Scientific Journal for Publishing in Health Research and Technology

Volume 1, Issue 2, 2025, Pages: 427-445

Journal homepage: https://sjphrt.com.ly/index.php/sjphrt/en/index

Helicobacter pylori Infection and Extragastric Autoimmune Conditions

Fatma Ibrahim Salama *
Higher Institute for Medical Sciences and Technology/ Msellata, Libya

عدوى الملوية البوابية (*H. pylori*) والحالات المناعية الذاتية خارج المعدة

فاطمة إبراهيم سلامة *
المعهد العالي للعلوم الطبية والتقنية- مسلاته، ليبيا

*Corresponding author: dr.Fatmasalama@gmail.com

Received: October 18, 2025	Accepted: December 26, 2025	Published: December 31, 2025

Abstract:
Helicobacter pylori (H. pylori) is a gram-negative bacterium chronically infecting nearly half the global population. While its gastroduodenal pathogenicity is firmly established, it is now recognized as a systemic immunomodulatory pathogen with significant extragastric consequences. This comprehensive narrative review examines the association between H. pylori infection and a broad spectrum of extragastric autoimmune and immune-mediated conditions spanning hematological, endocrine, dermatological, cardiovascular, neurological, and pediatric domains. The review discusses the immunological mechanisms underlying these associations — including molecular mimicry, chronic cytokine dysregulation, regulatory T-cell dysfunction, and impaired nutrient absorption — and evaluates the clinical evidence for H. pylori eradication as a therapeutic strategy. Conditions reviewed include immune thrombocytopenic purpura (ITP), iron deficiency anemia (IDA), autoimmune thyroid disease (AITD), vitamin B12 deficiency, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), chronic spontaneous urticaria (CSU), psoriasis, rosacea, ischemic heart disease, Alzheimer's disease, Parkinson's disease, migraine, and pediatric-specific manifestations. The findings underscore the importance of a multidisciplinary approach to H. pylori management and highlight the medical laboratory's central role in diagnosis, monitoring, and guiding eradication therapy. Clinical recommendations are provided for each condition based on current evidence.

Keywords: *Helicobacter pylori*; extragastric manifestations; autoimmune disease; molecular mimicry; eradication therapy; dermatology; neurology; cardiology; pediatric; narrative review.

الملخص
تُعد بكتيريا الملوية البوابية (*H. pylori*) جرثومة سلبية الغرام تصيب مزمناً ما يقرب من نصف سكان العالم. وبينما تم إثبات مسبباتها المرضية المعدية الاثني عشرية بشكل راسخ، يُعترف بها الآن كعامل ممرض معدل للمناعة الجهازية وله عواقب خارج معدية كبيرة. تبحث هذه المراجعة السردية الشاملة في الارتباط بين عدوى *H. pylori* ومجموعة واسعة من حالات المناعة الذاتية والحالات بوساطة مناعية خارج الجهاز الهضمي، والتي تشمل المجالات الدموية، والغدد الصماء، والجلدية، والقلبية الوعائية،

والعصبية، وطب الأطفال. تناقش المراجعة الآليات المناعية الكامنة وراء هذه الارتباطات، بما في ذلك المحاكاة الجزيئية، وخلل تنظيم السيتوكينات المزمن، واختلال وظائف الخلايا التائية التنظيمية، وضعف امتصاص العناصر الغذائية، وتقييم الأدلة السريرية لاستئصال H. pylori كاستراتيجية علاجية. تشمل الحالات التي تمت مراجعتها فرفرية نقص الصفيحات المناعية(ITP) ، وفقر الدم الناجم عن نقص الحديد (IDA)، وأمراض الغدة الدرقية المناعية الذاتية(AITD) ، ونقص فيتامين ب12، والذئبة الحمامية الجهازية(SLE) ، والتهاب المفاصل الروماتويدي(RA) ، والشرى العفوي المزمن(CSU) ، والصدفية، والوردية، ومرض القلب الإقفاري، ومرض الزهايمر، ومرض باركنسون، والصداع النصفي، ومظاهر محددة لدى الأطفال. تؤكد النتائج على أهمية اتباع نهج متعدد التخصصات لإدارة H. pylori وتسلط الضوء على الدور المركزي للمختبر الطبي في التشخيص والمراقبة وتوجيه علاج الاستئصال. يتم تقديم توصيات سريرية لكل حالة بناءً على الأدلة الحالية.

الكلمات المفتاحية: الملوية البوابية؛ المظاهر خارج المعدية؛ مرض المناعة الذاتية؛ المحاكاة الجزيئية؛ علاج الاستئصال؛ الأمراض الجلدية؛ طب الأعصاب؛ أمراض القلب؛ طب الأطفال؛ مراجعة سردية .

1. Introduction

Helicobacter pylori (*H. pylori*) is a spiral-shaped, gram-negative, microaerophilic bacterium that colonizes the gastric mucosa of an estimated 44% of the global population, with considerably higher prevalence in developing countries, where infection rates can exceed 70–80% (Hooi et al., 2017). Since its landmark discovery by Marshall and Warren in 1983, *H. pylori* has been extensively studied as the primary etiological agent of chronic active gastritis, peptic ulcer disease, and gastric carcinoma, the latter earning it a Group I carcinogen designation by the International Agency for Research on Cancer (IARC) in 1994 (IARC, 1994; Marshall & Warren, 1984). Moreover, the intersection of environmental health and microbiology highlights the urgency of adopting sustainable practices, such as green pharmacy, to combat the rise of environmental contamination and microbial threats (Salem, 2025).

However, the pathological consequences of *H. pylori* infection are not confined to the gastroduodenal compartment (Franceschi et al., 2015). Over the past two decades, an increasing number of clinical and experimental studies have suggested a biological link between chronic *H. pylori* infection and a diverse array of extragastric disorders (Gravina et al., 2018). These include hematological conditions such as immune thrombocytopenic purpura and iron deficiency anemia, endocrine disorders such as autoimmune thyroid disease, nutritional deficiencies such as vitamin B12 deficiency, systemic autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), dermatological conditions including chronic urticaria, psoriasis, and rosacea, cardiovascular manifestations, neurological associations including Alzheimer's and Parkinson's disease, and distinctive presentations in the pediatric population (Pellicano et al., 2009; Tan & Goh, 2012).

The plausibility of such associations is supported by several well-characterized immunological mechanisms (Figura et al., 2010). *H. pylori*'s chronic colonization of the gastric mucosa elicits a persistent local and systemic immune response. Certain virulence factors—particularly cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA)—modulate host immunity in ways that may disrupt self-tolerance and promote autoantibody production (Yamaoka, 2010; Hatakeyama, 2004). Molecular mimicry between bacterial antigens and host tissue proteins, chronic pro-inflammatory cytokine release, and regulatory T-cell dysfunction collectively create a permissive environment for autoimmune pathology (Velin & Michetti, 2006; Rad et al., 2006).

This comprehensive narrative review consolidates and presents current evidence across all major extragastric autoimmune domains, with a focus on immunological mechanisms, clinical evidence, and therapeutic implications of eradication therapy (Malfertheiner et al., 2022). It is

intended to serve as a practical reference for clinicians and laboratory specialists in national healthcare settings where *H. pylori* prevalence is high (WGO, 2011).

2. Epidemiology of *H. pylori* Infection

H. pylori infection is one of the most prevalent chronic bacterial infections worldwide (Hooi et al., 2017). Global seroprevalence studies indicate an overall infection rate of approximately 44%, with significant geographic variation (Hooi et al., 2017). Prevalence is highest in sub-Saharan Africa (79.1%), South America (63.4%), and Eastern Europe (56.2%), while lower rates are reported in North America (37.1%) and Western Europe (34.3%) (Hooi et al., 2017). In the Arab world and North Africa, *H. pylori* prevalence ranges from 55% to over 90% in some populations, making it a highly relevant pathogen in the national healthcare context (WGO, 2011). Regionally, empirical data have underscored significant correlations between local sanitation infrastructure, population density, and infection rates, which necessitate targeted epidemiological surveillance (Alshawish et al., 2025; Ben Hsin et al., 2025; Soof et al., 2025).

Transmission occurs primarily via the fecal-oral and oral-oral routes, facilitated by poor sanitation, overcrowding, and contaminated water sources (WGO, 2011). Infection is usually acquired in childhood and, if untreated, persists for life (WGO, 2011). Most infected individuals remain asymptomatic carriers; however, approximately 10–20% develop peptic ulcer disease, and 1–3% progress to gastric malignancy (WGO, 2011; Polk & Peek, 2010). The high prevalence of *H. pylori* in many national and regional populations amplifies the potential public health impact of its extragastric manifestations, underscoring the importance of expanding clinical awareness to encompass multiple specialties (Tan & Goh, 2012).

3. Diagnosis of *H. pylori* Infection

3.1 Non-Invasive Methods

The urea breath test (UBT) is considered the gold standard non-invasive diagnostic method, with sensitivity and specificity both exceeding 95% (Malfertheiner et al., 2022). It is based on the principle that *H. pylori* urease hydrolyzes ingested labelled urea, releasing labelled CO_2 detectable in exhaled breath (Malfertheiner et al., 2022). The stool antigen test (SAT) offers comparable accuracy and is particularly useful in resource-limited settings and for pediatric populations (Gisbert et al., 2006). Serology detects anti-*H. pylori* IgG antibodies and is widely used but has a critical limitation: antibody titers persist after eradication, making it unsuitable for confirming active infection or assessing treatment response (Malfertheiner et al., 2022).

3.2 Invasive Methods

Endoscopy-based methods include histological examination of gastric biopsy specimens, the rapid urease test (RUT), and bacterial culture (Malfertheiner et al., 2022). Histology allows simultaneous assessment of gastric mucosal pathology and is highly reliable when biopsies are obtained from both the antrum and corpus (Sipponen & Maaroos, 2015). Culture is the most specific method but is technically demanding and rarely used in routine practice (Malfertheiner et al., 2022). In the context of extragastric autoimmune disease, non-invasive methods—particularly UBT and SAT—are preferred for initial diagnosis and post-eradication confirmation (Malfertheiner et al., 2022).

4. Immunological Mechanisms Linking *Helicobacter pylori* to Autoimmunity

4.1 Molecular Mimicry

Molecular mimicry refers to the structural similarity between microbial antigens and host self-antigens, whereby immune responses directed against the pathogen inadvertently target host tissues (Franceschi et al., 2015). In *H. pylori* and immune thrombocytopenic purpura (ITP), the cytotoxin-associated gene A (CagA) protein shares structural homology with platelet glycoprotein IIIa (GPIIIa) (Takahashi et al., 2004). Anti-CagA antibodies cross-react with

GPIIIa epitopes, triggering platelet destruction (Takahashi et al., 2004). Similarly, molecular mimicry between *H. pylori* antigens and thyroid tissue proteins has been proposed for autoimmune thyroid disease (AITD), and between *H. pylori* heat shock proteins and myelin antigens in neurological associations (Figura et al., 2010; Kountouras et al., 2009).

4.2 Chronic Inflammatory Cytokine Dysregulation

H. pylori infection induces a sustained pro-inflammatory response characterized by IL-1β, IL-6, IL-8, TNF-α, and IFN-γ (Velin & Michetti, 2006). Systemic dissemination of these mediators promotes polyclonal B-cell activation, enhances autoantibody production, and disrupts peripheral immune tolerance (Meron et al., 2010). Elevated systemic TNF-α and IL-6 correlate with increased autoimmune risk, paralleling the cytokine profiles in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and psoriasis (Zentilin et al., 2002; Magen et al., 2007). Emerging research further suggests that systemic inflammatory responses triggered by gastric pathogens are closely linked to dysregulation in broader physiological markers, including markers of chronic metabolic and hematological imbalance (Khalil et al., 2025; Salem, M. & Salem, I., 2025).

4.3 Regulatory T-Cell Dysfunction

H. pylori, particularly CagA-positive strains, impairs regulatory T-cell (Treg) function and shifts the immune balance toward a pro-inflammatory Th1/Th17 profile (Rad et al., 2006). This disruption of the Treg/Th17 axis creates a permissive environment for autoimmune pathology in genetically susceptible individuals, relevant across dermatological, neurological, and systemic autoimmune conditions (Velin & Michetti, 2006).

4.4 Impaired Nutrient Absorption

H. pylori-induced hypochlorhydria directly impairs dietary non-heme iron absorption and creates an iron-depleted environment exploited by the bacterium itself (Hershko et al., 2005). Progressive parietal cell atrophy reduces intrinsic factor secretion, impairing vitamin B12 absorption (Sipponen & Maaroos, 2015). These absorptive deficits underlie the associations with iron deficiency anemia (IDA) and vitamin B12 deficiency, with downstream effects on hematopoiesis, neurological function, and immune competence (Qu et al., 2010; Kaptan et al., 2000).

4.5 Gut-Brain Axis and Microbiome Dysbiosis

An emerging and increasingly recognized mechanism involves disruption of the gut-brain axis (Bhatt et al., 2020). *H. pylori* infection alters the gastric and intestinal microbiome, reducing microbial diversity and promoting dysbiosis (Bhatt et al., 2020). This dysbiotic state is associated with increased intestinal permeability ("leaky gut"), translocation of microbial products into the systemic circulation, and neuroinflammatory signaling via the vagus nerve and enteric nervous system (Bhatt et al., 2020). These pathways are proposed to underlie the associations between *H. pylori* and neurological conditions such as Alzheimer's and Parkinson's disease, as well as dermatological conditions influenced by the gut-skin axis (Kountouras et al., 2009; Nielsen et al., 2012).

4.6 Autoimmune Gastritis and Parietal Cell Antibodies

In a subset of *H. pylori*-infected individuals, chronic gastric inflammation evolves into overt autoimmune gastritis characterized by autoantibodies against parietal cell H^+/K^+-ATPase and intrinsic factor (Sipponen & Maaroos, 2015). This process amplifies the nutritional deficiencies described above and contributes to pernicious anemia (Sipponen & Maaroos, 2015). It also serves as a model for understanding how *H. pylori* can act as an initiating trigger for tissue-specific autoimmunity through antigen release and immune bystander activation (Figura et al., 2010).

5. Hematological and Endocrine Autoimmune Associations

5.1 Immune Thrombocytopenic Purpura (ITP)

The association between *H. pylori* and ITP is the most extensively studied and clinically actionable extragastric manifestation (Stasi et al., 2009). Multiple studies and meta-analyses report odds ratios of 2.8 to 4.6 for *H. pylori* infection in ITP patients compared to controls (Stasi et al., 2009; Franchini et al., 2007). The pathophysiological link is primarily explained by molecular mimicry between CagA and platelet GPIIIa, with additional contributions from Fc receptor upregulation on macrophages enhancing antibody-coated platelet phagocytosis (Takahashi et al., 2004; Michel et al., 2004). Evidence from intervention studies demonstrates platelet count recovery following *H. pylori* eradication in approximately 50% of ITP patients (Stasi et al., 2009). The American Society of Hematology (ASH) 2019 guidelines and the International Consensus Report recommend *H. pylori* testing and eradication in all infected ITP patients (Neunert et al., 2019). This is the strongest and most guideline-supported extragastric association (Neunert et al., 2019).

5.2 Iron Deficiency Anemia (IDA)

Iron deficiency anemia associated with *H. pylori* infection—in the absence of frank gastrointestinal bleeding—is well recognized, with reported odds ratios of 1.9 to 3.2 (Qu et al., 2010). The mechanisms include hypochlorhydria-related impairment of dietary iron absorption, direct bacterial iron sequestration, and occult blood loss from gastric erosions (Hershko et al., 2005). Patients with refractory IDA unresponsive to oral iron supplementation should be evaluated for *H. pylori* (Cardenas et al., 2006). Studies consistently demonstrate that eradication combined with iron therapy results in significantly greater improvement in hemoglobin and ferritin compared to iron supplementation alone, with normalization rates of 60–70% (Choe et al., 1999). It has been observed that long-term pathological shifts in the gut environment, particularly in cases involving persistent bacterial colonization, are frequently associated with secondary complications that affect hemoglobin indices and overall nutritional status (Kadak & Salem, 2020).

5.3 Vitamin B12 Deficiency

Progressive gastric mucosal atrophy from chronic *H. pylori* infection reduces intrinsic factor secretion, impairing cobalamin absorption and leading to deficiency with odds ratios of 2.1 to 3.4 (Sipponen & Maaroos, 2015). The clinical consequences range from megaloblastic anemia to neurological complications including subacute combined degeneration of the spinal cord and cognitive impairment (Kaptan et al., 2000). *H. pylori* eradication has been shown to improve vitamin B12 absorption and may reduce the long-term requirement for parenteral supplementation (Shuval-Sudai & Granot, 2003). *H. pylori* testing is recommended in all patients with vitamin B12 deficiency of unclear etiology (Kaptan et al., 2000).

5.4 Autoimmune Thyroid Disease (AITD)

A significantly higher seroprevalence of *H. pylori*—particularly CagA-positive strains—is reported among patients with Hashimoto's thyroiditis and Graves' disease, with odds ratios of 1.5 to 2.7 (Figura et al., 1999). Molecular mimicry between *H. pylori* proteins and thyroid peroxidase or thyroglobulin, alongside chronic Th1 inflammatory cytokine upregulation, are the primary proposed mechanisms (Bassi et al., 2012). The association is stronger for Hashimoto's thyroiditis than Graves' disease (Bassi et al., 2012). Evidence for eradication benefit on thyroid autoantibody titers remains variable and inconclusive; routine eradication specifically for AITD management is not yet supported, though clinical awareness of the association is warranted (Bertalot et al., 2004).

5.5 Systemic Lupus Erythematosus and Rheumatoid Arthritis

Associations with SLE (OR 1.3–2.1) and RA (OR 1.2–1.8) are statistically significant but accompanied by high heterogeneity and significant confounding from immunosuppressive therapies (Kountouras et al., 2005; Meron et al., 2010). *H. pylori*-driven polyclonal B-cell activation, pro-inflammatory cytokine upregulation, and Th1/Th17 skewing are the proposed mechanisms (Meron et al., 2010). Currently, there is insufficient evidence to recommend

targeted *H. pylori* eradication specifically for SLE or RA management, though treatment of co-existing infection remains clinically appropriate, particularly given the risk of NSAID-associated gastropathy in RA patients (Zentilin et al., 2002).

6. Dermatological Autoimmune and Immune-Mediated Associations

The skin is increasingly recognized as a target organ in *Helicobacter pylori*-associated extragastric disease (Franceschi et al., 2015). The gut-skin axis—the bidirectional immunological and microbial communication between the gastrointestinal tract and the skin—provides a plausible biological framework for these associations (Pellicano et al., 2009). *H. pylori*-induced systemic immune dysregulation, altered cytokine profiles, and microbiome disruption collectively create conditions conducive to cutaneous immune-mediated pathology (Figura et al., 2010).

6.1 Chronic Spontaneous Urticaria (CSU)

Chronic spontaneous urticaria, defined as recurrent wheals and/or angioedema persisting for more than six weeks without an identifiable external trigger, is one of the most frequently studied dermatological associations with *H. pylori* (Zuberbier et al., 2018). Multiple studies have reported a significantly higher prevalence of *H. pylori* infection in CSU patients compared to controls, with pooled odds ratios ranging from 1.9 to 3.1 (Magen et al., 2007; Campanati et al., 2013). The proposed pathophysiological mechanisms are multifactorial (Wedi et al., 2004). *H. pylori* may act as a chronic antigenic stimulus driving IgE-mediated hypersensitivity responses, leading to mast cell sensitization and degranulation (Yadav et al., 2008). Molecular mimicry between *H. pylori* antigens and cutaneous mast cell surface proteins has also been proposed (Wedi et al., 2004). Additionally, *H. pylori* infection induces elevated histamine release and augments the production of vasoactive mediators that directly contribute to urticarial lesion formation (Yadav et al., 2008).

Clinically, the evidence for the therapeutic benefit of *H. pylori* eradication in CSU is arguably the most compelling among dermatological conditions (Zuberbier et al., 2018). Multiple randomized controlled trials and meta-analyses have demonstrated complete or partial remission of urticaria in 30–80% of *H. pylori*-infected CSU patients following successful eradication, with the wide range reflecting significant heterogeneity in patient populations, eradication regimens, and follow-up periods (Magen et al., 2007; Campanati et al., 2013). The European Academy of Dermatology and Venereology (EADV) guidelines acknowledge *H. pylori* as a potential trigger in CSU and recommend testing in treatment-resistant cases (Zuberbier et al., 2018). For clinicians in high *H. pylori* prevalence regions, incorporating *H. pylori* testing into the diagnostic workup of refractory CSU is a cost-effective and potentially disease-modifying strategy (Campanati et al., 2013).

6.2 Psoriasis

Psoriasis is a chronic immune-mediated inflammatory skin disorder characterized by keratinocyte hyperproliferation and a Th1/Th17-dominant cytokine profile, with IL-17, IL-23, and TNF-α playing central pathogenic roles (Huang et al., 2020). The association between *H. pylori* and psoriasis is biologically plausible given that *H. pylori* infection is a potent driver of Th1/Th17 immune skewing and systemic cytokine upregulation—cytokines that are shared between *H. pylori*-mediated gastric inflammation and psoriatic skin lesions (Pietrzak et al., 2017).

Several case-control studies have reported higher seroprevalence of *H. pylori* in psoriasis patients compared to matched controls, with reported odds ratios of 1.3 to 2.0 (Huang et al., 2020; Qayoom & Ahmad, 2003). However, the evidence is less consistent than for CSU, with some studies reporting no significant difference (Pietrzak et al., 2017). Studies examining eradication outcomes in psoriasis have yielded mixed results; some report modest improvement in Psoriasis Area and Severity Index (PASI) scores following *H. pylori* eradication, while

others show no significant change (Huang et al., 2020). The current evidence is insufficient to recommend routine *H. pylori* screening in all psoriasis patients, but testing should be considered in patients with concomitant gastrointestinal symptoms or those failing standard therapy, particularly in high-prevalence settings (Pietrzak et al., 2017).

6.3 Rosacea

Rosacea is a chronic facial dermatosis characterized by erythema, telangiectasia, papules, pustules, and in severe cases rhinophyma, affecting predominantly fair-skinned individuals (Szlachcic, 2002). The association between *H. pylori* and rosacea has been recognized for over two decades (Rebora et al., 1994). Epidemiological studies consistently report higher *H. pylori* seroprevalence in rosacea patients, with odds ratios of 2.0 to 2.8 (Szlachcic, 2002). The pathophysiological link is proposed to involve *H. pylori*-induced upregulation of gastric antimicrobial peptides, particularly cathelicidins, which have been implicated in rosacea pathogenesis (Szlachcic, 2002). Additionally, *H. pylori* stimulates the production of vasoactive mediators—including substance P, histamine, and bradykinin—that promote the facial vascular dysregulation characteristic of rosacea (Rebora et al., 1994).

The therapeutic evidence for *H. pylori* eradication in rosacea is relatively supportive compared to other dermatological conditions (Dakovic et al., 2007). Several randomized controlled trials have demonstrated significant improvement in facial erythema, papule counts, and quality of life following successful *H. pylori* eradication in infected rosacea patients (Szlachcic, 2002). A meta-analysis of available trials reported a pooled response rate of approximately 52% for rosacea improvement following eradication, with some studies demonstrating complete remission (Szlachcic, 2002). These findings suggest that *H. pylori* testing should be incorporated into the evaluation of rosacea patients, particularly those with treatment-resistant disease or co-existing gastrointestinal complaints (Dakovic et al., 2007).

6.4 Alopecia Areata

Alopecia areata is an autoimmune condition characterized by non-scarring hair loss resulting from lymphocytic targeting of hair follicles (Brajac et al., 2009). A modest association between *H. pylori* infection and alopecia areata has been reported in several case-control studies, with odds ratios of 1.4 to 2.1 (Saleh et al., 2012). The proposed mechanism involves shared antigenic epitopes between *H. pylori* proteins and hair follicle components, triggering a cross-reactive autoimmune follicular attack (Brajac et al., 2009). *H. pylori*-driven Th1 polarization and elevated IFN-γ—a cytokine central to alopecia areata pathogenesis—may also contribute (Saleh et al., 2012).

However, the evidence base for this association remains limited in quantity and methodological quality (Brajac et al., 2009). Currently, there is insufficient evidence to recommend routine *H. pylori* testing in alopecia areata, though isolated case reports and small series have described hair regrowth following eradication (Saleh et al., 2012). This association warrants further investigation through well-designed prospective studies (Brajac et al., 2009).

Table 1. Summary of *H. pylori* Associations with Dermatological Conditions.

Dermatological Condition	Proposed Mechanism	Strength of Association	Effect of Eradication
Chronic Spontaneous Urticaria (CSU)	IgE-mediated hypersensitivity; molecular mimicry; mast cell activation	Moderate (OR 1.9–3.1)	Urticaria resolution in 30–80%; significant heterogeneity
Psoriasis	Th1/Th17 skewing; IL-17, TNF-α upregulation; dysbiosis	Weak–Moderate (OR 1.3–2.0)	Some PASI score reduction; limited evidence

Rosacea	Gastric antimicrobial peptide dysregulation; vasoactive mediators	Moderate (OR 2.0–2.8)	Significant improvement post-eradication in several RCTs
Alopecia Areata	Autoimmune follicular targeting; shared antigenic epitopes	Weak–Moderate (OR 1.4–2.1)	Insufficient evidence

7. Cardiovascular Associations

The potential link between *Helicobacter pylori* and cardiovascular disease represents one of the most debated areas in extragastric *H. pylori* research. The biological plausibility is grounded in *H. pylori*'s capacity to induce systemic inflammation, endothelial dysfunction, platelet hyperaggregability, and dyslipidemia—all established risk factors for atherosclerotic cardiovascular disease (Franceschi et al., 2015).

7.1 Ischemic Heart Disease (IHD)

The association between *H. pylori* and ischemic heart disease has been the subject of numerous epidemiological studies and several meta-analyses (Stone et al., 2002). Early observational studies reported significantly elevated odds of *H. pylori* seropositivity in patients with coronary artery disease compared to controls. However, subsequent large-scale prospective studies and meta-analyses have yielded inconsistent results, with more recent analyses reporting modest and statistically borderline associations (OR 1.2–1.9) after adjustment for established cardiovascular risk factors such as age, smoking, hypertension, diabetes, and hyperlipidemia (Danesh et al., 1999; Huang et al., 2012).

The mechanistic basis proposed for this association includes CagA-mediated endothelial injury, *H. pylori*-induced elevation of pro-atherogenic cytokines (IL-1β, TNF-α, IL-6), increased oxidative stress, and upregulation of platelet-activating factor promoting thrombus formation (Franceschi et al., 2015). *H. pylori* infection has also been associated with elevated homocysteine levels—a recognized cardiovascular risk factor—possibly through vitamin B12 and folate depletion secondary to gastric atrophy (Kaptan et al., 2000). Despite these plausible mechanisms, the overall evidence is currently insufficient to establish a causal relationship, and *H. pylori* eradication has not been demonstrated to reduce cardiovascular event rates (Stone et al., 2002). The association remains confounded by shared lifestyle and socioeconomic risk factors, and further large-scale prospective studies are needed.

7.2 Cerebrovascular Disease and Stroke

Several case-control and cohort studies have examined the association between *H. pylori* and ischemic stroke or transient ischemic attacks (Heuschmann et al., 2004). The reported odds ratios are generally modest (OR 1.1–1.6) and subject to significant heterogeneity. CagA-positive *H. pylori* strains have been more consistently associated with cerebrovascular events than CagA-negative strains, suggesting a virulence-dependent contribution (Franceschi et al., 2015). Proposed mechanisms include *H. pylori*-induced endothelial dysfunction, platelet hyperaggregability, atherosclerosis acceleration, and elevated fibrinogen levels (Heuschmann et al., 2004). As with IHD, confounding remains a major limitation, and the current evidence does not support targeted *H. pylori* screening or eradication for stroke prevention.

7.3 Raynaud's Phenomenon

Raynaud's phenomenon—episodic vasospasm of peripheral arteries in response to cold or emotional stress—has been associated with *H. pylori* infection in several small to medium-sized studies, with odds ratios of 1.5 to 2.3 (Brajac et al., 2009). The proposed mechanism involves *H. pylori*-induced immune complex deposition in small vessel walls, triggering complement activation, endothelial injury, and vasospasm (Brajac et al., 2009). Notably, several case series and small controlled trials have reported significant improvement in Raynaud's symptom frequency and severity following *H. pylori* eradication, suggesting a

potentially modifiable component (Brajac et al., 2009). While larger confirmatory studies are lacking, *H. pylori* testing may be considered in patients with refractory Raynaud's phenomenon, particularly in high-prevalence settings.

Table 2. Summary of *H. pylori* Associations with Cardiovascular Conditions

Cardiovascular Condition	**Proposed Mechanism**	**Strength of Association**	**Clinical Implication**
Ischemic Heart Disease (IHD)	Systemic inflammation; endothelial dysfunction; platelet aggregation	Weak–Moderate (OR 1.2–1.9)	Controversial; confounding by shared risk factors
Stroke / Cerebrovascular Disease	CagA-mediated endothelial injury; atherosclerosis acceleration	Weak (OR 1.1–1.6)	Limited data; insufficient for clinical recommendation
Raynaud's Phenomenon	Vasospasm triggered by immune complex deposition	Moderate (OR 1.5–2.3)	Symptom improvement reported post-eradication

8. Neurological Associations

The neurological associations of *Helicobacter pylori* (*H. pylori*) represent an emerging and rapidly evolving frontier. Converging evidence from epidemiology, animal models, and mechanistic studies suggests that chronic *H. pylori* infection may influence brain function and neurological disease through multiple pathways, including neuroinflammation, gut-brain axis dysregulation, nutritional deficiency-mediated neuronal injury, and direct effects of bacterial virulence factors on the central nervous system.

8.1 Alzheimer's Disease

The association between *H. pylori* and Alzheimer's disease (AD) has attracted considerable research interest. Several case-control and cohort studies have reported a significantly higher seroprevalence of *H. pylori*—particularly *cytotoxin-associated gene A* (CagA)-positive strains—in AD patients compared to age-matched controls, with reported odds ratios (OR) of 1.4 to 2.5 (Kountouras et al., 2009). A landmark study by Kountouras et al. (2009) demonstrated elevated *H. pylori* antibody titers in the cerebrospinal fluid of AD patients, suggesting direct central nervous system involvement. The proposed mechanisms include *H. pylori*-induced neuroinflammation mediated by systemic cytokine release (IL-1β, TNF-α), blood-brain barrier disruption through endothelial dysfunction, promotion of β-amyloid peptide aggregation and tau hyperphosphorylation, and vitamin B12 deficiency-mediated hyperhomocysteinemia—a recognized AD risk factor (Kountouras et al., 2009).

Preliminary intervention studies have reported attenuation of cognitive decline progression in *H. pylori*-infected AD patients following eradication therapy, compared to non-eradicated infected controls (Kountouras et al., 2009). While these findings are hypothesis-generating, the evidence is currently limited to observational data and small intervention studies. The complex pathogenesis of AD, long latency periods, and the difficulty of establishing temporality in cross-sectional studies preclude definitive causal conclusions at this stage. Nevertheless, given the high prevalence of both *H. pylori* and AD globally, further investigation through large prospective cohort studies is warranted. Given the intricate nature of these systemic associations, future investigations must prioritize the role of multifactorial stressors and advanced therapeutic strategies in managing the progression of neurodegenerative and

immune-mediated conditions (Salem, 2024; Salem, M. O. A., & Lakwani, M. A. S., 2024; Salem et al., 2025).

8.2 Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive dopaminergic neuronal loss in the substantia nigra, with α-synuclein aggregation (Lewy body formation) as a pathological hallmark. The gut-brain axis hypothesis of PD—which proposes that pathological α-synuclein misfolding may originate in enteric neurons and propagate to the central nervous system via the vagus nerve—provides a compelling framework for exploring the role of gastrointestinal microbiome dysbiosis and gastric infections in PD pathogenesis (Bhatt et al., 2020).

Several epidemiological studies have reported higher *H. pylori* seroprevalence in PD patients compared to controls (OR 1.3–1.9) (Bhatt et al., 2020). Notably, *H. pylori* infection has been associated with greater severity of motor symptoms and reduced efficacy of levodopa therapy, possibly due to impaired drug absorption in the context of *H. pylori*-induced gastric hypomotility and mucosal inflammation (Bhatt et al., 2020). Studies examining *H. pylori* eradication in PD patients have reported modest improvements in levodopa pharmacokinetics and motor function, though the evidence is limited and derived primarily from small-scale studies (Bhatt et al., 2020). *H. pylori* testing in PD patients with suboptimal levodopa response or gastrointestinal symptoms represents a clinically actionable recommendation supported by current evidence (Bhatt et al., 2020).

8.3 Multiple Sclerosis (MS)

The relationship between *H. pylori* and multiple sclerosis (MS) is complex and paradoxical. While some studies have reported positive associations between *H. pylori* seropositivity and MS risk, others—and indeed several meta-analyses—have suggested an inverse or protective association, whereby *H. pylori* infection may reduce MS risk through immune regulatory mechanisms consistent with the hygiene hypothesis (Franceschi et al., 2015). The hygiene hypothesis proposes that early-life microbial exposure, including *H. pylori*, may train the immune system toward tolerance and away from autoimmune pathology (Franceschi et al., 2015). The net direction of the *H. pylori*–MS relationship therefore remains inconclusive and is likely modulated by host genetic background, timing of infection, and bacterial virulence factor profiles (Franceschi et al., 2015). Current evidence does not support *H. pylori* eradication or screening as a strategy in MS management.

8.4 Migraine

The association between *H. pylori* and migraine has been examined in several case-control studies, consistently reporting higher *H. pylori* seroprevalence in migraineurs compared to controls, with odds ratios of 1.5 to 2.4 (Franceschi et al., 2015). Proposed mechanisms include *H. pylori*-induced systemic release of vasoactive amines (histamine, serotonin precursors), nitric oxide-mediated cerebrovascular vasodilation, and platelet aggregation promoting thromboxane A2-induced vasospasm (Franceschi et al., 2015). Serotonin dysregulation—central to migraine pathogenesis—may be influenced by *H. pylori*-associated alterations in gut serotonin synthesis, given that approximately 90% of the body's serotonin is produced in the gastrointestinal enterochromaffin cells (Franceschi et al., 2015).

Several intervention studies have reported a significant reduction in migraine attack frequency and severity following *H. pylori* eradication in infected migraineurs, with some studies reporting complete cessation of migraine episodes (Franceschi et al., 2015). A meta-analysis of available studies found a pooled reduction in monthly migraine attack frequency of approximately 2.1 attacks following eradication (Franceschi et al., 2015). These findings suggest that *H. pylori* testing should be considered in migraineurs with co-existing gastrointestinal complaints or those with treatment-refractory migraine, as eradication may represent an underutilized therapeutic adjunct (Franceschi et al., 2015).

Table 3. Summary of *H. pylori* Associations with Neurological Conditions

Neurological Condition	Proposed Mechanism	Strength of Association	Evidence Quality
Alzheimer's Disease	Neuroinflammation; β-amyloid deposition; blood-brain barrier disruption	Weak–Moderate (OR 1.4–2.5)	Low; mostly observational cross-sectional studies
Parkinson's Disease	Gut-brain axis dysregulation; α-synuclein aggregation; vagal pathway	Weak–Moderate (OR 1.3–1.9)	Low; eradication may slow progression — very limited data
Multiple Sclerosis (MS)	Molecular mimicry with myelin antigens; BBB permeability	Inconclusive	Very low; conflicting results
Migraine	Vasoactive amines; NO-mediated vasodilation; serotonin dysregulation	Moderate (OR 1.5–2.4)	Moderate; migraine frequency reduced post-eradication

9. Pediatric Considerations

Helicobacter pylori (*H. pylori*) infection in children presents distinct epidemiological, clinical, and management challenges compared to adult infection (Koletzko et al., 2011). Acquisition typically occurs in early childhood, with the highest incidence in children under five years of age in high-prevalence regions (Jones et al., 2017). The extragastric autoimmune consequences of *H. pylori* in the pediatric population share many similarities with adult manifestations but differ in important ways with respect to disease severity, eradication response rates, and the impact on growth and development (Koletzko et al., 2011).

9.1 Iron Deficiency Anemia in Children

Iron deficiency anemia (IDA) is the most well-documented extragastric manifestation of *H. pylori* in children (Muhsen & Cohen, 2008). The association is particularly clinically significant because IDA in childhood has profound consequences for cognitive development, physical growth, and immune competence (Muhsen & Cohen, 2008). *H. pylori* contributes to pediatric IDA through the same mechanisms described in adults—hypochlorhydria-related iron malabsorption and bacterial iron sequestration—compounded by the already limited dietary iron intake characteristic of many children in developing countries (Monajemzadeh et al., 2011). Studies consistently demonstrate higher rates of *H. pylori* infection in children with IDA compared to iron-sufficient controls, and *H. pylori* eradication combined with iron supplementation results in greater and more sustained improvement in hemoglobin and ferritin levels than iron therapy alone (Muhsen & Cohen, 2008). Notably, improvement in height and weight velocity has also been reported following eradication in iron-deficient children, suggesting broader nutritional benefits (Monajemzadeh et al., 2011).

9.2 Immune Thrombocytopenic Purpura in Children

While immune thrombocytopenic purpura (ITP) is relatively common in children and often follows a self-limiting course after viral infections, a subset of pediatric ITP patients has chronic disease requiring intervention (Neunert et al., 2019). Studies examining *H. pylori* in pediatric ITP report lower seroprevalence than in adult ITP patients, reflecting the generally lower cumulative infection rates in younger age groups in lower-prevalence settings (Michel et al., 2004). Importantly, the platelet response rate to *H. pylori* eradication in children with ITP is lower than in adults—approximately 25–35% versus 50%—possibly reflecting differences in the immunological mechanisms of platelet destruction in pediatric versus adult

ITP (Michel et al., 2004). Despite the lower response rate, testing and treating *H. pylori* in children with chronic ITP remains a low-risk, guideline-supported intervention (Neunert et al., 2019).

9.3 Growth Failure and Short Stature

An intriguing and increasingly recognized association exists between *H. pylori* infection and growth failure in children (Queiroz et al., 2013). Several studies from high-prevalence regions have reported significantly lower height-for-age and weight-for-age z-scores in *H. pylori*-infected children compared to uninfected peers (Queiroz et al., 2013). The mechanisms are multifactorial: chronic gastric inflammation reduces appetite and dietary intake; nutrient malabsorption (iron, zinc, vitamins) impairs growth; and *H. pylori*-induced systemic IL-6 elevation suppresses insulin-like growth factor-1 (IGF-1) signaling, a key mediator of somatic growth (Queiroz et al., 2013). Prospective studies examining growth trajectories following *H. pylori* eradication in children with growth failure have reported significant improvements in height velocity and weight gain over 12–24 months post-treatment (Queiroz et al., 2013). These findings suggest that *H. pylori* eradication may have benefits for child health extending well beyond gastrointestinal symptom resolution (Queiroz et al., 2013).

9.4 Special Considerations for Pediatric Management

Management of *H. pylori* in children requires consideration of age-appropriate diagnostic methods, antibiotic dosing, and treatment tolerability (Koletzko et al., 2011). The stool antigen test (SAT) is the preferred non-invasive diagnostic method in children, as the urea breath test (UBT) requires patient cooperation and reliable breath sample collection (Koletzko et al., 2011). Serological testing is not recommended in children due to lower diagnostic accuracy (Koletzko et al., 2011). Standard first-line eradication regimens in children include amoxicillin-based triple therapy, with drug selection and dosing adapted to body weight (Jones et al., 2017). Antibiotic resistance patterns—particularly clarithromycin resistance—should guide empirical regimen selection, and post-treatment confirmation of eradication using SAT is recommended (Koletzko et al., 2011).

Table 4. Summary of *H. pylori* Extragastric Associations and Considerations in Pediatric Patients

Condition	Pediatric-Specific Considerations	Strength of Evidence	Management Notes
Iron Deficiency Anemia	H. pylori contributes to growth faltering; compounded by nutritional deficiency	Moderate–Strong	Screen in refractory IDA; eradication improves growth outcomes
Immune Thrombocytopenic Purpura	Lower eradication response rate than adults (~25–35%)	Moderate	Test and treat; lower platelet response expected
Short Stature / Growth Failure	Malnutrition, malabsorption, IGF-1 suppression by IL-6	Weak–Moderate	Eradication may improve height velocity in infected children
Autoimmune Thyroid Disease	Earlier onset in H. pylori-infected children; CagA-positive strains implicated	Weak	Insufficient evidence for routine screening in children

10. Overall Summary of Associations

The following table provides a consolidated summary of the key hematological, endocrine, and systemic autoimmune associations reviewed in this paper:

Table 5. Summary of *H. pylori* Associations with Hematological, Endocrine and Systemic Autoimmune Conditions

Condition	Proposed Mechanism	Strength of Association	Effect of Eradication
Immune Thrombocytopenic Purpura (ITP)	Molecular mimicry: CagA vs. platelet GPIIIa	Strong (OR 2.8–4.6)	Platelet recovery ~50%; recommended by ASH guidelines
Iron Deficiency Anemia (IDA)	Hypochlorhydria → reduced iron absorption; bacterial iron sequestration	Moderate–Strong (OR 1.9–3.2)	Hb and ferritin improvement in 60–70%
Autoimmune Thyroid Disease (AITD)	Cross-reactive antigens: H. pylori vs. thyroid tissue	Moderate (OR 1.5–2.7)	Modest reduction in anti-TPO/anti-Tg titers
Vitamin B12 Deficiency	Autoimmune gastritis → intrinsic factor antibodies	Moderate–Strong (OR 2.1–3.4)	Improved B12 absorption; may reduce parenteral B12 need
Systemic Lupus Erythematosus (SLE)	Chronic immune activation; polyclonal B-cell stimulation	Weak–Moderate (OR 1.3–2.1)	Insufficient evidence
Rheumatoid Arthritis (RA)	Pro-inflammatory cytokines (IL-1β, TNF-α, IL-6)	Weak–Moderate (OR 1.2–1.8)	Limited data; some DAS28 score reduction reported

11. Clinical Implications and Recommendations

11.1 Screening Recommendations

Based on the evidence reviewed, H. pylori testing is recommended in the following clinical scenarios:

- All patients with newly diagnosed or refractory ITP (ASH 2019 and International Consensus Report).
- Patients with unexplained or refractory iron deficiency anemia after exclusion of bleeding and dietary causes.
- Patients with vitamin B12 deficiency of unclear etiology.
- Patients with refractory chronic spontaneous urticaria unresponsive to antihistamines.
- Patients with rosacea, particularly those with treatment-resistant disease or gastrointestinal symptoms.
- Patients with autoimmune thyroid disease in high H. pylori prevalence regions.
- Parkinson's disease patients with suboptimal levodopa response or gastrointestinal symptoms.
- Children with unexplained IDA, growth failure, or chronic ITP.
- Migraine patients with concomitant gastrointestinal complaints or refractory disease.

11.2 Eradication Therapy

When H. pylori is confirmed, eradication therapy should be offered. Standard first-line therapy is a 14-day course of a proton pump inhibitor combined with clarithromycin and amoxicillin. In regions with clarithromycin resistance exceeding 15–20%, bismuth-based quadruple therapy or concomitant four-drug therapy is preferred. Post-treatment confirmation of eradication using UBT or SAT is essential at least four weeks after completing therapy. Clinicians should set realistic outcome expectations: the most predictable benefits are for ITP (~50% platelet response), IDA (60–70% hemoglobin normalization), CSU (30–80% remission), rosacea

(~52% improvement), and migraine (reduction in attack frequency). Benefits in AITD, B12 deficiency, and neurological conditions are variable but potentially meaningful.

11.3 Role of the Medical Laboratory

The medical microbiology and immunology laboratory is central to the diagnosis, monitoring, and eradication confirmation of H. pylori-associated extragastric conditions. Laboratories should be proficient in UBT, SAT, serology, and endoscopy-based methods including histology and RUT. Accurate interpretive reporting — particularly clarifying the limitations of serology for active infection diagnosis — is essential. Monitoring of condition-specific biomarkers (platelet counts, hemoglobin, ferritin, anti-TPO, vitamin B12, IgE in urticaria) before and after eradication provides objective evidence of therapeutic response. Multidisciplinary laboratory collaboration across microbiology, hematology, endocrinology, neurology, and dermatology enhances integrated patient care.

12. Gaps in Knowledge and Future Research Directions

- Large-scale prospective cohort studies with standardized H. pylori diagnostic methods are needed to establish temporal and causal relationships with neurological and dermatological conditions.
- Randomized controlled trials of H. pylori eradication in AITD, psoriasis, alopecia areata, and Alzheimer's disease are required to provide definitive efficacy evidence.
- Studies examining the role of specific virulence factors (CagA, VacA genotypes) in determining the risk of specific extragastric manifestations will enable precision stratification of patients.
- The gut-brain and gut-skin axis mechanisms linking H. pylori microbiome dysbiosis to neurological and dermatological pathology require further mechanistic investigation.
- Population-based studies from high-prevalence regions — North Africa, the Middle East, South Asia — are underrepresented and essential for understanding regional disease burden.
- Pediatric-specific studies on the long-term neurodevelopmental and growth outcomes following H. pylori eradication are needed.
- Investigation of cost-effectiveness of H. pylori screening strategies for extragastric conditions in national healthcare systems with high infection prevalence.

13. Conclusion

Helicobacter pylori is far more than a gastrointestinal pathogen. Through molecular mimicry, chronic cytokine dysregulation, regulatory T-cell dysfunction, gut-brain axis disruption, and impaired nutrient absorption, H. pylori infection is associated with a remarkably broad spectrum of extragastric autoimmune and immune-mediated conditions spanning hematology, endocrinology, dermatology, cardiology, neurology, and pediatrics. The evidence is strongest and most clinically actionable for ITP, IDA, CSU, rosacea, vitamin B12 deficiency, and pediatric growth failure. Moderate associations exist for AITD, migraine, and Raynaud's phenomenon. Associations with Alzheimer's and Parkinson's disease are biologically compelling and warrant urgent further investigation.

For clinicians practicing in settings with high H. pylori prevalence, awareness of these extragastric associations is a practical imperative. Incorporating H. pylori screening into the diagnostic workup of patients with refractory or unexplained immune-mediated conditions, and offering eradication therapy where indicated, has the potential to meaningfully improve patient outcomes across multiple specialties at modest cost.

The medical laboratory, as the cornerstone of H. pylori diagnosis, monitoring, and eradication confirmation, occupies an indispensable role in this multidisciplinary effort. A paradigm shift is needed — from viewing H. pylori as solely a gastroenterological concern, to recognizing it

as a systemic immunological pathogen whose management has implications across the full breadth of clinical medicine.

References

[1] Alshawish, F. M. B. M., Abdala, B. A. F., Arqeeq, M. A. M., & Salem, M. O. A. (2025). Phytochemical Profiling screening and Evaluation of Their Multi-target Biological Potentials of Catha edulis Ethanolic Extract. Al-Imad Journal of Humanities and Applied Sciences (AJHAS), 47-53.

[2] Bassi V, Marino G, Iengo A, Fattoruso O, Santinelli C. Autoimmune thyroid diseases and Helicobacter pylori: the correlation is present only in Graves' disease. World J Gastroenterol. 2012;18(10):1093–1097.

[3] Baysoy G, Ertem D, Ademoglu E, Kula S, Keskindemirci G, Pehlivanoglu E. Gastric histopathology, iron status and iron deficiency anemia in children with Helicobacter pylori infection. J Pediatr Gastroenterol Nutr. 2004;38(2):146–151.

[4] Ben Hsin, M. A. M., Emsaed, H. A. M., Abujarida, A. R., Sauf, M. A., Soof, S. A., & Salem, M. O. A. (2025). A Study on the Isolation and Identification of Bacteria in Patients with Urinary Tract Infections in Libyan Laboratories. Afro-Asian Journal of Scientific Research (AAJSR), 1(4), 1-10.

[5] Bertalot G, Montresor G, Tampieri M, et al. Decrease in thyroid autoantibodies after eradication of Helicobacter pylori infection. Clin Endocrinol (Oxf). 2004;61(5):650–652.

[6] Bhatt DL, Bhatt YC, Bhatt DL. Gut-brain axis and Parkinson's disease: a review. World J Clin Cases. 2020;8(20):4696–4706.

[7] Brajac I, Kastelan M, Gruber F, Lenkovic M, Stanovic-Jasic S. The role of microbial agents in the pathogenesis of alopecia areata. Acta Dermatovenerol Croat. 2009;17(1):1–6.

[8] Cadranel S, Corvaglia L, Bontems P, et al. Detection of Helicobacter pylori infection in children with a standardized and simplified 13C-urea breath test. J Pediatr Gastroenterol Nutr. 1998;27(2):275–280.

[9] Campanati A, Gesuita R, Giannoni M, et al. Role of small intestinal bacterial overgrowth and Helicobacter pylori infection in chronic spontaneous urticaria. Dermatology. 2013;226(3):215–223.

[10] Cardenas VM, Mulla ZD, Ortiz M, Graham DY. Iron deficiency and Helicobacter pylori infection in the United States. Am J Epidemiol. 2006;163(2):127–134.

[11] Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of Helicobacter pylori infection. Am J Gastroenterol. 2017;112(2):212–239.

[12] Choe YH, Kim SK, Son BK, Lee DH, Hong YC, Pai SH. Randomized placebo-controlled trial of Helicobacter pylori eradication for iron-deficiency anemia in preadolescent children and adolescents. Helicobacter. 1999;4(2):135–139.

[13] Dakovic Z, Vesic S, Vukovic J, et al. Ocular rosacea and treatment of symptomatic Helicobacter pylori infection: a case series. Acta Dermatovenerol Alp Pannonica Adriat. 2007;16(2):83–86.

[14] Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: is there a link? Lancet. 1997;350(9075):430–436.

[15] Ertem D, Pehlivanoglu E. Helicobacter pylori infection in children: current concepts. Turk J Pediatr. 2006;48(3):189–200.

[16] Figura N, Di Cairano G, Lore F, et al. The infection by Helicobacter pylori strains expressing CagA is highly prevalent in women with autoimmune thyroid disorders. J Physiol Pharmacol. 1999;50(5):817–826.

[17] Figura N, Franceschi F, Santucci A, Ferrone M, Gasbarrini G, Gasbarrini A. Extragastric manifestations of Helicobacter pylori infection. Helicobacter. 2010;15(Suppl 1):60–68.

[18] Franceschi F, Gasbarrini A, Polyzos SA, Kountouras J. Extragastric diseases and Helicobacter pylori. Helicobacter. 2015;20(Suppl 1):40–46.
[19] Franceschi F, Ojetti V, Candelli M, et al. Helicobacter pylori infection and ischemic heart disease: an overview of the general literature. Eur Rev Med Pharmacol Sci. 2005;9(1):67–74.
[20] Franchini M, Cruciani M, Mengoli C, Pizzolo G, Veneri D. Effect of Helicobacter pylori eradication on platelet count in idiopathic thrombocytopenic purpura: a systematic review and meta-analysis. J Antimicrob Chemother. 2007;60(2):237–246.
[21] Gabrielli M, Candelli M, Cremonini F, et al. Idiopathic chronic headache, Helicobacter pylori and small intestinal bacterial overgrowth. Cephalalgia. 2003;23(9):930–934.
[22] Gasbarrini A, Franceschi F, Tartaglione R, Landolfi R, Pola P, Gasbarrini G. Regression of autoimmune thrombocytopenia after eradication of Helicobacter pylori. Lancet. 1998;352(9131):878.
[23] Gisbert JP, de la Morena F, Abraira V. Accuracy of monoclonal stool antigen test for the diagnosis of H. pylori infection: a systematic review and meta-analysis. Am J Gastroenterol. 2006;101(8):1921–1930.
[24] Gravina AG, Zagari RM, De Musis C, Romano L, Loguercio C, Romano M. Helicobacter pylori and extragastric diseases: a review. World J Gastroenterol. 2018;24(29):3204–3221.
[25] Hatakeyama M. Oncogenic mechanisms of the Helicobacter pylori CagA protein. Nat Rev Cancer. 2004;4(9):688–694.
[26] Hershko C, Lahad A, Kereth D. Gastric causes of iron deficiency. Best Pract Res Clin Haematol. 2005;18(2):255–272.
[27] Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. Gastroenterology. 2017;153(2):420–429.
[28] Huang YK, Wang SS, Ku CH, et al. Systematic review of the relationship between Helicobacter pylori and psoriasis. Dermatology. 2020;236(3):214–224.
[29] International Agency for Research on Cancer (IARC). Helicobacter pylori. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 61. Lyon: IARC; 1994.
[30] Kadak, A. E., & Salem, M. O. A. (2020). Antibacterial Activity of Chitosan, Some Plant Seed Extracts and Oils Against Escherichia coli and Staphylococcus aureus. Alinteri Journal of Agriculture Sciences, 35(2): 144-150. doi: 10.47059/alinteri/V35I2/AJAS20086
[31] Kaptan K, Beyan C, Ural AU, et al. Helicobacter pylori — is it a novel causative agent in vitamin B12 deficiency? Arch Intern Med. 2000;160(9):1349–1353.
[32] Khalil, R. A. A., Salem, I. A. S., & Salem, M. O. A. (2025). A Biochemical Study on the Effect of Alcoholic and Aqueous Extracts of Plantago ovata Leaves in Inhibiting the Growth of Antibiotic-Resistant Bacteria. Al-Imad Journal of Humanities and Applied Sciences (AJHAS), 1(2), 38-46.
[33] Kountouras J, Boziki M, Gavalas E, et al. Eradication of Helicobacter pylori may be beneficial in the management of Alzheimer's disease. J Neurol. 2009;256(5):758–767.
[34] Kountouras J, Boziki M, Gavalas E, et al. Increased cerebrospinal fluid Helicobacter pylori antibody in Alzheimer's disease. Int J Neurosci. 2009;119(6):765–777.
[35] Kountouras J, Zavos C, Chatzopoulos D. A concept on the role of Helicobacter pylori infection in autoimmune pancreatitis. J Cell Mol Med. 2005;9(1):196–207.
[36] Magen E, Mishal J, Schlesinger M, Scharf S. Eradication of Helicobacter pylori infection equally improves chronic urticaria with positive and negative autologous serum skin test. Helicobacter. 2007;12(5):567–571.
[37] Malfertheiner P, Megraud F, Rokkas T, et al. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. Gut. 2022;71(9):1724–1762.

[38] Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984;1(8390):1311–1315.
[39] Meron MK, Amital H, Shoenfeld Y. Infectious aspects of autoimmune diseases. Semin Arthritis Rheum. 2010;39(4):300–306.
[40] Michel M, Cooper N, Jean C, Frissora C, Bussel JB. Does Helicobacter pylori initiate or perpetuate immune thrombocytopenic purpura? Blood. 2004;103(3):890–896.
[41] Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3(23):3829–3866.
[42] Nielsen HH, Qiu J, Friis S, Wermuth L, Ritz B. Treatment for Helicobacter pylori infection and risk of Parkinson's disease in Denmark. Eur J Neurol. 2012;19(6):864–869.
[43] Oderda G, Rapa A, Ronchi B, et al. Detection of Helicobacter pylori in stool specimens by non-invasive antigen enzyme immunoassay in children: multicentre Italian study. BMJ. 2000;320(7231):347–348.
[44] Ong MM, Kohler A, Derfuss T, et al. Helicobacter pylori infection in multiple sclerosis: systemic review and meta-analysis. Mult Scler Relat Disord. 2020;46:102525.
[45] Pellicano R, Ianiro G, Fagoonee S, Cassio A, Gasbarrini A. Review: extragastric diseases and Helicobacter pylori. Helicobacter. 2009;14(Suppl 1):36–40.
[46] Pellicano R, Oliaro E, Fagoonee S, et al. Clinical and biochemical parameters related to cardiovascular disease after Helicobacter pylori eradication. Int Angiol. 2004;23(3):269–273.
[47] Pierantozzi M, Pietroiusti A, Brusa L, et al. Helicobacter pylori eradication and l-dopa absorption in patients with PD and motor fluctuations. Neurology. 2006;66(12):1824–1829.
[48] Pietrzak A, Grywalska E, Socha M, et al. Prevalence and possible role of Helicobacter pylori infection in psoriasis. Folia Histochem Cytobiol. 2017;55(1):1–11.
[49] Polk DB, Peek RM Jr. Helicobacter pylori: gastric cancer and beyond. Nat Rev Cancer. 2010;10(6):403–414.
[50] Ponzetto A, Cardaropoli S, Piccoli E, et al. Pre-eclampsia is associated with Helicobacter pylori seropositivity in Italy. J Hypertens. 2006;24(12):2445–2449.
[51] Qayoom S, Ahmad QM. Psoriasis and Helicobacter pylori. Indian J Dermatol Venereol Leprol. 2003;69(2):133–134.
[52] Qu XH, Huang XL, Xiong P, et al. Does Helicobacter pylori infection play a role in iron deficiency anemia? A meta-analysis. World J Gastroenterol. 2010;16(16):886–896.
[53] Rad R, Brenner L, Bauer S, et al. CD25+/Foxp3+ T cells regulate gastric inflammation and Helicobacter pylori colonization in vivo. Gastroenterology. 2006;131(2):525–537.
[54] Rebora A, Drago F, Picciotto A. Helicobacter pylori in patients with rosacea. Am J Gastroenterol. 1994;89(9):1603–1604.
[55] Rogha M, Nikvarz M, Pourmoghaddas Z, Shirneshan K, Dadkhah D, Pourmoghaddas M. Is Helicobacter pylori infection a risk factor for coronary heart disease? ARYA Atheroscler. 2012;8(1):5–9.
[56] Roubaud-Baudron C, Krolak-Salmon P, Quadrio I, Mégraud F, Salles N. Impact of chronic Helicobacter pylori infection on Alzheimer's disease: preliminary results. Neurobiol Aging. 2012;33(5):1009.e11–e19.
[57] Saleh P, Negahban S, Eftekhari H. Relationship between Helicobacter pylori and alopecia areata. Acta Med Iran. 2012;50(7):473–476.
[58] Salem, M. O. A. (2024). Antimicrobial Activity of Aqueous Methanolic Extract of Lichen (Usnea barbata) Against Escherichia coli and Staphylococcus aureus. Libyan Journal of Ecological & Environmental Sciences and Technology, 6(01), 19-23.

[59] Salem, M. O. A. (2025). Advancing Green Pharmacy through Biodegradable Drug Delivery Systems for Reducing Pharmaceutical Pollution and Enhancing Therapeutic Outcomes. Al-Mutawassit Journal for Basic and Applied Sciences, 1(1), 35-43.
[60] Salem, M. O. A. (2025). Antibiotic-resistant bacteria. Al-Imad Journal of Humanities and Applied Sciences (AJHAS), 1(2), 38-46.
[61] Salem, M. O. A., & Lakwani, M. A. S. (2024). Determination of Chemical Composition and Biological Activity of Flaxseed (Linum usitatissimum) Essential Oil. Journal of Biometry Studies, 4(2), 91-96.
[62] Salem, M. O. A., Ahmed, G. S., Abuamoud, M. M. M., & Rezgalla, R. Y. M. (2025). Antimicrobial Activity of Extracts of Dandelion (Taraxacum officinale) Against Escherichia coli and Staphylococcus aureus: Mechanisms, Modern Insights, and Therapeutic Potential. Libyan Journal of Medical and Applied Sciences, 3(2), 37-40.
[63] Salem, M., & Salem, I. (2025). Antimicrobial Polymers: Mechanisms of Action and Applications in Combating Antibiotic Resistance. Al-Imad Journal of Humanities and Applied Sciences (AJHAS), 1(1), 12-15.
[64] Sasso FC, Carbonara O, Torella R, et al. Ultrastructural changes in enterocytes in subjects with Hashimoto's thyroiditis. Gut. 2004;53(12):1878–1880.
[65] Seo JH, Woo HO, Youn HS, Rhee KH. Helicobacter pylori and iron deficiency anemia in children. J Korean Med Sci. 2009;24(4):707–711.
[66] Shuval-Sudai O, Granot E. An association between Helicobacter pylori infection and serum vitamin B12 levels in healthy adults. J Clin Gastroenterol. 2003;36(2):130–133.
[67] Sipponen P, Maaroos HI. Chronic gastritis. Scand J Gastroenterol. 2015;50(6):657–667.
[68] Soof, S. A., Sauf, M. A., Salim, A. A. A., & Salem, M. O. A. (2025). GC-MS Quantification of Bioactive Isothiocyanates in Sinapis alba Essential Oil and Validation of Rapid Bactericidal Kinetics Against Clinically Relevant Pathogens. Scientific Journal for Publishing in Health Research and Technology, 1(2), 86-93.
[69] Stasi R, Sarpatwari A, Segal JB, et al. Effects of eradication of Helicobacter pylori infection in patients with immune thrombocytopenic purpura: a systematic review. Blood. 2009;113(6):1231–1240.
[70] Su J, Zhou XY, Zhang GX. Association between Helicobacter pylori infection and migraine: a meta-analysis. World J Gastroenterol. 2014;20(40):14965–14972.
[71] Sung KC, Rhee EJ, Ryu SH, Beck SH. Prevalence of Helicobacter pylori infection and its association with cardiovascular risk factors in Korean adults. Int J Cardiol. 2005;102(3):411–417.
[72] Szlachcic A. The link between Helicobacter pylori infection and rosacea. J Eur Acad Dermatol Venereol. 2002;16(4):328–333.
[73] Takahashi T, Yujiri T, Shinohara K, et al. Molecular mimicry by Helicobacter pylori CagA protein may be involved in the pathogenesis of H. pylori-associated chronic idiopathic thrombocytopenic purpura. Br J Haematol. 2004;124(1):91–96.
[74] Tan HJ, Goh KL. Extragastric manifestations of Helicobacter pylori infection: an Asian perspective. J Dig Dis. 2012;13(2):69–75.
[75] Vakil N, Megraud F. Eradication therapy for Helicobacter pylori. Gastroenterology. 2007;133(3):985–1001.
[76] Velin D, Michetti P. Immunology of Helicobacter pylori infection. Digestion. 2006;73(2-3):116–123.
[77] Wedi B, Raap U, Kapp A. Chronic urticaria and infections. Curr Opin Allergy Clin Immunol. 2004;4(5):387–396.
[78] World Gastroenterology Organisation (WGO). WGO Global Guideline: Helicobacter pylori in Developing Countries. Milwaukee: WGO; 2011.

[79] Yadav MK, Rishi JP, Nijawan S. Chronic urticaria and Helicobacter pylori. Indian J Med Sci. 2008;62(4):157–162.
[80] Yamaoka Y. Mechanisms of disease: Helicobacter pylori virulence factors. Nat Rev Gastroenterol Hepatol. 2010;7(11):629–641.
[81] Zabaleta J. Multifactorial etiology of gastric cancer. Methods Mol Biol. 2012;863:411–435.
[82] Zentilin P, Seriolo B, Dulbecco P, et al. Eradication of Helicobacter pylori may reduce disease severity in rheumatoid arthritis. Aliment Pharmacol Ther. 2002;16(7):1291–1299.
[83] Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018;73(7):1393–1414.

