Dated: 27th August 2014

We are pleased to submit a review article titled “Helicobacter pylori infection: An overview”.

We have previously worked and published on H pylori; our studies include the LOAD trial, ROAD trial and RENDER trial.

In this manuscript we wish to provide a comprehensive critical review of helicobacter infection, pathology and treatment regimens. Various clinical trials, guidelines and systematic reviews was performed through a Medline search.

We believe that this review article is appropriate for publication by the Scienpress Ltd Journal as it details Helicobacter pylori infection which is the most common chronic bacterial infection and cause of gastritis and gastric carcinoma for which various regimens exists and emerging resistance is a concern.

This review article has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose. Also, in case of acceptance of the manuscript copyright will be transferred to Scienpress Ltd Journal.

Thank you for your consideration!

Sincerely,

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Helicobacter Pylori infection: An overview

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Abstract

Background: Helicobacter pylori is the most common chronic bacterial infection and cause of gastritis and gastric carcinoma for which various regimens exists and emerging resistance is a concern.

Aim: To provide a comprehensive critical review of helicobacter infection, pathology and treatment regimens

Methods: Clinical trials, guidelines and systematic reviews of the same was performed through a Medline search. Papers with a Jadad score of 0-5 were incorporated. PubMed, Cochrane Library were the most commonly used websites for this review article.

Results: H. pylori is the major cause of peptic ulcer disease, gastric cancer and gastric MALT lymphoma. The prevalence varies by geographical location and socioeconomic conditions. H. pylori genomes and host-bacterial interactions have immensely contributed to better insights to the pathogenesis of the disease. Eradication rates vary between different therapies and geographical considerations should be taken into account. Triple therapy, quadruple therapy and sequential therapy are the options which could be used. Following therapy eradication testing should be opted for while continued symptomatic patients would require further investigations including esophagogastroduodenoscopy (to aid diagnosis) and proton pump inhibitors (for symptomatic relief).

Conclusions. The current aim of screening special population with an intention to treat and the newer emerging therapies could help eradicate one of the most common gastroenterology disorder which has infected half our population and has persisted for more than 58,000 years.

Key words: H pylori infection, H pylori diagnosis, H pylori treatment, gastritis, peptic ulcer disease, Helicobacter pylori, gastritis, peptic ulcer disease

Introduction

Helicobacter pylori (H. pylori) is the most common chronic bacterial infection in humans [1,2] Genetic sequence analysis suggests that humans have been infected with *H. pylori* since the time pre-historic homosapiens migrated out of Africa around 58,000 years ago[3]

H. pylori was initially known as Campylobacter pyloridis. In 1982 Marshall and Warren identified and subsequently cultured the gastric bacterium indicating for the first time the implications of gastric microbes [4]

H. pylori is one of the first eighteen species of the genus *Helicobacter.* It is a spiral shaped (0.5-1 μm (W) x 2.5–4 μm (L) microaerophilic gram negative rod. It has 2-7 unipolar flagella which facilitates its cork screw motion. Biochemically, *H. pylori* can be characterized into catalase, oxidase and urease producing. The urease activity is important for various diagnostic test.

Prevalence and transmission

Approximately 50% of the world's population is infected with *H. pylori.* Estimated infection rate is 50% in the United States by age 60 years [5]. It is more in Hispanics and African Americans which are indirectly related to the socioeconomic factors [6]. In developing countries the infection occurs at an earlier age of around age of 10 while the prevalence in adults peaks to around 80 % at around age of 50 [5]. *H. pylori* is a primary cause of Gastritis (non erosive, erosive), Peptic ulcer disease (duodenal, gastric), Gastric carcinoma and MALT lymphoma. WHO considers *H. pylori* a type 1 carcinogen

Transmission of *H. pylori* remains unclear and the possible routes of transmission are mainly person-to-person, as faeco-oral and oral-oral. Transmission usually occurs in early childhood. More than 90% of the *H. pylori* are found in the mucous layer with less than 1% in the gastric epithelium. Oral-oral transmission has not yet been proven. H. pylori has been isolated from dental plaques but the prevalence is low. *H. pylori* has been found in water sources, primates, cats and sheep. Children who regularly swim in rivers, streams, pools, drink stream water or eat

uncooked vegetables are more prone for *H.pylori* infection [7]. Iatrogenic infection has been documented with endoscopes and accessories. H. pylori can be cultured from vomitus and diarrheal stools [8,9].

The acute infection leads to transient hypochlorhydria. 80 to 90% of the times it is asymptomatic and is hence rarely diagnosed. Individuals with relatively higher acid output leads to antral predominant gastritis and duodenal ulcers. Individuals with low acid production have gastritis predominantly in the body of the stomach leading to gastric ulcerations and even gastric carcinomas. Chronic H. pylori infection can induce the formation of mucosa-associated lymphoid tissue, MALT lymphoma, from which malignant lymphomas could arise (which is a rare complication of chronic H. pylori infection)

Various risk factors for *H. pylori* infection [10,11] have been identified, as examples, a younger age of infection and a lower socioeconomic status – poor housing, overcrowding, higher number of siblings, bed sharing and lack of running water [12,13]. Chinese, Indian and Polynesian are more prone to be infected [14]. Underdeveloped countries have a higher incidence of infection and reinfection rates [14]. Pregnancy is a risk factor for *H. pylori* infection [14]. A high salty diet and diet low in antioxidant levels increases the possibility of persistent infection [14]. Hereditary associations have still not yet been proven.

The pathophysiology and the outcome depends on a complex interaction of the host genetic predisposition and the bacterial virulence factors [10,15,16], besides the external environment. The bacteria do not generally invade the gastric epithelium but does renders it more susceptible to infection. It induces an inflammatory cascade, which enhances tissue injury [
1].

Virulence factors of H.Pylori

Various factors are attributed to the colonization of *H. pylori.* These include the flagella, enzymes (urease, phospholipase, superoxide dismutase, catalase) and cagA, cagE, vacA, babA, sabA and OipA virulence factors.

Flagella

Flagella is essential for colonization and for movement through viscous mucus layer. The gastric mucin appears to be a natural antibiotic protecting against *H. pylori* infection [17]. The flagella produces mucolytic enzymes which facilitate its passage through the mucus layer to the gastric surface epithelium [18].

Urease, phospholipase & catalase

Urease is essential for acid neutralization as it converts urea into carbondioxide and ammonia which forms a protective region. The ammonia directly damages the epithelium. The urease enzyme is antigenic and chemotactic hence causing mucosal damage [19]. The production of the urease enzyme is decreased as pH increases (via the "urel gene" which encodes a pH dependent urea channel [20]. Urease may provide energy for flagellar motion. Also, the bacterial phospholipases alters the phospholipid content of the gastric mucosa affecting the permeability and enhancing lipolysis disrupting the epithelial integrity [21]. Superoxide dismutase has been isolated from *H. pylori*, which breaks down superoxide produced in polymorphonuclear leukocytes and macrophages and thereby prevents the killing of the organisms. Catalase acts as an anti-oxidant protecting *H. pylori* from oxygen metabolites permitting it to proliferate in an hostile environment [22]. The *H. pylori* almost exclusively adheres to gastric type mucosa [23]. Less than 1% of *H. pylori* adhere to gastric epithelium [Figure 1]

Adhesins

Bacterial adhesins selectively recognize and adhere to the expressed host receptors on the epithelium which alters the epithelium and activates virulence factors on the bacterium [24]. Adherent bacteria are 100-1000 times more resistant to antibiotics than non-adherent.

Cag-PAI

The cag Pathogenicity Island (cagPAI) is a 40 kb region of chromosomal DNA encoding

approximately 31 genes that forms a type IV secretion system. The Type IV secretion system translocates CagA into the epithelial cells by forming syringe like pilus structure. CagA is antigenic [25]. It induces IL-8 and leads to chronic inflammation due to neutrophil infiltration. This ultimately leads to epithelial injury, increased cell turnover and apoptosis [26]. 90% of biopsies of chronic active gastritis, peptic ulcers, MALT and gastric carcinoma has CagA-PAI present [27]. EPIYA is a specific amino acid sequence of the CagA protein which may be associated with higher risk of malignancy [28]. Another protein CagE (formly known as picA and picB) induces IL-8 release. VacA is a vacuolating cytotoxin A which causes epithelial damage. It increases the gastric epithelium permeability to urea creating a favorable environment for infectivity [29]. The adhesion is also mediated by adhesins and outer membrane proteins. Three Hop proteins BabA (HopS), OipA (HopH) and SabA (HopP) have been implicated [30]. BabA mediates the binding of lewis b blood group antigens to host cell [31]. OipA increases IL-8 expression [32]. SabA mediates the glycoconjugates containing sialic acid [33]. H. pylori can bind to class II MHC molecules on the epithelial cells and induce apoptosis [34].

Various *H. pylori* adherence antagonists have been observed. Sucralfate blocks interaction of *H. pylori* Liposaccaharide with laminin and gangliosides and decreases H. pylori mucinase activity. Co-magaldrox interferes with IL-8 secretion and reduces H. pylori surface expression of HSP 60 (Heat Shock Protein 60). *Lactobacillus salivarius* is a protobiotic agent having a possible activity against *H. pylori*. Bile acid, Omeprazole and Bismuth have unclear mechanism of *H. pylori* adherence antagonism. Milk inhibits Lewis b and sulfatide-mediated adherence; preventing *H. pylori* adherence. [35]

H. pylori is non-invasive but is antigenic and hence induces a strong immunological response. *H. pylori* produces antigenic substances including lipopolysaccharides, urease and HSP (heat shock protein) which are processed by macrophages of the lamina propria (after cellular disruption, especially the tight junctions) to activate T-cells. IL-1, IL-6, IL-8 and TNF (tumor necrosis factor) are released [36]. Also, the B-lymphocytes are stimulated which releases mainly IgG and IgA antibodies. Continued B cell stimulation leads to MALT lymphoma.
Chronic infection is contributed by B7-H1 (a member of the B7 family of proteins called “programmed death-1 ligand 1”). B7-H1 desensitizes the recruited T cells by inhibiting T cell

proliferation and IL-2 synthesis [37]. Host genetics with respect to IL-1 beta polymorphism determine the magnitude of inflammatory response. It also influences whether the individual is a hypo or hyper acid secretor; thus indicating its risk for gastric carcinoma [38,39].
CagA, CagE and VacA are potent IL-8 inducer which seems to be the major player in the inflammatory response in *H. pylori* infection [40]. TNF alpha augments IL-8 secretion. Upon treatment of H. pylori the levels of IL-8 and TNF alpha decline [41].

During acute infection, *H. pylori* binds to the gastric epithelial cells; the affinity of which depends on various host and bacterial factors. Whereas the pathogenicity depends on the presence of virulence factors, especially the cagPAI complex. This subsequently results in the production of chemokines (particularly IL-8), epithelial derived factors like ENA-78 (epithelial cell derived neutrophil activating factor) and GRO (growth related oncogene), certain intercellular messengers like NF-B (nulear factor-B) and AP-1 (early response transcription factor activator protein-1). These epithelial chemokines bind to proteoglycan scaffolding which facilitates neutrophils to be recruited.
The chronicity depends on the IL-1 beta polymorphism. Lymphocyte recruitment is via VCAM-1 (vascular-cell adhesion molecule-1) and ICAM-1 (intercellular adhesion molecule) which are the vascular addressins. Activated macrophages produce proinflammatory cytokines which activates T helper cells (Th1, Th1, Th2). The Th1 cytokines like interferons induce the expression of class II major histocompatibility complexes and B7-1 and B7-2 molecules (these molecules facilitates gastric epithelial cells to function as antigen presenting cells). Later the epithelial barrier is breached by TNF activated VacA and Fas mediated apoptosis. Cytokines disrupt mucus production. This leads to further translocation of bacterial antigens. TNF, IL-1 and IFN increase gastrin release and decrease antral D cells (which decreases somatostatin); thus increasing acid production [16]

Diseases associated with *H. pylori* infection

H. pylori infection has been associated with a spectrum of disorders from chronic gastritis, peptic ulcer disease (gastric and duodenal ulcers) to MALT lymphoma and gastric carcinoma [42].
World Health Organization's body *International Agency for Research on Cancer* (IARC)

declared *H. pylori* a class I carcinogen in 1994 based on the clear association with MALTOMA and gastric carcinoma [42].

Acute *H. pylori* gastritis is usually asymptomatic but has been demonstrated in volunteers with organism ingestion leading to mild epigastric tenderness, nausea, vomiting and pathological evidence of gastritis on gastric biopsy [43,44]. Mostly involves the gastric antrum. Acute infection on endoscopy usually demonstrates gastric numerous neutrophilic infiltration in the lamina propria and the neck region.

Chronic *H. pylori* gastritis affects two-thirds of the world's population [45]. Usually is detected in the antrum and the body of the stomach [46]. *H. pylori* generally resides in the gastric mucus layer adjacent to the gastric epithelial cells and also in the gastric pits.
Initially the acid production is elevated with increase in gastrin and decrease of somatostatin while later due to continued inflammation and loss of the gastrin and parietal cells the acid secretion decreases ultimately leading to atrophy and intestinal metaplasia [47]. Chronic proton pump infusion use also contributes to low acid secretion.
Duodenal ulcers are typically associated with antral predominant gastritis, minimal atrophy and increased acid production. Gastric ulcers and gastric carcinoma is typically associated with extensive gastritis, are corpus predominate, has atrophy and intestinal metaplasia and decreased acid production.

H. pylori-positive patients have a 10 to 20% lifetime risk of developing ulcer disease and a 1 to 2% risk of developing distal gastric cancer [31].
H. pylori interacts with von willebrand factor to facilitate platelet activation and aggregation leading to microvascular dysfunction and cytokine aggregation [48]. This may also explain cardiovascular manifestation and associated idiopathic thrombocytopenia [49].

Diagnosis testing of *H. pylori*

The first recommendation for diagnostic testing for *H. pylori* was by the NIH (National Institute of Health) in 1994 [50]. This was followed by the EHSG (European *Helicobacter* Study Group)

in 2006 [51] and then by the ACG (American College of Gastroenterology) in 2007 [52]
The ACG recommends testing in patients with MALT lymphoma, active or past documented peptic ulcer disease. The tests are performed only if treatment would be offered for positive test results. The test-and-treat strategy for *H. pylori* is a proven management strategy for patients with uninvestigated dyspepsia under the age of 55 years and with no alarming symptoms (bleeding, anemia, early satiety, unexplained weight loss, progressive dysphagia, recurrent vomiting, familial history of gastrointestinal cancer or previous esophagogastric malignancy).

Invasive testing

Invasive testing includes histopathological diagnosis, biopsy urease testing, brush cytology and real time polymerase chain reaction (RT-PCR). Histology is indicated as at times proton pump inhibitors may reduce the sensitivity of other modalities of diagnosis [53]. It is important to establish gastritis and even detect intestinal metaplasia or MALT lymphoma. *H. pylori* generally has variable distribution in the stomach and hence a combination of four biopsy sites (lesser and greater curvature of the mid antrum and the mid body) was deemed optimal for adequate detection [54]. Typical spiral bacilli on biopsy suggests *H. pylori.* However *H. pylori* can change its shape (U shaped, rod-like or coccoid forms) in response to hypochlorhydric states due to PPi's. Hematoxylin and Eosin stains can demonstrate *H. pylori* but usually other stains are used. Giemsa stain is the preferred method as it is inexpensive, consistent and easy to use. Silver stains such as Warthin-Starry and Genta methods – are expensive and sometimes not reliable [55]. Immunostaining techniques are expensive but reliable as it is highly sensitive and can detect even the coccoid forms) [56]. Upon treatment the neutrophilic infiltration disappears first followed by the lymphocytes and eosinophils. Intestinal metaplasia takes upto an year while the foveolar hyperplasia takes longer [57]. Biopsy urease testing is performed on the biopsy specimen and is less expensive than the histopathology. False positive is rare with 90 to 95& sensitivity and 95 to 100% specificity [52]. Brush Cytology is rarely used. It can be considered in patients with bleeding disorders. Real-time polymerase chain reaction (RT-PCR). Biopsy specimens of refractory cases of *H. pylori* could benefit from RT-PCR and in situ hybridization techniques [58]

Non-invasive testing

Non-invasive testing methods includes urease breath testing, serology, stool testing, salivary assays, urinary assays and 13C-urea serodiagnostic testing. *H. pylori* produces urease that splits urea to ammonia and carbon dioxide. This carbon atom is tagged and detected on breath samples. For the urease breath test the patient should ideally be off antibiotics for 4 weeks and off PPi's for 2 weeks [59]. The sensitivity is 88-95% while the specificity is 95-100% [60]. ELISA serology is used to detect IgG antibodies. It is inexpensive. However it is not recommended in low prevalence area since the sensitivity is 90-100% but the specificity is low at 76 to 96%. It may be positive for months to years after the infection [61]. *H. pylori* stool antigen testing is an antigen enzyme immunoassay test. The sensitivity is 94% while the specificity is 92% [62]. It is the less preferred method of *H. pylori* eradication (Second to UBT) after 4 to 6 weeks after completion of the antibiotic therapy. Salivary IgG assays of H. pylori are not as sensitive as other modalities and is not preferred [63]. Urinary ELISA assay is 96% sensitive but only 79% specific and hence not preferred [64]. 13C-urea serodiagnostic test requires two specimens. One serum sample is drawn before and one an hour after ingestion of a 13C-urea rich meal. Its cumbersome and expensive. It has a sensitivity of 92 to 100% and a specificity of 96 to 97% [65]. It is rarely used.

The confirmation of H. pylori eradication is indicated in certain conditions but presently recommended to be performed in all cases due to the easy availability, inexpensive and noninvasive methods. As per the ACG (American College of Gastroenterology) guidelines from 2007 [52] the confirmation of eradication is indicated in Patients with H. pylori associated ulcer, Persistent dyspepsia after treatment, H. pylori associated MALT lymphoma or anyone who has undergone resection of early gastric cancer. UBT performed after 4 weeks of antibiotic therapy is the test of choice. Stool antigen testing is less accurate [66].

Diseases associated with H. pylori infection

Dyspepsia is the most common symptom of H. pylori infection. Dyspepsia is defined as persistent or recurring symptoms consisting of upper abdominal pain, discomfort, nausea or bloating. The prevalence in western countries is approximately 25%. 60% of cases of functional

dyspepsia (FD) is associated with H. pylori and hence all patients should be assessed (depending on exposed risk factors) for possible H. pylori and treated if found positive. Alarm features that require prompt investigation include: gastrointestinal blood loss, weight loss, early satiety, dysphagia, persistent vomiting, or symptom onset after the age of 55 years [67]. H. pylori eradication leads to marginal improvement in symptoms of FD
In Corpus (Fundus) predominate gastritis due to H. pylori- the eradication of H. pylori will worsen GERD while in antral predominate gastritis due to H. pylori- the eradication of H. pylori will improve GERD symptoms [Table 1]

Majority of the patients with DU (Duodenal Ulcer) have associated H. pylori infection; but approximately 30% of patients with endoscopically documented duodenal ulcers do not have H. pylori infection [68]. The association is strong but not specific. Only 10 to 15% of H. pylori infection develop ulcer disease. Generally H. pylori eradication helps prevent development of DU. H. pylori status should be ascertained before starting treatment for H. pylori since H. pylori eradication could worsen the ulcers and even cause recurrent DU [69]. NSAID users with H. pylori infection were 61 times more prone for peptic ulcer disease and 1.8 to 4.9 times more prone for ulcer bleeding than non-infected individuals [70].

MALT Lymphoma is a complication of H. pylori infection. It is also known as MALToma, MALT type lymphoma, Extranodal marginal zone B-cell lymphoma of MALT type in the REAL classification. The incidence is 1 per 30,000-80,000 in US. Normal stomach does not contain significant lymphoid tissue [71]. H. pylori infection leads to T cell activation and B cell proliferation ultimately leading to the formation of lymphoid follicles. Various studies have demonstrated this association of H. pylori infection with MALT lymphoma [72,73]. 5-10% of gastric MALT lymphoma is H. pylori negative. The MALT lymphoma undergoes remission upon H. pylori treatment [74,75,76,77,78,79,80].

Gastric adenocarcinomas are of two types: Intestinal (well-differentiated, preserved intercellular adhesion molecules) and diffuse (undifferentiated, lack of adhesion molecules allows the tumor cells to invade adjacent structures) types. H. pylori is associated with the intestinal type while the diffuse gastric adenocarcinoma is more inherited. The intestinal type is more commonly seen in

high risk groups exposed to environmental factors such as diet, smoking or alcohol. Newer gene expression studies have classified gastric adenocarcinomas into intestinal (G-INT) and diffuse (G-DIF). Kaplan-Meier curves indicate better prognosis for G-INT when compared to G-DIF type with rapid disease progression and metastasis. Actually, H. pylori infection is associated both with intestinal type and diffuse type gastric adenocarcinoma, although in the diffuse type it is very important the genetic characteristics of the host.

The possibility of the development of gastric neoplasm depends on bacterial, genetic and environmental factors with a complex web of interplay of these factors. Animal models have demonstrated the association of H. pylori infection with gastric adenocarcinomas [81]. Also, human studies reveal the same association [82,83,84]. Gastric cancers develop only in 0.1 to 4% of H. pylori infected individuals. The IARC estimates that 36% and 47% of all gastric cancers in developed and developing countries are solely due to H. pylori infection. This adds up to an annual 350,000 gastric cancer cases worldwide.

The incidence of gastric cancer is about 1.5 to 3 times more common in the same family [85]. However studies have indicated that family history and H. pylori infection (despite the fact that H. pylori infection may cluster in the same family) are two independent risk factors for the development of gastric cancers [86].

The exact pathogenesis of H. pylori causing gastric cancer is not fully understood. However, it has been observed that the source of gastric cancer is from the bone marrow derived cells differentiating in the gastric epithelial cells in the presence of H. pylori and not from the gastric epithelial cells themselves [87]. Other hypothesis for the development of gastric cancer include neutrophil activation (CD11a/CD18-neutrophils and CD11b/CD18-neutrophils induced by ICAM-1), hypochlorhydria and ascorbic acid hypothesis [88]. IL-1 beta polymorphism and apoptosis pathways (following severe DNA damage).

Gastric cancer is inversely related to H. pylori duodenal ulcers. The incidence ratio of 0.6 in duodenal ulcer groups when compared to 1.8 in the gastric ulcer group [89].
The incidence of gastric cancer should decrease with the disappearance of H. pylori infection

particularly with the CagA-PAI complex (especially in high risk populations) [90]
Various factors in cancer development with H. pylori [91,92] include genetics, life style including diet and higher HbA1c. The presence of CagA-PAI is the most important bacterial factor. Cytokine polymorphisms (IL-1β, TNF-α), Diet (High salt and Nitrates, low fiber diet), Increased serum Gastrin and low Somatostatin (leading to Achlorhydria), Smoking and Alcohol consumption have been implicated. Higher HbA1c levels along with H. pylori infection is associated with higher incidence of gastric cancer [93].

Principal eradication treatments

Various H. pylori treatment options are available and have been suggested. These in general include the Triple therapy, Quadruple therapy and the Sequential therapy [Table 2].
Triple therapy should be used in areas where the Clarithromycin resistance is low (<15%). Initial therapy [52],[54] according to ACG First line of treatment includes:

- Patients **not** allergic to penicillin and who have not in the past received a macrolide: Lansoprazole 30 mg twice or Omeprazole 20 mg twice or Pantoprazole 40 mg twice or Rabeprazole 20 mg twice or esomeprazole 40 mg once daily plus clarithromycin 500 mg twice daily, and amoxicillin 1000 mg twice daily for 7-14 days. Eradication rates of 70 to 85 percent.

- Patients who are allergic to penicillin, and who have not in the past received a macrolide: Metronidazole 500 mg twice daily is replaced instead of Amoxicillin. Eradication rates of 70 to 85 percent.

Longer duration of therapy (14 days instead of 7 days) have shown a 5% increase of eradication rates [94].

Quadruple therapy is generally used in areas where the Clarithromycin or Metronidazole resistance is high (>15%) [95]. Bismuth subsalicylate 525 mg four times daily, metronidazole 250 mg four times daily, tetracycline 500 mg four times daily, Lansoprazole 30 mg twice or

Omeprazole 20 mg twice or Pantoprazole 40 mg twice or Rabeprazole 20 mg twice or esomeprazole 40 mg once daily. Doxycycline 100 mg twice daily could be replaced for Tetracycline [96]. Eradication rates of 75 to 90 percent [97]. LAC regimen: Lansoprazole, Amoxycycline and Clarithromycin- The eradication rate of 73.3. LOAD 7 and 10: Levofloxacin 500 mg daily, Omeprazole 40 mg daily, Nitazoxanide 500 mg twice daily and Doxycycline 100 mg daily for 7 or 10 days. Eradication rate of LOAD 7 was 88.9% while for LOAD 10 was 90% [98].

Sequential therapy includes proton pump inhibitors twice daily and Amoxicillin 1 g twice daily for 5 days followed by PPI twice daily and Clarithromycin 500 mg twice daily and Tinidazole/Metronidazole 500 mg twice daily for 5 days. Total of a 10 day treatment duration. Patients allergic to Penicillin or in areas with Clarithromycin resistance is high: Levofloxacin 250mg twice daily could be used [99]. Levofloxacin may be more cost effective than Clarithromycin.

Approximately 20% of patients fail H. pylori eradication on the first attempt [100]. Usually individuals who fail initial therapy are treated with Triple or Quadruple therapy for 14 days duration [101]. Antibiotics tried previously should be avoided. Sometimes a simpler regimen works better than twice daily quadruple regimen. Simpler regimen enhances compliance. Various combinations using other antibiotics have been used. These include Moxifloxacin, Levofloxacin [102,103] or Rifabutin [104,105].

H. pylori is naturally resistant to various antibiotics- including Vancomycin, Trimethoprim and sulfonamides [106]. H. pylori resistance may differ from region. Clarithromycin resistance is due to point mutations in A2143G, A2142G and A2143C. The resistance is highest in the mid-Atlantic and northeastern regions of the USA. Higher resistance rates of Metronidazole are observed in developing countries (up to 90%) secondary to use as anti-protozoal especially in females for gynecological issues. Tetracycline resistance is rare at approximately 2%. Macrolides resistance rates globally are as high as 20%. The resistance in USA is 10-15%. *In vitro* resistance equals *in vivo* resistance. The resistance is chromosomally mediated via point mutations A2142G and A2143G. The Amoxicillin resistance rate is low at approximately 1%. Also the MIC value required is low. However Penicillin allergy is the major concern. Resistance to Levofloxacin is as

high as 10%. The resistance is rising particularly in Asians and in other developing nations [107,108]. Nitazoxanide has potent *in vitro* activity against HP including metronidazole resistant strains [109]. H. pylori resistance HARP data base in USA indicates varied resistance rates to various antibiotics used so far. The resistance rates are as follows: Metronidazole 25% to 50%, Clarithromycin 12% to 30%, Amoxicillin 1% to 2%, Single antimicrobial resistance 55% while multiple drug resistance 40%.

Increasing drug resistance due to use of similar antibiotics for other medical conditions.
Problems with patient compliance (QID dosing, poor tolerability) are contributing factors to consider. Routine culture and testing for resistance and antibiotic sensitivity is not recommended but in patients who are refractory to therapy may be necessary as the incidence of resistance is high. Although 50% of patients report side events and approximately 10% discontinue therapy due to side events. Probiotic *Saccharomyces boulardii* administered along with triple therapy increases eradication rates (RR of 1.13) and decreases the adverse events (RR of 0.46). [110]
H. pylori is antigenic and hence a vaccine should be possible. However H. pylori can sometimes evade the immune response and the question of an effective vaccine becomes doubtful [111]. Immunization with crude sonicates of bacteria, [112], recombinant subunits of urease [113] and catalase [114] have shown to be safe and protect experimental animals from H. pylori exposure. Various trials (including human trials) for H. pylori vaccination have undergone clinical testing in various phases [115,116]. Lately the studies on vaccinations have broadened to the area of therapeutic immunizations [117].

Screening of H. pylori is debatable. The cost of screening and treating all patients worldwide would be a challenge. A recent article in Lancet demonstrated that selectively screening for H. pylori in American Japanese American population greater than 50 years of age was more cost effective than breast cancer treatment [118] Insufficient data exists to suggest screening in asymptomatic individuals for H. pylori to prevent gastric cancers. However, the decision to screen could be individualized by the clinicians based on associated risk factors.
Stool antigen is checked after 4 to 6 weeks of completion of treatment to assess for reinfection and again after a year. The reinfection rates are usually low. In adults it is less than 2 percent of persons per year [119,120].

The reinfection rates may be higher in children from developing countries with a low socioeconomic status and poor living conditions. The reinfection rates have been observed to be higher in dental technicians as compared to any other health care workers [121].
H. pylori can transform into its coccoid forms when exposed to strenuous conditions of nutrient depletion or when cultured in hostile media containing growth inhibitors such as bismuth, proton pump Inhibitors or antibiotics. These coccoid forms could survive for several years in river waters and could be further responsible for disease transmission and re-infection. The coccoid forms are the dormant phase and is resistant to antibiotics.

Conclusion

H. pylori is major cause of PUD and it should be eradicated in all patients testing positive. This complies with the non-invasive test and treat strategy for relatively young patients with no alarm features. H. pylori, a carcinogen also contributes to development of gastric cancer and MALT. Eradication rates vary between different therapies and geographical considerations should be taken into account. Triple therapy, quadruple therapy and sequential therapy are the options which could be used. Following therapy eradication testing should be opted for while continued symptomatic patients would require further investigations including esophagogastroduodenoscopy (to aid diagnosis) and proton pump inhibitors (for symptomatic relief). Screening and its autoimmune properties are debatable while a vaccination and newer therapies are on the horizon for the bacterium that has persisted for more than 58,000 years and infects half of our population.

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Figure 1 Pathophysiology of H.pylori on gastric mucosa (39)

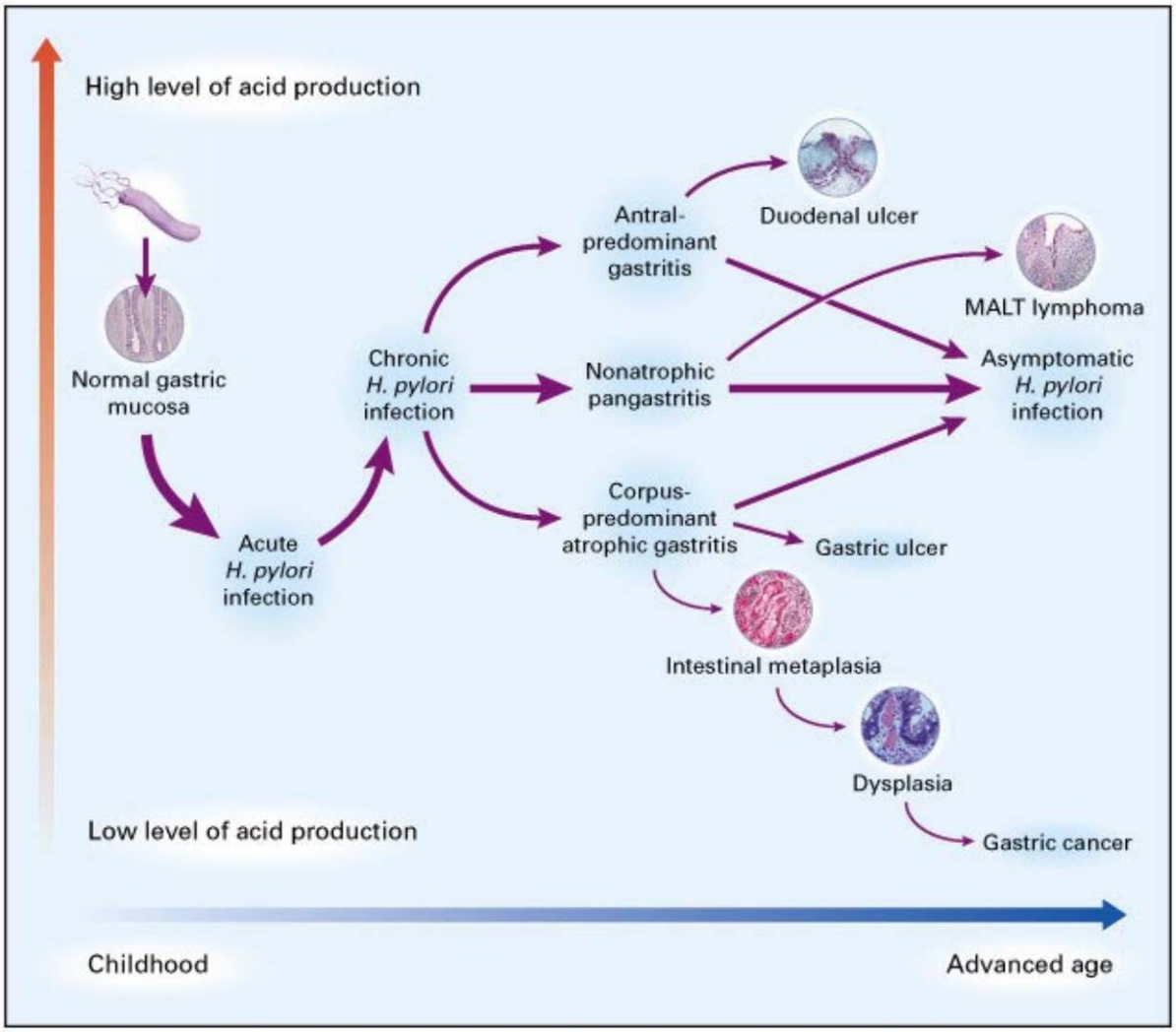

Table 1. Effects of H.pylorieradictionon antraland corpus gastritis, with or without competent esophaogastricjunction, hiatal hernia or acid clearance

	H pylori positive with GERD (incompetent EGJ, hiatal hernia, poor acid clearance)		**H pylori positive without GERD (normal EGJ, no hiatal hernia, good acid clearance)**	
	ANTRAL PREDOMINANT GASTRITIS	**CORPUS (FUNDUS) PREDOMINATE GASTRITIS**	**ANTRAL PREDOMINANT GASTRITIS**	**CORPUS (FUNDUS) PREDOMINATE GASTRITIS**
Acid secretion	Normal or increased	Normal or decreased	Normal or increased	Normal or decreased
DU risk	10% lifetime risk	----------	10% lifetime risk	----------
Gastric CA risk	----------	2-3 times increased risk	----------	2-3 times increased risk
Effect of H. pylori eradication	GERD may improve ↓DU recurrence	GERD worsens ↓ PPi efficacy ↓ risk of Gastric CA	GERD should not develop ↓DU recurrence	May unmask subclinical GERD ↓ PPi efficacy ↓ risk of Gastric CA

Table 2. First-Line Regimens for *Helicobacter pylori* Eradication

Regimen	**Duration**	**Eradication Rates**	**Comments**
Standard dose PPI b.i.d. (esomeprazole is q.d.), clarithromycin 500 mg b.i.d., amoxicillin 1,000 mg b.i.d.	10–14	70–85%	Consider in nonpenicillin allergic patients who have not previously received a macrolide
Standard dose PPI b.i.d., clarithromycin 500 mg b.i.d. metronidazole 500 mg b.i.d.	10–14	70–85%	Consider in penicillin allergic patients who have not previously received a macrolide or are unable to tolerate bismuth quadruple therapy
Bismuth subsalicylate 525 mg p.o. q.i.d. metronidazole 250 mg p.o. q.i.d., tetracycline 500 mg p.o. q.i.d., ranitidine 150 mg p.o. b.i.d. or standard dose PPI q.d. to b.i.d.	10–14	75–90%	Consider in penicillin allergic patients
PPI + amoxicillin 1 g b.i.d. followed by:	5	>90%	Requires validation in North America
PPI, clarithromycin 500 mg, tinidazole 500 mg b.i.d.	5		

PPI = proton pump inhibitor; pcn = penicillin; p.o. = orally; q.d. = daily; b.i.d. = twice daily; t.i.d. = three times daily; q.i.d. = four times daily.

*Standard dosages for PPIs are as follows: lansoprazole 30 mg p.o., omeprazole 20 mg p.o., pantoprazole 40 mg p.o., rabeprazole 20 mg p.o., esomeprazole 40 mg p.o.

Note: the above recommended treatments are not all FDA approved. The FDA approved regimens are as follows:

1. Bismuth 525 mg q.i.d. + metronidazole 250 mg q.i.d. + tetracycline 500 mg q.i.d. × 2 wk + H2RA as directed × 4 wk.
2. Lansoprazole 30 mg b.i.d. + clarithromycin 500 mg b.i.d. + amoxicillin 1 g b.i.d. × 10 days.
3. Omeprazole 20 mg b.i.d. + clarithromycin 500 mg b.i.d. + amoxicillin 1 g b.i.d. × 10 days.
4. esomeprazole 40 mg q.d. + clarithromycin 500 mg b.i.d. + amoxicillin 1 g b.i.d. × 10 days.
5. Rabeprazole 20 mg b.i.d. + clarithromycin 500 mg b.i.d. + amoxicillin 1 g b.i.d. × 7 days.

CONFLICT OF INTEREST STATEMENT

Dated: August 27th 2014

We are pleased to submit a review article titled "Helicobacter pylori infection: An overview".

All the three authors P. Patrick Basu, MD, MRCP, FACG, AGAF, Niraj James Shah, MD and Mark M Aloysius, MD, MRCS (Ed), PhD have contributed to the review article and none have any conflict of interest.

Guarantor of the article: P. Patrick Basu, MD, MRCP, FACG, AGAF

Specific author contributions:

P Patrick Basu; manuscript preparation

Niraj James Shah; manuscript preparation and background research

Mark M Aloysius; manuscript preparation

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Sincerely,

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