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Review Article

Review on Helicobacter Species Infections in Domestic Animals and Non-Human Primates and Their Significance for Human Health

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Abstract

It was first reported in 1984 that gastric ulcer disease in humans is caused by a bacterial. The causative agent, Helicobacter pylori, has also been associated with gastritis, peptic ulcer disease, gastric adenocarcinoma, and mucosa associated lymphoid tissue (MALT) lymphoma. This bacterium is very successful in the way that it colonizes the human stomach, since in developing countries, more than 80% of the population is infected with H. pylori, even at young age. In developed countries, the prevalence of H. pylori generally remains under 40% and is considerably lower in children and adolescents than in adults and elderly people. Current information about Helicobacter infections in humans and various domestic, wild, and research animal species that have been used or have the potential to be used as animal models of human disease is presented. The Helicobacter genus now includes at least 26 formally named species, with additional novel species in the process of being characterized. The natural history, host range with zoonosis potential, pathology, and diagnostic techniques are presented, along with examples of how Helicobacter infection has interfered with unrelated in vivo research. There are various techniques employed to detect H. pylori from specimens. These tests may be invasive or non-invasive. Endoscopy and gastric mucosal biopsy, microscopic examination of histological sections, PCR and rapid urease test are forms of invasive test that could be used. Non-invasive tests such as Urea Breath Test (UBT) make use of the ability of the organism to produce urease; enzyme linked immunosorbent Assay (ELISA), H. pylori stool antigen test, and latex agglutination tests are important non-invasive serological approaches employed to detect the presence of antibody or antigen from a specimen. Current recommendations for deriving and managing helicobacter-free animal colonies for research are provided., although it has become an increasingly treatable disease, there is still continuous ongoing research in the field of treatment for resistance and pharma compliance. Furthermore, in this field, probiotic therapy is considered a valid adjuvant.

INTRODUCTION

Background (Brief history of helicobacter disease, origin and date of emergence)

Helicobacter spp. are spiral-shaped mobile Gram-negative bacteria with tropism for the gastric mucosa of humans and animals [1]. *Helicobacter pylori (H. pylori)* was the first species isolated from the Helicobacter genus by Australian researchers [2]. Further research has shown that humans are the natural host of *H. pylori* and have established this species as the primary aetiology of peptic ulcers and gastric neoplasms [3].

It is new spiral bacteria were later classified by [4] as *Helicobacter heilmannii*. However, phylogenetic studies were later employed utilizing the 16 rRNA target gene, and these studies found instead that this bacterium belonged to a range of several *Helicobacter* species isolated from domestic and wild animals, such as *H. felis*, *H. bizzozeronii*, *H. salomonis*, *Helicobacter heilmannii sensu stricto* (*H. heilmannii s.s.*), *H. b´ilis*, *H. cynogastricus*, and *H. baculiformis* [5]. Therefore, in order to organize this large group of bacteria into a single term they were consensually denominated as *non-Helicobacter pylori Helicobacter* (NHPH) [6].

NHPH are the target of various studies due to their relationship with upper digestive tract illnesses in humans and their zoonotic importance [7]. Dogs are the natural hosts of NHPH and harbor these bacteria in their gastric mucosa, gut, and oral cavity; thus, gastric juice, saliva, and faeces are possible sources of transmission for these bacteria to infect humans [8,9]. In dogs, the main species of NHPH found are *H. heilmannii s.s*, *H. bizzozeronii*, *H. salomonis*, *H. felis*, and *H. canis* [8,9]. Chronic inflammation of the gastric mucosal tissue, peptic ulcers, and gastric mucosa

associated lymphoid tissue lymphoma are the clinical alterations described in humans with NHPH infection [10,11]. In human populations, NHPH has a prevalence of 0.5% in developed countries [12]. And 6.2%-15% in underdeveloped countries [13]. Thus, countries with lower socioeconomic development tend to have a higher prevalence of infected people with NHPH [14]. However, information regarding the importance of domestic dogs as reservoirs for these bacteria and the data related to the number of NHPH occurrences in the canine population of these countries has not yet been explicate [15].

Helicobacter pylori (*H. pylori*) infects approximately 50% of the human population worldwide and the infection could reach more than 70% in developing countries [16,17]. The consequences of infection have been associated with the development of different gastro-intestinal diseases, such as gastric ulcers, gastric cancer, mucosa-associated lymphoid tissue (MALT) lymphoma and biliary tract cancer [18]. Moreover, *H. pylori* infection has also been associated with extra gastric diseases, such us ischemic heart diseases [13] type 2 diabetes mellitus anemia [19], adverse metabolic traits in obese subjects [20] and insulin resistance [21] to mention but a few. Despite the existence of such associations, these diseases occur only in a small percentage of infected people, suggesting that the bacteria frequently persist in the human host without inducing any obvious signs of disease, and it has been suggested that *H. pylori* may also play a beneficial role in human health [22,23]. Indeed, recent studies indicate that the decreasing incidence of *H. pylori* in the developing world is paralleled by an increase in the incidence of allergies and autoimmune diseases [24].

However, despite the fact that about half the world's population carries *H. pylori*, only a small proportion develop ulcers or gastric cancer. This raises a number of questions, including how have H. pylori adapted to persistently colonize humans? And why (and how) does it cause disease in only a minority of those colonized? The other side of this coin is that although humans have been colonized for millennia by *H. pylori*, it is now disappearing [25,26]. Common differential diagnostics of chronic vomiting, such as drugs toxicity, foreign bodies, hepatic failure, or renal disease, were discarded by history, physical examination, complete blood count, serum biochemistry profile (keratinize, blood urea nitrogen, alkaline phosphatase, and albumin and alanine amino transaminase) and ultrasonography and/or radiography previous to procedure and by upper digestive endoscopy on the moment of study (Table 1).

The gastric mucosa of 75% of cheetahs above in table and 68% of free-ranging lynx to be colonized with "pet carnivore-associated" helicobacters. Those studies do not allow differentiation between H. felis, H. bizzozeronii, H. salomonis, H. baculiformis, H. cynogastricus, and Candidatus Helicobacter.

LITERATURE REVIEW

Etiology

***Helicobacter pylori*:** Infection with *H. pylori* occurs worldwide, but the prevalence varies greatly among countries and among population groups within the same country (Feldman RA). The overall prevalence of *H. pylori* infection is strongly correlated with socioeconomic conditions. (Malaty HM, Graham DY). The prevalence among middle-aged adults is over 80 percent in many developing countries, as compared with 20 to 50 percent in industrialized countries. The infection is acquired by oral ingestion of the bacterium and is mainly transmitted within families in early childhood, (Feldman RA, Rowland M, Kumar D, Daly L, O'Connor P, Vaughan D, Drumm B). It seems likely that in industrialized countries direct transmission from person to person by vomitus, Saliva, or feces predominates; additional transmission routes, such as water, may be important in developing countries [27,28].

There is currently no evidence for zoonotic transmission, although *H. pylori* is found in some nonhuman primates and occasionally in other animals [29,30]. *H. pylori* infection in adults is usually chronic and will not heal without specific therapy; on the other hand, spontaneous elimination of the bacterium in childhood is probably relatively common, [31] aided by the administration of antibiotics for other reasons. In industrialized countries, the rate of acquisition of *H. pylori* has decreased substantially over recent decades. Therefore, the continuous increase in the prevalence of *H. pylori* with age is due mostly to a cohort effect, reflecting more intense transmission at the time when members of earlier birth cohorts were children [25]. Mathematical modeling of prevalence trends in the United States has indicated that markedly improved Sanitation in the second half of the 19th century greatly reduced *H. pylori* transmission, initiating a decline in *H. pylori* infection that will ultimately lead to its elimination from the U.S. However, without intervention, *H. pylori* are predicted to remain endemic in the United States for at least another century [32]. The prevalence in humans is approximately 0.5 percent. *H. heilmannii* causes only mild gastritis in most cases, but it has been found in association with mucosa-associated lymphoid- tissue (MALT) lymphoma [33].

Pathogenesis

The gastric mucosa is well protected against bacterial infections. *H. pylori* is highly adapted to this ecologic niche, with a unique array of features that permit entry into the mucus, swimming and spatial orientation in the mucus, attachment to epithelial cells, evasion of the immune response, and, as a result, persistent colonization and transmission. The *H. pylori* genome (1.65 million bp) codes for about 1500 proteins [34]. Among the most remarkable findings of two *H. pylori* genome-sequencing projects were the discovery of a large family of 32 related outer membrane proteins (Hop proteins) that includes most known *H. pylori* adhesins and the discovery of many genes that can be switched on and off by slipped strand mispairing-mediated mutagenesis. Proteins encoded by such phase-variable genes include enzymes that modify the antigenic structure of surface molecules, control the entry of foreign DNA into the bacteria, and influence bacterial motility. The genome of *H. pylori* changes

Helicobacter species	Natural host (prevalence, %)	Associated with gastric disease in humans	Reference(s)
H. suis	Pig (60–80 in slaughter pigs), macaque (NA[b]), mandrill monkey (NA)	Yes	14, 42, 45, 167, 227, 230
H. felis	Dog (47), cat (63), rabbit (2–9), cheetah (NA[c])	Yes	45, 134, 166, 227, 230, 231, 234
H. bizzozeronii	Dog (70), cat (35)	Yes	45, 92, 227, 230
H. salomonis	Dog (9), cat (2), rabbit (0–4)	Yes	45, 115, 227, 230
"*Candidatus* Helicobacter heilmannii"	Dog (20–100), cat (20–100), wild felidae (NA[c]), nonhuman primates (66)	Yes	166, 227, 230
H. baculiformis	Cat (NA)	No	15
H. cynogastricus	Dog (NA)	No	233
"*Candidatus* Helicobacter bovis"	Cattle (NA)	Yes	44, 45
H. mustelae	Ferret (0–100)	No	66, 67, 68, 69, 70, 71, 85
H. auratii	Syrian hamster (50–100)	No	177
H. nemestrinae[a]	Macaque (NA)	No	24
H. acinonychis	Cheetah (low), tiger (NA)	No	60, 224
H. cetorum	Whales (NA), dolphins (NA)	No	97
H. muridarum	Mice (0–62)	No	86, 136, 183

Table 1 *Helicobacter* species naturally colonizing the stomachs of animals and their pathogenic significance for humans Source: [72].

continuously during chronic colonization of an individual host by importing small pieces of foreign DNA from other *H. pylori* strains during persistent or transient mixed infections [35,36].

Clinical Manifestations

It is well known that gastric mucosa is the main target of *H. pylori*, which colonizes and damages surface epithelium and induces a chronic inflammatory response in the lamina propria. Gland atrophy and intestinal metaplasia are among the long-term consequences of this process. In some cases, this organism elicits antibodies cross-reacting with epithelial components of the gastric mucosa, peri glandular T-cell infiltrates, and increased glandular cell apoptosis, which may cause diffuse corpus-fundus restricted, atrophic gastritis of autoimmune type [37]. Among the clinical consequences of this *H. pylori*-initiated autoimmune process are achlorhydria with secondary hypergastrinemia, with or without pernicious anemia, and increased risk for gastric enterochromaffin-like cell carcinoids and cancer [37]. Acute infection with *H. pylori* may cause a transient clinical illness, characterized by nausea and abdominal pain that may last for several days. After these symptoms resolve, the majority of people progress to chronic infection. However, there is no recognizable symptom complex or syndrome that can be ascribed to chronic gastritis, whether or not due to *H. pylori*. Peptic ulcers often present with dyspepsia. There may be pain at night; some patients report relief of pain with food or antacids and a recurrence of pain in two to four hours [38].

Once a person is infected, it can persist in the stomach for decades despite a systemic immune response. The reasons for the failure of the immune system to control infection may be attributed to the fact that *H. pylori* produces chemical components in their cell walls that are very much like molecules made by the stomach cells of the host. This creates a problem for the immune system, because it is designed to ignore molecules made by the host (self) and to recognize molecules produced by infectious agents (non-self). Once the immune system recognizes foreign molecules, it directs a vigorous attack that ordinarily destroys the foreign cells. To a certain extent, this mimicry disguises *Helicobacter* from the immune system so that the immune response is attenuated. This is thought as a probable reason why most people infected with *H. pylori* can't get rid of it, but instead remain infected for life unless they are treated with antibiotics. Respective immunological studies of systemic and local T- and B-cell responses in patients chronically infected with *H. pylori* have shown that the numbers of CD4+ and CD8+ T cells are increased in the gastric mucosa of patients with gastritis and that T cells isolated from the antrum region are able to produce gamma interferon [39,40]. Studies have revealed that infection by more virulent *cagA* positive strain is significantly associated with ischemic heart disease. These findings strongly suggest that the association between *H. pylori* and ischemic heart disease is related to the virulence of this bacterium [41].

Disease in Animals

Natural *Helicobacter* Infections in Cattle: *Helicobacter bovis'* is the proposed name for a helicobacter detected in the abomasum of cattle in Europe [42]. Although culture of *'H. bovis'* has not been successful, helicobacter-like organisms were detected in and biochemical and immunohistochemical methods. Bacterial 16S rDNA was abomasal biopsy specimens from adult cattle by use of electron microscopy amplified by use of PCR analysis and was sequenced. Phylogenetic analysis placed the organism, corresponding to the reference sequence R2XA, within the genus *Helicobacter*. A diagnostic PCR assay was designed that differentiated all of the bovine 16S rDNA sequences from *Helicobacter* and *Wolinella* species. *Helicobacter bilis* appears to be the most related species, but sequence similarity is low (92.8%), indicating that *'H. bovis'* is a novel *Helicobacter* species. In a separate survey of slaughter cattle, *'H. bovis'* was detected in 85% of the animals [43]. In the same survey, the abomasum of goats was tested and the results indicated failure to detect *Helicobacter* infection.

Gastric Non h. Pylori helicobacter nomenclature: the Need for clarification

Since the description of *H. pylori*, the number of species in the

genus *Helicobacter* has rapidly expanded. Today, a large number of non-*H. Pylori Helicobacter* species in a wide variety of animals and humans have been described, and the genus *Helicobacter* contains at least 32 species with validly published names (Table 2).

Gastric helicobacters in domestic animals' gastric helicobacters in domestic animals and nonhuman primates: an overview

A summary of gastric lesions described in domestic animals and nonhuman primates naturally or experimentally infected with helicobacters is presented in Table 3. Below, infections with gastric helicobacters in pigs, dogs, cats, rabbits, ferrets,

Hamsters, ruminants, horses, and nonhuman primates are considered. Guinea pigs and Mongolian gerbils are also often kept as pets, but natural infections with gastric helicobacters have not been described in these animal species.

Gastric Helicobacters Associated with Pigs: The main *Helicobacter* species colonizing the stomachs of pigs is *H. suis*. Its prevalence at slaughter age in most reports is 60% or more. *H. suis* causes gastritis in experimentally and naturally infected pigs. It has also been associated with ulcers of the no glandular part of the stomach [44] although the exact role of *H. suis* in porcine gastric pathology remains to be elucidated. Indeed [45], did not find this association (Table 3).

Gastric Helicobacters in Domestic Animals and Primates (Figure 1).

Transmission and Prevalence in Africa

H. pylori, the principal species of the genus *Helicobacter*, are a common human pathogen, which is responsible for a variety of gastroduodenal pathologies in the developing world. Infections have been reported to be higher in the developing countries, especially in Africa. Epidemiologic studies have addressed a variety of factors such as bacterial host, genetic and environmental factors to determine the causative links to *H. pylori* infection, but knowledge of reservoirs and transmission still remains elusive [46-48]. There appears to be a [47]. There appears to be a substantial reservoir of the organism aside from the human stomach. Other animals, e.g., cats, harbor organisms that resemble *H. pylori* [49] but under particular circumstance [1]. Thus, the major question of transmission is how *H. pylori* is transmitted from the stomach of one person to that of another. The first and least common is Iatrogenic, in which tubes, endoscopes or specimens in contact with the gastric mucosa from one person are introduced to another person [50]. Improved disinfection of endoscopes has reduced the incidence of transmission [51]. Interestingly, endoscopists, especially those who do not wear gloves during procedures, are at risk of becoming infected [33]. Occupationally acquired infections also have been reported [52].

Faecal-oral transmission is perhaps the most important. Although *H. pylori* has been isolated from the faeces of young children infected with the organism [46], faecal isolation is not common; this could indicate that shedding is intermittent. Faecally contaminated water maybe a source of infection [53], but the organism has not been isolated from water. Food borne transmission has not been substantiated. Transmission probably occurs mostly by the faecal- oral and oral- oral routes and via recently contaminated food and water and unclean hands [54]. Oral-oral transmission has been identified in the case of African women who pre masticate foods given to their infants [55]. There is no identified association of infection with sexual transmission, therefore, if it occurs, it is uncommon. Transmission via aspiration of the organism from vomitus is another possibility but has not been documented [56].

Disease in Human

Epidemiology: *Helicobacter pylori* (*H. pylori*) is a microorganism that invades the gastric and duodenal mucosa linings and is notoriously known to cause Gastric and Duodenal Ulcers, commonly diagnosed as Peptic Ulcer Disease (PUD) by Clinicians. The pathogenicity of *H. pylori* spans between three major factors. These include:

Characteristic	*H. baculiformis*	*H. cynogastricus*	*H. bizzozeronii*	*H. felis*	*H. salomonis*	*H. pylori*	*H. suis*	"*Candidatus* Helicobacter heilmannii"	*H. mustelae*	*H. nemestrinae*[b]	"*Candidatus* Helicobacter bovis"	*H. aurati*
Length (μm)	10	10–18	5–10	5–7.5	5–7	2.5–5	2.3–6.7	5–10	2	ND	1.5–2.5	4–8
Cell width (μm)	1	0.8–1.0	0.3	0.4	0.8–1.2	0.5–1.0	0.9–1.2	0.5–0.6	0.5	ND	0.3	0.6
Nitrate reduction	+	+	+	+	+	−	−	ND	+	−	ND	−
Urease	+	+	(+)	(+)	+	+	+	+	+	+	+	+
Alkaline phosphate hydrolysis	+	+	V	V	V	+	+	ND	+	+	ND	−
γ-Glutamyl transpeptidase	+	+	+	+	+	+	+	ND	+	ND	ND	+
Indoxyl acetate hydrolysis	−	−	(−)	(−)	(−)	(−)	−	ND	+	−	ND	+
Growth at 42°C	−	−	V	V	−	(−)	−	ND	V	+	ND	+
Growth on 1% glycine	−	−	(−)	−	−	−	−	ND	−	−	ND	−
Periplasmic fibril	+	+	−	+	−	−	−	−	−	−	−	+
No. of flagella/cell	11	6–12	10–20	14–20	10–23	4–8	4–10	10–20	4–8	4–8	≥4	7–10
Distribution of flagella	BP	BP	BP	BP	BP	MP	BP	BP	LP	BP	ND	BP

Table 2 Data of heterotypic synonym of H. pylori Source: [72,87].

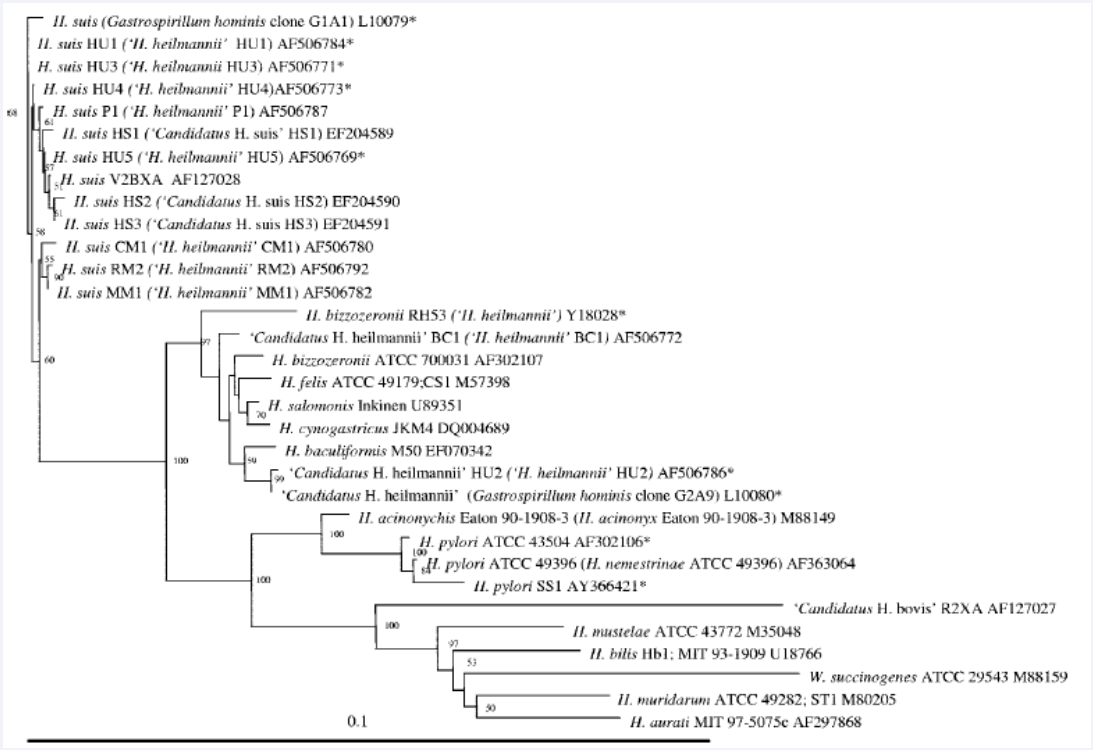

Table 3 *Helicobacter* species and other related species.

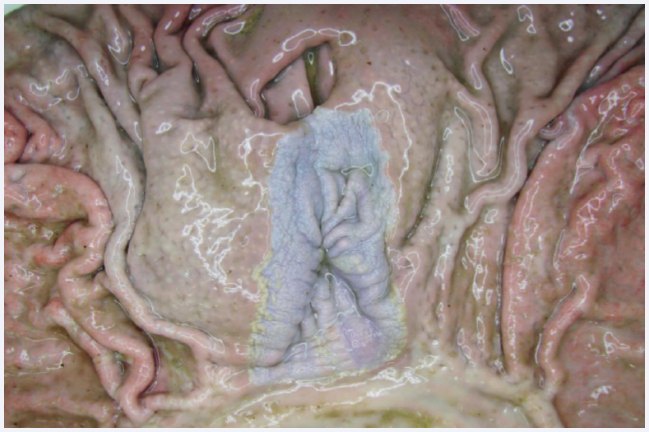

Figure 1 In the normal porcine stomach, there is a small rectangular area around the cardia which is covered by a slightly keratinized squamous Epithelium presenting as a white, slightly irregular surface on visual inspection. This area is named the pars esophageal, since the epithelium is similar to that of the esophagus.

1. Entry to, adherence to, and Colonization of the human gastric and (or) duodenal mucosa.
2. Avoidance, subversion and exploitation of the body's immune system, and
3. Multiplication, tissue damage and ultimate transmission to a new susceptible host individual.

A Combination of these factors enables this bacterium to thrive and cause infection in humans. *H. pylori* produce Urease that aids in the colonization of the host by neutralizing gastric acid and providing ammonia for its protein synthesis and continued survival. The *H. Pylori* bacterium

Consequently, weakens the protective mucous (mucosa) coating of the stomach and duodenum, thus allowing acid to get through to the sensitive lining beneath. The irritation symptoms are caused by both physical presence of the bacterium and the acid flux.

The *H. pylori* bacterium cause disease by attacking the gastric mucous lining leaving part of the stomach exposed to the acid which altogether irritate the stomach cancer ulcers and gastritis and sometimes stomach cancer.

Reservoirs for pylori: The human stomach appears to be the environment most suitable for the organism's growth; there are no significant animal or environmental reservoirs for strains infecting humans. H. pylori have been isolated from domestic, commercially reared cats [57,1] and it has been suggested that it might be a zoonotic pathogen with transmission occurring from cats to humans. Dog-is reservoir for NHPHB species.

Transmission routes: The mode of transmission of H. pylori remains poorly understood; no single pathway has been clearly identified [58] demonstrated that the housefly has the potential to transmit H. pylori mechanically, and thus fly

excreta might theoretically contaminate food. This hypothesis may be of the most significance in areas of the world with poor sanitation. Person-to-person contact is considered the most likely transmission route. Three possible routes of transmission from the stomach of one person to that of another have been described [59] and are presented below.

Sign in humans: The most common symptoms of *H. pylori* infection include:

1. Burning pain in the abdomen especially in the epigastric region
2. Abdominal pain that worsens that worsens on empty stomach and during at night
3. Nausea
4. Loss of appetite
5. Bloating and others [60].

Diagnostic Methods

Initial Diagnosis: When endoscopy is required, the current diagnostic invasive approaches are biopsy and histology, immunohistochemistry, urease detection, culture assay, and polymerase chain reaction (PCR). The implementation of sequencing technologies is subject to the recommended guidelines for the management of H. pylori infection. The determination of the gold standard among all methods remains controversial, especially for epidemiological studies. Because of the declining sensitivity of invasive tests, non-invasive tests, including serology, stool antigen test and urea breath test, have been largely used for detecting H. pylori. Urea breath test and stool antigen test, among the non-invasive tests, are the best methods to detect the active infection. The sensitivity of serology tests is high but the specificity is relatively low. The guidelines show that no test can be considered the gold standard for diagnosing H. pylori and there are advantages and disadvantages of all methods [61,62].

Confirmation of Eradication: Confirmation of H. pylori eradication is always recommended. Stool antigen test and urea breath test can be used to confirm eradication when endoscopy is not required and have to be accomplished at least 4 weeks after the end of the therapy [62,63]. Since it is known that PPIs exert transient negative effects on H. pylori viability, morphology, and urease test, cessation of these drugs at least 14 days before testing for eradication could help avoid false-negative results (Maastricht V) [64] (Figure 2-4).

Treatment in Human and Animals

Treatment of H. pylori Infection

First-Line Treatment: Considering the choosing of the regimen for H. pylori eradication, previous exposure to antibiotics should be accounted. The triple clarithromycin-based therapy must be confined to patients without prior exposure to macrolides living in areas with a low resistance to clarithromycin.

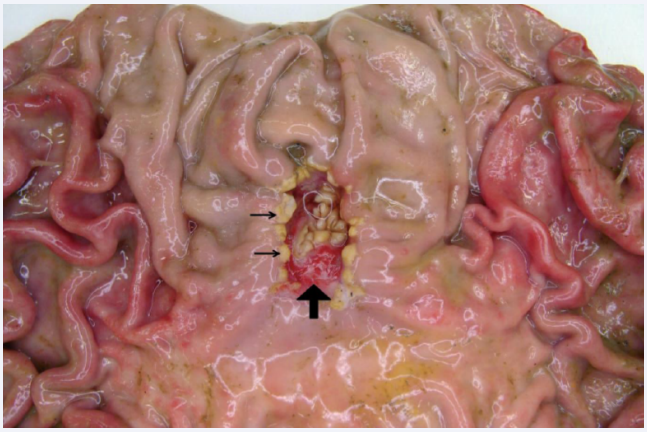

Figure 2 Gastric *Helicobacter* Paylori Disease

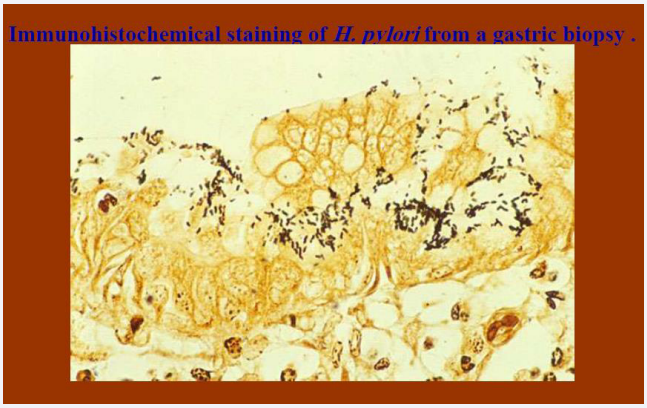

Figure 3 The Biohit Helicobacter Pylori Quick test is a novel rapid (1-2 min.) biopsy urease test.

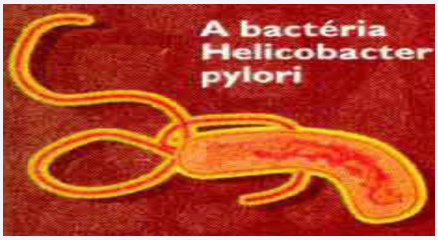

Figure 4 *H. Pylori* (a bacteria).

At present, bismuth quadruple therapy or concomitant non-bismuth quadruple therapy (PPI, amoxicillin, clarithromycin and nitroimidazole) should be the preferred regimen. This has been shown to be most effective in overcoming antibiotic resistance. After the failure of the first-line therapy, the rescue regimen should avoid antibiotics that have been used before. If the patient has received first-line treatment containing clarithromycin, the preferred treatments are bismuth salts schemes or levofloxacin. With clarithromycin, should also be recommended after failure of quadriceps containing bismuth [65,66].

Second-Line Treatment: The failure of the first-line therapy

for H. pylori infection requires a second-line therapy which is challenged due to potential microbiological resistance to the antibiotics included initially [67]. There is no "golden" standard in rescue eradication therapy after failure of first-line treatment. The advice of the Maastricht V/Florence Consensus Report is in favor of quadruple bismuth therapy or triple/quadruple fluoroquinolone–amoxicillin therapy as a second-line therapy [64]. Meta-analyses proved that the eradication results of quadruple bismuth therapy and levofloxacin-amoxicillin therapy are almost equal, while the first has more adverse effects than the second. The rate of eradication of triple and quadruple Levofloxacin-based therapies are suboptimal. In case of fluoroquinolone resistance, the triple or quadruple levofloxacin–amoxicillin therapy has a lower efficacy of eradication. A 10-day therapy consisting of PPI, bismuth, tetracycline and levofloxacin was recently developed, which achieved a significantly higher degree of eradication compared to triple therapy with PPI–levofloxacin–amoxicillin (98% vs. 69%) in patients after failure of standard therapies [67,68]. As a second-line treatment, the tetracycline-levofloxacin, bismuth-based or levofloxacin– amoxicillin quadruple therapies could be administered for H. pylori eradication. Recent data suggest that 10-days tetracycline-levofloxacin therapy is an effective scheme and a candidate for rescue treatment after failure of eradication by all first-line schemes for H. pylori infection. A document comparing the recommendations in the guidelines of expert groups in Europe, Canada and the United States has been published.

Third-Line (and Further) Treatment: After two failed therapies, susceptibility-guided treatments have been administered as a third-line strategy. This could be a rescue treatment. Nevertheless, evidence in favor of this therapy is insufficient and the cure rate is moderate [69]. The efficacy of the third-line therapies for H. pylori is suboptimal, even after a bacterial culture. Resistance to many antibiotics is the main factor for treatment failure. The effectiveness and safety of 2-weeks eradication using high doses of amoxicillin, metronidazole and esomeprazole in patients with two previous failures of therapy has been assessed. Triple therapy with esomeprazole 40 mg twice daily, amoxicillin 1 g three times daily and metronidazole 500 mg three times daily for 14 days has been implemented as third-line therapy after first therapy, including clarithromycin, and a second-line treatment, including quinolone [70].

Adding an Adjuvant Treatment: Probiotics have inhibitory effect on H. pylori and have been used as adjunctive therapy in H. pylori eradication. Probiotics have improved eradication rate of H. pylori and side effects of antibiotic treatment. Treatment outcomes are conflicting due to species, doses, and length of administration. Additional studies on the safety of adjuvant probiotics in eradication therapy of H. pylori are needed [71].

Relapse and Reinfection

Recurrence can occur either through relapse or through reinfection. To determine relapse or reinfection, and to match the treatment and follow-up of patients to the nature of relapses, it is mandatory to study genotype [72]. Compared to reinfection, the relapse time window is usually shorter, followed by a recurrence of H. pylori-related diseases. Reinfection after an effective eradication therapy is very rare [73]. Several factors are responsible for H. pylori reinfection, such as the presence of H. pylori positive family members, poor living conditions, and health status. The factors for H. pylori relapse need further study [74].

Resistant Infections: Unfortunately, an increasing number of infected individuals are found to harbor antibiotic-resistant bacteria. This results in initial treatment failure and requires additional rounds of antibiotics. For resistant cases, a quadruple therapy may be used. Resistance is common with metronidazole. For the treatment of clarithromycin-resistant strains of H. pylori the use of levofloxacin as part of the therapy has been recommended. Endoscopy and biopsy with C&S of the Pylori strain can be done in some resistant cases.

Prevention and control

Vaccination: Prophylactic and therapeutic vaccination against Helicobacter infection has been successful in a variety of animal models (Blanchard and Czinn, 2000). Intranasal delivery of antigen with CpG oligodeoxynucleotide induced a strong systemic immune response and a mucosal immunoglobulin A (IgA) response [48]. Further studies are necessary to determine the efficacy of such vaccines in prevention of H. pylori infections. Post-treatment with catechins/sialic acid decreased the bacterial load and gastritis score and eradicated up to 60% of H. pylori infections in a dose-dependent manner. This is the first demonstration to our knowledge of a non-probiotic, nonantibiotic treatment that is 100% effective in preventing and has promising possibilities for treating H. pylori infection. Further studies are needed to confirm this result in humans [75-91].

CONCLUSION AND RECOMMENDATION

The genus *Helicobacter* has rapidly expanded due to the isolation of new species from a wide range of animals. Many domestic and wild animal species have not been systematically and valuated for *Helicobacter* infections; therefore, more novel isolates can be anticipated with future efforts. The genus now includes 26 formally named species as well as numerous other novel helicobacters currently being characterized. Continued study of the genus *Helicobacter* is yielding new information for varied disciplines within biology and medicine. The zoonotic potential of *Helicobacter* spp. has been established, but is likely under reported. Diagnostic evaluations of human and veterinary patients will increasingly include *Helicobacter*-associated disease in the differential list of potential diagnoses. Advanced molecular techniques have given investigators the ability to study these fastidious organisms when culture has been difficult or appeared unachievable. The advances of evaluating host and bacterial gene expression using microarray technology is in its infancy and will be very applicable to the study of interactions between Helicobacter spp. and their hosts.

- ✓ Genomic studies of *Helicobacter* spp. as pathogens and of their hosts will no doubt shed light on critical genes

and associated molecular events that could be targets for preventing or treating infectious diseases in the future.

- ✓ As examples, new insights are emerging concerning the dysregulated host response to enteric flora thought to be the basis for IBD of humans. Particularly noteworthy, mouse models of *Helicobacter*-associated disease are strengthening the link between chronic infections and the associated tissue damage from chronic inflammation and the progression of dysplastic lesions to cancer in the liver and gastrointestinal tract.

- ✓ As more is learned about the helicobacters that naturally infect the species that biomedical research historically has, and will continue to rely on as predictable models of human disease, management of helicobacter free research colonies will continue to gain in importance.

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