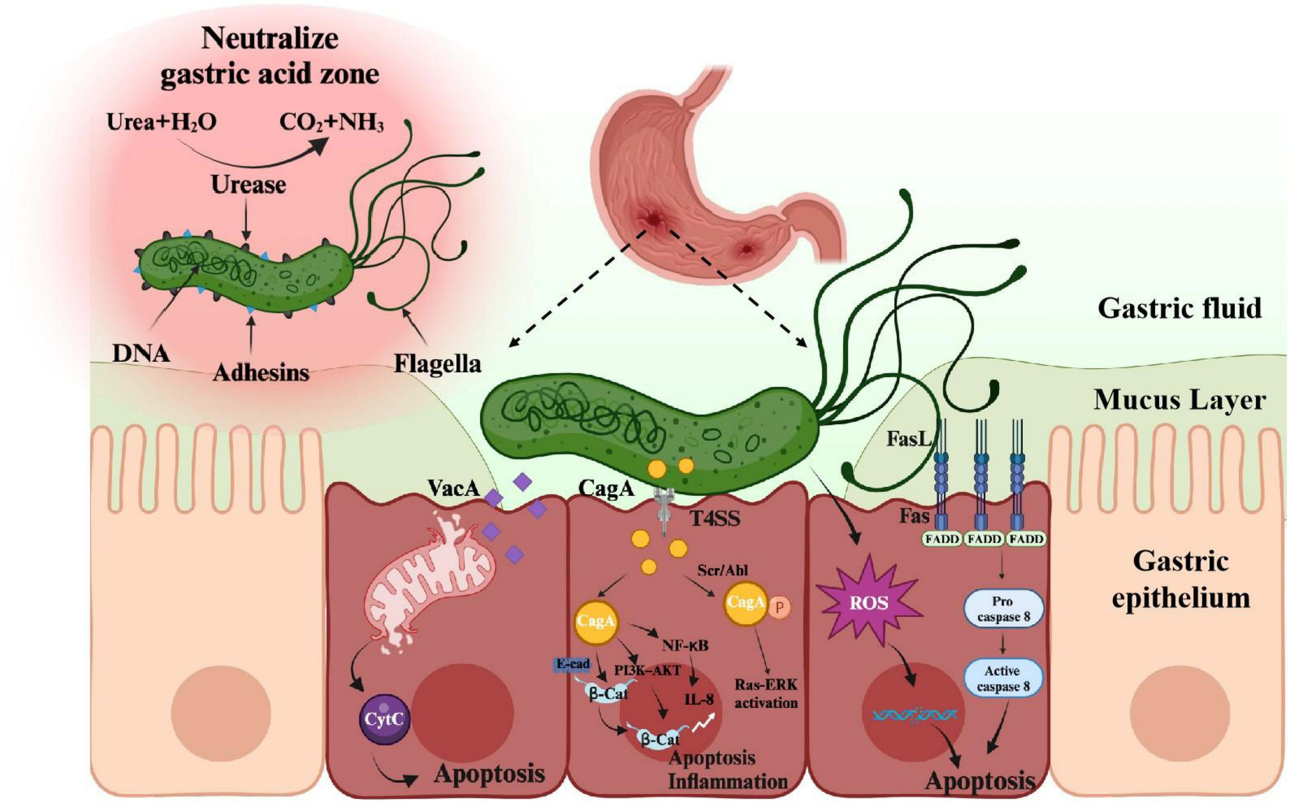

Figure 1 Schematic illustrates the cellular apoptosis responses to *H. pylori* infection. Created in BioRender. Smith, Z. (2025) https://BioRender.com/l5rgaq5.

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Bacterial Virulence Factors

Vacuum-Activated Cytotoxin A (VacA)

VacA is a major virulence factor of *H. pylori*, forming anion-selective channels in the cell membrane that disrupt calcium and potassium ion balance, leading to intracellular disturbances.[32–34] This disruption compromises the integrity of the gastric epithelial barrier, thereby increasing its permeability. Furthermore, VacA disrupts the mitochondrial membrane potential and activates the release of pro-apoptotic BAX proteins from the BCL-2 family, releasing cytochrome c and activating the mitochondrial apoptotic pathway. Repeated immune responses to VacA in host epithelial cells are crucial for the progression of gastritis to cancer.

Cytotoxin-Associated Gene A (CagA)

CagA is another key virulence factor of *H. pylori* that affects host cells through its phosphorylated and non-phosphorylated forms.[35,36] Once injected into host cells via the Type IV secretion system (T4SS),[37] CagA can be phosphorylated by host cell kinases, such as Src and Abl. The phosphorylated form of CagA (p-CagA) interacts with various signaling pathways to induce pathogenesis. p-CagA activates SHP-2, promoting cell motility and elongation.[38] It also disrupts intercellular junctions in epithelial cells, thereby increasing permeability. In addition, p-CagA activates the MAPK/ERK pathway, ultimately leading to cytoskeletal rearrangement, inflammatory responses, and apoptosis. Non-phosphorylated CagA disrupts intracellular signaling pathways. CagA interacts with E-cadherin, disrupting the E-cadherin–β-catenin complex and causing the nuclear accumulation of β-catenin, which promotes the transcription of genes linked to carcinogenesis.[39] Additionally, CagA activates the PI3K-AKT signaling pathway, directly activating β-catenin and enhancing the expression of pro-inflammatory cytokines such as IL-8 by activating NF-κB.[40] Notably, the function and pathogenicity of CagA exhibit significant strain- and geography-specific differences, particularly between East Asian-type[41] and Western-type strains.[42] These differences primarily lie in the structure of the EPIYA (Glu-Pro-Ile-Tyr-Ala) motifs.

The pathogenicity of CagA is closely associated with the number and type of its EPIYA motifs. East Asian-type CagA typically carries EPIYA-A, EPIYA-B, and EPIYA-D motifs, whereas Western-type CagA predominantly contains EPIYA-A, EPIYA-B, and one or more EPIYA-C motifs. Studies have shown that the EPIYA-D motif exhibits significantly higher phosphorylation efficiency compared to the EPIYA-C motif, which enhances the ability of East Asian-type CagA to activate SHP-2 phosphatase.[43] Excessive activation of SHP-2 not only promotes cell migration and morphological changes but is also closely associated with the carcinogenesis of gastric epithelial cells.

In addition, the pathogenicity of East Asian-type CagA is further reflected in its stronger ability to disrupt signaling pathways. For instance, studies have revealed that East Asian-type CagA more effectively activates the MAPK/ERK and NF-κB pathways, thereby exacerbating the expression of pro-inflammatory cytokines (eg, IL-8), as well as cell apoptosis and inflammation.[44] This functional enhancement may help explain the significantly higher incidence of gastric cancer in East Asia compared to Western regions.

Beyond the differences between East Asian-type and Western-type CagA, some studies have also observed notable strain-specific variations in *H. pylori* CagA in other regions, such as South Asia,[45] the Middle East,[46] and Latin America.[47] These variants differ not only in the diversity of EPIYA motifs but also in CagA sequence variations, the number of phosphorylation sites, and the activation of downstream signaling pathways. Therefore, the geography- and strain-specific differences in CagA not only determine the virulence of *H. pylori* but also have a profound impact on the severity and type of associated diseases.

The Death Receptor Pathway

The death receptor pathway (extrinsic apoptosis pathway) is a crucial mechanism by which *H. pylori* induces apoptosis in the host cells. Following *H. pylori* infection, the expression of death receptors on the surface of gastric epithelial cells is markedly upregulated. The central death receptors include Fas, TNFR1, and TRAIL receptors (DR4 and DR5).[48] Upregulation of these receptors increases the sensitivity of cells to their corresponding ligands (FasL, TNF-α, and TRAIL), thereby facilitating the initiation of apoptotic signaling and inducing gastric mucosal damage.

Environmental and Host Cell Responses

Oxidative Stress

H. pylori infection markedly elevates intracellular reactive oxygen species (ROS) levels, including superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH\cdot$).[49] ROS can damage cellular DNA, proteins, and lipids, compromising cellular integrity and function. Mitochondria, the primary sites of ROS production, may suffer from mitochondrial DNA damage and electron transport chain dysfunction, thereby creating a vicious cycle. Additionally, oxidative stress activates various signaling pathways, promoting apoptosis and inflammation.

Inflammatory Response

H. pylori infection induces a robust inflammatory response in the gastric mucosa. Bacterial lipopolysaccharide (LPS) activates immune cells to release pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6).[50,51] These cytokines recruit and activate additional immune cells, thereby intensifying the inflammation. IL-1β and TNF-α are potent inducers of apoptosis, which activate death receptors and initiate the extrinsic apoptotic pathway.

Autophagy

Autophagy is a cellular mechanism that breaks down and recycles damaged organelles and proteins, thereby promoting cell survival under stressful conditions.[52] Following *H. pylori* infection, autophagy acts as a protective mechanism by removing damaged cellular components and limiting bacterial replication. However, excessive or dysregulated autophagy can also lead to cell death. *H. pylori* can manipulate autophagy via its virulence factors. For example, VacA can induce autophagosome formation, whereas CagA can interfere with the maturation and function of autophagosomes. Overstimulation of autophagy can result in autophagic cell death, which is characterized by the extensive degradation of cellular components and organelles, ultimately triggering apoptosis. Additionally, defective autophagy may lead to the accumulation of damaged mitochondria, increase ROS production, and further promoting apoptosis.[53]

Disease Associations

The infection of *Helicobacter pylori* not only triggers a strong immune response in the host but also successfully achieves long-term colonization through a series of complex immune evasion mechanisms. These mechanisms lay an important foundation for the progression of gastric diseases. Firstly, the lipopolysaccharide (LPS) of *H. pylori*, characterized by low endotoxin activity, attenuates the activation of Toll-like receptor 4 (TLR4), significantly diminishing the host's innate immune responses.[54] In addition, *H. pylori* secretes virulence factors such as VacA and CagA, which directly disrupt the maturation of dendritic cells and the process of antigen presentation, thereby preventing the effective activation of T cells and weakening the adaptive immune system's ability to eliminate the bacteria.[55] More importantly, *H. pylori* manipulates immune cell polarization, inducing T helper cells (Th cells) to shift towards a Th2 or regulatory T cell (Treg) phenotype. Tregs secrete immunosuppressive cytokines, such as IL-10 and TGF-β, which further inhibit the activity of effector T cells and macrophages, creating an immune-tolerant environment.[56,57] These mechanisms not only enable *H. pylori* to persist within the gastric mucosa but also induce chronic low-grade inflammation and immune dysregulation.

Due to these immune evasion strategies, *H. pylori* infection gradually progresses into a spectrum of gastric diseases, including gastritis, peptic ulcers, and even gastric cancer. The following sections will explore the specific progression of these diseases in greater detail.

Gastritis

Molecular Mechanisms

H. pylori is the leading cause of chronic gastritis.[58] Its virulence factors, CagA and VacA, disrupt intracellular signaling, induce oxidative stress, and promote epithelial cell apoptosis, resulting in mucosal damage. The World Health Organization (WHO) classifies *H. pylori* as a Group I carcinogen due to its strong association with gastric cancer and MALT lymphoma.[59] Infection triggers an inflammatory response, with increased secretion of cytokines such as IL-1β,

TNF-α, and IL-6, and immune cell infiltration. Chronic *H. pylori*-related inflammation is considered the initial step of the Correa cascade, leading to gastric malignancy. The Maastricht VI/Florence Consensus highlights eradication of *H. pylori* as central for preventing gastric cancer and related complications.[60]

Histopathological Changes

H. pylori gastritis is characterized histologically by infiltration of neutrophils and mononuclear cells in the gastric mucosa, epithelial degeneration and apoptosis, and glandular atrophy. Persistent infection can progress to atrophic gastritis, intestinal metaplasia, and dysplasia, which are considered precancerous changes. The updated Sydney System, recommended by WHO and international guidelines, standardizes the assessment and grading of these lesions.[61]

Clinical Implications

H. pylori infection is often asymptomatic but may cause nonspecific symptoms such as epigastric discomfort or nausea. Chronic infection weakens the gastric barrier, increasing the risk of peptic ulcers, MALT lymphoma, and gastric cancer. Since 1994, WHO has identified *H. pylori* as the main cause of gastric cancer, with an estimated global infection burden of around 440 million people, especially in developing countries.[62] The American College of Gastroenterology (ACG) guidelines recommend testing and eradication therapy for symptomatic or high-risk individuals, such as those with a family history of gastric cancer or atrophic gastritis.[63]

Ulcers

Molecular Mechanisms

H. pylori is one of the primary etiological factors of gastric ulcers. According to WHO and epidemiological studies, approximately 60%–80% of gastric ulcers worldwide are associated with *H. pylori* infection, with even higher rates observed in developing countries (eg, around 70% in China).[64] The development of ulcers arises from an imbalance between gastric mucosal defense mechanisms (such as the mucus barrier) and aggressive factors (such as gastric acid and pepsin). *H. pylori*, through virulence factors like CagA and VacA, increases the generation of reactive oxygen species (ROS), promotes the release of pro-inflammatory cytokines such as IL-1β and TNF-α, and induces apoptosis of gastric epithelial cells. These processes collectively weaken the mucosal barrier, ultimately leading to ulcer formation.

Histopathological Changes

H. pylori-associated gastric ulcers are characterized by deep mucosal necrosis, fibrosis, and granulation tissue formation at the base of the ulcer, often accompanied by marked infiltration of neutrophils and mononuclear cells (including lymphocytes and plasma cells). There is increased epithelial cell apoptosis, significant glandular destruction, and proliferative repair with chronic inflammation observed at the ulcer margins. Pathological assessment commonly employs the updated Sydney System and staging with OLGA/OLGIM systems may be used to evaluate the risk of malignant transformation.[65]

Clinical Implications

Clinically, gastric ulcers typically present with symptoms such as epigastric pain and dyspepsia, while severe cases may develop complications including gastrointestinal bleeding or perforation. *H. pylori* infection significantly elevates the risk of ulcer recurrence, with recurrence rates reaching 50%–80% in cases where the infection is not eradicated. The Maastricht VI/Florence Consensus (2022) recommends a 14-day bismuth-containing quadruple therapy or other eradication regimens, which can reduce ulcer recurrence rates to 5%–10%.[66]

Gastric Cancer

Molecular Mechanisms

According to the WHO International Agency for Research on Cancer (IARC), about 89% of non-cardia gastric cancers worldwide are linked to *H. pylori* (IARC, 2012).[67–69] *H. pylori* virulence factors (eg, CagA, VacA) induce chronic oxidative stress and inflammation, leading to epithelial cell injury, apoptosis, and increased DNA damage. Chronic infection promotes genetic mutations, genomic instability, and impairs autophagy, all of which contribute to malignant transformation.

Histopathological Changes

H. pylori-associated gastric cancer typically follows the Correa cascade, progressing from chronic gastritis to atrophic gastritis, intestinal metaplasia, dysplasia, and finally adenocarcinoma. Key histological features include glandular distortion, marked cellular atypia, and tumor invasion into deeper layers, often with stromal and inflammatory cell infiltration.

Clinical Implications

Early gastric cancer is often asymptomatic; advanced cases may present with epigastric pain, weight loss, or gastrointestinal bleeding. WHO estimates *H. pylori* causes around 800,000 gastric cancer cases globally (2020), especially in high-incidence regions like East Asia. Given this clear association, WHO and the Maastricht VI/Florence Consensus (2022) recommend *H. pylori* screening and eradication in high-risk populations as a primary preventive measure.[70]

Detection of *H. Pylori* Infection and Apoptosis

H. Pylori Infection Detection

Previous studies have shown that *H. pylori* infection is associated with several diseases. When detected and treated early, *H. pylori* infection can significantly prevent the onset and progression of these diseases, improve patient quality of life, and reduce medical costs. Currently, both conventional and innovative diagnostic techniques are effectively used to diagnose *H. pylori* infection, encompassing non-invasive[71] and invasive methods, as illustrated in Figure 2. Noninvasive

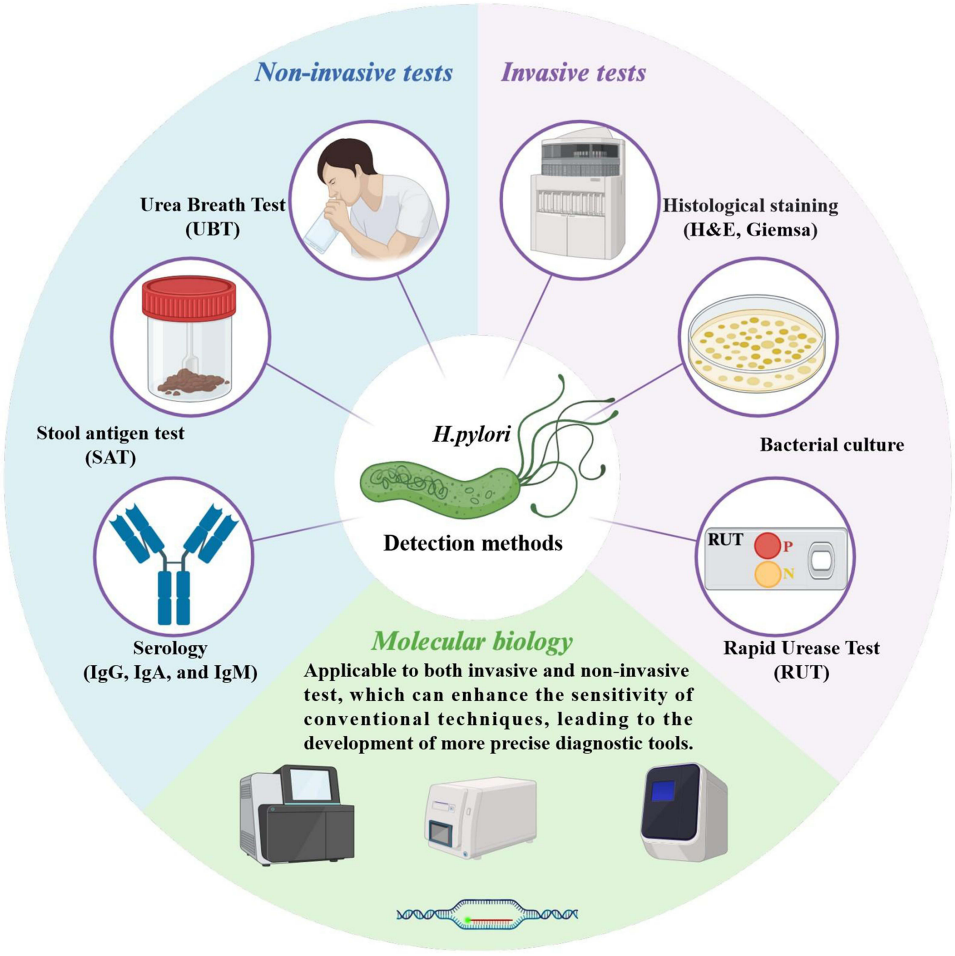

Figure 2 Commonly used *H. pylori* detection strategies. On the left are non-invasive methods. On the right are invasive methods. At the bottom are newly developed molecular biology methods applicable to both non-invasive and invasive detection. These diverse techniques provide comprehensive options for diagnosing *H. pylori*, enhancing the effectiveness of detection strategies. Created in BioRender. Smith, Z. https://BioRender.com/a62utpp.

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methods detect bacterial antigens, related antibodies, or nucleic acid sequences in bodily fluids. For example, the urea breath test (UBT), which detects labeled carbon dioxide in a patient's breath to assess *H. pylori* urease activity, is safe, convenient, and well accepted by patients, making it suitable for initial screening and post-treatment evaluation, and it is characterized by a sensitivity of 90%–95% and a specificity of 95%–98%.[60,72–75] However, it is relatively costly, may be influenced by the patient's recent diet and medications, and requires specialized equipment.[66] Stool antigen testing is relatively simple, avoids patient discomfort and risk, and has around 85%–95% sensitivity and 90%–100% specificity.[76] However, handling stool samples is inconvenient, and cross-reactivity may lead to false positives.[66,77] Serological testing for antibodies can provide results within a few hours and is suitable for large-scale screening with 80%–95% of sensitivity and specificity. However, it cannot distinguish between current and past infections.[66,76,78]

Invasive methods involve examination of tissues obtained via gastrointestinal endoscopy. Histological examination can directly detect the presence of *H. pylori* with 80%–95% sensitivity and 98%–100% specificity,[79,80] but causes significant discomfort to patients and is highly dependent on the quality and location of the sample. Bacterial culture methods with 80%–95% sensitivity and 98%–100% specificity and can be used to confirm *H. pylori* infection for clinical treatment; however, they require long culture times, stringent culture conditions, high costs, and complex operations.[80–82] Rapid urease tests are quick and straightforward, providing results within an hour with 80%–95% sensitivity and 80%–100% specificity; however, their sensitivity is affected by the sample size and bacterial load, leading to potential false positives.[80,83–85] Finally, molecular biology methods applicable to both non-invasive and invasive testing, such as PCR techniques for analyzing *H. pylori* DNA and high-throughput sequencing technologies (NGS) with quite high sensitivity and specificity,[86–88] can comprehensively analyze the *H. pylori* genome in samples, providing detailed genetic information and antibiotic resistance analysis.[89–91] These methods enhance the sensitivity of traditional detection techniques and offer more precise diagnostic tools, facilitating early detection and treatment of *H. pylori* infection. The relevant details are presented in Table 1.

Table 1 Recent *H. Pylori* Infection Detection Method Summary

Diagnostic Methods	Principle	Advantages	Disadvantages	Sensitivity	Specificity	Ref
Non-Invasive Test						
Urea Breath Test (UBT)	Measure the concentration of labeled carbon dioxide in the breath after the patient ingests labeled urea	Rapid diagnosis, simple operation, low cost, high specificity, non-invasive, high patient acceptance	Previous use of antibiotics, proton pump inhibitors, etc., can cause false negatives	90%–95%	95%–98%	[74,75]
Stool antigen test (SAT)	Identify the presence of bacterial antigens in a stool sample	Easy to collect samples, low cost, relatively high sensitivity and specificity, suitable for large-scale screening	Not applicable to all patients, high transportation condition requirements	85%–95%	90%–95%	[76,77]
Serology	Measure specific antibodies against the bacteria in the patient's blood	Easy sample collection, rapid diagnosis, suitable for large-scale screening	Cannot distinguish past infection, unable to assess treatment efficacy	80%–95%	80%–95%	[76,78]
Invasive test						
Histology	Stain and directly observe *H. pylori* in gastric biopsy samples under a microscope	Visualization, detailed information about gastric mucosa, simultaneous pathology assessment, permanent record	Time-consuming, high cost, operator and sample quality dependence	80%–95%	98%–100%	[79,80]

(*Continued*)

Table 1 (Continued).

Diagnostic Methods	Principle	Advantages	Disadvantages	Sensitivity	Specificity	Ref
Rapid urease test (RUT)	Identify the presence of urease enzyme activity in gastric biopsy samples	Rapid diagnosis, simple operation, cost-effective, high specificity and sensitivity, on-site testing.	Invasive, false negatives, sample quality and location dependence, non-quantitative	80%–95%	80%–100%	[80,84,85]
Bacteria culture	Grow the bacteria from gastric biopsy samples in a controlled laboratory environment	Provides direct evidence of *H. pylori* presence, high specificity, allows for antibiotic susceptibility testing	Invasive, time-consuming culture, high cost, high technical requirements	80%–95%	98%–100%	[80,82]
Molecular biology						
PCR	Amplification of specific *H. pylori* DNA fragments to detect targeted genes such as CagA, VacA	Fast, highly sensitive, low cost, simple operation, capable of detecting specific genes	Limited information, risk of false negatives and false positives, unable to comprehensively analyze resistance, invasive sampling may be required in some cases	75%~95%	95%	[87,88]
NGS	High-throughput sequencing to analyze the entire genome of *H. pylori*, identifying genes, mutations, virulence factors, and resistance markers	Comprehensive genomic analysis, high sensitivity, strong resistance detection capability, applicable to various sample types.	High cost, time-consuming, requires advanced technology, higher risk of false positives, unable to distinguish current infection from past infection	95%	95%	[86]

Apoptosis Detection

Apoptosis plays a crucial role in the pathogenesis of various diseases, and its detection provides deeper insights into disease onset and progression. Recent studies have demonstrated that the assessment of apoptotic markers—such as cleaved caspase-3, BAX, and BCL-2—not only reflects the extent of *H. pylori*-induced gastric mucosal damage but is also closely associated with disease severity and patient prognosis. For example, elevated expression of cleaved caspase-3 and higher apoptotic indices in gastric mucosal biopsies are often indicative of advanced gastritis, increased mucosal atrophy, and a heightened risk of gastric cancer.[92] In patients with gastric cancer, a low BCL-2/BAX ratio or persistently high levels of apoptotic markers are generally correlated with poorer prognosis and reduced overall survival.[93,94] Moreover, patients who exhibit a significant decrease in apoptotic marker levels following *H. pylori* eradication therapy frequently experience symptom relief and histological improvement, such as resolution of inflammation and glandular restoration, suggesting that these markers may serve as early indicators of therapeutic response.

Therefore, the incorporation of apoptotic marker detection into clinical practice holds significant potential for risk stratification, prognostic assessment, and personalized treatment in *H. pylori*-associated gastric diseases. Currently, standard methods for detecting apoptosis include TUNEL staining,[95] caspase activity assays,[96] Western blotting[97] and flow cytometry (as shown in Table 2).[98] TUNEL staining directly observes DNA fragmentation in cells, revealing the degree and location of apoptosis. Its advantages include intuitive and accurate localization; however, it requires cell fixation and permeabilization, which makes the procedure complex. Caspase activity assays detect changes in the activity of critical enzymes during apoptosis and offer high specificity and sensitivity. However, this method can only indirectly reflect the apoptotic state and cannot provide specific information about the apoptotic cells.

Flow cytometry can accurately quantify the proportion of apoptotic cells, offering rapid and precise quantitative analysis. However, this method requires the preparation of single-cell suspensions, complex procedures, and expensive equipment. Western blotting was used to detect the expression levels of apoptosis-related proteins (such as BAX, BCL-2,

Table 2 Recent Apoptosis Detection Method Summary

Diagnostic Methods	Principle	Advantages	Disadvantages	Ref
Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL Assay)	Label and detect DNA strand breaks (hallmark of apoptosis)	High sensitivity, capable of detecting both early and late apoptotic cells	Detect non-specific DNA damage, false positives	[95]
Caspase Activity Assays	Measure the activity of caspases, enzymes activated during apoptosis (eg, caspase-3, caspase-8, caspase-9)	High specificity, distinguish different apoptotic pathways	Indirectly reflect the apoptotic state, require specialized equipment and reagents	[96]
Western Blot	Detect expression levels of apoptosis-related proteins (eg, Bax, Bcl-2, cleaved PARP)	Quantify changes in apoptotic protein expression	Time-consuming, technically demanding	[97]
Flow Cytometry	Use fluorescent labeling to detect and quantify apoptotic cells	High throughput, analyze large numbers of cells quickly	Require expensive flow cytometry equipment and skilled personnel	[98]

and Caspase-3). This method has high sensitivity and specificity and can detect multiple proteins; however, it involves cumbersome steps and relatively complex quantitative analysis.

Combined diagnostic methods should be considered to effectively assess the progression of *H. pylori*-induced apoptosis and to evaluate its severity. For example, combining Western blotting and PCR can simultaneously provide information on the expression levels of apoptosis-related proteins and direct evidence of *H. pylori* infection. This can aid in an in-depth study of the mechanisms by which *H. pylori* induces apoptosis. Flow cytometry and TUNEL staining can be used for quantitative analysis, providing accurate proportions of apoptotic cells and levels of *H. pylori* infection. Comprehensive application of these methods can improve diagnostic accuracy and facilitate the early detection of *H. pylori* infection and its induced apoptosis, providing opportunities for early intervention. Physicians can develop individualized treatment plans based on comprehensive detection results to improve therapeutic outcomes. However, combined methods typically require more complex procedures and higher equipment and reagent requirements, making them less accessible.

Future Directions

Challenges and Opportunities

Current diagnostic methods for detecting *H. pylori* infection and its apoptosis-inducing effects have established a solid foundation for clinical application. However, challenges persist in terms of sensitivity, specificity, accessibility, and adaptability to diverse clinical and geographical settings. Non-invasive methods, such as urea breath tests and stool antigen tests, are convenient but can be affected by recent antibiotic use or dietary factors, limiting their accuracy. Invasive methods, including histological examination and rapid urease tests, rely heavily on sample quality and technical expertise, making them less feasible in resource-limited settings. Specifically in low- and middle-income nations, these challenges are further amplified by the lack of adequate healthcare infrastructure, limited access to specialized diagnostic equipment, and financial constraints faced by both healthcare providers and patients. For instance, the high cost of molecular diagnostics and advanced imaging technologies often renders them inaccessible in these regions, despite their potential to improve detection accuracy. Moreover, logistical barriers, such as poor supply chain management and lack of maintenance for diagnostic equipment, further hinder the implementation of advanced diagnostic techniques. Addressing these unmet needs requires a focus on developing diagnostic solutions that prioritize affordability, simplicity, and adaptability to resource-constrained environments. Innovations such as low-cost point-of-care testing,[99,100] multiplex molecular diagnostics,[101] AI-driven data analysis for simplified diagnostics, and portable molecular diagnostic devices could provide transformative solutions for in low- and middle-income nations.

Emerging Trends in Research

Emerging technologies offer significant potential to improve the diagnosis of *H. pylori* infection and its apoptosis-inducing effects. For instance, loop-mediated isothermal amplification (LAMP) and NGS enable rapid and highly sensitive detection of *H. pylori*, including virulence factors such as CagA and VacA, facilitating early diagnosis and strain typing.[102] Advances in imaging technologies, such as confocal laser endomicroscopy (CLE),[103] allow the real-time visualization of cellular changes during infection, including apoptotic processes. These tools not only contribute to a more precise understanding of apoptosis mechanisms but also enable detailed evaluation of tissue damage caused by *H. pylori* infection.

The rapid development of nanotechnology has created new opportunities for *H. pylori* diagnosis. Owing to their high sensitivity and specificity, nanoparticles can be used to efficiently and cost-effectively detect *H. pylori*-related biomarkers efficiently and cost-effectively.[104] Moreover, ongoing research is focusing on the development of "theragnostic" tools that utilize nanoparticles for targeted drug delivery while simultaneously monitoring the infection status and advancing precision medicine.

Artificial intelligence (AI) and machine learning have also provided innovative approaches for *H. pylori* diagnosis. These technologies can analyze complex datasets, such as genomic or multi-omics data, improving diagnostic accuracy and efficiency, while enabling automated diagnostic processes. CRISPR-Cas systems have recently been developed as novel molecular diagnostic tools capable of rapid and specific detection of *H. pylori* genes, further strengthening the capabilities of molecular diagnostics.[99]

Despite these advancements, several fundamental challenges remain. Patient compliance is a critical issue, particularly in resource-limited settings where the acceptance of new diagnostic technologies may be low. Additionally, the widespread adoption of these technologies in clinical practice and by the general public requires further validation. The regional variability of *H. pylori* strains also highlights the necessity of developing localized diagnostic tools tailored to specific strain characteristics. Finally, the lack of standardized diagnostic protocols remains a significant challenge. Establishing globally unified detection guidelines and technical standards is essential to ensure comparability and reliability of diagnostic results.

Discussion

This review systematically summarizes the molecular mechanisms by which *H. pylori* induces gastric mucosal cell apoptosis, in conjunction with the progression of related diseases such as gastritis, ulcers, and gastric cancer. It also provides a comprehensive analysis of both conventional and emerging diagnostic techniques for *H. pylori* infection and apoptosis. Compared to previous literature, this review focuses on the systematic integration of multiple mechanisms—including virulence factors such as CagA and VacA, with disease evolution, histopathological changes, and clinical manifestations. In addition, it offers a comparative evaluation of the clinical value, limitations, and applicable scenarios of various detection methods.

Future research should emphasize the combined application of multiple diagnostic approaches to comprehensively assess the impact of *H. pylori* on disease progression and to explore novel therapeutic strategies for improving clinical outcomes. Furthermore, efforts are needed to promote the clinical translation of research findings by incorporating innovative molecular detection and apoptosis marker assays into routine clinical practice, thereby enhancing early diagnosis and personalized treatment. Special attention should also be given to the needs of low- and middle-income countries, including the development of low-cost, portable, and user-friendly diagnostic methods to improve the screening and management of *H. pylori*-associated diseases, and to promote global disease prevention and health equity.

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Disclosure

The authors declare no conflicts of interest in this work.

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