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REVIEW: *HELICOBACTER PYLORI* AND EXTRAGASTRIC DISEASES

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Abstract – Infection with *H. pylori* causes chronic gastritis and is the most important risk factor for gastric cancer. Besides gastric disease, infection is also thought to play a role in the development of other human diseases. *H. pylori* has been predominantly associated with gastrointestinal, metabolic, cardiovascular, respiratory, and neurological disorders. In the past year, novel evidence has demonstrated a significant impact on human morbidity and mortality, mostly derived from association studies. In addition, novel experimental data have revealed direct and indirect mechanisms through which *H. pylori* affects extragastric organs. This article provides an update on the current knowledge of extragastric diseases associated with *H. pylori* infection.

Keywords: *H. pylori*, Gastrointestinal disease, Metabolic disorder, Cardiovascular disease, Respiratory disease, Neurological disorders.

INTRODUCTION

Helicobacter pylori (*H. pylori*) are gram-negative, microaerophilic bacteria that specifically colonize and persist lifelong in the stomachs of around 45% of the world's population[1,2]. Infection with *H. pylori* is the most important risk factor for gastric cancer. Recent discoveries regarding the induction of chronic systemic inflammation, the effects on gastric stem cells, and the identification of bacterial factors in the systemic circulation raise the question of whether and to what extent infection is linked to extragastric diseases. While the evidence for *H. pylori*-related gastric diseases, such as chronic gastritis, ulceration, and gastric cancer, is epidemiologically and experimentally well-established, the evidence for an association with extra gastric diseases remains less compelling since it is based on only a limited number of association studies from different fields, with partly heterogeneous results. There is, therefore, an ongoing debate on the role of *H. pylori* in common human diseases such as type 2 diabetes (T2DM) and coronary artery disease (CAD). Since these conditions are highly prevalent, understanding a potential interplay with a bacterium carried by almost half of all people is of emerging interest and may lead to novel diagnostic, preventive, and therapeutic strategies. In addition to a potentially causal role in extra gastric disease, *H. pylori* also seems to have a protective effect, e.g., against the onset of autoimmune diseases, which is assumed to relate to its ability to modulate the host immune system long-term in order to maintain a life-long infection. Here, we provide an overview of new evidence in this field published last year.

METHODS

A semi-systematic search of the MEDLINE database was conducted. As the particular focus of this review includes the recent advances in *H. pylori* and extragastric diseases, we considered only studies published between January 2023 and June 2024. The search term "*H. pylori*" was combined with terms relating to the clinical disciplines or medical conditions "gastrointestinal disease", "inflammatory bowel disease", "colorectal cancer", "metabolic disorder", "dyslipidemia", "atherosclerosis", "diabetes", "MASLD", "NAFLD", "cardiovascular disease", "coronary artery disease", "respiratory disease", "asthma", "neurological disorders", "stroke", and "dementia". Following the database search, titles and abstracts were screened for eligibility. Eligible studies, including retrospective or prospective clinical studies and experimental studies, were reviewed in full text for confirmation of a contribution to *H. pylori*-related extragastric disease pathophysiology, diagnosis, or therapy. Some studies have been added *via* hand search. Studies that have already been reviewed in "The Year in Helicobacter 2023" special issue collection were excluded.

MAIN

Gastrointestinal Disease

H. pylori has been epidemiologically associated with a nearly two-fold increased risk for colorectal cancer (CRC)[5]. However, this association has been challenged by recent studies using genome-wide association study (GWAS) datasets[6,7]. Nonetheless, an experimental causality has been provided by infection of adenomatous polyposis coli (APC) mutant mice ($Apc^{+/min}$ and $Apc^{+/1638N}$), which showed nearly two-fold increased tumor development in the small intestine and colon compared to uninfected mice, driven by upregulation of pro-inflammatory and pro-carcinogenic signals, e.g., activation of nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3) signaling, as well as a reduction of regulatory T cells (Treg)[8]. In addition, gut bacteria and gut phages may contribute to intestinal tumorigenesis in *H. pylori*-infected mice[8-10]. More specifically, the expansion of gut phages and the presence of phage-encoded virulent genes, e.g., flgJ, cwlJ, and sleB, was reported in *H. pylori*-infected mice. These phages potentially infect other bacteria, such as *Enterococcus faecalis*, which are associated with CRC. This indicates that infection as a second "hit" in a tumor-prone genetic environment strongly drives intestinal pathology – and that it does so *via* environmental changes, enabling other microbiota species to promote disease development in the gut. Importantly, early eradication therapy reduced STAT3 levels and prevented accelerated tumorigenesis in these mice[8]. A retrospective study analyzing nearly 100,000 patients in Hong Kong who received eradication therapy found that the long-term rectal cancer incidence declined compared to the general population after more than 10 years of eradication (SIR 0.90, 95% CI: 0.81-0.999). However, the opposite was true for colon cancer (SIR 1.20, 95% CI: 1.12-1.29)[11]. In the face of the new valuable experimental data revealing how *H. pylori* triggers colorectal carcinogenesis, future prospective studies should identify patients at risk and determine the optimal timing of *H. pylori* testing and eradication to prevent CRC.

The most common and rapidly increasing chronic liver disease is metabolic dysfunction-associated steatotic liver disease (MASLD), which involves various metabolic and inflammatory signals[12]. Several clinical trials have now provided convincing evidence for an association between *H. pylori* infection and MASLD, providing a treatment option in the form of *H. pylori* eradication[13-16]. In patients with MASLD, *H. pylori* was shown to be an important contributor to altered glucose metabolism and expression of pro-inflammatory cytokines, such as IL-18[17]. Possible mechanisms derived from experimental studies are either indirect effects, such as disruption of the gastrointestinal barrier, systemic inflammation, insulin resistance, and dyslipidemia, or direct effects, e.g., mediated *via* outer membrane vesicles (OMV)[13]. These secreted nanovesicles contain various proteins (not related to major virulence factors such as CagA and VacA) that can enter the systemic circulation and affect distant organs. For example, human hepatic stellate cells cultured with *H. pylori* OMVs have demonstrated

an increased expression of pro-fibrogenic genes, such as beta-catenin, that may explain the induction of liver fibrosis[18]. One major complication of liver cirrhosis is hepatic encephalopathy (HE), often triggered by dehydration or diverse infections. A recent meta-analysis showed that *H. pylori* infection increases the risk of HE by 32% (OR 2.32, 95% CI: 1.78-3.04)[19]. After *H. pylori* eradication, the risk of HE was reduced by 64% in this analysis. It should be noted that most data are derived from Asian countries, and data in Europe had a lower association[20], while in the US population, the association could not be verified[21]. Nonetheless, the retrospective US data showed that *H. pylori*-infected patients had a higher overall rate of cirrhosis-related complications, such as gastrointestinal bleeding and hepatorenal syndrome[21]. However, a direct causal relationship could not be identified in either of these studies.

Of note, another retrospective study found that active *H. pylori* infection (determined *via* urea breath test) is associated with ultrasound detection of gallbladder stones (age- and sex-adjusted HR 1.74, 95% CI: 1.01-2.98)[22]. In a large meta-analysis, *H. pylori* infection was associated with an increased risk of irritable bowel syndrome (IBS) (OR 1.68, 95% CI: 1.29-2.18), while eradication improved IBS symptoms[23]. However, these data have been challenged, as no causal association between *H. pylori* infection and IBS has been identified using a European GWAS dataset[24].

In several other gastrointestinal disorders, *H. pylori* infection is considered to be a protective factor. One example is inflammatory bowel disease (IBD). While the prevalence of *H. pylori* infection has declined in the last decade, the prevalence of IBD has increased[2,25]. In line with this, an inverse association between both diseases has been reported in several studies, as recently reviewed[26]. Definitive evidence for a causal association is missing, however, and the potential underlying mechanisms remain mostly obscure. An analysis of the association between *H. pylori* and IBD in a large US database revealed that the prevalence of IBD was lower in *H. pylori*-infected *vs.* non-infected patients (2.01% of patients with *H. pylori* had Crohn's disease compared to 2.63% of patients without *H. pylori* ($p < 0.001$), 1.95% of patients with *H. pylori* had ulcerative colitis compared with 2.29% of patients without *H. pylori* ($p < 0.001$)[27]. Conflicting with earlier data, patients who received eradication therapy also had a lower risk of developing IBD within the 5-year follow-up[27]. Future research needs to clarify this association in long-term follow-up.

A further inverse association with *H. pylori* infection was recently shown for eosinophilic esophagitis (OR 0.20, 95% CI: 0.04-0.91), but the results are limited by the small sample size[28]. A large meta-analysis found that erosive esophagitis, as part of gastroesophageal reflux disease (GERD), is also inversely associated with *H. pylori* infection (OR 0.56, CI: 0.48-0.66) and atrophic gastritis (OR 0.51, CI: 0.31-0.86)[29]. In addition, *H. pylori* has been inversely associated with esophageal adenocarcinoma[30]. It is thought that upon gastric atrophy caused by *H. pylori*, the lack of gastric acid production is a preventive factor for GERD (and hence the development of Barrett's esophagus and esophageal adenocarcinoma). Importantly, eradication of *H. pylori* promoted neither Barrett's esophagus[31] nor esophageal adenocarcinoma (SIR 0.89, 95% CI: 0.82-0.97)[32]. These novel data with 24 years of follow-up suggest that eradication is safe from an esophageal cancer perspective.

Metabolic Disorder

A major impact on human morbidity is due to metabolic syndrome, which is more frequently diagnosed in *H. pylori*-positive than -negative patients[33-35]. *H. pylori* infection has been associated with atherosclerosis driven by *H. pylori*-induced foam cell formation and altered expression of pro-inflammatory cytokines and lipoproteins[36]. In fact, infection has been found to increase the carotid intima-media thickness (CIMT), a hallmark of atherosclerosis[36,37]. Using GWAS data, *H. pylori* outer membrane protein (OMP) antibodies have been linked to peripheral atherosclerosis, while VacA antibodies have been linked to coronary atherosclerosis[38]. Using animal experiments with a combination of a high-fat diet and *H. pylori* infection, a study showed that this combination synergistically drives a pro-atherogenic environment with increased LDL levels and transformation of macrophages into foam cells[39]. Notably, liver sections showed the most intense steatosis upon a combination of a high-fat diet and *H. pylori* infection. Recent studies confirmed that *H. pylori*-positive patients have a dyslipid-

emic profile with hypertriglyceridemia, elevated LDL, reduced HDL, and omega-3 fatty acid levels compared to negative patients[7,40]. However, others could not confirm this association and a worldwide meta-analysis found that the *H. pylori* prevalence in obese patients (as a metabolic endpoint) is not greater than that of the general population[41,42]. Nonetheless, in a retrospective study, the eradication of *H. pylori* increased HDL levels in female, but not in male patients[43].

In a non-diabetic Asian population, *H. pylori* infection has been identified as an independent risk factor for elevated fasting plasma glucose and HbA1c levels[44]. In addition, a nonlinear correlation has been identified between HbA1c and *H. pylori* infection, while eradication led to decreased HbA1c levels[45]. Novel genetic evidence obtained by analyzing European GWAS data suggested an association of *H. pylori* with T2DM[46]. A further study identified several inflammation-related key genes and pathways, e.g., Toll-like receptor 4 (TLR4) signaling, in *H. pylori*-infected but not uninfected patients with T2DM, which could play a role in the pathogenesis of T2DM in infected individuals[47]. Importantly, eradication in T2DM patients is as efficient as in the general population in the US[48]. An association of *H. pylori* with type 1 diabetes (T1DM) has been identified in a recent meta-analysis (OR 1.77, 95% CI: 1.47-2.12)[49]. Infected patients with T1DM had higher HbA1c levels compared to uninfected T1DM patients. In addition, *H. pylori* infection was shown to be an independent risk factor for diabetic retinopathy[50].

Of note, other diverse metabolic associations have been identified. For example, in Chinese women aged 40 or over, *H. pylori* infection correlates with low skeletal muscle mass[51], and a further study showed an association with osteoporosis[52].

Cardiovascular Disease

Cardiovascular disease (CVD) is considered a major outcome of the metabolic syndrome. Whether *H. pylori* infection is also a risk factor for CVD is controversially discussed. Chronic systemic inflammation and metabolic disorders caused by *H. pylori* infection may promote CAD. Recently, a large meta-analysis found that after a median follow-up of 6.3 years, *H. pylori* infection was associated with only a mildly increased risk of composite CVD (RR 1.10, 95% CI: 1.03-1.18) and CAD (RR 1.10, 95% CI: 1.02-1.18) compared to subjects without *H. pylori* infection[53]. Importantly, the association was significantly stronger for CagA+ compared to CagA- *H. pylori* infections (RR 1.58, 95% CI: 1.03-2.41), but only analyzed in a limited number of heterogeneous studies. The all-cause mortality was not associated with infection in this meta-analysis – although this data was only available in a subset of analyzed cohort studies[53]. As CagA was previously identified in exosomes in the systemic circulation[4], an experimental study analyzed its effect on coronary artery smooth muscle cells (CASMCs) *in vitro*. In CASMCs, CagA increased pro-inflammatory signals, including IL-1β, and induced calcification, likely through bone morphogenic protein (BMP) signaling[54]. The exact origin of systemic CagA (either directly from bacteria or *via* gastric cells) and the mechanisms that induce BMP signaling have not been studied in extragastric tissues. An association with inflammatory markers was retrospectively identified in *H. pylori*-infected patients with myocardial infarction, pointing towards a potential role of bacteria-induced inflammation in the pathogenesis of myocardial infarction[55]. Further prospective studies should address whether eradication prevents the development of atherosclerosis and its complications.

Vascular pathology also includes changes in the aorta, as *H. pylori* was associated with abdominal aortic aneurysm in a population-based study in Taiwan[56]. However, the exact cause of aortic pathology in *H. pylori* infection was not reported.

As patients with CAD frequently use anti-thrombotic therapy, the risk for gastrointestinal (GI) bleeding may be aggravated in combination with *H. pylori* infection. However, screening and eradication of *H. pylori*, is not yet performed in routine cardiology practice due to the lack of evidence from powered randomized trials. In 2022, the HEAT trial (Helicobacter Eradication Aspirin Trial) identified a significant reduction of upper GI bleeding by routine *H. pylori* screening and eradication in unselected low-dose aspirin users in the UK[57]. The results had some limitations, mainly caused by a transient effect of bleeding prevention followed by loss of benefits after 2.5 years of follow-up, uncertainties of risk groups, and optimal timing for testing and

eradication. Thus, novel randomized trials are currently ongoing, which may lead to the establishment of routine screening and eradication in patients receiving anti-thrombotic agents[58,59]. However, the efficacy of this approach is currently under debate[60].

Respiratory Disease

H. pylori is thought to play a protective role in allergic airway diseases, such as childhood asthma. As the prevalence of asthma has increased and eradication reduces its risk in experimental studies, a strong inverse correlation with *H. pylori* infection was identified[61]. Recently, two animal studies found that treatment with VacA reduced a variety of asthma hallmarks: bronchoalveolar lavage eosinophilia, lung inflammation, goblet cell metaplasia, tolerogenic dendritic cells and Treg cells[62,63]. Importantly, VacA treatment showed efficacy in both an acute and a chronic disease model. These data suggest that regardless of its known pathological effects in the stomach and other organs, VacA (and potentially other *H. pylori* virulence factors) could represent a possible treatment option for asthma.

The potential involvement of *H. pylori* infection in other highly prevalent respiratory diseases, such as chronic obstructive pulmonary disease (COPD), is still under debate[64]. Analysis of the UK Biobank revealed a significant association with an impact on respiratory-associated mortality (HR 2.16, 95% CI: 1.48-2.84)[7]. However, prospective studies are needed to clarify this association.

Neurological Disorders

H. pylori seropositivity and serointensity have been associated with cognitive dysfunction in a study analyzing a set of cognitive tasks in 40-70-year-old participants of the UK Biobank[65]. In line with this, *H. pylori* antibodies have been associated I) with biomarkers of neurodegeneration, e.g., tTau and pTau181, in cognitively intact individuals[66] and II) with poorer white matter integrity in cognition-related regions in magnetic resonance imaging (MRI)[67]. A case-control study with 11 years of follow-up identified a moderately elevated risk of developing Alzheimer's disease upon *H. pylori* infection among individuals aged ≥50 years (OR 1.11; 95% CI: 1.01-1.21)[68]. A prospective cohort of retired French farmers aged ≥65 years with 7 years of follow-up found, after risk factor adjustment, a significant correlation of *H. pylori* seropositivity with dementia (HR 1.70, 95% CI: 1.05-2.74), which was even stronger for Alzheimer's disease (HR 2.85, 95% CI, 1.58-5.12)[69].

Whether this is due to indirect or direct effects is currently under investigation[70]. Recently, an interesting experimental approach was used in two studies. Labeled *H. pylori* OMVs were detected in mouse brains after oral or intravenous administration[71]. Detection of OMVs coincided with astrocyte reactivity and neuronal damage *in vivo*. Astrocytes treated with OMVs *in vitro* secreted interferon-γ in dependence on NF-κB, causing neurotoxicity. Analysis of the composition of isolated OMVs revealed urease as the dominant component. Urease activity promotes hyperammonemia, which may be neurotoxic and cause permeability of the blood-brain barrier[71]. The presence of OMVs in the brain and uptake by astrocytes was confirmed in the second study, which also found a critical role for complement C3-C3aR signaling in mediating pathological crosstalk between brain cells that ultimately accumulate amyloid-β, driving cognitive impairment[72]. Another study identified *H. pylori*-induced STAT3-mediated neuroinflammation in neuron-astrocyte co-cultures[73]. These experimental data highlight how secreted *H. pylori* factors are able to cross epithelial barriers to reach and damage brain cells.

An association between anti-*H. pylori* IgG and stroke (OR 1.43, 95% CI: 1.25-1.46) was identified in a meta-analysis in 2021[74]. Recently, analysis of data from the UK Biobank showed that specifically VacA antibodies are causally associated with stroke (OR 1.04, 95% CI: 1.01-1.07)[75]. Multivariate analysis indicated that CRP, as a marker for (VacA-induced) inflammation, may mediate this association independently of peptic ulcers. In the face of this data, a prospective controlled trial in Japan analyzed *H. pylori* patients for up to 20 years following eradication. Eradication did not alter the incidence of ischemic stroke (HR 0.531, 95% CI: 0.221-1.270)[76]. However, this study identified a non-significant trend for lower risk in women after eradication,

warranting further investigation. *H. pylori* infection and intracerebral hemorrhage share inflammatory pathways and key NF-κB-related cytokines, such as Cxcl1 and Cxcl2[77]. However, the association between both is limited because the datasets in this study did not include patients who had both diseases.

Of note, the previously suggested protective effect of *H. pylori* seropositivity against the development of multiple sclerosis was not evident in a recent meta-analysis[78], although a definite conclusion on this is outstanding.

CONCLUSIONS

Novel retrospective analyses, such as GWAS data derived from well-characterized, community-based datasets such as the UK Biobank, have improved our understanding of *H. pylori*-associated extragastric disease burden in the last year, while prospective studies contributed only a limited amount of data. *H. pylori* was positively associated with colorectal cancer, IBS, metabolic disorder, atherosclerosis, MASLD, T1DM, T2DM, CVD including stroke, and neurodegenerative diseases and negatively associated with IBD, eosinophilic esophagitis, erosive esophagitis, esophageal adenocarcinoma, and asthma. At the same time, experimental studies uncovered several causal mechanisms that link *H. pylori* infection, either directly or indirectly, to metabolic and inflammation-driven diseases. These include MASLD, CAD, neurotoxicity, and neoplasms such as colorectal cancer.

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Authors' Contributions

JW performed the literature search, wrote the original draft manuscript, and reviewed and edited the manuscript. MS supervised the project and reviewed and edited the manuscript. All authors approved the final version of the article.

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Conflict of Interest

Jonas Wizenty has served as an advisory board member for Janssen-Cilag GmbH. Michael Sigal has no conflict of interest to declare.

AI Statement

No artificial intelligence was used for the preparation of the manuscript.

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