

REVIEW

## ***HELICOBACTER PYLORI* AND RECURRENT ABDOMINAL PAIN: A REVIEW OF THE LITERATURE**

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*Helicobacter pylori* (HP) was first described in 1983 by Warren and Marshall.<sup>1</sup> It is a spiral-shaped bacterium measuring 2-4µm x 0.5-1.0µm. Since it was discovered, the organism has rarely been isolated from sites other than the stomach.<sup>2</sup> Available evidence, therefore, points to the human stomach as the normal habitat of this bacterium. The infection is contracted primarily in childhood.<sup>3</sup> It has been shown that colonisation by HP is rare under the age of five years, but thereafter, it becomes gradually more frequent, and by sixty years of age more than 50% of individuals may be affected.<sup>4</sup>

The close relationship between HP and peptic ulcer disease is well-recognised. In adult studies, over 90% of duodenal ulcer and 70-90% of gastric ulcer patients have the infection.<sup>5</sup> In paediatric studies, HP is discovered in 92% (range 33% to 100%) of children with duodenal ulcers and in 25% (range 11% to 75%) of children with gastric ulcers.<sup>6</sup> In such cases, the relationship between the organism and abdominal pain appears clear.

However, most patients infected with the organism do not have peptic ulcer disease and are asymptomatic. Infection with the organism is likely to result in the development of gastritis in all subjects.<sup>7</sup> but the significance of this remains unclear. Furthermore, the majority of infected humans will continue to be free of symptoms throughout their lifetime; a small minority will get peptic ulcer disease (lifetime risk 15%) and an even smaller proportion will

develop gastric cancer, including mucosa-associated lymphoid tissue lymphoma and adenocarcinoma (lifetime risk 0.1%).<sup>8,9</sup>

The question arises as to whether HP plays a role at all in children with recurrent abdominal pain. There have been numerous studies on this topic but the answer is not always straightforward and clear-cut. At times, the evidence is only indirect. This article looks at the problem based on available studies in answer to the following queries:

1. How common is HP infection in children today?
2. How common is recurrent abdominal pain in children with HP?
3. How common is HP in children with recurrent abdominal pain?
4. What is the effect of eradicating HP in children with recurrent abdominal pain?

### **How common is *Helicobacter pylori* infection in children today?**

When considering the extent to which HP infection contributes towards recurrent abdominal pain, it would be helpful to know the prevalence of the organism among children in general, especially among asymptomatic children.

In a large cross-sectional study in southern China, Mitchell<sup>10</sup> found that by the age of five years, a high proportion (23%) of children were already infected with HP. Over this age, the difference in seroprevalence of HP for each age group increased by about 1% a year. The overall

prevalence is 44.2%.

In Belo Horizonte, Brazil Oliveira,<sup>11</sup> using a serological test, found the prevalence of HP among 249 children to be 34.1% and was similar in boys (35.8%) and girls (32.2%). It was noted that the prevalence increased significantly ( $p=0.001$ ) with age as follows: 1 month–2 years, 16.4%; 3–5 years, 36.7%; 6–8 years, 29.5%; 9–11 years, 48.8%; 12–14 years, 42.8% and 15–18 years, 64.3%.

Lanciers found the prevalence of HP seropositivity in a population of 833 symptom-free children to be 8.2%.<sup>12</sup> A significant difference was observed between symptom-free Caucasian and non-Caucasian children ( $p < 0.001$ ). Tsai<sup>13</sup> collected serum samples from 428 apparently healthy children under the age of twelve years in Taipei city in Taiwan and found an overall prevalence of HP infection of 8.4%. The prevalence was low in the age groups one to three years (0.9%) and three to six years (3.7%). After six years of age, the prevalence increased significantly, reaching 19.4% at nine to twelve years of age. It was concluded that HP infection was independent of gender but increased with age.

Blecker<sup>14</sup> studied the seroprevalence of HP in 466 asymptomatic children from different ethnic backgrounds all born in Belgium. Thirty four (7.3%) had positive titres for HP. A significant increase was noted in the number of seropositive patients with advancing age (5.4% in the age group two to eight years and 13.4% in the age group eight to fourteen years;  $p>0.001$ ). They also found a significant difference in the prevalence of HP seropositivity between Caucasian Belgian children and non-Caucasian children of different ethnic backgrounds.

The relatively high prevalence of HP seropositivity particularly in asymptomatic older children shown in Tsai's (19.4%) and Blecker's (13.4%) studies suggest that the infection can be present without necessarily causing recurrent abdominal pain.

In Malaysia, the overall prevalence of HP

among asymptomatic children is 10.3%.<sup>15</sup> Seropositivity was most common in the Indians and lowest in the Malays ( $p=0.001$ ). A significant rise was noted with increasing age ( $p=0.009$ ). Among 11 to 17 year olds, as many as 16.7% of asymptomatic children were seropositive for HP. The Malaysian experience therefore also adds to the body of evidence cited earlier that the organism may be present without symptoms.

#### **How common is recurrent abdominal pain in children with *Helicobacter pylori*?**

Raymond<sup>16</sup> found that recurrent abdominal pain was present in 63.3% of 77 children with HP, determined by endoscopy, histology and cultures, as compared to 48.6% of a control group of 74 age-matched children negative for the organism. Weight loss was present in 6.5% of positive children versus 0% of control children while a family history of peptic ulcer was present in 14.2% of positive children versus 5.4% of controls. Based on these findings, Raymond suggested that HP should be looked for in children with recurrent abdominal pain.

On the other hand, Bode<sup>17,18</sup> using a <sup>13</sup>C-urea breath test to determine the presence of HP, found that among 127 infected children, the infection was not positively related to specific gastrointestinal symptomatology. In fact, infected children had even fewer symptoms when compared with uninfected children. They concluded that HP infection in children is mostly asymptomatic and not associated with specific gastrointestinal symptoms.

In a London-based study, O'Donohoe<sup>19</sup> recorded a HP seropositivity of 16.7% among school-children aged between four and thirteen years. However, they could not demonstrate any relationship between HP seropositivity and a personal or family history of recurrent abdominal pain or the nature of the pain.

#### **How common is *Helicobacter pylori* in children with recurrent abdominal pain?**

The prevalence rates of HP infection in children with recurrent abdominal pain are quite variable in different countries. Many studies have already been done on this topic and new studies are constantly being published. The following paragraphs review some of the available studies. In Denmark, Wewer<sup>20</sup> obtained positive cultures for HP in the gastric antrum of six out of thirty seven (16%) children aged five to sixteen years with recurrent abdominal pain. Five children had concomitant histological inflammation or gastritis, but none had endoscopic changes. Among the thirty one HP negative children, seven (23%) had inactive chronic gastritis and one (3%) had inactive chronic duodenitis, the significance of which is not clear.

Heldenberg<sup>21</sup> found a high prevalence of HP (54%), indicated by Gram stain and urease test, among 80 Israeli children undergoing upper gastrointestinal endoscopy for recurrent abdominal pain. Of these HP positive children, endoscopic findings were abnormal in 46.5% (antral nodularity, antral erythema, gastric or duodenal ulceration), but histological examination revealed chronic gastritis in 97.7%. Conversely, of the HP negative children, 86.5% were normal endoscopically and 94.6% normal histologically.

In Greece, Roma<sup>22</sup> endoscoped 396 children complaining of recurrent abdominal pain and found that, histologically, there was HP in 113 patients (28.5%) and mucosal inflammation in 338 children (85.4%). Factors that differentiated HP positive from negative children included older age 11 years versus 8.1 years ( $p < 0.001$ ) and male gender ( $p < 0.001$ ). No significant difference was noted regarding incidence and character of the presenting symptoms. Histologically confirmed gastritis was the most marked finding in HP positive children compared with negative ones (98.2% versus 19%,  $p < 0.001$ ). The incidence of peptic ulcer was also higher in positive children (5.3% versus 1%,  $p < 0.05$ ).

In Singapore, forty-eight children with recurrent

abdominal pain were studied endoscopically for the presence of gastritis and HP infection.<sup>23</sup> Fifteen children had histological evidence of gastritis with eight of them also having HP infection. The majority of infected patients had severe degrees of acute following chronic gastritis. In Thailand, sixty five children with recurrent abdominal pain underwent gastrointestinal endoscopy which revealed HP gastritis without duodenal ulcer in 16.9% of cases.<sup>24</sup> The prevalences of infection in recurrent abdominal pain and asymptomatic children were not found to be different.

In Arkansas, USA, Fiodorek<sup>25</sup> studied twenty children with a previous diagnosis of functional recurrent abdominal pain using a <sup>13</sup>C-urea breath test and serology. Only two had evidence of HP infection. In the Netherlands, van der Meer<sup>26</sup> found antibodies to HP in seven of eighty two patients with recurrent abdominal pain (8.5%) and two of thirty nine controls (5.1%). The difference is not significant and van der Meer concluded that recurrent abdominal pain is only rarely caused in children by HP infection.

In Australia, Hardikar<sup>27</sup> carried a prospective case-control serological study in children with recurrent abdominal pain. Interestingly, a negative association between HP and recurrent abdominal pain was found: five subjects (5.1%) and fourteen controls (14.3%) had raised serum IgG antibodies to HP (adjusted OR, 0.21; 95% CI, 0.05–0.85). Hardikar concluded in the study that HP is unlikely to have an important causative role in recurrent abdominal pain.

In Malaysia, a preliminary endoscopic study of 10 children with recurrent abdominal pain showed that none of the children had any evidence of HP.<sup>28</sup> The study is still ongoing and more data will be available in due course.

Thus, various studies appear to give different answers. In order to assess the evidence for a cause-and-effect relationship between HP infection, antral gastritis, peptic ulcer disease and recurrent abdominal pain Macarthur<sup>6</sup> performed a MEDLINE search from January

1983 through July 1994 and retrieved a total of 45 studies (case series, cross-sectional surveys and treatment trials). He found the rate ratio of antral gastritis in children with HP infection as compared with uninfected children ranged from 1.9 to 71.0 (median, 4.6). However, prevalence rates of infection in children with recurrent abdominal pain were not inconsistent and ranged from 0% to 81% with a median of 22%. In children meeting Apley's criteria, the rates were even lower with a range of 0% to 9% and a median of 6%. He concluded that although there is strong evidence for an association between HP and antral gastritis, there was weak or no evidence for an association with recurrent abdominal pain. In 1999, Macarthur<sup>29</sup> did another MEDLINE search for papers between January 1983 and July 1998, restricting it this time to prospective, controlled studies reporting empirical data on children up to the age of eighteen years. Again, he came to the conclusion that current evidence does not support an association between HP infection and recurrent abdominal pain in children.

#### **The effect of eradicating *Helicobacter pylori* in children with recurrent abdominal pain?**

Some studies have shown that there may be a group of children with recurrent abdominal pain with gastritis and HP who respond to eradication of the organism. For example, Heldenberg<sup>21</sup> eradicated the organism in thirty four children with recurrent abdominal pain and managed to achieve a sustained symptomatic improvement in all of them.

However, the relationship may not be as clear as it seems. Oderda<sup>30</sup> treated children with recurrent abdominal pain and HP with amoxicillin. Symptoms that were present before treatment disappeared within a fortnight in most cases. On endoscopy 3 months later, HP gastritis recurred in 73% but symptoms recurred in only 13%.

#### **Conclusion**

While the relationship between HP and peptic ulcer disease is relatively clear-cut, the question whether HP gastritis in the absence of peptic ulcer disease as a contributing factor in recurrent abdominal pain is still difficult to answer with complete confidence although most authorities are of the opinion that it is not. Hence, unless there is peptic ulcer disease, current evidence does not support eradicating the organism in children on the basis of tests such as serology. More studies, especially long-term follow-up studies, are required on the relationship between HP gastritis and recurrent abdominal pain.

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