

Determinants of disease outcome following *Helicobacter pylori* infection in children

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NL Jones, AS Day, PM Sherman. Determinants of disease outcome following *Helicobacter pylori* infection in children. *Can J Gastroenterol* 1999;13(7):613-617. *Helicobacter pylori* infection is primarily acquired during childhood, causes chronic, active gastritis and peptic ulcer disease, and is associated with the development of gastric malignancies. However, only a small number of infected individuals ever develop the more severe sequelae of peptic ulcer disease and gastric cancers. Therefore, the identification of bacterial and host factors that play a role in determining the outcomes and pathophysiology of infection is a major focus of current research. Recent advances in the understanding of disease pathogenesis are critically considered, with particular reference to the pediatric population.

Key Words: Gastric cancer; Gastritis; *Helicobacter pylori*; Pediatrics; Peptic ulcer disease

Déterminants de l'évolution de la maladie à la suite d'une infection à *Helicobacter pylori* chez les enfants

RÉSUMÉ : L'infection à *Helicobacter pylori* s'acquiert principalement pendant l'enfance, cause une gastrite évolutive et chronique et l'ulcère gastro-duodéal, et est associée au développement de tumeurs gastriques malignes. Cependant, seul un petit nombre des sujets infectés vont développer les séquelles les plus sévères de l'ulcère gastro-duodéal et des cancers gastriques. Par conséquent, l'identification des facteurs bactériens et imputables à l'hôte, et qui jouent un rôle dans l'évolution de la maladie et dans la physiopathologie de l'infection, constitue le centre d'intérêt majeur de la recherche actuelle. Les avancées récentes dans la compréhension de la pathogénie de la maladie sont examinées de façon critique, et s'adressent particulièrement à la population pédiatrique.

Helicobacter pylori is an important causative agent in the development of chronic, active gastritis and peptic ulcer disease (1). *H pylori* was the first bacterial pathogen classified as a type 1 carcinogen because of the strong epidemiological association between chronic infection and the development of gastric malignancies (2). More recently, an animal model that develops gastric cancer during *H pylori* infection has been identified (3). Even though no cases of gastric adenocarcinomas caused by infection with *H pylori* have been documented in children, isolated cases of mucosal-associated lymphoid tissue lymphomas (4) and lymphoma (5) have been reported in individuals under 18 years of age.

Although *H pylori* infection is generally acquired in child-

hood, the development of complications associated with infection is rare in this age group. It has been estimated that over half of the world's population is infected with the organism. However, the majority of infected individuals will not suffer from clinical sequelae. The lifetime risk of acquiring peptic ulcer disease during infection is estimated to be approximately 10%, while the lifetime risk of developing gastric cancers, including adenocarcinomas and lymphomas, is less than 1% (6). Therefore, an increased understanding of both host and bacterial factors that place an individual at risk for the development of these complications is an area of great interest because it has implications for diagnostic testing, therapeutic strategies and vaccine development.

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FACTORS MEDIATING PEPTIC ULCER DISEASE

Vacuolating cytotoxin: One bacterial virulence factor initially suggested to play a role in the development of peptic ulcer disease is the vacuolating cytotoxin. Although all *H pylori* strains possess the gene *vacA* coding for a vacuolating cytotoxin, only approximately 50% of strains induce vacuolation of the cytoplasm of infected eukaryotic cells in vitro (7). Therefore, due to the variable expression of the cytotoxin, the possibility that VacA is involved in mediating disease outcome was considered.

In one study of *H pylori* isolates obtained from children, VacA activity was detected in 21% (three of 14) of strains from subjects with gastritis alone and 24% (six of 25) of strains isolated from those with peptic ulcer disease (not significant) (8). These findings are in agreement with those of a preliminary study of 26 Brazilian children in whom the presence of vacuolating cytotoxin activity was identified in 30% (three of 10) of isolates obtained from children with peptic ulcer disease and 31% (five of 16) of strains isolated from children with gastritis alone (not significant) (9). Therefore, a lack of association between vacuolating cytotoxin activity and peptic ulcer disease is evident in pediatric populations.

Studies in adult populations have demonstrated an inconsistent association between infection with strains exhibiting cytotoxic activity and peptic ulcer disease. A possible explanation for these variable findings is the considerable diversity of the *vacA* gene among different *H pylori* strains (10). Expression of VacA activity in vitro is dependent on the genotype, at least in certain eukaryotic cell types (10,11). The *vacA* genotype is determined by a combination of the variants of two main regions within the gene – a midregion (including types m1 and m2) and a region encoding the signal sequence (including at least three subtypes referred to as s1a, s1b and s2).

Few studies have investigated the relationship between the *vacA* genotype and disease complications in children. A study of isolates obtained from 32 children (three with peptic ulcer) found a lack of correlation between the degree of gastric mucosal inflammation observed in antral biopsy specimens and the vacuolating cytotoxic genotype (12). However, a preliminary study of Brazilian children has identified an association between infection with *vacA* s1m1 strains and peptic ulceration (13). Eleven of 37 children with gastritis were infected with s1m1 strains compared with 14 of 16 children with duodenal ulcer ($P=0.01$).

Adult studies characterizing the association between *vacA* genotype and disease complications have had varying results. Atherton and colleagues (10) identified an association between infection with *vacA* s1 strains and peptic ulcer disease. Similarly, a study of 94 gastric biopsy specimens obtained from adult patients in The Netherlands found that infection by a strain with the *vacA* s1 genotype correlated with the presence of peptic ulcer disease (14). In contrast, a recent study of *vacA* genotypes in *H pylori* isolates obtained from Japanese patients identified much less genetic heterogeneity with a predominance of the s1a/m1 alleles (15). As

such, there was no detectable association between the *vacA* genotype and clinical outcome.

An additional mechanism by which the toxin may mediate disease is through the alteration of host signal transduction pathways. Toxin-treated epithelial cells display a dose-dependent increase in the second messengers cytosolic calcium and inositol phosphates (16). Recent evidence indicates that VacA disturbs epidermal growth factor (EGF) signalling, which may have important implications for gastric cytoprotection and ulcer healing (17). Pai et al (18) showed that exposure of gastric epithelial cells to VacA inhibits both EGF-stimulated phosphorylation of the EGF receptor and enhanced expression of the downstream signalling molecules ERK2 and *c-fos*. Similarly, dialyzed *H pylori* broth culture filtrate from a cytotoxin-expressing strain inhibited EGF-mediated proliferation of gastric epithelial cells in vitro (19). In contrast, dialyzed broth filtrate from the isogenic *vacA*-deficient mutant had no effect on proliferation. Taken together, the results from these studies indicate that the vacuolating cytotoxin is capable of disrupting EGF signalling in vitro.

***cagA* and the *cag* pathogenicity island:** CagA, a 120 kDa bacterial outer membrane protein of unknown function, has also been considered as a virulence factor. An initial study reported that adult patients with peptic ulcer disease more commonly have serological evidence of infection with CagA-positive strains (20). Few studies have investigated the role of CagA in *H pylori*-infected children. A French study of 45 *H pylori*-infected children identified *cagA*-positive strains in 40% of the isolates (21). A higher frequency of severe histological gastritis was detected in gastric biopsy specimens obtained from children infected with *cagA*-positive strains (88.8%) compared with children infected with *cagA*-negative strains (55.5%, $P=0.017$). A comparable study of 84 *H pylori* isolates obtained from Polish children identified a high prevalence of the *cagA* gene (80%) (22). Neither of these studies was able to address the role of *cagA* in ulcerogenesis because none of the *H pylori*-infected children had peptic ulcer disease.

To investigate the potential role of *cagA* in mediating peptic ulcer disease, the prevalence of *cagA* in *H pylori* isolates obtained from 13 children with peptic ulcer disease and 16 children with gastritis alone was determined (23). In this study, 92% (12 of 13) of isolates obtained from children with duodenal ulcers were *cagA*-positive compared with 81% (13 of 16) of isolates from children with gastritis alone ($P=0.6$).

Recent studies in adults also indicate that the correlation between infection with *cagA*-positive strains and more severe disease outcomes is not so convincing. For example, Miehle et al (24) identified an equivalent prevalence of *cagA* positivity in clinical isolates obtained from asymptomatic subjects and those with duodenal ulcer. Similarly, a recent serological study failed to identify an association between CagA positivity and peptic ulcer disease (25).

cagA is located among a larger cluster of genes carried on a pathogenicity island (26). Therefore, *cagA* may serve as a marker for the presence of other genes on the island that

code for virulence factors (27). Genetic variability within the pathogenicity island exists among *H pylori* strains. Initial characterization of the pathogenicity island with the use of mutagenesis studies identified several genes, including *cagE* (also referred to as *picB*), which are involved in mediating the secretion of the potent neutrophil chemokine interleukin-8 (26,27). Mutational analysis of the *cagA* gene suggests that the 120 kDa outer membrane protein is not responsible for inducing the transcription of interleukin-8 (28). These findings indicate that products encoded by other genes contained within the pathogenicity island may well be important in determining bacterial virulence.

We investigated the association between infection with *cagE*-positive strains and the presence of duodenal ulcer disease in 29 *H pylori*-infected children from Toronto (23). By polymerase chain reaction analysis, 12 of 13 (92%) children with *H pylori*-mediated duodenal ulcer disease were *cagE*-positive compared with only five of 16 (31%) children with gastritis alone ($P=0.0018$). These findings are in agreement with those of a recent study of *H pylori*-infected adult patients. Fallon and colleagues (29) identified the presence of *cagE* in 36.9% of isolates obtained from 84 subjects with gastroduodenal pathology defined by the presence of either peptic ulcer disease or gastric cancer compared with 20.7% of isolates from 92 subjects with either nonulcer dyspepsia, normal endoscopy or another diagnosis such as esophagitis ($P=0.02$). In contrast, Jenks et al (30) detected the *cagE* gene in 13 of 17 (76%) *H pylori* isolates obtained from adult subjects with nonulcer dyspepsia and 51 of 56 (91%) isolates from adults with duodenal ulcers ($P=0.19$). Further studies are required to confirm these findings in other patient population groups and to understand the mechanisms by which *cagE* mediates disease.

Gastric metaplasia: It is clear from animal studies that, in addition to bacterial factors, the host responses to infection play an important role in determining disease outcome (31,32). In the murine model of helicobacter infection, a variable response to infection – ranging from minimal inflammatory infiltration to severe mucosal inflammation with atrophic changes – is dependent on the genetic background of the mouse. For example, C57BL/6 mice infected with *Helicobacter felis* develop a more severe gastritis than *H felis*-infected BALB/c mice (31,32).

Although the exact host factors involved remain to be identified, the development of gastric metaplasia in response to infection has been investigated. *H pylori* exhibits tropism for binding to gastric epithelial cells. Therefore, areas of gastric metaplasia in the duodenum may permit colonization of the organism and, thereby, mediate the development of mucosal injury and ulceration in the duodenum. A retrospective study identified an increased frequency of gastric metaplasia in *H pylori*-infected children (13 of 31) compared with children with secondary gastritis (two of 33) or noninflamed controls (one of 33, $P<0.001$) (33). The presence of duodenal inflammation also correlates with *H pylori* infection. However, the appearance of gastric metaplasia or duodenitis was no more common in *H pylori*-infected children

with duodenal ulcer than in those with gastritis alone. Another retrospective study identified gastric metaplasia in 23 of 173 duodenal biopsies obtained from children undergoing upper endoscopy (34). However, in contrast to the previous study *H pylori* infection was not associated with a higher prevalence of gastric metaplasia.

A prospective study of 148 children identified gastric metaplasia in 34 children of whom 11 had *H pylori* infection. Duodenal inflammation was present in 89% of those with gastric metaplasia. Furthermore, six of seven *H pylori*-infected children with duodenal ulceration had gastric metaplasia compared with five of 18 *H pylori*-infected children with gastritis alone ($P<0.001$) (35). Thus, the presence of gastric metaplasia in the duodenum likely is associated with the development of duodenal ulcer in *H pylori*-infected children.

FACTORS MEDIATING THE DEVELOPMENT OF H PYLORI-ASSOCIATED GASTRIC CANCERS

The mechanisms by which infection with *H pylori* results in the development of gastric cancers are not known. The recent development of an animal model, the Mongolian gerbil, which develops gastric cancers following chronic infection with the organism, is likely to help elucidate the bacterial factors involved (3,36).

Enhanced cell turnover and apoptosis: Increases in both gastric epithelial cell proliferation and apoptosis observed during *H pylori* infection may play a role in the development of gastric cancers. During chronic infection, increased apoptosis and enhanced proliferation have the potential to expand the target cell population for further mutagenic events (37). The potential for genotoxic damage occurring during *H pylori* infection has been investigated. For instance, Baik et al (38) detected an increase in oxidative DNA damage within gastric biopsy specimens obtained from children infected with *H pylori*.

The mechanisms for the induction of apoptosis following *H pylori* infection remain incompletely defined. In vitro studies are beginning to elucidate bacterial factors that mediate the induction of programmed cell death. Current evidence indicates that the bacterium can directly transduce the death signal in infected gastric epithelial cells (39,40). It remains controversial whether bacterial adhesion is required to induce cell death. Chen and colleagues (41) demonstrated that bacterial contact with tissue culture cells is required to stimulate a maximal apoptotic effect. Fan et al (42) showed that binding of bacteria to major histocompatibility complex (MHC) class II molecules is required to transduce the cell death signal. Cells that either constitutively or following transfection express MHC class II molecules are sensitive to *H pylori*-stimulated apoptosis. In contrast, cells that lack MHC class II molecules are resistant to bacterial-mediated apoptosis. However, results from two other studies indicate that both purified *H pylori* lipopolysaccharide (43) and soluble extracts from a cytotoxic *H pylori* strain (39) can stimulate gastric cell apoptosis in vitro.

Several groups have begun to investigate the molecular

pathways involved in transducing the apoptotic signal during *H pylori* infection. Enhanced expression of the tumour suppressor *p53* is detected in gastric biopsy specimens obtained from *H pylori*-infected children (44) and during *H pylori* infection of gastric epithelial cells in vitro (45). In addition, the phenotype observed in *H felis*-infected *p53* hemizygous mice differs from that seen in infected wild-type mice (46). Mice with one copy of the *p53* gene develop hyperplastic lesions in the gastric mucosa in response to infection. In similar studies, mutation of the tumour suppressor adenomatous polyposis coli (APC) did not enhance the development of disease in *H felis*-infected mice, indicating that the APC protein does not play a major role (47).

Evidence also implicates members of the Bcl-2 family in regulating *H pylori*-induced programmed cell death. Enhanced expression of the pro-apoptotic homologue Bak is associated with induction of apoptosis of *H pylori*-infected gastric epithelial cells in vitro (41). Furthermore, an increase in Bak expression is detected in gastric epithelial cells within biopsy specimens obtained from *H pylori*-infected adult subjects (48). Taken together, the results of these studies indicate that several different regulatory pathways mediate the cell death caused by infection with the bacterium.

In addition to a direct effect of the bacterium, mucosal inflammation stimulated by *H pylori* infection may affect cell turnover kinetics (37). Following standard eradication therapy, the enhanced degree of apoptosis observed in gastric tissue obtained from *H pylori*-infected children returns to baseline levels only if both the bacterium is eradicated and inflammation resolves (44). Cytokines produced during *H pylori* infection, including interferon-gamma and tumour necrosis factor-alpha, potentiate *H pylori*-triggered pro-

grammed cell death in vitro (39,42). Furthermore, infection with the bacterium is associated with upregulation of the Fas death receptor on gastric epithelial cells both in vitro (40) and in vivo (49). In vivo studies demonstrate that expression of the Fas ligand is increased in infiltrating mucosal lymphocytes as well as in gastric epithelial cells (49). Taken together, these findings indicate that *H pylori* infection may increase immune-mediated cell death through Fas signalling as well as fratricidal and suicidal cell death of gastric epithelial cells that express both the Fas receptor and the Fas ligand. Future studies in relevant animal models should elucidate the relative importance of programmed cell death and Fas signalling in *H pylori* disease pathogenesis.

CONCLUSIONS

The complex interplay between the host and infecting bacterium is certain to be important in determining the ultimate clinical outcome during chronic infection with *H pylori*. Continued research should allow the identification of bacterial products and host factors that place an infected individual at increased risk for the development of disease complications including peptic ulceration, gastric adenocarcinomas and gastric lymphomas.

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