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Advances in Helicobacter pylori-Associated Extragastric Diseases: Postprint

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Abstract

Helicobacter pylori (Hp) is a common Gram-negative bacillus that infects the gastrointestinal tract, primarily residing on the surface of gastric epithelial cells and in mucus, and is associated with gastric ulcers, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma. Studies have shown that H. pylori may induce or exacerbate certain extragastric diseases, and recent research has also reported an association between H. pylori and coronavirus disease 2019; it participates in the onset and progression of diseases indirectly or directly by stimulating the production of inflammatory cytokines or through cross-immune reactions. Furthermore, H. pylori can also enter Candida cells, release toxins to participate in extragastric diseases, and evade the immune system and drug effects. This article summarizes recent foreign research reports on H. pylori-associated extragastric diseases, aiming to raise clinical awareness of H. pylori-associated extragastric diseases, disseminate interdisciplinary knowledge, and prevent H. pylori from exacerbating or inducing other diseases.

[Keywords] Helicobacter pylori; extragastric diseases; cross-immune reaction; coronavirus disease 2019

Full Text

Research Progress on Helicobacter pylori-Related Extragastric Diseases

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Abstract

Helicobacter pylori (Hp) is a common gram-negative bacterium that infects the gastrointestinal tract. It primarily resides on the surface of gastric epithelial cells and within mucus, and is associated with gastric ulcer, gastric cancer, and gastric mucosa-associated lymphoma. Some studies have shown that H. pylori may induce or aggravate certain extragastric diseases. Recently, research has reported an association between H. pylori and novel coronavirus pneumonia (COVID-19). H. pylori participates in the occurrence and development of diseases indirectly or directly by stimulating the production of inflammatory factors or triggering cross-immune responses. Additionally, H. pylori can enter Candida cells, release toxins, contribute to extragastric diseases, and evade both the immune system and drug effects. This paper summarizes recent international research reports on H. pylori-related extragastric diseases, aiming to raise clinical awareness of these conditions, disseminate relevant knowledge, and prevent the exacerbation of H. pylori infection or other diseases.

Keywords: Helicobacter pylori; extragastric diseases; cross-immune response; novel coronavirus pneumonia

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The global infection rate of Helicobacter pylori exceeds 50% [1], with significantly higher prevalence in developing countries compared to developed nations [2]. Beyond gastric diseases, mounting evidence demonstrates that H. pylori infection correlates with disorders of the cardiovascular [3], immune [4], and nervous systems [5,6]. Recent studies have also reported an association between H. pylori and COVID-19 [7]. H. pylori infection complicates the treatment of certain diseases, and clinicians often overlook its relevance to extragastric diseases during early infection stages, leading to exacerbation of patients' existing conditions.

H. pylori is a spiral-shaped gram-negative bacterium. Its pathogenicity is associated with flagella, adhesins, cytotoxin-associated protein A (CagA), and vacuolating toxin A (VacA) [8]. CagA represents the most characteristic virulence factor—an immunodominant protein encoded by the cagA gene within the cag pathogenicity island, with a molecular weight of approximately 140 kDa [9].

These virulence factors can directly damage the host or induce inflammatory responses that increase inflammatory cytokines and trigger disease. For example, CagA can stimulate the production of interleukin-6 (IL-6) and tumor necrosis factor, promoting thyroid cell apoptosis and inducing thyroid disease [10]. Therefore, neutralizing certain toxins secreted by H. pylori should be considered in clinical treatment strategies.

Recent research indicates that H. pylori can form a prokaryotic-eukaryotic symbiont with Candida [11]. When internalized by Candida, H. pylori can continuously release virulence factors extracellularly while evading antibiotic effects [12], thereby exerting persistent influence on the host. Furthermore, some H. pylori-infected individuals remain asymptomatic [13] and do not receive timely treatment, allowing continuous production of virulence factors that affect extragastric diseases. This review summarizes selected H. pylori-related extragastric diseases and briefly describes their pathogenic mechanisms, aiming to broaden clinical perspectives on H. pylori treatment and highlight the importance of intervening against specific virulence factors.

1.1 Lung Cancer

Lung cancer is the leading cause of cancer mortality in China, typically classified as non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). Its etiology remains unclear. Recent studies have implicated certain pathogenic microorganisms—including H. pylori—in lung carcinogenesis [14]. Data from Beijing, China, demonstrate that H. pylori infection correlates with tumor marker levels: infected lung cancer patients exhibit higher carcinoembryonic antigen (CEA) levels but lower alpha-fetoprotein (AFP) and CA724 levels [15]. Elevated CEA indirectly reflects cancer progression or recurrence, suggesting that H. pylori may play a role in specific cancers. This provides clinical insight: for H. pylori-infected patients, clinicians should recognize that tumor marker levels may be influenced by the infection and consider whether H. pylori should be incorporated into overall assessment of cancer progression and treatment. For such patients, international research has identified “tailor-made” therapeutics such as biocompatible silver nanoparticles, which can both target lung cancer cells and inhibit H. pylori [16].

Additionally, H. pylori infection significantly reduces interferon and IL-6 expression in NSCLC patients receiving immunotherapy, impairing treatment efficacy—likely due to VacA-mediated inhibition of myeloid cell activity [17]. These findings suggest that: (1) neutralizing H. pylori toxins is as important as eradicating the bacterium; (2) serological testing for H. pylori could be incorporated into evaluating the expected efficacy of immunotherapy for NSCLC; and (3) this concept warrants further investigation and may be extended to other tumors to assess treatment effectiveness.

1.2 COVID-19

COVID-19, caused by the novel coronavirus, is among the deadliest pandemics in history. The virus enters cells by binding to the angiotensin-converting enzyme-2 (ACE-2) receptor [18], causing respiratory and other clinical manifestations. Research indicates that H. pylori upregulates ACE-2 receptor expression on intestinal cells, facilitating viral entry and resulting in more severe gastrointestinal symptoms such as abdominal pain and diarrhea compared to uninfected individuals [19]. Moreover, H. pylori stimulates production of inflammatory mediators including tumor necrosis factor-alpha and IL-8, which together with the virus mediate acute lung injury [20].

Beyond the infection phase, a *Gut* study demonstrated that proton pump inhibitor (PPI) use during H. pylori treatment increases susceptibility to COVID-19 and correlates with severe clinical symptoms, possibly due to PPI-induced elevation of plasma chromogranin A (CgA) levels [22]. CgA levels serve as an independent predictor of early mortality in COVID-19 patients [23], highlighting its potential role in disease pathogenesis.

2.1 Alzheimer's Disease

Since H. pylori does not directly invade the nervous system, early medical research overlooked its role in neurological diseases. Alzheimer's disease (AD) is a neurodegenerative disorder characterized by neuronal loss in the cerebral cortex and subcortical regions. In recent years, scholars have begun investigating the relationship between AD and pathogenic microbial infections, with H. pylori emerging as a potential etiological factor [25].

Some researchers believe a clear association exists between H. pylori and AD [26], with proposed mechanisms including: (1) outer membrane vesicles released by gram-negative bacteria can carry virulence factors [27], and H. pylori vesicles can cross the blood-brain barrier, induce glial cell activation, and impair neuronal function, accelerating AD development; (2) H. pylori urease possesses pro-inflammatory activity and can activate the immune system, triggering neuroinflammation and neurodegeneration [28]; and (3) H. pylori increases intestinal mucosal permeability and causes gut dysbiosis, serving as a key initiating factor for AD [29].

2.2 Other Neurological Diseases

The relationships between H. pylori and other neurological diseases, along with potential mechanisms, are summarized in Table 1 . In Parkinson's disease, H. pylori can inhibit levodopa absorption during treatment, reducing plasma drug concentrations [33]. In multiple sclerosis, the association may relate to H. pylori-induced cellular and humoral immune responses [35]. For migraine, the connection may involve H. pylori-stimulated release of inflammatory mediators and disruption of the gut microbiota [37].

2.3 Significance of H. pylori Treatment for Neurological Diseases

These H. pylori-associated neurological diseases demonstrate that H. pylori-induced pathology extends beyond the stomach and digestive system. While most neurological diseases have unclear etiologies, H. pylori has been widely reported in association with them. These findings reveal the importance of H. pylori treatment in neurological diseases: (1) H. pylori outer membrane vesicles are detectable only three weeks after infection [27], underscoring the importance of early detection and eradication; (2) the studies highlight the significance of gut microbiota for the nervous system, with scholars metaphorically terming this relationship the "gut-brain axis" [38]—a multi-mechanism connection between the enteric and central nervous systems that includes microbial participation, while H. pylori can affect the native gut flora [39]. Therefore, researchers have proposed the hypothesis that probiotic treatment may be effective for neurological diseases [40], a hypothesis confirmed by studies showing that long-term oral probiotics can delay AD progression in mice and help reduce H. pylori treatment side effects [41].

3.1 Hyperemesis Gravidarum

Hyperemesis gravidarum is a condition characterized by nausea and vomiting during pregnancy due to altered progesterone levels. Research has linked H. pylori to this condition [42]. Another study detected H. pylori-specific antigens in amniotic fluid via amniocentesis, finding higher hyperemesis gravidarum incidence in patients with positive amniotic fluid H. pylori compared to negative controls [43]. This research broadens clinical approaches to H. pylori detection. Additionally, studies have demonstrated that H. pylori infection during pregnancy adversely affects fetal development (e.g., smaller biparietal diameter, lower birth weight, and smaller head circumference) [44], indicating that detection in amniotic fluid warrants prompt eradication to avoid dual maternal and fetal impacts. While amniotic fluid testing directly suggests intrauterine H. pylori presence, the study did not compare positivity rates with stool testing. If stool-positive patients also harbor H. pylori antigens in amniotic fluid, patients and clinicians would prefer non-invasive testing.

3.2 Male Infertility

Male infertility involves complex pathogenic mechanisms [45], with many cases remaining idiopathic [46]. Recent international research suggests an association between H. pylori infection and male infertility [47], with infected individuals showing reduced sperm motility, concentration, and fertility index [48]. One study found that androgen-deprivation therapy for prostate cancer patients with H. pylori infection resulted in lower mortality, leading researchers to speculate that H. pylori may affect male androgen levels [49]. Additionally, research has identified partial structural homology between tubulin—the main component of sperm flagella—and H. pylori flagellin, CagA, and VacA, suggesting that H.

pylori may trigger cross-immunity [50] and induce anti-sperm antibodies that impair sperm quality.

3.3 H. pylori Treatment in Special Populations

Given the impact of H. pylori on both mother and fetus during pregnancy, early detection and eradication are crucial. Current H. pylori treatment recommendations involve two antibiotics plus a proton pump inhibitor (PPI) and bismuth. However, pregnancy requires cautious antibiotic use, as known risks include transplacental effects on the fetus and reduced IgG levels in breast milk, compromising neonatal immunity [51]. Furthermore, PPI use increases risks of preeclampsia and gestational diabetes in pregnant women [52]. *In vitro* studies show that pantoprazole impairs sperm capacitation by increasing protein phosphorylation and preventing membrane hyperpolarization [53], while esomeprazole—a new-generation PPI—reduces total motile sperm count within 60 minutes of administration [54]. Therefore, H. pylori treatment in special populations requires particular care. Probiotic supplementation is recommended as an adjunct therapy for the following reasons: (1) probiotics during pregnancy reduce preeclampsia and gestational diabetes incidence [55]; (2) in male infertility patients, probiotics improve semen quality by modulating gut microbiota [56]; and (3) probiotics enhance antibiotic efficacy and reduce H. pylori recurrence [57].

4.1 Transmission Routes

Traditional H. pylori transmission routes are considered fecal-oral and oral-oral [58]. However, since 2008, researchers have proposed sexual transmission [59], with studies showing significantly higher H. pylori prevalence among sexual partners compared to controls [60]. Evidence supporting sexual transmission includes: (1) detection of H. pylori in the oral cavity [61,62], demonstrating its ability to colonize this environment; and (2) identification of H. pylori virulence genes in the female vagina [63]. Therefore, H. pylori may be sexually transmitted, possibly even vertically from mother to child. Clarifying specific transmission routes would facilitate scientific prevention and reduce extragastric disease. However, limitations remain: for example, the study showing higher prevalence among sexual partners [60] only measured positivity rates without confirming H. pylori homology between spouses. Nevertheless, one point is certain: H. pylori readily spreads within families [64]. We recommend that, given diverse transmission routes, H. pylori screening and prevention should be family-based.

4.2 Formation of Eukaryotic-Prokaryotic Symbionts

Candida is a fungus that inhabits the female vagina, while H. pylori is the only bacterium known to live in the stomach—making their association unlikely. However, recent research has detected H. pylori-specific nucleic acids within Candida from female vaginal secretions [65]. *In vitro* experiments also show that H. pylori enters Candida to escape unfavorable conditions: while gastric

H. pylori catalyzes urea to produce ammonia that reduces gastric acidity, the low urea content in the vagina prompts H. pylori to enter Candida cells, forming a eukaryotic-prokaryotic symbiont [65-67] through H. pylori internalization by Candida, which can enhance bacterial pathogenicity [68]. H. pylori within Candida can still release CagA extracellularly, indicating its potential to produce virulence factors that cause extragastric disease (see Figure 1 [Figure 1: see original paper]). Therefore, H. pylori eradication and screening should not be limited to the stomach but must also disrupt these symbionts. Research shows that Candida cell wall alterations under nutrient deficiency prevent H. pylori entry [66], offering new strategies to prevent symbiont formation.

5. Summary and Outlook

In recent years, substantial evidence has demonstrated that H. pylori infection produces complex manifestations and associates with numerous systemic diseases. As summarized in this review for respiratory, neurological, and reproductive systems, H. pylori need not directly invade these systems—even H. pylori within Candida can release virulence factors. Through virulence factors and cross-reactive antigens, H. pylori can cause extragastric disease, indicating that treatment and screening require comprehensive consideration. However, given the many H. pylori subtypes, future research should focus on clarifying associations between specific subtypes and different diseases, as well as targeted therapies.

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Note: Figure translations are in progress. See original paper for figures.

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