

## REGULAR REVIEW

# 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.<sup>1</sup> 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.<sup>2</sup> Subsequent studies in adults and children have confirmed this association as well as a strong association with duodenal ulcer disease.<sup>3 4</sup>

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*'.<sup>5</sup> 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.<sup>3 6</sup> 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.<sup>7 8</sup> *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.<sup>8</sup>

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.<sup>7</sup> There is also depletion of intracellular mucin. Ultrastructural studies have demonstrated *H pylori* adhering to the surface of the gastric epithelium.<sup>3</sup> 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.<sup>3 5</sup>

*H pylori* can be successfully cultured under conditions of reduced oxygen but does not grow under aerobic or anaerobic conditions.<sup>5</sup> 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 haemin source is always necessary for growth. Growth in liquid broth is possible when brucella broth is supplemented with fetal bovine serum.<sup>5</sup>

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.<sup>5</sup>

To date no serotyping system has been developed. It appears possible to distinguish between strains using restriction endonuclease enzyme DNA digest pattern.<sup>9</sup> 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.<sup>3 4</sup> 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.<sup>6 10</sup>

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.<sup>11 12</sup>

*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,<sup>13</sup> and it was subsequently possible to demonstrate rising titres

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of *H pylori* specific antibody after the onset of gastritis.<sup>14</sup> It should be noted that Morris became transiently achlorhydric when he ingested *H pylori*.<sup>12</sup> 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.<sup>15</sup> A closely related organism, *Helicobacter mustelae*, has been identified on the gastric mucosa of ferrets.<sup>5</sup> 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*.<sup>16</sup>

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.<sup>17-20</sup>

### ***H pylori* and peptic ulceration**

#### **DUODENAL ULCER DISEASE**

Duodenal ulcer disease is associated with chronic antral gastritis.<sup>21</sup> 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.<sup>3 4</sup> The organism is present on the gastric mucosa in approximately 80% of adults with duodenal ulcers.<sup>4</sup> *H pylori* does not colonise the duodenal mucosa except at sites of gastric metaplasia.<sup>7 8</sup> This tropism 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.<sup>8</sup>

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.<sup>17</sup>

#### **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.<sup>4</sup> 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.<sup>6 10 22-26</sup> There also appears to be a strong association between *H pylori* associated antral gastritis and chronic duodenal ulcer disease in children.<sup>6 22 26</sup>

In 1987, a prospective study in Toronto,

examined antral biopsy specimens from 67 of 71 children who underwent upper gastrointestinal endoscopy.<sup>6</sup> 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.<sup>10</sup> 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.<sup>22 27</sup> Colonisation increases progressively with age.<sup>27</sup> The prospective study in Toronto found *H pylori* gastritis in only 10% of children undergoing endoscopy for upper gastrointestinal symptoms.<sup>6</sup> Hill *et al* found the organism in six of 38 (16%) children studied in Australia.<sup>23</sup> Cadranet *et al* found *H pylori* in eight of 25 children (32%) studied in Belgium.<sup>24</sup> More recently Glassman *et al* detected the organism in 10% of children undergoing upper endoscopy in New York.<sup>25</sup> Studies of children, in Western societies, indicate that colonisation almost never occurs below 8 years of age.<sup>6 10 22 23 25</sup>

#### **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.<sup>6 22</sup> 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.<sup>26</sup> 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.<sup>28</sup>

#### **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.<sup>6 24 25</sup> Children with duodenal ulcer disease have more noticeable symptoms than those with gastritis alone.<sup>19</sup>

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.<sup>19</sup> Oderda *et al* found that clearing *H pylori* from the gastric mucosa using amoxicillin alone resulted in the disappearance of symptoms in children.<sup>29</sup> 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.<sup>22 27</sup> 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.<sup>6 18</sup> 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.<sup>5 6</sup> 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.<sup>5</sup>

##### 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.<sup>6 22</sup> However, these stains are tedious to perform. Simpler methods include the use of a giemsa stain which is also very effective.<sup>7 29</sup>

##### 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.<sup>30</sup> Commercial tests for urease production can identify *H pylori* in approximately 90% of biopsies from colonised children.<sup>29</sup>

Urease breath tests have been developed to

detect *H pylori* colonisation by non-invasive means. Labelled urea (<sup>13</sup>C or <sup>14</sup>C) 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.<sup>31 32</sup> Quantitation of expired labelled carbon dioxide allows for the indirect diagnosis of *H pylori* gastritis. These tests are extremely sensitive. A <sup>13</sup>C 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.<sup>22</sup> 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.<sup>27</sup> 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*.<sup>22 27</sup> The incidence of infection increases progressively with age until approximately 50–60% of the population are colonised at 60 years.<sup>27</sup> 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.<sup>33</sup>

*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.<sup>34</sup> 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.<sup>22</sup> 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.<sup>9</sup> Furthermore, it appears that an individual can harbour more than one strain of the organism simultan-

eously.<sup>35</sup> Further studies are therefore needed to clarify this issue.

### Treatment

Eradication of *H pylori* from the gastric mucosa is correlated with healing of antral gastritis in adults and children.<sup>17-20 36</sup> This occurs irrespective of the particular agent that is used to clear the organism. While *H pylori* is sensitive to many antibiotics in vitro, this sensitivity is not correlated with clearing of the organism in vivo.<sup>37</sup> It has been postulated that the failure of antibiotic monotherapy adequately to clear *H pylori* in vivo may be due to the lack of efficacy of the antibiotics in the acid environment of the stomach.<sup>37</sup>

*H pylori* is optimally cleared from the gastric mucosa using combinations of bismuth salts and various antibiotics.<sup>20 37</sup> Treatment with bismuth salts alone is successful in clearing *H pylori* from the gastric mucosa in approximately 50% of adult patients.<sup>17 18 20</sup> Recurrence of infection is common after treatment of *H pylori* by bismuth alone or antibiotic monotherapy.<sup>20 29</sup>

Oderda *et al* treated children with amoxicillin. Immediately after treatment the organism was absent from gastric biopsy specimens in 85% of treated children.<sup>29</sup> However, three months later the infection was present in 73% of these children. Combination therapy using a bismuth preparation and an antibiotic such as ampicillin or metronidazole increases the percentage of adult patients in whom the organism is cleared.<sup>20 37</sup> Studies from Leeds and Toronto have reported clearing of *H pylori* from the antral mucosa in 70% of children treated with bismuth subsalicylate or tripotassium dicitrate bismuthate and oral ampicillin (MJ Mahony, JI Wyatt, JM Littlewood; British Society of Gastroenterology, Autumn 1989).<sup>19</sup> In Italy, 94% of children treated with amoxicillin and tinidazole were successfully cleared of *H pylori* and six months later 75% of them remained clear.<sup>36</sup> There are, however, ethical considerations in performing repeat endoscopies on asymptomatic children and long term relapse rates will be difficult to determine. More recently triple therapy using bismuth combined with two antibiotics, such as amoxicillin and metronidazole, has been reported to be successful in long term eradication of *H pylori*. Evidence is accumulating that *H pylori* rapidly develops resistance to antibiotics such as metronidazole, however, although resistance is less likely to occur when the antibiotic treatment is combined with bismuth. Such triple therapy is not presently justified in situations other than controlled trials.

### DUODENAL ULCER DISEASE

H<sub>2</sub> antagonists have appreciably reduced the morbidity associated with chronic peptic ulcer disease. However, relapse of ulcer disease occurs in most patients (children and adults) after treatment is stopped.<sup>17 28</sup> These agents have no effect on *H pylori* colonisation or on the chronic gastritis that is invariably associated with duodenal ulcer disease.<sup>18 20</sup> Bismuth salts

are as successful as H<sub>2</sub> antagonists in healing duodenal ulcers. More importantly, duodenal ulcer disease relapses less frequently after treated with bismuth.<sup>38</sup> This appears to be due to the effect of bismuth on *H pylori* associated antral gastritis.<sup>17</sup> Recent studies have shown a considerable reduction in the rate of relapse of duodenal ulcer disease if *H pylori* is cleared from the gastric mucosa during treatment.<sup>17</sup> Recurrence of ulcer disease in such patients is associated with reinfection with *H pylori*.

### RECOMMENDATION ON TREATMENT

While the search is continuing for the optimal treatment of *H pylori* associated gastritis, we have to define who requires treatment. There is, at present, no evidence to indicate that treatment is necessary for *H pylori* associated gastritis in the absence of ulcer disease. Chronic duodenal ulcer disease in children has a natural history identical to duodenal ulcer disease in adults.<sup>28</sup> The evidence from studies in adults would seem to justify treating children with duodenal ulcer disease using colloidal bismuth subcitrate (bismuth chelate, tripotassium dicitrate bismuthate) for four weeks combined with an antibiotic such as ampicillin or metronidazole for two weeks. Mahony *et al* used colloidal bismuth subcitrate, 240 mg twice a day in children and did not encounter bismuth toxicity (MJ Mahony, JI Wyatt, JM Littlewood; British Society of Gastroenterology, Autumn 1989).

### 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 if we are to fully understand the role of this bacterium in peptic disease. There have been hypotheses published to explain how *H pylori* colonisation could result in chronic duodenal ulcer disease. These hypotheses have relied on the ability of *H pylori* to break down mucus. A recent study indicates that *H pylori* is not effective in degrading mucus.<sup>39</sup> This association between antral gastritis, *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.

I wish to acknowledge Dr Liam Carroll for providing a critical review of this manuscript and Sharon Bennis for typing and proof reading.

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