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REVIEW – NON-*HELICOBACTER PYLORI* HELICOBACTERS

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Abstract: Over the past 12-months, almost 50 original publications concerning non-*Helicobacter pylori* Helicobacters were published. This review summarizes these main findings. A paragraph concerning the importance of Helicobacters in the environment is also presented. Three novel *Helicobacter* species were proposed: '*Helicobacter delphinicola*' sp. nov. was isolated from the stomach of dolphins; '*Helicobacter monodelphidis*' sp. nov. and '*Helicobacter didelphidarum*' sp. nov. were isolated from the feces and the large intestine of opossums. Data showed the virulence of *Helicobacter suis* in mammals, supported its transmission from pigs to human, and highlighted the relevance of testing *H. suis* in gastric biopsies from patients negative for *H. pylori* infection. Data proposed longer duration treatment for successful eradication of *Helicobacter cinaedi* in humans. A role for *Helicobacter bilis* in inflammatory bowel disease and colorectal carcinogenesis was also shown in humans and new data supported the zoonotic importance of *Helicobacter* spp. in dogs. Several studies in *Helicobacter felis*-infected mice models akin to human gastric cancers have shown the importance of serine-phosphorylated-STAT3, PD-1/PD-L1 pathway and NLRC5 signaling in the promotion of gastric cancer, as well as the therapeutic potential of CCL28 blockade in gastric cancer progression. Using susceptible mice infected with enterohepatic *Helicobacter* spp. akin to human inflammatory bowel diseases, epigenetic dysregulation following chronic inflammation was shown to participate in the initiation of colorectal cancer; the protective effects of the inhibition of ALDH1A enzyme by WIN 18,446 was shown in Smad3$^{-/-}$ mice; and *Helicobacter hepaticus* GroEL/Hsp60 was identified as a driver of colitis in a CD40-mediated model of colitis and its CDT promoted colitis development by activating the JAK-STAT signaling pathway. Finally, the wax moth larvae, *Galleria mellonella*, was reported to be a useful and fast model to assess virulence of enterohepatic *Helicobacter* spp.

Keywords: Animal disease, Animal models, Genomics and evolution, Human disease, Non-*helicobacter pylori*, Helicobacter, Pathogenesis.

NON-*HELICOBACTER PYLORI* HELICOBACTER (NHPH) INFECTIONS IN HUMANS

Helicobacter suis is a gastric Helicobacter naturally hosted by non-human primates and pigs and may be transmitted to humans. Although its prevalence is underestimated in humans, *H. suis* is the second most prevalent *Helicobacter* species in the human stomach where it is associated with gastric MALT lymphoma. A concomitant infection with *Helicobacter pylori* and *H. suis* lymphoma was described in a 53-year-old woman, who was diagnosed with atypical gastric mucosa-associated lymphoid tissue (MALT) lymphoma with multiple lymphomatous polyposis (MLP), most likely associated with *H. suis*[1]. Eradication of *H. pylori* and *H. suis* cured the MALT lymphoma, but multiple granular elevations remained in the gastric body[1]. Based on

Koch's postulates, Rimbara et al[2] demonstrated the virulence of human *H. suis* isolates during infection in mice. Comparative genomics of human and porcine *H. suis* isolates revealed very similar genomes, suggesting its transmission to humans[2]. Additionally, *H. suis* lacks orthologs of the two major virulence factors of *H. pylori*, i.e., CagA and VacA, but contains highly plastic genomic regions encoding putative strain-specific virulence factors, including type IV secretion system-associated genes.

Two Japanese studies suggested that the prevalence of NHPH may be significant and previously underestimated. A retrospective study[3] showed NHPH-associated gastritis in 50 out of 3,847 Japanese patients (1.30%) over the last decade and the prevalence increased to 3.35% (30 of 896 patients) during the last 28 months. Analysis of the latter 30 positive cases identified 28 as NHPH: 26 as *H. suis* and two as *Helicobacter heilmannii*/*Helicobacter ailurogastricus*. None of these NHPH-infected patients were co-infected with *H. pylori*. Almost all NHPH-positive patients were asymptomatic but presented gastritis. This suggests that NHPH infection should be investigated in patients with gastritis whose *H. pylori*-based serology is negative[3]. Another study[4] analyzed gastric biopsies obtained in 17 hospitals in Japan including 236 patients without *H. pylori* infection and who did not receive any *H. pylori*-eradication treatment. Forty-nine cases (20.8%) were positive for NHPH, of which 22 cases could not be identified, seven cases were positive for *H. heilmannii sensu stricto*/*H. ailurogastricus*, and 20 cases were positive for *H. suis*. Forty-five patients had been treated with one of the four types of triple therapy used for *H. pylori* eradication, leading to eradication of NHPH in all cases[4]. The prevalence of five NHPH was also analyzed in Iranian patients without *H. pylori* infection who were not treated with *H. pylori*-based eradication therapy. Among the 60 gastric biopsies included from dyspeptic patients, *Helicobacter salomonis*, *H. heilmannii*, *H. suis*, *Helicobacter felis* and *Helicobacter bizzozeronii* were found in 20, 13, 10, 10, 13 and 7 cases, respectively[5]. None of these NHPH were found in Iranian stray cats according to publications of this year[6].

With regard to enterohepatic *Helicobacter* spp. (EHH), a case of *Helicobacter canis*-related bacteremia with underlying multilevel degenerative lumbar spinal stenosis was reported in a 65-year-old woman with rheumatoid arthritis treated with Tofacitinib, a Janus kinase inhibitor (JAKi), known to interfere with the host immune system[7]. The patient was in close contact with her pet dogs. This case hints at a possible zoonotic *H. canis* transmission favored by the immunosuppressive medication and highlights the increased risk of opportunistic infections with JAKi used in the treatment of rheumatoid arthritis[7].

Helicobacter cinaedi infections are associated with a wide variety of clinical presentations ranking this *Helicobacter* species among emerging human pathogens. The number of new clinical cases involving *H. cinaedi* infection increased this year and suggests that it is an underdiagnosed cause of febrile illness[8]. *H. cinaedi*-associated refractory cellulitis was reported in 2 patients with X-linked agammaglobulinemia (XLA)[9] and eradication required a long duration of antibiotic treatment. *H. cinaedi* co-infection with Campylobacter and Parainfluenza virus was diagnosed in a child with XLA and chronic abdominal pain[10]. Analysis of five cases of *H. cinaedi* infection revealed that the time required for a *H. cinaedi*-positive blood culture is relatively longer than that of *Campylobacter* species, especially for patients with underlying diseases, reaching up to 17 days[11,12]. Extended treatment duration should also be considered, as a 45-day treatment was required for a patient with rhabdomyosarcoma[12]. *H. cinaedi* infection also occurred in immunocompetent humans[8]. A case of *H. cinaedi* bacteremia secondary to diarrhea in an immunocompetent patient provided evidence that one route of bacteremia occurs through translocation from the intestinal tract to the bloodstream[13]. *H. cinaedi* is a fastidious, underdiagnosed pathogen whose culture from human blood samples is improved with the use of FAPlus/FNPlus bottles[14].

The role of *Helicobacter* bilis was investigated in inflammatory bowel disease (IBD) (n=20), colorectal cancer (CRC) (n=58) and adenoma (AD) (n=20). Compared to normal colorectal mucosa (NC) (n=40), the study revealed a higher abundance of *H. bilis* in CRC than in IBD, AD and NC[15]. Similarly, the average number of $CD4^+CD45RB^+$T was also higher in CRC than in IBD and NC, with a positive correlation between the *H. bilis* abundance and density of $CD4^+CD45RB^+$T in 30 colorectal tissues. *H. bilis* detection was also associated with higher levels of IFN-γ. Taken together, these data suggest that *H. bilis* may play a role in the initiation of IBD and colitis-associated carcinogenesis, by promoting the transformation of T cells into $CD4^+CD45RB^+$T cells and increasing the expression of IFN-γ[15].

A study[16] in Guatemala (n=424) revealed the lack of association between *Helicobacter* species (*H. hepaticus*, *H. bilis* and *H. pylori*) and non-alcoholic fatty liver disease and related metabolic conditions.

NON-*HELICOBACTER PYLORI* INFECTION IN ANIMALS

Three novel *Helicobacter* species have been proposed. '*Helicobacter delphinicola'* sp. nov. was isolated from the gastric fluid of captive common bottlenose dolphins with gastric disease[17]. This rod-shaped bacillus with tightly coiled spirals with two to four turns and two to six bipolar, sheathed flagella, is resistant to 2% NaCl. This species, closely related to *Helicobacter cetorum*, secretes a vacuolizating factor, like the *H. pylori* VacA toxin[17]. The two other proposed species were isolated from the fecal, cecal and colon contents of grey short-tailed opossums, clinically asymptomatic with and without prolapses[18]. '*Helicobacter monodelphidis*' sp. nov. is spiral-shaped, urease-negative and resistant to nalidixic acid, whereas '*Helicobacter didelphidarum'* sp. nov., has a fusiform morphology with periplasmic fibers, is urease-positive and susceptible to nalidixic acid. Both species appear to be closely related to *Helicobacter canadensis*[18].

Whole genome sequencing of '*Helicobacter himalayensis*' isolated from the gastric mucosa of Himalayan marmots[19], revealed a 1,829,936 base-pair long genome with a G+C content of 39.89%, a predicted genomic island named HhiG1, and a total of 1,769 predicted coding sequences[20]. The genome contains 42 virulence factor genes, including those related to flagellar motility and cytolethal distending toxin (CDT). Phylogenetically, '*H. himalayensis*' clustered close to *H. cinaedi* and *H. hepaticus*[20].

H. suis and *H. pylori* infection were explored in a colony of symptomatic and asymptomatic rhesus macaques (n=21) used in research[21]. Nineteen macaques were positive for *H. suis* and 5 of them were also positive for *H. pylori*. Serology was an inadequate biomarker for *H. suis* diagnosis. In this study, the clinical relevance of *H. suis* remained unclear but one macaque presented a gastric ulcer strongly associated with the infection[21]. *H. pylori* and *H. suis* DNA were also detected in two free-range wild boars[22].

Helicobacter species colonize healthy wild and captive marmosets and tamarins, and appear to form part of the normal microbiota. Chronic recurrent diarrhea and weight loss is a common problem in captive tamarins. Changes in the fecal microbiota of pied tamarins, a new world monkey, in a zoo in England, revealed that *Helicobacter jaachi* may be associated with chronic, recurrent diarrhea in captive callitrichids[23].

NHPH can cause disease in humans, and pets are a natural reservoir for many of these species. A rare case of hypertrophic canine gastropathy, Ménétrier-like disease, was reported in a dog with a simultaneous manifestation of granulomatous gastritis, with the presence of *Helicobacter* spp. and Leishmania[24]. The dog's clinical improvement was significant after treatment for the helicobacteriosis and leishmaniosis but vomiting persisted probably due to the Ménétrier-like disease. The presence of *Helicobacter* species was also analyzed in fecal samples (n=390) from domestic dogs without gastrointestinal symptoms in Chile[25]. These dogs commonly carry *Campylobacter* (173/390) and *Helicobacter* species (60/390) in their stools, mainly *Campylobacter upsaliensis* (169/390), *H. canis* (23/390), *Helicobacter canicola* (20/390), *H. bilis* (14/390), *Campylobacter jejuni* (8/390) and the proposed '*Helicobacter winghamensis*' species (5/390)[25]. Another study[26] revealed a high prevalence (94.3%) of *Helicobacter* species in dogs (n=35) in Brazil. These Helicobacters were closely related to *H. heilmannii sensu stricto*, *H. salomonis*, *H. felis*, and *H. bizzozeronii*[26]. An investigation of microbiota composition in dogs (n=33) showed that the colonic crypt of healthy dogs was mainly composed of *Helicobacter* species[27]. These studies support the zoonotic importance of *Helicobacter* spp. in dogs.

The prevalence of *Helicobacter* species was also analyzed in the digestive tract of stray cats (n=30) in Iran. This study revealed the presence of *H. pylori* (60%), *H. canis* (43.3%) and *H. bilis* (26.7%) in their duodenum (50%), ileum (60%), colon (50%) and liver (43.3%) and a concurrent infection of the duodenum and liver was observed[6]. Antimicrobial susceptibility testing of feline *H. heilmannii* and *H. ailurogastricus* revealed that acquired resistance to azithromycin, spectinomycin, enrofloxacin, and lincomycin occasionally occurs in feline *H. heil-*

mannii isolates[28], suggesting that antimicrobial resistance to these antibiotics should be taken into account for human eradication treatment, as pets may constitute a reservoir for human zoonosis. Dysbiosis of fecal microbiota in cats infected with protozoal *Tritrichomonas foetus* revealed increased prevalence and abundance of Megamonas and *Helicobacter*[29].

HELICOBACTER SPP. AND THE ENVIRONMENT

Improvements in the feed efficiency of chickens should decrease production costs and reduce the demand of land area for feed production, while also reducing the environmental impact of broiler production. Metagenomics of cecal contents from chickens showed that low feed efficiency increased the abundance of *Campylobacter avium* in females and *Helicobacter pullorum* in males, suggesting that gender and food intake play a role in the colonization of chickens with these *Campylobacterales*[30].

Analysis of treated urban wastewater reused for irrigation in Spain[31] provided evidence of the presence of *Helicobacter* species such as *H. pylori*, *H. hepaticus*, *H. pullorum* and *H. suis* in wastewater samples, even after disinfection treatment[31], suggesting an increased risk for environmental safety.

MODELS FOR HELICOBACTER INFECTION

Several *H. felis* mice models akin to human gastric cancer were used. Myd88$^{-/-}$ mice infected with *H. felis* constitute a fast-progressing gastric cancer model which allowed the early detection of tumor cells in bone marrow and peripheral blood during cancer progression[32]. Cytokeratins, epithelial to mesenchymal transition markers, and cancer stem cell biomarkers were pertinent and useful markers to detect aggressive forms of gastric cancers in this model[32]. In *H. felis*-infected Myd88$^{-/-}$ mice, *Lactobacillus* spp. may contribute to a faster development of gastric cancer and may serve as a potential biomarker for gastric cancer[33]. Another model, *H. felis*-infected mice treated with N-methyl-N-nitrosourea (MNU), was used to demonstrate an immunosuppressive role of tumor-intrinsic β-catenin signaling and the therapeutic potential of CCL28 blockade in gastric cancer progression[34]. The effects of 5-fluorouracil and oxaliplatin were assessed in gastrin-deficient mice infected with *H. felis* and treated with MNU[35]. These chemotherapeutic agents reduced numbers of myeloid-derived suppressor cells (MDSC) to increase the effects of anti-programmed cell death-1 (PD-1), which promotes tumor infiltration by CD8+ T cells[35]. An adverse effect was the induction of PD-1 ligand (PD-L1) by tumor cells, which increases tumorigenesis and accumulation of depleted MDSC, and promotes tumor progression[35]. PD-L1 induction should be considered in the design of therapeutic regimens. Infection of dendritic cell-depleted mice with *H. felis* showed that the PD-1/PD-L1 pathway modulates the immune function of gastric dendritic cells that protects the gastric mucosa from Helicobacter-induced inflammation but allows persistent Helicobacter colonization[36]. In other mice models of *H. felis* infection, dendritic cell-derived TGF-β were shown to mediate the induction of mucosal regulatory T-cell response to *H. felis,* essential for the maintenance of immune tolerance in mice[37]. In another study using *H. felis* and *H. pylori* mice models of B-cell lymphomagenesis, as well as gastric tissues from *H. pylori*-infected patients, NLRC5 (nucleotide-binding oligomerization domain-like receptors (NLR) family CARD domain-containing 5), an innate immune molecule, was shown to be a negative regulator of gastric inflammation and mucosal lymphoid formation in response to both infections. Aberrant NLRC5 signaling in macrophages can promote B-cell lymphomagenesis during chronic Helicobacter infection[38]. The model of chronic *H. felis* infection in mice deficient for serine-phosphorylated-STAT3 revealed the key role of serine-phosphorylated-STAT3 in promoting Helicobacter-induced gastric carcinogenesis[39]. Different genetically modified mice were infected with *H. felis* to study the regulation of Mist1-positive stem cells upon the gastric injury and inflammation induced by *H. felis*[40]. Mist1 transcription factor is a marker for this corpus stem cell population that can give rise to cancer. This study showed that gastric Mist1+ isthmus cells are the main supplier of regenerated glands and are activated in part through the Wnt5a pathway and expand in response to injury and inflammation in mice[40].

In *H. felis*-infected mice, a vaccine with silk fibroin hydrogel as the mucosal vaccine carrier was evaluated. Data showed that gastric tissue-resident memory CD4+T (CD4+T_{RM}) cells protect against the infection, and the influence of neutrophils on gastric intraepithelial CD4+T_{RM} cell formation was shown[41].

H. hepaticus infection of susceptible mice is widely used to study human IBD. Antibody therapies blocking signaling through the CD40-CD40L axis are promising treatments for IBD. The DC-LMP1/CD40-mediated colitis mouse model of spontaneous fatal colitis and dysbiosis lacks intestinal CD103+ dendritic cells and fails to induce regulatory T cells (iTreg). In these mice whose immunity is compromised, *H. hepaticus* rapidly promotes a strong intestinal inflammation and the bacterial chaperonin GroEL/Hsp60, the main specific antigen, is targeted in the absence of iTregs[41]. This study showed that improper immune regulation triggers IBD and colitis and highlights the importance of CD103+ DC- and iTreg-mediated immune tolerance to maintain a healthy intestinal balance during pathobiont infection[42]. Multi-omics analyses were performed to characterize IBD-induced hyperplasia/dysplasia in $Rag2^{-/-}$/$IL10^{-/-}$ mice infected with *H. hepaticus*[43]. In this model, Helicobacter-induced chronic inflammation promotes changes in methylation and hydroxymethylation patterns in the genome, altering the expression of key tumorigenesis genes and suggesting a role for epigenetic dysregulation in the initiation of colorectal cancer[43].

$Rag2^{-/-}$/$IL10^{-/-}$ mice were co-infected with *H. pylori* and *H. hepaticus* to study IBD onset[44]. Despite a similar gastric and colonic *H. pylori* colonization for both genders, only co-infected males developed more severe colitis and dysplasia, when compared to mice infected with *H. hepaticus* only. In these co-infected males, inflammatory colonic mRNA levels were upregulated. Thus, *H. pylori* and *H. hepaticus* co-infection enhances the inflammatory responses in the colon of susceptible male mice, which results in more severe colitis and dysplasia[44].

Using $Smad3^{-/-}$ mice infected with *H. bilis*, Seamons et al[45] showed the protective effects of ALDH1A enzyme inhibition using WIN 18,446, a non-selective potent ALDH1A inhibitor known to decrease all-trans-retinoic acid levels with minimal side effects. WIN 18,446 attenuates IBD and deserves to be evaluated in other IBD models.

Dextran sodium sulfate (DSS) chemically induced colitis in mice is an IBD model. C57BL/6 mice infected with *Helicobacter muridarum* with and without DSS and indole-3-carbinol (I3C), a natural plant product[46], revealed the beneficial effect of I3C on colitis because it exerts an agonist function of the aryl hydrocarbon receptor and affects bacteria and bacterial byproducts. *H. muridarum*-infected mice are a pertinent IBD model as the immune response to *H. muridarum* mimics responses seen during DSS-chemically induced colitis and human IBD in terms of local and systemic cytokine responses and microRNA changes. Additionally, *H. muridarum* does not alter the activity of the I3C compound[46]. When studying the effects of native starches on the onset of colitis in DSS-chemically induced colitis in mice, the authors showed the beneficial effects of some native starches from potato, pea, and Chinese yam, that could be used to alleviate colitis and also to inhibit *H. hepaticus*[47].

The wax moth larvae from the *Pyralidae* family, *Galleria mellonella*, was recently proposed as a model to study the virulence of different pathogens. The virulence of *H. bilis*, *H. canicola*, *H. canis*, and proposed '*H. winghamensis*' isolated from domestic dogs was assessed using the *G. mellonella* model[48]. These larvae were susceptible to Helicobacter infection after four hours of infection and *H. canicola* was the highest virulent *Helicobacter* species in this model. Histopathology revealed cellular and humoral immune response, accumulation of hemocytes, nodulation, and melanin deposition in different tissues[48].

VIRULENCE FACTORS

In vitro experiments showed that soluble factors secreted by *H. felis* stimulate IL-10-producing B cells which suppress differentiation of *H. felis*-activated stimulatory dendritic cells[49].

The main virulence factor of EHHs is CDT, a genotoxin which triggers DNA breaks. The nuclear remodeling following CDT-induced DNA damage can be associated with the formation of messenger ribonucleoprotein particles concentrated and invaginated in the nuclei of giant surviving cells[50]. These structures, called nucleoplasmic reticulum (NR), were observed both *in vitro* and in *H. hepaticus*-infected mice and concentrate the RNA binding proteins UNR/CSDE1

and P62/SQSTM1[50,51]. CDT-induced NR formation is associated with cell survival and involves autophagy, which leads to selective removal of CDT-induced micronuclei-like structures and protects the cells against induced apoptotic cell death[51]. In another study, *IL10*$^{-/-}$ male mice infected with *H. hepaticus* and its corresponding CDT isogenic mutant strain[52] showed that CdtB promotes colitis development by induction of an inflammatory response and activation of the JAK-STAT signaling pathway. In this model, CDT did not affect the colonization efficiency of *H. hepaticus* and increased the NO content in the proximal colon[52].

H. pullorum commonly colonizes the gastrointestinal tract of poultry causing gastroenteritis. It is an emerging zoonotic *Helicobacter* species that causes digestive diseases in humans through ingestion of contaminated meat. The genetic characteristics of *H. pullorum* (n=23) from different sources (poultry, meat and animals) and countries (Asian and Western countries) revealed that *H. pullorum* exhibits a high genetic diversity and two subtypes of type 6 secretion system[53].

Conflict of interest

The author declare that they have no conflict of interest.

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