

Chapter 8

Gastric Non-*Helicobacter pylori* *Helicobacter*: Its Significance in Human Gastric Diseases

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Abstract In the post-*H. pylori* eradication era, the clinical significance of gastric non-*H. pylori* helicobacters (NHPH; also referred to as *H. heilmannii*-like organisms and *H. heilmannii sensu lato*) is gradually increasing. This group of bacteria may inhabit the stomach of domestic and wild animals including cats, dogs, pigs, primates, rodents, cheetahs, and rabbits. NHPH are zoonotic microorganisms, meaning that they may transmit between animals and humans. They may be distinguished from *H. pylori* regarding their microbiology involving larger cells with more distinct spiral shape and bipolarity, localization in the stomach layer and regional distribution, urease activity and virulence factors, and relation to gastric diseases where gastric NHPH infection is often associated with milder gastritis than *H. pylori* but higher risk of gastric MALT lymphoma. At present, pure culture of NHPH species remains a challenge, but the full genome sequences of some of the species have been reported. Recent and ongoing prevalence studies indicate a higher clinical relevance of these bacteria than earlier impressions suggested. Current efforts in improving cultivation and detection methodology are contributing to an increased understanding of their microbiology, prevalence, and relevance to human diseases.

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8.1 Introduction

Recently, many spiral bacteria belonging to the *Helicobacter* genus other than *H. pylori* have been described in many tissues, organs, and animals. They are generally longer than *H. pylori* with a size ranging from 4 to 10 μm, spiral shaped, highly motile with three to eight coils, up to 14 uni- or bipolar flagellae, and no periplasmic filaments [1]. These bacteria also differ from *H. pylori* when considering traits such as zoonosis, distribution/sublocations in the stomach, relation to gastric diseases, urease activity, and response to antibiotics. To date, 35 species belonging to the *Helicobacter* genus have been identified (Fig. 8.1) that may be divided into gastric helicobacters and enterohepatic helicobacters. In this chapter, we would like to focus on the gastric helicobacters and further aim at the gastric helicobacters other than *H. pylori*, the so-called non-*H. pylori* helicobacters (NHPH), and discuss these bacteria regarding their microbiology, pathogenesis, and significance for human health.

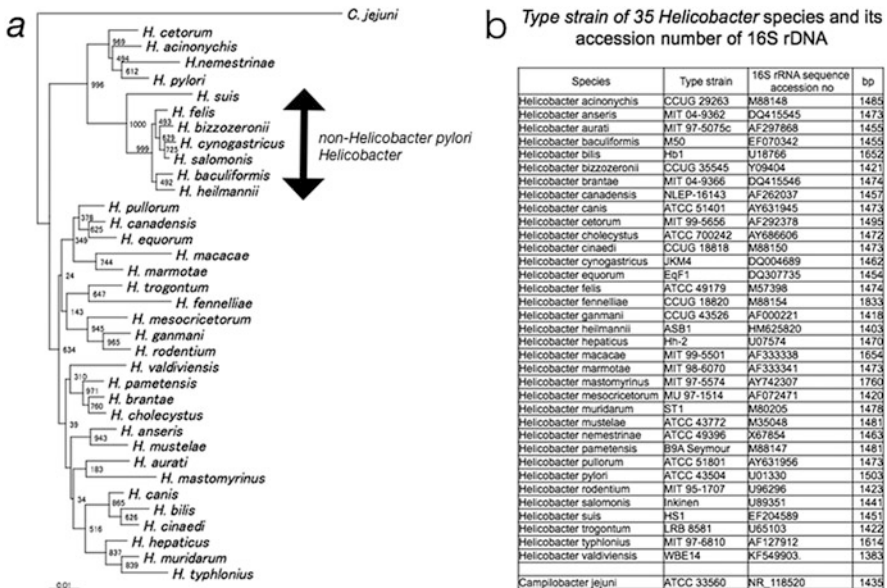


Fig. 8.1 Phylogenetic tree of 35 *Helicobacter* species (a) and type strains (b)

8.2 History

At first, we would like to introduce the reader to the somewhat complicated story of NHPH and nomenclature as this has been subject to some confusion in discussions and in published papers. In fact, the first discovery of spiral-shaped microorganism in the stomach from an animal dates back to 1881, a study conducted by Rappin using light microscopy [2]. Bizzozero and Salomon also showed similar studies [3, 4], and in 1906 the German scientist Krienitz reported spiral-shaped microorganisms in the human stomach [5]. In 1919, Kasai and Kobayashi were the first to achieve an interventional study by using salvarsan, an arsene compound, to treat infection [6]. In 1962, Weber et al. found spiral-shaped bacteria in the gastric mucosa of cats and dogs by using electron microscopy [7]. As 1984 will be remembered for the paramount discovery of gastric *H. pylori* by Warren and Marshall [8], 3 years later was marked by a German report by Heilmann who detected gastric spiral bacteria in 39 patients (0.25 %) with upper gastrointestinal symptoms. The report was later published in an English journal [9]. Among the patients examined 34 patients had chronic active gastritis and 4 had chronic gastritis, and they were all treated with the bismuth treatment. Following this report, Dent and McNulty found spiral-shaped bacteria in 6 human cases and further reported that they were incapable of cultivating these bacteria in vitro [10, 11]. They designated these spiral-shaped bacteria *Gastrospirillum hominis*. In 1988, they proposed that these spiral-shaped bacteria could transmit from cat to human [12]. Three years later, Ito and Takahashi found urease-positive gastric bacteria in a cynomolgus monkey [13], a strain that would turn out to be used for later experimentation [14]. In 1993, Solnick et al. analyzed the 16S rRNA of this bacterium and discovered that this bacterium was phylogenetically close to *H. felis* [15]. *Gastrospirillum hominis* was from that point renamed to *H. heilmannii*. Further phylogenetic analyses revealed that *H. heilmannii* did not only encompass one species, but rather a group of bacteria. Further renaming resulted in *H. heilmannii* type 1 and 2, of which type 1 was identical to the type found in pigs also called *H. suis* [16]. Type 2 represents a group of bacteria which includes, for instance, *H. felis*, *H. bizzozeronii*, and *Candidatus H. heilmannii*. Challenges in in vitro cultivation have hampered identification and phylogenetic analyses of these bacteria, but recent efforts have resolved many of the species that belong to the *Helicobacter* genus. In order to avoid further confusion, Haesebrouck proposed to use the terms *H. heilmannii* sensu stricto and sensu lato [17, 18]. Another commonly applied term is *H. heilmannii*-like organisms (HHLO), which may be further subdivided into types 1, 2, and 4 [19]. More recently, the term non-*H. pylori* helicobacters (NHPH) has been applied as it covers all “the other” helicobacters than *H. pylori* without manifesting to one such species of historical reason [20]. The term is per definition the same as *H. heilmannii* s.l. and will be used throughout this chapter.

8.3 Characteristics of NHPH

8.3.1 Zoonosis

Unlike *H. pylori*, NHPH show a zoonotic infection pattern. Reported animal hosts for gastric NHPH include dogs, cats, primates, pigs, cheetahs, rodents, and rabbits [21]. Stolte et al. conducted a study in which the relationship between infection in humans and contact with domestic animals was made. In NHPH-positive cases, 70 % of the patients had a history of contact with pet animals, while in the general population, 37 % has a history of contact with pet animals [22]. In addition, the rate of coinfection with NHPH and *H. pylori* was found to be very low, suggesting that NHPH infection might conflict with and somehow prevent an *H. pylori* infection (although opposing reports do exist as mentioned later in this chapter). Another report demonstrated the transmission of NHPH from a cat to a veterinarian who was treating the cat [23]. The relationship between pet keeping and risk of infection for NHPH has also been demonstrated in a prevalence study conducted in Korea by Chung and colleagues [24]. Although transmission from animals to humans is a commonly accepted concept, studies that raise important questions also exist. For example, Priestnall et al. have reported that the NHPH most transmitted to human is HHLO type 1, or *H. suis*, which is a pig-specific species of NHPH. The type of NHPH predominant in cats and dogs are presumably HHLO type 2 and 4, suggesting that pet keeping is not necessarily the main transmission route of NHPH from animal to human [18]. A prevalence study conducted in China of more than 1500 patients all positive for *H. pylori* showed that of those who were coinfecting with NHPH, about half was infected with *H. suis* [25]. An ongoing prevalence study in Japan by Øverby and Nakamura of gastric disease patients negative for *H. pylori* also suggests the pig-specific species *H. suis* to be the predominant type found in humans. Considering the number of people who are in contact with pet animals compared to the number of people who are in contact with live pigs, it is likely that there is a missing piece to this controversial puzzle of how humans are infected with NHPH. Flahou and Haesebrouck have shown that NHPH may be detected in minced meat from pork from the supermarket, suggesting that transmission through diet may also be a possibility [26].

8.3.2 Distribution in the Stomach

As for the localization in the gastric mucosa, it has been reported that the majority of the bacteria inhabit the mucus layer like *H. pylori* but that they also may reside in the fundic glandular tissue as shown, which is clearly detected in our histochemical observation in Fig. 8.2 [27]. A more precise pathological observation revealed that most of the cells residing in the fundic gland were actually in the intracellular canaliculi in the parietal cells [28]. However, by using electron microscopy, some

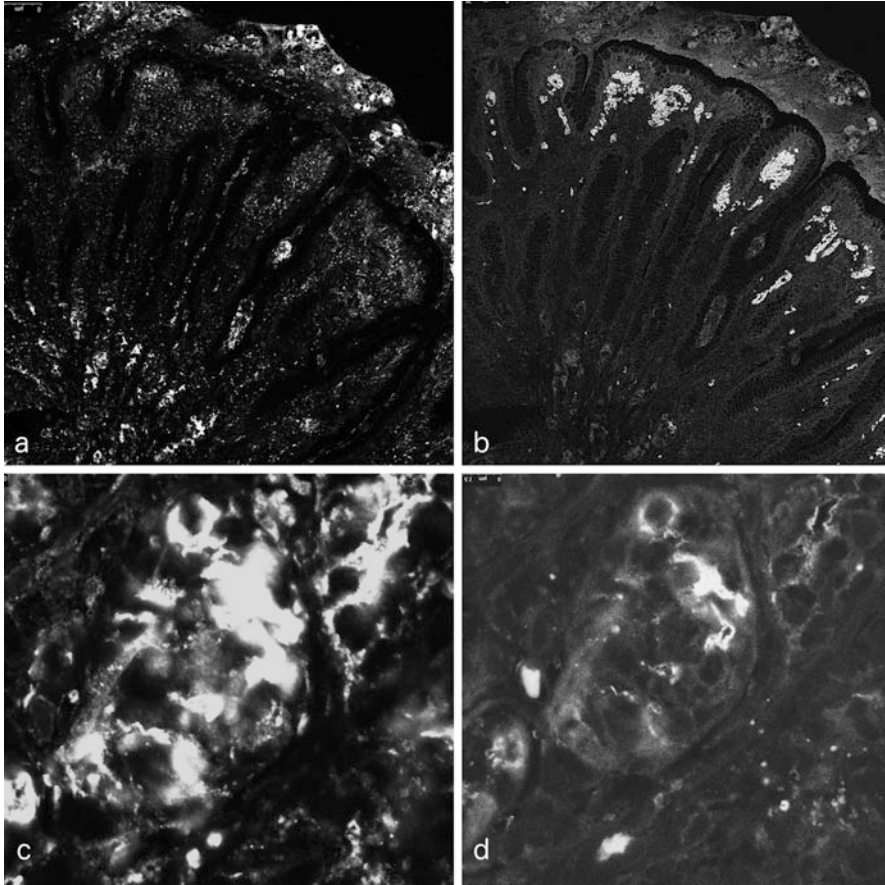


Fig. 8.2 Immunohistochemical observation of *Helicobacter suis* in the human fundic mucosa. (a, b) *Helicobacter suis* are localized in the base of the fundic mucosa as well as in the mucus layer above the surface epithelial cells. (c, d) In the base of the fundic glands, *Helicobacter suis* are localized mainly in the actin-rich parietal cells. (a, c) Stained with *Helicobacter* antibody to the *Helicobacter suis*-positive human gastric mucosa. (b, d) stained with FITC-phalloidin showing the actin-rich erythrocytes in the tip portion and parietal cells in the base of the fundic mucosa. (a, b) x200, (c, d) x800

of the bacteria were found to be localized in the lamina propria mucosae as well as in the intracellular canaliculus. This resulted in the adjacent parietal cells to become apoptotic suggesting a relation to gastric MALT lymphoma formation [23].

8.3.3 Prevalence of NHPH

Up until 2001, O'Rourke performed meta-analysis of 500 NHPH-positive cases [29–31], and she found that the infection rate is very diverse. In Western countries, the prevalence of NHPH in the general population was less than 0.5 %, while in East Europe and Asia, it varied from 1.2 % to 6.2 %. In a prevalence study conducted in China mentioned above with *H. pylori*-positive patients with symptoms of a gastric disease, close to 12 % was shown to coinhabit an NHPH infection [32]. In an ongoing study in Japan based on patients with a gastric disease but negative for *H. pylori*, more than half appear to be infected with NHPH (Øverby and Nakamura, unpublished data).

8.3.4 NHPH and Human Diseases

Stolte et al. compared the disease formation by *H. pylori* and NHPH and found that NHPH induced a milder gastritis than *H. pylori* but that NHPH was a stronger inducer of gastric MALT lymphoma than *H. pylori* [33, 34]. They used histochemistry, specific immunoabsorbent method, and PCR analysis using 16S rDNA, and five MALT lymphoma cases were *H. pylori* negative and NHPH positive. From the survey of the patients from 1988 to 1998, 1745 out of 263, 680 cases were *H. pylori* positive (0.66 %), while 8 out of 543 cases were NHPH positive (1.47 %) and confirmed the stronger relation of NHPH to the gastric MALT lymphoma formation. Okiyama et al. found 15 NHPH-positive cases out of 4074 serial cases, among these 11 patients constituted chronic gastritis cases, and 4 patients were diagnosed with gastric MALT lymphoma [35]. The relationship between NHPH infection and gastric cancer is still a controversial topic. Foschini et al. have reported that all NHPH-positive cases had gastritis, and 1 gastric cancer case was coinfecting with NHPH and *H. pylori* [36]. The relation to the gastric dysplasia to NHPH infection was suggested in cases in Thailand [31]. Sasaki has recently reported a patient case positive for NHPH infection and with nodular gastritis, which is thought to be one of the precancerous lesions of the gastric cancer [37].

8.3.5 Diagnosis, Culture, and Genome Sequence Studies

Detection of NHPH may be performed with different approaches. However, PCR analysis of the 16S rDNA is the most reliable method but is also time-consuming. The pathological identification of gastric spiral bacteria may sometimes be inaccurate, as under certain conditions *H. pylori*, for instance, may display a different morphology than typically seen including a longer shape [38]. At present, serum serological test and fecal bacterial detection tests are not available for NHPH,

somewhat limiting the detection methodology in patients. Difficulties in cultivation NHPH have hampered the identification of these microorganisms. Lee et al. reported culture of a spiral bacterium isolated from the antrum area of the stomach from a cat [39]. In 1996, Andersen et al. reported a presumably successful cultivation of *H. heilmannii* (s. s.) but later turned out to be identified as *H. bizzozeronii* [40, 41]. As a new diagnostic method, Trebesius et al. used fluorescent in situ hybridization of the 16S rDNA and reported five species of NHPH from human cases, most of which coincided with *H. suis* [42]. In 2003, Chisholm et al. invented a novel PCR method for NHPH detection from biopsy specimen and found 2.3 % positive cases from dyspeptic cases in New England, which was quite higher compared with their former report highlighting the importance of appropriate detection methodology [43]. In 2004, O'Rourke et al. analyzed 26 human and animal samples positive for NHPH infection and showed that 15 (28 %) of these were very infected with *H. suis*. The rest were identified as *H. felis*, *H. bizzozeronii*, *H. salomonis*, and *Candidatus H. heilmannii* [44]. In 2008, Baele et al. reported the first pure culture of *H. suis* isolated from pig stomach [45]. In 2011, the whole genome sequences of *H. suis* and *H. felis* were reported [46, 47]. When compared with *H. pylori*, the genome sequence of *H. suis* was shown to lack *cagA* but did contain *hpaA* and *horH*; *comB*, related to type IV secretory system and similar genes to *H. pylori* neutrophil-activating protein; γ -glutamyl transpeptidase (GGT); and flavodoxin vacuolating cytotoxin A gene. In *H. felis*, the genome sequence was shown to lack *cagPAI* and *vacA* but contain *comB*, GGT-encoding gene, immunomodulator (*napA*), collagenase and secretory serine protease *htrA*, and several chemotaxis sensors and restriction/modification system [48]. The sequence of *H. bizzozeronii* isolated from a gastritis patient [49] and the sequence of *H. heilmannii* isolated from cat [50] were subsequently reported.

8.4 Conclusion

Infection with the zoonotic NHPH is becoming an increasing issue in the clinic and eventually in the general population. Recent studies have shown NHPH to be linked to human gastric diseases especially gastric MALT lymphoma, require up-to-date sensitive methodology in order to be detected, and be more prevalent than what was previously thought. In the post-*H. pylori* eradication era, gastric infection with NHPH is likely to become a significant burden and should be subject to further investigation in order to resolve its issues linked with gastric MALT lymphoma and gastric cancer.

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