

## Transmission Of *Helicobacter Pylori*

Anthony T. R. Axon

*Centre for Digestive Disease, General Infirmary, Leeds, United Kingdom*

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*Helicobacter* gastroduodenitis is a serious chronic infectious disease that is responsible for widespread morbidity and mortality. An understanding of the way in which it spreads is fundamentally important when considering measures for its control. Its prevalence is highest in the developing world and in individuals with a disadvantaged socio-economic childhood. The disease is believed to be contracted during the early years of life.

A faeco-oral mode of transmission is considered by many to be the most likely mode of spread, however, the organism is difficult to culture both from faeces and from the environment and unlike other enteric organisms *Helicobacter* does not give rise to a diarrhoeal illness that would facilitate its transmission. An oro-oral route of spread has also been suggested, however, *Helicobacter* cannot be cultured from saliva, and if it was spread orally there is no reason why childhood should be the most frequent age for its acquisition.

A third possibility is that the bacterium is transmitted gastro-orally. In favor of this hypothesis, the infection is easily acquired following gastric intubation with inadequately disinfected equipment. Children have a greater tendency to vomit than adults, and tend to explore with their fingers and place foreign objects in their mouths. Initial *Helicobacter* infection causes a dyspeptic illness characterised by mucous vomiting, which may provide a vehicle for transmission. Furthermore, during the acute infection the organism induces achlorhydria in the host, possibly enabling the organism to survive longer in vomited mucus in the absence of acid. This theory fits best with the epidemiological data. Those most at risk are children living in an overcrowded environment who share beds with one another and live in houses that do not possess a fixed hot water supply (thus making cleaning up of vomit more difficult). It is also commoner in institutionalized children and is associated with school catchment areas.

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### NATURAL HISTORY

*Helicobacter* gastritis is probably the commonest chronic infectious disease in the world, affecting over 50 percent of its population. The condition is usually acquired in childhood but can occur at any age. Following infection there is an incubation period of 1-7 days and this is followed by a dyspeptic illness characterised by epigastric pain, malaise, foetor, eructation and mucous vomiting [1]. The illness usually persists for up to two weeks, but in 50 percent of adults the initial infection is asymptomatic. During the acute phase of *Helicobacter* gastritis the stomach is macroscopically inflamed with edema, hemorrhage and erosions, and in some cases these may be macroscopic ulceration or even a pseudo-tumor appearance. Histologically there is an acute inflammatory infiltrate within the mucosa associated with large numbers of polymorphonuclear leucocytes and degeneration in the superficial epithelium. These changes are associated with

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<sup>a</sup>To whom all correspondence should be addressed: Professor Anthony T.R. Axon, Centre for Digestive Disease, General Infirmary, Great George Street, Leeds LS1 3EX United Kingdom. Tel: 44-113-292 2125; Fax: 44 113 292 6968.

<sup>b</sup>Abbreviations: MALT, mucosal associated lymphatic tissue.

achlorhydria and an absence of pepsin from the gastric juice. Following the acute phase of infection the cellular infiltrate changes to a chronic inflammation though a variable number of polymorphonuclear leucocytes persists. The inflammation usually lasts for a lifetime. It may preferentially affect the antrum of the stomach or involve the whole of the stomach. The degree of inflammation varies from patient to patient, and over the years gastric atrophy may occur together with the development of intestinal metaplasia. These changes lead to a diminution in acid secretion, and under these conditions colonization with *Helicobacter pylori* may decline and the organism may disappear altogether. The complications of *Helicobacter* gastritis are duodenal ulcer, gastric ulcer, mucosal associated lymphatic tissue (MALT)<sup>b</sup>, lymphoma and gastric cancer, the likelihood of complications developing is influenced by the virulence of the organism, other environmental factors and the host response to the infection.

*Helicobacter* gastroduodenitis is responsible for 95 percent of duodenal ulcers, 70 percent of gastric ulcers and increases the risk of developing gastric cancer by a factor of nearly eight [2].

### ECONOMIC IMPLICATIONS OF *HELICOBACTER* GASTRODUODENITIS

It is a serious cause of morbidity, mortality and health care costs. Non-invasive methods are available for detecting *Helicobacter* infection and treatments have been developed that enable 90 percent of patients to be cured. In the United Kingdom the cost of non-invasive testing is about £30.00, and the drug costs for treatment £20.00; these figures suggest that in the developed world a therapeutic eradication campaign is financially feasible, while in developing countries this approach would be impractical. Considerable interest has been expressed in the development of vaccines for *H. pylori*, and preliminary studies in animals suggest that a vaccine may not only protect against *Helicobacter* but be effective in curing patients already infected [3]. In the developing world, however, where up to 80 percent of the population is infected, preventative measures may be more effective; but if this is to be achieved it is essential to identify the way in which *H. pylori* is transmitted. In spite of enormous interest in this area, however, its mode of transmission is unknown.

### EPIDEMIOLOGY

*Helicobacter* gastritis is a disease of the under-privileged. Its prevalence is greater in the developing world [4] and in those with a lower income and educational attainment [5]. The differences in the developed world are associated with childhood socioeconomic disadvantage rather than adulthood economic status.

In the West, the prevalence of infection increases with age. There are two possible explanations for this, either individuals acquire infection as the years go by or alternatively older members of the community may have been at greater risk of acquiring infection during childhood, that is to say the changes with age do not result from continual acquisition but represent a cohort effect whereby older people were at greater risk of developing infection in their youth, perhaps reflecting the socio-economic standards that prevailed at that time. Present data suggest that the cohort theory is correct [6, 7]. It seems likely that some of the social conditions that prevailed in Europe at the beginning of the twentieth century were comparable with those experienced in the developing world today. The decline in the incidence of peptic ulcer and gastric cancer that has occurred in most developed countries in recent years may reflect the decline in *H. pylori* infection that has taken place over the past seventy years.

Analysis of the epidemiological data for *H. pylori* and its surrogate markers, peptic ulcer and gastric cancer, suggest, therefore, that infection usually occurs in childhood. Once the disease has been eradicated in adult patients with peptic ulcer recurrence of

infection is uncommon. This may be due to immunological protection. Alternatively, it could be that adults are either less susceptible to infection or come into contact with it less frequently.

### CONDITIONS ASSOCIATED WITH CHILDHOOD INFECTION

Children at risk from infection are not only socio-economically disadvantaged in terms of parental income and subsequent educational attainment, they are also more likely to have lived in overcrowded surroundings, to have shared a bed with a sibling and to have been raised in a house without a fixed hot water supply [8]. They are more likely to have contracted infection if they have lived in an institution, and the school catchment area may also be of relevance. That is to say children from a more advantaged background are still at risk if they attended a school that catered for children of a disadvantaged socio-economic background [9].

### FECO-ORAL TRANSMISSION

Many believe that *H. pylori* is passed by a feco-oral route, analogous to the transmission of hepatitis A. The data in support of this, however, are sparse. Although hepatitis A is usually contracted in childhood the community as a whole is also at risk, not just children. Poor hygiene, although perhaps more relevant in childhood, nevertheless affects the whole community where “flies, fingers, food and feces” apply to all. Most bacterial pathogens that affect the gastrointestinal tract characteristically cause diarrhea. Diarrheal illness in these cases is not a fortuitous event, but rather is a symptom generated by the pathogen usually through specific toxins in order to enable it to spread more readily. It is difficult in an over-crowded community to prevent transmission of a diarrheal illness where hygiene is poor or where the water supply is unsafe. Certain organisms specialize in transmission through food such as salmonella or the water supply (cholera). *H. pylori* does not cause a diarrhea disease. Intestinal commensals such as *E coli* are readily culturable from feces, and pathogens can usually be identified in feces during periods of a diarrhoeal epidemic. It has been difficult to culture *H. pylori* from stool. Two groups have succeeded in culturing the organism, in one study *Helicobacter* was grown from Gambian children with diarrhea, and in another report the organism was identified from freshly obtained fecal material [10]. However, these data have not been confirmed by other workers, and the organisms cultured did not all have the typical genotype of *H. pylori*, their colonial appearance was unusual and somewhat surprisingly the organisms were still cultured from stool after apparently successful eradication from stomach. A number of workers have been able to demonstrate the presence of *H. pylori* DNA within the stool using a PCR technique. However in spite of the high sensitivity of PCR techniques it is surprising that others have experienced difficulty in identifying the DNA within the stool [11]. This may reflect technical difficulties or the presence of inhibitors of the technique within stool or it may suggest that the amount of DNA within the stool itself is sparse. In any event the presence of DNA within the stool does not necessarily imply that viable organisms are present. The evidence in favor of a feco-oral route of transmission is tenuous and while it remains a possibility the data in its favor are unconvincing.

### ORO-ORAL TRANSMISSION

*H. pylori* infects the stomach and it is not unreasonable to presume that from time to time gastro-oesophageal regurgitation will occur and possibly give rise to transient or even permanent oral colonization, that could lead to oro-oral transfer. A number of centers have attempted to identify *H. pylori* in saliva. Those where saliva has been tested before (rather than after) endoscopy have been unsuccessful in culturing the organism. Attempts to grow

the organism from dental plaque has met with mixed success, however most have been unsuccessful and inappropriate methods of diagnosis have been employed in other studies. To date there is little evidence that the organism is present in significant numbers within the mouth. Some epidemiological studies have suggested that an oro-oral transfer may be possible quoting an increased incidence of infection in children within communities where mothers pre-masticated food for their children [12] and in parts of China where a communal bowl is used for people eating with chopsticks. Whilst an oro-oral route of transfer remains a possibility the evidence in its favour is small.

### ENVIRONMENT

It is known that *H. pylori* can remain viable within water for long periods [13] and studies in South America have suggested that *H. pylori* may be transmitted through the water supply [14]. These data are based on experiments that compared different groups of people supplied by separate water supplies. In these communities the source of water supply appeared to be more important than the socio-economic status of the individuals infected. The study however does not rule out the possibility that other factors such as school catchment area might have been a more important common factor. It seems intrinsically unlikely that in developed countries the water supply could be responsible for infection. Whilst water supply remains a possibility for infection in certain areas it seems an unlikely explanation bearing in mind the widespread nature of *H. pylori* infection.

### GASTRO-ORAL TRANSMISSION

If the organism is not passed feco-orally, oro-orally or by an infected water supply what other possibilities are there? *H. pylori* is easily passed from stomach to stomach. Most of the data that we have on acute infection come from case reports that have occurred as a result iatrogenic infection, usually following gastric intubation studies. Two large epidemics [15, 16] arose in separate intubation studies prior to the identification of *H. pylori* but in retrospect there is little doubt that in both *H. pylori* was responsible. Indeed a review of the literature indicates that serial gastric intubation between patients is an effective way of transmitting infection [1]. More recently unequivocal data has shown inadequate disinfection of endoscopes to lead to transmission of the infection [17] and the so called "post endoscopic syndrome" recognised in Japan is often the result of *H. pylori* infection [18]. The increased incidence of *Helicobacter* infection in endoscopists also implicates a gastro-oral route as a potential mode of transfer. It will be argued that each of these examples represent "unnatural" spread in that serial intubation between individuals is not part of normal life. The question arises, however, as to whether gastric juice itself might be the vehicle for *Helicobacter* transmission, in which case vomiting could be the underlying mechanism whereby the disease is spread.

It is possible to infect experimental animals with *Helicobacter* organisms. Early recorded experiments were in 1919 when Kasai and Kobayashi infected rabbits and mice with *Helicobacter felis* [19]. This was done by direct gastro-oral transfer of material. More recently Lee and colleagues have carried out similar experiments on rodents. Rodents are easily infected with *H. felis* using these techniques but in spite of being coprophagic uninfected animals in the same cage do not become infected [20]. This is in contrast to dogs where the organism is readily passed between beagles. One possible explanation for this difference lies in the fact that rodents are unable to vomit whereas dogs and cats do so, and this argues that a gastro-oral rather than a feco-oral route may be the usual method of transfer for *Helicobacter* organisms. These data however have to be considered critically in that *H. felis* is a natural infection of dogs and cats, whereas it is an artificial model when transmitted in rats and mice.

As previously noted, *H. pylori* does not cause diarrhea, it does, however, in the acute phase, cause an illness characterised by mucousy vomiting. Could this be an adaptive feature of *Helicobacter*? That is to say does the organism cause the vomiting illness in order to enable it to spread? This would certainly fit with the epidemiological data. It is a common observation that children tend to vomit more readily than adults, and it is possible that acute *H. pylori* infection causes vomiting in children more commonly than in adults. Whereas adults are careful to avoid being sick in public and from experience know that pangs of nausea mean they should seek privacy and an appropriate receptacle, children lack this experience and control, furthermore children have a tendency to handle, feel and explore with their fingers and then put their fingers and foreign objects in their mouths. There is a possibility therefore that the usual route of transmission of *Helicobacter* in humans may be epidemic vomiting in childhood. If this is the case, infection would be commoner in an over-crowded situation where siblings were sharing beds. In the absence of a fixed hot water supply, it is more difficult to clean up mucousy vomit. One study looking at the relationship between children with infection and parents has demonstrated a relationship between mothers and infected children [21]. The presumption to date has been that it was the mother who possibly infected the children through preparing food, however an alternative construction that it is the mother who has become infected from the children as a result of cleaning up infectious vomit.

One difficulty with the gastro-oral hypothesis is that gastric juice is normally acidic, and although *H. pylori* is resistant to acid by virtue of the urease that it secretes it is unlikely that the organism continue to protect itself indefinitely in an acid medium. It might be to its advantage if it were to be spread in a medium that evaporated slowly and was at neutral pH. One of the characteristics of acute *Helicobacter* infection as indicated earlier is that it is characterized by a period of achlorhydria occurs during the phase of mucus vomiting. It is possible that achlorhydria is caused by the acute inflammation within the gastric mucosa, an alternative explanation, however, is that the organism has adapted in such a way that when it first invades its host it secretes a toxin that switches off acid secretion. For it to do this would in a sense be to its own detriment in a sense in that it has evolved to live in an acidic environment that protects it from competition from other organisms. However, it may be that for the temporary period of initial infection it gains an advantage by providing a suitable medium of achlorhydric mucus transmission.

## SUMMARY

The method whereby *H. pylori* spreads remains unclear. No direct evidence supports any of the proposed mechanisms to date. A gastro-oral mode of transmission perhaps fits best with the available data [20, 22] but requires objective experimentation before it can be generally accepted.

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