Summary and Conclusions
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INTRODUCTION

One of the most profound changes to occur in the field of gastroenterology over the past one and a half decades has been realisation of the association between the presence of \textit{H pylori} in the stomach and gastroduodenal diseases. Even though this organism is present in a large number of Indians, only a small fraction of them will develop peptic ulcer and other gastroduodenal diseases. The epidemiology of \textit{H pylori} in India differs from that observed in developed countries. Data concerning the prevalence of \textit{H pylori} in normal populations or in patients with upper alimentary tract disorders is scanty, especially from South India. Reports on \textit{H pylori} and its relationship to complicated duodenal ulcer are few and limited in their ambit.

This study was conducted in the Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) Hospital, Pondicherry, India from September 1994 to September 2000.

AIMS

The following were the primary aims of this study:

a) To document the prevalence of \textit{H pylori} infection in asymptomatic adults and children without any gastrointestinal disorders.
b) To determine *H pylori* prevalence in patients with various alimentary disorders such as non-ulcer dyspepsia, duodenal ulcer, gastric ulcer, carcinoma of the stomach, chronic gastritis, erosive gastritis and stomal ulcer.

c) To study the prevalence of *H pylori* infection in complications of duodenal ulcer such as bleeding, obstruction and perforation.

d) To document the relationship between prevalence of *H pylori* infection in the postoperative period to medium and long term ulcer recurrence following simple closure of a perforated duodenal ulcer.

e) To determine whether a fall in anti-*H pylori* IgG antibody titres can indicate eradication of the organism without need for endoscopy. If so, to determine, the appropriate level of percentage fall.

**SUBJECTS OF STUDY**

A total of 955 patients were included in this study in four groups;

**GROUP I -ASYMPTOMATIC ADULTS AND CHILDREN (n=205):**

- Group IA (n=105) - Children (≤ 15 years of age)
- Group IB (n=100) - Adults
GROUP II - UPPER GASTROINTESTINAL TRACT DISORDERS (n=458):

Group IIA (n=166) - Duodenal ulcer
Group IIB (n=53) - Gastric ulcer
Group IIC (n=50) - Non-ulcer dyspepsia
Group IID (n=51) - Carcinoma stomach
Group IIE (n=50) - Chronic gastritis
Group IIF (n=58) - Erosive gastroduodenitis
Group IIG (n=30) - Stomal ulcer

GROUP III - COMPLICATED DUODENAL ULCER OTHER THAN PERFORATED DUODENAL ULCER (n = 142):

Group IIIA (n=30) - Bleeding duodenal ulcer
Group IIIB (n=112) - Duodenal ulcer with gastric outlet obstruction

(These patients also formed part of Group IIA)

GROUP IV - PERFORATED DUODENAL ULCER (n=262):

Group IVA (n=202) - Perforated duodenal ulcer (Prospective)
Group IVB (n=60) - Perforated duodenal ulcer (Retrospective)

The diagnosis of various upper alimentary tract disorders was made using upper gastrointestinal endoscopy and histology wherever necessary. The diagnosis of \textit{H pylori} infection was established by urease test, serology by ELISA for IgG anti-\textit{H pylori} antibodies and histology (Giemsa stain).
Criteria of positivity for *H pylori* infection

In asymptomatic children and in patients with perforated duodenal ulcer (prospective group) only serology was used to detect the prevalence of *H pylori*. Per-operative endoscopy, urease test and histology were not done in patients with perforated duodenal ulcer (prospective group) due to ethical reasons. In all the other groups any two of the above mentioned three tests, if positive, was taken as indicative of a positive *H pylori* state. If only one test was positive it was not considered as indicative of a positive *H pylori* state.

Statistical analysis

Statistical analysis was done using Epi Info Software (Version 6.04) and SPSS (Version 6). Chi-square ($\chi^2$) for linear trend, Chi-square test, Fisher’s exact test, analysis of variance (ANOVA), Student’s ‘t’ test and logistic regression analysis were used where appropriate.

METHODOLOGY

In groups I and II the prevalence of *H pylori* was determined as mentioned earlier. The prevalence in asymptomatic controls was compared with the prevalence seen in patients with various upper alimentary disorders.

In group III, the prevalence of *H pylori* infection in patients with bleeding duodenal ulcer was compared with uncomplicated duodenal ulcer and asymptomatic
controls. Also the prevalence in patients with obstructed duodenal ulcer was compared to that seen in patients with non-obstructed active duodenal ulcer.

In group IV, 202 patients were included on a prospective basis and 60 patients were studied retrospectively.

In the prospective group patients were followed up to a maximum period of two years following simple closure of perforated duodenal ulcer. They were randomized to receive ranitidine or quadruple therapy consisting of ranitidine, colloidal bismuth subcitrate, metronidazole and tetracycline in the postoperative period. The eradication rate and the correlation of ulcer recurrence with *H pylori* infection was studied at different intervals of follow-up. Whether fall in IgG serology titres can indicate eradication of *H pylori* was also assessed. The side effects of therapy were noted.

In the retrospective group sixty patients who had a simple closure of a perforated duodenal ulcer five or more years prior to inclusion in the study were entered and the long term ulcer recurrence was correlated with *H pylori* status.

**RESULTS**

**Asymptomatic adults and children**

Group I included 105 children and 100 adults. The children were further sub-grouped into (i) the under fives (n = 37), (ii) 6-10 years of age (n = 36) and (iii) 11-15
years of age (n = 32). The prevalence of *H pylori* in these groups was 46%, 44%, and 44% respectively with no intergroup difference. 50% of infants below 1 year of age had antibodies to *H pylori*. The ability to mount an immune response at this age is uncertain and in the absence of maternal IgG levels, it cannot be said whether these antibodies have been transplacentally transferred to the infants. The overall prevalence rate of *H pylori* in children was 45%. Gender did not affect *H pylori* status in children. The level of anti-*H pylori* IgG antibody titres did not show any significant difference in the different subgroups of children.

69% of adults were infected with *H pylori*. The prevalence increased with age upto 21-40 years with a minimal decline thereafter. There was a significant difference in the prevalence of *H pylori* between children and adults (p = 0.0007). Gender did not affect the *H pylori* state in adults. The anti-*H pylori* antibody levels too showed a significant rise with age upto 41-60 years (p = 0.0007). Thus, it appears that *H pylori* infection starts in early childhood and the rate of infection continues to rise with increasing age reflecting a pattern similar to that seen in other developing countries.

**Upper gastrointestinal disorders**

The prevalence of *H pylori* infection in patients with various upper alimentary disorders is shown below:

- Non-ulcer dyspepsia .. 72%
- Chronic gastritis .. 74%
Erosive gastroduodenitis .. 59%
Gastric ulcer – Overall .. 77%
   Type I and III gastric ulcer - 67%
   Type II gastric ulcer - 83%
Stomal ulcer .. 80%
Carcinoma of the stomach .. 57%
Duodenal ulcer .. 87%

The *H pylori* prevalence rate in upper gastrointestinal disorders was not significantly different from controls except for patients with duodenal ulcer who had a prevalence of 87% which was significantly higher than the asymptomatic controls (*p = 0.0008*). There was a trend towards higher positivity in patients with Type II gastric ulcers (gastric ulcers with active or healed duodenal ulcers) and stomal ulcers which, however, did not reach significance due to small numbers. The serological titres of anti-*H pylori* IgG antibodies did not show any significant difference in various upper gastrointestinal disorders.

No change in prevalence was seen in patients with carcinoma of the stomach when related to the site of tumour although a trend towards higher positivity was seen for tumours of the fundus. The rate of infection for tumors of the fundus, body, antrum and the whole stomach was 80%, 44%, 67% and 50% respectively (*p >0.05*).
In patients with erosive mucosal disease, the *H pylori* infection rate was not different between NSAID users (52%) and NSAID non-users (63%). Site of erosions in the stomach or duodenum did not affect the *H pylori* status. Smoking or alcohol abuse did not have a significant effect on the prevalence of *H pylori* in patients with erosive gastroduodenitis.

Patients with gastric ulcer and associated duodenal ulcer (Type II gastric ulcer) had a relatively higher prevalence of *H pylori* (83%) than in other gastric ulcers (67%). However, the difference was not significant. Number of ulcers, smoking, alcohol or analgesic intake did not affect *H pylori* state in patients with gastric ulcer. In patients with duodenal ulcer also, size of the ulcer, number of ulcers, smoking, alcohol or analgesic intake did not affect the *H pylori* state.

Overall our study showed that the infection rate with *H pylori* in various gastroduodenal disorders is not significantly different from asymptomatic controls with the exception of patients with duodenal ulcer and possibly Type II gastric ulcers and stomal ulcers. In the latter two diseases there is a trend towards a higher infection rate which failed to reach significance probably due to small numbers.

**Complicated duodenal ulcer other than perforated duodenal ulcer**

In patients with bleeding duodenal ulcer, there was a trend towards a high prevalence rate of 80%. This was not significantly different from that seen in active duodenal ulcer without bleeding or asymptomatic controls probably again due to
small numbers. Size of the ulcer or NSAID use did not affect *H pylori* prevalence in these patients.

Comparison of *H pylori* status in patients with duodenal ulcer with and without gastric outlet obstruction showed that patients with active duodenal ulcer whether or not associated with gastric outlet obstruction have a significantly higher prevalence than patients with gastric outlet obstruction without an active ulcer. Serological titres too followed a similar pattern. A significantly higher level of titres was seen in patients with gastric outlet obstruction and active ulcer as opposed to those who had only gastric outlet obstruction but no active ulcer (*P* = 0.024). This indicates that high *H pylori* positivity is responsible for continued/recurrent reactivation of the duodenal ulcer.

**Perforated duodenal ulcer**

Age related seroprevalence of *H pylori* in patients with perforated duodenal ulcer studied on a prospective and retrospective basis showed maximum colonization in young adults between 21 to 30 years of age. There was no gender related difference as regards *H pylori* status. Size of the perforation, acute or chronic nature of the disease based on duration of preperforation symptoms, smoking or alcohol abuse did not affect *H pylori* status.
Effects of therapy

At every interval of follow up, after simple closure of perforation, *H pylori* eradication rates were higher with quadruple therapy as opposed to ranitidine alone. In the quadruple group the eradication rate dropped from 80% at 8 weeks to 33% at 2 years, whereas in the ranitidine group it fell from 57% to 28%. The difference in the eradication rates was significant at 8 weeks alone. Thereafter no significant difference was seen perhaps due to limited number of patients returning for follow up. The percentage of patients with perforated duodenal ulcer in the prospective group returning for follow up at 8 weeks, 6 months, 1 year, 18 months and 2 years was only 88%, 78%, 55%, 23% and 10% respectively. However, it appears that a combination regimen consisting of ranitidine and classical triple therapy is unsuitable for eradication of *H pylori* in our country probably due to high resistance to metronidazole. Regimens without nitroimidazoles may be more suitable for a country like India. Side effects of quadruple therapy were not very marked. Nausea and diarrhoea were most common at 37% and 21% respectively.

*H pylori* status and recurrence of duodenal ulcer

Correlation between the *H pylori* status with presence of recurrent or residual ulcers at various intervals of time after perforation closure in the prospective group showed that a positive *H pylori* status is significantly higher in all patients who have recurrent or residual ulcer compared to those in whom the ulcer had remained healed. The positivity status varied between 76% to 94% in those who had
persistent recurrent ulcer and between 11% to 38% only in those who had no ulcers. In the retrospective group also, the *H pylori* positivity status was very much higher at 90% in those who had recurrent ulcers compared to 19% in those who had no ulcer (*P* < 0.0001). It appears that perforated duodenal ulcer is related to *H pylori* in a heterogeneous manner. The overall prevalence of *H pylori* in patients with perforated duodenal ulcer is higher but not significantly different from controls in our study but the presence of a residual or recurrent ulcer in the postoperative period following simple closure of perforated duodenal ulcer is significantly associated with *H pylori*. Thus, it can be stated that, in spite of the heterogeneous nature of the relationship between *H pylori* and perforated duodenal ulcer, eradication of *H pylori* should be recommended in all patients with perforated duodenal ulcer and a positive *H pylori* state to prevent recurrence of ulcer.

Value of serology as a test for eradication

When serological titres were studied in the follow up period and correlated with eradication rates, it was seen that at 6 months followup, 71% of the eradicated patients had a fall in titre of more than 20% compared to basal titres as opposed to only 45% in the non-eradicated group (*p* < 0.012). A similar difference was seen at one year also with corresponding figures of 72% and 17% (*p* < 0.0001). When a decline of >20% titre levels in EU/ml was used as a test of eradication, it was found to have a sensitivity of 71% at 6 months and 72% at 1 year with corresponding specificity rates of 55% and 83%. When the cut off of IgG titres was raised to 25%, 30% and 50% it was seen that with the increase in percentage decline in titre levels
as a test of eradication, the sensitivity progressively decreased and the specificity increased. At 10% cut-off the sensitivity increased to 78% with a decline in specificity. Overall the highest sensitivity of 78% was obtained for a 10% cut-off. Though the sensitivity and specificity of serology to determine eradication was not very high in this study, further studies to evaluate the decay in antibody titre levels with appropriate fixation of cut-off levels can help in increasing the efficacy of this test to monitor the results of antimicrobial therapy without need for invasive investigation such as upper gastrointestinal endoscopy.
The following conclusions could be drawn from the study. *H pylori* infection is acquired in early childhood and increases progressively with age. Among the various upper gastrointestinal disorders only duodenal ulcer had a significantly higher prevalence of *H pylori* infection. A trend towards higher positivity is also seen for patients with Type II gastric ulcers and stomal ulcers which may reach significance with larger numbers. Bleeding and obstructed duodenal ulcer have high prevalence rates of *H pylori*. However, beneficial effects of eradicating *H pylori* in these conditions has to be further studied. Patients with perforated duodenal ulcer with a positive *H pylori* state should always be recommended for eradication of *H pylori*. Nitroimidazole containing regimes have a low efficacy probably due to resistance. Serology can be considered as a crude but non-invasive test to monitor results of antimicrobial therapy from 6 months to one year after therapy with an appropriate cut-off to increase the accuracy.