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REVIEW

Helicobacter heilmannii sensu lato: An overview of the infection in humans

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Abstract

Helicobacter heilmannii sensu lato (*H. heilmannii* s.l.) is a group of gastric non-*Helicobacter pylori Helicobacter* species that are morphologically indistinguishable from each other. *H. heilmannii* s.l. infect the stomach of several animals and may have zoonotic potential. Although the prevalence of these infections in humans is low, they are associated with gastric pathology, including mucosa-associated lymphoid tissue lymphoma, making them a significant health issue. Here, the taxonomy, epidemiology, microbiology, diagnosis, and treatment of these infections will be reviewed. The gastric pathology associated with *H. heilmannii* s.l. infections in humans will also be addressed. Finally, the features of the complete bacterial genomes available and studies on species-specific pathogenesis will be reviewed. The understanding of the mechanisms that underlie gastric disease development mediated by the different bacterial species that constitute *H. heilmannii* s.l. is essential for developing strategies for prevention and treatment of these infections.

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Key words: *Helicobacter heilmannii sensu lato*; Gastric non-*Helicobacter pylori; Helicobacter* species; Pathogenesis; Diagnosis; Treatment; Genomes

Core tip: *Helicobacter heilmannii sensu lato* is a group of non-*Helicobacter pylori Helicobacter* species that infect the stomach of animals and humans. In the human stomach, these infections are associated with several pathologies, but it is currently unknown whether certain species are more often associated with a certain disease outcome than others. The access to bacterial genomes together with the availability of increasing numbers of *in vitro* isolates will allow significant advances in the understanding of species-specific bacteria-host interactions in disease pathogenesis and will be essential for future development of strategies to prevent and treat these infections.

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INTRODUCTION

The first descriptions of spiral bacteria colonizing the stomach of animals date from the end of the 19th century[1], and reports of such microorganisms in the human stomach date from the beginning of the 20th century[2]. Also, by that time, the presence of urease activity in the stomach was reported[3], but no associations were made between this observation and the presence of microorganisms in the stomach. The occurrence of spirochetes in stomachs from autopsied individuals and in fresh gastric surgical specimens was reported later[3,4]. None of these findings received much attention, as the stom-

Table 1 Natural hosts and characteristics of *Helicobacter heilmannii* s.l. species that infect humans

Species	Natural host	Length/width (μm)	Number and distribution of flagella	Periplasmatic fibrils	*In vitro* isolation from humans	Ref.
H. heilmannii s.l.						
H. bizzozeronii	Cat, dog, fox ,lynx	5-10/0.3	10-20, bipolar	No	Yes	[17,42,81,106]
H. felis	Cat, dog, rabbit, cheetah	5-7.5/0.4	10-17, bipolar	Yes	Yes	[17,45,68,80]
H. heilmannii s.s.	Cat, dog, fox, lynx, non-human primates	3.0-6.5/0.6-0.7	4-10, bipolar	No	No	[15,17,82,106]
H. salomonis	Cat, dog, rabbit	5-7/0.8-1.2	10-23, bipolar	No	No	[17,43,106]
H. suis	Pig, non-human primates	2.3-6.7/0.9-1.2	4-10, bipolar	No	No	[17,44,83]
H. pylori		2.5-5.0/0.5-1.0	4-8, unipolar	No	Yes	[6]

ach was considered sterile and a hostile environment for bacteria. This view started to change only in 1982, when Marshall and Warren[5] successfully cultured *Helicobacter pylori* (*H. pylori*), a spiral-shaped, Gram-negative bacterium from a gastric biopsy specimen. Further studies have since shown that *H. pylori* is the most common chronic infection in humans, and established this species as the main etiologic factor in peptic ulcer disease, gastric carcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[6]. Since the discovery of *H. pylori*, many new *Helicobacter* species that infect human or animal hosts have been described, and the *Helicobacter* genus now includes more than 30 formally named species[7]. Here, we will review the gastric non-*H. pylori Helicobacter* species generally referred to as "*Helicobacter heilmannii*", focusing on those that infect humans and on their impact in human disease.

TAXONOMY

A spiral-shaped bacterium colonizing the human gastric mucosa that was different from *H. pylori* was reported for the first time by Dent *et al*[8] in 1987. Two years later, the same authors described this bacterium and proposed a new genus and species-*Gastrospirilum hominis*[9]. Later 16S rRNA gene sequencing analysis led to its reclassification within the *Helicobacter* genus[10]. It was then provisionally renamed as *Helicobacter heilmannii* (*H. heilmannii*), in acknowledgement of Konrad Heilmann, the German pathologist who first studied the pathologic features of this infection in the human stomach[11]. Further 16S rRNA analysis of an increasing number of samples led to the sub-classification of *H. heilmannii* into type 1 and type 2[10,12]. It was shown that *H. heilmannii* type 1 represented a single species, *H. suis*, that colonizes the stomachs of pigs[13], whereas *H. heilmannii* type 2 represented a group of species that colonize the stomachs of cats and dogs and includes *H. felis*, *H. bizzozeronii*, *H. salomonis*, *H. cynogastricus*, *H. baculiformis*, and *H. heilmannii* sp. nov.[14]. The latter had been provisionally named "Candidatus *H. heilmannii*" in 2004, based on urease gene sequence analysis and because it could not be cultured *in vitro* at that time[14]. In fact, only very recently and after successful *in vitro* isolation, *H. heilmannii* was formally recognized as a valid species name[15].

To avoid further confusion in nomenclature, in 2011 the introduction of the terms *Helicobacter heilmanni sensu lato* (*H. heilmanni* s.l.) was proposed to refer to the non-*H. pylori Helicobacter* species detected in the stomachs of humans or animals if only histopathological, electron microscopy, or crude taxonomic data are available; and *Helicobacter heilmannii sensu stricto* (*H. heilmanni* s.s.) or the other species names if definite identification at the species level is achieved[16].

EPIDEMIOLOGY AND TRANSMISSION

As many as 11 different *H. heilmannii* s.l. have been described colonizing the stomach of domesticated and wild animals[17], 5 of which have been found in the human stomach, namely *H. suis*, *H. felis*, *H. bizzozeronii*, *H. salomonis*, and *H. heilmannii* s.s. (Table 1).

In Western countries as well as in Japan, the prevalence of *H. heilmannii* s.l. in human gastric biopsies is generally lower than 1%, both in adults and in children[18-23]. Reports from China and Thailand indicate that the prevalence of the infection can reach 2% and 6%, respectively[24,25].

Because of the nomenclature problems and due to the difficulty of cultivating these bacteria to allow species differentiation, there are few studies addressing the prevalence of each species individually. In gastric biopsy samples with histological evidence of *H. heilmannii* s.l., polymerase chain reaction (PCR)-based techniques showed that *H. suis* is the most prevalent *H. heilmannii* s.l. species infecting the human stomach, with prevalence ranging from 14% to 37%[26,27]. *H. salomonis* was present in 21%, *H. felis* in 15%, *H. heilmannii* s.s. in 8%, and *H. bizzozzeronni* in 4% of cases[27]. Infection with two or more *H. heilmannii* s.l. species or *H. pylori* and *H. heilmannii* s.l. can be present in the same gastric biopsy[28,29].

While *H. pylori* is known to colonize mainly humans and few non-human primates, *H. heilmanni* s.l. species have other non-human and probably more important hosts, such as cats, dogs, and pigs[17]. In addition to being present in the stomach, *H. heilmannii* s.l. species have also been reported in the oral cavity of domestic dogs and cats and, recently, *H. bizzozeronii* and *H. salomonis* were detected in canine saliva[30-32]. Several reports have suggested the transmission of *H. heilmanni* s.l. from pets to their owners by direct contact[33-36]. A higher prevalence of *H. heilmanni* s.l. infection among people that live in rural areas and of those who often have contact with dogs, cats, cattle, or pigs has been described[37-39]. It has

further been suggested that *H. suis* might be transmitted to humans by consumption of contaminated raw pork meat, where the bacterium can viably persist for up to 48 h[40]. Given this evidence, it has been hypothesized that *H. heilmannii* s.l. infection is a zoonosis.

MICROBIOLOGY

All *H. heilmannii* s.l. species are Gram-negative, microaerophilic, and catalase- and urease-positive[17]. The first descriptions of *H. heilmannii* s.l. used the term "corkscrew-like" bacteria because of their morphology[41]. As a group, these bacteria are microscopically very similar, with spiral and coiled shape, with 4-6 helical turns and 2.3-10 μm in length (Table 1)[11,15,42-45]. *H. heilmannii* s.l. have varying number of flagella, which have bipolar distribution, and fix themselves to a blunt undulated part of the cell wall[11]. *H. felis* is the only *H. heilmannii* s.l. species that has periplasmatic fibrils[15,42-45]. *H. suis* has several contrasting features when compared with other *H. heilmannii* s.l. species, since it may be shorter in length and have fewer flagella[15,42-45].

H. HEILMANNII S.L.-ASSOCIATED DISEASES IN HUMANS

The relationships between *H. heimannii* s.l. and disease in humans are mostly based on publications that have only identified the agent as gastric non-*H. pylori Helicobacters*.

The initial description by Dent *et al*[8] of *H. heimannii* s.l. in the gastric mucosa of 3 patients with gastritis was followed by several other publications, mostly case reports[46-49]. Since then, *H. heilmannii* s.l. infection has been reported in cases of peptic ulcer disease[19,24,39,50], gastric carcinoma[50-52], and gastric MALT lymphoma[21,50,53]. Infected patients may be asymptomatic or present dyspeptic symptoms, such as chronic epigastric pain, nausea, vomiting, heartburn, dysphagia, and post-prandial discomfort[11,19,50,54].

Heilmann and Borchard were the first to report the histopathological and ultrastructural features of a large series of 39 cases with *H. heilmannii* s.l. infection[11]. Bacteria were more frequently found colonizing the antrum although 20% of the cases presented microorganisms also in the fundus. *H. heilmannii* s.l. were found as single microorganisms or in small groups, located underneath the mucous layer, above the surface cells, and deep in the lumen of the foveolae. In ultrastructural analyses, the close contact of some bacteria with the membrane of surface mucous cells, in association with degenerative changes of the cell membrane and partial destruction of the microvilli was reported[11]. The presence of *H. heilmannii* s.l. inside mucous and parietal cells and inside parietal cell canaliculi in the corpus mucosa was also observed[11,50]. *H. heilmannii* s.l.-infected cases mostly presented mild active chronic gastritis in the antrum and mild inactive gastritis in the fundus.

Some years later, Stolte *et al*[50] undertook a study to compare the parameters of gastritis between 202 German patients infected with *H. heilmannii* s.l. and 202 matched control patients infected with *H. pylori*. In agreement with the previous findings[11], they observed that *H. heilmannii* s.l. colonization occurred predominantly in the antrum and mainly focally[50]. They also observed that the grading of the parameters of gastritis, such as the density of lymphocytic and neutrophilic infiltration, the replacement of foveolae by regenerative epithelium, and mucus depletion were significantly milder in *H. heilmannii* s.l. infection than in *H. pylori* infection. Additionally, the presence of lymphoid follicles and intestinal metaplasia were less common in *H. heilmannii* s.l. gastritis[50]. Similar findings were reported in studies comparing the histopathological changes in the gastric mucosa between *H. heilmannii* s.l. and *H. pylori* infections in patients from other geographic areas, including Thailand, Japan, and Korea[21,24,55].

Interestingly, Stolte *et al*[50] observed a relatively high prevalence of gastric MALT lymphoma in *H. heilmannii* s.l. gastritis (3.5%), which prompted them to investigate their material from a 10-year period[56]. They observed 8 MALT lymphomas among patients with *H. heilmannii* s.l. gastritis (1.5%) in comparison with 1745 MALT lymphomas among 263680 patients with *H. pylori* gastritis (0.7%), suggesting that patients infected with *H. heilmannii* s.l. develop MALT lymphoma more frequently than those with *H. pylori*[56].

Although in the previous studies there was not a clear identification of the bacteria at a species level, in experimentally infected animal models the administration of *H. heilmannii s.s.*-positive gastric biopsy homogenates to BALB/c and to C57BL/6 mice induced gastric MALT lymphoma[57-59]. Furthermore, infection with pure bacterial isolates of *H. felis*[60-62] and of *H. suis*[63] were shown to induce gastric MALT lymphoma-like lesions in the BALB/c and in the Mongolian gerbil models, respectively.

The contribution of *H. heilmannii* s.l. to the pathogenesis of the aforementioned diseases is highlighted in reports in which eradication treatment of the bacteria is followed by symptomatic relief[11,36] and complete regression of the infection-associated lesions[11,64], including low-grade gastric MALT lymphoma[21,53,55].

DIAGNOSIS

The diagnosis of *H. heilmannii* s.l. infection poses a complex challenge in comparison to the well-established tests for *H. pylori*. The diagnosis of *H. pylori* can be achieved by non-invasive tests, which are based on detection of antibodies, bacterial antigens, or urease activity in samples such as blood, breath or stools; and invasive tests, which involve an endoscopy with collection of gastric biopsy specimens for histology, culture, urease test, or molecular methods[6].

The diagnosis of *H. heilmannii* s.l. has been based mainly on histological detection, and for this, silver staining-based techniques, such as the Steiner and the Whartin-Starry stains are preferable to hematoxylin and eosin[41].

There are currently no specific antibodies available for immunohistochemical detection of *H. heilmannii* s.l.[65]. Importantly, and although there may be morphological differences in size, number of spirals, and tightness of coils among *H. heilmannii* s.l species, and between these and *H. pylori*, these criteria are not accurate for species identification, as different species may be morphologically very similar, and variation in morphology within a single species may also occur[9,11,17,41].

The use of rapid urease tests allowing the detection of urease activity directly in the gastric biopsy specimens may not be sensitive enough[66], as the colonization density of *H. heilmannii* s.l. is lower than that of *H. pylori*, and also will not be helpful for species identification.

The use of *in vitro* culture as a diagnostic test is also not feasible due to the very fastidious nature of these bacteria. So far, very few laboratories have succeeded in the isolation of *H. heilmannii* s.l. from the gastric mucosa of cats, dogs, or pigs[15,44,45,67] and only *H. bizzozeronii* and *H. felis* have been isolated from the human gastric mucosa[35,68-70].

Currently, the most accurate method available for conclusive species identification is the use of PCR, followed by sequencing of specific target genes. These include the urease A and B (*ureA*, *ureB*) genes, the heat shock protein 60 (*hsp60*) gene, and the gyrase subunit B (*gyrB*) gene[44,71-74]. Sequencing of the 16S rRNA gene and of the 23S rRNA gene allows distinction of *H. suis* from the rest of the *H. heilmannii* s.l. species[13,44].

TREATMENT

H. heilmannii s.l. eradication treatment is indicated in patients that present with severe pathology and clinical symptomatology associated with the infection[17]. No randomized trials have been performed to evaluate the most suitable treatment for *H. heilmannii* s.l. infection. The treatment strategies used are identical to the triple therapy regimen for *H. pylori* eradication, which include a proton pump inhibitor and clarithromycin combined with amoxicillin or metronidazole for 2 wk[64,75,76]. An *in vitro* antimicrobial susceptibility study of *H. bizzozeronii*, *H. felis*, and *H. salomonis* isolates obtained from cats and dogs showed that they were sensitive to ampicillin, clarithromycin, and tetracycline, among other pharmacological agents[77]. However, acquired resistance to metronidazole was observed for some *H. bizzozeronii* and *H. felis* isolates[77]. More recently, it was confirmed that *H. bizzozeronii* had a rapid *in vitro* acquisition of resistance to metronidazole, which should be taken into account when treating this species[78]. In a mouse model of infection used for evaluating the antibiotic susceptibility of 2 different *H. suis* isolates to amoxicillin and omeprazole, a difference in susceptibility between the bacterial isolates was observed[79].

COMPLETE GENOMES OF H. SUIS, H. FELIS, H. BIZZOZERONII, AND H. HEILMANNII S.S.

Only after successful *in vitro* isolation of these extremely fastidious microorganisms did pure bacterial isolates become available. The complete genomes of 4 of the 5 human-infecting *H. heilmannii* s.l. have now been published[80-83] (Table 2). The sequencing of these genomes showed that *H. suis*, *H. felis*, *H. bizzozeronii*, and *H. heilmannii* s.s. share many homologues to genes associated with colonization and virulence properties of *H. pylori* and of other bacteria[80-83]. These include the urease gene cluster, encoding a key enzyme to bacterial survival in the acidic gastric environment[6], the neutrophil-activating protein NapA, the γ-glutamyl transpeptidase, as well as complete or almost complete *comB* secretion system, required for DNA uptake by natural transformation[84]. Although these species contain homologues of genes encoding several outer membrane proteins of *H. pylori*, they do not harbor homologues to the BabA and SabA adhesins. They also lack homologues of the *H. pylori cag* pathogenicity island, including the gene encoding CagA, and of the vacuolating cytotoxin VacA. The *H. suis* genome is an exception, since it contains a *vacA* homologue[83]. The dissimilarities between the genomes of *H. heilmannii* s.l species and the *H. pylori* genome, including the lack of homologues to well-known *H. pylori* virulence factors associated with disease, may partially explain some of the differences between *H. pylori* and *H. heilmannii* s.l.-associated pathology[80-83].

Comparative genome analysis also provided a putative molecular basis for the zoonotic nature of *H. heilmannii* s.l species[85]. In comparison to *H. pylori*, *H. bizzozeronii*, *H. felis*, and *H. suis* have a higher metabolic versatility and a higher number of methyl-accepting chemotaxis proteins, possibly facilitating their adaptation and survival in the gastric environment of different host species[80,83,85].

PATHOGENESIS OF H. HEILMANNII S.L. INFECTIONS

The lack of pure isolates has also limited the information available on the pathogenesis and host responses of individual *H. heilmannii* s.l. species. The major exception is *H. felis* for which experimental models of infection have existed since the early 1990's, and for which different mice strains have been well-established as models of chronic gastritis[86], gastric atrophy[87-89], gastric MALT lymphoma[60], and gastric carcinoma[90,91]. Infection with *H. felis* in these models are often also used to study the pathogenesis of infection and the host immune response to *H. pylori*[92-95].

Table 2 General features of the available *Helicobacter heilmannii* s.l. species genomes and homology to *Helicobacter pylori* virulence genes

	H. suis		*H. felis*	*H. bizzozeronii*	*H. heilmannii* s.s.
Strain	HS1	HS5	CS1 (ATCC 49179)	CIII-1	ASB1
Host, Country	Pig, Belgium	Pig, Belgium	Adult cat, Australia	47-yr-old female patient with severe gastric symptoms, Finland	Kitten with severe gastritis, Belgium
Genome size (MB)	1635	1670	1673	1755	1805
G + C content	39.9%	39.9%	44.5%	46%	47.4%
CDSs	1266	1257	1671	1894	1918
Function assigned	1072	1066	1387	1280	1183
Plasmids	Not found	Not found	One (6.7 Kb; 5 CDSs)	One (52.1 Kb; 77 CDSs)	Not found
VacA	Yes (63% homology)	Yes (22% homology)	No	No	No
CagA	No[1]	No[1]	No	No	No
Ref.	Vermoote *et al*[83]		Arnold *et al*[80]	Schott *et al*[81]	Smet *et al*[82]

[1]Two members of the *cag* pathogenicity island (cag23/E and cagX) were identified in the *H. suis* genomes. CDSs: Coding sequences.

More recently, *H. suis*, *H. bizzozeronii*, and *H. heilmannii* s.s. pure isolates have been used in experimental models of infection[63,96-99]. Experimental infections with *H. suis* in Mongolian gerbils, BALB/c mice, and C57BL/6 mice showed that while in gerbils *H. suis* mainly colonized the antrum, in both mice strains *H. suis* was able to colonize the entire stomach[63]. Colonization with *H. suis* induced parietal cell necrosis in the 3 animal strains, epithelial cell hyperproliferation, and inflammation. *In vitro* data confirmed that *H. suis* causes apoptosis and necrosis of gastric epithelial cells, and indicated that the γ-glutamyl transpeptidase (GGT) virulence factor is involved in epithelial cell death[100]. *H. suis* GGT was also shown to inhibit T lymphocyte proliferation, and bacterial outer membrane vesicles were identified as a putative delivery route of GGT to the lymphocytes residing in the deeper mucosal layers[101].

Further experimental infections of BALB/c and C57BL/6 mice using 9 *H. suis* strains, showed that all *H. suis* isolates induced a predominant T-helper (Th)17 response, but only mild upregulation of the Th2 cytokine interleukin (IL)-4, and no upregulation of Th1 markers, including interferon (IFN)-γ[98]. This contrasts with previously published data which showed that *H. suis* induced a predominantly Th1 local immune response, and IFN-γ had a major role in the gastric inflammatory process[99,102]. A possible explanation for these differences is that previous experimental infection studies have used homogenized gastric specimens from mice, pigs or non-human primates instead of pure bacterial isolates[99,102].

In the Mongolian gerbil model, infection with *H. suis* led to the development of MALT lymphoma-like lesions in some animals[63], and in experimentally infected pigs, *H. suis* induced severe gastritis and a significant reduction in weight gain[103].

Concerning *H. bizzozeronii*, experimental infections in BALB/c, C57BL/6, SJL, and CFW mice showed that bacteria were mainly located in the gastric pits, dispersed through the mucous layer of the surface epithelium, or in close association with the parietal cells[104]. In the Mongolian gerbil model, *H. bizzozeronii* induced mild to moderate lymphocytic and neutrophilic infiltration in the gastric antrum of some animals, which was sometimes accompanied by mild parietal cell loss[105]. In the same study, transmission electron microscopy of *H. bizzozeronii*-infected gerbils showed neither necrotic parietal cells nor bacteria adhering to the epithelium[105]. Overall, *H. bizzozeronii* appears to be associated with a lower pathogenicity than *H. pylori* or *H. felis*[85].

Infection with 9 different *H. heilmannii* s.s. isolates in the Mongolian gerbil model showed that strains had different abilities to colonize the gerbil stomach. Furthermore, only 78% of the strains were able to induce chronic active gastritis and lymphocytic aggregation, caused by upregulation of IL-1β[96]. *H. heilmannii* s.s. strains with higher colonization ability were associated with higher fundic gastrin expression and reduced antral expression of the of H^+/K^+ ATPase pump[96].

Overall, these studies demonstrate that not only are there differences in the bacterium-host interactions between diverse *H. heilmannii* s.l. species, but there are also differences in the pathogenic potential in strains within the same species. Further studies will be necessary to address this question, namely the virulence factors involved and their putative associations with disease.

CONCLUSION

It is now recognized that *H. heilmannii* s.l. does not represent a single species, but rather several distinct *Helicobacter* species. *H. heilmannii* s.l. infect the stomach of several animals and may have zoonotic potential. Although the prevalence of these infections in humans is low, they are associated with gastric pathology and confer a higher risk of gastric MALT lymphoma than that of *H. pylori* infection, making them a significant health issue. So far, there are no studies that permit a clear stratification of the characteristics of the diseases according to each individual species that constitutes the group of gastric non-*H. pylori Helicobacter* species known as *H. heilmanni* s.l. Therefore, methods that allow bacterial identification at a species level are necessary to better clarify the prevalence of the infection in humans. Access to the full bacterial genome sequences together with the availability of in-

creasing number of *in vitro* isolates will allow significant advances in the understanding of bacteria-host interactions in disease pathogenesis and will be essential for developing strategies of prevention and treatment.

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