Other helicobacters involved in human diseases

James G. Fox

Division of Comparative Medicine, Massachusetts Institute of Technology, Cambridge.

Introduction

Spiral, motile bacteria have evolved to inhabit the mucus of the intestinal crypts. The best known of these spiral, microaerobic organisms is *Campylobacter jejuni*. We now recognize that the intestinal crypts of a variety of animals, as well as humans are also the natural reservoir of many members of the genus Helicobacter. Indeed, *H. cinaedi* and *H. fennelliae,* previously classified as camyplobacters, were first isolated from inflamed tissues of homosexual males suffering from procitits and colitis (1). Other recently named helicobacters, *H. pullorum, H. canis, H. canadensis* and '*H. rappini*' have been isolated from the diarrheic feces of humans (2,3,4, 5). With the exception of *H. canadensis,* these helicobacters also have been isolated from the feces of animals with and without diarrhea (3). Rodent helicobacters, *H. hepaticus* and *H. bilis* have been linked to both chronic hepatic and intestinal disease and are increasingly being used in mouse models to understand the pathogenesis of helicobacter induced gastrointestinal disease (6,7,8). Of the gastric helicobacters, *H. pylori*, is the best known and the most important in terms of global impact on human disease. However, two other gastric helicobacters, *H. heilmannii* and *H. felis* are associated with gastric disease in humans and are worthy of discussion (9,10). Today at least 23 formally named helicobacters have been identified and an additional 35 or more novel helicobacters are awaiting formal naming. The purpose of this review will be to highlight the expanding role that other helicobacters, though not as well known as *H. pylori*, play in gastrointestinal disease in humans.

Isolation of fastidious enterohepatic *Helicobacter spp.*

It should be stressed that many hospital laboratories have difficulty in isolating enteric helicobacters. Because of the slow growth of *H. cinaedi* and other enteric helicobacters under microaerobic conditions, laboratory diagnosis is unlikely if blood culture procedures which rely on visual detection of the culture media are utilized (11,12). Dark field microscopy or use of acridine orange staining of blood culture media, rather than Gram staining, increases likelihood of seeing the organism. Likewise, fecal isolation is difficult ; selective antibiotic media are required and recovery is facilitated by passing fecal homogenates through at 0.45 µ filter (13). Also, in a recent study, several strains of both *H. cinaedi* and *H. fennelliae* were inhibited by concentrations of cephalothin and cetazolin used frequently in selective media for isolation of enteric microaerophilic bacteria (12). These organisms also require an environment rich in hydrogen for optimum in vitro growth. *H. cinaedi* and *H. fennelliae* can grow under anaerobic conditions but this anaerobic growth may be only under laboratory conditions where the organisms have adapted to the controlled anaerobic environment.

In our experience, for the best recovery of enterohepatic helicobacters, fecal samples should be placed in glycerol medium for transportation. Higher H_2 levels (5-10%) are required for optimal enteric *Helicobacter* spp. isolation. Unfortunately, this atmosphere is not available in the commercially available diagnostic kits used for campylobacter isolation. Current identification of multiple species of microaerobic bacteria in feces poses a particular challenge, particularly when these microaerobes grow on similar media in comparable atmospheric conditions. Primary isolation of *Campylobacter* spp. may be misleading, because *Helicobacter* spp. may be present in smaller numbers, and grow at a slower rate than *Campylobacter* spp. Their similar phenotypic traits and biochemical profiles, also complicate a diagnosis. Using genus specific campylobacter and helicobacter PCR assays should allow discrimination between the two species (14).

South Africa investigators have developed a protocol in use since 1990 which has allowed primary isolation of multiple species of campylobacter and helicobacter from individual childrens' diarrheic specimens. The technique, uses selective filtration, the filtrates are placed onto antibiotic free blood agar plates and incubated in an H_2 enriched atmosphere (15,16). The authors not only documented an increase in number of CLO's isolated but they were able to culture *C. upsaliensis* for the first time. The authors have reported a 16.2% prevalence of multiple species of CLO's based on primary isolation, biochemical characterization, and serologic confirmation. They frequently recovered between 2-5 CLO

Correspondence and requests for reprints : James G. Fox, D.V.M., Professor and Director, Division of Comparative Medicine, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Bldg. 16, Rm. 825C, Cambridge, MA 02139. E-mail : jp-fox&mit.edu.
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species from one stool sample, with *C. jejuni* (with different serotypes), *C. coli, C. upsaliensis, H. fennelliae* and *H. cinaedi* being commonly isolated (15).

It also has been suggested by several investigators that the true prevalence of *H. pullorum* in both chickens and as a purported cause of gastroenteritis in humans may be under reported because of the difficulties associated with isolation and species identification (17). *H. pullorum* is sensitive to polymyxin which is used in Skirrow-selective media for isolation of CLO's ; its use for isolation of *H. pullorum* is therefore not warranted. Like many helicobacters, *H. pullorum* is inert in most biochemical tests commonly used in diagnostic laboratories and even when isolated on bacterial media may be easily misidentified (Table 1). For example it can't be distinguished from *Campylobacter coli* except by its lack of indoxyl acetate, and is indistinguishable from *C. lari* except for its lack of tolerance to 2% NaCl and sensitivity to nalidixic acid. One report describes the use of fatty acid profiles to differentiate *H. pullorum* from *C. lari* (18). Other authors have strongly recommended that species specific PCR assays based on 16S rRNA genes be used for definitive diagnosis (19,20). More recently, several enteric helicobacters have been assayed for cytolethal distending toxin. Its presence or absence may assist in distinguishing among closely related species (3,21,22,23).

Direct PCR of fecal samples as well as other body fluids for diagnosis of enteric helicobacters, has been hampered by the presence of inhibitory substances. To circumvent these difficulties, a screening technique for detecting *Helicobacter* spp in rodents was developed whereby reproducible PCR results are obtained following a simple and quick purification protocol (24). In this technique, bacteria are released from the fecal material by treatment with PVPP, an agent used to isolate bacteria from soil. The best results with the PVPP treated samples were obtained at 4°C with efficacy of the PCR reaction decreasing when the treatment was performed at higher temperatures, probably reflecting an increased release of inhibitors at higher temperatures. As reported in other laboratories, the addition of a Chelex 100 treatment enhanced the final PCR reaction (25,26). The use of a new commercially available QIAamp Tissue Kit (Qiagen, Inc., Chatsworth, CA) for DNA extraction from fecal samples has also proven extremely useful in detection of enteric helicobacters by PCR (27). This or similar PCR techniques on human stool may prove useful as an adjunct for diagnosis for these fastidious microaerophiles.

Human Enterohepatic Helicobacters

Helicobacter cinaedi. In 1984, a group of microaerobic. campylobacter like organisms were isolated from rectal swabs of male homsexuals (1,28). These bacteria could be broadly classified into three major DNA homology groups. One of these was *Helicobacter cinaedi,* previously classified as *C. cinaedi* (CLO-1A). The second CLO2 was named *C. fennelliae* and the third still unnamed organism was classified as CLO3 (29). Although *H. cinaedi* has been primarily recovered from immunocompromised individuals, the organism has also been isolated from chronic alcoholics, immunocompetent males and females, and children (30,31). For example, Tee *et al.* isolated nine strains of apparent enteric helicobacters from fecal cultures of over 1000 patients with gastroenteritis ; three were classified biochemically and by DNA/DNA hybridization as *H. cinaedi* (32).

Since *H. cinaedi* has been isolated from normal intestine flora of hamsters, it has been suggested that the pet hamsters serve as a reservoir for transmission to humans (13,33) (Table 2). This fastidious microaerophile was recovered from blood of a neonate with septicemia and meningitis (30). The mother of the neonate had cared for pet hamsters during the first two trimesters of her pregnancy (30). The mother had a diarrheal illness during the third trimester of pregnancy ; the newborn was likely to have been infected during the birthing process, though this was not proven. Further studies are needed to confirm zoonotic risk of handling *H. cinaedi* infected hamsters (13). Also of interest is the isolation, based on cellular fatty acid and identification analysis, of *H. cinaedi* from the feces of dogs and a cat (12). We have recently isolated *H. cinaedi* from an inflamed colon, mesenteric lymph node, and liver of a rhesus monkey with chronic idiopathic colitis and hepatitis (34). This case highlights the ability of enteric helicobacters to translocate across the intestinal epithelia. The isolation of other novel helicobacters from inflamed colons of monkeys is also consistent with the increasing recognition of enteric helicobacters in children with gastroenteritis who reside in developing countries (15,35,36).

In an attempt to understand the pathogenesis of *H. cinaedi* and *H. fennelliae* infection, pigtailed macaques (*Macaca nemestrina*) were experimentally challenged by the oral route with the organisms (37). Both *H. cinaedi* and *H. fennelliae* caused bacteraemia, diarrhea and focal colonic lesions. One of five monkeys infected with *H. fennelliae* also had acute proctitis and *H. cinaedi* induced lymphoid hyperplasia (37).

H. cinaedi has also been isolated from the blood of homosexual patients with human immunodeficiency virus (HIV) as well as children and adult females (30,31, 38,39,40,41,42,43,44). In a retrospective study of 23 patients with *H. cinaedi*-associated illness, 22 of the cases had the organism isolated from blood using automated blood culture system where a slightly elevated growth index was noted (11). This study also described a new *H. cinaedi* associated syndrome, consisting of bacteremia and fever accompanied by leukocytosis and thrombocytopenia. Recurrent cellulitis and/or arthritis are also noted in a high percentage of infected immunocompromised patients (11,45).

Table 1. — **Characteristics which differentiate nongastric *Helicobacter* species**[a]

Taxon	Catalase production	Nitrate Reduction	Alkaline phosphatase hydrolysis	Urease	Indoxyl acetate hydrolysis	ψ-glutamyl transpeptidase	Growth at 42°C	Growth with 1 % glycine	Susceptibility to : Nalidixic acid (30-µg disc)	Susceptibility to : Cephalothin (30-µg disc)	Peri-plasmic fibers	No. of flagella	Distribution of flagella	G+C Content (mol%)
H. canadensis	+	+	–	–	+	–	+	+	R	R	–	2	Bipolar	ND
H. rodentium	+	+	–	–	–	–	+	+	R	R	–	2	Bipolar	ND
H. pullorum	+	+	–	–	–	ND	+	ND	R	S	–	1	Monopolar	34-35
H. westmeadii	+	+	+	–	ND	ND	–	ND	+	–	–	1	Bipolar	ND
H. fennelliae	+		+	–	+	–	–	+	S	S	–	*2*	Bipolar	35
H. trogontum	+	+	–	+	ND	+	+	ND	R	R	+	5-7	Bipolar	ND
H. muridarum	+		+	+	+	+	–	–	R	R	+	10-14	Bipolar	34
H. hepaticus	+	+	ND	+	+	ND	–	+	R	R	–	2	Bipolar	ND
H. canis			+		+	ND	+	ND	S	1	–	2	Bipolar	48
H. bilis		+	ND	+	–	ND	+	+	R	R	+	3-14	Bipolar	ND
«H. rappini»	+		–	+	ND	+	+	–	R	R	+	10-20	Bipolar	34
H. cinaedi	+	+	–	–	–	–	–	+	*S*		–	1-2	Bipolar	37-38
H. pametensis	+	+	+	–	–	–	+	+	*S*	S	–	2	Bipolar	38

a+, positive reaction ; -, negative reaction ; S, susceptible ; R, resistant ; 1, intermediate ; ND, not determined.

Table 2. — **Non *H. pylori* helicobacters isolated from humans (as of 2000)**

Species	Other Hosts	Primary site	Other sites	References
*"H. rappini"**	Sheep, dog, mice	Intestine	Blood (humans) Liver (sheep), stomach (dogs)	(2,54,56,60,61)
*H. canis**	Dog, cat	Intestine	Blood (humans) Liver (dog)	(4,52,53)
*H. cinaedi**	Hamster, rhesus monkey	Intestine	Blood, soft tissue, joints (humans) Liver (monkey)	(13,14,33,35)
H. fennelliae	Dog, macaque	Intestine	Blood	(1,11,28)
*H. pullorum**	Chicken	Intestine	Liver (chicken)	(5)
H. canadensis		Intestine		(3)
H. westmeadii		Blood		(46)
*'H. heilmannii'**	Dogs, cats, monkeys, cheetahs, wild rats, swine	Stomach		(9,54,76,77)
H. felis	Dogs, cats, cheetahs	Stomach		(10,102)

* Some data suggest zoonotic potential.

'Helicobacter westmeadii'. In 1997, a novel helicobacter, *H. westmeadii* was cultured from the blood of two HIV infected patients (46). '*H. westmeadii',* though morphologically and biochemically similar to *H. cinaedi,* was previously distinguished by its ability to hydrolyze hippurate and ability to grow anaerobically. Also, the authors stated that results of ribotyping, fatty acid analysis, and 16S rRNA ribosomal sequences made it distinctly different from *H. cinaedi* and *H. fennelliae.* By electron microscopy, there is little morphological difference between *H. cinaedi, H. fennelliae,* and *H. westmeadii,* all having single, sheathed, polar flagella. *H. cinaedi* and *H. fennelliae* are longer (2.5 to 5 µm) and thicker (0.5-1 µm than *H. westmeadii* which 1.5-2 µm by 0.5 µm in diameter). A recent paper by Vandamme *et al.* raises the question whether *H. westmeadi* is a separate species or instead a junior synonym of *H. cinaedi.* They based their results on numerical analysis of whole-cell protein electrophoresis, extensive biochemical analysis, and DNA-DNA hybridization experiments (47).

Helicobacter fennelliae. Like *H. cinaedi, H. fennelliae* previously known as *C. fennelliae,* was first isolated from rectal swabs of homosexuals (1,28). However, unlike *H. cinaedi,* this enteric helicobacter does not often cause bacteremia in adults (39,48). It has however been isolated from a child with leukemia (49) and was responsible for septic shock in a non HIV-infected heterosexual patient (50). However, this patient was undoubtedly immunocompromised because of liver cirrhosis and diabetes mellitus, as well as pre-existing disseminated fungal infections. One HIV seropositive patient, suffering from successive bacteremia, had both *H. cinaedi* and *H. fennelliae* isolated from his blood at differing time points (39). These patients also have diarrhea concurrent with the isolation of *H. fennelliae* from their blood. Although *H. fennelliae* has been identified in the feces of a dog and macaque, no direct evidence of zoonotic transmission has been reported (12).

Helicobacter canis. A *H. fennelliae-like organism* was isolated from the feces of a child suffering from gastroenteritis (51). *H. canis* also has been isolated from bacteremic humans (29,52). The bacteria were distinguished from *H. fennelliae* by their ability to grow at 42°C, failure to produce catalase, and its marked tolerance to bile. Morphologically, the bipolar, sheathed flagella of *H. canis* are similar to those in *H. cinaedi* and *H. fennelliae,* and are useful in characterizing the organism as a helicobacter. Subsequently, the same bacteria were isolated from feces of normal and diarrheic dogs and was classified, based on 16S rRNA sequencing, as a novel helicobacter and named *H. canis* (4). It has been isolated from a colony of cats with endemic diarrhea (53). Our laboratory has also identified *H. canis* based on 16S rRNA data from the liver of a puppy diagnosed as having an active, multifocal hepatitis (52). Whether this organism is capable of experimentally inducing diarrhea and/or hepatitis in dogs or cats or importantly, occurs as a natural liver infection in humans requires further study.

Additional investigations will be required to ascertain whether *H. canis* in dogs and cats constitutes a potential reservoir for zoonotic, transmission to man. The fact that other microaerophilic bacteria, i.e. *Campylobacter jejuni* and *C. coli* are associated with zoonotic transmission to humans, especially children handling young puppies and kittens, strengthens the argument that dogs and cats may be responsible for zoonotic infection of *H. canis* in humans (4). It is also important to note that both helicobacters and campylobacters can be isolated from diarrheic feces of individual pet animals and humans ; careful diagnostic efforts are therefore needed to properly identify mixed infections with these microaerobic bacteria (15,53).

'H. rappini'(Flexispira rappini). The bacteria, with periplasmic fibers that entwine the surface of the organism and multiple bipolar sheathed flagella, were first noted on electron microscopic examination of dog stomachs (54). Subsequently, a similar bacterium was cultured from aborted ovine fetuses and given the provisional name '*Flexispira rappini*'(29,55,56). '*F. rappini* can cross the placenta in pregnant sheep, induce abortions, and cause acute hepatic necrosis in sheep fetuses (55,56). Experimentally, '*F. rappini*' causes abortions and necrotic hepatitis in guinea pigs (55). Isolation of the organism from the blood of infected guinea pigs 1.5 weeks after inoculation indicates the ability of these organisms to cause bacteremia. This bacteria has also been isolated from the feces of asymptomatic mice (57). By 16S rRNA analysis, this organism also belongs in the genus *Helicobacter* (57). Our recent 16S rRNA analysis of numerous '*H. rappini*' strains from multiple sources indicates that there are at least 10 species of closely related '*H. rappini*' taxons (58).

'Helicobacter rappini' was first reported in two humans with chronic diarrhea (2). Since then the organism has been increasingly cited as a cause of bacteremia. It was recently isolated from a 9 year old bacteremic child with pneumonia (59). The organism was grown in a pediatric bottle (BACT/Alert Microbial detection system Organon Technika). The child was successfully treated with erythromycin. Also, '*H. rappini*' was isolated on two occasions from the blood of an HIV negative 65 year old febrile patient undergoing hemodialysis for end stage renal disease (60). He had a history of chronic pancreatitis due to alcoholism and also had secondary diabetes which required insulin therapy. Two months prior to the septic episode with '*H. rappini,* the patient had suffered from cellulitis, secondary to a cat scratch. The strains were recovered from aerobic blood culture media (Bactec Plus Aerobic /F), but not from anaerobic culture media (Bactec Anaerobic/F). By whole protein numerical analysis, and biochemical characteristics, the organism was indistinguishable from the LMG 8738 strain (ATCC 43879) first described by Archer (2). The '*H. rappini*' from this patient was

> 99% similar by 16S rRNA analysis to that of '*H. rappini*' strain ATCC 43966 (60).

Recurrent bacteremia over a period of several months due to *H. rappini*, despite several courses of antibiotics has also been noted in a patient with prolonged cellulitis and X-linked agammaglobulinemia (61). This organism was also first grown in aerobic pediatric BacTAlert (Organon Tekmika Corp, Durham, NC) blood culture media. It was then successfully subcultured using microaerobic conditions that included H_2. The use of phase contrast microscopy of blood culture to observe the characteristic darting motility of these bacteria proved very helpful for selecting conditions for incubation of subcultures (61). Interestingly, this organism was urease negative, similar to the novel *Helicobacter* sp isolated from cotton top tamarins with chronic diarrhea (36). Given that identical '*H. rappini*' strains have been isolated from dogs and their owners and the occurrence of *H. rappini* associated cellulitis following a cat scratch, there is an apparent likelihood of zoonotic transmission with this organism (2,60,62).

Helicobacter pullorum. Novel helicobacters, named *H. pullorum* isolated from ceca of normal chickens, the livers and intestinal contents of chickens with hepatitis, and feces of humans with gastroenteritis have been characterized biochemically, by DNA hybridization, and 16S rRNA sequencing (5). This bacterium is urease negative and can be distinguished from most other helicobacters by lack of sheathed flagella. Like *H. hepaticus, H. canis* and *H. bilis* (all 3 capable of colonizing the liver), *H. pullorum* is tolerant to bile. The potential of *H. pullorum* to cause serious gastrointestinal disease is evidenced by isolation of the organism from a young woman and a young man, both of which suffered from chronic diarrhea of one month's duration (63). The young man also had elevated liver enzymes, which though not proven, may have been induced by invasion of the liver by *H. pullorum,* in a manner similar to the organism's ability to cause hepatitis in chickens. Since then *H. pullorum*-associated gastroenteritis has been increasingly recognized in both Europe and North America (20,64).

H. pullorum along with *H. bilis* and *H. rappini* have been identified by PCR, cloning, and 16S rRNA analysis in Chilean patients with chronic cholecystitis (65). Nilsson *et al.* recently have found *Helicobacter* spp (including *H. pylori)* by using *Helicobacter* spp specific PCR in livers of PSC patients as well as patients with primary biliary cirrhosis, another idiopathic biliary disease. Interestingly, *Helicobacter* spp were not identified in control patient's livers or in patients with non-cholestatic liver disease (66). *Helicobacter* spp were also noted in cases of liver carcinoma (67,68). Unfortunately, in none of these reports were the investigators able to isolate *Helicobacter spp* from affected tissues. Further studies are needed to assess the significance of these interesting findings.

A cytotoxic activity that is a member of the cytolethal distending toxin (CDT) family of bacterial toxins has been reported in a number of enterohepatic helicobacters including *H. pullorum* (21,23). CDT activity is characterized by the appearance of cellular distension, cytoskeletal abnormalities, G_2/M cell cycle arrest and cytolethality in cultured cell lines treated with bacterial culture supernatants or sonicates of bacteria expressing the toxin (21,23). However, *H. fennelliae* and *H. cinaedi* do not appear to possess the *cdt* gene cluster, nor do they possess typical CDT activity (21). Although the mode of action of enterohepatic helicobacters Cdt on eukaryotic cells is unknown, it was recently shown that bacterial Cdt-induced cell cycle arrest in *Escherichia coli* and *C. jejuni* was associated with a DNase activity intrinisic to the CdtB polypeptide. This toxin may play a role in the pathogenesis of enterohepatic disease by targeting lymphocytes and causing cell cycle arrest (69,70).

H. canadensis. We recently analyzed 11 helicobacter isolates cultured from diarrheic patients in Canada. These isolates had been characterized biochemically, by RFLP (*Alu*I, Hhal), and fatty acid analysis as *H. pullorum.* However, four of the isolates varied biochemically from *H. pullorum* by their inability to hydrolyze indoxyl acetate and their resistance to nalidixic acid. Using complete 16S rRNA analysis we determined that these four strains clustered near *H. pullorum* but had a sequence difference of 2% and therefore represent a novel *helicobacter, Helicobacter canadensis* (3). This novel helicobacter could also be distinguished from *H. pullorum* by RFLP using *Apa*LI and the lack of cytolethal distending toxin (3,22). This finding highlights the importance of careful molecular analysis in addition to standard biochemical tests in speciating the increasing number of *Helicobacter* spp isolated from humans and animals.

Treatment of enterohepatic helicobacters

Antimicrobial in vitro testing of 22 strains of *H. cinaedi* provide the clinician with a variety of antibiotics to use in treating infected patients (71). Tetracycline and various aminoglycosides appear to be effective in treating infections with *H. cinaedi*. Apparent relapses of *H. cinaedi* bacteremia in patients treated with ciprofloxicin (despite its previous use to successfully treat *H. cinaedi* infection) and the occurrence of in vitro resistance of *H. cinaedi* isolates to ciprofloxicin suggest that this antibiotic should be used with caution (11,12,71).

Non standardized in vitro testing suggest that *H. fennelliae* is susceptible to a variety of antibiotics including ciprofloxacin, doxycycline, gentamicin, rifampin and sulfamethoxazole (71). Intravenous chloramphenicol also has been used to treat bacteremic patients (39). One patient with *H. fennelliae* bacteremia responded clinically to intravenous ampicillin-sulbactam and ceftazidine followed by ampicillin-sulbactam. The patient

remained well at follow-up, 6 months after being discharged from the hospital (50).

A '*H. rappini*' recovered from a patient with end stage renal disease and alcoholism appeared by in vitro criteria (using inhibition zones of > 30 mm around antibiotic discs) to be more sensitive to antibiotics than the Archer strain (2). The strain was susceptible to ceftriaxone, meropenem, erythromycin, clindamycin, clarithromycin, doxycycline, gentamicin, amikacin, ciprofloxacin, nitrofurantoin, and metronidazole. This '*H. rappini*' strain was considered to be resistant to penicillin G and cefazolin because no zone of growth inhibition was observed. Susceptibility to ampicillin and co-trimoxazole appeared to be decreased (inhibition zone diameters of 28 and 22 mm, respectively) (60). These results were consistent with the clinical failure in this patient when treated with co-trimoxazole and clinical cure when treated with meropenem. In another case of bacteremia, the '*H. rappini*', by in vitro antibiotic testing using E-test strips, indicated the bacteria were resistant to ampicillin, azithromycin, ceftriaxone, chloramphenicol, ciprofloxacin and clindamycin (61). The organism was sensitive to imipenem, metronidazole, minocycline and rifampin and showed intermediate sensitivity to doxycycline. Based on these findings, the patient was initially treated with doxycline and metronidazole with noted clinical improvement of the cellulitis. Blood cultures remained positive however, and treatment was changed to oral amoxcillin-clavulanic acid, minocycline, and rifampin (61). Initial improvement was again noted but recurrence of symptoms followed. Intravenous gentamicin and imipenem was then initiated and continued for 5 months which achieved resolution of systemic infection and negative follow up on blood cultures (61).

One HIV infected individual who had '*H. westmeadi*' bacteremia was admitted because of pyrexia and neutropenia following chemotherapy. His medications on admission consisted of dapsone (100 mg daily), fluconazole (400 mg daily) and acyclovir (200 mg twice daily). After recovery of a gram negative rod from his blood, he was treated empirically with tricarcillin-clauvlamate and tobramycin. His fever subsided and his leukocyte count became elevated. However, he died 11 months later with advanced Kaposi's sarcoma. In the second bacteremic patient, there was a previous history of being HIV positive and having related diseases including oral candidiasis, diarrhea, and weight loss. He was subsequently admitted with a 4 week history of cellulitis in the right leg. He had '*H. westmeadi*' isolated from a blood culture and was treated with penicillin and flucloxacillin without clinical improvement. He developed a maculopapular rash and oral candidiasis ; his treatment was changed to cephalothin, to which he initially responded. He later developed recurrent lesions on both legs which resolved with time ; however, the patient died several months later of HIV related illness (46).

Non *H. pylori* gastric helicobacters isolated from humans

'Helicobacter heilmannii' (Gastrospirillum hominis). Of the known gastric *Helicobacter* spp. *'H. heilmannii'*, (a large spiral organism, ~ 5-10 µm long with 4 or 6 spirals and 0.3 µm wide, without periplasmic fibers) has the largest number of known mammalian hosts. These gastric helicobacter-like organisms (GHLO's) have commonly been observed microscopically in the stomachs of dogs, cats, cheetahs, swine, various species of non-human primates, and in a small percentage of humans with gastritis (9,10,72,73,74,75,76,77). Characterization of these bacteria have relied on 16S rRNA analysis because of their inability to grow the organisms on artificial media. Maintenance of the bacteria in the laboratory, other than in a frozen state, has relied on preparation of these gastric spirals in the stomachs of mice (78). Recently however, investigators from Finland have been able to culture a large spiral bacteria from gastric biopsies of dogs (79). They have named the organism *Helicobacter bizzozeronii* in honor of the Italian pathologist who was one of the first scientists credited with the observation of these organisms in the stomach of mammals (79). For *in vitro* growth, the organism required a fresh, moist medium containing antibiotics, a microaerobic environment, and 5 to 10 day incubation period (79,80). A case report of isolation of a *H. heilmannii* like organism was also reported in a human with gastritis (81). This isolate was susceptible to amoxicillin, metronidazole and tetracycline.

A diagnosis of humans infected with *H. heilmannii* first observed and reported in three humans in 1987, has been made on morphological grounds by a variety of authors assessing human gastric biopsies (9,72,82,83,84, 85,86). The frequency of occurrence is between 0.25% to 0.60% depending on the study. However, as high as 6% of patients in Thailand and China have been reported to be infected with '*H. heilmannii*' (87,88). Heilmann and Borchard (9) examined 15, 180 gastric biopsies and observed the gastric helicobacter in 39 German patients, 34 of whom had a chronic, active gastritis, and the remaining 5 had a chronic gastritis consisting of a lymphoplasmacytic inflammation. *H. heilmannii* is located in the deep part of the gastric pits of human patients, whereas *H. pylori* colonizes more frequently the mucus layer of surface epithelia. The GHLOs can also invade parietal cells in a manner similar to GHLO in other mammals. Authors have also systematically compared the histology of '*H. heilmannii*' and *H. pylori* in a large group of patients (89). Two hundred and two patients with '*H. heilmannii*' infection were compared with an equal number of *H. pylori* infected individuals. '*H. heilmannii*' associated gastritis was more mild when compared to the *H. pylori* gastritis cases (89). These helicobacters can persist in humans for years, and presumably the same is true for other mammals.

In the Heilmann study, 34 of the 39 patients complained of upper abdominal discomfort. Other reports indicate patients infected with GHLOs can have intermittent epigastric pain, and occasional bleeding is noted from gastric ulcers (9,86,90,91,92,93,94,95).

Using a questionnaire, 125 German patients infected with GHLOs provided information regarding animal contact. Of these, 70.3% had contact with one or more animals (as compared with 37% in the "normal" population). More than a threefold preponderance of male over female patients with GHLOs was recorded (72). In addition to dogs and cats as potential zoonotic hosts of these gastric helicobacters, swine may also be a source of infections to humans (96).

"H. heilmannii" also has been associated with primary gastric low grade lymphoma in humans (83,97). Similar to *H. pylori* associated lymphoma, clinical remission of the lymphoma was noted in five patients after antibiotic eradication of the gastric helicobacter (83,98,99). Eradication of "*H. heilmannii*" by antimicrobial therapy also has resulted in the resolution of gastritis and peptic ulcer disease (9,82,100). *"H. heilmannii"* infections have been successfully treated with bismuth alone and with combination therapies that included metronidazole or amoxicillan (9,81,82).

Helicobacter felis. Lee *et al*. isolated a tightly coiled spiral organism from the gastric mucosa of cats in 1988 (10). The bacterium had tufts of bipolar sheathed flagella and a body entwined with periplasmic fibers, which usually occurred in pairs (10). The bacteria were urease, catalase, and oxidase positive, typical biochemical features of other gastric helicobacters. In subsequent studies using 16S rRNA sequencing analysis and further biochemical characterization, the organism was named *Helicobacter felis* (101). Gastric spiral bacteria with similar morphology (based on electron microscopy) have also been identified in the stomachs of dogs and cheetahs (54,73). The organism is infrequently observed in human gastric biopsies in the gastric tissue of humans (102). In one case study, a researcher performing physiological studies with cat stomachs developed an acute gastritis, presumably caused by *H. felis* based on electron microscopy (102). Similar gastric spiral bacteria were shown in gastric mucosa of cats being used by this scientist. The gastritis observed in *H. felis* infected dogs and cats is similar to that observed with *"H. heilmannii"*. Interestingly, BALB/c mice infected with *H. felis* develop a lymphoma-like gastric lesion, which if treated with antimicrobials reduces the development of these gastric lesions (103). Also, the recent observation that *H. felis* infection in INS/GAS transgenic C57/BL mice induces gastric cancer adds credence to isolated case reports of '*H. heilmannii*' associated gastric carcinoma (104,105,106). Coinfection with *H. felis* and *"H. heilmannii" is* often observed in animals and perhaps in humans as well. Indeed, it is impossible to distinguish the two organisms histologically by light microscopy.

Conclusion

During the past 20 years, the genus *Helicobacter* has evolved rapidly due to the isolation of novel species from a wide range of animals and humans. The genus now includes at least 23 formally named species as well as numerous other helicobacters not formally named. Thirteen of these formally named helicobacters are found in the intestinal mucus of animals, six in humans and two in birds. Many of these helicobacters can also colonize the biliary tract of the liver and induce hepatitis (and in some cases hepatic cancer) or cause bacteremia and systemic disease in immunocompromised hosts (6,7,8). Discovery of these helicobacters provides the scientific community with an excellent opportunity to study and better understand the finely balanced ecological relationship between these bacteria which persistently colonize the gastrointestinal tract and host, and with this knowledge, appreciate how fluctuations in this intricate balance results in clinically significant disease.

Infection with *Helicobacter* spp and their associated diseases in numerous hosts allow us the means to assess pathogenic mechanisms as well as the utility of in vivo models to develop various therapeutic and prophylactic modalities to eradicate or prevent helicobacter-induced gastrointestinal disease in humans. In addition, it is important to understand the pathogenesis and epidemiology of helicobacter induced diseases in animals and where these helicobacter infections pose a clinical threat, or potentially interfere with interpretation of experimental results develop methods to treat and eliminate infection in these animals as well. The ultimate goal in these studies will be to eliminate afflictions causing significant human morbidity and mortality in both the developed and developing worlds.

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