FOCUS ON CURRENT TRENDS IN THE TREATMENT OF HELICOBACTER PYLORI INFECTION: AN UPDATE

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Accepted on: 23-03-2011; Finalized on: 01-07-2011.

ABSTRACT
One of the most vulnerable gastro intestinal tract infections affecting the human population worldwide are H pylori infections. It causes complicated gastric problems such as gastritis, gastro duodenal ulcers, gastric cancer and primary B-cell gastric lymphoma. The current dosage regimens proposed by the international guidelines which are in practice to abate this chronic destructive bacterial infection (combination of two antibiotics (clarithromycin plus amoxicillin or metronidazole) with a PPI for at least 7 days for the eradication of H pylori) were still found to be unsatisfactory. So there is a need of hour to design and develop alternative drug delivery systems viz. gastro retentive delivery systems, site specific delivery systems and probiotics. This review focuses the issues related to the diagnosis and treatment of H pylori infection including herbal formulations.

Keywords: Gastric lymphoma, diagnostic tests, bismuth salts, herbal formulations, gastrorententive systems, lipobeads.

INTRODUCTION

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Helicobacter pylori were the first isolated microaerophilic gram-negative bacteria from the gastric mucosa of gastritis patients by Marshall and Warren in 1980s. It is a spiral-shaped, highly motile organism with a unipolar flagellum that harbors within and beneath the mucous layer of the stomach and often found attached to gastric mucosa. It is a worldwide common infection with prevalence rates in the general population ranges from not only 30-40% in United States, 80-90% in South America and 70-90% in Africa but also in developing countries like India, China from the age of teenagers 20% to 50-60% of elderly subjects1, 2. The infection is usually acquired in early childhood, either through the fecal to oral / oral to oral route. Acute infection with H pylori during childhood can be accompanied by diarrhea and slowing of weight gain. In adults, however, acute infection usually passes unnoticed except for transient and mild dyspepsia, nausea and vomiting3. According to the statistics, it causes peptic ulcer disease approximately one in six (17%) persons and each year 1% to 2% of these will experience a major or life threatening complication, such as bleeding or gastric outlet obstruction4. H pylori is such a threat that the World Health Organization’s (WHO) International Agency for Research into Cancer (IARC) in 1994 has classified as a “Class-I-Carcinogen”5.

The location of H pylori in stomach is shown in Figure 1. The series of steps or pathogenic mechanisms of H pylori in the stomach are6, 6

- Attachment - The H pylori bacteria enter into the stomach and attach themselves to the lining of the stomach to establish an environment in which to grow.
- Toxin production - H pylori produce poisonous substances to increase the secretion of water and electrolytes in the stomach and cause cell death in the cells of the stomach lining. This will help the bacteria take over the stomach environment and will lessen the competition for required nutrients.
- Cell invasion - The bacteria will enter into the stomach lining cells for protection and then kill the cells they are in (their host cells) so that they can move on to invade more stomach-lining cells. This process will continue, thus creating tissue damage. This tissue damage will become the ulcer formation in the stomach.
- Loss of microvilli/villi - The substances released into the host cell during the ‘Cell Invasion’ step cause a change in the stomach-lining cells. This change results in fewer calories getting absorbed by the stomach. The body will get fewer nutrients from the food eaten at every meal.

Figure 1: H pylori location within the stomach
The situations provoking for the growth of *H pylori* are,

1. *H pylorus* is a curable chronic destructive bacterial infection. Once *H pylori* acquired, it penetrates the gastric mucus layer and fixes itself to various phospholipids and glycolipids on the epithelial surface including phosphatidyl ethanolamine, GM3 ganglioside and Lewis antigen. Therefore the organism exclusively resides on the luminal surface of the gastric mucosa under the mucus gel layer in the acidic environment of the stomach.

2. Bitterly violent factors exhibited by *H pylori* are motility (help to swim in mucosa), adherence (increases mucosal contact), CagA (antigenic protein-increases the mucosal inflammatory response), Urease (urea is broken down into bicarbonate and ammonia; this protects the bacterium in the acid milieu of stomach). These special factors of *H pylori* promote the colonization and tissue injury in the stomach.

3. *H pylori* cause physiological changes in the stomach by decreases or inhibit mucin synthesis via inhibition of UDP-galactosyltransferase. This effect may certainly impair the gastric mucosal barrier and contribute to the mucosal injury which leads to interaction between *H pylori* and phagocyte cells and activation of the mast cells, which shows the acute and chronic inflammatory response associated with *H pylori* infection. Inflammation caused by *H Pylori* was depicted in Figure 2.

![Figure 2: Survival of *H pylori* in the stomach (Acidic Environment)](image)

**DISEASES CAUSED BY *H PYLORI***

*H pylori* infection not only causes the physiological changes in the stomach but also causes several diseases depending on progression of infection; the process is depicted in Figure 3 and 4.

![Figure 3: Sequential diseases caused by long term *H pylori* infection](image)

1. **Gastritis**

*H pylori* infected gastric mucosa causes epithelial cell damage due to polymorphonuclear and mononuclear inflammatory cells; and lymphoid follicles. The lymphocytic component of the inflammatory response is known as mucosa-associated lymphoid tissue (MALT). Inflammation tends to spread upwards from the gastric antrum to corpus, thereby causing a reduction in acid secretion and eventual loss of parietal cells, leading to gastric atrophy. Chronic gastritis is the precursor lesion for the development of gastric atrophy, which in turn can progress to gastric carcinoma.

![Figure 4: Ulcerogenic and carcinogenic effects of *H pylori*](image)
2. Peptic ulcer Disease

H pylori infection is responsible for nearly all duodenal ulcers and approximately 70% of gastric ulcers. These ulcers are occurring due to imbalance caused by H pylori between aggressive factors (gastric acid and pepsin) and protective factors (gastric mucus, bicarbonate, prostaglandins). When H pylori causes inflammation in the antrum results in constant stimulation of gastrin secretion there by increases the acid secretion. It leads to the lowering of the pH in the duodenum, causes the removal of bile acids (which inhibit growth of H pylori in the small intestine). Due to this colonization of H pylori occurs. Sometimes the infection spreads to proximal part of stomach and invades the mucosa by binding to class II major-histocompatibility-complex (MHC) molecules on the surface of the epithelia, inducing apoptosis of the gastric epithelial cells. The produced antibodies cross-react with surface antigens on the gastric parietal cells, enhancing the inflammatory injury to the mucosa lead to gastric ulcer.

3. Gastric Cancer

The risk for developing gastric cancer is most closely related to the degree of damage of gastric mucosa by H pylori. The risk is highest in case of pangastritis with intestinal metaplasia, hypochlorhydrin and lowest in predominantly antral gastritis. The mechanism for the development of gastric carcinoma is multifactorial such as development auto antibodies that cross-react with gastric antigens. Patients with these auto antibodies have a higher frequency of glandular atypia and neoplastic transformation, which may explain progression of gastritis to atrophy and metaplastic changes in some patients. Once the precursor lesion has developed (atrophic pangastritis), the risk of gastric cancer appears to be relatively constant across age groups and populations.

4. Gastric (MALT) Lymphoma

The normal stomach lacks organized lymphoid tissue. Chronic H pylori infection prolonging the antigen stimulation due to this lymphocytes form MALT. Over time, MALT can develop into lymphoma. Gastric MALT lymphomas are typically low grade, T cell dependent, B cell lymphomas whose antigenic stimulus is thought to be H pylori. Complete resolution of MALT lymphomas usually occurs following cure of the H pylori infection, provided that the lymphoma is localized to the stomach. MALT lymphomas may exist in apparently normal mucosa and therefore require histological examination.

Diagnostic tests for H pylori

H pylori easily spread through the fecal-oral, oral-oral route by contaminated sources, poor sanitation and crowded living condition. Immediate diagnosis is necessary for identification of infection and for treatment. The list of diagnosis tests were given in Table 1.

Eradiation of H pylori is difficult because of the organism’s habitat in the stomach under the mucus layer. For effective H pylori eradication therapeutic agents have to penetrate the gastric mucus layer to disrupt and inhibit the mechanism of colonization. The agents used for eradication of H pylori infection are

1. Antimicrobial agents

The antimicrobial agents are act topically and systemically to eradicate the H pylori.

Metronidazole: H pylori are highly sensitive to metronidazole. It is a prodrug that undergoes activation by nitro reductase of bacteria, then acting on helical structure of bacterial DNA, break strand, which causes impairment of bacterial function and it has a pH independent activity. Unfortunately, H pylori rapidly developed resistance to this drug.

Clarithromycin: It is very effective for treatment of H Pylori. It is a 14-membered ring macrolide antibiotic, binds to bacterial ribosome and disrupts protein synthesis, leading to cell death. It is relatively stable in the acid environment, it having lowest minimum inhibitory concentration (MIC). When given in conjunction with a PPI, its concentration in the mucous layer increases markedly.

Amoxicillin: It inhibits the synthesis of the bacterial cell wall by acting topically and systemically. It is more stable in acidic environment. It has significant effect against bacteria along with anti secretory agent. Resistance to amoxicillin is uncommon but has been reported.

Tetracycline: It is a derivative of the polycyclic naphtacene-carboxamides and acting on bacterial cell. It inhibits protein synthesis by specifically binding to the 30S ribosomal subunit there by prevents the addition of amino acids to the growing peptide chain. It is active at low pH.

2. Anti secretory Agents

These shows indirect action on H pylori i.e. they increase the antibiotic concentration in stomach by decrease gastric juice volume. The anti secretory agents are proton pump inhibitors (blocks the H+ K+ ATPase pump on the gastric parietal cell. e.g. omeprazole and lansoprazole) and H2 receptor antagonists (Cimetidine, ranitidine, famotidine).

3. Bismuth

It is directly acting on bacterial cell walls and disrupt their integrity by accumulating in the periplasmic space and leads to bacterial lysis. H pylorus is unable to develop resistance to the various bismuth salts, but the drawbacks are discoloration of tongue and black stool. e.g.: bismuth subsalicylate, ranitidine bismuth citrate.

Most antibiotics have very low in vitro minimum inhibitory concentrations (MIC) against H pylori (MIC 90 ≤
1mg/L, no single antibiotics was able to eradicate this organism effectively. Currently, drug combination therapies are using to increase healing rates of *H pylori* by acting luminally as well as systemically.

**Dual Therapies (approved but not recommended):** A PPI or bismuth plus any one of the antibiotic (Amoxicillin or Clarithromycin). The cure rate after completion of course is only 70%.

**Triple Therapies:** A PPI or bismuth plus any 2 of the antibiotics (Amoxicillin, Clarithromycin, Metronidazole and Tetracycline). The course of the therapy is 10 days to 2 weeks and cure rate is 85%. This treatment is fairly complicated (20 pills/day). The options for triple therapy are given in Table 2.

**BMT Quadruple Therapy Includes (all given for 2 weeks):** This therapy consisting Bismuth subsalicylate 2 tablets QID, Metronidazole 500 mg TID, Tetracycline 500 mg QID, proton pump inhibitor (Omeprazole 20 mg BID or Lansoprazole 30 mg BID). The cure rate is only 66.7% and side effects were more than above therapies. FDA approved regimens for *H pylori* infection are listed in Table 3.

Main drawback of above therapies is expensive, poor patient compliance and developed resistance power for antibiotics to *H pylori*.

### Table 1: Diagnostic tests for *H. pylori*

<table>
<thead>
<tr>
<th>Test</th>
<th>What does it measure</th>
<th>Sensitivity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive (requiring endoscopic biopsy)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Steiner's stain of gastric biopsy specimen</td>
<td>Histological identification of organism</td>
<td>82 to 95%</td>
<td>Considered the &quot;gold standard.&quot;</td>
</tr>
<tr>
<td>2. Rapid Urease test (CLO test, Delta Wenst, Bently, Western Australia)</td>
<td>Urease activity of biopsy specimen</td>
<td>85-90%</td>
<td>Sensitivity decreased by acid suppression and acid bleeding.</td>
</tr>
<tr>
<td>3. Culture</td>
<td>Presence of organisms; antimicrobial sensitivities</td>
<td>70-80%</td>
<td>Especially useful for the research and to guide management in treatment failure; requires experienced laboratory.</td>
</tr>
<tr>
<td><strong>Noninvasive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Serology: laboratory based ELISA</td>
<td>IgG</td>
<td>90-96%</td>
<td>Accurate, convenient for initial infection, titers diminishes slowly after eradication and may remain positive after one year.</td>
</tr>
<tr>
<td>2. Whole blood: office based ELISA</td>
<td>IgG</td>
<td>50-85%</td>
<td>Less accurate, but fast, convenient and inexpensive.</td>
</tr>
<tr>
<td>4. Urease breath test</td>
<td>Urease activity</td>
<td>95-100%</td>
<td>Sensitivity reduced by acid suppression.</td>
</tr>
<tr>
<td>5. String Test (swallowed and recovered polymeric string)</td>
<td>Culture or polymerase chain reaction on gastric mucosa</td>
<td>75-80%</td>
<td>Minimally invasive method to obtain viable organisms, but retrieval rate less than with endoscopy.</td>
</tr>
<tr>
<td>6. Urine ELISA</td>
<td>IgG</td>
<td>70-96%</td>
<td>Greater patient acceptance and convenience than stool test; not yet readily available.</td>
</tr>
<tr>
<td>7. Saliva</td>
<td>ELISA</td>
<td>82-91%</td>
<td>Greater patient acceptance and convenience than stool test; not yet readily available.</td>
</tr>
</tbody>
</table>

CLO=Campylobacter-like organism; ELISA=enzyme-linked immunosorbent assay; HpSA = *H. pylori* stool antigen

### Table 2: Options for triple therapy

<table>
<thead>
<tr>
<th>Option 1</th>
<th>Option 2</th>
<th>Option 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton-Pump Inhibitors</td>
<td>Proton-Pump Inhibitors</td>
<td>Bismuth compounds</td>
</tr>
<tr>
<td>E.g, Omeprazole, Pantoprazole, Lansoprazole</td>
<td>E.g, Omeprazole, Pantoprazole, Lansoprazole</td>
<td>e.g., Bismuth subsalicylate</td>
</tr>
<tr>
<td>Clathromycin</td>
<td>Clathromycin</td>
<td>Metranidazole</td>
</tr>
<tr>
<td>Brand names : Biaxin, Klaricid, Klabax, Claripen, Calidar, Fromilid, Calcid</td>
<td>Brand names: Biaxin, Klaricid, Klabax, Claripen, Calidar, Fromilid, Calcid</td>
<td>Brand name: Flagyl</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Metranidazole</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Brand names: Amoxil, Dispermox, Trimox</td>
<td></td>
<td>Brand names: Sumycin, Terramycin, Tetracycin, Panmycin</td>
</tr>
</tbody>
</table>
Table 3: FDA approved regimens for treatment of H pylori infection

<table>
<thead>
<tr>
<th>ABRREVIATION</th>
<th>DRUG</th>
<th>DESIGN</th>
<th>EFFICIENCY</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC</td>
<td>Omeprazole</td>
<td>40mgqAM 500mg TID</td>
<td>70-80</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC+C</td>
<td>Ranitidine bismuth citrate</td>
<td>400mg BID 500mg TID</td>
<td>70-85</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMT+H2 ANTAGONIST</td>
<td>Bismuth subsalicylate</td>
<td>2 tabs QID 250mg QID</td>
<td>70-90</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tetracycline HCl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAC</td>
<td>Lansoprazole</td>
<td>30mg BID 1mg BID 500mg BID</td>
<td>80-95</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>Lansoprazole</td>
<td>30mg BID 1mg BID</td>
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<td>14</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAC</td>
<td>Omeprazole</td>
<td>20mg BID 1mg BID 500mg BID</td>
<td>80-95</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Gastro retentive drug delivery systems against H pylori

GRDDS are designed to localize the action of drug on gastric region and prolong the gastric residence time of the drugs. Now a day’s research is going on these dosage forms for effective treatment of H pylori. Drug delivery to the site of infection i.e. gastric mucosa may help to solve the problems associated with the above therapies. The major gastro retentive drug delivery formulations for eradication of H pylori are

#### 1. Floating drug delivery systems

These systems have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time and localize the drug activity. Various floating drug delivery systems for eradication of H pylori infection are listed in Table 4 and represented diagrammatically in Figure 5. They are,

a) **Hydrodynamically balanced systems**

![Figure 5a: Floating drug delivery systems - Hydrodynamically balanced](image)

These are single unit dosage forms containing hydrocolloid (HEC, HPMC, NaCMC, Poly saccharides) and matrix forming polymer (polycarbophil, polyacrylates and polystyrene) incorporated either in tablets or in capsules.

Up on oral administration hydrocolloid starts to hydrate due to gastric fluid and forming a gel surface and maintains a relative integrity of shape and a bulk density of less than one. The resultant gel structure then controls the rate of diffusion of solvent in and drug out of the dosage form. As the exterior surface of the dosage form goes into solution, the gel layer is maintained by the immediate adjacent hydrocolloid layer becoming hydrated. As a result the drug dissolves in and diffuses out with the diffusing solvent creating a ‘receding boundary’.

b) **Gas-Generating Systems**

![Figure 5b: Floating drug delivery systems - Gas generating system](image)

Floatability of this type system can be achieved by generating gas bubbles. This system formulated as matrices by a swellable polymer such as HPMC or polysaccharides (Chitosan) and carbonates or bicarbonates which reacts with acid either natural gastric acid or co-formulated ingredients such as citric and tartaric acid. When the matrices are in contact with the acidic environment CO₂ was librated and entrapped in swellable hydrogels, produces upward motion by decreasing specific gravity.
c) Low density systems (hallow microspheres)

Low density systems are globular shells apparently having lower density than that of gastric fluids. The buoyancy of this system achieved by low-density carriers like popcorn, poprice, polystrol, polypropylene. The surface of the empty shells is coated with sugar or with polymeric materials such as methacrylic polymer and cellulose acetate phthalate. The under coated shell is then coated by mixture of drug with polymers such as Ethyl cellulose or HPMC, on contact with GI fluid the tablet forms a water impermeable colloid gel barrier around its surface and maintains the bulk density less than one. Due to that it shows good buoyancy and target action.

d) Raft Forming System

This system has received much attention in drug delivery for GI infections mainly for *H pylori*. It contains a gel forming agent (alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft), when in contact with gastric fluids. The raft thus formed floats on the gastric fluids because low bulk density created by the formation of CO₂ and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus.

![Figure 5c: Floating drug delivery systems - Raft forming system](image)

**Figure 5c:** Floating drug delivery systems - Raft forming system

2. Mucoadhesive drug delivery systems

Mucoadhesive drug delivery systems prolong the residence time of the dosage form at the site of application and improved therapeutic performance of the drug. The absorption of an antibiotic into the mucus through the mucus layer (from the gastric lumen) is believed to be more effective for *H pylori* eradication than absorption through the basolateral membrane (from blood). A preparation that spreads out adheres to the gastric mucosal surface and continuously releases antibiotic should be highly effective against *H pylori*. Various mucoadhesive drug delivery systems have been proposed for *H pylori* eradication is listed in Table 5 and system was depicted in Figure 6.

![Figure 6: Mucoadhesive drug delivery system](image)

**Figure 6:** Mucoadhesive drug delivery system

### Table 4: Floating drug delivery system

<table>
<thead>
<tr>
<th>Drug delivery system</th>
<th>Method</th>
<th>Materials</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrodynamically balanced system (HBS)</td>
<td>Direct compression technique</td>
<td>HPMCK4M, HPMCK125M, sodium bicarbonate</td>
<td>Buoyancy duration less than 12hr, and buoyancy lag time 49sec.</td>
</tr>
<tr>
<td>Gas generating system</td>
<td>Expendable asymmetric triple layer tablet</td>
<td>Tetracycline HCL, Metronidazole HCL</td>
<td>Buoyancy duration (0.1NHCL),6-8hr Buoyancy lag time 17-28min.</td>
</tr>
<tr>
<td>Raft forming system</td>
<td>Compressed tablet</td>
<td>Triclosan, Alginic acid, Sodium bicarbonate, Calcium carbonate and Mannitol</td>
<td>In acidic conditions bicarbonate salts produced effervescent causes the buoyancy of raft structure formed by alginate.</td>
</tr>
<tr>
<td>Low density system</td>
<td>Polycarbonate micro balloons by Emulsion (o/w) solvent evaporation technique</td>
<td>Antiurease drug (acetohydroxamic acid (AHA), poly carbonate</td>
<td>Buoyancy duration (stimulated gastric-fluid) is 12hrs and shows sustain release.</td>
</tr>
</tbody>
</table>
### Table 5: Mucoadhesive drug delivery system\(^{19-22}\)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Method</th>
<th>Materials</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microsphere (250-335(\mu)m)</td>
<td>Spray chilling method</td>
<td>Amoxicillin (drug), carboxyvinyl (Bioadhesive polymer), Curdlan (Polysaccharide)</td>
<td>Microspheres adhesion on Mongolian gerbil’s stomach wall after 4hr is 20% and having 10 times greater activity than suspension.</td>
</tr>
<tr>
<td>Microspheres</td>
<td>Emulsion/evaporation method</td>
<td>Amoxicillin, polymer (carpobol 934P)</td>
<td>The remained amount of drug in rat stomach after 4hr is 63.6± 21.9% and higher effectiveness than powder.</td>
</tr>
<tr>
<td>Sustain release liquid preparation</td>
<td>Sodium alginate form a firm gel contact with acid or di or trivalent metal ions</td>
<td>Ampicillin, sodium alginate</td>
<td>The remained amount of drug in rat stomach is 87% after 60min.</td>
</tr>
<tr>
<td>Chitosan microspheres</td>
<td>Chemical (glyxal) crosslinking method</td>
<td>Tetracycline, glyxal</td>
<td>It fasted gerbils the cross linked chitosan microspheres in stomach is 17% and 10% at 2 , 10 hr respectively</td>
</tr>
</tbody>
</table>

### 1. Drug delivery systems with specific interaction

a) Some strains of H. pylori express an adhesin, BabA2, it interact with the fucosylated histo-blood antigen Lewis b (Le\(^b\)) in the stomach. Therefore, formulations having fucose as ligand is suitable for targeting to H pylori.

  e.g.: Umamaheshwari et al. developed chitosan-glutamate nanoparticles by ionotropic gelation method and covalently bind the L-fucose. A “plug and seal” effect between H pylori and nanoparticles was observed. In vitro growth inhibition studies showed that L-fucose-conjugated chitosan-glutamate nanoparticles exhibited 2-fold inhibitory efficacy compared to chitosan-glutamate nanoparticles and the plain drug\(^{21}\).

b) Receptor-mediated drug delivery system: PE is a predominant lipid in the antrum of the human stomach and function as a receptor for H pylori adhesion\(^{24}\).

  e.g.: Anti Urease drug, acetylhydroxamic acid (AHA) was formulated into lipobeads. The system consists of a lipid bilayer shell (PE) that is anchored on the surface of a hydrogel polymer (polyvinyl alcohol xerogel) core. The specific binding between lipobeads and PE specific surface receptor of H pylori was confirmed by in situ adherence and radiolabelling assays with human stomach cells and KATO-III cells respectively. The in vitro growth inhibition studies showed a better efficacy of PE-lipobeads than polyvinyl alcohol (PVA) bare beads and plain AHA (the three formulations containing the same amount of AHA). The % growth inhibition rate of lipobeads, PVA-bare beads and plain AHA are 100%, 25% and 35% respectively\(^{25, 26}\). The system was depicted in Figure 7.

### Herbal formulations for H pylori eradication

The widespread use of antibiotics not only causes the side effects but also increases the resistance power of all pathogenic bacteria. Therefore, need a non-antibiotic agent which is both effective and free from side effects. For centuries, herbs have been used as traditional medicine to treat a wide range of ailments including gastrointestinal (GI) disorders such as dyspepsia, gastritis and peptic ulcer disease (PUD). Commonly used medical plants for treatment of H pylori are

1. **Black myrobalan**: The aqueous extract of black myrobalan (*Terminalia chebula* Retz) has uniform antibacterial activity against ten clinical strains of *H pylori*. The antibacterial activity of aqueous extracts of black myrobalan against *H pylori* was significantly higher than that of ether and alcoholic extracts. The minimum inhibitory concentration and minimum antibacterial activity of the extract is 150 and 175mg/L respectively\(^{27}\).

2. **Ginger**: Ginger root (*Zingiber officinale* Rosc) traditionally used for the treatment of gastrointestinal ailments such as motion sickness and dyspepsia. The constituents such as 6-, 8- and 10-gingerol and 6-shogaoal were isolated from Ginger rhizome in menthol. The isolated compounds eradicate 19 strains of *H pylori*, including 5Cag A-positive. The methanol extract of ginger rhizome inhibited growth of all strains in vitro with MIC range of 6.25-50\(\mu\)g/mL. One fraction of the crude extract containing gingerol inhibited all strains of *H pylori* including CagA-positive strain with an MIC 0.78 to 12.5\(\mu\)g/mL\(^{28}\).

3. **Turmeric**: The derived chemical constituents of turmeric (*Curcuma longa* L) are curcumin, a polyphenolic which prevent gastric and colon cancer in rodents. A methanol extract of the dried powered turmeric rhizome and curcumin inhibited growth of 19 strains of *H pylori*, including 5 Cag A-positive in vitro with MIC range of 6.25 to50\(\mu\)g/mI\(^{29, 30}\).

4. **Thyme**: It is a popular herbal remedy in ancient Egypt, Greece and Rome. Thyme was mainly used for headaches, digestive problems, respiratory illness, and as a mood-enhancer. Researcher who investigated the antimicrobial properties of 21 essential oils against five important food-borne pathogens, including *H pylori* noted that thyme was very effective at inhibition activity\(^{31}\).

5. **Liquorice**: In a recent study at the Institute of Medical Microbiology and Virology, Germany, researchers found that liquorice extract produced a potent effect against strains of *H pylori* that are resistant against Clarithromycin\(^{32}\).
6. **Berberine**: Berberine is a plant alkaloid isolated from the roots and bark of several plants including golden seal, barberry, *Coptis chinensis* Franch and *Yerba mansa*. Berberine-containing plants have been used medicinally in ayurvedic medicine, and are known to have antimicrobial activity against a variety of organisms including bacteria, viruses, fungi, protozoans, helminthes, and Chlamydia. More recently, berberine had been demonstrated to be effective against *H pylori*.[33]

**Probiotics**[34,35]

Probiotics are defined as live, non-pathogenic microbial feed or food supplements that exert a positive influence on the host by altering the host's microbial balance. Currently, probiotics are accepted as being useful in the prevention and/or treatment of certain pathological conditions, mainly (but by no means exclusively) infections of GI tract. Several in vitro studies show that lactobacilli or their cell-free cultures having an inhibitory effect on *H pylori* and increases the eradication rate of *H pylori*. In vivo models demonstrate that pre-treatment with a probiotic can prevent *H. pylori* infections and/or that administration of probiotics markedly reduced an existing infection. The mechanisms of probiotics to counteract *H. pylori* induced functional effects are shown in Figure 8.

1. Inducing aggregation.
2. Competing with host-cell binding sites.
3. They could modulate inflammatory responses.
4. Strengthen the mucosal barrier.
5. Probiotics with a high fraction of CpG sequences can possibly reduce *H. pylori* colonization.
6. Differential modulation of cytokine production recognized by Toll-like receptors (TLR).
8. Decreases tumor necrosis factor (TNF)-α production by macrophages could have a role in *H. pylori* infection.
9. Probiotics could down-regulate the production of virulence factors of *H pylori*.
10. Induce mucin release from epithelial cells.
11. They could compete with *H. pylori* in binding to dendritic cell (DC) receptor specific intercellular adhesion molecule 3-grabbing nonintegrin (SIGN).
12. Modulate DC function and regulatory T (Tr) cell development.

Probiotics are a promising alternative among individuals who have adverse reactions to antibiotics because they help the gastrointestinal flora resist gastrointestinal aggression brought on by antibiotics.

![Figure 7: Site specific drug delivery system](image)

![Figure 8: Mechanisms of probiotics to counteract *H pylori* induced functional effects](image)
Eventually, the need for the design and development of GRDDS or site specific drug delivery systems to eradicate H. pylori infection is immense. But high mucous turnover rate and low retention time of dosage form in stomach and guaranteed clearance of swallowable systems after appropriate time are the most challenging aspects of designing GDDS. In addition, much more knowledge about the pathogen in terms of identification of certain specific receptors on the surface of the bacterium will be possible for ligand targeted action. However, further investigation on the coccoïd form of the bacterium H. pylori existing either as degenerative type or resistant type along with its virulence factors will certainly gain an advantage to understand its physiology. Moreover, the recent advent of herbal drugs in conjunction with novel drug delivery systems can be a fruitful alternative option. Thereby, a more effective therapy can be rendered to protect from the diseases caused by H pylori infection.

Acknowledgements: The authors are thankful to Chalapathi Educational Society, Guntur for providing the necessary facilities.

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