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REVIEW OF NON-*HELICOBACTER PYLORI* HELICOBACTER SPECIES: INSIGHTS INTO PATHOGENESIS, EPIDEMIOLOGY, AND CLINICAL IMPLICATIONS

M. Kroiß, B. Teodorescu, T. Song, R. Vasapolli

Department of Medicine II, University Hospital, LMU Munich, Germany

Markus Kroiß and Bianca Teodorescu contributed equally and share first authorship

Corresponding Author: Markus Kroiß, MD; email: Markus.Kroiss@med.uni-muenchen.de

Abstract – Non-*Helicobacter pylori* Helicobacters (NHPHs) represent a group of bacteria distinct from H. pylori. They are commonly found in the gastrointestinal tracts of animals, such as poultry, swine, and domestic pets. Recent studies have demonstrated that these organisms have implications beyond animal hosts, indicating a potential role in human gastric diseases and raising concerns about the possibility of zoonotic transmission. Different NHPH species can cause gastritis, ulcerations, and even systemic effects like bacteremia in human individuals. A comprehensive literature search protocol on MEDLINE (PubMed) from the last twelve months was employed, resulting in the identification of 24 articles and case studies on NHPHs in animals and 12 in humans, respectively. Furthermore, we conducted a search for Helicobacter species other than *H. pylori* that are referenced individually in the National Library of Medicine database. The most recent studies have focused on the clinical manifestations and diagnostic challenges of NHPHs-related diseases in animal models and human cases. An important subject was the transmission of disease between different species, particularly those associated with livestock farming. The results suggest that NHPHs, especially *H. pullorum*, *H. suis*, and *H. cinaedi*, may be a significant contributing factor in the development of gastrointestinal diseases in humans, particularly in instances where H. pylori is not present. Although there has been a significant improvement in the overall awareness regarding NHPH infections, it remains a challenge to identify new species and distinguish between low and high pathogenicity levels. Further research is needed to understand how NHPH impacts human health, with a focus on improved diagnostic tools and treatment strategies.

Keywords: Non-*Helicobacter pylori* Helicobacter, Gastric Helicobacter species, Human dysbiosis, Zoonosis.

INTRODUCTION

Non-*Helicobacter pylori* Helicobacters (NHPHs) are a group of bacteria usually found in the gastrointestinal tract, which genetically and phenotypically differ from *H. pylori*[1]. These species are typically associated with animals and exhibit notable differences in their overall morphology, particularly in the form of the spiral structure and the number, location, and configuration of their flagella[2].

In recent years, studies on NHPH have expanded beyond the traditional focus on poultry and pigs to include a wider range of host species, such as dolphins and domestic animals. These

studies have yielded valuable data on the prevalence of NHPH amongst broader populations of zoological species and its impact on their gastrointestinal health. Additionally, several research groups have investigated potential zoonotic transmission routes with varying outcomes. Our literature search indicates an overall growing interest in investigating the role of NHPHs in the onset of disease and therapeutic approaches within the human gut[3-5]. The accurate identification of NHPH species in the human body that cause dysbiosis and eventually promote disease could potentially serve as a novel diagnostic indicator for patients otherwise negative for *H. pylori*.

The following work contains the main data published on NHPH in the past twelve months, covering a wide range of topics, from studies on animal models to clinical case discussions. Thus, we provide insights into the epidemiology, transmission dynamics, pathogenic mechanisms, and clinical manifestations associated with NHPH infections.

METHODS

In order to gain a comprehensive understanding of the current state of research on NHPH, we conducted a comprehensive analysis of all relevant publications published between the 1st of April 2023 and the 31st of March 2024. A literature search protocol was employed, resulting in the identification of 24 articles and case studies on NHPH in animals. In addition, 12 newly published original research articles or clinical case studies were identified that focus on gastric NHPHs in humans. The search protocol on MEDLINE (PubMed) was as follows:
–"Helicobacter" NOT "pylori",
– "Non-Helicobacter pylori Helicobacter",
– "NHPH".

Additionally, we searched for Helicobacter species other than *H. pylori* that are mentioned individually in the National Library of Medicine[6]. To ensure the highest level of scientific rigor, we excluded all review studies and any publications published as abstracts, posters, editorials, or that were not written in English. The following three review articles will not be further discussed, as they were excluded based on the aforementioned criteria: a bibliometric analysis and assessment of research concerning NHPHs from 1993 to 2023[7], a literature review focusing on *H. pullorum* as a main foodborne pathogen[8], and a literature minireview of NHPH gastric mucosa-associated lymphoid tissue lymphoma[9]. In the past twelve months, three new NHPH species were newly described (Table 1).

NHPH SPECIES IN ANIMAL STUDIES

Poultry

As in previous years, the primary focus within the field of NHPH research was once again on poultry and the risk of foodborne infections. A few articles examined the role of *H. pullorum*

TABLE 1. AN OVERVIEW OF THE NEWLY DESCRIBED NHPH SPECIES AND THEIR CHARACTERISTICS.

Species name	Isolated from	Closest relative	Type strain	Urease	Catalase	Reference
H. ibis	Fecal samples of wild birds in Southern Chile	*H. burdigaliensis* and *H. valdiviensis*	A82T (=LMG 32718T= CCCT 22.04T)	-	+	Lopez-Cantillo et al[50]
H. zhangjianzhongii	Fecal samples of canines in Beijing, China	*H. canis*	XJK30-2T = GDMCC 1.3695T	-	-	Wang et al[51]
H. kumamotonensis	Human fecal sample	*H. equorum*	PAGU 1991T (=GTC 16810T= CCUG 75774T)	-	+	Kawamura et al[48]

in this context. It is well known that *H. pullorum* colonizes the gastrointestinal tract of poultry and can cause gastritis in animals. However, there are instances where *H. pullorum* has been linked to conditions such as colitis, hepatitis, and bacteremia in humans[10-12]. The bacteria can be transmitted to humans by uncooked poultry meat. A study by Quaglia et al[13] investigated the occurrence of *H. pullorum* in retail chicken meat. 240 samples were analyzed by two identification methods, one following a microbiological protocol and the other one performing a PCR test using the 16S rRNA gene. As a result, 35% of the samples analyzed by the microbiological protocol and 45% of the PCR tests were positive for *H. pullorum*. The data from this study indicate that there is a high probability of transmission through the consumption or preparation of raw chicken meat.

Given the high prevalence of *H. pullorum* and the potential for human infestation, another study examining the functional molecular characterization of a transmission route for multidrug-resistant *H. pullorum* should be considered. Qumar et al[14] isolated *H. pullorum* from 11 free-range and broiler chickens and infected HepG2 cells with the isolates. It was shown that all isolates adhered to HepG2 cells. Interestingly, there was a difference in the invasiveness between free-range and broiler chicken isolates. The last mentioned were significantly more invasive than the free-range isolates. Another difference between the two isolates was the upregulation of cdtB, flhA, and flaB genes of *H. pullorum* post-infection in broiler chicken isolates. However, all isolates created a similar biofilm on the liquid-air interface of the glass coverslips and sidewalls of the wells. These findings indicate that there is a chance of transmission from poultry to humans, and thus, *H. pullorum* potentially represents a risk to public health as a food-borne, multidrug-resistant bacterium.

Swine

The following paragraph focuses on *Helicobacter spp.* in swine. Pegu et al[15] conducted a study about the incidence of Helicobacter infections in the gastric mucosa of pigs and in the stool of their farmers in India. The analysis was conducted on 403 stomach samples and 74 necropsy samples obtained from the animals, along with 97 stool samples collected from the farmers. The findings revealed that around 20% of the pigs suffering from gastritis were positive for *Helicobacter spp.* (not closer classified), whereas only 3% of pigs with a physiological mucosa tested positive. Through PCR analysis it was proven that almost 20% of the pig stomach samples were colonized by *H. suis,* a species with significant pathogenic effects in humans[16]. Around 3% of the farmers' stool samples showed a positive result for *H. suis*. The results indicate that there is a relevant transmission route of *Helicobacter spp.* in livestock farming.

Taillieu et al[17] were able to identify *H. suis* as a causative infectious agent for ulceration in the pars oesophagea of slaughtered pigs. A histological examination of 150 stomachs from slaughtered pigs revealed the presence of lesions in all cases. *H. suis* was found in 78% of the samples. A positive correlation between a high infectious load and the severeness of the gastric lesions was then concluded. The underlying cause is supposed to rely on a reduction in the diversity of the microbiome in the oesophagus, mediated by the bacterium. There was no proven effect of the food on the presence of gastric lesions.

Dolphins

A singular study this year investigated the role of *Helicobacter spp.* in dolphins. Former studies already underlined the role of *H. cetorum* and *H. delphinicola* in gastric infections of dolphins[18-20]. Segawa et al[21] collected data on the incidence of *H. cetorum* and *delphinicola* in 21 facilities in Japan and put their findings in relation to the occurrence of gastric diseases. Out of 82 dolphins, 96% were positive for *H. cetorum*, and 55% were positive for *H. delphinicola*. There was a significant correlation between the infection with *H. delphinicola* and the presence of gastric disease, whereas no such correlation was found for *H. cetorum*. *H. delphinicola*-positive dolphins were found in 55% of the examined facilities.

Felines and Canines

A study conducted by Guendulain et al[22] investigated the potential transmission of *Helicobacter spp.* from dogs to their human owners. 30 gastric samples of human patients with symptoms of clinical gastritis and samples of their associated dogs were collected and analyzed for *Helicobacter spp*. *H. pylori* was detected in 83% of the human samples, whereas the canine species tested positive for *H. bizzozeronii*, *H. felis*, *H. salomonis*, and *H. heilmanii*. No cases of the same species being transmitted from dogs to humans were identified, which brings the authors to the conclusion that a transmission from dogs to their human owners is unlikely.

A study published by Taillieu et al[23] aimed at identifying potentially novel Helicobacter-like species in gastric samples of cats and dogs. Samples of 27 dogs and 20 cats were analyzed using different PCR assays, followed by a histopathological and immunohistochemical evaluation. In a first 16S rRNA assay, 83% of the samples showed positive results for infection with a canine/feline gastric NHPH. Following the initial round of a nested PCR targeting 23S RNA (*Helicobacter genus*-specific), 77% of the animals tested were found to be positive. This was followed by a second round of PCR, this time only targeting *H. pylori*, in which all samples were found to be negative. The histopathological analysis showed a low pathogenic effect of the gastric *Helicobacter spp.* present in cats and dogs. This study comes to the conclusion that known *Helicobacter spp*. are unlike *H. pylori* in humans, and cannot represent a main cause of gastric diseases in cats and dogs.

Wild Mice

Mice studies analyzing the effect of *Helicobacter spp.* on the intestinal microbiome have become of increased interest over the past years. A study by Zhao et al[24] found that colonization with *Helicobacter spp.* reduces the growth of lethal *Citrobacter rodentium* and consequently also weakens the *Citrobacter rodentium*-induced gut inflammation in wild-type mice. The protective effects might be moderated by the interference of *Helicobacter spp.* with the tissue attachment of *Citrobacter rodentium* by lowering the amount of mucus-derived sugars.

A study by Druffner et al[25] tried to identify the difference between infection with a mouse-adapted strain of *H. pylori*, and the natural murine pathogen *H. felis* has on the gastric inflammation and metaplasia. Their experiments showed a much higher immunogenic effect of *H. felis* compared to *H. pylori*. In mice, *H. felis* leads to a substantially higher CD4+ T-cell activation, a process linked to gastric cancer risk in humans. In conclusion, when designing studies on the pathogenesis and initiation of gastric cancer, it seems that the *H. felis* infection is a more suitable model than *H. pylori*, whereas *H. pylori* should be considered for studies on colonization.

In the past year, apart from the vast amount of research that focused on gastrointestinal diseases, one group has also examined the role of *Helicobacter spp.* in Parkinson's disease. Ahn et al[26] found that augmented levels of *H. hepaticus* in the gut microbiota of mice aggravate the symptoms of Parkinson's, especially *via* dopaminergic degeneration and, thus, motoric disorders. The effect seems to be transmitted through an activation of asparagine endopeptidase, which creates α-Synuclein pathologies and motoric impairments.

NHPH SPECIES IN HUMAN STUDIES

H. suis, naturally hosted by swine, is considered the most prevalent gastric NHPH found in human subjects[27]. It has been associated with gastric disease and exhibits virulence-associated features and survival characteristics indicative of pathogenicity[28]. Infection with *H. suis* changes glycosylation, reducing gastric mucins' ability to effectively inhibit pathogen growth[29]. In a joint report of four cases of *H. suis* infection of the duodenal mucosal (with moderate infiltration of inflammatory mononuclear cells and neutrophils), Agawa et al[30] revealed that the entry of gastric contents into the duodenum could lower the pH within the duodenum, thereby facilitating the survival and growth of the pathogen.

The endoscopic features typical of *H. suis* gastritis tend to resemble those of *H. pylori* gastritis and have not yet been widely characterized. In a study conducted by Okamura et al[31] a

cohort of 2,087 patients undergoing endoscopy was examined, of whom 134 exhibited positive biopsy results for *H. pylori* and 9 for *H. suis*, respectively. The objective of the study was to identify unique characteristic endoscopic findings of NHPHs in order to facilitate a more accurate macroscopic diagnosis in *H. pylori*-negative patients. While the proportion of subjects exhibiting a cracked-like or white-marbled appearance of the mucosa was similar in both subjects infected with *H. pylori* and *H. suis*, findings of diffuse redness were significantly less frequent in the *H. suis* group ($p < 0.001$). The authors argue that the average neutrophil infiltration and Helicobacter density scores[32] were higher in the *H. pylori* group (both $p<0.01$), which could explain the observed endoscopic differences. Although no particular endoscopic feature was identified that would enable a more precise diagnosis of NHPH gastritis, evaluation for diffuse redness during endoscopy may prove helpful to the investigating physician when dealing with unusual cases. In line with these findings, Takeda et al[33] described characteristic changes of the gastric mucosa in chronic gastritis using Linked-Color Imaging (LCI) and Blue-Laser Imaging (BLI) in a *H. suis*-positive patient. While no endoscopic findings of diffuse redness, patchy redness, or atrophy were identified by white-light endoscopy, detection of erosions, nonuniform redness, and nodularity by LCI and BLI were suggestive of chronic gastritis[34].

Tests that rely on the activity of *H. suis* urease, such as the urea breath test and rapid urease test, frequently yield negative results. Given the lack of a reliable clinical method for diagnosing *H. suis* infection without gastric biopsy samples, Matsui et al[35] evaluated the diagnostic accuracy of a serological test based on the application of whole-bacterial cell ELISA that simultaneously assesses *H. suis* and *H. pylori* infection in humans. This novel approach presents a non-invasive test method using serum from patients susceptible to NHPH. The results of the ELISA test in the *H. suis* infection group demonstrated 100% sensitivity, 92.6% specificity, a positive predictive value of 76.9%, and a negative predictive value of 100%.

H. cinaedi stands out as the most frequently studied species within the group of NHPH in the past 12 months and appears to play a pivotal role in various diseases, including bacteremia, vascular diseases, myalgia, and cellulitis. In immunocompromised individuals, it is known to cause invasive infections of high severity.

A case report presents the case of a child with nephrotic syndrome who suffered from mild transient febrile illness with spontaneous remissions caused by a bacteremia with *H. cinaedi*[36]. To date, there are only 6 cases of pediatric *H. cinaedi* bacteremia in the medical literature. All pediatric patients were either neonate or immunocompromised, and all of them suffered from a severe infection with complications such as meningitis, cholangitis, or arthritis. Although the number of cases is relatively limited, it is evident that the severity of bacteremia with *H. cinaedi* can widely range from mild to life-threatening. The diffuse symptoms pose a diagnostic challenge, and the bacteria itself requires special treatment for cultivation.

As dangerous as *H. cinaedi* for children might potentially be, data show that, in adults, severe complications from an infection with *H. cinaedi* are rare. Izuta et al[37] collected data from all patients with an *H. cinaedi* infection presenting to the emergency room at Kobe City General Hospital in Japan between November 2011 and December 2020. Only 22 patients in total exhibited *H. cinaedi* in blood cultures. The symptoms were non-specific (fever, shivering and localized pain were the main complaints). Seven out of the 22 patients had a more complex infection, such as osteomyelitis, infected aortic aneurysm, or infected renal/pancreatic cysts. None of the patients died, and only one required surgical treatment.

Two case reports of human patients with *H. cinaedi* bacteremia were published. Shimada et al[38] detailed the case of a 78-year-old man who presented to the hospital with tenderness in both gastrocnemius muscles and erythema from the left lower leg to the ankle. Symptoms have existed for more than two weeks, and the patient was afebrile. Five days after getting hospitalized, the blood cultures tested positive for *H. cinaedi.* Further examinations excluded immunodeficiency or any tumor burden. The patient was treated with intravenous ampicillin, and symptoms improved.

In the second case report, *H. cinaedi* was not detected *via* blood culture but through metagenomic next-generation sequencing[39]. The patient suffered from primary agammaglobulinemia and developed a pyoderma gangrenosum-like ulcer. Adequate treatment was provided.

A study by Horii et al[40] investigated the association between *H. cinaedi* and clinically uninfected abdominal aortic aneurysms. Samples of 39 arterial walls, deriving from patients who underwent elective surgery between June 2019 and June 2020, were genetically analyzed.

The PCR target gene region was the *H. cinaedi*-specific cytolethal distending toxin subunit B. In 9 of the 39 patients *H. cinaedi* was detected. As a control, non-aneurysmal iliac arteries were obtained from six of the nine patients who tested positive, and from 14 of the 30 patients who tested negative for the pathogen in the abdominal aortic aneurysm. Notably, *H. cinaedi* was absent in non-aneurysmal arterial walls.

There is no general consensus on how *H. cinaedi* attaches itself to host cells and initiates the infection process. Aoki et al[41] investigated a novel autotransporter protein, HcaA, and its role in *H. cinaedi* disease onset. *In vivo* investigations were conducted with mice that were either orally infected with wild-type or HcaA-knockout strains of *H. cinaedi*, respectively. Samples from the intestinal tract were assessed after 7, 14, and 28 days post-infection. The results demonstrated that the overall bacterial colonization was significantly lower in mice exposed to the HcaA-knockout strain compared to the wild-type strain. Following the knockout of HcaA, the authors were able to significantly reduce the cytotoxic effect of *H. cinaedi* infection on colon epithelial cells. This supports the existence of a new virulence factor based solely on adhesion capacities.

In their study, which used retrospective (n = 464) and prospective (n = 65) patient samples from populations of gastric patients who tested negative for *H. pylori*, Taillieu et al[43] were able to demonstrate a pathophysiological involvement of NHPHs in disease development for chronic gastritis, peptic ulcer disease and gastric MALT lymphoma, and a positive correlation between the clinical and/or histological remission and the canonical *H. pylori* eradication therapy. DNA extracted from biopsy and saliva samples underwent subsequent analysis using different *Helicobacter genus*-specific PCR assays to confirm the presence of gastric NHPHs. The prevalence was 29.1% in the retrospective biopsy samples, whereas the prospective cohort demonstrated a prevalence of 27.7% in gastric tissue and 20.6% in saliva, respectively. Prospectively enrolled patients were then administered a triple eradication therapy for *H. pylori* (in most cases, a combination of amoxicillin, clarithromycin, and proton pump inhibitors). Patients suffering from MALT lymphoma received the triple therapy in combination with rituximab monotherapy. A total of 12 of 17 patients achieved clinical remission, 7 out of 9 achieved gastritis histological remission (histologically confirmed by a negative follow-up gastroscopy), and 4 out of 8 achieved eradication.

Unlike earlier research findings, Taillieu et al[42] revealed that the canine/feline gastric NHPHs *H. bizzozeronii* and *H. felis* were the predominant species in their cohort, rather than *H. suis*. Two case reports of patients with severe refractory gastric ulcers from the past year also highlight upon histopathologic examination the presence of NHPHs from cats and dogs (*H. ailurogastricus*, *H. bizzozeronii*)[43,44]. Gastric NHPHs that are commonly found in dogs and cats have prevalence rates ranging from 60% to 100%[45]. A retrospective study of children in the New England region of the United States analyzed the outcomes of *H. heilmannii* infection and its association with epigastric abdominal pain, nausea, and macroscopic and microscopic signs of chronic gastritis on endoscopy[46]. 84% of the infected children exhibited endoscopic findings, such as gastric nodularity (55%) and erythema (26%). Histological evidence of chronic gastritis was present in all children, even those with normal endoscopic examinations. As mentioned before in this work, *H. heilmannii* is another NHPH commonly found in the gastric systems of dogs and cats.

During our literature search, we have encountered one publication that showed no significant association between NHPHs infection and gastritis or gastric cancer development[47]. The authors retrospectively screened formalin-fixed paraffin-embedded tissue probes that were collected from 73 gastric cancer patients. The patient cohort was then divided into three groups: 21 patients with current *H. pylori* infection, 37 patients with previous *H. pylori* infection, and 15 patients with no history of *H. pylori* infection. The tissues were analyzed for NHPHs *via* PCR, with overall negative association results between NHPH-positive and negative patients and gastric disease in all three groups.

NEW SPECIES

Our literature search protocol resulted in three research articles published between April 2023 and March 2024 with novel Helicobacter species, one human and two animal strains, respec-

tively. Kawamura et al[48] reported the isolation of a gram-stain-negative, spiral bacterium from the blood of a patient with diffuse large B-cell lymphoma. The bacterium (*H. kumamotonensis*) closely resembles a pathogen that is already known to originate from the horse gastrointestinal tract[49]. The only two species novae from animals that we identified were *H. ibis*, which was isolated from fecal samples from wild birds in southern Chile[50], and *H. zhangjianzhongii*, obtained from multiple dogs in Beijing, China[51].

DISCUSSION

The majority of the present literature on NHPH from the past year was centered on examining the correlation between Helicobacter species and gastric disease in animal hosts, with a focus on the ability of NHPH to induce gastritis, ulcerations, and other gastrointestinal disorders. The spread of disease among different animal species, particularly those linked to livestock farming, was a recurring topic. Several studies found NHPH in raw meat and fecal samples from various animals involved in common food production. Similar results were yielded in pets and small rodents. These findings may be transferable to human individuals and could assist in understanding the etiology of their similar diseases, underlining the importance of exploring host-pathogen interactions across species boundaries. The effects of different NHPHs on human health were also highlighted, with *H. suis* and *H. cinaedi* being the most studied pathogens. NHPH species do not solely interact with the human gut but appear to have a broader systemic effect, particularly in immunocompromised individuals or young children.

One could argue that progress in the diagnosis and treatment of NHPH infections has become substantial, although it remains a challenge to detect novel species and differentiate between low and high pathogenicity levels.

CONCLUSIONS

In summary, our review provides a comprehensive overview of current research on NHPH and demonstrates their diverse roles and influence across multiple species. By analyzing the results of our literature search, we were able to encompass the epidemiology, transmission dynamics, pathomechanisms, and clinical manifestations of NHPH infections. Our research shows how important it is to consider NHPHs in addition to *H. pylori* in order to understand the complexity of the gastrointestinal microbiome and its influence on health and disease. In the future, further studies on the immunogenicity, virulence, and potential for zoonotic transmission of NHPH are necessary to better understand their influence on human health and disease.

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Authors' Contributions

M.K. and B.T. formulated the study concept, contributed to all stages of the review process, performed the literature search and data extraction, wrote the first draft of the manuscript, and acted as first reviewers. T.S. oversaw the review conceptualization and execution and acted as a second reviewer. R.V. acted as a third reviewer for discrepancies and revisions of the manuscript. All authors contributed equally to preparing the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Ethics Statement

As this manuscript is a review, it does not involve original research with human participants. Therefore, informed consent was not required. The paper synthesizes and analyses the existing literature on the subject, ensuring compliance with all relevant ethical guidelines for review articles.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

ORCID ID

Bianca Teodorescu: https://orcid.org/0000-0002-4333-5965
Riccardo Vasapolli: https://orcid.org/0000-0001-7150-5864

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