Discussion
DISCUSSION

*Helicobacter pylori* is certainly the most common infection worldwide affecting nearly half the population. Its mere frequency of occurrence, however, is not in itself a problem; it is the propensity of this organism for causing illness that determines its public health significance. This spiral, microaerophilic bacterium has been identified as the cause of chronic gastritis, peptic ulcer disease, gastric adenocarcinoma and MALT lymphoma. Less well accepted is its role in non-ulcer dyspepsia and its more indirect influence on coronary artery disease, rosacea, diarrhoeal diseases in children in developing countries and hepatic encephalopathy [4-6].

Higher *H pylori* infection rates with increasing age have been reported from all over the world [15,274-275]. It is seen to be more prevalent in certain ethnic groups. African and Hispanic Americans have higher infection rates compared to Caucasian Americans [276-277]. However, regardless of the ethnic background, people in developing countries acquire infection earlier than those in developed countries.

The epidemiology of *H pylori* in India differs from that observed in developed countries [10]. While the medical, economic and social significance of *H pylori* has been recognized in the West, the situation in India is not fully clear. Data concerning the prevalence of *H pylori* in the normal population or in patients with upper alimentary tract disorders is scanty, especially from South India [167].
Establishment of prevalence rates of *H pylori* in 'normals' and 'abnormals' will help in understanding the relationship between *H pylori* infection and different upper gastrointestinal disorders in this region. Likewise, the determination of the prevalence rates of *H pylori* in complications of duodenal ulcer such as bleeding, gastric outlet obstruction and perforation will help to evaluate the role of *H pylori* in complicated ulcer disease.

Though *H pylori* infection and its relationship to bleeding duodenal ulcer has been studied in the West, reports on the correlation of infection with this organism with other complications of peptic ulcer such as obstruction and perforation are very limited [18,137-139,142]. It is well accepted that *H pylori* is closely associated with uncomplicated duodenal ulcer; whether a similar relationship exists with perforated duodenal ulcer is not known. Contradictory reports in literature only serve to keep the question on association of *H pylori* and perforated duodenal ulcer wide open [24,25].

To summarise, the following are the chief lacunae in data from India:

- There is no large study on prevalence rates in the asymptomatic population particularly in children.
- There is no large study on prevalence rates in upper gastrointestinal disorders other than peptic ulcer.
- Methods of diagnosis are not uniform and acceptable.
- Data on complications of duodenal ulcer are scanty and contradictory.
This study was, therefore, planned to document the prevalence rate of *H pylori* in asymptomatic adults and children, in patients with various upper alimentary tract disorders including complications of duodenal ulcer such as bleeding and gastric outlet obstruction. A major area of emphasis was to study the prevalence rate of *H pylori* in patients with perforated duodenal ulcer and to correlate the *H pylori* status with short, medium and long term ulcer recurrence following simple closure of a perforated duodenal ulcer.

**RATIONALE OF TESTS USED FOR DIAGNOSIS OF *H PYLORI* IN THIS STUDY**

There are many methods to detect the presence of *H pylori*. An ideal test should have high sensitivity and specificity and high positive and negative predictive values. It should be inexpensive and easy to perform and be minimally invasive for better patient acceptance. The various diagnostic methods used for detection of *H pylori* can be categorized as –

a) direct and

b) indirect

Histology, culture and polymerase chain reaction (PCR) provide direct evidence of presence of *H pylori*. Indirect tests rely on detecting a characteristic of the bacteria such as the ability to hydrolyze urea or the response of the immune system to the presence of the organism. These include urea breath tests, urease test and serology.
Because of their high degree of specificity, direct tests are commonly regarded as the standard with which the indirect tests are compared [70]. However, in most centres, culture is considered to be technically demanding and time consuming. Even in well established laboratories an isolation rate of only 70% to 90% makes this test only moderately sensitive and of limited use [75]. The isolation rates from India range widely from 5% to 80% [11]. Though PCR can detect *H pylori* from feces or saliva its use for diagnosis is limited to experimental studies due to cost and limited availability of the technique in most clinical laboratories [95]. Urea breath tests though non-invasive and accurate for detection of *H pylori* involve high cost in establishing the facility for doing the test.

In this study *H pylori* infection was diagnosed by the urease test on gastric mucosal biopsy, serology for IgG antibodies against *H pylori* and histology of gastric mucosa using Giemsa stain.

**Urease test**

The urease test was done by a urea solution prepared and standardized in our institution [267]. This had a high accuracy. The sensitivity and specificity of this urea solution was 93% and 92% respectively compared to histology. The commercial CLO urease test has a sensitivity ranging from 89% to 98% and a specificity between 93-98% [74]. Though there is a possibility of uneven or patchy distribution of *H pylori*, the gastric antrum appears to be more uniformly involved and
two biopsies from within 2-5 cm of pylorus are generally held to be sufficient for diagnosis [74,268]. There may be false negative results within two to three weeks of stopping antimicrobial therapy [79]. Hence, no patients who had taken antibacterial therapy, proton-pump inhibitors or H₂ blockers within a month of presentation were included in the study. False positive results are rare with the urease test as the solution used for urease test contains a bacteriostatic agent [81] which inhibits the growth of other urease producing organisms. Sterilized endoscopes and biopsy forceps were used, which makes it unlikely that bacterial contamination can occur from exogenous sources. The endoscopes and biopsy forceps were sterilized between patients using 2% glutaraldehyde solution as per standard procedure. Following sterilization, the endoscopy and biopsy forceps were cleaned with sterile saline as residual glutaraldehyde may also produce suppression of *H pylori*.

**Serology**

Serology was done with a second generation Microwell ELISA assay for the detection of IgG antibodies; its sensitivity and specificity were validated at our centre by comparing it to histology and urease test [267]. This was done as many of these commercial kits are developed and validated in Western countries and need revalidation before use in other countries [278]. This commercial kit had a high accuracy. Serology was used as one of the methods of detecting *H pylori* status as *H pylori* is a chronic infection that does not resolve spontaneously and elevated titres indicate current infection unless the patient is known to have been treated for *H pylori* in the recent past [38]. *H pylori* specific serum IgG response is both highly
specific (99%) and sensitive (96%) in detecting *H pylori* colonization [64]. This test when validated at our centre was found to have a sensitivity of 91% and a specificity of 84% compared to the urease test. On comparison with histology the sensitivity and specificity was 93% and 88% respectively.

In patients infected with *H pylori* both IgG and IgA antibodies are significantly elevated. IgM titres, however, are similar in *H pylori* positive and negative individuals, probably because the IgM seroconversion which occurs in the early phase of infection is transient and falls to negative levels very early [31]. IgG and IgA serum antibodies detect *H pylori* colonization with fair degree of accuracy. The use of antigenic material of higher specificity such as high molecular weight cell membrane associated protein, has yielded sensitivity and specificity of 98.7% and 100% respectively with IgG ELISA [88]. This high accuracy obviates the need to do IgA antibody titres for *H pylori* detection. Serology might not be useful to assess immediate effects of antibacterial therapy. However, studies have reported that a fall in titre might give a clue to *H pylori* eradication [92,93]. Serological testing for *H pylori* for determination of prevalence at the time of perforation was carried out both immediately and after an interval period of 8 weeks, to detect those patients who had been infected just prior to perforation. This was similar to the study by Reinbach et al in patients with peptic ulcer perforations studied prospectively [25]. The possibility that acute perforated duodenal ulceration could be associated with the early phase of *H pylori* infection before IgG seroconversion has had time to
occur must be considered, hence repeat serology at 8 weeks from presentation is necessary.

**Histology**

Histology was done with the help of two endoscopic gastric mucosal biopsies taken from the pyloric antrum within 2 cm of the pylorus. Histology is reported to have a high degree of sensitivity ranging from 93% to 99% and a high specificity of 95% to 99% for detection of *H pylori* [74]. The paraffin embedded histological sections were stained with Giemsa stain for identification of *H pylori* [269]. The stained sections were reported separately by two pathologists without knowledge of the clinical findings, endoscopic data or urease and serological results. The *H pylori* status by Giemsa stain was considered positive if it was reported positive by one or both pathologists. The *H pylori* status was considered negative if both the pathologists reported the slide as negative for *H pylori*. This method was adopted to increase the accuracy of the test. Giemsa stain was used as it is considered cheap, easy to perform and a stain superior in detecting *H pylori* [72]. Though there is a possibility of sampling error due to patchy distribution of the organism in the stomach, it is thought to be minor provided the biopsies are taken within 5 cm of the pylorus [74]. Histology has an additional advantage that the specimen can be re-examined and preserved to provide a permanent record.
Criteria of Positivity

In asymptomatic children and patients with perforated duodenal ulcer (prospective group) only serology was done to detect the prevalence of *H pylori* as reported in other studies [7,25,60]. As general anaesthesia would be required in most of the children for doing endoscopy, it was considered unethical to subject them for endoscopy and invasive tests for detection 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 other groups if any two of the above mentioned three tests were positive, it was taken as a positive *H pylori* state. This is similar to other studies reported in literature [268,270-272,279]. If only one test was positive then it was not considered as indicative of a positive *H pylori* state.

PREVALENCE IN ASYMPTOMATIC ADULTS AND CHILDREN

Rationale for the Control Group:

Most investigators find it difficult to get a representative control group for comparing prevalence rates. Tests for absolutely ruling out upper gastrointestinal disorders are invasive and consent for these is difficult to obtain in the general population or blood donors. Also, one cannot rule out upper gastrointestinal disorders on history and examination alone. Hence, controls have to be drawn from hospital based patients admitted for other reasons who volunteer to undergo endoscopy. However, since endoscopy involves general anaesthesia in children, it
is precluded on ethical considerations and exclusion of alimentary disorders has to be only on clinical grounds without resorting to endoscopy. This also rules out endoscopy based tests for \( H \text{pylori} \). Facilities for examination of stool for \( H \text{pylori} \) or urine elisa tests are not widely available. The only non-invasive test (breath test) is costly. Since controls were recruited only for getting an idea of baseline prevalence in the asymptomatic population for comparison with the diseases group, it was not considered appropriate to relate presence of the organism to epidemiological and socioeconomic parameters. Most studies in India and abroad have used only hospital based patients admitted for other disorders as controls [7,9].

The prevalence of \( H \text{pylori} \) infection varies world wide. Higher colonization rates are seen in developing countries compared to developed ones [280]. Xia et al in their review of the natural history of \( H \text{pylori} \) in humans, concluded that natural acquisition of \( H \text{pylori} \) infection occurs mostly in childhood with the rates being relatively lower in developed countries than in developing ones [280]. Low socioeconomic status is a major risk factor for the acquisition of \( H \text{pylori} \) infection. \( H \text{pylori} \) is thought to be spread by the feco-oral route and has been cultured from diarrhoeal stools [52-53] and drinking water [57]. Prevalence of \( H \text{pylori} \) was higher if more than one person shared a room or if there was no hot running water in the house [56]. Nosocomial transmission between patients undergoing endoscopies has been reported [58]. As one of the major risk factors for acquiring this infection is a low socioeconomic status, this infection is widely prevalent in India.
In Western countries, *H pylori* infection is rare in patients less than 5 years of age [8]. This prevalence increases with age and more than 50% of individuals above fifty years have serologic evidence of infection. Prieto et al reported a prevalence rate of 3.3% in the first two decades of life from Spain [9]. In France, 3-5% of patients were infected in the first decade of life [9]. On the other hand, in countries such as Algeria, Ivory Coast and Gambia 45% to 90% of children are infected during the first decade of life [9,60]. Fiedorek et al studied 245 healthy children (under 20 years of age) who presented for day surgery in Arkansas in the USA for serologic evidence of *H pylori* infection using ELISA for IgG antibodies. 31% of these children were infected with *H pylori* with the frequency of infection in blacks at 50% being twice as much as in whites [7].

Blecker et al in their large series of 466 asymptomatic children also used serology for diagnosis of *H pylori* [281]. These children were admitted for a day for elective surgery. Other studies have also used serology for documenting *H pylori* infection in asymptomatic children [6]. The only study which used endoscopy in children was by Prieto et al who studied *H pylori* infection in children referred for abdominal pain using histology and culture for diagnosis [9]. Those who were endoscopically negative were taken as normals. Hence, serology by ELISA is the most widely used method of diagnosing *H pylori* infection in asymptomatic children. This was done in the present study also. Wu et al reported a prevalence rate of 61% in asymptomatic controls from China reflecting the higher colonization rate seen in developing countries [282].
Age related studies documenting *H pylori* infection from India show the same trend seen in developing countries; viz. occurrence of infection at an earlier age [10]. Dore et al reported a high prevalence of *H pylori* infection (82%) in school children using $^{13}$C urea breath test [283]. In a study from Mumbai, India, age related prevalence rate in 82 control subjects in the age groups 10-19 years, 20-29 years, 30-39 years, 40-49 years and 50 years and above was 44%, 55%, 58%, 36% and 33% respectively [14].

In our study too, children less than 5 years had a relatively high prevalence of *H pylori* (46%) compared to their western counterparts. When prevalence rates in the under fives was analysed further antibodies for *H pylori* were present in 4 out of 8 children under one year of age. 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 transplacently transferred to the infants. The prevalence rate in children in our study was almost the same through the different age groups of 6-10 years and 11-15 years suggesting a steady colonization rate compared to young adults where it rises significantly to 74% (P = 0.0002). Our study reflects a similar pattern of *H pylori* infection as seen in Mumbai showing a steady rise upto 40 years and thereafter a slight decline in the later years of life (Fig.1.2). Gill et al reported an *H pylori* seroprevalence rate of 22%, 56% and 87% in the 0-4, 5-9 and 10-19 years age groups [274]. Though their prevalence in the under fives was low compared to our study, it was higher in older children.
A study from Chennai in South India, showed a seroprevalence of only 21.1% in children between 12-20 years of age [15]. This low prevalence in children from India might be due to the inclusion of subjects from educated upper class population where the living standards are good. There was a rising trend in seroprevalence, with a prevalence rate of 41.1%, 58.6%, 54.7%, 54.7%, 47.8% and 76.2% in the 21-30, 31-40, 41-50, 51-60, 61-70 and more than 70 years age groups respectively. Though the prevalence increased with age the overall colonisation rate appeared to be low compared to our study especially in young adults. This can be explained again on the basis of better living conditions and better socioeconomic status of the group studied by Alaganantham et al [15]. These authors also noted that individuals belonging to larger families had a higher risk of infection. Table D-1 in next page shows the high prevalence of *H pylori* infection in children from developing countries and the low infection rates from developed countries.

In a Japanese study in 1994, the age specific seroprevalence rate of *H pylori* increased significantly with age starting from 0 to 9 years and reached a peak in the 50-59 year age group. It then decreased in the 60-69 year age group [275]. The seroprevalence rate was not related to gender. This overall tendency of increasing seropositivity with age upto 60 years and thereafter a decline seen by them was similar when stored samples taken from the years 1974 and 1984 were tested [275]. However, in comparison with the *H pylori* infection rate in 1974, the 1984 and 1994 infection rates with this organism was less in those under 45 years of age.
### TABLE D1. SEROPREVALENCE OF H. PYLORI INFECTION IN CHILDREN FROM DEVELOPING AND DEVELOPED COUNTRIES.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Age group (years)</th>
<th>H. pylori Positivity (%)</th>
</tr>
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<tbody>
<tr>
<td>Buhanover et al⁶</td>
<td>1996</td>
<td>France</td>
<td>0-10</td>
<td>3.5</td>
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<td></td>
<td></td>
<td></td>
<td>11-20</td>
<td>16.3</td>
</tr>
<tr>
<td>Blecker et al²³</td>
<td>1994</td>
<td>Belgium</td>
<td>2-8</td>
<td>5.4</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>9-14</td>
<td>13.4</td>
</tr>
<tr>
<td>Prietto et al⁹</td>
<td>1992</td>
<td>Spain</td>
<td>0-20</td>
<td>3.3</td>
</tr>
<tr>
<td>Megraud et al¹²</td>
<td>1993</td>
<td>Algeria</td>
<td>0-10</td>
<td>45.2</td>
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<td></td>
<td></td>
<td></td>
<td>11-20</td>
<td>73.0</td>
</tr>
<tr>
<td>Sullivan et al⁶</td>
<td>1990</td>
<td>Gambia</td>
<td>0-5</td>
<td>31.4</td>
</tr>
<tr>
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<td>1994</td>
<td>Brazil</td>
<td>0-8</td>
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<td>9-14</td>
<td>45.8</td>
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<td></td>
<td>15-18</td>
<td>64.3</td>
</tr>
<tr>
<td>Graham et al¹³</td>
<td>1991</td>
<td>India</td>
<td>0-9</td>
<td>60.0</td>
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<td></td>
<td></td>
<td></td>
<td>10-19</td>
<td>69.0</td>
</tr>
<tr>
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<td>India</td>
<td>12-20</td>
<td>21.1</td>
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<tr>
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<td>2000</td>
<td>India</td>
<td>0-5</td>
<td>46.0</td>
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<td>6-10</td>
<td>44.0</td>
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<td></td>
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<td></td>
<td>11-15</td>
<td>44.0</td>
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</table>
This could be related to the better sanitation in the eighties and nineties compared to the earlier decades. Thus it appears that the prevalence of *H pylori* in asymptomatic adults and children varies from region to region. Significant differences are seen within a country like India. Hence, whenever a study is done for determining the prevalence in the diseased patients, controls should preferably be taken from the same area due to the variation in the geographical distribution of infection.

In the present study, gender did not affect the *H pylori* status in children. The infection rate was 47% and 41% in boys and girls respectively. In adults too, though women showed a higher rate of infection of 83% compared to men (66%), the difference was not significant. Graham et al in their study on an asymptomatic population in the United States, also reported an equal frequency of *H pylori* infection in men and women [61]. An Indian report from Chennai also found equal seroprevalence rates of *H pylori* infection in men (53.2%) and women (45.9%) [275].

When prevalence rates established by urease, histology or serological positivity are compared to actual levels of anti-"H pylori" IgG antibodies it was seen that the mean titres in different age groups more or less had a similar peak at 21-40 years and 41-60 years with a steady decline thereafter. The increase in the titre levels might suggest a continued or repeated attacks of re-infection producing a booster dose effect. This increase in the IgG titre levels differs significantly from the
childhood prevalence and response \( (P = 0.0007) \) suggesting that though the infection starts in children, it will last throughout the individual's life.

**UPPER GASTROINTESTINAL DISORDERS**

One of the most significant changes in gastroenterology over the past one and half decades has been the realization of the association between the presence of *H pylori* in the gastric mucosa and gastroduodenal diseases. *H pylori*, is a pathogen which causes gastritis. This *H pylori* induced gastritis may lead to duodenal ulcer disease, gastric carcinoma and MALT lymphoma [285].

While this organism is present in a large number of Indians, only a fraction of them will develop peptic ulcer or other gastroduodenal diseases or even exhibit any symptoms. Most of the work on the bacteriologic properties of *H pylori*, its pathogenic factors of its relationship to duodenal ulcer or other gastroduodenal disorders have been determined in the West. This organism has now been recognized by the World Health Organisation as a Group I carcinogen [286]. Though studies from all parts of India have documented the prevalence of *H pylori* in diseases like non-ulcer dyspepsia (NUD), duodenal ulcer (DU), gastric ulcer (GU) and carcinoma of the stomach, the reports are few and limited in their ambit [164,166,200].

The distribution of *H pylori* in gastroduodenal diseases in Indian and other series is shown in Table D-2 (Next page). In most of the Indian and foreign series,
TABLE D-2. DISTRIBUTION OF H. PYLORI IN GASTRODUODENAL DISEASES IN INDIAN AND FOREIGN SERIES

<table>
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<tr>
<th>Author</th>
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<th>Number</th>
<th>Diagnosis of H. Pylori</th>
<th>DU</th>
<th>GU</th>
<th>Chronic gastritis</th>
<th>Carcinoma stomach</th>
<th>NUD</th>
<th>Stomal ulcer</th>
<th>Erosive gastroduodenitis</th>
<th>Controls</th>
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<td>UH</td>
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DU-duodenal ulcer, GU-gastric ulcer, NUD-non-ulcer dyspepsia, U-urease test, H-histology, S-serology, C13-urea breath test.
the maximum colonization rate is seen in patients with duodenal ulcer. Other disorders show a relatively low prevalence in most of the studies. About half the control subjects are infected by this bacteria. A study from Malaysia by Uyub et al, however, shows a very low prevalence of *H pylori* in all the disorders studied by them[290]. A low frequency of peptic ulcers was also noted in this study. Studies from South India show a similar distribution of *H pylori* as seen in the present study [164-165,200].

**Duodenal Ulcer**

*H pylori* is undoubtedly one of the most important factors in the etiology of peptic ulcer disease. Due to the multifactorial nature of this disease there is an interplay of other disease modifiers such as acid-pepsin secreting potential, smoking, genetic predisposition and other environmental factors [121]. This might explain the discrepancy between the high frequency of *H pylori* infection in the general population in the region of about 50% and a low overall lifetime prevalence of duodenal ulcer disease which is only about 10% [121]. The prevalence of *H pylori* infection in duodenal ulcer has consistently been found to be between 90-100% [122-124,293]. In the present study too it was 87%, a rate which was significantly more than controls. When adjusted for age and sex, *H pylori* infection in duodenal ulcer was significantly higher than controls. Prasad et al also reported a high prevalence rate of 93% for *H pylori* infection in patients with duodenal ulcer [165]. A North Indian study reported a prevalence rate of 95% in patients with duodenal ulcer.
However, Joshi et al from Western India reported a relatively low prevalence of 66%.

Studies conducted in duodenal ulcer patients in the United States have reported the prevalence of *H. pylori* infection in these patients to range from 61% to 100% [125,294-297]. In those studies where only serum IgG antibodies were used as the method of detecting *H. pylori*, the positivity rate for *H. pylori* infection was high ranging from 92-100% [294-296]. In another study where a CLO test or histology was used as the method of detection, 61% of the patients only were positive for *H. pylori* [297]. The difference in prevalence is probably related to the test used for detection of *H. pylori*. Serology alone is accurate for detecting current or past infection which since then might have been eradicated whereas a CLO test or histology detects only current infection. The latter estimation may be an under approximation due to widespread misuse of over the counter drugs (both antibiotic and anti-ulcer) leading to temporary suppression of the organism below the threshold of detection by CLO or histology. Other studies also showed a high prevalence of *H. pylori* ranging from 86% to 99% in patients with duodenal ulcer [201,258,288-289,298-299]. These studies suggest a high prevalence of *H. pylori* infection in patients with duodenal ulcer disease.

Duodenal ulcer in children:

There is a strong correlation between duodenal ulceration and *H. pylori* infection in children. In a prospective study from Toronto, all 13 children with
duodenal ulceration had *H pylori* associated chronic antral gastritis [64]. Hassall and Dimmick have reported 27 children from British Columbia who were found to have duodenal ulcers over a six year period [300]. Twenty three of these children had chronic *H pylori* associated antral gastritis. Retrospective studies from Toronto and Cleveland found evidence of *H pylori* gastritis in between 90% and 100% of patients with duodenal ulcer disease in children [301-302]. De Oliveira et al found *H pylori* infection in all of 20 children with duodenal ulcer disease [303]. They also found that the serum anti-*H pylori* IgG concentration was significantly higher (*P* = 0.0003) in children with duodenal ulcer than in those without ulceration. They used a second generation ELISA kit to estimate the IgG levels.

*H pylori* negative duodenal ulcer:

McCull et al in their study of *H pylori* negative chronic duodenal ulceration reported 12 patients presenting with chronic duodenal ulcer disease with no evidence of current or recent *H pylori* infection [304]. The patients were considered *H pylori* negative when microscopy, $^{14}$C-urea breath test, urease test and *H pylori* IgG serology were negative. In half of these patients, some explanation for the ulcer was apparent. Four of the patients were taking regular NSAIDs, one patient had Zollinger-Ellison syndrome and one patient had histological changes in duodenal biopsies consistent with Crohn's disease. Some other studies have also reported NSAID intake and evidence of Crohn's disease in *H pylori* negative duodenal ulceration [305-306]. In the remaining six patients in McCull's series, there was no other explanation for the ulceration. These were labelled as idiopathic duodenal
ulcers. These patients with idiopathic duodenal ulcers showed disturbances of gastric function such as hypergastrinemia, increased basal and peak gastric output and rapid gastric emptying [304].

Size and number of ulcers and *H pylori* infection:

Size of the duodenal ulcer did not affect *H pylori* status in our patients. Patients with several ulcers too showed no greater predilection for *H pylori* colonization, indicating that *H pylori* association with duodenal ulcer is independent of the size or the number of ulcers.

Smoking and duodenal ulcer:

Cigarette smoking is an important factor in peptic ulcer disease. There are conflicting reports on the influence of cigarette smoking on healing in patients with duodenal ulcer [307]. Roxburgh et al studied the effect of acute cigarette smoking on gastric secretion and concluded that cigarette smoking causes a significant fall in gastric secretion resulting in increased gastrin levels which in turn produced a trophic effect on the parietal cell mass with consequent increase in acid secretion [308-310]. The net result was an increased capacity for gastric secretion in chronic smokers.

The relationship of duodenal ulcer, smoking and *H pylori* infection is controversial. Bateson reported a strong association between *H pylori* infection and smoking in patients with normal endoscopy or with duodenal ulcer [258]. In his
study, a higher prevalence of \textit{H pylori} infection was seen in cigarette smokers (49.6\%) compared with non-smokers at 35.5\% (p < 0.01). In the same study, 85\% of patients with duodenal ulcer were infected with \textit{H pylori} compared to 40\% of patients with normal findings on endoscopy (p < 0.005). It was also noted in this study that 51.8\% of duodenal ulcer patients smoked compared to 31.8\% in controls. This difference in number of smokers was highly significant (p < 0.001). He concluded that current cigarette smokers are predisposed to peptic ulcer because of increased susceptibility to \textit{H pylori} infection. A study from North India too found \textit{H pylori} infection more commonly in smokers than non-smokers [311]. On the contrary in our study we did not find any significant difference in \textit{H pylori} infection in patients with duodenal ulcer who were smokers or non-smokers (Table 2.5.2). Chan et al reported that continued smoking did not predispose to a peptic ulcer relapse after successful eradication of \textit{H pylori} infection [312].

Alcohol and duodenal ulcer:

Alcohol has a strong antimicrobial activity besides stimulating gastric acid secretion. Alcohol consumption may affect the colonization of the stomach by \textit{H pylori} [313]. In the present study, the \textit{H pylori} infection in alcoholic and non-alcoholic patients with duodenal ulcer disease was similar with no significant difference. Studies have shown that moderate alcohol consumption facilitates spontaneous elimination of \textit{H pylori} infection and hence a decrease in the prevalence rate is seen in alcoholics [313,314]. However, this was not seen in our study. Brenner et al suggested that alcohol in the form of wine as compared to beer
might have a greater antibacterial activity [314]. As our patients belonged to a low socioeconomic strata most of them consumed only locally made liquor which may have minimal bactericidal action. Also the amount consumed was usually small.

NSAID use and duodenal ulcer:

The prevalence of *H pylori* infection in patients using NSAIDs has been reported to range from 22.5% to 63% [188,189]. Most studies have shown no significant difference in *H pylori* prevalence between NSAIDs users and non-users [189]. In the present study NSAID use did not alter the *H pylori* status in patients with duodenal ulcer. The prevalence rate in NSAID users was 100% compared to 86% in non-users. Other reports suggest that though the evidence for a synergistic relationship between NSAID use and *H pylori* in producing duodenal ulcer is weak, this association should not be ignored because of the therapeutic implications [315]. However, Heresbach et al reported that among patients taking NSAIDs, *H pylori* infection was present more frequently in those who presented with gastropathy than in those without any lesions [292]. They concluded that *H pylori* could be a risk factor in NSAID induced gastropathy.

Gastric Ulcer

The relationship between *H pylori* infection and gastric ulceration is less clear as compared to gastritis or duodenal ulcer. Most of the studies show that *H pylori* infection ranges from 70-80% in patients with gastric ulcer [37,316-317]. Gastric ulcers developing in non-infected patients are thought to be mainly due to ingestion
of anti-inflammatory agents. If these drug induced ulcers and other known causes such as Zollinger-Ellison syndrome are excluded, then the \( H \) pylori prevalence approaches 96% in patients with gastric ulcer also similar to that seen in duodenal ulcer [124,151]. In our study also, while overall prevalence rate of infection in patients with gastric ulcer was only 77%, when NSAID users were excluded it rose to 82% \((p = 0.23)\). The overall prevalence of \( H \) pylori at 77% was not significantly different from that seen in controls at 69% \((p = 0.37)\). Some other studies from India have reported a lower frequency of positivity of \( H \) pylori ranging from 50-65% in patients with gastric ulcer [318-319]. Prasad et al reported an \( H \) pylori prevalence of 81% in their study [165]. Joshi et al showed that both patients with gastric ulcer in their study were positive for \( H \) pylori. In a study on Chinese patients 36% of patients with gastric ulcer were positive for \( H \) pylori [201]. Bateson reported a rate of infection of 55.8% in patients with gastric ulcers [258]. This was significantly higher than his controls in whom it was only 40% \((p < 0.01)\). Majority of our patients (66%) with gastric ulcer had associated healed or active duodenal ulcer. In literature there is no specific rate of prevalence mentioned for Type I, II or III gastric ulcers. 83% of our patients with Type II gastric ulcers were positive for \( H \) pylori status suggesting a similar link etiologically as is seen in duodenal ulcer disease (Table 2.4.1). On the contrary only 67% of the other gastric ulcers without evidence of duodenal ulcer were infected with \( H \) pylori.
NSAID use and gastric ulcer:

In the present study, 37% of patients with gastric ulcer were NSAID users. The *H pylori* positivity rate was 82% in patients who had not taken analgesics compared to 70% in patients who were NSAIDs users. However, there was no significant difference in the *H pylori* positivity status in NSAID users and non-users.

Martin et al reported that NSAID users with *H pylori* infection more often had gastric ulcers than those without *H pylori* [320]. However, most other studies report that the presence of *H pylori* was not a significant additional risk factor for NSAID induced gastric ulcer [321-323]. A study from Western India showed an *H pylori* infection rate of 37% in patients on NSAIDs as compared to 57% in patients with arthritic disorders prior to starting NSAID therapy. A 60% positive *H pylori* status was seen in healthy volunteers in this study [190]. The authors concluded that long term NSAID use does not lead to increased risk of *H pylori* infection nor does presence of *H pylori* correlate with gastroduodenal damage in NSAID users. Sung et al found that gastric ulcers unrelated to NSAIDs, healed better with antibacterial treatment than with medication to suppress gastric acid [324].

As in patients with duodenal ulcer, the number of gastric ulcers did not alter the *H pylori* status.
Smoking and alcohol:

Smokers did not have a significantly higher *H. pylori* positivity status in our patients with gastric ulcers when compared to non-smokers. Bateson who reported a significantly higher prevalence of *H. pylori* in patients with gastric ulcer than that seen in controls, found that more patients were smokers (48.8%) in the gastric ulcer group than the 31.8% seen in controls (p < 0.01) [258]. Though alcohol is reported to have an anti-microbial activity towards *H. pylori* [313,314] in our study on patients with gastric ulcers, alcoholics had a marginally but not significantly higher *H. pylori* prevalence rate of 83% than non-alcoholics (77%) (p = 0.59). This was similar to our findings in duodenal ulcer also.

Stomal Ulcer

In the present study of 30 patients with stomal ulcer following gastroenterostomy for chronic duodenal ulcer 80% were infected with *H. pylori*. This frequency of colonization was only next to that found in duodenal ulcer. The difference in infection rate from controls did not reach statistical significance, probably due to the small number of patients with stomal ulceration. A Jordanian study which included only 2 patients with stomal ulceration showed that only one of them was positive for *H. pylori* infection [291]. A trend towards a high positivity rate in patients with stomal ulceration as seen by us (Table 2.1.1) mandates that measures to control stomal ulceration should include anti-*H. pylori* therapy in addition to surgery, where warranted, to achieve complete and permanent healing and to
reduce the incidence of relapse of these ulcers and consequent further complications such as perforation and gastrojejunocolic fistula.

**Erosive Gastroduodenitis**

The involvement of *H. pylori* in the pathogenesis of chronic antral gastritis is well known [325-326]. However, the role of this organism in erosive gastritis, one of the most frequent causes of upper gastrointestinal bleeding is not clearly established. Some studies show a significant relationship between NSAID use, *H. pylori* infection and erosive mucosal disease. Taha et al in their study of the relationship between *H. pylori* and mucosal erosions in patients on long term NSAID use, found that in the group of patients with *H. pylori* infection there were significantly more patients with erosions [259]. Another report also found *H. pylori* infection more frequently in patients with bleeding mucosal erosions [292].

On the other hand, other authors have shown contradictory findings. Kulkarni et al studied the effect of *H. pylori* on the gastroduodenal mucosa and found that it did not increase the risk of gastroduodenal damage [190]. Graham et al found a greater number of submucosal haemorrhages and erosions in *H. pylori* negative NSAID users suggesting that the presence of *H. pylori* had no influence on the prevalence of such lesions due to the administration of NSAIDs [323].

In the present study, in patients with erosive gastritis, the *H. pylori* infection rate was more in NSAID non-users (63%) compared to NSAID users (52%). The
difference, however, was not significant. This appears to be in agreement with the earlier mentioned Indian study by Kulkami et al and other cited reports [190,327]. NSAIDs lead to a histologic picture similar to bile reflux gastritis in patients with history of gastroduodenal surgery. This is characterised by foveolar hyperplasia, vasodilatation, oedema, lack of inflammatory cells and presence of muscle fibres in lamina propria [327]. *H pylori* infection has been noted to be rare in the presence of bile reflux gastritis. This has been noted in our earlier report [328,329]. Hence, the changes produced by NSAIDs may also make the environment hostile for the organism.

It appears from our study that patients on NSAID therapy do not have an increased risk of *H pylori* infection. Hence eradication of *H pylori* in patients on NSAIDs therapy might not be beneficial.

The body of the stomach was the predominant site of erosions in our study. This has also been reported in literature [141]. Patients with erosions in the fundus had the maximum *H pylori* colonization rate of 100% compared to other sites in the stomach or the duodenum. However, the difference was not significant (Table 2.3.1). Smokers and alcoholics had a higher prevalence of *H pylori* infection than non-smokers or non-alcoholics but the difference again was not significant (Table 2.3.2). Another Indian study from Northern India also did not find any association between *H pylori* infection and smoking [330].
Chronic gastritis

Chronic gastritis, one of the most common inflammatory conditions of humans has been difficult to study and characterize in clinical, epidemiological and aetiological terms [331]. It was first described as a clinical entity by Osler [332].

In the present study, diagnosis of chronic gastritis was entirely by endoscopy. This showed an appearance of congestion of the gastric mucosa in the pyloric antrum. However, there are limitations in diagnosis of chronic gastritis on endoscopy [261,262]. Since endoscopically normal appearing mucosa may on histology show the typical picture of antral gastritis and vice versa. Hence, biopsies were taken for histological confirmation according to standard established criteria of the Sydney system [263]. The prevalence of \textit{H pylori} in chronic antral gastritis ranges from 48 to 100\% in literature [32,167,181-183]. Characteristically, \textit{H pylori} gastritis predominantly affects the antrum. In the present study, 74\% of patients had a positive \textit{H pylori} status which was marginally higher than that in the controls. Other studies from India have reported a lower prevalence of 48-50\% in patients with chronic gastritis [167,183]. However, Katelaris et al in their study on Tibetans exiled in India found a close association between chronic gastritis and \textit{H pylori} [333]. A correlation between the number of bacteria present and severity of gastritis was also noted in this study. A higher density of the bacteria were seen in patients with severe forms of gastritis. Even though the prevalence of \textit{H pylori} in patients with chronic gastritis has a wide range, other gastropathies like portal hypertensive
gastropathy or gastritis related to postoperative bile reflux show a low prevalence of *H pylori* infection [184-185]. Balan et al reported a prevalence of only 40% in patients with portal hypertensive gastropathy [184]. 90% of chronic active gastritis patients were infected with *H pylori* in the same study.

In an earlier study from our center the effect of vagotomy and drainage for chronic duodenal ulcer on *H pylori* colonisation was studied [329]. 43 patients with obstructed duodenal ulcer who were preoperatively positive for *H pylori* by the urease test on antral mucosal biopsy specimens were recalled for repeat endoscopy and urease test from the same site at 1 month, 3 months, 6 months and more than 1 year after surgery. The *H pylori* positivity declined from 100% preoperatively to 69%, 71%, 73% and 80% at these intervals postoperatively respectively. The fall in *H pylori* status after surgery was significant at all intervals. This was attributed to bile reflux following gastroenterostomy which reduces the frequency of *H pylori* infection [185,187].

**Non-Ulcer Dyspepsia**

The data in literature associating *H pylori* infection and non-ulcer dyspepsia (NUD) are conflicting and contradictory. There is some evidence to suggest a role for this organism in NUD as some studies report a higher prevalence of *H pylori* infection in patients with NUD [157,159-162]. This higher prevalence than controls in NUD is more commonly reported from developed countries. In our study, we found a prevalence rate of 72% in patients with NUD which was similar to that seen
in controls. Reports from India show similar prevalence rates of 44-76% in NUD [164-167]. Some authors have shown symptomatic improvement in the dyspeptic symptoms following eradication of _H pylori_ in patients with NUD [157,170-172]. On the other hand other studies failed to improve dyspeptic symptoms [175-176]. The lack of consistent results by various modalities of therapy used to treat NUD suggests that NUD is of a heterogenous nature. Various arbitrary classifications of NUD have been developed on the basis of different types of symptom clusters. These include reflux like, ulcer like, dysmotility like and unspecified or non-specific NUD [334].

Balamourougane in his study from our centre, found symptomatic improvement in 63.9% of patients following eradication of _H pylori_ in patients with NUD at 6 weeks which dropped to 31.6% at 6 months [174]. The position paper on _H pylori_ in India suggests an association of _H pylori_ with NUD in only about 60% of patients. The paper recommends no treatment for _H pylori_ in this condition [11]. However, the results of our earlier study show that one-third of the patients with NUD do have a symptomatic and sustained improvement following eradication of _H pylori_ [174]. In a recently concluded another study at our centre, 53% of patients with NUD had symptomatic improvement at 3 months following eradication of _H pylori_. This dropped to 43% at 6 months follow up [335]. The Maastricht consensus report also recommends eradication therapy in _H pylori_ positive patients with NUD as _H pylori_ eradication therapy resulted in amelioration of symptoms, reduction in drug consumption and prevented long term sequelae of infection [336].
Cancer of the Stomach

Evidence for the role of *H pylori* in gastric adenocarcinoma and lymphoma of the mucosa associated lymphoid tissue (MALT) is increasing. Recognition of the causal role of *H pylori* in the induction of gastric cancer theoretically presents a tool for prevention of cancer. Association of gastric metaplasia, a precursor of gastric cancer with *H pylori* is well known [337]. The intestinal type of adenocarcinoma is strongly associated with *H pylori* [60,338]. Support for the role of *H pylori* in gastric cancer comes from cross-sectional studies, longitudinal studies and some studies paralleling the epidemiologic features of cancer and *H pylori* infection [117,195]. Geographic studies of *H pylori* prevalence and gastric cancer in regions like Peru, Mexico and Columbia have shown high colonization rates of *H pylori* in those populations where gastric cancer rates reach almost epidemic proportions [117,195].

Cross sectional studies report a prevalence rate of 50-100% for *H pylori* infection in patients with adenocarcinoma of the stomach [196-198]. Danesh in his review of *H pylori* and gastric cancer analysed papers published before 1998. He found a risk ratio of 2.5 for gastric cancer in people seropositive for *H pylori* antibodies suggesting that gastric cancer is 2 or 3 times more common in those chronically infected with *H pylori* [339]. However, in our present study a prevalence of only 57% for *H pylori* infection in patients with gastric carcinoma was seen. This was less than the rate in controls (69%). Other reports from India are conflicting. Prabhu et al reported a low prevalence of 38% from Western India in patients with
gastric carcinoma. They suggested that although *H. pylori* infection and chronic atrophic gastritis are common in Indians, the incidence of intestinal metaplasia is low; hence there is a doubt on the role of *H. pylori* in the pathogenesis of gastric carcinoma in India [166]. On the contrary Sivaprakash et al reported higher rates ranging from 56-62.6% by different tests in patients with gastric carcinoma which was significantly higher than in controls [200].

A Chinese study reported an *H. pylori* seroprevalence rate of 60.8% and 58.8% in gastric adenocarcinoma and healthy volunteers respectively [201]. This was not statistically significant. The Eurogast Study Group on an extensive review of gastric cancer and *H. pylori*, found a six fold higher risk of gastric cancer in patients infected with *H. pylori* [205].

In our study, correlation of *H. pylori* infection rates with the site of malignancy did not reveal any significant difference though in patients with tumours of the fundus there was an increased *H. pylori* prevalence as compared to patients with tumours of the body, the antrum or diffuse growths of the stomach (Table 2.2.1). A relatively lower prevalence rate in antral tumours could be due to endoscopic biopsy necessarily being taken from the body and not from the antrum for diagnosis of *H. pylori*. Natural colonisation rates are known to be lower in the proximal stomach when compared to the antrum. Yamaoka et al reported a significant association of *H. pylori* infection with distal and intestinal type of gastric cancers [340]. They did not find any association with diffuse or proximal type of gastric cancer. Though distal
gastric cancer is associated with a greater risk of *H pylori* in many reports, the limited number of patients in our study did not suggest such an association. It is likely that *H pylori* is only one of the carcinogens which requires several co-carcinogens to initiate malignancy. Hence, even a low infection rate in the presence of co-carcinogens may lead to malignant change [117-119].

According to the Maastricht consensus report MALT lymphoma is a condition in which eradication of *H pylori* is recommended especially when it is a low grade lymphoma [337]. Some other studies also have shown an association of *H pylori* with MALT lymphoma with a prevalence rate ranging from 90-93% [207]. It is reported that these tumours are driven by a continuing *H pylori* antigenic stimulus and regress when *H pylori* is treated effectively [208]. We did not have any patients with MALT lymphoma in our study. It is, however, clear that with good results being reported in the treatment of MALT gastric lymphoma with *H pylori* therapy, this can be the initial step in the treatment of proven gastric lymphoma.

**COMPLICATED DUODENAL ULCER OTHER THAN PERFORATED DUODENAL ULCER**

There are many difficulties in associating *H pylori* with disease in view of the high natural prevalence seen especially in developing countries. Hence, criteria of establishing cause effect relationship have to be stricter than usual. When studying the relationship between *H pylori* infection and complicated duodenal ulcer disease it
needs to be seen whether these studies address the following three questions regarding \textit{H pylori} infection and complicated duodenal ulcer disease.

(i) Whether patients with ulceration are associated with a positive \textit{H pylori} status as opposed to the non-ulcer state being negative for \textit{H pylori}.

(ii) Whether treatment of \textit{H pylori} infection at the time of complication reduces ulcer recurrence rate and further complications.

(iii) In patients who have recurrence, is there also a significantly higher \textit{H pylori} positivity rate. This study set out to answer these questions.

The major complications of peptic ulcer disease are bleeding, perforation and gastric outlet obstruction.

**Bleeding**

Bleeding is one of the common complications of chronic ulcer disease. 30% of patients with duodenal ulcer have massive bleeding [136]. Of patients who present with bleeding ulcers, approximately one-third will develop recurrent bleeding in the following 1-2 years if left untreated after initial ulcer healing [16]. In recent years accumulated data suggest that \textit{H pylori} eradication may reduce the rate of peptic ulcer recurrence and re-bleeding [17, 341]. Graham et al reported in patients with bleeding ulcer that \textit{H pylori} eradication could prevent re-bleeding over a median follow up of seven months [341]. Labenz and Borsch reported that the rebleeding rate at 17 months following eradication of \textit{H pylori} was nil whereas in patients with
persistent *H pylori* infection it was 37% [17]. In two other randomized trials, Rokkas et al [139] and Jaspersen et al [342] reported separately that none of the 16 and 29 patients with bleeding peptic ulcer cured of *H pylori* infection and followed up for 12 months had rebleeding. In contrast, only 5 of 15 and 6 of 22 control patients with untreated infection suffered a rebleeding episode. Santander et al too concluded that antimicrobial therapy for *H pylori* reduces the risk of recurrent haemorrhage from the ulcer more effectively than long term maintenance anti-secretory therapy [140]. Sung et al reported recurrence of bleeding in 3 patients on maintenance acid suppression therapy compared to none in the group treated with antibiotics for *H pylori* infection [343]. Kadayifc reported a high prevalence of *H pylori* in patients with bleeding duodenal ulcer (80%) compared to uncomplicated duodenal ulcer (67%) and recommended *H pylori* eradication therapy to prevent recurrent bleeding [137].

In the present study, the prevalence of *H pylori* in patients with bleeding duodenal ulcer was high at 80% compared to 69% in controls. The difference was not significant perhaps due to the small number of patients with bleeding duodenal ulcer (Table 3.1.1). The prevalence rate of *H pylori* in active duodenal ulcer at 93% again was not significantly different from bleeding duodenal ulcers. This high prevalence of *H pylori* in both bleeding and non-bleeding ulcers suggests an important role for *H pylori* in both these disorders. A study from North India found an 80% prevalence rate of *H pylori* in patients with bleeding duodenal ulcer which was
significantly higher than in uncomplicated duodenal ulcer (60%) or controls at 33% [344].

Size of the ulcer did not affect *H pylori* status in patients with bleeding DU. NSAID use also did not affect the *H pylori* state in this group. Graham et al found no difference in *H pylori* prevalence in NSAID users and healthy volunteers and suggested that NSAID induced damage to the gastroduodenal mucosa does not lead to an increased susceptibility to *H pylori* infection [323]. However, Aalykke et al have shown that *H pylori* infection potentiates the gastrointestinal toxicity of NSAIDs with a two-fold increased risk of ulcer bleeding [345]. On the contrary, Wu et al found no synergistic effect of *H pylori* and NSAIDs use in increasing the risk of peptic ulcer bleeding [346]. Table D-3 (next page) shows studies depicting the prevalence of *H pylori* infection in bleeding duodenal ulcer.

With growing evidence that successful eradication of *H pylori* reduces recurrent ulcer bleeding, the Maastricht Consensus report also strongly recommended *H pylori* eradication therapy for this condition [337]. Besides there appears to be a consensus from other reports [293,347].

**Gastric Outlet Obstruction**

Long standing duodenal ulcers with recurrent episodes of healing and recrudescence lead to cicatrical stenosis of the pyloric channel or the duodenum leading to gastric outlet obstruction. Gastric emptying is impaired in gastric outlet
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obstruction [141]. Apart from conventional surgery for this complication of duodenal ulcer, endoscopic balloon dilatation has also been recommended [142,348]. De Boer and Driessen successfully treated two patients with pin-point pyloric stenosis by quadruple therapy alone aimed at eradication of *H pylori* [18]. This was suggested as an alternative to surgery and balloon dilatation for patients with gastric outlet obstruction with *H pylori* infection. In some patients with gastric outlet obstruction and active ulcer, high prevalence rates and higher titres of anti-*H pylori* may indicate that obstruction is largely due to edema due to active infection. This may point to possible amelioration of symptoms by anti-*H pylori* therapy.

In the present study, patients with active duodenal ulcer with or without gastric outlet obstruction had a positive *H pylori* status exceeding 90% whereas it was only 74% in patients with gastric outlet obstruction without any active ulcer (Table 3.2.1). The difference was significant and continued to be so when adjusted for age and sex in the three groups. This significant difference in *H pylori* status in patients with and without active ulcers suggests that persistent high colonisation prevents complete healing of ulcer. Chung also found a relatively low prevalence of *H pylori* (50%) in their patients with pyloric stenosis without an active ulcer [293].

In our study, we found higher levels of antibody titres in patients with an active ulcer with or with gastric outlet obstruction compared to patients with no active
ulcer and gastric outlet obstruction. The antibody levels followed a similar pattern to the prevalence of *H. pylori* in the three groups (Table 3.2.2).

**PERFORATED DUODENAL ULCER**

Surgical treatment of perforated duodenal ulcer can be either an omental patch repair of the perforation or definitive surgery for the ulcer performed at the time of perforation closure. However, unacceptably high recurrence rates of relapse of duodenal ulcer ranging from 42% to more than 50% makes it imperative to consider some form of therapy to reduce the morbidity in the form of reperforation, haemorrhage, obstruction or intractability [19]. Definitive surgery as an alternative treatment has the disadvantage that in the long term it might cause side effects which are troublesome, especially in those patients who might otherwise have been cured by simple closure alone [20]. Also, selecting patients for definitive surgery on operative evidence of chronicity is difficult due to oedema around the ulcer [149].

The poor results of simple closure and the problems of definitive surgery have led to the use of *H*₂ blockers and proton pump inhibitors in this condition. However, the results of the studies are conflicting. There are reports suggesting a reduced incidence of reperforation and relapse after surgical closure of perforation with the use of these drugs [21,349]. On the contrary Sevvel et al found that postoperative ranitidine therapy did not appear to promote healing or prevent recurrence of ulcer following simple closure of a perforated duodenal ulcer [20]. Recurrent perforation despite continuously being on *H*₂ blockers has been reported
Another study from India reported a beneficial effect of H₂ blockers following simple closure of duodenal ulcer in reducing the subsequent need for definitive surgery [350].

Attention has recently been focussed on the role of *H pylori* in perforated duodenal ulcer. At present, there are only few reports regarding the significance of *H pylori* infection in perforated duodenal ulcer [23-25]. None of these studies addresses the question of eradication of *H pylori* on the natural history of the perforated duodenal ulcer.

**Prevalence of *H pylori* infection in perforated duodenal ulcer**

A significant relationship between perforated duodenal ulcer and *H pylori* has been suggested by some authors. Sebastian et al reported *H pylori* in 24 out of 29 patients with perforated peptic ulcer by radioactive $^{13}$C urea breath test done on the eighth postoperative day [24]. Peroperative antral mucosal biopsies were also taken in 25 patients for the urease test. At 6 weeks follow up, all patients who had persistent duodenal ulcer were positive for *H pylori*. Eradication therapy was recommended in all patients with perforated peptic ulcer associated with this organism by these authors [24]. Ng et al reported that 70% of patients with perforated duodenal or prepyloric ulcers were infected with *H pylori* [271]. In this study, the diagnosis of *H pylori* infection was done by taking antral biopsies from gastrectomy specimens or by performing an intraoperative per oral gastroscopy. Rapid urease test, culture and histology were the methods adopted. Patients were
defined as *H pylori* positive when two of the three tests were positive for *H pylori*. This *H pylori* positivity rate of 70% was not significantly different from the prevalence seen in the local population (55%). However, when subclassified into NSAIDs users and nonusers, 80% of non-NSAIDs related perforations were infected with *H pylori* compared to only 23% of NSAID users. The authors concluded that *H pylori* plays an important role in the pathogenesis of non-NSAIDs related perforated duodenal ulcer [271].

Chu et al from Hongkong found *H pylori* in 47.2% of patients with past duodenal ulcer perforations [351]. This was a retrospective study in which 163 consecutive patients with history of perforated duodenal ulcer unrelated to non-steroidal anti-inflammatory drugs were included. Upper gastrointestinal endoscopy was performed at a mean of 74.5 ± 7.1 months after operation for perforated duodenal ulcer. The diagnosis of *H pylori* was made by the urease test and histology on endoscopic antral biopsy specimens. *H pylori* was present in 77 (47.2%) patients. Recurrent duodenal ulcer was found in 29 (17.8%) patients. Even though less than half the patients in this group were infected with *H pylori*, positive *H pylori* status was considered an independent risk factor associated with recurrent duodenal ulcer.

Tokunaga from Japan in their study of the histological density of *H pylori* infections with peptic ulcer perforation reported that 92% of their patients with perforated ulcer had *H pylori* [352]. Also patients with perforated ulcer were
associated with significantly higher density of bacteria compared to bleeding and stenotic ulcer indicating a close relationship between *H pylori* and perforated duodenal ulcer [352].

However, other papers have shown contradictory findings. Jensen et al reported a prevalence rate of only 48% for *H pylori* in patients with acute perforated duodenal ulcer [23]. This low prevalence rate in Jensen’s study could be due to the NSAIDs use by patients with acute perforated duodenal ulcer. Reinbach et al reported a 47% (38/80) positivity rate for *H pylori* in patients with perforated duodenal ulcer which was similar to the 51% seen in controls [25]. In this study, the diagnosis of *H pylori* infection was made by performing anti-*H pylori* IgG serology within five days of the patient’s admission for acute perforated duodenal ulcer. A further blood sample was obtained from these patients at 4 weeks after discharge for a repeat *H pylori* serology so as to reassess the *H pylori* positive status since some patients with recent infection may not have had IgG seroconversion in the early post-perforation phase. For control purposes, patients admitted for other disorders were included. The authors concluded that there was no association between *H pylori* and perforated duodenal ulcer. The difference in the prevalence of *H pylori* in their study and that reported by Sebastian et al could be due to the use of NSAIDs by patients in Reinbach’s study.

In another study from India, Chowdhary et al did not find any patient with duodenal ulcer infected with *H pylori* in a group of 15 patients with duodenal ulcer.
perforations [353]. Peroperative antral punch biopsies were taken for diagnosis of \textit{H pylori} by culture, rapid urease test and Giemsa staining. A review on \textit{H pylori} from India too suggested that \textit{H pylori} is not related to perforated duodenal ulcer [354]. However, it had included only one study of Chowdhary et al [353] in their report for this conclusion. Another Japanese study reported that \textit{H pylori} infection is not aetiologically related to perforated peptic ulcer [355]. The authors found a high prevalence rate of 95% for \textit{H pylori} in perforated duodenal ulcer and a 100% prevalence in perforated gastric ulcer by ELISA for IgG antibodies. However, the number of patients with perforated duodenal ulcer at 20 and gastric ulcer at 5 was relatively low. As the difference in the prevalence of \textit{H pylori} between uncomplicated duodenal ulcers (93%) and uncomplicated gastric ulcers (86%) was not significantly different from that seen in the perforated group, the association of \textit{H pylori} and perforated peptic ulcer was not considered to be aetiologically linked [355]. Debouguie et al found a prevalence rate for \textit{H pylori} of 56% in patients with perforated gastroduodenal ulcers [356]. The diagnosis of \textit{H pylori} in the perforated ulcer group was made on antral biopsy specimen obtained by endoscopy done prior to or at least two months after perforations by urease and histology. In blood donors used as controls, \textit{H pylori} status was established by serology. Patients with uncomplicated ulcer had endoscopy and confirmatory tests for \textit{H pylori} – viz. urease and histology. The prevalence rate in patients with perforated duodenal ulcers was in between that seen in healthy blood donors (36%) and patients with uncomplicated ulcers (86%). This suggested to them that perforated ulcers belong to a heterogenous group.
The major lacunae in literature regarding *H pylori* infection and perforated duodenal ulcer are:

i) Most of the studies included only a limited number of patients.

ii) Although some studies had compared prevalence in perforated duodenal ulcer with controls, other studies did not include controls.

iii) Most of the reports studied association of *H pylori* with perforated ulcer. Very few of them addressed the question of eradication of *H pylori* on the natural history of perforated duodenal ulcer.

iv) Very few studies reported correlation of ulcer recurrence with an *H pylori* positive status on prospective basis. The follow up was also relatively short ranging from few weeks to few months only.

Hence, this study was planned to eliminate these deficiencies. Patients with perforated duodenal ulcer were included on a prospective and a retrospective basis. As the maximum followup in the prospective group was only for 2 years it could only relate *H pylori* and ulcer recurrence to short and medium duration of follow up after surgery. Hence, a retrospective group of patients operated for perforated duodenal ulcer with the procedure of simple closure five or more years prior to presentation were also studied. This group was included to determine the relationship of *H pylori* to recurrent duodenal ulceration in the long term. The retrospective group was only included to assess prevalence rates of infection and association of a positive
*H pylori* status with recurrent ulceration and not for determining the effect of *H pylori* on them.

In our present study, the *H pylori* status in the prospective group of patients with perforated duodenal ulcer was determined by serology for anti-*H pylori* antibodies at presentation and after 8 weeks. Peroperative endoscopy, urease test and histology were not done in these patients at presentation due to ethical problems which may arise by instrumentation through the perforation which could result in further trauma and widening of the perforation with consequent complications following closure.

In the present study, a 73% seropositivity rate for *H pylori* was seen in patients with perforated duodenal ulcer in the prospective group. The serological method for documenting *H pylori* in patients with perforated duodenal ulcer has been used earlier [25]. Though the prevalence was high, it was not significantly different from controls (69%) in our study. The prevalence rate in patients with perforated duodenal ulcer varied from 58% in patients between 51-60 years and 100% in those over 70 years of age. A steadily increasing rate was seen from 11-20 years with a maximum colonization rate of 78% to 81% seen in young adults (20-40 years) (Fig.4.1.1) when the few patients over 70 years were ignored, then a decline was seen as age advanced beyond 40 years. The difference in prevalence rates in different age groups did not reach statistical significance.
In the retrospective group, 53% of the patients were infected with *H pylori*. The maximum colonization was seen in young adults between 21-30 years of age (Fig.4.1.2). The difference between various age groups was significant. The trend was similar to that in the prospective group, although patients between 31-40 years of age had a lower prevalence of 45%.

**Gender / size / chronicity / smoking / alcohol / NSAID use and *H pylori* infection**

Gender did not affect *H pylori* status in either the prospective or the retrospective group. In both groups, males predominated and there were very few females. The lack of statistical difference in prevalence rates may be due to this factor.

Size of the perforation did not correlate with *H pylori* status in either group.

Since it is difficult to determine chronicity at the time of laparotomy [149], the only acceptable way of classifying ulcers with acute or chronic is by the pre-perforation duration of symptoms. When classified thus using 3 months as the cut off, no difference in *H pylori* positivity was seen in acute or chronic ulcers. Ng et al had suggested that acute ulcers are usually NSAIDs related and have a relatively low prevalence of *H pylori* [271]. This was not seen in the present study as most of the acute ulcers (dyspeptic symptoms of less than 3 months) did not have history of NSAIDs use. The titres of anti-*H pylori* IgG antibodies too did not show any significant difference between acute and chronic duodenal ulcer perforation.
Smoking and alcohol did not alter the \textit{H pylori} status in either group of perforated duodenal ulcers similar to the findings noted by us in non-perforated duodenal and gastric ulcers. The effect of analgesic intake (NSAIDs use) could not be separately analysed as there were very few patients on NSAIDs.

In the prospective group, there were only four patients on NSAIDs. Two of these were positive for \textit{H pylori}. One patient in the retrospective group used NSAIDs but was \textit{H pylori} negative. Non-NSAID users had infection rates similar to controls in both prospective and retrospective groups.

**Antimicrobial therapy for \textit{H pylori}**

The introduction of effective \textit{Helicobacter pylori} eradication therapy has made possible the eradication of \textit{H pylori} in patients with gastroduodenal diseases and active infection. The aim of therapy in treating patients with \textit{H pylori} infection is complete eradication and not temporary suppression of the organism. Efficacy is the most important criterion for choosing anti-\textit{H pylori} therapy. Most successful treatment schedules comprise of an acid suppressing agent in combination with two antibiotics in seven to fourteen day courses. This will reliably cure around 85\% of infected individuals. When treating patients it is necessary to be aware of antibiotics that induce resistance so that these drugs can be avoided if initial eradication attempts fail. Also, knowledge of resistance pattern in different countries helps in choosing primary drugs. For example, in India, it has been reported that there is a high native resistance to drugs like nitroimidazoles, erythromycin, etc. due to
widespread over the counter misuse of these drugs [357]. Hence, the same regimes may yield different eradication rates in different countries / socioeconomic groups.

Bismuth based triple therapy using colloidal bismuth subcitrate, tetracycline and metronidazole for two weeks was considered the gold standard and the first practical choice if antibiotic sensitivity testing was not available some years back [153,217-218]. Since the present study was started about six years back this classical triple therapy was used for treatment of patients with duodenal ulcer perforation for the eradication of *H pylori*. This therapy had provided consistent and predictably high *H pylori* eradication rates from studies in the West [220,222]. Chiba et al in a meta-analysis, reported a high eradication rate of 94.1% using this regime [221]. In our study, we did not find the eradication rate to be satisfactory. The major disadvantages of the classical bismuth based triple therapy include a complicated regimen, poor compliance and frequent occurrence of side effects [221-222]. Besides, the use of metronidazole containing triple therapy may have unacceptability low eradication rates due to antimicrobial resistance to nitroimidazoles [135]. The resistance to these drugs in developing countries might reach 80-90% compared to the 25% seen in Europe [223-225]. Such a high primary resistance rate may be associated with previous treatment with metronidazoles for other infectious diseases or parasitic infestations in patients already infected with *H pylori* [215]. In a pooled analysis of eleven studies involving 699 patients, a 92% eradication rate was achieved in nitroimidazole sensitive strains whereas eradication treatment failed in 56% of patients with resistant strains [135].

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In the present study, it was seen that at every interval of follow up, eradication rates as expected were higher with quadruple therapy as opposed to ranitidine alone. In the quadruple therapy 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%. Surprisingly, at all intervals of follow up except at eight weeks, there was no significant difference in the eradication rate between the two regimes (Table 4.5.2, Fig.4.5.2). A high eradication rate at eight weeks by the quadruple therapy might be a temporary suppression of the organism leading to its recrudescence at subsequent follow ups. As the sensitivity pattern of the organism was not available, anti-microbial resistance to metronidazole could be one of the factors responsible for a low and decreasing eradication rate with longer duration of follow up.

In the short term, eradication rates with triple therapy in India have been low. In a study from Northern India, Dayal et al reported a 67% eradication rate for *H pylori* by classical triple therapy at one month [287]. This low eradication rate was presumed to be due to bacterial resistance. Goenka et al in another study from northern India, reported a 63.3% eradication rate at four weeks follow up using the triple therapy of bismuth subcitrate, amoxicillin and metronidazole [358]. On the other hand, Ahuja et al reported more than 80% eradication rates using lansoprazole, amoxicillin and secnidazole or lansoprazole, clarithromycin and secnidazole combinations [359]. These higher eradication rates were obtained inspite of regimes containing a nitroimidazole. Probably, presence of a proton pump
inhibitor might have enhanced the eradication rates in these studies. An Asian report has shown metronidazole resistance in 50% of all strains of \textit{H pylori} in Singapore and Hongkong and in 80 to 90% of all strains in India [357]. This high antimicrobial resistance might be the cause of the difference in eradication rates in Asia compared to the West [357].

Studies have shown that regardless of the antibiotics administered with metronidazole (either amoxicillin or tetracycline) and regardless of the duration of the treatment, significant differences in eradication rates were found between susceptible strains [224,360-361]. Metronidazole resistance is due to mutations in the rdxA gene, which encodes a novel nitroreductase that is responsible for the reductive activation of the drug [362]. Products of metronidazole activation are mutagenic and can be demonstrated to increase both the mutation frequency and the frequency at which antibiotic resistance arises in \textit{H pylori}. Surprisingly, Sung et al from Hong Kong reported good eradication rates with metronidazole based triple therapy [363-364]. One of the regimens used by Sung et al was a combination of ranitidine bismuth citrate, amoxicillin and clarithromycin for one week. This produced an eradication rate of 94% [363]. The other regime had the classical triple therapy for one week and yielded an eradication rate of 83.6% [364]. These good results may be due to either suppression rather than eradication of \textit{H pylori} due to short term follow up of six weeks or the high prevalence of metronidazole sensitive strains of \textit{H pylori} in patients.
Side effects of *H pylori* antimicrobial therapy

In the present study, the side effects of quadruple therapy were not very marked. Nausea and diarrhoea were the most common symptoms in the present study (Fig. 4.6.1). Other side effects like abdominal pain, metallic taste and vomiting were relatively infrequent. This led to better compliance. There was no need for discontinuation of therapy in any of the patients.

Role of Serology in diagnosing eradication

Serology was carried for detection of anti-*H pylori* IgG antibodies. Although serum IgA antibodies also detect *H pylori* with same accuracy [81], IgG serology alone with use of antigenic material of high specificity is considered of high accuracy [88]. IgM titres are not useful as seroconversion is transient [81]. As the commercial kit used in the present study was a validated second generation Microwell ELISA assay using purified solid phase antigens, estimation of IgA titres was not considered necessary.

Overall, there was no significant difference in the percentage of *H pylori* positive patients as determined by serology at presentation, six months or one year follow up. The proportion of positive patients was 73% at presentation, 64% at 6 months and 68% at 1 year.
When serological titres at various intervals of follow up were compared to the titres at presentation, it was seen that between 53% to 67% of patients had a fall in titres below 20%, whereas 33% to 47% had a fall of more than 20%. These titres pertained to the group as a whole without separating the titres in patients who were eradicated or not eradicated. Thus it appears that overall serological positivity does not convey any important information. Though serology cannot monitor immediate effects of antimicrobial therapy because of the delay between bacterial eradication and the decline in the antibody levels, studies have shown that more than 20% fall in IgG titre can indicate eradication of *H pylori* 12-21 months after treatment with good accuracy [92].

In the present study, 71% of the eradicated patients (confirmed by negative urease and histology) had a fall in titre of more than 20% compared to basal titres as opposed to only 45% in the non-eradicated group at 6 months follow up. This difference was significant suggesting that serological titres do play an important role in assessing eradication even though true seroconversion to a negative value is uncommon (Table 4.7.3). A similar difference was seen at one year follow up also with corresponding figures of 72% and 17%. The sensitivity for *H pylori* eradication by a serological decline in titres of 20% was 71% and 72% at 6 months and 1 year respectively. The specificity was 55% and 83% at 6 months and 1 year respectively. When the cut off of IgG titres was altered to 10%, 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 while the specificity increased (Table 4.7.4).
Increasing specificity was associated with increasing positive predictive value (PPV) and declining sensitivity with decrease in negative predictive value (NPV). The accuracy ranged from 62% to 65% at 6 months and 75% to 78% at 1 year follow up.

Marchildon et al reported a 87.5% sensitivity and 100% specificity when more than 25% decline in serology titres at 6 months follow up was taken as a cut-off for detecting eradication of *H pylori* [365]. These were done serially with separate ELISA plates. When parallel estimations were done with the same ELISA plate similar results were seen. They concluded that a 25% decline in the titre at 6 months after therapy is a sensitive and specific marker for the eradication of the infection and serial or parallel estimations of IgG titres offer equivalent diagnostic accuracy. In the present study a parallel estimation was done using the same ELISA plate and all the samples were seen concurrently.

Kist et al found a significant decrease in IgA and IgG titres at the end of one year follow up following eradication therapy of *H pylori*. However, the seroconversion to negative state was only 47% for IgA and 24% for IgG class of antibodies [366]. They did not recommend serology for monitoring treatment success. A Japanese study in children found that when a 30% decrease in the titres was taken as a cut off to indicate eradication, a 90.5% sensitivity and 100% specificity was seen for IgA and IgG class antibodies at one year follow up [367]. Seroconversion rates were relatively low at 53% and 48% for IgG and IgA antibodies respectively at 12 months. When done at 2 years follow up it showed a good
seroconversion rate to a negative state at 86% and 81% for IgG and IgA antibodies respectively thus indicating that it may take a long time for antibody titres to become negative after eradication.

At present, it appears that due to unsatisfactory sensitivity rates, percentage fall in IgG titres can at best serve as a crude test of eradication. It, however, has the advantage of not requiring endoscopy or costly equipments needed for the $^{13}\text{C}$ or $^{14}\text{C}$ breath tests.

**Recurrent / Residual ulcer and *H pylori* infection**

Studies on duodenal ulcer relapse rates have shown a high relapse rate in patients in whom *H pylori* was not eradicated [368]. A meta analysis of 19 studies reported a 67% rate of relapse of duodenal ulcer in 353 patients with persistant *H pylori* and only 6% in 331 patients in whom *H pylori* was eradicated [368]. Another analysis of 27 papers involving 1881 patients with duodenal ulcer, reported 58% and 2.6% relapse rates in *H pylori* positive and negative patients respectively [369]. Tovey et al too found a relatively high rates of relapse of 22.2% to 25% in patients with duodenal ulcer at one year follow up [370]. There are only three studies with long term follow up available from India on ulcer relapse and *H pylori* infection [287,371,372]. The mean relapse rate was 17% among 99 *H pylori* eradicated patients compared to 62% among 85 infected patients during an average follow up of one year. In these studies the ulcer relapse rates were evaluated following
confirmation of _H pylori_ eradication. In most of the other studies, ulcer relapse rates were not stratified according to eradication status.

Work on duodenal ulcer has shown a beneficial role for _H pylori_ eradication in preventing duodenal ulcer relapse both from India and abroad. However, there are very few papers relating _Helicobacter pylori_ infection and relapse of duodenal ulcer following simple closure of perforated duodenal ulcer. Most of these include only small number of patients with limited follow up. There is no study from India on this aspect. Sebastian et al reported _H pylori_ infection by a positive $^{13}$C urea breath test and urease test in seven patients who had persistent or recurrent duodenal ulcers following simple closure of duodenal ulcer perforation at 6 weeks follow up [24]. They recommended eradication of _H pylori_ in patients with duodenal ulcer perforation. Debonjnie et al reported symptomatic relapse in seven out of nine patients with duodenal ulcer perforations who had not received any _H pylori_ antimicrobial therapy after 12 months of follow up [356]. One patient without _H pylori_ infection had a second perforation which was the only relapse in this group of six patients. The authors suggested an association between _H pylori_ and recurrent ulcer disease after perforation closure.

In the present study, the _H pylori_ positive status was significantly higher in the prospective group at all intervals of follow up upto 2 years in patients with recurrent or residual ulcer after previous duodenal ulcer perforation compared to those in whom the ulcer had remained healed (Table 4.8.1, Fig.4.8.1). The positive
status varied from 76% to 94% in those who had persistent recurrent ulcer which was significantly higher than the 11% to 38% seen in those who had no residual ulcer. When further analysis was done with adjustment for age and sex, \textit{H pylori} was significantly associated with relapse of duodenal ulcer (Table 4.8.1A). At 2 years follow up the patients with recurrent ulcer had a high \textit{H pylori} positivity at 86% as opposed to 42% in those without ulcer. This difference did not reach significance at 2 years probably due to small numbers. A study from Hongkong reported endoscopic follow up in patients who had a history of closure of duodenal ulcer perforation in the past at a mean of 74.5 ± 7.1 months. It was found that recurrent duodenal ulcers were seen in 17.8% of patients and were significantly associated with \textit{H pylori} infection of 47.2% [351]. The authors also mention that a positive \textit{H pylori} state is an independent risk factor of recurrence.

In our study when \textit{H pylori} state was correlated with recurrent duodenal ulcer disease in patients who had a simple closure of perforation more than 5 years primarily in the retrospective group it was found that 90% of patients had \textit{H pylori} positivity when they had recurrent ulcer disease as compared to only 19% in those who had no ulcer (Table 4.8.2, Fig.4.8.2). This suggests that there is a close association between \textit{H pylori} and recurrent duodenal ulcer disease after perforation closure in the long term also. When adjusted for age and sex in both groups (i.e. with and without ulcer) (Table 4.8.2A) \textit{H pylori} was still significantly associated with recurrent duodenal ulcer.
It appears, therefore, from the present study that the recurrent or relapse of duodenal ulcer following simple closure of perforated duodenal ulcer is significantly related to \textit{H pylori} infection. Eradication of \textit{H pylori} should, therefore, be recommended in all patients with perforated duodenal ulcer with a positive \textit{H pylori} status at the time of perforation.

**CONCLUSIONS**

**ASYMPTOMATIC ADULTS AND CHILDREN**

Almost half the asymptomatic patients in the pediatric group were infected with \textit{H pylori}. No significant difference in the prevalence of \textit{H pylori} was seen in children less than 5 years, 6-10 years of age and 11-15 years of age. A relatively high prevalence rate of 46\% was found even in the under 5 years at 46\%. Under one year of age four out of eight children had antibodies to \textit{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 prevalence rate was similar in male and female children. No significant difference in the levels of antibody titres were seen in children of different age groups. However, there was a trend to higher titres in older age groups.

69\% of adult asymptomatic patients were infected with \textit{H pylori}. There was no significant difference between men and women. \textit{H pylori} prevalence increased significantly with age and was maximum in young adults between 21 to 40 years of age.
age. Thereafter, there was a minimal decline in prevalence with advancing age. The anti-\textit{H pylori} antibody levels too followed a similar pattern with an age related difference. There was a significant difference in the prevalence of \textit{H pylori} infection between children and adults.

Infection of approximately half the children and two-thirds of adults indicates a high prevalence of \textit{H pylori} in normals in South India.

\textbf{UPPER GASTROINTESTINAL DISORDERS}

A significantly high prevalence of \textit{H pylori} was seen in patients with duodenal ulcers compared to controls. The size of the ulcer or the number of ulcers did not affect \textit{H pylori} status. Smoking, alcohol or analgesic abuse did not appear to alter the prevalence of \textit{H pylori} in patients with duodenal ulcer disease. \textit{H pylori} status in patients with gastric ulcer was lower compared to duodenal ulcer patients. NSAID use, number of ulcers, smoking or alcohol did not affect the \textit{H pylori} status in patients with gastric ulcer. When gastric ulcer was associated with duodenal ulcer, the prevalence was high at 83\%. No significant difference was noted between normals and patients with other gastric ulcers not associated with active or healed duodenal ulcer.

A lower prevalence rate of \textit{H pylori} was seen in patients with gastric cancer compared to controls. The difference was, however, not significant. Site of the malignancy in the stomach did not affect the \textit{H pylori} status. In patients with erosive
gastritis the overall prevalence was low. NSAID therapy did not increase the risk of *H pylori* infection in patients with erosive mucosal disease (EMD). The site of the erosions, smoking and alcohol abuse did not affect the *H pylori* status. A marginally higher prevalence of *H pylori* compared to controls was seen in patients with non-ulcer dyspepsia. The subtype of "ulcer like" non-ulcer dyspepsia may have a closer association with *H pylori* compared to "reflux like" or "dysmotility like" dyspepsia. In patients with gastritis too, a marginally higher prevalence of *H pylori* infection was seen. Patients with stomal ulcer had a high prevalence at 80%. However, a significant difference could not be reached from controls due to limited numbers.

The distribution of *H pylori* in the different gastroduodenal diseases in South India suggests a high prevalence in duodenal ulcer. Other disorders showed no increase in prevalence compared to controls. However, a trend towards higher positivity was seen in Type II gastric ulcers and patients with stomal ulcers. Routine *H pylori* eradication is, therefore, indicated in patients with duodenal ulcer. A high prevalence in patients with stomal ulcer and gastric ulcer associated with duodenal ulcer although not reaching statistical significance still indicates need for eradication in these patients. However, larger studies are required in other upper gastrointestinal disorders to substantiate the association of *H pylori* with them and the need for eradication therapy.
COMPLICATED DUODENAL ULCER OTHER THAN PERFORATED DUODENAL ULCER

In patients with bleeding duodenal ulcer, a higher prevalence of *H pylori* was seen compared to controls although the difference did not reach significance. Size of the ulcer and NSAID use did not affect *H pylori* status. However, the higher prevalence seen by us and data from literature both suggest necessity of eradication to prevent recurrent duodenal ulcer bleeding.

The prevalence of *H pylori* infection was high in patients with active duodenal ulcer with or without gastric outlet obstruction. The difference in positivity status was significantly different from those patients with gastric outlet obstruction who had no active ulcer. The anti-*H pylori* antibody levels too followed a similar pattern with a significantly higher titres in patients with active ulcer and gastric outlet obstruction compared to those with gastric outlet obstruction but no active ulcer. Thus, it appears that *H pylori* presence leads to continued or recurrent activation of the ulcer. A corresponding immune response resulting in high titres is seen in patients with active ulcer. The prevalence and the immune response to *H pylori* is lowered over a period of time once the ulcer heals.

PERFORATED DUODENAL ULCER

In patients with perforated duodenal ulcer the prevalence of *H pylori* was higher but not significantly so from controls. However, recurrent or relapse of
duodenal ulcer following simple closure of perforated duodenal ulcer was significantly related to *H pylori* infection. Inspite of the heterogenous nature of the relationship between *H pylori* and perforated duodenal ulcer, eradication of *H pylori* should be recommended in patients with perforated duodenal ulcer with a positive *H pylori* status to prevent reperforation or recurrence.

Gender, size of the ulcer, chronicity of the ulcer, smoking or alcohol did not affect the *H pylori* status. The quadruple combination therapy had a very low eradication rate probably due to native metronidazole resistance. Eradication rate achieved in 80% of the patients at eight weeks fell progressively indicating suppression of *H pylori* rather than eradication. This combination therapy of ranitidine and classical triple therapy is unsuitable for eradication of *H pylori* in our country although it is considered a gold standard abroad. Further studies from India are required to evaluate and document the nitromidazole resistance and assess the efficacy of regimes which do not contain nitroimidazoles. The side effects of quadruple therapy were not very marked and did not affect compliance.

A fall in serological titres can be used as a crude test to monitor the results of antimicrobial therapy without need for invasive investigations. Further serological studies in future to document the time of disappearance of the antibody from circulation may lead to an optimum cut-off value for increasing the efficacy of this test to monitor results of antimicrobial therapy.
LIMITATIONS OF THE STUDY

1. Hospital based patients without gastrointestinal disorders were included as asymptomatic subjects as consent for the test for diagnosis of *H pylori* was not possible in the general population. Other studies have also used hospital based controls or “blood donor” as controls. This, however remains a limitation.

2. The number of patients in the stomal ulcer and bleeding duodenal ulcer groups was small leading to limitation in conclusions.

3. In the prospective perforated duodenal ulcer group antibiotics had to be given to all patients for a conventional period for peritonitis. Though follow up tests were done at 8 weeks some interference in *H pylori* diagnosis is possible.

4. Facilities for noninvasive test (urea breath test) were not available to detect eradication, hence endoscopic tests had to be done.

5. Culture though highly specific was not used for documenting prevalence due to its moderate sensitivity. However, use of culture would have given information on drug resistance pattern of native organisms and enabled choice of appropriate drugs for therapy.
6. Though the duration of follow up in the prospective perforated duodenal ulcer
group was up to two years for correlating recurrence rate of ulcer with *H pylori*
infection, less than 25% came for review at 1½ years and 2 years. This reduced
the strength of the study in the medium term.

7. A very low efficacy of the quadruple therapy probably due to nitroimidazole
resistance made it difficult to differentiate reinfection from recrudescence of
suppressed organism.

8. No attempt was made by us for testing for cytotoxin associated gene A (Cag A)
or vacuolating cytotoxin associated gene A (Vac A) to determine virulent strains
of *H pylori*.

**RECOMMENDATIONS**

1. Any work on *H pylori* should first document natural prevalence in control in that
area before drawing conclusion based on association.

2. All patients with complicated duodenal ulcer should mandatorily receive anti-*H
pylori* therapy at first presentation.

3. Monitoring of eradication can be done by less invasive and less expensive
methods not requiring endoscopy such as serology.

4. Knowledge of native drug resistance is important in planning anti-*H pylori*
regimes.
SUGGESTIONS FOR FURTHER RESEARCH

A study with a larger sample size taken from the general population from South India will give a more representative picture of the seroprevalence of *H pylori* infection in asymptomatic population. A long term longitudinal study in a cohort would be more appropriate to evaluate the *H pylori* status in children and the natural history of *H pylori* infection in them. A prospective randomized controlled trial for treatment of stomal ulcer and bleeding duodenal ulcer by *H pylori* eradication with a longer follow up from India will confirm that *H pylori* eradication benefits these patients.

A larger study using a combination more likely to be successful in a developing country like India with more complete long term follow up is required to confirm the role of antimicrobial therapy in the healing of perforated duodenal ulcer. The study should also relate the prevalence of *H pylori* in the postoperative period to medium and long term ulcer recurrence following simple closure of perforated duodenal ulcer.