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CURRENT CONTROVERSIES ASSOCIATED WITH *HELICOBACTER PYLORI* INFECTION IN THE PEDIATRIC POPULATION

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1. ABSTRACT

Helicobacter pylori is a human bacterial gastric pathogen, fulfilling each of Koch's postulates for causal inference for ulceration in children and adults. In addition many reports purport to show that the organism causes a variety of extra-intestinal manifestations in children. This review of the English language literature provides evidence that *H. pylori* is likely a cause of unexplained iron deficiency (sideropenic) anemia in children, even in the absence of gastrointestinal bleeding. Much stronger evidence is required however, before *H. pylori* infection can be considered as an etiologic agent in recurrent abdominal pain of childhood, unexplained short stature, protracted diarrhea in pre-schoolers and sudden infant death syndrome.

2. INTRODUCTION

The first successful culture of *Helicobacter pylori* was accomplished in the early 1980's by Dr. Barry Marshall in Perth, Australia (1). The organism was cultured using endoscopic biopsies taken from the pre-pyloric region of Australian adults with chronic active gastritis and peptic ulcer disease. Subsequently, the organism has been shown to fulfill each of Koch's postulates as a pathogen for gastritis and peptic ulcer disease (2, 3). In addition, the organism may be involved in the pathogenesis of gastric adenocarcinoma and mucosa associated lymphoid tissue (MALT) lymphoma (4).

Soon after the discovery of *H. pylori*, clinical investigators in Australia (5), Europe (6) and North America (7-9) showed that the organism causes gastritis in children and adolescents. Also, recent consensus conferences in Europe (10), Canada (11) and the United States (12), provide compelling evidence that *H. pylori* is a cause of peptic ulceration in children and adolescents. Eradication therapy is warranted in this setting as it changes the natural history of peptic ulcer disease by dramatically reducing ulcer recurrence rates. Therefore, eradication therapy leads to reduced hospitalization, reduced surgery, less requirement for blood transfusion, and an improved quality of life.

Increasingly, it is recognized that H. pylori infection is acquired in childhood and infection is life-long unless eradication therapy is instituted. Some reports suggest that pre-school children may acquire and then spontaneously clear the gastric infection. Such studies, however, have relied on indirect assays of *H. pylori* infection, which may be inaccurate diagnostic tools in young children. Monotherapy antibiotic regimens - used with great frequency in children to treat episodes of acute otitis media and pharyngitis - are not effective in eradicating *H. pylori* from the surface mucous layer overlying epithelial cells in the antrum of the stomach (13). The environmental reservoir of infection is not known, although some studies report that contaminated drinking water may be a potential vehicle of transmission of infection.

There is intra-familial clustering of *H. pylori* infection (14). Historically (prior to the identification of *H. pylori*) it was recognized that peptic ulceration in children was familial. Indeed, peptic ulcer was considered to be an autosomal dominant genetic condition related to hyperpepsinogenemia I. The data now show that the increase in pepsin and mucosal ulceration are, in fact, responses to an infectious agent colonizing the antrum of the stomach (15).

Table 1. Case reports and case series of sideropenic refractory anemia associated with *H.Pylori* infection

Country	# of Subjects	Journal Citation
Belgium	1	Eur J Pediatr 1991;150:560-1
Italy	1	JPGN 1993;17:225-7
France	1	Ann Pediatr 1993;40:367-8
Russia	23	Gasslini 1996;28:168-9
Italy	4	JPGN 1999;28:116-9
Japan	4	JPGN 2000;31:52-6
Italy	1	Scan J Gastro 1997;32:617-22

It appears that parental (particularly maternal) transmission of the organism is a primary route of acquisition of infection during childhood. Living in crowded social settings also is a risk factor for childhood acquisition of infection. As a result, children in developing nations are at higher risk of infection, compared with their peers in first world countries. In developed nations, low socioeconomic status and children of immigrants from the third world are risk factors for colonization with *H. pylori*.

The consequences of gastric infection remain controversial. It appears that almost all children develop an inflammatory response in the gastric mucosa. There is one report, however, contending that *H. pylori* can colonize the stomach of children in the absence of an inflammatory cell response (16). Regardless, most humans will harbor the infection for life without adverse consequences. It has been estimated that only fifteen percent of infected subjects will develop a peptic ulcer as a consequence of infection (17). Lifetime rates of gastric cancer and gastric lymphoma are orders of magnitude lower.

Recent reviews have critiqued the plethora of reports describing manifestations of *H. pylori* infection in adults extending beyond the gastrointestinal tract (18, 19). This review will critically examine current controversies with respect to the role of *H. pylori* in children. The issues that will be considered include whether *H. pylori* causes abdominal pain in the absence of mucosal ulceration, if the infection causes refractory iron deficiency anemia in the absence of peptic ulcer disease in children, and whether *H. pylori* infection has extra-digestive manifestations - including growth impairment, diarrheal disease and sudden infant death syndrome - in infants and children.

3. ABDOMINAL PAIN

Two meta-analyses, which evaluated the role of H. *pylori* as a cause of dyspepsia in adults have recently been published. The two studies provide conflicting conclusions. The first study reported that *H. pylori* infection is more frequent in subjects with epigastric abdominal symptoms, compared with age-matched controls (20). Moreover, eradication of the infection provided symptomatic relief in colonized subjects. This meta-analysis was criticized for using a restricted search strategy and pooling the results of individual studies that were clinically and statistically heterogenous. In contrast, a more recent meta-analysis provided the opposite conclusion: prevalence of infection was no more common in symptomatic subjects when compared with age-matched controls (21). This meta-analysis addressed the limitations of the previous review. Therefore, methodological differences likely account for the discordant conclusions of the two analyses.

Similar contradictions are apparent in the literature on children. Critical reviews by Macarthur (22, 23) found, on average, no difference in the prevalence of infection in children with functional recurrent abdominal pain of childhood, compared with age and community matched controls. Of six studies addressing the issue, one reported a significantly higher prevalence of *H. pylori* infection in symptomatic children (24). In contrast, another study found a significantly higher rate of gastric colonization in the asymptomatic group compared with children with symptoms referable to the gastrointestinal tract (25). The remainder of the controlled studies found no difference in the prevalence of *H pylori* infection in children with and without abdominal pain (26-29).

Neither individual clinical symptoms nor a constellation of symptoms help distinguish *H. pylori*-infected children from those not harboring the gastric pathogen (30). Epigastric pain, nocturnal pain, and episodic abdominal pain are predictors of peptic ulceration rather than *H. pylori* infection. Although often used as criteria for decision making in the context of diagnostic esophagogastroduodenoscopy, such symptom complexes are neither sensitive nor specific for infection. A single small sample study from Ireland reported that resolution of such symptoms, however, occurs more frequently in children with peptic ulceration as a complication of *H. pylori*, compared with infected subjects with gastritis alone (31).

A major limitation in the published clinical research is the absence of controlled studies to follow the frequency and severity of abdominal pain in the year or more following a course of eradication therapy, compared with either acid suppression treatment alone or placebo. Ideally, a randomized, double-blind, placebo-controlled trial of eradication therapy would provide “gold standard” evidence. The plethora of case reports and case series reporting clinical improvement following antibiotic therapy are not helpful, given the potential for selection bias and the inevitable placebo effect.

4. SIDEROPENIC ANEMIA

There have been a number of case reports, primarily in children (32-37) but also in an adult (38), describing refractory iron deficiency anemia, which resolves following the eradication of *H. pylori* infection (Table 1). As summarized in Table 2, case control studies report lower mean levels of ferritin and iron in *H. pylori*-infected subjects, compared with age-matched community members who are not colonized with the gastric pathogen (39-42). Ferritin levels rise following successful eradication of bacteria in the stomach (Table 3) (43, 44).

Table 2. *Helicobacter Pylori* and iron deficiency

Subjects	#	Finding	Citation
Yupik Adults	140	Iron Deficiency	JAMA1997;277:1135-9
Danish adults	2,794	Reduced ferritin (comparable Fe intake)	Gastroenterology 1998;115:274-8
Australian adults	160	Reduced ferritin (comparable hemoglobin)	Med J Austr 1998;169:188-90
German adults	1,806	Reduced ferritin (comparable Fe intake)	Am J Gastroenterology 2001;96:1014-8

Table 3. Effect of *H. Pylori* eradication on iron deficiency anemia

Subjects	No	Findings	Citation
Italian adults	30	Rise in Hb, ferritin	Ann Intern Med 1999;131:668-72
Korean teens	21	Rise in Hb, ferritin	Acta Paediatr 2000;89:154-7
Korean teens	660	Rise in Hb, ferritin	J Pediatr 2001; 139:100-4

Table 4. *HelicobacteR Pylori* & iron deficiency

Potential Mechanisms	
• Occult blood loss	JAMA 1997;277:1135-1139
• Reduced duodenal iron absorption	
• Iron scavenging by the microbe	Mol Microbiol 2000;37:274-286 Res Microbiol 1999;150:475-481 Infect Immun 1997;65:514-518

Initial studies (39) hypothesized that reduction in total body iron in *H. pylori*-infected subjects was due to bleeding from ulceration or erosions associated with chronic gastritis and duodenitis (Table 4). The majority of subjects with sideropenic refractory anemia, however, have no evidence of occult blood loss from the gastrointestinal tract. More recently, it has been suggested that uptake of ingested iron and heme by *H. pylori* may compromise iron uptake by the infected host (45-47). Genome sequencing of *H. pylori* indicates that the organism possesses several distinct mechanisms to take up and utilize iron from its immediate microenvironment. Impaired duodenal iron absorption is also a theoretical alternate explanation. Such an explanation for sideropenic anemia in infected humans, however, has not been confirmed, to date, by experimental observations.

Current consensus conference reports have not addressed the issue of searching for *H. pylori* infection in subjects with unexplained iron deficiency. Given the increasing evidence supporting a cause-and-effect relationship between *H. pylori* infection and iron deficiency in the absence of mucosal ulcers, future expert panels should critically review the relevant literature and provide updated clinical practice guidelines.

5. SHORT STATURE

A report from the Gambia (48) first suggested that *H. pylori* infection of pre-school children is a risk factor for undernutrition and impaired linear growth. Subsequently, a number of studies have been published on the issue. As shown in Table 5, the findings are contradictory. Several studies, conducted both in developed nations and in the developing world, suggest that gastric infection is associated with a reduction in height velocity (49-53). In contrast, other investigations do not support this contention (54-59).

An evaluation of children referred to short stature clinics might provide interesting data. For example, it has been recently confirmed that asymptomatic gluten-sensitive enteropathy can present to the pediatric endocrinologist as unexplained short stature (60). Similarly, it would be worthwhile to define the prevalence of *H. pylori* infection in children with short stature. The prevalence of gastric colonization in such children could be compared with age-matched and community-matched children with other endocrine disorders in which linear growth is not affected. Additional population-based studies are also required to settle the current controversy about the relationship of *H. pylori* infection in childhood with linear growth velocity.

6. DIARRHEA

Two studies (48, 61) have reported that *H. pylori* infection in childhood predisposes to episodes of diarrhea. As shown in Table 6, not all reports have confirmed these initial observations (62). Given the morbidity and mortality associated with diarrheal diseases in children, however, this is an important issue deserving additional investigation. The precise mechanism underlying these observations is uncertain. Nevertheless, there is potential biologic plausibility given that acute *H. pylori* infection may cause reduced acid production in the stomach. Hypochlorhydria is well defined as an independent risk factor for bacterial-induced diarrhea.

Longitudinal studies that document the number and duration of episodes of diarrhea and resulting nutritional status in cohorts of children with and without *H. pylori* infection are required. To maximize the generalizability of the findings, such studies need to be conducted in developed and developing nations and in a variety of settings; for example, day-care centers.

7. SUDDEN INFANT DEATH SYNDROME (SIDS)

As summarized in Table 6, a report by Pattison and Marshall (63) speculated whether *H. pylori* infection in young infants could be a risk factor for sudden infant death

Table 5. Impaired linear growth in *H. Pylori*-infected children

Country	No.	First Author	Citation
Negative impact of infection on linear growth			
Gambia	**361**	**Sullivan**	**Arch Dis Childh 1990; 65:189-91**
Scotland	554	Patel	BMJ 1994;309:1119-23
Italy	216	Perri	Arch Dis Childh 1997;77:46-9
England	1,020	Fall	Arch Dis Childh 1997;77:310-4
Gambia	101	Dale	JPGN 1998;26:393-397
Turkey	30	Demir	Arch Dis Childh 2001;84:89-93
Turkey	56	Buyukgebiz	J Pediatr Endocrinol Metab 2001;14:549-51
No effect of H. pylori infection on height velocity			
France	151	Raymond	J Clin Microbiol 1994; 32: 461-3
Italy	134	Oderda	BMJ 1998;317:514-5
Italy	338	Cacciari	J Ped Endo Metab 1999;12:197-01
Guatemala	211	Quinonez	Am J Trop Med Hyg 1999;61:395-8
France	48	Sauve-Martin	JPGN 1999;28:354-5
Korea	385	Choe	Arch Dis Child 2000;82:136-40
Egypt	187	Naficy	Int J Epidemiol 2000;29:928-32

Table 6. Reported extra-digestive manifestations of *H. Pylori* infection in children

DIARRHEA			
Evidence in favor			
No.	Country	Authors	Citation
361	Gambia	Sullivan	Arch Dis Childh 1990;65:189-91
2,477	Germany	Rothenbacher	J Inf Dis 2000;182:1446-9
SUDDEN INFANT DEATH SYNDROME			
Evidence in favor			
No	Authors	Citation	
0	Pattison & Marshall	Medical Hypothesis 1997;49:365-9	
32 cases/ 8 controls	Kerr et al	Arch Dis Childh 2000;83:429-34	
Scathing editorial			
No	Authors	Citation	
0	Rowland & Drumm	Lancet 2001;357:327	

syndrome. Subsequently, one publication from the United Kingdom suggested that *H. pylori* was commonly identified in infants under six months of age who died unexpectedly (64). A recent editorial (65) highlighted serious deficiencies in the purported association. Concerns were raised about the control group employed and the measures used to define the presence of *H. pylori* infection. Clearly, additional studies are required before any definitive conclusions can be drawn.

8. CONCLUSIONS

H. pylori is primarily acquired during childhood and acquisition of the gastric pathogen depends primarily on whether other family members also harbor the infection. Current evidence for an association between *H. pylori* infection and several clinical conditions including abdominal pain, sideropenic anemia and extra-digestive manifestations is contradictory and controversial. Therefore, methodologically sound clinical research in children is required to definitively answer these unresolved controversies. Additional resources, in the form of research funding, to support such clinical research is also required. To prove most beneficial, studies need to be undertaken in a variety of settings around the globe. Multicenter collaborative research programs must also be strongly encouraged, supported and facilitated so as to advance the field in a timely and expeditious manner.

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