Helicobacter pylori

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Spiral organisms have been noted on the gastric mucosa on many occasions over the last 100 years. In 1975, Steer and Colin-Jones associated the presence of Gram negative bacteria on the gastric mucosa with gastritis. However, their failure to culture the organism resulted in the finding being ignored. It was not until Warren and Marshall’s report, in 1983, describing an association between the presence of spiral organisms on the gastric mucosa and antral gastritis in adults, that interest in a pathogenic role for bacteria in gastritis was rekindled. Subsequent studies in adults and children have confirmed this association as well as a strong association with duodenal ulcer disease.

This bacterium was initially referred to as a campylobacter like organism because of its morphologic resemblance to Campylobacter jejuni. After its successful culture, in 1984, the name ‘Campylobacter pyloridis’ was applied to the organism but this was later changed, for grammatical reasons, to Campylobacter pylori. It has recently been designated as the type species of a new genus—termed ‘Helicobacter’. The organism, now called Helicobacter pylori, has been the dominant issue in recent studies on peptic ulcer disease.

_H pylori_ is present on the gastric mucosa beneath the gastric mucus layer and within it. The bacterium does not invade the epithelium. It is usually found on the antral mucosa but may also be present in other parts of the stomach. The organism colonises gastric tissue only. _H pylori_ may be isolated from other sites such as the duodenum, oesophagus, and rectum but only if there is gastric metaplasia at these sites.

Antral biopsy specimens from colonised individuals show an increase in the number of mononuclear cells and in most cases there is an increased number of neutrophils present. There is also depletion of intracellular mucin. Ultrastructural studies have demonstrated _H pylori_ adhering to the surface of the gastric epithelium. This adherence is associated with pedestal formation, a feature identical to that seen with enteropathogenic Escherichia coli attaching to intestinal cells.

**Microbiological features of _H pylori_**

_H pylori_ is a spiral or curved, Gram negative, motile organism which has multiple unipolar flagellae. It produces large amounts of urease and is also catalase and oxidase positive.

_H pylori_ can be successfully cultured under conditions of reduced oxygen but does not grow under aerobic or anaerobic conditions. Growth is optimal at 37°C. It has a long incubation period of five to seven days when grown in primary culture. _H pylori_ can be grown on solid media such as charcoal, blood, or Skirrow’s medium. A haematin source is always necessary for growth. Growth in liquid broth is possible when brucella broth is supplemented with fetal bovine serum.

The bacterium is sensitive in vitro to penicillin, ampicillin, amoxycillin, erythromycin, gentamicin, kanamycin, rifampicin, metronidazole, tetracycline, and cephalothin. It is also sensitive to bismuth salts. Resistance to vancomycin, sulphonamides, trimethoprim, and nalidixic acid has been documented.

To date no serotyping system has been developed. It appears possible to distinguish between strains using restriction endonuclease enzyme DNA digest pattern. Using this method, isolates from each individual are almost always different, although the same strain can be isolated sequentially from an individual.

**H pylori and gastritis**

After Warren and Marshall’s observation there have been many reports confirming an association between the presence of these organisms and gastritis in adults. Almost all individuals with chronic antral gastritis are colonised. It was postulated that the organism could be colonising gastric tissue as a result of inflammation rather than as a cause of it. Subsequent studies in children demonstrated not only an association of _H pylori_ with gastritis, however, but that the organism is associated specifically with primary or unexplained gastritis.

Further evidence implicating _H pylori_ as a gastric pathogen has come from volunteer studies. Two volunteers have ingested the organism and both developed gastritis after gastric colonisation.

_H pylori_ appears to have been associated with ‘epidemic gastritis’. In 1979, Ramsey et al reported 17 healthy volunteers and one patient with Zollinger-Ellison syndrome who became profoundly hypochlorhydric while undergoing studies of acid secretion. These subjects simultaneously developed gastritis, and it was subsequently possible to demonstrate rising titres...
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of H pylori specific antibody after the onset of gastritis. It should be noted that Morris became transiently achlorhydric when he ingested H pylori. The reasons for this apparent achlorhydria at the time of acute infection with H pylori are not understood.

Newell et al have described the presence of H pylori in primates and found a similar association with gastritis in these animals. A closely related organism, Helicobacter mustelae, has been identified on the gastric mucosa of ferrets. This organism is also associated with gastritis. Ferrets are frequently found to have gastritis and peptic ulcer disease. Gnotobiotic piglets can be experimentally infected with H pylori. These piglets develop gastritis in association with gastric colonisation by H pylori.

Perhaps the strongest evidence supporting a pathogenic role for H pylori in gastritis comes from treatment studies. These have demonstrated that eradication of H pylori from the stomach is associated with resolution of antral gastritis.

H pylori and peptic ulceration

DUODENAL ULCER DISEASE

Duodenal ulcer disease is associated with chronic antral gastritis. It is not surprising therefore that a strong association has now been demonstrated between the presence of H pylori on the gastric antrum and chronic duodenal ulcer disease. The organism is present on the gastric mucosa in approximately 80% of adults with duodenal ulcers. H pylori does not colonise the duodenal mucosa except at sites of gastric metaplasia. This trophism for gastric tissue makes H pylori an unlikely candidate to cause directly duodenal ulceration. It has been proposed that gastric metaplasia in the duodenum serves as a precursor of duodenal ulceration by providing a nidus for H pylori colonisation and subsequent inflammation.

Although the role of H pylori in duodenal ulceration is not understood, its importance in this condition is demonstrated by the effect of clearing this organism on duodenal ulcer disease. Relapse rates for duodenal ulcer disease are appreciably reduced when H pylori is cleared from the gastric mucosa.

GASTRIC ULcer DISEASE

The association of H pylori and antral gastritis with gastric ulcer disease is less noticeable. The organism is found in approximately 60% of adults with gastric ulceration. This may be due to the fact that a significant number of gastric ulcers are secondary, being related to drug and other ingestions.

H pylori in children

Several studies have confirmed an association between gastric colonisation with H pylori and antral gastritis in children. There also appears to be a strong association between H pylori associated antral gastritis and chronic duodenal ulcer disease in children.

In 1987, a prospective study in Toronto, examined antral biopsy specimens from 67 of 71 children who underwent upper gastrointestinal endoscopy. Forty nine of these children had normal antral histology and 18 had histological gastritis. Of these 18, 10 had unexplained gastric inflammation whereas eight had an underlying cause identified (gastroduodenal Crohn's disease, eosinophilic gastroenteritis, drug ingestion). Seven of the 10 children with primary or unexplained gastritis had H pylori isolated from the gastric mucosa. In contrast none of the children with secondary gastritis had H pylori isolated. Also none of the 49 children with normal histology had the bacterium cultured from biopsies. A retrospective study using gastric biopsy specimens, obtained over a three year period, resulted in identical findings. These studies provided strong evidence implicating H pylori as a gastric pathogen.

The number of children colonised with H pylori is very low, in Western societies, in comparison with the number of adults colonised. Colonisation increases progressively with age. The prospective study in Toronto found H pylori gastritis in only 10% of children undergoing endoscopy for upper gastrointestinal symptoms. Hill et al found the organism in six of 38 (16%) children studied in Australia. Cadamel et al found H pylori in eight of 25 children (32%) studied in Belgium. More recently Glassman et al detected the organism in 10% of children undergoing upper endoscopy in New York. Studies of children, in Western societies, indicate that colonisation almost never occurs below 8 years of age.

PEPTIC ULCER DISEASE

In two prospective studies from Toronto H pylori was found in association with duodenal ulcer disease in all 13 cases in which ulcers were detected. In a retrospective study Kilbridge et al found H pylori to be present on the antral mucosa in eight of nine patients who had duodenal ulcer disease. Therefore, although duodenal ulcer disease is uncommon in children, there is a strong correlation between the presence of such ulceration and H pylori associated antral gastritis. An association with gastric ulcer disease has not been clearly demonstrated as primary gastric ulceration is rare in children.

SYMPTOMs

There has been no major prospective study of presenting symptoms in children colonised with H pylori. Epigastric pain and vomiting appear to be major presenting symptoms. Children with duodenal ulcer disease have more noticeable symptoms than those with gastritis alone. Clearing of H pylori from the gastric mucosa and resultant improvement or healing of gastritis is associated with a definite improvement in symptoms. This improvement in symptoms is, however, primarily seen in those patients who have associated duodenal ulcer disease. Oderda et al found that clearing H pylori from the gastric mucosa using amoxycillin alone resulted in the disappearance of symptoms in children. Although the infection recurred in
most of the children, however, very few developed a relapse of symptoms. Therefore, *H. pylori* associated gastritis, in the absence of ulcer disease, may not be a significant cause of symptoms. This supposition is supported by the finding that *H. pylori* colonisation is widespread in the adult community as well as in siblings of children with documented *H. pylori* gastritis.22 Large prospective studies of children undergoing endoscopy will be needed to clarify this issue.

**ENDOSCOPIC FINDINGS**

Children and adults with *H. pylori* associated gastritis often have normal endoscopic findings.6 15 It is essential to obtain antral biopsy specimens during endoscopy. These specimens may demonstrate appreciable gastritis microscopically in the absence of endoscopic findings.

**Diagnosis of *H. pylori* infection**

**CULTURE**

The 'gold standard' for diagnosis of *H. pylori* infection is culture of the organism from an antral biopsy specimen. The specimen can be ground and the material used to inoculate blood agar, chocolate agar, or Skirrow's medium.6 10 These inoculations should be done within 60 minutes of the biopsy being taken. The plates are incubated at 37°C under microaerophilic conditions for up to seven days. *H. pylori* colonies are very small and translucent and usually very few colonies are present on a primary culture from a child. The organism is identified as *H. pylori* if it is positive for urease, catalase, and oxidase and produces a negative reaction for hippurate hydrolysis and nitrate reduction.5

**STAINING TECHNIQUES**

Because of its spiral appearance and unique location within and beneath the gastric mucus layer, *H. pylori* can be demonstrated by various stains on histological sections. The Warthin-Starry silver stain has been widely used to demonstrate the organism. The silver stain allows for easy identification of darkly staining bacteria against a bright background. This method of identifying *H. pylori* correlates very well with culture in children.6 10 However, these stains are tedious to perform. Simpler methods include the use of a giemsa stain which is also very effective.7 29

**UREASE TESTS**

A positive urease reaction occurring when a gastric biopsy specimen is incubated in a urea medium is usually indicative of the presence of *H. pylori* on the gastric mucosa. The biopsy specimen is placed on a Christensen's urea slope and a positive reaction is indicated by a change in colour of the medium from tan to pink.30 Commercial tests for urease production can identify *H. pylori* in approximately 90% of biopsies from colonised children.29

Urease breath tests have been developed to detect *H. pylori* colonisation by non-invasive means. Labelled urea (13C or 14C) is ingested by individuals and the breakdown of urea by bacterial urease results in the appearance of labelled carbon dioxide in the expired air of colonised subjects.31 32 Quantitation of expired labelled carbon dioxide allows for the indirect diagnosis of *H. pylori* gastritis. These tests are extremely sensitive. A 13C label is more ideal for use in children as it is not radioactive. The label, however, is very expensive and the test requires the use of mass spectrometry.

**SEROLOGY**

A *H. pylori* specific IgG serologic response is both highly sensitive (96%) and highly specific (99%) in identifying children with *H. pylori* associated gastritis.55 Enzyme linked immunosorbent assay systems are now widely used to detect this serological response using various *H. pylori* antigenic preparations. The IgG immune response is the most sensitive indicator of infection. The IgA immune response is also used whereas specific IgM measurements are not reliable.27 Serological testing may therefore, present a very good diagnostic test for *H. pylori* associated gastritis in children.

**Epidemiology**

Serology has provided the optimal means of studying the incidence of *H. pylori* colonisation. In Western countries, studies have shown that children and young adults are rarely colonised by *H. pylori*.22 27 The incidence of infection increases progressively with age until approximately 50–60% of the population are colonised at 60 years.27 The reason for this increase in colonisation with age is not known. There are indications that colonisation occurs earlier in life and ultimately affects almost the entire population in less developed countries.33

*H. pylori* has not been isolated from a site outside of the gastrointestinal tract. There is a single report of successful culture of the organism from dental plaque.34 There is no known natural reservoir in the environment for this bacterium. A recent study of children and their families provides strong evidence supporting person to person transmission of this organism.35 In this study, 73% of parents of *H. pylori* positive children had a *H. pylori* specific serological response, whereas only 24% of parents of children who were not colonised had such a response. The strongest evidence of person to person spread was provided by studies on the siblings of the *H. pylori* colonised children. Eighty one percent of these siblings were found to have serological evidence of *H. pylori* colonisation in comparison with 13% of controls.

It is unclear whether members of a family are colonised by the same strain of *H. pylori*. Strain identification using DNA digest patterns has shown the same strain infecting several members of the same family in Europe. In Canada, however, young siblings were shown to be colonised by different strains.9 Furthermore, it appears that an individual can harbour more than one strain of the organism simultan-
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duodenal morbidity. Chronic gastritis that accompanies ulcer disease in children is often associated with duodenal ulcer disease. However, relapse of ulcer disease occurs in most patients (children and adults) after treatment is stopped. This phenomenon is not due to the organism being eradicated by the treatment or to antibiotic resistance. Rather, it is due to the persistence of the organism in the stomach and its subsequent re-colonization after the treatment is stopped. This issue is critical and needs further investigation.

**Conclusion**

H. pylori is a cause of chronic antral gastritis. Furthermore, clearing of H. pylori from the gastric mucosa reduces the rate of relapse of duodenal ulcer disease. Several questions still need to be studied, including the role of this bacterium in peptic disease. There have been hypotheses published to explain how H. pylori colonization could result in chronic duodenal ulcer disease. These hypotheses have been based on the ability of H. pylori to break down mucus. A recent study indicates that H. pylori is not effective in degrading mucus. This association between antral gastritis and H. pylori, and duodenal ulceration is therefore still not understood. Why does the organism colonise gastric tissue only? How does H. pylori cause inflammation? Is there a natural reservoir for this organism in the environment? Research projects are presently being undertaken in several centres that will hopefully provide answers to these questions.

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Campylobacter pylori and Campylobacter mustelae to Helicobacter gen nov as Helicobacter pylori comb nov and Helicobacter mustelae comb nov, respectively. *International Journal of Systematic Bacteriology* 1989;39:397–405.


See related paper on p 1212.


