ACVIM Consensus Statement

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The Relationship of *Helicobacter* Spp. Infection to Gastric Disease in Dogs and Cats*

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The discovery of the association of *Helicobacter pylori* with gastritis, peptic ulcers, and gastric neoplasia has led to fundamental changes in the understanding of gastric disease in humans.[1–3] Investigation of the relationship of gastric disease to *Helicobacter* spp in other animals has resulted in the discovery of *H mustelae* in ferrets with gastritis and peptic ulcers, *H acinonychis* in cheetahs with severe gastritis, and *H heilmannii* in pigs with gastric ulcers.[4] The presence of gastric *Helicobacter*-like organisms (HLO) in the stomachs of dogs and cats has been known for many years,[5–7] but the relationship of those organisms to gastric disease is controversial.[8–17] This article is the Consensus Statement of an ACVIM study group on the relationship of *Helicobacter* spp infection to gastric disease in dogs and cats.

Helicobacter are spiral-shaped or curved, or sometimes coccoid gram-negative bacteria that inhabit the glands, parietal cells, and mucus of the stomach.[4] The large gastric HLO in dogs and cats are morphologically indistinguishable by light microscopy, in which they are seen as large, 5–12-μm-long spirals. They have been classified into several *Helicobacter* spp. on the basis of 16s rRNA sequencing, DNA hybridization, and electron microscopic appearance.[15,18–22] *H felis, H bizzozeronii, H salomonis, H bilis, Flexispira rappini,* and *H heilmannii*-like organisms ("*H heilmannii*"; also called *Gastrospirillum hominis*) have been found in the gastric mucosa of dogs[16,17,23] and *H felis, "H heilmannii,"* and *H pametensis* in the gastric mucosa of cats.[13,20,24] *H pylori* has been isolated from the stomachs of a group of colony-housed cats but not from pet cats or dogs.[25]

There is a high prevalence of gastric *Helicobacter* infection in dogs and cats.[8–14,16,20,22,26–31] HLO have been observed in gastric biopsies from 41 to 100% of clinically healthy and 57 to 100% of vomiting cats (Table 1). The prevalence of infection in dogs is 67–100% in clinically healthy pets, 72–90% in those presented for investigation of recurrent vomiting, and 100% of healthy laboratory beagles (Table 2).

The prevalence of individual *Helicobacter* spp. has not been thoroughly investigated, as it requires specialized techniques. *H felis* has been cultured from 3 of 21 *Helicobacter*-infected cats in Finland,[20] whereas "*H heilmannii*" was identified by polymerase chain reaction (PCR) in 38 of 49 Swiss cats.[13] Preliminary results of PCR studies in *Helicobacter*-infected cats in the USA have identified 9 of 17 with "*H heilmannii,*" 1 of 17 with *H felis,* 3 of 17 coinfected with *H felis* and "*H heilmannii,*" and 4 cats with unclassified *Helicobacter* spp. (K. Simpson and D. Strauss-Ayali, unpublished observations, 1999). In *Helicobacter*-infected dogs, culture of gastric tissue was positive in 48 of 95 dogs: 21 *H bizzozeronii,* 8 *H felis,* 8 *H salomonis,* 3 mix, 2 *F rappini.*[20] PCR was positive in 59 of 60 dogs: 19 *H bizzozeronii/salomonis,* 12 "*H heilmannii,*" 2 *H felis,* 6 mix, 31 unclassified.[22] Electron microscopic examination of gastric biopsies from infected dogs has also demonstrated coinfection with *H felis, F rappini,* and other large gastric spiral organisms.[15,32]

H pylori infection has been reported in a group of laboratory cats in the USA but has not been reported in pet cats in the USA or Europe to date.[25] It has been proposed that *H pylori* is an anthroponosis—an animal infection with a human pathogen.[29]

The cause of gastritis in dogs and cats is seldom determined, and in the absence of systemic disease, ulcerogenic or irritant drugs, gastric foreign objects, and in rare instances fungal infections, has usually been attributed to dietary allergy or intolerance, parasites, or a reaction to bacterial antigens. The association of *Helicobacter* infection with gastric disease in humans, ferrets, cheetahs, pigs, and experimentally infected laboratory animals suggests that spiral organisms may have a role in the pathogenesis of gastritis in dogs and cats.[4] The results of studies of dogs and cats with naturally acquired gastric *Helicobacter* infection can be summarized as follows:

The high prevalence of gastric colonization with HLO in healthy and sick dogs and cats indicates that there is no simple "infection = disease" relationship in dogs and cats.[8–14,16,20,22,26–31] This observation has been interpreted by some to imply that *Helicobacter* spp. are not pathogenic in dogs and cats. However, this view may be somewhat naive as *H pylori* prevalence in people reaches 80–90% in some countries, but only a relatively small number (10–15%) of these individuals have overt clinical signs of infection. Eradication of *H pylori* infection in symptomatic humans has been associated with resolution of symptoms and gastric abnormalities. An uncontrolled treatment trial of dogs and cats with gastritis and *Helicobacter* infection showed that clinical signs in 90% of 63 dogs and cats responded to treatment with a combination of metronidazole, amoxicillin, and famotidine, and that 74% of 19 animals re-endoscoped had no evidence of *Helicobacter* in gastric biopsies.[33] Controlled clinical trials are required to confirm these observations.

The majority of studies in dogs and cats with naturally

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Table 1. Prevalence of gastric *Helicobacter*-like organisms in Dogs.

State of Health	Infected (%)	# Of Dogs	Authors
Healthy	100	15	Weber 1958[12]
Healthy	100	30	Henry 1987[26]
Healthy	100	30	Hanninen 1996[17]
Healthy	100	10	Happonen 1996[8]
Healthy	67–100	54	Eaton 1996[16]
Healthy	93	68	Neiger 1998[22]
Healthy	86	21	Yamasaki 1998[27]
Healthy	96	25	Happonen 1998[28]
Sick	74	42	Geyer 1993[9]
Sick	82	122	Hermanns 1995[10]
Sick	61	56	Yamasaki 1998[27]
Sick	90	21	Happonen 1998[28]

Table 2. Prevalence of gastric *Helicobacter*-like organisms in Cats.

State of Health	Infected (%)	# Of Cats	Authors
Healthy	100	12	Weber 1958[12]
Healthy	41	29	Geyer 1993[9]
Healthy	97	32	Otto 1994[11]
Healthy	100	25	El-Zataari 1997[29]
Healthy	100	15	Papasouliotos 1997[14]
Healthy	90	10	Yamasaki 1998[27]
Healthy	94	32	De Majo 1998[30]
Healthy	91	58	Neiger 1998[13]
Healthy	100	15	Norris 1999[31]
Sick	57	60	Geyer 1993[9]
Sick	76	127	Hermanns 1995[10]
Sick	64	33	Yamasaki 1998[27]
Sick	100	24	Papasouliotos 1997[14]

acquired *Helicobacter* infections demonstrate that the fundus and cardia are more densely colonized with bacteria than the pylorus.[8,11,27,30] Large HLO colonize the superficial mucus and gastric glands and may also be observed intracellularly. Degeneration of gastric glands, with vacuolation, pyknosis, and necrosis of parietal cells is more common in infected dogs and cats than uninfected dogs and cats.[12,27]

The gastric mucosal inflammation present in *Helicobacter*-infected dogs is generally mononuclear in nature, and ranges in severity from "normal" to moderate.[8,9,16,22] There is overlap in the type and severity of inflammation in infected and uninfected dogs. In cats, like dogs, gastritis is generally mononuclear and ranges from mild to moderate in severity.[8,13,14,31] However, in cats, a correlation between the presence of HLO and the extent of histopathological changes in the gastric corpus has been demonstrated.[8,10] The paucity of uninfected dogs and cats in most studies precludes more definitive statements at this time.

The lack of standardization of histopathological grading schemes also makes comparison between studies difficult. Adoption of a standardized grading scheme such as that employed by Happonen et al[28] would be useful for future studies. Interestingly, gastric histopathology was normal in 52% of asymptomatic dogs with naturally acquired HLO infection versus 19% of symptomatic dogs with naturally acquired HLO infection.[28] This observation raises the possibility that differences in the host response to infection or the specific species of *Helicobacter* present in an individual may affect the clinical outcome of infection.

The gastritis observed in infected dogs and cats is less severe than that observed in *H pylori*-infected humans, where neutrophilic aggregates and moderate to severe gastritis are commonly encountered.[1] A more severe gastritis characterized by marked lymphoid follicular hyperplasia and infiltration of neutrophils and eosinophils has been observed in cats with *H pylori* infection.[25,34]

Gastric lymphoid hyperplasia appears to be more common and more extensive in *Helicobacter*-infected than uninfected dogs and cats.[8,10,11,25,26] Studies in cats that have examined full-thickness gastric biopsies have demonstrated a strong association between infection and lymphoid follicle hyperplasia. In addition to this local immune response, a systemic immune response characterized by circulating anti-*Helicobacter* IgG has been detected in sera from naturally infected dogs and cats.[35,36]

To date there has been no association made between *Helicobacter* infection and gastrointestinal ulcers or gastric neoplasia in dogs and cats. However, the relatively low prevalence of these diseases coupled with the small number of animals evaluated to date means that such a relationship cannot be discounted.

In people infected with *H pylori,* increased acid secretion is associated with antral gastritis and duodenal ulceration,[37,38] whereas achlorhydria is observed shortly after infection with *H pylori* and when the gastric fundus and body is inflamed or atrophied.[39,40] Eradication of *H pylori* has been associated with decreased acid secretion in patients with acid hypersecretion and increased acid secretion in achlorhydric patients.[37–39] Decreased inhibition of gastrin release by somatostatin, with resultant hypergastrinemia and increased parietal cell mass, has been postulated as the cause of hyperacidity and duodenal ulceration.[41] Inhibition or destruction of parietal cells is considered responsible for achlorhydria.[39] In contrast to the variability of gastric acid secretion that accompanies *H pylori* infection, the magnitude of hypergastrinemia in asymptomatic individuals, those with achlorhydria, and those with duodenal ulcers is similar.[39–42]

The effect of naturally acquired *Helicobacter* infection on the gastric secretory axis has been evaluated in dogs.[32] Unstimulated gastric pH and fasting, postprandial and bombesin-stimulated plasma gastrin were similar in both infected and uninfected dogs, though a trend toward higher meal-stimulated gastrin was observed in infected dogs at 60 minutes. Pentagastrin stimulated maximal acid output (mmol HCl/kg$^{.75}$/h) and titratable acidity (mmol HCl/mL) were similar in both infected and uninfected dogs, but gastric pH during maximal acid output was lower ($P < .01$) in uninfected dogs. Acid secretion, plasma gastrin, and mucosal inflammation were not affected by the transient suppression of *Helicobacter* spp. by amoxicillin metronidazole famotidine (AMF). These findings suggest that gastric secretory function in dogs is not markedly perturbed by naturally acquired *Helicobacter* spp. infection

The effect of naturally acquired *Helicobacter* infection

on the gastric secretory axis of cats has not been critically examined.

In contrast to humans, in whom *H pylori* infection predominates, the investigation of pathogenicity in dogs and cats is complicated by the fact that they can be colonized by a variety of *Helicobacter* spp., and simultaneous colonization with multiple species has been frequently observed.[13,15,20] Experiments to determine the pathogenicity of individual *Helicobacter* spp. have demonstrated gastritis (subglandular infiltrates of lymphocytes, plasma cells, and eosinophils were widespread) and a humoral immune response in gnotobiotic dogs after infection with *H felis* and *H pylori*.[43,44] Specific pathogen free (SPF) dogs infected with *H felis* did not develop any morphological or functional abnormalities.[45] In an electron microscopic study of dogs with naturally acquired infection, *H felis*-like organisms were associated with more cellular damage than *H bizzozeronii*-like organisms in dogs.[46] Most recently, conventional beagles infected with *H pylori* developed vomiting and diarrhea that was associated with a transient neutrophilic gastritis and expression of mucosal interleukin-8, seroconversion, and progression to chronic gastritis.[47] This is the first time that clinical signs have been observed in response to experimental *Helicobacter* infection in cats or dogs.

Studies of the pathogenicity of *H felis* in laboratory cats have demonstrated gastritis, lymphoid follicular hyperplasia, and seroconversion.[48] *H pylori* infection in cats is associated with a more severe gastritis, with more frequent neutrophilia, than cats with experimental *H felis* infection, and naturally acquired *Helicobacter* infection.[25,34,36] However, clinical signs associated with gastritis, such as inappetance and vomiting, were absent in those cats. Changes in gastric acid secretion and serum gastrin that are known to occur in humans with *H pylori* infection have not been demonstrated in cats with experimental *Helicobacter* infections.

The general lack of knowledge of the pathogenicity of gastric *Helicobacter* spp. has meant that veterinarians are faced with the dilemma of either treating, or ignoring, spiral bacteria observed in biopsies from patients with chronic vomiting and gastritis. Eradication of *H pylori* infection in symptomatic humans has been associated with resolution of symptoms and gastric abnormalities.[37–42] In light of their pathogenicity in man and other animals, it would seem reasonable that eradication of gastric *Helicobacter* spp. is considered prior to initiating treatment with immunosuppressive agents to control gastritis. An uncontrolled treatment trial of dogs and cats with gastritis and *Helicobacter* infection lends support to this approach. Clinical signs in 90% of 63 dogs and cats responded to treatment with AMF and 74% of 19 animals re-endoscoped had no evidence of *Helicobacter* in gastric biopsies.[33] However, controlled therapeutic studies in asymptomatic dogs and cats suggest that it is difficult to eradicate gastric *Helicobacter* spp. In naturally infected dogs treatment with AMF for 2 weeks was highly successful when evaluated by light microscopy, urease, and ^{13}C-urea breath test 3 days after therapy, but 28 days later GHLO were present and the urea-breath test was positive in most dogs again.[49] Further analysis of gastric tissues from these dogs revealed that PCR was positive throughout the study.[32] Similar results were observed in naturally infected cats treated either with azithromycin, tinidazole, bismuth, and ranitidine or with clarithromycin, metronidazole, bismuth, and ranitidine for 4 or 7 days when evaluated by urea-breath test.[50] After 3 weeks of amoxicillin, metronidazole, and omeprazole, cats with *H pylori* infection were culture negative, but five out of six cats were positive in a species-specific PCR in dental plaque, saliva, and/or gastric fluid samples.[51]

It is unclear if in most studies antibiotic failure was due to reinfection or recrudescence, although the persistence of *Helicobacter* by PCR suggests recrudescence is likely. The preliminary results of a study in dogs infected by GHLO appear more promising, with an 80% eradication rate after a 1-week course of triple therapy when evaluated 30 days post-therapy with urea-breath test, rapid-urease test, and histology.[52]

In order to help clarify the role of *Helicobacter* as a gastric pathogen and the efficacy of eradication strategies, there is a clear need for placebo-controlled, blinded trials in dogs and cats with clinical signs, biopsy-confirmed *Helicobacter* infection, and gastritis.

It is clear that our current state of knowledge with regard to *Helicobacter*-associated gastritis in dogs and cats is incomplete and that further clinical and experimental studies need to be performed to determine the role of *Helicobacter* infection as a cause of gastritis in cats and dogs. The results of studies to date support the following conclusions: (1) *Helicobacter* spp. are highly prevalent in healthy and sick dogs and cats. (2) There is no simple relationship of infection = disease. (3) Degeneration of gastric glands appears related to infection. (4) The gastric inflammatory response is variable in severity and is generally lymphoplasmacytic—too few uninfected animals have been studied to make more definitive statements. (5) Infected animals generally mount an immune response that is characterized by lymphoid follicular hyperplasia and seroconversion. (6) Marked abnormalities in gastric function have not been observed in dogs with naturally acquired infection and cats with experimental infections. (7) There are apparent differences in the pathogenicity of various *Helicobacter* spp.: *H pylori* seems more pathogenic than large gastric *Helicobacter* spp. in both cats and dogs. (8) The role of antimicrobial therapy in the treatment of sick cats and dogs with *Helicobacter* infection and gastritis is unclear.

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