Chapter 10
Non-*Helicobacter pylori Helicobacter* Infections in Humans and Animals

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Abstract Since the first description of the human pathogen *Helicobacter pylori* in the early 1980s, the number of known species in the genus *Helicobacter* has increased largely. Currently, 45 different *Helicobacter* species have been identified. Bacteria belonging to this genus can roughly be divided into two major groups, gastric and enterohepatic species. Gastric helicobacters express urease at a high level which helps them to survive in the acidic environment of the stomach, whereas most enterohepatic helicobacters do not. The best-known gastric *Helicobacter* species is *H. pylori*. This chapter, however, deals with non-*H. pylori* helicobacters (NHPH). Most NHPH are animal-associated bacteria, but some of them are of zoonotic significance. First, gastric infections with these bacteria in humans are considered. Thereafter, an overview of natural and experimental gastric infections in animal hosts is given, with emphasis on the gastric helicobacters that are mainly associated with dogs, cats, and pigs. Finally, enterohepatic *Helicobacter* species are briefly discussed.

Keywords Gastric non-*Helicobacter pylori* helicobacters • Enterohepatic helicobacters • Zoonotic significance • Gastric disease • Enterohepatic disease • Animal models

10.1 Introduction

Since the original description of the human pathogen *H. pylori* in 1983, the number of known species in the genus *Helicobacter* has increased largely (Warren and Marshall 1983). Currently this genus includes 45 identified species. An overview is shown in Fig. 10.1. The *Helicobacter* bacteria can roughly be divided into gastric and enterohepatic species. Gastric *Helicobacter* species are able to survive the acidic environment in the stomach by expressing high levels of urease (Pot et al. 2007). Enterohepatic species do not normally colonize the gastric mucosa.

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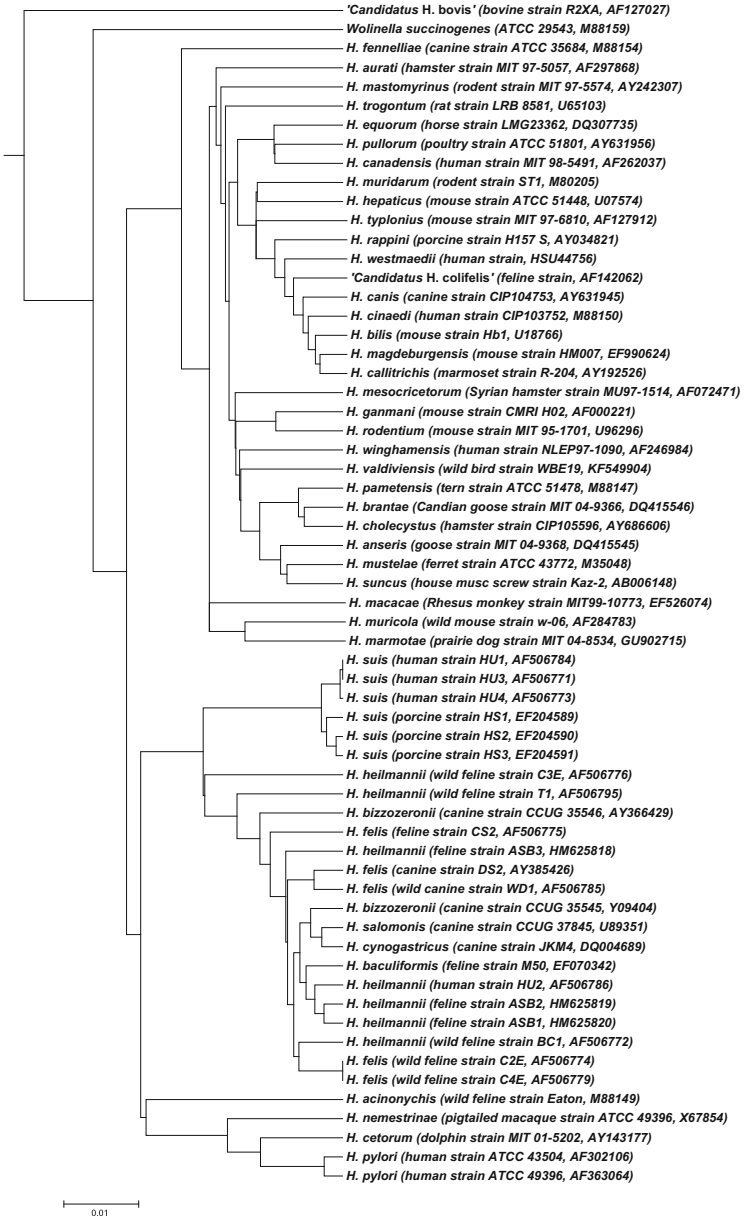

Fig. 10.1 Phylogenetic tree based on the near-complete 16s rRNA gene sequences from all gastric and enterohepatic *Helicobacter* species described so far. The alignment of the sequences and the construction of the phylogenetic tree were performed as described before (Smet et al. 2012)

Instead, they thrive at the mucosal surface of the intestinal tract and/or the liver (Sterzenbach et al. 2007). To date, *Helicobacter* spp. have been detected in nearly 150 vertebrate species, including animals from every continent and all four non-fish vertebrate taxonomic classes (Schrenzel et al. 2010). Animal-associated helicobacters, and especially the gastric species, are characterized by their extremely fastidious nature, which to date has resulted in a low number of in vitro isolates available worldwide (Haesebrouck et al. 2009). Several of these species have a pathogenic potential in different animal hosts, and some are capable of causing disease in humans (Table 10.1). The presence and diversity of helicobacters in the vertebrate fauna and their transfer possibilities between hosts are critical factors on how fast the *Helicobacter* ecology will evolve and what their impact is on animal and human health (Schrenzel et al. 2010). This chapter mainly focuses on the biology and pathogenesis of animal-associated gastric *Helicobacter* infections in humans and animals. An overview of the significance of enterohepatic *Helicobacter* spp. in human and animal disease is summarized at the end of this chapter.

10.2 Gastric *Helicobacter* Infections in Humans

In the early years of *H. pylori* research, pathologists examining human gastric biopsies already reported the presence of bacteria with a long spiral-shaped morphology. These microorganisms were similar to bacteria reported in the stomach of pigs, cats, dogs and nonhuman primates and were originally referred to as *Gastrospirillum hominis* (McNulty et al. 1989). Later on, they were renamed to *H. heilmannii* (Heilmann and Borchard 1991). Although at that time the name *H. heilmannii* had no official standing in nomenclature, it was used for many years to refer to the group of long spiral-shaped bacteria in the human stomach, which actually comprises several different *Helicobacter* species. Later on these microorganisms were reclassified into *H. heilmannii* type 1, representing *H. suis* from pigs, and *H. heilmannii* type 2, comprising a group of canine and feline *Helicobacter* spp. (Haesebrouck et al. 2009). The valid description of *H. heilmannii* further added some confusion on the nomenclature of this complex and expanding group of microorganisms (Smet et al. 2012). Therefore, the terms *H. heilmannii* (sensu lato), referring to the group of gastric non-*H. pylori Helicobacter* spp. (NHPH), and *H. heilmannii* (sensu stricto), referring to the species, have been proposed (Haesebrouck et al. 2011).

To date, these microorganisms have been associated with gastritis, gastric and duodenal ulcers, and low-grade mucosa-associated lymphoid tissue (MALT) lymphoma in humans. Gastric NHPH have microscopically been detected in 0.2–6 % of humans with severe gastric complaints undergoing a gastroscopy, but this is most probably an underestimation of their true prevalence (Haesebrouck et al. 2009). It cannot be excluded that infections with these bacteria sometimes remain unapparent or cause mild disease signs which are often not thoroughly examined.

Table 10.1 *Helicobacter* spp. and their hosts

Taxon	Natural hosts	Zoonotic potential
Gastric *Helicobacter* spp.		
'*Candidatus* H. bovis'	Cattle	Yes
'*Candidatus* H. homininae'	Chimpanzee, gorilla	Unknown
H. acinonychis	Cheetah, tiger, lion	Unknown
H. ailurogastricus	Cat	Unknown
H. baculiformis	Cat	Unknown
H. bizzozeronii	Cat, dog	Yes
H. cetorum	Whale, dolphin	Unknown
H. cynogastricus	Dog	Unknown
H. felis	Dog, cat, cheetah, New Guinea wild dog, rabbit	Yes
H. heilmannii	Dog, cat, cheetah, bobcat, tiger, lynx, leopard, puma	Yes
H. mustelae	Ferret	Unknown
H. pylori	Human	/
H. salomonis	Cat, dog, rabbit	Yes
H. suis	Pig, mandrill monkey, rhesus macaque, crab-eating macaque	Yes
Enterohepatic *Helicobacter* spp.		
'*Candidatus* H. colifelis'	Cat	Unknown
H. anseris	Goose	Unknown
H. aurati	Hamster	Unknown
H. bilis	Mouse, rat, gerbil, dog, cat, sheep	Yes
H. brantae	Goose	Unknown
H. callitrichis	Marmoset	Unknown
H. canadensis	Bird, pig	Yes
H. canis	Dog, cat	Yes
H. cholecystus	Hamster	Unknown
H. cinaedi	Hamster, rat, cat, dog, rhesus monkey, baboon	Yes
H. equorum	Horse	Unknown
H. fennelliae	Dog	Yes
H. ganmani	Mouse	Yes
H. hepaticus	Mouse, gerbil	Yes
H. macacae	Rhesus monkey, baboon	Unknown
H. marmotae	Woodchuck, cat	Unknown
H. magdeburgensis	Mice	Unknown
H. mastomyrinus	Rodents	Unknown
H. mesocricetorum	Hamster	Unknown
H. muricola	Wild mouse	Unknown
H. muridarum	Mouse, rat	Unknown
H. pamatensis	Bird, pig, cat	Yes
H. pullorum	Poultry	Yes
H. rappini	Mouse, sheep, dog	Yes

(continued)

Table 10.1 (continued)

Taxon	Natural hosts	Zoonotic potential
H. rodentium	Mouse, rat	Unknown
H. suncus	House musk shrew	Unknown
H. trogontum	Rat, pig, sheep	Unknown
H. typhlonius	Mouse, rat	Unknown
H. valdiviensis	Wild birds	Unknown
H. westmeadii	Human	/
H. winghamensis	Human, wild rodents	Yes

Clinical symptoms associated with gastric NHPH infections include acute or chronic epigastric pain, nausea, dyspepsia, reflux esophagitis, heartburn, vomiting, hematemesis, abdominal pain, irregular defecation frequency and consistency, and dysphagia, often accompanied by a decreased appetite (Haesebrouck et al. 2009).

In patients undergoing an endoscopy, a variety of lesions can be observed ranging from a normal to slightly hyperemic mucosa, mucosal edema, nodular inflammation, and the presence of ulcerations in the antrum of the stomach or in the duodenum (Haesebrouck et al. 2009; Sykora et al. 2003). Histopathological examination of gastric biopsies reveals infiltration with lymphocytes and plasma cells, sometimes organized in lymphocytic aggregates (Joosten et al. 2013b). Other lesions, such as intestinal metaplasia, have occasionally been described in patients infected with NHPH, and some of these patients were also infected with *H. pylori* (Stolte et al. 1997; Yakoob et al. 2012). Compared to an *H. pylori*-associated gastritis, gastritis associated with NHPH is often less active and less severe. On the other hand, the risk of developing MALT lymphoma is higher with NHPH than with *H. pylori* (Haesebrouck et al. 2009).

Tests to rapidly diagnose infection with gastric NHPH are currently unavailable. Urea breath tests, used to diagnose infection with *H. pylori*, are often negative in patients infected with animal-associated *Helicobacter* spp. (Matsumoto et al. 2014). This can be explained by the fact that infections with these bacteria are, in contrast to *H. pylori* infections, more often focal and predominantly found in the antrum of the stomach (Stolte et al. 1997). Due to the fastidious nature of gastric NHPH, isolation of these bacteria is not an option for routine diagnostic purposes. Until now, only *H. bizzozeronii* (Andersen et al. 1999; Kivisto et al. 2010) and *H. felis* (Wüppenhorst et al. 2013) have been cultured from gastric biopsies. Therefore, analysis of gastric biopsies by molecular microbiological methods and histology is so far the only way to determine infections with these microorganisms. A German study analyzed 89 human gastric biopsies, previously shown to be NHPH positive (Trebesius et al. 2001). Eighty percent of these samples were positive for *H. suis*, 17 (19 %) samples were positive for *H. heilmannii*, and 5 (6 %) hybridized with a probe specific for *H. felis*, *H. bizzozeronii*, and *H. salomonis*. De Groote and co-workers (2005) screened paraffin-embedded gastric biopsies from 101 patients

with confirmed gastric NHPH infection. Fourteen samples were positive for *H. suis*, whereas 49 were infected with helicobacters from cats and dogs. Another Belgian study showed similar results. *H. suis* was the most prevalent species (37 %), followed by *H. salomonis* (21 %), *H. felis* (15 %), *H. heilmannii* (8 %), and *H. bizzozeronii* (4 %) (Van Den Bulk et al. 2005b). A Polish study evaluated the incidence of gastric NHPH infection in dyspeptic children at the age of 4–18 years and found a prevalence of 0.2 % (Iwanczak et al. 2012). Another study focused on the association between coinfection with canine and feline NHPH and *H. pylori* and gastric pathology in patients with dyspepsia. *H. pylori* was found in 67 % of the patients, and only 6 % and 4 % of them were coinfected with *H. heilmannii* and *H. felis*, respectively (Yakoob et al. 2012). Recently, a remarkably high prevalence (27 %) of *H. suis* DNA was found in gastric biopsies from human patients with idiopathic parkinsonism. The putative significance of this bacterium in Parkinson's disease requires further investigation (Blaecher et al. 2013).

Evidence is accumulating that pigs, cats, and dogs constitute reservoir hosts for gastric *Helicobacter* spp. with zoonotic potential (Haesebrouck et al. 2009). *Helicobacter* DNA has been detected in saliva from cats, dogs, and pigs, indicating that the oral cavity of these animals may act as source of NHPH infection for humans (Ekman et al. 2013; Casagrande Proieti et al. 2010; Shojaee Tabrizi et al. 2010). Fecal-oral transmission has also been suggested as a possible route for infection in cats (Ghil et al. 2009). Besides direct contact with animals, other routes of transmission of NHPH should not be neglected. It has been shown that *H. felis* is able to survive in water for several days, highlighting the possible role for water in the transmission of this species (Azevedo et al. 2008). Recently, De Cooman and co-workers (2013) demonstrated that *H. suis* can be present on and survive in minced pork. This indicates that raw or undercooked pork may also constitute a source of *H. suis* infection for humans. Nowadays, the prevalence of *H. pylori* in humans from the Western world is decreasing from generation to generation, leaving a niche for possible infection with these animal-associated gastric *Helicobacter* spp.

For patients with severe clinical symptoms and pathology, treatment is necessary. There is, however, a lack of clinical trials, and only a few reports deal with antimicrobial susceptibility and acquired resistance of gastric NHPH (Vermoote et al. 2011b; Van den Bulck et al. 2005a). Triple therapy using the combination of a proton-pump inhibitor and two antimicrobial agents, like clarithromycin, metronidazole, amoxicillin, or tetracycline, may be effective in most cases but not always. A Finnish patient infected with *H. bizzozeronii* received a triple therapy of tetracyclines, metronidazole, and lansoprazole for 1 week. The symptoms subsided, but the infection was not cleared and the patient continued to suffer from mild nausea. *H. bizzozeronii* was isolated from the stomach, and determination of its antimicrobial susceptibility showed resistance against tetracycline and metronidazole (Schott et al. 2012). Furthermore, it was demonstrated that acquired resistance to metronidazole in *H. bizzozeronii* was due to the contingency nature of an oxygen-insensitive NAD(P)H-nitroreductase. This phenomenon was also described for *H. heilmannii* (Kondadi et al. 2013).

10.3 Natural and Experimental Gastric *Helicobacter* Infections in Animal Hosts

10.3.1 Gastric Non-H. pylori Helicobacter *spp. Associated with Dogs and Cats*

10.3.1.1 Prevalence in Dogs and Cats

In pet animals, gastric *Helicobacter* spp. have been frequently described with a prevalence of 67–86 % in clinically healthy dogs, 61–100 % in dogs presenting chronic vomiting, and 41–100 % in healthy cats as well as cats showing chronic vomiting (Haesebrouck et al. 2009; Shojaee Tabrizi et al. 2010). Ghil and colleagues (2009) reported that the prevalence of *Helicobacter* spp. in feral cats was approximately twofold higher than in domestic cats. Often cats and dogs are naturally infected with multiple gastric *Helicobacter* spp. (Haesebrouck et al. 2009). The first *Helicobacter* species isolated from the stomach of cats and dogs was *H. felis* (Lee et al. 1988). Later on, *H. bizzozeronii*, *H. salomonis*, and *H. cynogastricus* were isolated from the canine gastric mucosa, whereas H. baculiformis, H. heilmannii and H. ailurogastricus isolates were obtained from the stomach of cats (Haesebrouck et al. 2009; Smet et al. 2012; Joosten et al. 2015). It has been shown that *H. bizzozeronii* is the most predominant species in the canine stomach, whereas *H. felis* and *H. heilmannii* are the predominant *Helicobacter* spp. in cats (Priestnall et al. 2004; Svec et al. 2000; Wiinberg et al. 2005). The prevalence of *H. cynogastricus* and *H. baculiformis* in pet animals as well as their zoonotic potential is so far unknown. Only few data is available on the transmission of NHPH infections in dogs and cats. Transmission of *H. salomonis* from a dam to her puppies, as well as between infected and noninfected pups, has been described (Hänninen et al. 1998). It has been suggested that in this case, transmission occurred through oral-oral or gastric-oral contact, as nursing dogs have very close contact with their offspring and puppies eat material vomited by the dam (Hänninen et al. 1998).

10.3.1.2 Role of *Helicobacter* spp. in the Development of Gastric Pathologies in Dogs and Cats

In general, canine and feline *Helicobacter* spp. have been associated with chronic active gastritis (Haesebrouck et al. 2009). Histological changes in the lamina propria include mild mononuclear inflammatory infiltration, the presence of lymphoid follicles, fibrosis, and glandular degeneration in the stomach of cats naturally infected with *H. heilmannii* (Takemura et al. 2009). One study reported a correlation between *Helicobacter* infection and the presence of feline lymphoma (Bridgeford et al. 2008). Gastric and duodenal ulcers have been rarely reported among cats and dogs, and an association with *Helicobacter* infections has not been

made (Haesebrouck et al. 2009). To study the pathogenesis of NHPH infections in dogs and cats, several experimental infection studies have been performed. A mononuclear infiltration throughout the gastric mucosa, with follicular organization of the inflammatory cells, has been demonstrated in the stomach of *H. felis*-infected-specific pathogen-free (SPF) cats (Scanziani et al. 2001). Another experimental infection study with *H. felis* in young gnotobiotic dogs described lymphoid hyperplasia in the fundus and body of the stomach (Diker et al. 2002). On the contrary, Simpson and co-workers (1999) found a similar degree of inflammation in both *H. felis*-infected SPF dogs and uninfected control dogs. These contradictory results may be explained by differences in virulence between *H. felis* strains. The review by Haesebrouck and colleagues (2009) suggested that the pathogenic significance of gastric helicobacters in cats and dogs may be related to (1) the species expressing its own virulence which may be increased in cases of mixed infections due to synergistic effects, (2) differences within strains from the same species, or (3) host differences. An Italian study investigated the localization of *Helicobacter* spp. in the fundic mucosa of laboratory beagle dogs. They demonstrated that *H. bizzozeronii* was present in the superficial and basal portions of the fundic glands, while *H. felis* was only detected in the superficial portions of the glands. Additionally, these helicobacters were also located free in the cytoplasm or within lysosomes of parietal cells (Lanzoni et al. 2011). The urea breath test, widely used for rapid and noninvasive detection of *H. pylori* infection in humans, has recently been applied on laboratory beagle dogs. A sensitivity and specificity of 89 % was reported suggesting the usefulness of this technique to monitor gastric *Helicobacter* infections in dogs (Kubota et al. 2013).

10.3.1.3 Genomics, Genetics, and Experimental Studies in Rodents on the Pathogenesis of Canine and Feline *Helicobacter* Infection

Recently the genomes of *H. felis*, *H. bizzozeronii*, and *H. heilmannii* have been sequenced (Arnold et al. 2011; Schott et al. 2011; Smet et al. 2013). These genomes contain genes encoding homologues of known *H. pylori* virulence factors discussed in Chaps. 3, 4, 5, 6, and 7. These genomes possess a complete *comB* system conferring natural competence, but they all lack the cytotoxin-associated gene pathogenicity island (*cag*PAI), a functional vacuolating cytotoxin A (VacA), and the *H. pylori* adhesins identified so far. Amorim and colleagues (2014) showed that several canine and feline helicobacters, like *H. felis* and *H. heilmannii*, are able to adhere to the canine gastric mucosa. Which adhesins are involved is so far unknown.

Besides SPF pets, rodent models have also been shown to be useful experimental infection models to obtain insights into the pathogenesis of gastric NHPH infections in animals and humans (O'Rourke et al. 2004a). *H. felis* infection in mice is often used as an animal model to study *H. pylori*-related gastric pathology in humans. Due to the lack of several important *H. pylori* virulence factors, researchers must be

aware that *H. felis* might not always have similar outcomes in pathogenicity compared to *H. pylori*. Extrapolation of data obtained in an *H. felis* infection mouse model to *H. pylori* infections in humans should therefore be done with caution. To date, many reports studied the pathogenesis of canine and feline *Helicobacter* infection in rodent models. One of the very first steps in the pathogenesis of gastric infections caused by these microorganisms is colonization of the gastric mucosa in which binding to mucins (MUC) plays an important role. MUC1, MUC5AC, and MUC6 are the major mucins covering the gastric mucosa. Liu and colleagues (2014) investigated the gastric mucin expression pattern in the stomach of *H. heilmannii*-infected BALB/c mice. They showed a remarkable increased expression of Muc6 and Muc13 in the first 9 weeks postinfection. Since Muc6 is expressed by the gastric glands and, unlike *H. pylori*, *H. heilmannii* was mainly localized in the deep glands of the gastric mucosa, the potential role of Muc6 in *H. heilmannii* colonization was suggested. The MUC13 mucin is normally not expressed in a healthy stomach and has so far only been described as a marker for gastric cancer in humans. The increased expression already in the early stages of infection highlights its role in *H. heilmannii* colonization (Liu et al. 2014). The mucin Muc1 is constitutively expressed by the gastric mucosa and is likely the first point of contact between the host stomach and adherent pathogens. It has been shown that Muc1 limits *H. felis* binding to gastric epithelial cells. However, it does not limit colonization and gastric pathology following infection (Every et al. 2008). The pathological changes in the mouse stomach infected with *H. salomonis*, *H. bizzozeronii*, or *H. felis* have been evaluated as a means of distinguishing different NHPH species in terms of virulence. *H. salomonis* was not able to colonize the murine stomach. *H. bizzozeronii* showed moderate pathological changes, while *H. felis* induced the most severe inflammatory changes (De Bock et al. 2005). Another study by the same research group demonstrated that *H. felis* and *H. bizzozeronii* induce gastric parietal cell loss in Mongolian gerbils, highlighting the preference of these bacteria for parietal cells as was also demonstrated in their natural host (De Bock et al. 2006). Takaishi and co-workers (2009) studied the effect of gastrin on *H. felis*-associated gastric carcinogenesis using hypergastrinemic, gastrin-deficient, and wild-type C57BL/6 mouse models. Gastrin is released by G cells mainly in the antrum of the stomach in response to food intake and stimulates the secretion of gastric acid by parietal cells. Severe corpus dysplasia with mild gastric atrophy was noted in *H. felis*-infected hypergastrinemic (INS-GAS) mice, while mild to moderate antral dysplasia was seen in the gastrin-deficient and wild-type mice. Gastrin deficiency did not result in an alteration of *H. felis* colonization, but it was shown that gastrin is an essential cofactor for the development of gastric dysplasia in *H. felis*-infected C57BL/6 mice. Joosten et al. (2013a) demonstrated that chronic *H. heilmannii* infection in Mongolian gerbils was associated with decreased gastric acid secretion and increased gastrin mRNA levels stimulated by interleukin-1 beta (IL-1β). This latter finding could be considered as a reaction to the *H. heilmannii*-induced hypochlorhydria. Another study investigated the role of *H. felis* infection in the etiology of iron deficiency in INS-GAS C57BL/6 mice. Decreased serum iron concentrations were associated

with a concomitant reduction in the number of parietal cells, strengthening the association between hypochlorhydria and gastric *Helicobacter*-induced iron deficiency. Additionally, the marked changes in gastric iron concentrations and the reduced number of parietal cells following *Helicobacter* infection may be relevant to the more rapid development of carcinogenesis in *H. felis*-infected INS-GAS mice (Thomson et al. 2012). The loss of parietal cells can lead to two distinct types of mucous metaplasia: intestinal metaplasia and spasmolytic polypeptide-expressing metaplasia (SPEM). It has been suggested that intestinal metaplasia induced by *Helicobacter* infection develops in the presence of preexisting SPEM, supporting the role of SPEM as a neoplastic precursor in the carcinogenesis cascade (Liu et al. 2014; El-Zaatari et al. 2013). Several reports uniformly showed that *H. felis* predominantly causes a T helper (Th)1/Th17 immune response in mice, as has also been described for *H. pylori* (Ding et al. 2013; Obonyo et al. 2011; Sayi et al. 2011; Stoicov et al. 2009, Hitzler et al. 2012). Other gastric NHPH, like *H. heilmannii*, have been shown to cause a predominant Th2/Th17 host immune response in BALB/c mice which clearly differs from what is observed during *H. felis* infection (Liu et al. 2014). In BALB/c mice chronically infected with *H. heilmannii*, MALT lymphoma-like lesions were observed (Liu et al. 2014; O'Rourke et al. 2004a). Similar pathological findings have also been described in BALB/c mice chronically infected with *H. felis* suggesting that this mouse model can be seen as a critical model to study gastric MALT lymphoma (Stolte et al. 2002).

*10.3.2 Gastric Non-*H. pylori Helicobacter *spp. Associated with Large Felines*

Besides domesticated cats, *Helicobacter* spp. like *H. felis* and *H. heilmannii* have occasionally been found in the stomach of wild felines, such as lynx, leopards, pumas, bobcats, tigers, and cheetahs (Hamir et al. 2004; Mörner et al. 2008; O'Rourke et al. 2004b; Luiz de Camargo et al. 2011). In cheetahs, gastritis caused by these bacteria is characterized by the infiltration of lymphocytes and plasma cells in the epithelium and lamina propria with gland destruction and parietal cell loss. In some cases lymphoid follicles were observed, especially in captive animals and less frequently in wild animals (Terio et al. 2005; Munson et al. 2005). Terio and colleagues (2012) further investigated the local immune response in cheetahs with varying degree of *Helicobacter*-associated gastritis. The type of cells involved was similar among all types of gastritis with the exception that a large number of lamina proprial activated $CD79a^{+}CD21$-B cells and plasma cells were only seen in cheetahs with severe gastritis (Terio et al. 2012). Another and more frequently found *Helicobacter* species in big cat predators is *H. acinonychis*. This species has been associated with severe chronic gastritis in cheetahs, tigers, and lions (Tegtmeyer et al. 2013). Cattoli and co-workers (2000) demonstrated that eradication of this bacterium from the stomach using antimicrobial treatment resulted in

the resolution of gastric lesions in tigers. *H. acinonychis* has been described as the most closely related species to *H. pylori* (Tegtmeyer et al. 2013). Eppinger and colleagues (2006) sequenced the *H. acinonychis* genome and showed that this species arose after a single host jump of *H. pylori* from humans to large felines approximately 43,000–56,000 years ago. Comparison between the *H. acinonychis* and *H. pylori* genomes revealed that both species share a high number of core genes (Tegtmeyer et al. 2013). The *H. acinonychis* genome also possesses unique features that confirmed the direction of the host jump from humans to large felines. Interestingly, *H. acinonychis* lacks a *cag*PAI and a functional VacA as has been described for other animal-associated gastric helicobacters as well. Additionally, the *H. acinonychis* genome contains a high number of fragmented genes due to frameshifts and/or stop codons which are probably caused by niche changes and host specialization (Gressmann et al. 2005). So far, only little information is available about the interaction of *H. acinonychis* with its host. Dailidiene and co-workers (2004) showed that *H. acinonychis* was able to infect mice and to coexist and recombine with *H. pylori* in the stomach.

10.3.3 Gastric Helicobacter *Infection in Pigs*

In 1990, large spiral-shaped bacteria were described for the first time in the gastric mucus layer and on the mucosal surface of pig stomachs (Mendes et al. 1990; Queiroz et al. 1990). Initially, *Gastrospirillum suis* was proposed as a name, but subsequent characterization showed that this organism in fact belonged to the genus *Helicobacter* (De Groote et al. 1999b). A new name, '*Candidatus* Helicobacter suis', was then proposed, and despite numerous attempts worldwide, the first successful in vitro isolate was only obtained in 2007, by using a new biphasic culture method, which finally led to the description of *H. suis* as a new species (Baele et al. 2008). Sequence analysis of 16S rRNA, 23S rRNA, partial *hsp60*, and partial *ureAB* gene sequences confirmed that *H. suis* is identical to the previously called *H. heilmannii* type 1. Besides pigs and humans, this species also colonizes the stomach of nonhuman primates, such as mandrills, macaques, and baboons (O'Rourke et al. 2004b).

10.3.3.1 Prevalence of *Helicobacter suis* in Pigs

The reported prevalence of *H. suis* infection in pigs depends on the study. In general, this bacterium is detected in more than 60 % of the European, Asian, and South and North American pigs at slaughter age (Barbosa et al. 1995; Grasso et al. 1996; Cantet et al. 1999; Park et al. 2004; Hellemans et al. 2007b; Kopta et al. 2010). Most likely, *H. suis* is transmitted via the oral-oral route through saliva or via the gastric-oral route through vomiting or regurgitation, but this remains to be investigated. Despite a very high prevalence in adult pigs, far lower degrees of

infection have been shown in younger animals. Hellemans and co-workers (2007b) detected a prevalence of only 2 % in suckling piglets, which however increased rapidly after weaning.

So far, *H. suis* has not been detected in the stomach of wild boars. In a Polish study, the authors did find gastric *Helicobacter* spp., but interestingly, these bacteria were shown not to be *H. suis* (Fabisiak et al. 2010). More worldwide studies are, however, required to draw firm conclusions on the presence of *H. suis* in these wild ancestors of domesticated pigs.

10.3.3.2 *Helicobacter suis* and Its Role in the Development of Gastric Pathology in Pigs

H. suis has been shown to cause gastritis in experimentally and naturally infected pigs, mainly in the antrum (Mendes et al. 1991; Grasso et al. 1996; Queiroz et al. 1996; Park et al. 2000; Hellemans et al. 2007a; De Bruyne et al. 2012). Besides an occasional neutrophilic infiltrate, the inflammation mainly composes of a diffuse lymphocytic/plasmacytic infiltration as well as lymphocytic aggregates and lymphoid follicles. In experimentally infected pigs, this gastritis shows a spatial association with the main sites of colonization: the antrum and fundus (Hellemans et al. 2007a; De Bruyne et al. 2012). Interestingly, diffuse lymphocytic infiltration and lymphoid follicles have been shown to be present in the stomach, and mainly in the cardiac region, of newborn piglets without *Helicobacter* infection (Driessen et al. 2002; Mazzoni et al. 2011). Most likely, germinal centers in lymphoid follicles are formed in the presence of an antigenic stimulus, for instance, during *H. suis* infection.

Besides the strong association with gastritis, *H. suis* infection has also been associated with ulceration of nonglandular stratified squamous epithelium of the *pars esophagea* of the stomach, although *H. suis* bacteria probably do not colonize this specific stomach region (Barbosa et al. 1995; Queiroz et al. 1996; Choi et al. 2001; Roosendaal et al. 2000; Hellemans et al. 2007b; De Bruyne et al. 2012). Other research groups did not find this association (Grasso et al. 1996; Cantet et al. 1999; Melnichouk et al. 1999; Park et al. 2000; Szeredi et al. 2005), so the exact role of *H. suis* in the development of these lesions remains to be elucidated. Sapierzyński and colleagues (2007) demonstrated that *H. suis* infection in pigs results in an increased number of gastrin-producing cells and a decreased number of somatostatin-producing cells in the antrum. Since gastrin stimulates and somatostatin inhibits the secretion of hydrochloric acid by parietal cells, this may influence gastric acid production, which may also be altered due to the tropism of this bacterium for parietal cells (Hellemans et al. 2007a). An altered gastric acid secretion could in turn be involved in the development of ulceration of the *pars esophagea*. The discrepancies found in literature may be due to differences in laboratory techniques, different sampling practices, or differences in virulence between *H. suis* strains. In any case, hyperkeratosis and ulceration of the nonglandular part of the stomach have been reported in many countries. Up to

80 % of the market pigs in Australia (Robertson et al. 2002) and 60 % of the sows (Hessing et al. 1992) in the Netherlands have been described to be affected.

The development of lesions in the *pars esophagea* is most likely a process involving different factors, including stress, transport, the presence in the stomach of short-chain fatty acids, and pelleting and fine grinding of the feed (Haesebrouck et al. 2009; Argenzio and Eisemann 1996). The latter factor may have an influence on the fluidity of gastric contents (Elbers and Dirkzwager 1994), leading to an increased contact of the stratified squamous epithelium of the nonglandular region with the luminal content of the distal part with acid, bile (refluxed from the duodenum), and pepsin.

Ulceration of the porcine gastric nonglandular mucosa may result in decreased feed intake, a decrease in daily weight gain, and even sudden death due to fatal hemorrhage (Ayles et al. 1996; Haesebrouck et al. 2009), thus leading to significant economic losses. There is also little doubt that this disease can cause pain and discomfort. Interestingly, a decrease in daily weight gain of up to 10 % has been observed in pigs experimentally infected with *H. suis*, however, without a clear association with the development of lesions in the nonglandular part (De Bruyne et al. 2012).

Besides *H. suis*, other *Helicobacter* species have been described in the stomach of pigs, including an *H. pylori*-like bacterium, responsible for ulceration of the *pars esophagea* in gnotobiotic piglets (Krakowka and Ellis 2006), *H. bilis* and *H. trogontum* (Hänninen et al. 2003, 2005). The main site of colonization of the latter two is most probably the lower intestinal tract, and it remains to be determined whether these bacteria are able to colonize the porcine stomach and cause gastric pathology.

10.3.3.3 Genomics, Genetics, and Experimental Studies on the Pathogenesis of *H. suis* Infection

Genome sequencing of *H. suis* (Vermoote et al. 2011a) revealed the presence of homologues of *H. pylori* genes involved in acid acclimation, motility, chemotaxis, oxidative stress resistance, and adhesion to gastric epithelial cells. These include genes encoding urease A and B subunits and urease accessory proteins, genes encoding different components of the flagellar apparatus, several *che* and *tlp* genes, *katA*, *sodB*, genes encoding several members of the major *H. pylori* outer membrane families, and *hpaA*. In addition, *H. suis* harbors a near complete *comB* type IV secretion system and homologues of the *H. pylori* neutrophil-activating protein and γ-glutamyl transpeptidase, but it lacks most members of the *cag*PAI as well as a functional VacA.

In literature, several studies describe experimental infection of mice with *H. heilmannii*. Sometimes, however, this name might be misleading, as several of these studies have in fact used *H. suis* bacteria, obtained from mucus, or homogenized gastric tissue of infected mice, pigs, or nonhuman primates, because of the lack of in vitro isolated strains. Infection of mice with these inocula induces

inflammation, already 7 days after inoculation (Moura et al. 1993). During long-term infection studies of up to 2 years, infiltration of the gastric mucosa with lymphocytes and plasma cells with subsequent development of lymphoid follicles has been observed, both in studies using mucosal homogenates and pure in vitro isolated *H. suis* strains (Park et al. 2008; Flahou et al. 2010). Conflicting reports have been published regarding the immune response underlying *H. suis*-induced gastritis. Several authors have described the inflammation and formation of gastric lymphoid follicles to be mainly driven by a Th1 response (Cinque et al. 2006; Mimura et al. 2011). Others have described a mixed Th1/Th2 response (Park et al. 2008), whereas studies using pure in vitro isolated *H. suis* strains revealed that experimental *H. suis* infection causes an upregulation of IL-17, IL-10, and IL-4 expression, in the absence of interferon (IFN)-γ upregulation (Flahou et al. 2012), which also clearly contrasts to the immune response elicited by *H. pylori* in this same animal model. Recently, however, Liang and colleagues (2015) described a strong upregulation of IFN-γ expression in *H. suis*-infected Mongolian gerbils.

The resulting chronic gastritis has been shown not to depend upon the presence of Peyer's patches in the small intestine, in contrast to what has been described for *H. pylori* (Nobutani et al. 2010). Often, this chronic gastritis evolves to more severe histopathological lesions. In BALB/c mice experimentally infected with different *H. heilmannii* bacteria, "isolated" in vivo in mice and originating both from humans and animals, gastric MALT lymphoma has been shown to develop starting from 18 months postinfection (O'Rourke et al. 2004a). In this study, the most severe pathological changes were seen in mice infected with in vivo "isolates" from a human patient, a bobcat, a crab-eating macaque, and mandrill monkeys. Except for the strain from the bobcat, these strains were in fact shown to be *H. suis*. Similar lesions were observed in C57BL/6 mice infected for at least 6 months with an in vivo "isolate" of '*Candidatus* H. heilmannii', which in fact was shown to belong to the species *H. suis* (Nakamura et al. 2007; Haesebrouck et al. 2009), as well as in Mongolian gerbils infected with an in vitro isolated strain of *H. suis* (Flahou et al. 2010). These histopathological changes resemble inflammation-related changes in the stomach of humans infected with NHPH, including *H. suis*.

In addition to the involvement of several cytokines, including IL-4 and chemokine (C-X-C motif) ligand 13 (CXCL-13) (Flahou et al. 2012; Yamamoto et al. 2014), several mechanisms have been described to stimulate lymphomagenesis in this setting. An overexpression of miR-142-5p and miR-155, as well as increased lymphangiogenesis and angiogenesis, has been shown to be involved in *H. suis*-induced gastric MALT lymphoma (Saito et al. 2012; Nakamura et al. 2008). The latter changes are accompanied by an increased expression of vascular endothelial growth factors (VEGF), such as VEGF-A and VEGF-C, and some of its receptors, including Flt-1 and Flt-4 (Nishikawa et al. 2007; Nakamura et al. 2007, 2008, 2010). In addition, the formation of peripheral lymph node addressin (PNAd)- and mucosal addressin cell adhesion molecule 1 (MadCAM-1)-expressing high endothelial venule-like vessels plays a role (Suzuki et al. 2010). These alterations may cause a sustained "homing" of lymphocytes to the gastric mucosa. Interestingly, the administration of antibodies raised against certain of the

abovementioned factors, including CXCL-13, Flt-1, and Flt-4, induces a marked reduction of the size of the region affected by gastric MALT lymphoma, which may have implications for the future treatment guidelines of *Helicobacter*-induced gastric MALT lymphoma (Nakamura et al. 2010, 2014; Yamamoto et al. 2014).

Besides inflammation-related pathological changes, *H. suis* also interacts with the mucosal epithelium. In infected humans, the majority of *H. pylori* bacteria remain in the mucus layer, whereas a limited number adhere to gastric epithelial (mucus-secreting) cells (Lindén et al. 2008). *H. suis*, on the other hand, is most often observed in the vicinity of or inside the canaliculi of acid-producing parietal cells in pigs, humans, and experimentally infected mice and Mongolian gerbils (Hellemans et al. 2007a; Joo et al. 2007; Flahou et al. 2010). Regularly, these parietal cells show signs of degeneration or oncosis. Many questions remain unanswered with regard to the mechanisms underlying the epithelium-related changes observed during *H. suis* infection. As described above, several important *H. pylori* virulence factors, such as the *cag*PAI and VacA, are absent or nonfunctional in *H. suis* (Vermoote et al. 2011a). So far, the *H. suis* γ-glutamyl transpeptidase (GGT) is the only virulence factor from *H. suis* with a confirmed role in death of gastric epithelial cells. In vitro research using a human gastric epithelial cell line (AGS) has shown that the enzyme causes apoptosis or necrosis, depending in part on the amount of reactive oxygen species (ROS) generated through degradation of reduced glutathione (GSH), an important antioxidant (Flahou et al. 2011). Besides its role in death of epithelial cells, the same enzyme has been shown to impair lymphocyte function, which is in line to what has been published for *H. pylori* (Zhang et al. 2013). Supplementation of GGT-treated cells with known substrates of the enzyme was shown to modulate the observed effects: glutamine restored normal proliferation of lymphocytes, whereas supplementation with reduced glutathione strengthened *H. suis* GGT-mediated inhibition of proliferation. Most likely, depletion of glutamine and the generation of reactive oxygen species through degradation of GSH are involved. In this same study, *H. suis* outer membrane vesicles were identified as a possible delivery route of *H. suis* GGT to lymphocytes residing in the deeper mucosal layers.

Parallel to the cell death it induces, *H. suis* infection also causes an increased proliferation of progenitor cells in the isthmus of gastric glands (Flahou et al. 2010). A direct effect of the bacteria may be involved (Fast et al. 2011), or alternatively, this may reflect a compensatory hyperproliferation due to increased epithelial cell loss (Shirin and Moss 1998).

10.3.4 Gastric Helicobacter *Infection in Nonhuman Primates*

Captive rhesus macaques are commonly infected with *H. pylori* (Drazek et al. 1994). The anatomy and physiology of the stomach resemble that of humans, which suggests that the rhesus monkey model can serve as a good experimental

model to study *H. pylori* infection. For instance, it has been shown that socially housed rhesus monkeys rapidly acquire *H. pylori* infection, particularly during the peripartum period (Solnick et al. 2003, 2006). Once acquired, infection is associated with chronic gastritis resembling that seen in humans.

Besides *H. pylori*, nonhuman primates can be naturally infected with gastric NHPH. Although an exact species designation of the colonizing *Helicobacter* species is sometimes lacking, *H. suis* seems to be the species involved (O'Rourke et al. 2004b; Martin et al. 2013; Nakamura et al. 2007; Matsui et al. 2014). In the stomachs of rhesus monkeys, gastric NHPH which were not identified to the species level have been observed in the mucus covering the surface epithelial cells, as well as in the lumina of gastric glands. These microorganisms were shown to be able to invade and on occasion damage parietal cells, which was however often accompanied by an apparent hyperchlorhydria. This contrasted with *H. pylori* infection in this model, which appeared to cause a more pronounced gastritis, while apparently not modifying the acid output (Dubois et al. 1991). In another study, *H. suis* was shown to be present in the stomach of all rhesus monkeys that were used for determining the effects of an experimental *H. pylori* infection on the gastric microbiota. Interestingly, the populations of *H. suis* and *H. pylori* were shown to be highly dynamic, and a potential competitive inhibition/exclusion was observed between both species (Martin et al. 2013).

NHPH infection in baboons has been associated with the development of gastritis by Mackie and O'Rourke (2003) but not by others (Curry et al. 1989). NHPH have been described to be naturally present in the stomachs of cynomolgus monkeys from different geographic regions (Reindel et al. 1999; Drevon-Gaillot et al. 2006). Again, *H. suis* seems to be the species involved (O'Rourke et al. 2004b), and these microorganisms can be found in the gastric pits, in the superficial glands, or on the surface epithelium. In one study, no correlation was observed between these bacteria and the infiltration of lymphoplasmacytic cells and inflammatory lesions in these gastric tissues (Drevon-Gaillot et al. 2006).

Recently, a putative new gastric *Helicobacter* species was detected in wild chimpanzees and gorillas, which was provisionally named '*Candidatus* H. homininae' (Flahou et al. 2014).

10.3.5 Gastric Helicobacters Associated with Ruminants and Horses

'*Candidatus* Helicobacter bovis' has been demonstrated in the pyloric part of the abomasum of calves and adult cattle. So far, this bacterium has not been cultivated in vitro (De Groote et al. 1999a), and its involvement in bovine gastric disease is unknown. Although gastric ulcers regularly occur in calves and adult cattle (Haringsma and Mouwen 1992; Jelinski et al. 1995; Ok et al. 2001), no association between gastric ulceration and *Helicobacter* colonization was observed in a recent

study, since no *Helicobacter* bacteria could be detected in the animals that were sampled (Valgaeren et al. 2013). *H. pylori* has been demonstrated in the stomach of sheep (Dore et al. 2001), and so far, no helicobacters have been demonstrated in the stomach of goats (Gueneau et al. 2002; Momtaz et al. 2014). Interestingly, *H. pylori* has also been detected in milk from cows, sheep, and other ruminants (Quaglia et al. 2008; Angelidis et al. 2011; Rahimi and Kheirabadi 2012). Although Rahimi and colleagues claim to have isolated *H. pylori* bacteria, most studies used polymerase chain reaction or fluorescence in situ hybridization to detect *H. pylori*. Further studies are therefore needed to assess whether *H. pylori* or *H. pylori*-like bacteria are involed. In addition, it needs to be confirmed whether milk consumption can serve as a route of transmission for *H. pylori*.

Although some studies describe the absence of *Helicobacter* spp. in the stomach of horses (Husted et al. 2010; Perkins et al. 2012), others describe the presence of *Helicobacter*-like organisms or their DNA in this niche. So far, however, helicobacters have not yet been cultivated from the equine stomach (Scott et al. 2001; Contreras et al. 2007), so their possible role in the development of gastric ulcers, which are common in horses (Haesebrouck et al. 2009), remains speculative.

10.3.6 Gastric Helicobacters Associated with Other Animal Species

10.3.6.1 Marine Mammals

Urease-positive helicobacters have been isolated from the main stomach or feces of various cetaceans, including stranded wild Atlantic white-sided dolphins and captive Pacific white-sided dolphins, Atlantic bottlenose dolphins, and a beluga whale (Harper et al. 2002, 2003a). In 2002, these bacteria were characterized and described as *H. cetorum* (Harper et al. 2002). The results of a health study, in which 20 wild Atlantic bottlenose dolphins were sampled, showed that the prevalence in these animals was at least 50 % (Harper et al. 2003a). In addition to the studies described above, helicobacters with a high homology to *H. cetorum* have been isolated from or detected in fecal samples from captive seals and sea lions from Australia, South American fur seals, the stomach of an Atlantic spotted dolphin, gastric fluids, dental plaques, saliva and gastric tissue of captive dolphins and a killer whale from Argentina, fecal material from wild and captive Yangtze finless porpoises, the stomach of common dolphins, an Atlantic white-sided dolphin and a striped dolphin from European waters, and the aquatic environment of captive dolphins (Oxley and McKay 2005; Goldman et al. 2009a, b, 2011; Suárez et al. 2010; McLaughlin et al. 2011; Davison et al. 2014).

Some of the captive animals from which *H. cetorum* was recovered showed clinical signs, such as intermittent inappetence, lethargy, or chronic regurgitation. Endoscopic or gross examination revealed the presence of esophageal and

forestomach ulcers, as well as gastric mucosal hemorrhages (Harper et al. 2002; Davison et al. 2014). Cytological examination of gastric fluid of some animals indicated the presence of inflammation in the stomach (Harper et al. 2002). This was confirmed by histopathological analysis, revealing *Helicobacter* colonization of the epithelial surface accompanied by a diffuse lymphoplasmacytic gastritis in the main stomach and to a lesser extent in the pyloric stomach, and a mild distortion of the adjacent glands (Harper et al. 2002; Suárez et al. 2010).

In a recent study, two genomes of *H. cetorum* were sequenced: one strain originated from a dolphin and one strain isolated from a captive Beluga whale (Kersulyte et al. 2013). Although these genomes, differing markedly from one another in gene content, appeared to be larger than *H. pylori* genomes, the strains were shown to be more closely related to *H. pylori* and *H. acinonychis* than to other known species. They lack the *cag*PAI but do possess novel alleles of the *vacA* gene. In addition, they reveal an extra triplet of *vacA* genes, metabolic genes distinct from *H. pylori*, as well as genes encoding both an iron- and nickel-cofactored urease.

Besides *H. cetorum*, other putative novel *Helicobacter* spp., distinct from *H. cetorum*, have been detected in the gastric fluids, gastric mucosa, or dental plaque from dolphins, harp seals, and a sea lion with chronic gastritis (Harper et al. 2003b; Oxley et al. 2004, 2005; Goldman et al. 2011).

10.3.6.2 Ferrets

Not so long after the discovery and description of *H. pylori* in humans, spiral organisms were isolated from a gastric ulcer of a ferret and from the gastric mucosa of two healthy ferrets (Fox et al. 1986). In 1989, these organisms were named *Helicobacter mustelae* (Goodwin et al. 1989). Only a minority of ferrets younger than 6 weeks are colonized by this bacterium, in contrast to the vast majority of adult ferrets (Fox et al. 1988), indicating that widespread colonization and persistence occur after weaning (Fox et al. 1991a; Forester et al. 2000). Keeping in mind the ease by which ferrets vomit, oral-oral and gastric-oral contact most likely play a role in transmission of *H. mustelae* (Fox et al. 1991a). Fecal-oral transmission has, however, also been suggested. *H. mustelae* has indeed been isolated successfully from feces of ferrets, and successful isolation correlated with periods of transient hypochlorhydria, which may allow larger numbers of bacteria to exit the stomach (Fox et al. 1992).

H. mustelae colonizes the mucosal surface in the corpus region, which often induces only a superficial gastritis (Marini and Fox 1999). In the antrum, however, *H. mustelae* colonizes the surface, gastric pits, and superficial portion of the glands, leading to the development of a diffuse mononuclear gastritis with inflammatory cells often occupying the full thickness of the mucosa (Fox et al. 1991b).

The incidence of gastric ulceration in ferrets varies between 1.4 and 35 % (Andrews et al. 1979). Both gastric and duodenal ulcerations have been reported in ferrets infected with *H. mustelae* (Fox et al. 1986, 1990). Given the high prevalence of *H. mustelae* in adult ferrets, long-term observations of experimentally

infected pathogen-free ferrets are needed to elucidate the exact role of *H. mustelae* infection in the development of peptic ulcer disease. An increased epithelial cell proliferation has been detected in the gastric mucosa of ferrets infected with *H. mustelae*, which may play a role in the development of gastric tumors (Yu et al. 1995). Indeed, gastric adenocarcinoma has been described in the pyloric mucosa of two ferrets infected with *H. mustelae* (Fox et al. 1997). In both cases, the invasion of neoplastic tubules into the deep submucosa was described. Gastric MALT lymphoma, accompanied by destruction of the gastric glands, has also been described in the antrum of ferrets infected with *H. mustelae* (Erdman et al. 1997). For both tumor types, however, evidence remains so far circumstantial (Solnick and Schauer 2001).

H. mustelae adheres firmly to the gastric epithelium, and only a few bacteria are seen lying in the mucus (O'Rourke et al. 1992). In *H. mustelae* infected ferrets, the gastric mucosal hydrophobicity is reduced, which correlates with the degree of mucosal inflammation (Gold et al. 1996). This may promote the attachment of *H. mustelae*, which is thought to be mainly hydrophilic. *H. mustelae* binds to the same receptor lipids as *H. pylori*, in particular phosphatidylethanolamine (Gold et al. 1995). Like other gastric helicobacters, *H. mustelae* possesses a urease enzyme and flagella, consisting of a body, hook, and flagellar filament composed of FlaA and FlaB subunits. Clyne and coworkers (2000) showed that these flagella do not play a direct role in promoting adherence of *H. mustelae* to gastric epithelial cells. Double mutants of *H. mustelae* in *flaA* and *flaB* genes were shown to be completely nonmotile and unable to colonize the ferret, whereas single-gene *flaA* and *flaB* mutants have a decreased motility but are still able to colonize the ferret's stomach (Andrutis et al. 1997; Josenhans et al. 1995). An isogenic urease-negative mutant of *H. mustelae* was shown to fail to colonize the ferret stomach (Andrutis et al. 1995; Solnick et al. 1995). In addition to the standard nickel-dependent UreAB, *H. mustelae* has been shown to possess a second, nickel-independent urease (Stoof et al. 2008). Instead, this UreA2B2 is activated with ferrous ions in the absence of auxiliary proteins. This unique metalloprotein is sufficient for the bacteria to survive an acid shock in the presence of urea, and it is thought to play a role in survival of the bacteria in the stomach of carnivores, with a diet rich in iron and low in nickel (Stoof et al. 2008; Carter et al. 2011, 2012).

H. mustelae produces an array of surface rings, which seem to be unique to this *Helicobacter* species. They are composed of the *Helicobacter* surface ring (Hsr) protein, comprising approximately 25 % of the total envelope protein of *H. mustelae* (O'Toole et al. 1994). These surface rings have been shown to play a role in bacterial colonization and the pathogenesis of *H. mustelae* infection, as shown by reduced numbers of bacteria recovered from mutant-dosed ferrets (Patterson et al. 2003). Moreover, animals inoculated with the Hsr-negative strain show less inflammation compared to ferrets infected with the wild-type strain. Like other animal-associated gastric *Helicobacter* species, *H. mustelae* lacks a *cag*PAI and VacA.

10.3.6.3 Hamsters and Mice

H. aurati has been isolated from the inflamed stomachs and ceca of adult Syrian hamsters (Patterson et al. 2000a). Certain features, including the fusiform shape and the presence of periplasmic fibrils, distinguish it from other enterohepatic *Helicobacter* species detected in hamsters, such as *H. cholecystus*, *H. mesocricetorum*, and *H. cinaedi* (Solnick and Schauer 2001; Whary and Fox 2004; Ceelen et al. 2007a). Although *H. aurati* possesses urease activity, the fact that bacteria were recovered from cecal samples more often than from antral samples indicates that the preferential colonization site of *H. aurati* in hamsters is probably the intestinal tract (cecum) with subsequent spreading of this bacterial agent to the stomach in some animals, possibly due to the coprophagic behavior of hamsters (Patterson et al. 2000b). The precise role of *H. aurati* in gastric diseases in hamsters has not yet been fully elucidated, although the organism has been identified in hamsters suffering from chronic gastritis and intestinal metaplasia (Patterson et al. 2000a, b). In the stomach of these same hamsters, the authors reported the presence of another helical, urease-negative *Helicobacter* species, as well as a smaller, urease-negative *Campylobacter* species. Likewise, natural infection with different *Helicobacter* species, including *H. aurati*, was reported in a Syrian hamster with gastritis-associated adenocarcinoma (Nambiar et al. 2005). There are no indications that *H. aurati* is of zoonotic significance.

Also in mice, urease-positive helicobacters have been described in the stomach. In line with what has been described for *H. aurati* infection in Syrian hamsters, *H. muridarum* has occasionally been detected in the stomach, with or without concurrent inflammation, although these bacteria are found more frequently in the ileal and cecal mucosa of the animals (Lee et al. 1992). *H. suncus* has been isolated from the stomach of house musk shrews with chronic gastritis (Goto et al. 1998).

10.3.6.4 Rabbits

Only two reports describe the presence of *H. felis* and *H. salomonis* DNA in the stomach of rabbits. So far these bacteria have not been cultivated from rabbits, and their pathogenicity toward these animals is unknown (Haesebrouck et al. 2009; Van den Bulck et al. 2006).

10.4 Enterohepatic *Helicobacter* Species

The NHPH species described above are mainly found colonizing the stomach of their hosts. A large number of *Helicobacter* species, however, prefer to settle in the lower intestinal tract or the liver of a wide variety of mammalian, reptilian, avian, or amphibian host species as well as humans (Schrenzel et al. 2010; Hansen et al. 2011).

Several enterohepatic *Helicobacter* species are found in rodents with or without signs of intestinal or hepatic disease, including *H. bilis*, *H. hepaticus*, *H. cholecystus*, *H. muridarum*, *H. mastomyrinus*, *H. typhlonius*, *H. rodentium*, *H. mesocricetorum*, *H. magdeburgensis*, *H. aurati*, *H. cinaedi*, *H. ganmani*, *H. trogontum*, and *H. muricola* (Lee et al. 1992; Fox et al. 1994, 1995; Patterson et al. 2000a; Vandamme et al. 2000; Robertson et al. 2001; Solnick and Schauer 2001; Won et al. 2002; Shen et al. 2005; Traverso et al. 2010). Several models of experimental enterohepatic *Helicobacter* infection, including *H. hepaticus* infection in immunodeficient IL-10$^{-/-}$ knockout mice, are used to model the development of colitis/inflammatory bowel disease in humans (Solnick and Schauer 2001; Hansen et al. 2011).

H. canis has been detected in or isolated from healthy dogs and cats as well as dogs suffering from endemic diarrhea or necrotic hepatitis (Solnick and Schauer 2001; Shen et al. 2001). Several other enterohepatic *Helicobacter* species have been demonstrated in dogs and cats, including *H. bilis*, *H. cinaedi*, '*Candidatus* H. colifelis', *H. marmotae*, and *H. fennelliae* (Solnick and Schauer, 2001; Fox et al. 2002; Misawa et al. 2002; Hänninen et al. 2005; Rossi et al. 2008; Otte et al. 2012; Castiglioni et al. 2012). The pathogenic significance of these microorganisms for dogs and cats remains uncertain.

H. equorum has been isolated from the feces of healthy horses (Moyaert et al. 2007a, b). The prevalence of this microorganism in different adult horse populations varies between 0.8 % and 7.9 % but is much higher (66 %) in 1- to 6-month-old foals (Moyaert et al. 2009). Experimental infections revealed that this microorganism colonizes the cecum, colon, and rectum of adult horses without causing apparent pathological changes (Moyaert et al. 2007c).

Several *Helicobacter* spp., including *H. trogontum*, *H. bilis*, and *H. canis*, have been identified or isolated from sheep, and infection with the first two species has been associated with abortion and the presence of hepatic necrosis in aborted lambs (Dewhirst et al. 2000; Solnick and Schauer 2001; Hänninen et al. 2003, 2005; Swennes et al. 2014). Enterohepatic *Helicobacter* species have not been described in other ruminants, including cattle and goats.

H. pamatensis (Seymour et al. 1994), *H. trogontum* (Hänninen et al. 2003), *H. bilis* (Hänninen et al. 2005), and atypical *H. canadensis* strains (Inglis et al. 2006) have been isolated from the gastrointestinal tract or feces of pigs, but their pathogenic significance for this animal host is not known.

H. pullorum has been isolated from the ceca and feces of apparently healthy chickens, as well as from laying hens with vibrionic hepatitis (Stanley et al. 1994). In two in vivo studies, experimentally infected chickens remained clinically healthy although mild lesions were observed in the ceca (Neubauer and Hess 2006; Ceelen et al. 2007b). *H. pullorum* or its DNA have also been detected in other bird species, including turkeys (Zanoni et al. 2011) and a parakeet suffering from diarrhea (Ceelen et al. 2006b). Other *Helicobacter* species detected in birds include *H. canadensis*, which has mainly been associated with geese but also with chickens, guinea fowl, and pheasants (Fox et al. 2000; Nebbia et al. 2007; Robino et al. 2010). *H. anseris* and *H. brantae* have been isolated from the feces of resident Canada

geese (Fox et al. 2006), and still now, new species are being discovered, including *H. valdiviensis*, isolated from wild bird fecal samples (Collado et al. 2014).

Also in monkeys, enterohepatic helicobacters have been detected, including *H. callitrichis* in common marmosets, *H. cinaedi* and *H. macacae* in rhesus macaques and baboons, and several enterohepatic *Helicobacter* spp. in gorillas and chimpanzees (Fernandez et al. 2002; García et al. 2006; Fox et al. 2007; Won et al. 2007; Flahou et al. 2014). It has been suggested that infection with *H. macacae* plays a role in the development of chronic idiopathic colitis and intestinal adenocarcinoma in rhesus macaques (Lertpiriyapong et al. 2014).

Several enterohepatic *Helicobacter* species have been associated with disease in humans. These reports include associations between *H. canis*/*H. winghamensis* and gastroenteritis; *H. hepaticus* and cholecystitis, liver carcinogenesis, or chronic pancreatitis; *H. bilis* and chronic cholecystitis, biliary duct, and gallbladder cancer; *H. ganmani* and liver disorders; *H. pullorum* and enteritis or diarrhea; *H. canadensis* and enteritis; and *H. cinaedi*/*H. fennelliae* and chronic diarrhea, enteritis, proctitis, or proctocolitis in homosexual men (Totten et al. 1985; Stanley et al. 1994; Steinbrueckner et al. 1997; Fox et al. 2000; Melito et al. 2001; Solnick and Schauer 2001; Matsukura et al. 2002; Murata et al. 2004; Tolia et al. 2004; Kobayashi et al. 2005; Apostolov et al. 2005; Nilsson et al. 2006; Zhang et al. 2006; Hamada et al., 2009). Enterohepatic *Helicobacter* species have also been associated with the various forms of inflammatory bowel disease (Hansen et al. 2011), and several species, including *H. cinaedi*, *H. fennelliae*, *H. canadensis*, *H. canis*, *H. westmaedii*, and *H. rappini*, have been isolated from (immunosuppressed) patients with bacteremia (Solnick and Schauer 2001; Tee et al. 2001, Matsumoto et al. 2007; Prag et al. 2007; Abidi et al. 2013; Rimbara et al. 2013).

Most enterohepatic *Helicobacter* species do not contain an urease enzyme, although there are exceptions, including *H. hepaticus* and *H. bilis*. A large number of enterohepatic *Helicobacter* species contain a bacterial toxin called the cytolethal distending toxin (CDT). The toxic effects of this major virulence factor involve cellular distension, actin cytoskeleton remodeling, G2/M cell cycle arrest, and cytolethality (Ceelen et al. 2006a; Varon et al. 2014). CDT is typically composed of three subunits: CdtA, CdtB, and CdtC, which are all required for a maximal cytotoxic activity (Liyanage et al. 2013; Varon et al. 2014). Other factors involved in host-bacteria interactions include a type VI secretion system, which is expressed by several enterohepatic helicobacters, including *H. hepaticus*, *H. pullorum*, *H. cinaedi*, and *H. trogontum* (Chow and Mazmanian 2010; Goto et al. 2012; Kaakoush et al. 2013; Sirianni et al. 2013).

10.5 Conclusions and Outlook

There are clear indications that gastric NHPH species can cause disease in humans. Some distinct features, such as the association with gastric MALT lymphoma, indicate that these zoonotic bacteria should not just be considered as a “light”

version of *H. pylori*. There are clear indications that domestic animals constitute reservoir hosts for these gastric *Helicobacter* species with zoonotic potential. A correct diagnosis to the species level remains sometimes problematic. Therefore, diagnostic methods enabling the correct identification of these bacteria are needed to help clarify the epidemiology and pathology of these infections in humans. The successful in vitro isolation of several of these species has opened new perspectives for understanding the pathogenesis of non-*H. pylori Helicobacter* associated gastric pathology in their natural hosts as well as humans. An increased knowledge may in the end contribute to the development of new treatment and prevention measures.

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