Peptic ulcer disease (PUD) is a common problem encountered by physicians in day-to-day practice. Its prevalence varies from country to country and from place to place within the country. Till recently a number of factors were incriminated as the cause of the disease. These included food habits, smoking, heredity, physical stress, psychological stress, alcohol, coffee, drugs, infectious agents like virus, etc. All these factors were thought to be responsible for increased acid output, which is the requirement for the occurrence of the ulcer. It was believed that “no acid, no ulcer”. During the last two decades there has been a tremendous progress in understanding the aetiology, pathogenesis and management of the disease. Now, it is certain that the bacterial infection by *H. pylori* is the main aetiological agent of peptic ulcer. Of course, acid remains in the limelight and it does play an important role. This review deals with the role of *H.pylori* in peptic ulcer and its management.

**Epidemiology and Prevalence**

Humans are the only host for *H.pylori*, which is found in stomach, and in duodenum, oesophagus and rectum on areas of metaplastic gastric epithelium. Other helicobacter species have been isolated from the animals. Animal models of Helicobacter infection have been developed due to shared characteristics of other Helicobacters like *H.mustelae and H. felis* with *H.pylori*.

*H.pylori* exists the world over and its prevalence in the population increases with age. In developed countries, prevalence increases about 1% per year of age where it is rare in children, and reaches 70% in the seventh decade. In developing countries, more than 50% children acquire the infection by the age of 10 years, and more than 80% of the population gets infected by the age of 20 years. In asymptomatic individuals prevalence of *H.pylori* infection varies from 31%-84%.

*H.pylori* infection is chronic and once acquired remains life long, unless eradicated by antibiotics given for some other conditions. Humoral and tissue immune response by the host is usually not sufficient to clear the infection. Though the mode of transmission is not yet well established, most probably it takes place by oral-oral or faeco-oral route and important risk factors are socio-economic status and age. Overcrowding, poor socio-economic status and poor hygiene are associated with high infection rate. Re-infection rate after eradication is quite high in developing countries due to the above mentioned risk factors.

Colonisation of *H.Pylori* occurs by producing urease and gastric acid inhibitory protein. It can colonise only in gastric type epithelium and cannot stay anywhere else in the GI tract in absence of gastric mucosa. Metaplasia, which is present in more than 90% of patients of duodenal ulcer, occurs by replacing the columnar cells, normally covering the duodenal villi, by gastric type epithelium. Adhesion of *H.pylori* to the gastric epithelium occurs by tissue specific proteins. Colonisation of the duodenal bulb by *H.pylori* leads to mucosal inflammation which makes it vulnerable to attack by acid or pepsin or bile resulting into ulceration, however, factors leading to gastric metaplasia in the duodenal bulb are not known. Stimulation of the immune system of *H.pylori* contributes to host damage and it evades the immunological clearance.

**Bacterial Factors**

Direct damage to the host occurs by urease and other enzymes and toxins produced by the
bacteria. Depending on the enzymes and toxins production, *H. pylori* strains phenotypically can be divided into two groups, i.e., type 1 and type 2. Type 1 contains vacuolating toxin, encoded by the gene vacA (94-kda vacA) and cytotoxin associated protein encoded by the gene cagA (120-128-kcagA). The second group, i.e., type 2 contains non-cytotoxic vacA and cagA negative strains. It has been observed that type 1 strains cause more intensive inflammation than type 2. Such strain diversity may explain why some infected individuals do not develop diseases while some may develop peptic ulcer and gastric cancer which may be due to different type of strains. The studies from other countries have reported that about 70% of strains isolated from patients with DU produce this toxin compared to about 30% isolated from non-ulcer dyspepsia. There is also some evidence to suggest that the degree of inflammation and subsequently clinical consequences of *H. pylori* infection are related to density of bacterial colonisation. The enzyme produced by both types of strains plays an important role in the pathogenesis. Urease hydrolyses urea into ammonia and creates alkaline surroundings, thus creating a neutral microenvironment for the bacteria. It may also have a role in *H. pylori* metabolism as a part of nitrogen cycle. It has been presumed that the ammonia produced by the urease activity works with cytotoxin inducing vacuoles.

Though *H. pylori* is strongly antigenic and leads to humoral and cellular immune response, the human host is unable to clear the infection which may persist life long. The local inflammatory response leads to accumulation of a number of different cytokines which includes IL-8 and tumour necrosis factor alpha. These two cytokines play an important role in the formation of inflammatory infiltrate. Type 1 *H. pylori* strains have been shown to induce significantly higher IL-8 than type 2 strains.

Effects on Gastric Secretions

Gastrin produced by the G cells stimulates the acid secretion and has a trophic action on mucosal cells in the stomach. It has been found that *H. pylori* increases the fasting serum gastrin levels in healthy subjects and also in patients with duodenal ulcer. The main inhibitor of gastrin secretion and excretion somatostatin is produced by the D cells. Somatostatin levels are decreased in *H. pylori* positive individuals. *H. pylori* also decreases the gastric body mucosal histamine. There are two main opposite effects of *H. pylori* on acid secretion function of the stomach, viz., its effect on fundal histamine decreases acid output while the effect on somatostatin leading to hypergastrinaemia increases the gastric acid output. The basal and peak acid output changes after eradication of *H. pylori* supports the hypothesis that *H. pylori* causes impairment in the inhibitory control of gastric acid. In the early stage of infection acid output increases, leading to gastric metaplasia in duodenum, which in turn gets infected with *H. pylori* and development of duodenal ulcer. With diffuse disease the acid output falls.

Diseases associated with *H. Pylori*¹²⁻¹⁴

*H. pylori* infection is found to be associated with gastritis, non-ulcer dyspepsia (NUD), duodenal ulcer, gastric ulcer, gastric cancer, gastric lymphoma of mucosa associated lymphoid tissue (MALT), non-Hodgkin’s lymphoma and even coronary heart disease. It has now been well established that *H. pylori* is the cause of almost all duodenal ulcers (DU) and chronic benign gastric ulcers (GU) which are not associated with NSAIDs. More than 95% of DU and 90% of GU are associated with *H. pylori* infection and there is a dramatic decrease in their relapse rate after the *H. pylori* eradication. Right now there is no convincing evidence that NUD symptoms are due to *H. pylori* infection. Prevalence of *H. pylori* infection is comparable between healthy individuals and patients with the symptoms of NUD. Recurrent abdominal pain in children suggestive of NUD subsides after the eradication of *H. pylori* which indirectly associates *H. pylori* infection with NUD. However, further studies are necessary in this regard and at present there is no
indication to eradicate *H. pylori* in NUD.

Association between *H. pylori* and gastric cancer has been reported in several retrospective epidemiological studies. It is postulated that starting with acute gastritis, *H. pylori* infection leads to chronic atrophic gastritis, intestinal metaplasia, dysplasia and ultimately progression to gastric adenocarcinoma. High *H. pylori* infection rate has been reported in patients with gastric cancers compared to healthy subjects. The WHO has put *H. pylori* in group I, a definite carcinogen. *H. pylori* has also been found to be associated with development of MALT and subsequent transformation to malignant lymphoma. Eradication of *H. pylori* has shown regression of low-grade b cell gastric lymphoma of MALT type. There is some epidemiological evidence that *H. pylori* infection is associated with non-Hodgkin’s lymphoma which is comparatively rare in stomach.

**Diagnosis**

A number of invasive and non-invasive tests with almost comparable sensitivity and specificity are available. Invasive tests require upper GI endoscopy and biopsy from stomach for histology, bacterial culture, rapid urease test (RUT) and PCR.

Biopsy is fixed in 10% formalin and stained with haematoxylin and eosin or by modified Giemsa stain. Biopsy can also provide additional information on gastritis, metaplasia and dysplasia. In experienced hands histology has >90% sensitivity and >95% specificity. Biopsy specimen can also be used for bacterial culture in selective or non-selective media. Though the sensitivity and specificity of this test is >95% and >80% respectively, it is time consuming and expensive and also it is not easy to culture this bacteria.

RUT is 90% sensitive and 100% specific, inexpensive and provides results within 20 minutes. Urease produced by the bacteria hydrolyses urea into ammonia. A change in pH changes colour of the indicator from yellow to pink. In case of low urease activity it may take as long as 24 hours to change the colour. False negative result may be there if the number of bacteria in the specimen is less or if the antral biopsy is taken after one week of proton pump inhibitors, antibiotics or bismuth treatment, when *H. pylori* colonize in body or fundus.

PCR is highly sensitive and specific but it may detect DNA of non-viable bacteria also giving false positive results and also has a limited role in confirming eradication of *H. pylori* after treatment. It is usually used for molecular typing of *H. pylori* and for research.

Non-invasive tests include serology and urea breath test (UBT). Commercially available ELISA kits detect IgG antibodies in sera. This test is useful to screen the patients for *H. pylori* infection, usually to find out prevalence of *H. pylori* infection in the community. It is a relatively sensitive and specific test and also inexpensive. But it has a limited role in diagnosing acute infection and in confirming eradication.

UBT is a good non-invasive test. Although it is expensive, it is highly sensitive (95%) and specific (100%) and also ideal to check the post-treatment eradication. Detection of labelled CO₂ (¹³C or ¹⁴C) in expired air indicates hydrolysis of urea and presence of urease producing organism in stomach. Difference between ¹³C UBT and ¹⁴C UBT are shown in Table I.

**Table I: ¹³C- and ¹⁴C-UBT**

<table>
<thead>
<tr>
<th></th>
<th>¹³C-UBT</th>
<th>¹⁴C-UBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>90-100%</td>
<td>90-100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>90-100%</td>
<td>90-100%</td>
</tr>
<tr>
<td>Radioactive</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Analysis</td>
<td>Isotope ratio mass Spectrometry</td>
<td>Liquid scintillation counter</td>
</tr>
<tr>
<td>Advantages</td>
<td>Simple to do</td>
<td>Cheap</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>High Cost</td>
<td>Nuclear Medicine</td>
</tr>
</tbody>
</table>

Follow-up tests to check the eradication should be done at least four weeks after the completion of treatment to minimize the likelihood of false negative results. At present, no single test is the
gold standard for diagnosis of \textit{H. pylori}. The combination of two or more of above mentioned tests are used for this purpose.

**Treatment**\textsuperscript{18-23}

The main aim of treating \textit{H. pylori} is to eradicate the organism from the foregut. Eradication is defined as negative test results for \textit{H. pylori} four weeks or longer after the antibacterial therapy. The National Institute of Health of USA recommends eradication of all \textit{H. pylori} in all patients with active peptic ulcer disease or a history of it and proved infection.

Antimicrobial treatment of \textit{H. pylori} is difficult, as the bacteria are located below the mucus layer, adherent to gastric mucosa where the access of antimicrobial drugs, given either by enteral or parenteral route is limited and \textit{H. pylori} may acquire resistance to commonly or frequently used antibacterial drugs. These vary from country to country depending on the use of different antibacterial drugs. For example, resistance of \textit{H. pylori} to clarithromycin in UK is less than 5% while in Spain and France it is as high as 15-17%. It is because of this problem, the treatment regimens using two or three antimicrobial agents have been developed.

The ideal therapy for any infection should be simple, safe, free from side effects, with 100% efficiency and low cost and same applies to \textit{H. pylori} infection also. The ideal treatment regimen has not yet been established, so there is no definite recommendation for the optimal treatment schedule. The treatment for \textit{H. pylori} should be given only after the clinical diagnosis and proper indication for eradication. Eradication therapy should not be taken lightly. All the treatment schedules have side effects but they are mild and usually do not interfere with patient’s compliance if given with proper instructions.

Effect of the antimicrobial agent depends on the acid environment of stomach which may decrease the effectiveness of some antibiotics. Usually the concentration of antibiotics is low in stomach. Colloidal bismuth subcitrate (CBS) penetrates transmucosally, and has been shown to block adhesion of \textit{H. pylori} to epithelial cells and to form protective complexes with glycoproteins and to stimulate mucosal bicarbonate secretion. In \textit{vitro} studies have shown bacteriostatic effect of proton pump inhibitors (PPI) on \textit{H. pylori}. PPI also may interfere with energy production of bacteria. All the PPI have also been found to cause decrease in antral \textit{H. pylori} density during the therapy, although the fundal count may increase leading to fundal gastritis. This is an important effect one has to keep in mind while keeping the patient on maintenance therapy for gastroesophageal reflux disease. Clarithromycin is one of the most effective antimicrobial agent against \textit{H. pylori} \textit{in vitro}. It is quickly absorbed and at pH 5.5, obtained with the help PPIs, it is the most effective antimicrobial agent.

**Indication for \textit{H. pylori} Eradication**

Treatment for \textit{H. pylori} in asymptomatic carrier, in order to decrease reservoir of infection in community and to prevent the development of various conditions caused by \textit{H. pylori}, is controversial and supported by only a few studies. It is advised that it should be treated only if chronic carrier status is proved to initiate the disease process.

**Non-ulcer Dyspepsia**

Treatment for \textit{H. pylori} associated with symptoms of non-ulcer dyspepsia is also controversial and at present there is no convincing evidence that \textit{H. pylori} is responsible for these symptoms. Moreover, prevalence of \textit{H. pylori} in this group of patients is not higher than the general population without symptoms. Although a subset of patients may have their symptoms due to presence of \textit{H. pylori}, there is no clear evidence that they benefit after \textit{H. pylori} eradication. At present there is no indication that patients with non-ulcer or functional dyspepsia should be treated for \textit{H. pylori}, till the results from large trials are available.
Duodenal and Gastric Ulcer

It has now been well established that *H. pylori* is the main cause of most of the duodenal ulcers and chronic benign gastric ulcers that are not associated with NSAIDs. More than 95% of patients with duodenal ulcer are positive for *H. pylori* and eradication of infection results in rapid healing and a dramatic decrease in relapse rate to less than 5% each year. Duodenal ulcer heals completely after the eradication therapy and a course of antisecretory drugs after healing is not required, unless it is associated with complications like recent haemorrhage, perforation, etc. There is some data suggesting prevention of recurrence of bleeding from ulcer after eradication of *H. pylori*. Those who have recurrence of symptoms after successful eradication, without recurrence of duodenal ulcer, other causes for such symptoms, like gastroesophageal reflux disease, gallstones should be investigated. The clinical benefit of *H. pylori* eradication in NSAIDs induced duodenal or gastric ulcer is not well established. However, there is some evidence that NSAIDs induced mucosal damage may be less in the absence of *H. pylori* and thus there is some justification to eradicate *H. pylori* in NSAIDs induced gastric or duodenal ulcer.

Though there is a strong circumstantial evidence to link the *H. pylori* infection with the development of gastric adenocarcinoma and WHO has classified *H. pylori* as a group I definite carcinogen, less than 1% of *H. pylori* infected individuals will ever develop gastric cancer and so far there is no evidence that, eradication of *H. pylori* will decrease the risk of gastric cancer. It is also not known where exactly the point of no return is in the gastritis-atrophy-metaplasia-dysplasia-cancer sequence of events. With a family history of gastric cancer, if an individual has an evidence of atrophy, metaplasia or dysplasia in early life, he may be offered *H. pylori* eradication treatment. *H. pylori* infection has been associated with MALT lymphoma, which subsequently develops into malignant lymphoma. It has been found that *H. pylori* specific T-lymphocytes act as a growth stimulant for MALT, which suggests that early tumour may respond if this stimulus is withdrawn. *H. pylori* eradication therapy results in regression of low-grade b-cell gastric lymphoma of MALT type.

Epidemiological evidence has suggested that *H. pylori* infection is also associated with non-Hodgkin’s lymphoma but there is no data on effect of *H. pylori* eradication in this condition. *H. pylori* infection has been found in more than 90% patients with hypertrophic gastropathy (Menetrier’s disease). Eradication of *H. pylori* has been reported to return the stomach and protein concentration to normal in this condition.

**Eradication Regimens**

*H. pylori* infection can be cured with antibacterial therapy and with presently available combination more than 90% eradication can be achieved. The present therapeutic standards are clear, eradication in atleast 90% after one week of treatment and less than 5% of the patients dropout from the treatment because of side effects. It should be remembered that all currently available treatments are associated with side effects. Various therapeutic regimens that have been tried are as follows:

**Monotherapy**: Single drug therapy is not effective in eradication of *H. pylori*. With a single antibiotic, eradication rate has been reported from 0-54%. Clarithromycin has been found as the most effective single drug. However a single antibiotic should not be prescribed as it is not only ineffective but also it may produce a resistant strain. *H*<sub>2</sub> receptor antagonists have no effect on *H. pylori* and despite *in vitro* effect of PPI on *H. pylori*, they are not effective in eradicating the bacteria. Bismuth compounds do suppress the *H. pylori*, but as monotherapy, bismuth does not eradicate this bacteria. Due to the ineffectiveness and possibility of development of resistant strain, monotherapy is not recommended.

**Dual therapy**: Combinations that have been tried for eradication of *H. pylori* include two antibiotics;
H₂ receptor antagonists with antibiotics; bismuth with antibiotics; omeprazole (PPI) with amoxycillin; and omeprazole (PPI) with clarithromycin. Combination of any two antibiotics is not effective in H. pylori eradication. High dose H₂RAs given along with antibiotic (amoxycillin or clarithromycin) for two weeks may eradicate H. pylori in up to 60% of patients. Colloidal bismuth subcitrate (CBS) with metronidazole have been found effective in almost 85% in small studies. Ranitidine bismuth citrate (RBC) in combination with either amoxycillin or clarithromycin given for two weeks has shown eradication rate from 65% to 80% depending upon the dosage.

Triple Therapy: Various combinations of three drugs have been tried. Drugs that have been used in triple therapy are CBS, RBC, H₂RA, PPI, amoxycillin, tetracycline, clarithromycin, metronidazole and tinidazole. There are wide dosage variation and different treatment schedules with eradication rate varying from 35 to 95% have been reported in the literature. Such different findings are because of dissimilarities in patient populations, resistance to metronidazole and other antibiotics and variation in compliance by the patients. Classical triple therapy given for seven days has not been always successful. On the contrary, there is no further benefit if the treatment is given for 14 days or more. Tetracycline or amoxycillin based therapy has no significant difference in eradication. The combinations used for triple therapy are; bismuth+antibiotics+PPI, H₂RA+metronidazole+amoxycillin, PPI+metronidazole/tinidazole+amoxycillin/clarithromycin. Newer PPIs like lansoprazole and pantoprazole also have been used in these combinations. Various combinations with their efficacies are shown in Tables II-IV.

Quadruple Therapy: Combination of four drugs also have been tried, though these have more side effects and compliance problems. Drugs that have been given for one week in this combination were omeprazole (20mg bid), CBS(120mg bid), tetracycline (500mg bid) and metronidazole (500 mg bid). The eradication rate was 96%.

Table II : Dual therapy with amoxycillin

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Dosage</th>
<th>Duration</th>
<th>Hp Eradication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Amoxycillin</td>
<td>20-40 mg b.i.d.</td>
<td>2 weeks</td>
<td>50-85%</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Bismuth Citrate</td>
<td>400-800 mg b.i.d.</td>
<td>2 weeks</td>
<td>65%</td>
<td>Diarrhoea</td>
</tr>
</tbody>
</table>

Table III: Dual therapy with clarithromycin

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Dosage</th>
<th>Duration</th>
<th>Hp Eradication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Clarithromycin</td>
<td>40 mg b.i.d.</td>
<td>2 weeks</td>
<td>60-80%</td>
<td>Taste disturbances, Diarrhoea</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Bismuth Citrate</td>
<td>400 mg b.i.d.</td>
<td>2 weeks</td>
<td>80%</td>
<td>Taste disturbances, Diarrhoea</td>
</tr>
</tbody>
</table>

Table IV: Low-dose, 1 week triple therapies

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
<th>Dosage</th>
<th>Duration</th>
<th>Hp Eradication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>Clarithromycin</td>
<td>Amoxycillin</td>
<td>o.d. or b.i.d.</td>
<td>7 days</td>
<td>85-95%</td>
<td>Nausea</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Omeprazole</td>
<td>Amoxycillin</td>
<td>b.i.d.</td>
<td>7 days</td>
<td>75-90%</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Amoxycillin</td>
<td>Metronidazole</td>
<td>Clarithromycin</td>
<td>o.d.</td>
<td>7 days</td>
<td>75-90%</td>
<td>Diarrhoea</td>
</tr>
</tbody>
</table>

Table V: Triple therapy combinations with amoxycillin and metronidazole

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
<th>Dosage</th>
<th>Duration</th>
<th>Hp Eradication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBS</td>
<td>Omeprazole</td>
<td>Metronidazole</td>
<td>120 mg q.i.d.</td>
<td>2 weeks</td>
<td>60-90%</td>
<td>Diarrhoea, Nausea</td>
</tr>
<tr>
<td>Amoxycillin</td>
<td>PPI</td>
<td>Metronidazole</td>
<td>500 mg q.i.d.</td>
<td>1 week</td>
<td>75-80%</td>
<td>Diarrhoea, Nausea</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Ranitidine</td>
<td>Amoxycillin</td>
<td>300 mg q.i.d.</td>
<td>12 days</td>
<td>68-90%</td>
<td>Diarrhoea, Nausea</td>
</tr>
</tbody>
</table>

It is very difficult to eradicate metronidazole resistant H. pylori. Combination therapy consisting
metronidazole may not be very effective against metronidazole resistant strains (eradication rate may be less than 50%). Primary or acquired metronidazole resistance of *H. pylori* is 20-30% in western countries and as high as 66% in India. Metronidazole or tinidazole resistance may be reduced by combining with bismuth or by giving quadruple therapy for 10 days.

In spite of large available data, it is yet not possible to give final recommendation as to the best regimen to eradicate *H. pylori* as there are very few large trials. It is quite likely that there is no significant difference between triple and quadruple regimens. The effective eradication also depends upon other factors like compliance, metronidazole resistant status and side effects of the drugs. Cost is also an important consideration and also the relapse rate. However, for all practical purposes the triple drug regimen in a suitable combination is preferable for the treatment of *H. pylori* infection. In high metronidazole resistant areas preference should be given to a combination without metronidazole.

References


