Editorial

Helicobacter pylori Infection

The understanding of pathogenesis of peptic ulcer disease has been revolutionized during the last decade with the introduction of a new pathogen *Helicobacter pylori.* This organism has received a lot of attention not only because of its changing nomenclature from *Campylobacter pyloridis* to *Campylobacter. pyloris* to the present one but also because of a strong epidemiological association between *Helicobacter pylori* infection and both duodenal and gastric ulcers, and gastric cancer in adults. In addition, evidence suggests that eradication of the bacterium from the gastric antrum reduces the chances of recurrence of peptic ulcers. However, the clinical spectrum of H. *pylori* infection in younger children has not yet been clearly established. The increasing use of endoscopy as a diagnostic modality in gastroduodenal diseases in children has raised many questions regarding the role of *H. pylori* in causing a wide range of symptoms which may need eradication therapy.

H. pylori infection in children assumes a greater importance particularly in India, where infection is acquired in early childhood and seroprevalence has been observed to reach 58% by 19 years of age(l). Poor hygienic living conditions resulting in consumption of contaminated water has been regarded as a major reason for the higher prevalence of *H. pylori* infection in developing countries since the infection is more common among lower socio-economic groups with low parental education, family income and general living conditions(2-4). Transmission of the infection is believed to be from person to person, possibly fecal-oral, as the seroprevalence is increased in the family contacts and in institutionalized children, even though some of them have been observed to harbor clonal variants of different strains.

Pathogenesis

H. pylori is a spiral shaped, Gram negative bacterium with flagella, that has a urease enzyme which hydrolyzes urea into ammonia and bicarbonate. The alkaline microenvironment produced by this action protects the organism from gastric acid. Active motility of the organism by virtue of its flagella allows it to penetrate the mucus layer of the gastric mucosa. Pathogenesis of gastroduodenal injury due to H. *pylori* infection is explained by 'leaking roof hypothesis. *H. pylori* infection is believed to injure submucosal tissue by causing a 'leak' in its protective coating of mucin gel and epithelial cells ('the roof) thereby making it susceptible to gastric acid ('the rain'). Secretion of urease, specific adhesion-receptor interaction, cytotoxins (including hemolysin), superoxide desmutase, heat shock proteins, mucinase, lipase and phospholipase are some of bacterial virulence determinants. Increased levels of gastrin and pepsinogen I have also been detected in the sera of children infected with H. *pylori.* Several host factors like gastric acid and mucus production, and quality of gastric mucosa are also critical in determining the outcome(5).

Infection with *H. pylori* has demonstrated a remarkable variability with normal healthy seropositive people on one end of the spectrum and serious life threatening upper gastrointestinal disease on the other end. A complex host-

bacterium relationship seems to be the primary determinant. *H. pylori* strains from ulcer patients are genetically different from those isolated from asymptomatic individuals. Presence of an *H. pylori* 128 k protein (the product of the cag A gene) may be associated with an enhanced probability of ulcer disease. Studies on PCR-amplified DNA sequences in *H. pylori* genome have shown specific fragments in duodenal ulcer patients which are not present in simple gastritis(2). Specific antibodies against cytotoxins have also been identified in patients with ulcer disease suggesting that it is the strain of the organism which is the most important variable for clinical manifestation of the disease. Certain genetic factors like Lewis blood group and HLA-DQAI gene of the host may also contribute to the susceptibility or resistance of *H. pylori* infection(3).

Clinical Manifestations

In adults there is sufficient proof to believe that *H. pylori* is the primary cause for gastric inflammation rather than a secondary colonizer of inflamed tissue since the inflammation could be induced by challenging animals and humans by oral administration of the bacteria(3). Since the infection is supposed to be acquired in early childhood, simply identifying *H. pylori* in a child without any symptoms or with nonspecific symptoms does not provide evidence that the detection of this organism is of any consequence, particularly because of high seroprevalance in age and community matched controls. The clinical manifestations of *H. pylori* infection in children are, therefore not very clearly defined. The clinical spectrum may be related to simple colonization of gastric mucosa by *H. pylori* without any specific symptoms, non-ulcer dyspepsia and peptic ulcer disease.

Colonization of H. pylori

Colonization of gastroduodenal mucosa by *H. pylori* appears to be the primary event in the pathogenesis of the infection. Infection is always accompanied by an inflammatory response in the underlying mucosa but the inflammation caused by *H. pylori* is not always detected endoscopically. It is well known that *H. pylori* resides exclusively in gastric mucosa, but can be found in remote areas that have undergone metaplastic changes in which gastric epithelial cells are present such as esophagus, duodenum or Meckel's diverticulum. A higher concentration of bacteria is found in the antral area. A typical 'cobblestone appearance' or nodularity of antral mucosa has been documented on endoscopy in many reports ranging from 30-100% which is much higher than that seen in adults since nodularity is accompanied by increased number of lymphoid follicles in the gastric mucosa in children. Colonization of *H. pylori* without any evidence of non-ulcer dyspepsia (gastritis/duodenitis) or peptic ulcer may be associated with symptoms for which a child has been subjected to endoscopic examination. Conversely, detection of *H. pylori* in association with some other gastroduodenal disease for which endoscopy has been performed may be a chance finding. In the former group, there is a proposed link between *H. pylori* infection and recurrent abdominal pain (RAP), reported to range from 5-34%(4). However, by applying Hills criteria for causal inference, *H. pylori* infection does not fulfill Koch's postulates with regard to RAP(5). Duodeno-gastric reflux, esophagitis, protein losing enteropathy and chronic diarrhea have also been associated with colonization by *H. pylori* but the exact significance has not been established as yet. Therefore, at present mere detection of *H. pylori* from gastric mucosa seems to be of no consequence.

Non-ulcer Gastroduodenal Disease

Since peptic ulcers have not been commonly encountered in children less than 12 years by most of the workers, attention needs to be focussed on association of nonulcer dyspepsia identified as gastritis and /or duodenitis in these cases which might be followed by an ulcer in later life. Prevalence of *H. pylori* and antral gastritis has been reported to

range from 8-56% in children with a rate ratio ranging from 1.9 to 71 from different countries(4). Even though DNA sequences in *H. pylori* genome are different in patients with peptic ulcer as compared to simple gastritis(2), endoscopic/histologic evidence of inflammation of gastric/antral mucosa would suggest that the bacterium results in slow inflammatory changes which may eventually lead to chronic active type B gastritis and mucosal ulceration of stomach and duodenum. What proportion of these children may eventually develop peptic ulcer in later life can only be estimated by a long term follow up to know the natural history of *H. pylori* infection in these cases. Causal inference can also be enhanced if the effect of eradication of *H. pylori* on the persistence of these endoscopic/histologic findings and subsequent development of peptic ulcer can be evaluated. Therefore, presence of antral gastritis and duodenitis seem to be important findings associated with *H. pylori* infection. Histological changes may precede morphological changes of inflammation and ulcer formation. At present the clinical significance of this group is not conclusive. Recent improvement in the ability to genetically manipulate helicobacters and develop animal models is expected to provide some answers to these questions.

Peptic Ulcer

Peptic ulcers are infrequent in children and most of the gastric ulcers are secondary rather than primary. It is, therefore, difficult to estimate its association with *H. pylori* infection. However, *H. pylori* has been demonstrated in association with peptic ulcer in 5-100% of children by different workers (3,4). Using the adult model for older children with peptic ulcer disease, the clinical significance and therapeutic options may remain essentially the same.

Diagnosis

Endoscopically a typical 'cobblestone appearance' has been described with *H. pylori* infection in children. *H. pylori* can be detected by a number of direct and indirect methods. The organism can be directly identified in the gastric mucosa by culture, histology and polymerase chain reaction (PCR). Indirect evidence is based on the biochemical properties of the bacteria of hydrolyzing urea *{e.g.,* urease test, urease breath test). However, no ideal evaluation has emerged as yet and in most of the cases accurate diagnosis relies on a combination of tests. Serological tests (antibodies detected by bacterial agglutination, complement fixation and ELISA) are mainly useful for epidemiological or screening purposes and do not provide any proof of existing infection. Of the available serological tests, ELISA is the technique of choice and is currently available as 'rapid office test' which is not a quantitative test (using commercial kits for serum, saliva and gingival secretions making it particularly appropriate for children) and the 'machine-read, laboratory-based' serology tests which are more accurate and provide quantitative results. These tests may be useful in identifying children with RAP who require further investigations and also avoids unnecessary invasive procedures in seronegative patients.

Therapeutic Approach

Epidemiological data associates acquisition of *H. pylori* infection in childhood with development of gastric cancer in adulthood which may imply that *H. pylori* should be eradicated in every infected child or adolescent whether or not there is non-ulcer dyspepsia or an ulcer. But the argument against this conclusion is that gastric cancer is very rare, whereas *H. pylori* infection is relatively common. Moreover, infection without peptic ulcer does not represent a pre-symptomatic stage, but rather a different (genetically determined) entity in the evolution of *H. pylori* infection(5). A consensus statement published by the National Institute of Health Consensus Development Conference on *Helicobacter pylori* in Peptic Ulcer Disease recommends

treatment of ulcer patients with *H. pylori* infection with antimicrobial agents in addition to antisecretory drugs whether on first presentation with the illness or in recurrence. Eradication therapy is not recommended for nonulcer dyspepsia associated with *H. pylori* infection(3). However, no consensus exists at present for the treatment of *H. pylori* associated gastroduodenal disease in children.

There is compelling evidence to support eradication therapy in children with primary duodenal ulcers like in adults since eradication of *H. pylori* infection reduces the recurrences. It is, therefore recommended that children and adolescents harboring *H. pylori* who have endoscopic evidence of mucosal ulceration in the stomach or duodenum should be treated(5). Several regimens of treatment have been used for eradication of *H. pylori* in children. The most widely used protocols are triple and dual therapies employing bismuth or H_2 blockers and one or two antimicrobial agents. Bismuth salts remain the most effective single agent in eradicating *H. pylori* as compared to H_2 blockers, antibiotics and metronidazole used singly. Therefore, a combination therapy with a H_2 blocker or bismuth salt (bismuth subcitrate), an antibiotic (amoxycillin) and metronidazole is currently the recommended therapy.

However, increasing resistance of metronidazole may severely limit the usefulness of triple therapy especially in developing countries. Treatment schedules of 4 weeks and more have been reduced to 1 week. Clarithromycin has a good anti *H. pylori* activity *in vitro* and has proved to be relatively effective when used as a monotherapy and highly effective in combination with omeprazole and other antimicrobials. *H. pylori* seems to be resistant to cimetidine, sucralfate and antacids.

Children with non ulcer dyspepsia (endoscopic and/or histological evidence of antral gastritis/duodenitis) constitute a distinct group which deserves attention. One of the views put forward in this context is that most of the children do not have any clinical symptoms in the absence of mucosal ulceration and therefore, there seems to be no justification in treating all children with *H. pylori* associated non-ulcer dyspepsia(3). On the other hand there are definite reports suggesting that a subgroup of these children with antral gastritis/ duodenitis do have symptoms for which they seek medical attention which are severe enough to warrant endoscopic examination. It is still not clear whether histological and endoscopic inflammation is a precursor of an ulcer or not and whether an early eradication of the bacteria will prevent development of an ulcer. Hence it may not be justified to leave these children untreated even after making a definite diagnosis. Secondly, eradication therapy may provide them the much desired symptomatic relief which is patient's primary concern. Symptomatic relief of abdominal pain following antihelicobacter treatment(6) may justify treatment of such cases. Kumar *et al.(7).* have also observed a good therapeutic response with triple therapy in children with antral gastritis and upper abdominal pain. Symptomatic improvement correlated very well with eradication of *H. pylori* in these children. However, such an intervention poses the question as to what happens to these children after initial satisfactory response. *H. pylori* infection is very closely related to environment and even after eradication the chances of reinfection are quite high. It may, therefore, not be justified to offer *H. pylori* eradication therapy only for a 'brief symptomatic relief. More randomized placebo controlled trials with longer and sequential follow up are required to offer a definite answer to this problem.

Prevention

The current status of *H. pylori* infection suggests that the infection is acquired in childhood even though the disease manifests beyond the pediatric age group. In order to prevent resultant morbidity in adult life, it may be necessary to initiate

preventive measures in the pre-school years. In the developing countries, existing measures targeted at preventing communicable disease transmission through fecal-oral route would go a long way to reduce the risk of gastroduodenal diseases associated with *H. pylori* infection.

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