LEADING ARTICLE

HELICOBACTER PYLORI AND GASTRODUODENAL DISEASE

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Spiral organisms were first described in the gastric mucosa by Bizzozero in 1893[1] and rediscovered by Warren and Marshall in 1983[2].They were initially called *Campylobacter-like* organisms, then *Campylobacter pylori* and now *Helicobacter pylori* (HP)[2,3]. The clinical importance of this organism is controversial.

There is an established correlation between increased HP colonization of gastric mucosa and increasing age among normal adults[4]. At least 50% of those over the age of 50 years are positive for HP[5,6]. Certain ethnic groups who have a high incidence of duodenal ulcer (DU) also have a high incidence of HP infection[7]. The frequency of HP infection was similar in different races locally[8]. Little is known about the source and the transmission of HP although initial observations indicate spread associated with close personal contact. Water supply and animals in the food chain may be important sources for human infections.

The crucial question is whether this organism is a commensal colonizing an abnormal mucosa or whether it is indeed a pathogen. HP is found beneath the gastric mucus layer that lines the surface epithelium of the stomach. It can degrade mucus glycoprotein and alter the viscosity of the mucus barrier, thus enhancing its penetration to the epithelial cell surface[9]. The abundant urease activity of HP produced at the epithelial surface is probably a major pathogenetic factor[10], resulting in back diffusion of H^+, local hyperchlorhydria and ulceration. An intense inflammatory infiltrate is also associated with HP colonization. Acute infection with the organism causes an acute gastritis with achlorhydria and continuation to chronicity may occur in some subjects. There is no data to date as to what host factors lead to chronicity.

Whether these organisms are involved in the pathogenesis of peptic ulcer diseases is much less clear. There is now substantial evidence that colonization of the stomach by HP is causally related to type B gastritis which affects the antrum of the stomach mainly. As duodenal ulceration is invariably associated with type B antral gastritis, there is strong correlation between HP colonization and DU. HP is found in over 95% of patients with DUs and 65% of patients with gastric ulceration (GU)[11]. It has been postulated that gastric metaplasia occurs within the duodenum and HP spreads distally from antrum and colonizes the metaplastic tissue in the duodenum which eventually leads to ulceration[12]. Evidences favouring a causal relationship between HP gastritis and ulceration, include (1) the strong association between HP and gastritis, the topographical association between the organism and inflammation[13], (2) ingestion of HP caused acute histological gastritis[14,15] and (3) gastritis resolves with eradication of the organism and relapse rate is high if the organism persists. However, there have been reports of the isolation of HP in the absence of histological gastritis[13] and the mere presence of HP does not necessarily imply that it is the cause of gastrointestinal symptoms. Furthermore, the organisms have been found for years in the stomach with associated inflammation in entirely asymptomatic population[13]. The link of HP with gastric ulcers is also difficult to demonstrate as the proportion of GU patients with HP is hardly more than that of patients without ulcers. Although there is limited evidence to support a role for HP in the genesis of the gastric ulcer crater, the discovery of HP lends support to the theory that DU and GU are part of a continuum[16].

The role of HP in non-ulcer dyspepsia (NUD) remains unproven A high incidence of HP infection is also noted in NUD[17]. This is associated with chronic antral gastritis which is found in as high as 70% of NUD[18,19]. However, the role of HP as the cause of symptom of NUD is controversial. Some workers are of the opinion that there is probably a subgroup of NUD patients whose symptoms are associated with the presence of HP and eradication of this organism appear to improve symptoms in these patients[20-24]. It must be stressed that the placebo response is high in NUD and gastritis is known to increase with age and there is no clear correlation between the presence of gastritis and symptomatology[25].

Type A gastritis which is associated with pernicious anaemia, has been reported to be a precancerous lesion in human stomach. There are some data[26,27] that suggest a similar association for gastric carcinoma and type B gastritis which is the lesion associated with HP infection. There is no evidence to date of a causal link between the carriage of HP and the subsequent development of gastric carcinoma. However, high prevalence of HP colonization was found in a study which screened subjects with high risk of developing gastric carcinoma[28].

HP may be detected by several methods. The organism grows best on moist chocolate agar under microaerophilic conditions at 37°C, producing small colonies within 3 to 4 days. Culture of biopsy specimens will yield growth of organism in 90% of cases[17]. Failure to culture the organism may result from technical problems during tissue sampling or transport or if only a small number of organisms are present in the biopsy. However, culture is the most specific test for the identification of HP and is the only definite proof that the organism is present. The presence of HP on routine histology is most commonly used for the diagnosis of HP infection. Routine hematoxylin-eosin stain, acridine orange, Giemsa or Wartin-starry silver stains have similar sensitivity in the detection of HP though the latter three stains provide better and easier visualization of the organism. Alternatively, HP can be detected by monoclonal antibodies or DNA probes on histologic sections. Based on the production of abundant quantities of urease by the bactrium, rapid diagnostic tests such as CLO, campyQuick or C7-test, all of which require biopsy specimens, have been developed. The

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sensitivity for most rapid urease tests is over 90%. This is also shown in our local study[29]. The urea breath test (^{13}C or ^{14}C - labelled urea) and serology (anti-HP) are indirect and non-invasive tests. The main disadvantage of the urea breath test is the expensive equipment required to perform the test and the use of radioactivity in the ^{14}C-test. Non-invasive tests can also be used for mass screening and follow up. Urea breath test has a sensitivity of 95% and specificity of 98% while serology gives a sensitivity of 70 - 84% and specificity of 95-99%[30].

Should HP be eradicated routinely when treating patients with peptic ulcer disease? Acid suppressive therapy has no effect on HP status and does not reduce the inflammatory changes in the gastroduodenum. Bismuth subcitrate treated patients showed lower ulcer relapse rates than conventional treatment. It is possible that the bactericidal effect of bismuth result in clearance of HP and amelioration of underlying gastritis. A recent report[31] however showed that treatment with sucralfate has significantly lower ulcer relapse rates but sucralfate, unlike bismuth has no effect on HP both in vivo or in vitro. Hence clearance of HP is not the only factor involved in preventing ulcer relapses. Elimination of HP should be considered before surgery in patients with resistant DUs and those who have multiple recurrences after treatment with H_2 blockers, and may represent an alternative to long term maintenance therapy. Despite the in vitro susceptibility of HP to a large number of antibiotics, including amoxycillin, erythromycin, tetracycline, metronidazole and tinidazole, the in vivo eradication is not easy. It is probably due to the fact that systemic antibiotics do not penetrate reliably to the organisms' habitat beneath the mucus gel layer and bacterial resistance develop during treatment when used alone. Currently, the most effective treatment regimen appears to be a combination of a bismuth salt (such as colloidal bismuth subcitrate 120 mg qds), a nitroimidazole (metronidazole 500 mg qds or tinidazole 500 mg bd) and tetracycline (500 mg qds) or amoxycillin (500 mg qds). The total course lasts two weeks and such a combination apparently gives high eradication rates and a low incidence of side effects and relapse rates. The optimal length of treatment is still unknown[30]. Routine treatment is not yet recommended, especially for asymptomatic carriers as the ideal method of eradication is as yet uncertain. A significant proportion of patients have relapse of ulcer despite being cleared of the organisms. It is not clear what action should be taken in this group of patients. Further studies of the effect of eradicating the organism on the natural history of gastritis and peptic ulcer disease are needed to assess its role in these conditions.

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