HELICOBACTER

Animal Group(s) Affected	Transmission	Clinical Signs	Severity	Treatment	Prevention and Control	Zoonotic
Multiple taxa: primates; felids (primarily cheetahs, but lions, tigers and domestic cats, and other small felids have been reported); canids, rodents. Disease is described best in humans, but induced and natural disease has been reported in multiple species.	Not well understood but probably through conspecific grooming and fecal-oral transmission.	Gastro-intestinal signs, primarily gastritis but hepatic and intestinal disease occurs in some species; signs range from asymptomatic to anorexia, vomiting, regurgitation, stomach ulceration, diarrhea with undigested food in feces, and weight loss.	Non-clinical or mild to severe; depending on immune status of animal and co-factors that are not well understood.	Multimodal symptomatic treatment to reduce *Helicobacter* spp. load can reduce gastric irritation and clinical signs, but reinfection/ recrudescence is likely.	Difficult but iatrogenic exposure can be prevented through appropriate cleaning of endoscopy equipment.	Possibly

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Susceptible animal groups: Humans are the most broadly susceptible group. Within the veterinary field, felids (in particular cheetah), ferrets, non-human primates and rodents are susceptible. Gastritis associated with *Helicobacter*-like organisms is a profound cause of morbidity and mortality in the cheetah (S. African cheetah, 40% of the mortalities; Cheetah Research Council indicated that 86% of cheetah study population is affected). A few reports of *Helicobacter*-like organisms have been reported in association with gastritis in other species including felids (bobcat, *Felis rufus*; Pallas cat, *F. manul*; Canada lynx, *F. lynx canadensis*; fishing cats, *F. viverrina*; margays, *F. wiedii*; sand cats, *F. margarita;* African lion, *Panthera leo*; snow leopards, *P. uncia*; Siberian tiger, *P. tigris altaica;* jaguar, *P. onca*), domestic dogs, and non-human primates (cynomolgus monkeys). Laboratory induced infections to study *Helicobacter* spp. primarily have involved macaques, pigs, guinea pigs, hamsters and mice.

Causative organism: The genus *Helicobacter* was created in 1989 with approximately 20 species currently described across all taxa. The essential property of almost all *Helicobacter* spp. is the presence of sheathed flagella, and in most species, possession of strong ureolytic (urease producing) ability, particularly those associated with gastric mucosa. Considerable diversity in cell morphology is present with respect to cell length, number and location of flagella, and presence of periplasmic fibrils. *H. pylori* has a global distribution and infects human gastric mucosa (predominately the gastric cardia) with evidence for infection in cats. The most commonly described pathogenic species of *Helicobacter* include: *H. pylori* (human), *H. heilmannii* (cat, dog), *H. felis* (mouse model), *Helicobacter acinonychis (*formerly *H. acinonyx;* persists in the gastric fundus in cheetah) and *H. mustelae* (ferrets). *H. acinonychis* lacks the *cag* pathogenicity island (PAI), but is otherwise

the most closely related *Helicobacter* to *H. pylori*. The PAI is the characteristic component causing the human neutrophilic inflammatory response, but has not been associated with *Helicobacter* spp. infecting cheetah. Multiple strains of *H. acinonychis* have been reported, but the demographic of these strains within North America and other populations of felids is poorly understood.

The urease produced by *Helicobacter* and the flagella allow the organism to survive in the gastric environment over a wide spectrum of pH, penetrate into gastric mucous layer, and reach the gastric epithelium where it can then attach to cells. Both cellular immune response and humoral response to *H. pylori* are believed to contribute to disease pathogenesis.

In cheetah, gastritis is associated with single species or multi-species infections of *Helicobacter* spp. (*H. pylori*-like, *H. heilmannii*, *H. felis*, or *H. acinonychis* (formerly *H. acinonyx*)). *Helicobacter*-associated gastritis causes morbidity and mortality in captive cheetah, but this reaction to *Helicobacter* spp. is not seen in free-ranging cheetahs when infected with the same *Helicobacter* spp. It has been hypothesized that immunomodulation caused by chronic stress (elevated glucocorticoids) or other factors may play a role in the pathogenesis of cheetah gastritis. Pet cats are frequently colonized by *H. heilmannii* without substantial correlation between infection and degree of gastritis. Differences in the pathogenicity of *Helicobacter* spp. across taxa are apparent making understanding the pathogenesis, epidemiology and treatment difficult.

An occurrence of natural infection with *H. pylori* in a group of cynomolgus monkeys was associated with chronic active gastritis and gastric erosions. *H. pylori* were isolated from these monkeys in different countries within Asia with multiple strains isolated.

Zoonotic potential: The exact route of transmission of *H. pylori* among people is unknown. Several routes of transmission of *H. pylori* have been proposed including fecal-oral, oral-oral, gastro-oral, and via respiratory droplets. In humans, familial associated spread from person-to-person is appropriate. Under controlled laboratory conditions, human sourced *H. pylori* has been shown to infect non-human primates. However, *H. pylori* occurring naturally in monkeys (or other species) are unlikely to represent a major route of transmission to humans, since close contact between nonhuman primates and humans is typically limited. *H. pylori* has been cultured from feline salivary and gastric sections, and *H. pylori* DNA has been found in in feline feces and dental plaque raising the possibility that *H. pylori* could be transmitted from cats to humans via saliva, vomit, or feces. *H. pylori* in humans can be excreted through several routes, with concentrations highest in vomitus. In developing countries, it is suspected that *H. pylori* may have an environmental reservoir (e.g. untreated water or contaminated food). Transmission of *Helicobacter* and subsequent clinical disease between humans and animals is poorly studied, but veterinarians should be careful and take personal protective precautions for potential exposure. In humans, *H. pylori* is associated with gastric cancer and is a known carcinogen of the stomach. Human medical endoscopists and endoscopy nurses have significantly higher rates of *H. pylori* than other medical professionals. Because of this, appropriate precautions using proper personal protective equipment (gloves, masks) should be used by veterinary staff conducting endoscopy, performing dental procedures, handling saliva or fecal material.

Distribution: *H. pylori* is the most common bacterial infection in the world affecting people, with estimates that it infects half of the people worldwide but causes clinical disease in only a small percentage of those infected. The discrepancy between infection and clinical disease is a problem for physicians discerning when to treat patients. To help with this challenge, standardized human medical guidelines recommend only treating people suffering from peptic ulcer disease or mucosally associated lymphoma.
The distribution of *Helicobacter* spp. in animals is poorly understood and under studied. Hand raised cheetah have been found to be *Helicobacter* negative until introduced to other cheetah (personal comm. S. Citino). But

it can be assumed that most cheetah (free-ranging and captive) have been exposed to various *Helicobacter* spp. of varying strains.

Incubation period: Unknown

Clinical signs: Clinical signs range across taxa, but most are consistent with gastrointestinal signs. Cheetah with *Helicobacter*-associated gastritis display partial or full anorexia as the most common clinical sign leading to vomiting, regurgitation, diarrhea with undigested meat in feces, gastroesophageal reflux disease (GERD), acquired lower esophageal sphincter dysfunction, acquired hiatal hernia, and weight loss.

Clinical pathological, gross, and histopathological findings: *Helicobacter*-associated gastritis cannot be identified by gross evaluation of the stomach by endoscopy. Gastric ulcers can be identified via ante-mortem endoscopy evaluation or post-mortem gross evaluation, but further testing is needed to identify *Helicobacter*. As a spiral shaped bacterium, cytology can be helpful when diagnosing *Helicobacter*-associated gastritis. Histopathologic and immunological findings in cheetah with *Helicobacter*-associated gastritis are described as florid lymphocyte and plasma cell infiltrates within the gastric lamina propria and glandular epithelium, parietal cell apoptosis, leading to gland hyperplasia, goblet cell metaplasia, fibrosis and atrophy of the glandular fundus. Cheetahs with severe gastritis have larger numbers of active B cells and plasma cells.

Diagnosis: Rapid urease test, C-13-urea breath test (UBT), serology, gastric biopsy with histopathology, and touch cytology are all highly accurate invasive diagnostic tests for gastric *Helicobacter* organisms, whereas culture and polymerase chain reaction are the only means to identify *Helicobacter* to the species level.

Material required for laboratory analysis: Stomach (multiple fundic biopsies recommended for cheetah) biopsies for histopathology, once initial diagnosis and grading of gastritis has been performed, non-invasive C-13-urea breath test (UBT) can offer an alternative to repeated biopsies for therapeutic monitoring.

Relevant diagnostic laboratories:
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Treatment: Triple therapy with a proton pump inhibitor (PPI), in combination with amoxicillin and clarithromycin is the established treatment for *H*. pylori. Metronidazole is used in the place of amoxicillin as part of the triple therapy for penicillin hypersensitive patients. Metronidazole is an important treatment for *Helicobacter*, but resistance among strains of *H. acinonychis* and *H. pylori* have been reported. For human cases of *H. pylori*, resistance to metronidazole has been reported in up to 80%, and resistance to clarithromycin in 2-10% of strains cultured. Resistance to one antibiotic, when triple therapy is attempted reduces the efficacy of therapy up to 50%. For *H. pylori*, quadruple therapy incorporating a bismuth compound with a PPI, tetracycline and metronidazole has been a choice for rescue therapy if triple medication course is not successful. Ranitidine-bismuth citrate has been shown to over-come metronidazole and clarithromycin resistance, and can be used in place of a PPI for rescue therapy as studied in humans. PPI triple therapy has been shown to provide the most consistent and durable therapy in humans. The exact mechanism by which PPI exert their effect on *H. pylori* eradication is not clear, but it is suspected that the potent acid suppression creates an optimal pH for bacterial growth and cell division allowing the key antibiotics amoxicillin and clarithromycin to act more effectively on the bacterium. *H. pylori* resistance to amoxicillin is not often reported, but amoxicillin is less

effective when used alone on *H. pylori* than clarithromycin or metronidazole.
Because treatment of *Helicobacter* requires the use of several medication, compliance is a significant challenge to success. Resistance of *H. pylori* toward levofloxacin is rising worldwide, due to a point mutation reducing quinolone susceptibility. Because the quinolones are used for second line therapy when triple or quadruple courses are ineffective, a major concern for human medicine exists. Resistance to amoxicillin and tetracycline is low due to the need for multiple simultaneous mutations in genes. The comparison of drug resistance across different *Helicobacter* species is poorly studied, but *H. acinonychis* is used to model *Helicobacter* drug resistance.
In cheetah, optimal treatments are described as lansoprazole/clarithromycin/amoxicillin treatment group which produced a short-term decrease in inflammation when compared to controls. Lansoprazole has been shown to have direct bacteriocidal activity against *Helicobacter* spp. Prednisone should not be used because it has no effect on gastric inflammation and does not reduce *Helicobacter* load. Further treatment protocols recommend omeprazole/clarithromycin/amoxicillin or tetracycline/metronidazole/Pepto-Bismol for 28 days to achieve short-term *Helicobacter* eradication in cheetahs. Alternative treatments for delayed gastric emptying in cheetah associated with bacterial gastritis have been described using both Y-U pyloroplasty and incisional gastropexy. This procedure was combined with *Helicobacter* multi-therapy for tetracycline, metronidazole, and bismuth subsalicylate for one week.

Prevention and control: Personal protective equipment such as wearing barrier gloves and hand washing is recommended to prevent exposure. Proper cleaning of endoscopy equipment requires use of a detergent (enzymatic cleaner) and brush (mechanical cleaning over manual cleaning preferred) to remove blood, mucus, and tissue from the endoscope channels prior to disinfection. The World Congresses of Gastroenterology recommends that endoscopes be soaked in 2% activated glutaraldehyde for at least 10 minutes after cleaning to prevent transfer of *Helicobacter* between patients. Sterilization of biopsy forceps, or the use of disposable biopsy forceps is preferred to prevent transfer of *Helicobacter*. Typically, as biopsy forceps penetrate the gastric mucosa, they are difficult to clean and pose a significant risk for cross transfer among patients.

Suggested disinfectant for housing facilities: None

Notification: None

Measures required under the Animal Disease Surveillance Plan: None

Measures required for introducing animals to infected animal: None

Conditions for restoring disease-free status after an outbreak: Because transmission is poorly understood, it is suspected there cannot be a disease-free status for susceptible species. *Helicobacter* associated disease does not present as an "outbreak". It is believed that secondary factors are necessary to result in clinical disease (i.e., gastritis) associated with *Helicobacter* across all taxa.

Experts who may be consulted:

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