

Transmission of *Helicobacter pylori*: a role for food?

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Helicobacter pylori colonizes and grows in human gastric epithelial tissue and mucus. Its presence is associated with gastritis and there is substantial evidence that it causes peptic and duodenal ulcers and chronic gastritis. Since 1994, *H. pylori* has been classified as carcinogenic to humans.

In industrialized countries, as many as 50% of adults are infected with the pathogen, while in the developing world, prevalence values of about 90% have been reported. As little is known about the mode of transmission, a literature search was carried out to determine whether food acts a reservoir or vehicle in the transmission of *H. pylori*. Although growth of the pathogen should be possible in the gastrointestinal tract of all warm-blooded animals, the human stomach is its only known reservoir. Under conditions where growth is not possible, *H. pylori* can enter a viable, but nonculturable state. *H. pylori* has been detected in such states in water, but not in food. Person-to-person contact is thought to be the most likely mode of transmission, and there is no direct evidence that food is involved in the transmission of *H. pylori*.

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Introduction

Helicobacter pylori, formerly known as *Campylobacter pylori*, colonizes and grows in human gastric epithelial tissue and mucus. Its presence is associated with gastritis; substantial evidence indicates that it causes peptic ulcers, duodenal ulcers, and chronic gastritis and that it is also involved in the development of gastric cancer (1–3). *H. pylori* was identified in 1984 (4): 10 years later, the International Agency for Research on Cancers classified *H. pylori* as carcinogenic to humans (5).

In industrialized countries as many as 50% of adults are infected, although the prevalence of infection seems to be decreasing (6). In the developing world, the prevalence is higher, with figures of about 90% having been reported (7, 8). Once acquired, *H. pylori* infection usually persists for life unless treated by antimicrobial therapy (7). Two

types of treatment are recommended: one is a combination of bismuth and antibiotics; the other is a combination of a proton-pump inhibitor and antibiotics (9). Many infected individuals, however, do not develop clinically apparent disease. Vaccines are currently being tested in animal models (10).

H. pylori seems to be transmitted in various ways, including oral–oral and faecal–oral routes (7, 11). In this study we have investigated the possible role of food as reservoir or vehicle in the transmission of *H. pylori*. We examined literature published from 1995 onwards, and the relevant references included in these publications.

Physiology and growth conditions

The physiological characteristics of *H. pylori* have received relatively little attention. It is a Gram-negative spiral-shaped bacteria, although its morphology is not constant. Under adverse conditions it becomes coccoid, but there is controversy about the nature of the coccoid form. Some researchers have stated that this form is either a contaminant or a dead bacterium (12), but others consider it to be a metabolically active form that cannot be cultured in vitro (13, 14). It has also been suggested that some cocci can revert to their original spiral shape (15).

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H. pylori is microaerophilic; optimal growth occurs in the presence of 5–15% oxygen (16). Incubation in air results in reduced survival (17) and it grows poorly under anaerobic conditions (18). The presence of 5% CO₂ seems to provide optimal conditions, while 10% CO₂ led to a loss in cultivability in one study (19).

Carbon source

Glucose is not necessary for growth (20, 21). Cell yield is not influenced by the presence of glucose, pyruvate, succinate, or citrate, but survival is enhanced by their presence. Prolonged incubation with carbon sources improves the viability of the organism (20). *H. pylori* depends on the presence of various amino acids for growth, including arginine, histidine, isoleucine, leucine, methionine, phenylalanine, and valine. Some strains also need alanine, serine, proline, and tryptophan (21).

pH and water activity

H. pylori can be cultured in environments within a pH range of 4.5–9 (22). At low pH values (e.g. 3.5), the addition of urea increases survival (22). NaNO₂ has no effect if concentrations range from 0 µg/ml to 400 µg/ml; growth is not possible at NaCl concentrations of ≥2.5 g/l (22). The pathogen is sensitive to environments with a low water activity (A_w): growth is inhibited at values <0.98. In one study, *H. pylori* concentrations became undetectable in nutrient-rich laboratory medium within three days when the A_w was 0.96 (22).

Temperature

H. pylori only grows at temperatures of 30–37 °C. All the required growth conditions are met in the gastrointestinal tract of all warm-blooded animals. At temperatures below 30 °C, *H. pylori* could survive in some foods, such as fresh fruit and vegetables, fresh poultry or fish, fresh meats, and some dairy products (23). *H. pylori* survived at 30 °C in laboratory media (22), water (17), and milk (24), and survived longer at lower temperatures (22).

Reservoirs

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* has been isolated from domestic, commercially reared cats (25, 26) and it has been suggested that it might be a zoonotic pathogen with transmission occurring from cats to humans. However, there have been no data to support this hypothesis. For example, after adjusting for potential confounders in a study of 447 factory workers in the United Kingdom, there was no association between *H. pylori* seropositivity and cat ownership during childhood (27). In Ulm, Germany, in 1996–97 among schoolchildren in first grade,

neither contact with pets in general nor contact with specific kinds of animals was positively associated with infection (28).

The possibility that *H. pylori* might be a zoonotic pathogen transmitted from animals other than cats has also been considered (7, 26), but the organism has never been isolated from animals slaughtered for consumption, such as pigs (26). It has been isolated from some non-human primates, such as macaque monkeys. However, because contact between humans and other primates is rare, it is unlikely that these other animals play an important role in the transmission to humans. It is possible that the inability to isolate the organism from other animals may be due to the difficulty of detecting the bacterium in materials other than gastric tissue (26).

Transmission routes

The mode of transmission of *H. pylori* remains poorly understood; no single pathway has been clearly identified. Grubel et al. (29) 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 (7) and are presented below.

Iatrogenic

The first, and most frequent, mode of transmission is iatrogenic, in which tubes or endoscopes that have been in contact with the gastric mucosa of one individual are used for another patient (30). Occupationally acquired infections — usually in which infection is transmitted from a patient to staff member — have also been reported, especially among endoscopists and gastroenterologists (7, 31, 32). However, in quantitative terms the iatrogenic route is considered to be marginal.

Faecal–oral

The second possible route is faecal–oral. *H. pylori* has been isolated from the faeces of infected young children (7, 31), but isolation from adults' faeces has been rare (33–36). Failure to recover the bacterium from faeces might be due to the toxic effect of faeces (37) or the methods used may not have been suitable (38). Several studies have investigated the association between the seroprevalence of *H. pylori* and hepatitis A virus (39–44). An association between the two was proposed, suggesting similar modes of transmission for both organisms, that is, faecal–oral. However, results from these studies have been contradictory (39–44).

Faeces-contaminated water may be a source of infection; an association between *H. pylori* and the absence of hot running water was found in some studies (45). In addition, an increased risk of infection was observed in children who swam in rivers, streams, or swimming pools in the southern Colombian Andes (46). However, the organism has not been isolated from water (45) except in two instances in which it was detected using the polymerase chain reaction on samples from Aldana, Colombia, and Lima, Peru (47, 48). In Sweden, exposure to sewage among sewage workers did not cause an increased risk of infection (49).

Three epidemiological studies South America have suggested that transmission occurred through food or water. In Chile, consumption of uncooked vegetables that had been irrigated with water contaminated with untreated sewage was associated with *H. pylori* seropositivity. More than 60% of 1815 Chileans younger than 35 years old and of lower socioeconomic groups were found to be *H. pylori* seropositive (50). Children who obtained their drinking water from local streams in the Columbian Andes were also found to have an increased prevalence of *H. pylori* (46). A case-control study of 407 children aged 2 months to 12 years in Peru also concluded that water was the vehicle of infection: children who used the municipal water supply had a higher prevalence of *H. pylori* infection than children who used private wells (51). These results were confirmed by another study that identified *H. pylori* in drinking water in Peru (48). Although these studies suggest that transmission may occur via water and food in developing countries, comparable results have not been observed in industrialized countries. The possible route of transmission via food that has been contaminated with faeces has not been substantiated (7).

Oral-oral

The third possible route of transmission is oral-oral. Few reliable studies have cultured *H. pylori* from the oral cavity; only sporadic isolates from dental plaque and saliva have been recorded (36, 38). *H. pylori* infection is uncommon among dental professionals (52). In addition, studies using the polymerase chain reaction have given contradictory findings (7). There have been problems with the specificity of bacterial cultures and the polymerase chain reaction from samples from the oral cavity. Possible oral-oral transmission has been investigated in the eating of premasticated foods among some ethnic groups, the use of the same spoon by both mother and child, intimate oral-oral contact, and aspiration from vomit (7, 38, 53). There is no direct evidence for transmission via the last two routes, but possible transmission via intimate oral-oral contact has been suggested indirectly by the fact that spouses and children of individuals infected with *H. pylori* were more often seropositive than spouses and children of non-infected individuals (38). Without specifying the

exact mode of transmission, evidence for oral-oral exposure has been suggested by a population-based study in Victoria, Australia, in 1994-95: a significant association was found between positive test results for *H. pylori* and increased number of tooth surfaces with plaque (54).

Intrafamilial clustering of infections and the higher prevalence found in institutionalized populations may indicate that person-to-person contact is a route of transmission, but this could also indicate that there had been a common source of transmission, such as contaminated drinking water or food. The use of molecular typing on bacterial strains isolated from infected members of a family might indicate whether there had been a common source. In a small study of six families in Lithuania, in only two families did two members harbour the same strain (55). In the other four families, each member carried a different strain. Additional studies addressing this issue are warranted.

Outbreaks of *H. pylori* have not been described, except for the few observed following infection after endoscopy (38).

Risk factors for infection

H. pylori is found in all parts of the world, although the prevalence is higher in developing countries. Almost all infections occur before the age of 10 years (7, 8, 53, 56). In industrialized countries *H. pylori* seroprevalence in children younger than 5 years of age is 1-10%, whereas in developing countries rates of more than 50% are common in children of the same age group (45).

In industrialized countries a decrease in the risk of infection is observed in successive generations (a cohort effect) (45, 53). The acquisition of infection does not appear to be seasonal. Infection seems to occur equally commonly among men and women, although one study found a higher risk in men and another found a higher risk in boys aged 3-9 years (7, 46).

In industrialized countries, individuals of higher socioeconomic status are often less likely to be infected, with the exception of those in some ethnic subgroups (7). Intrafamilial clustering of infection is common, and, especially in industrialized countries, infection occurs more often in individuals who live in crowded environments (45, 53, 57). An association has been observed between infection and type of housing: high infection rates have been documented in orphanages, institutions for mentally or physically handicapped people, hospitals for people with severe learning difficulties, and homes for the elderly (45, 57-59). The number of family members in the house (46, 54, 57, 60, 61) and whether beds were shared during childhood (45, 53) were also important risk factors for infection. Some studies have shown a dose-response effect between the extent of overcrowding and risk of infection quantified by the number of people per room or the length of time children shared a bed (45, 60).

High-density crowding is often associated with low socioeconomic status. Several studies have also observed an association with the father's or mother's educational level, the family's income, or parents' occupation (54, 57, 61). In developing countries factors related to the community and religion might be as important as characteristics of the family or home (62). Genetic background also appears to play an important part (53).

An increased prevalence of infection has been associated with increased consumption of food from street vendors (63), supporting the role of food prepared under unhygienic conditions as a probable mechanism of transmission. In a study by Goodman et al. (46) in the southern Colombian Andes, the quantity of raw vegetables (especially lettuce) eaten per day was identified as a risk factor, with a positive dose-response effect.

Detection and identification of *H. pylori*

Several tests are available to detect *H. pylori*. In an infected individual's stomach, *H. pylori* is the only organism that expresses urease: thus *H. pylori* can be detected indirectly by identifying urease in a biopsy specimen (64).

Foods and faeces are not routinely tested for *H. pylori*. When they are tested, isolation and detection of the pathogen can be obscured by many factors (described below), leading to false negative results. Furthermore, the incubation time of the infection might be too long to allow a connection to be made between the source of infection and apparent clinical disease.

H. pylori can enter a viable but nonculturable state under adverse conditions, such as those present in faeces (37); under fully aerobic conditions (17); and in low water activity environments (22). Using specific and sensitive polymerase chain reaction techniques for detecting *H. pylori* might solve this problem, but sensitivity values have been shown to vary (7).

Misidentification as *Campylobacter*

Helicobacter and *Campylobacter* are closely related. Detection of *Campylobacter* species involves enrichment followed by plating on selective media containing a mixture of antibiotics (65). As *H. pylori* is also resistant to many of the antibiotics (7), it may be present but not identified among colonies formed on selective media (during incubation under microaerophilic conditions in the presence of 5–10% CO₂ at 37 °C), as used for detection of *Campylobacter* species. A study by Atabay, Corry, & On identified *Helicobacter pullorum* after closer examination of *Campylobacter*-like isolates from poultry (66).

Species of *Helicobacter* and *Campylobacter* also share immunological features: antibodies have shown cross-reactivity with *Campylobacter jejuni* (37), thus limiting the role of serological identification techniques.

Conclusions

Knowledge about the reservoirs and modes of transmission could help to explain the high prevalence rates found for *H. pylori*. Most studies have been cross-sectional and have focused on the prevalence of and risk factors for *H. pylori* infection. Prevalence is high in developing countries (90%), whereas in industrialized countries the figure is lower (50%) and is decreasing. Childhood is the critical period for infection, and transmission most probably occurs from person to person. The iatrogenic route certainly exists, but is considered relatively unimportant. Much debate surrounds the oral-oral and faecal-oral routes, which are probably more significant.

The human stomach is the only known reservoir of *H. pylori*. However, the possibility that there are other reservoirs cannot be excluded, as the conditions required for growth are met in the gastrointestinal tract of all warm-blooded animals. *H. pylori* has only been isolated from primates, but other *Helicobacter* species have been isolated from other animals. This suggests the presence of host-specific binding sites, although the techniques required for isolation of *Helicobacter* species might differ between various hosts.

H. pylori has been found in faeces, and survival and transmission via faeces-contaminated water can occur. Two studies have suggested possible occurrences of waterborne transmission. A third study reported transmission from uncooked vegetables that had been irrigated with water contaminated with sewage. Other potential vehicles, such as fresh fruit and vegetables, fresh poultry or fish, fresh meats, and some dairy products, have not been found to be contaminated with *H. pylori*, although consuming uncooked lettuce or food from street vendors has been recognized as a risk factor for infection.

H. pylori is unlikely to grow in food, but it may survive in a viable but nonculturable form. This might lead to an underestimation of its prevalence in food. It is not clear how conversion from a viable nonculturable state to a viable state occurs. This remains to be resolved, particularly since it is not known whether coccoid forms of *H. pylori* are able to infect humans.

Molecular-typing techniques, such as ribotyping or restriction fragment length polymorphism, are expected to help trace the route of transmission in future. Epidemiological studies of transmission should be longitudinal and adequately controlled for the numerous likely confounders of the association between risk factors and *H. pylori* infection. ■

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Résumé

Transmission de *Helicobacter pylori*: quel est le rôle des aliments ?

Chez l'homme, *Helicobacter pylori* colonise l'épithélium et le mucus gastrique et s'y développe. Sa présence est associée à la survenue de gastrites et de nombreux arguments indiquent qu'il est à l'origine des ulcères gastroduodénaux et des gastrites chroniques. Depuis 1994, *H. pylori* est rangé parmi les agents cancérogènes pour l'homme.

Dans les pays industrialisés, on observe jusqu'à 50 % des adultes infectés par cet agent pathogène, tandis que dans les pays en développement, on a signalé des taux de prévalence voisins de 90 %. On connaît peu de choses sur le mode de transmission et une étude de la littérature a donc été entreprise pour déterminer si les

aliments jouent le rôle de réservoir ou de véhicule dans la transmission de *H. pylori*. Si la multiplication du germe paraît possible dans les voies digestives de tous les animaux homéothermes, le seul réservoir connu est l'estomac de l'homme. Dans les conditions où sa multiplication n'est pas possible, *H. pylori* peut entrer dans un état viable mais où il ne cultive pas. Il a été identifié sous cette forme dans l'eau mais pas dans les aliments. Le contact interhumain serait le mode de transmission le plus probable, et il n'existe aucune observation directe impliquant les aliments dans la transmission de *H. pylori*.

Resumen

Transmisión de *Helicobacter pylori*: ¿intervienen los alimentos?

Helicobacter pylori coloniza el epitelio y el moco gástricos en el hombre. Su presencia se asocia a gastritis y hay pruebas sustanciales de que causa úlceras pépticas y duodenales y gastritis crónica. Desde 1994 se considera que *H. pylori* es carcinógeno para el ser humano.

En los países industrializados, hasta un 50% de los adultos están infectados por ese patógeno, mientras que en el mundo en desarrollo se ha informado de prevalencias cercanas al 90%. Dado lo poco que se sabe sobre el modo de transmisión, se llevó a cabo una búsqueda en la literatura para determinar si los alimentos pueden actuar como reservorio o como

vehículo en la transmisión de *H. pylori*. Aunque el agente patógeno debería poder proliferar en el aparato digestivo de todos los animales de sangre caliente, el estómago humano es el único reservorio conocido. En las condiciones en que la proliferación no es posible, *H. pylori* puede adoptar un estado en el que es viable, aunque no cultivable. Se ha detectado esa forma de *H. pylori* en el agua, pero no en alimentos. Se considera que el contacto personal es la vía de transmisión más probable, y no hay ninguna prueba directa de que los alimentos intervengan en la transmisión de *H. pylori*.

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