Extradigestive manifestations of *Helicobacter pylori* infection in children and adolescents

Philip M Sherman MD FRCPC, Frank YH Lin MD FRCPC

**Abstract**

*Helicobacter pylori* infection fulfills each of Koch’s postulates as a human pathogen causing chronic active gastritis. Disease consequences that develop in a subset of infected subjects include peptic ulcerations, gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma. More recently, multiple publications have advocated a role for *H pylori* infection in causing a variety of extraintestinal manifestations. Many of these reports suffer from being case reports or case series without adequate controls. As a result, purported manifestations may simply be coincidental in nature. On the other hand, increasing evidence supports *H pylori* infection as a cause of sideropenic (refractory iron deficiency) anemia. Moderate evidence supports *H pylori* gastric infection as a cause of some cases of immune thrombocytopenic purpura due to molecular mimicry. Guidelines should be adjusted in accordance with advancing knowledge in the field.

**Key Words:** Anemia; Children; Food allergy; *H pylori*; Short stature; Thrombocytopenia

Since the first successful culture of *Helicobacter pylori* in the early 1980s by Barry Marshall and Robin Warren in Perth, Australia, much has been learned about this gastric pathogen (1). Each of Koch’s postulates and all of Hill’s criteria for causal inference have been fulfilled, showing that *H pylori* causes a chronic active, superficial gastritis in infected individuals (1). Although most humans remain asymptomatic throughout their lifetime, a subset of infected persons develop disease complicating the gastric infection.

There is compelling evidence that *H pylori* infection is a cause of gastric and duodenal ulcers (2). The natural history of ulcer recurrence can be altered by eradicating the gastric infection (3). Similarly, there is strong epidemiological evidence supporting the contention that *H pylori* infection increases the risk of developing gastric adenocarcinoma later in life (4). In addition, certain animal models (5) support the contention that *H pylori* infection is a risk factor promoting the complex cascade of events that ultimately determine carcinogenesis. Multiple reports (6) indicate that at least a subset of mucosa-associated lymphoid tissue lymphomas can regress following eradication of *H pylori* infection.

Interest has arisen on the potential for related *Helicobacters* to cause disease in the intestinal tract and in the hepatobiliary system (reviewed by Gasbarrini et al [7]). Much of this work has arisen from studies in animal models. For example, it is clear that inflammatory bowel disease in interleukin-10-deficient mice is much more severe in mice that are colonized with *Helicobacter hepaticus* compared with animals clear of the infection (8). Similarly, colitis in the cotton-topped tamarin appears dependent on colonization of the large bowel by a novel *Helicobacter* (9).

The potential for *H pylori* – or a novel related *Helicobacter* species – to cause disease in the human hepatobiliary tract is being evaluated (10). For instance, several investigators (11) have detected the presence of *Helicobacter*-specific DNA (using the polymerase chain reaction) in samples obtained from subjects with primary sclerosing cholangitis. However, the successful culture of viable organisms from biliary epithelium has not been reproducible.

More recently, an increasing number of reports have considered the possibility that *H pylori* infection of the stomach may have consequences for adverse health effects outside of the gastrointestinal tract (Table 1). For instance, multiple studies have considered the potential for an infectious etiology of coronary artery disease. However, the current consensus (based on available literature) does not provide support for the contention that there is a cause and effect relationship between *H pylori* gastric infection and atherosclerotic heart disease.

**Research Institute:** Hospital for Sick Children, University of Toronto, Toronto, Ontario

**Correspondence:** Dr Philip M Sherman, Gastroenterology and Nutrition, Hospital for Sick Children, 555 University Avenue, Room 8409, Toronto, Ontario M5G 1X8. Telephone 416-813-7734, fax 416-813-6531, e-mail sherman@sickkids.ca

**Can J Gastroenterol Vol 19 No 7 July 2005**

©2005 Pul漕 Group Inc. All rights reserved

421
disease (reviewed by Gasbarrini et al [7]). Similar weaknesses in study design limit enthusiasm for supporting the contention that H pylori is a causative agent in a variety of other purported disease conditions. For instance, just in the past year, H pylori infection has been considered a potential cause of nongonococcal urethritis (12), aphthous stomatitis (13) and glaucoma (14). However, the level of supporting evidence is limited and certainly insufficient for current consensus conferences to advocate therapeutic interventions in such clinical settings.

The present review will focus on reported extradigestive manifestations of H pylori infection in the pediatric age group (Table 2). A critical review of the available information is provided, together with recommendations for updating current consensus conference recommendations based on advances in knowledge in the field.

**Sideropenic (refractory iron deficiency) anemia**

A series of case reports, both in children and adults, first indicated that H pylori infection could be a potential cause of otherwise unexplained sideropenic anemia (reviewed by Barabino [15]). Sideropenic anemia that does not respond to supplemental iron therapy can resolve following successful eradication of H pylori from the antrum of the stomach (16).

Subsequent case controlled studies have confirmed these findings by showing higher rates of H pylori infection in patients with unexplained sideropenic anemia compared with age- and sex-matched controls without iron deficiency (17). Lower iron stores are also evident in H pylori-infected subjects compared with age- and sex-matched controls without gastric infection (18). Controlled studies confirm that eradication of H pylori results in increased hemoglobin levels, whereas iron supplementation alone has no effect (19).

The biological explanation for H pylori infection causing sideropenic anemia remains uncertain. Initial considerations focused on occult blood loss due to chronic active superficial gastritis induced by H pylori (20). However, subsequent studies (21) have not confirmed evidence of occult blood loss. Infection with H pylori may cause impairment in iron uptake and increases in iron demand. Hypoacidity because of paragastrostis (21) and low ascorbic acid levels in the stomach of H pylori-infected patients also could result in impaired duodenal iron absorption (22). In addition, gastric mucosa levels of lactoferrin, an iron-binding protein, are elevated in H pylori-infected patients with iron deficiency (23), indicating a possible role between increased lactoferrin sequestration and iron utilization by the organism. Alternatively, H pylori may compete with the infected host for available dietary iron. For example, H pylori possesses multiple iron acquisition systems, which can avidly and efficiently take up iron available in the microenvironment of the lumen of the stomach (24).

**TABLE 1**

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Neurological</th>
<th>Autoimmune</th>
<th>Dermatological</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic heart disease, stroke</td>
<td>Parkinson's disease, migraine</td>
<td>Immune thrymboctyopenic purpura, Raynaud's phenomenon, Sjogren's syndrome, diabetes mellitus</td>
<td>Chronic urticaria, angioedema, rosacea, alopecia areata</td>
<td>Halitosis, hyperemesis gravidarum, anorexia of aging</td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Immune thrombocytopenic purpura</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sideropenic (refractory iron deficiency) anemia</td>
</tr>
<tr>
<td>Immune thrombocytopenic purpura</td>
</tr>
<tr>
<td>Short stature</td>
</tr>
<tr>
<td>Impaired weight velocity</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Food allergy</td>
</tr>
<tr>
<td>Sudden infant death syndrome</td>
</tr>
</tbody>
</table>

**Immune thrombocytopenic purpura**

A subset of patients with chronic immune thrombocytopenic purpura will respond to eradication of H pylori with an increase in platelet count (reviewed by Franchini and Veneri [25]). However, such a positive response has not been observed in every case series (26). The potential for molecular mimicry, with antiplatelet antibodies in serum recognizing the cytotoxin-associated gene A protein of H pylori (27), provides a biological explanation for the apparent association. Reports in children with chronic idiopathic thrombocytopenic purpura provide conflicting results (28,29). Accordingly, additional studies focusing on large numbers of children with chronic immune thrombocytopenic purpura (30) are warranted before guidelines are revised to include this entity as an extradigestive manifestation of H pylori infection.

**Short stature, impaired weight velocity and diarrhea**

A number of prospective (31) and cross-sectional (32) studies suggest that H pylori infection in children has an adverse effect on linear growth; however, other case-controlled studies have not supported such an assertion (33). Socioeconomic status likely plays a major confounding role in adversely influencing growth velocity. Sex may also prove to be a contributing factor; for example, Richter et al (32) found that only boys with H pylori infection were shorter and had lower weight gain compared with noninfected controls. Additional reports indicate an adverse effect on body weight, but no effect on linear growth (reviewed by Sherman and Macarthur [34]). The impact of maternal H pylori infection on impaired growth of the fetus in utero has also been suggested (35).

Biological explanations for a reduction in growth velocity remain to be defined. Initial considerations raised the potential that young children infected with H pylori were at an increased risk for episodes of diarrhea; a known risk factor for impaired growth with repeated episodes and associated under-nutrition. Although some studies support such a contention (36), other reports indicate no such effect (37-40). Indeed, other investigators suggest that H pylori infection might even protect children against infection from other intestinal pathogens causing diarrheal disease (41). Choe et al (42) suggested that iron deficiency induced by H pylori infection, rather than the bacterial infection per se, accounts for short stature in Korean children between 10 and 15 years of age.

An alternative explanation for the potential impact of H pylori infection on growth velocity in children could be effects of the organism (or resulting gastritis) on hormones that control appetite. Recent findings demonstrate that the stomach is a source of both ghrelin and leptin. Nwokolo et al (43) found that plasma ghrelin levels increased in 10 healthy adult...
patients after successful eradication of *H. pylori*. However, this finding requires confirmation because another study did not find differences in levels of plasma ghrelin between 24 *H. pylori*-infected female patients and 15 uninfected women matched for body mass index (44). Azuma et al (45) showed that eradication of *H. pylori* infection resulted in a reduction of gastric leptin, even though serum levels of the hormone were not altered. If confirmed by future studies conducted in children, the net effect of *H. pylori* colonization and chronic active gastritis on increasing levels of leptin and lowered ghrelin could be to impair appetite and reduce energy intake (the potential for an impairment of body mass index). Before firm guidelines regarding the role of *H. pylori* infection in growth are considered, additional prospective controlled studies need to be conducted to precisely delineate the factors involved in impairing body weight and reducing linear height.

**Food allergies**

One study has reported higher *H. pylori*-specific immunoglobulin G titres in serum samples obtained from 30 children with food allergies, compared with an equal number of subjects with either asthma or inflammatory bowel disease (46). A provocative review by Matysiak-Budnik and Heyman (47) considers potential underlying mechanisms which may explain this apparent association. Additional confirmatory studies from other centres are required before considering the merits of undertaking intervention studies to determine if altered gastric permeability and atopic symptoms might be reversible following *H. pylori* eradication.

**Sudden infant death syndrome**

A speculative report by Pattison and Marshall (48) raised the potential that sudden infant death syndrome (SIDS) could be due to *H. pylori* infection in infants. This hypothesis appeared to be supported by a subsequent publication (49) which reported the identification of *Helicobacter*-like DNA in the respiratory tract of autopsy materials obtained from infants who died of SIDS, but not in a smaller number of controls who were older in age. That report raised considerable alarm, guilt and concern among parents who had previously suffered the tragedy of an otherwise healthy baby dying suddenly and unexpectedly.

Following that report, a subsequent editorial (50) and letters (51) scathed the analysis, with much concern addressing the lack of appropriate controls and the absence of culture of the organism; that is, the molecular approach employed may well have provided false-positive results. Notably, two subsequent studies (52,53) failed to demonstrate the presence of *H. pylori* organisms in the stomach and trachea of babies who had died of SIDS. In addition, an equal number of subjects with and without SIDS tested positive for the presence of *H. pylori* DNA using the polymerase chain reaction. Thus, it appears likely that the molecular approach employed to detect *H. pylori*, in fact, does result in false-positive findings. Alternatively, postmortem cross-contamination could have occurred during tissue handling and processing.

**CONCLUSIONS AND RECOMMENDATIONS**

Sufficient evidence is now available to consider *H. pylori* infection a cause of otherwise unexplained sideropenic anemia. In such a clinical setting, once gluten-sensitive enteropathy has been excluded as an alternate explanation, it seems reasonable to consider a test-and-treat strategy for *H. pylori* infection. Clinical practice guidelines and treatment recommendations should be updated and revised accordingly to reflect that *H. pylori* can indeed cause sideropenic anemia in infected humans. Currently, available data are not sufficiently compelling to consider adding other reported extradigestive manifestations of *H. pylori* infection to the list of conditions in which a test-and-treat strategy should be considered. On the other hand, when new and compelling information arises in the context of well-designed studies with appropriate control and comparison groups, there will be a need to reassess this cautious recommendation in the future.

**ACKNOWLEDGEMENTS:** FYH Lin is the recipient of a Canadian Institutes of Health Research – Industry (Canadian Association of Gastroenterology/AstraZeneca Canada) Research Initiative Award. PM Sherman is the recipient of a Canada Research Chair in Gastrointestinal Disease.

**REFERENCES**

5. Peek Jr RM, Blaser MJ. *Helicobacter pylori* infection in infants. This hypothesis appeared to be supported by a subsequent publication (49) which reported the identification of *Helicobacter*-like DNA in the respiratory tract of autopsy materials obtained from infants who died of SIDS, but not in a smaller number of controls who were older in age. That report raised considerable alarm, guilt and concern among parents who had previously suffered the tragedy of an otherwise healthy baby dying suddenly and unexpectedly.

**Additional references**

22. Ashorn M. Acid and iron disturbances related to
Submit your manuscripts at http://www.hindawi.com