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Association of gastritis and peptic ulcers with *Helicobacter pylori* and their symptoms and cure

Varsha and Girish Chandra Pandey

Abstract
Gastritis is the inflammation in the gastric mucosa of stomach and untreated gastritis developed into ulcers. Main cause of Gastritis and peptic ulcers are *Helicobacter pylori* bacterium and others cause like stress, smoking and diet. Helicobacter pylori are a micro aerophilic and gram negative bacteria found in the upper gastrointestinal tract. Helicobacter pylori produce urease enzyme, urease use urea as a substrate and convert urea into ammonia and bicarbonate ions, these are basic in nature and protect bacteria from acid produce in the stomach. Gastritis is identified by greater number of uninuclear cells, predominantly lymphocytes, plasma cells and macrophages. For diagnosis various test are used like urea breath test, stool antigen test, serology etc. For treatments various antibiotics like Amoxicillin, Clarithromycin are used. In some countries dual, triple and quadruple therapies are used.

Keywords: Association, gastritis, peptic ulcers, *Helicobacter pylori*

Introduction
Gastritis is the inflammation in the gastric mucosa. The term gastritis was given by German Physician, Georg Ernst Stahl in 1728 to describe the general inflammation in the gastric mucosa of stomach. Untreated gastritis can develop into ulcers. Ulcers are the deep sores in the stomach lining. Gastritis only affects the stomach and ulcers can develop in the intestine, stomach & oesophagus or food pipe.
The stomach has a mucous layer which protects stomach from acid. *Helicobacter pylori* bacterium attack on mucous lining of stomach and damage the lining of stomach and leaves to expose the part of stomach to acid. Both bacteria and acid irritate the stomach lining and causes ulcers, gastritis and stomach cancer. Peptic ulcers are of two types: Gastric ulcers: Sores developed in the stomach lining. Duodenal ulcers: Sores develop in mucosa of the upper part of the small intestine.
Gastritis is of two types acute or chronic: Acute gastritis: Acute gastritis start suddenly and last for a short time period. Chronic gastritis: Chronic gastritis is long lasting diseaese. Gastritis is of two types be erosive or non-erosive**:** -Erosive gastritis: Erosive gastritis cause inflammation in the inner lining of the stomach, and causes erosions, shallow breaks in the stomach lining or ulcers. Non- erosive gastritis: Non- erosive gastritis cause only inflammation in the stomach lining, not causes formation of erosions or ulcers. Chronic stomach inflammation can develop in the stomach cancer.

Aetiology of gastritis or peptic ulcers: Aetiology of peptic and gastritis diseases is multifactorial.
Helicobacter pylori bacterium is the main cause of gastritis and ulcers, stress, Smoking, alcohol, cocaine and diet, injury or death of mucus producing cells, hypercalcemia, due to Hypercalcemia the volume, Acidity and pepsin content of gastric secretion increase, the chances of developing of ulcers are more in the offspring's if their parents are affected, during childhood some factors such as socioeconomic status, environmental factors, household density, cooking habits etc. are responsible to get the *Helicobacter pylori* infection during childhood. J. Robin Warren and Barry J. Marshall discovered the *H. pylori* bacteria in 1982. Both scientists cultured the bacteria from inner lining of human stomach and show the association with gastric inflammation. They both are awarded by noble prize in 2005 for the discovery of bacteria and they also explain that how bacteria cause gastritis and ulcers.
It is a gram- negative bacterium, shape of bacteria is spiral, catalase-positive motile bacteria & microaerophilic bacteria, size is 2um, and multiple flagella present. Microaerophilic bacteria require a reduced oxygen concentration for growth. Microaerophilic bacteria are aero tolerant anaerobes. Due to spiral shape of bacteria and presence of flagella, bacteria are able to penetrate the mucus layer of the stomach and can either be found in the gastric mucosa or

can found attached to epithelial cells. *H. pylori* bacteria found in the inner lining of the stomach and previously it is known as *Campylobacter pylori.* Greater than fifty percentage of the global population *H. pylori* infection found in the upper gastrointestinal tracts. In developing nation's majority of children are infected before the age of 10 and in adult infection is more than 80% before age 50. In children the evidence of infection is very rare in developed countries but it become more common during adulthood. *Helicobacter pylori* has copious amount of urease enzyme. All the gastric *Helicobacters* colonize and increase their number into the stomach of animals like monkey, cat, dog, tiger etc.
Adhesins are produced by *Helicobacter pylori* bacteria which bind to the lipids which are associated with the membrane and carbohydrates and helps in adhesion to the epithelial cells. Urease enzyme breaks down urea (NH_2CONH_2) into ammonia and bicarbonate ions.

Defence mechanism of *Helicobacter pylori:* Once *Helicobacter pylori* are located in the mucus, it is able to fight with acid produce in stomach with the help of an enzyme. Urease converts urea (urea is supply in stomach from gastric juices and saliva) into bicarbonate ion and ammonia, they both are strong bases. These forms a cloud of acid neutralizing chemicals around the *Helicobacter pylori* bacteria and these chemicals protecting it from the acid in the stomach.

Transmission of *Helicobacter pylori*: *Helicobacter pylori* transmit from one individual to another individual via fecal to oral route, oral to oral route, by contaminated water and food.

Reservoirs of *Helicobacter pylori*: Main reservoir of *H. Pylori* are humans' stomach's, and others are cats, dogs and primates.

Virulence factors: These bacteria have an incredible amount of virulence factors, like urease, catalase, and cytotoxin associated gene, adhesin, acid inhibitory protein, flagella, cytotoxin and mucinase.

Symptoms: Pain in the chest or upper abdomen, sharp or sudden pain, Indigestion, heartburn, nausea, passing excessive amount of gas, vomiting, Blood in vomiting and in fecael material, weakness, paleness and black stools, poor appetite, weight loss, fatigue, perforation (hole in the stomach wall), Stomach cancer, Gastrointestinal bleeding.

Diagnosis: Endoscope, blood test, urea breath test, stool & tissue test.

Medications used for treatment of ulcers and gastritis
Antibiotics like Clarithromycin (Biaxin), Amoxicillin or Metronidazole, proton pump, acid blockers/ histamine (H2) blockers like Ranitidine, Famotidine, Nizatidine and Cimetidine. Antacids like magnesium hydroxides, Aluminium hydroxides, H_2 receptors antagonists like Ranitidine, cimetidine are widely used to treat ulcers and gastritis.

Gastritis
Gastritis is the inflammation in the gastric mucosa of the stomach. Acute infection leads to development of hypochlorhydria and neutrophilic infiltration on (Kuiper's *et al.* 2004) gastric biopsy. Majority of severe gastritis develops into long lasting gastritis.
Gastric mucosa of healthy person constitutes some dispersed uninuclear cells. Lymphoid follicles and polymorph mononuclear granulocytes mainly absent in gastric mucosa. When an individual infected with *Helicobacter pylori* the histological picture of mucosal layer changes immediately and in chronic gastritis histology of tissue is completely changes such as increases the number of mononuclear cells, more number of lymphocytes, plasma cells number also gets increases and macrophages, lymphoid follicles with germinal centre are mainly increases(Fox *et al*. 1989; Rosh *et al.* 1992; Genta *et al.* 1994). Other histopathological feature due to *Helicobacter pylori* infection is thinning of the gastric mucosa and formation of erosions in the epithelial tissue. *Helicobacter pylori* infection mainly occurs during childhood and if it is persisting for longer period chronic disorder occur.

Peptic ulcer disease: The risk of peptic ulcer depends on the extent of inflammation that is occurring due to colonization of *Helicobacter pylori* strain in the stomach. Mainly risk of peptic ulcer is higher in those individuals who are infecting by a strain which is producing the vacuolating cytotoxinor protein i.e. Cag protein. Duodenal mucosa secretes bicarbonate ions in response to acid exposure is also a factor which induce peptic ulceration. Due to Helicobacter *pylori* infection ulcers developed in the stomach and in the duodenum (Hussein NR, 2010). Large numbers of peoples are infected by *Helicobacter pylori*, for the treatment of this bacterial infection eradication therapy are used for several weeks (Wong *et al.* 2013).
According to Goh *et al*. studies about 95% of ulcers are treated within 6 weeks without the use of additional antisecretory therapies. *Helicobacter pylori* eradication inhibits bleeding and perforation.

Effect of Antral predominant gastritis on the production of acid & gastrin:
Antral predominant gastritis occurs due to *Helicobacter pylori* infection and due to infection hypersecretion of acid takes place and this is linked to the duodenal ulcers (Dixon,1991).Individuals with antral predominant non-atrophic gastritis, hypersecretion of acid takes place dueto the *Helicobacter pylori* gastritis, and this stimulates the release of more amount of gastrin hormone which spreads and activates the body of the stomach for the production of acid (El-Omar *et al.* 1993; El-Omar *et al.*1995).Hormone gastrin produced by the antral mucosa and the increased gastrin predominantly affecting antral mucosa. The level of Gastrin-17 is increases due to eating and hypergastrinemia condition arises due to more level of gastrin-17 hormone.

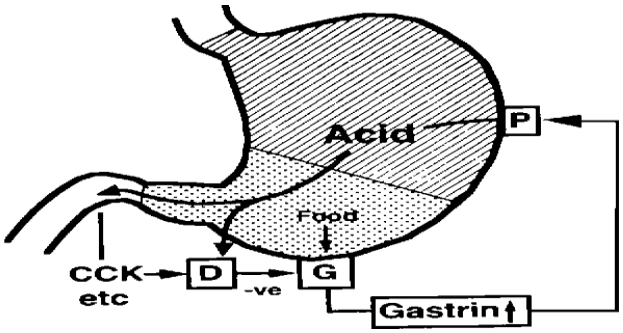

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Fig 1: Physilogical regulation of gastrin release by antral nucosa. CCK = chole- stokinin, P = parietal ell, D somatosatain producing cell G = astrin producing cell

Helicobacter pylori associated antral gastritis causes hypergastrinemia. The release of gastrin hormone by the antral mucosa is under physiological inhibitory control in order to control secretion of gastric acid. When antral luminal pH decreases (below 3), Gastrin release is suppressed. Cholecystokinin and other enterogastrones released from the small intestine exert an inhibitory control on release of gastrin hormone. Gastric acid and cholecystokinin inhibit the release of gastrin hormone and it is mediated by the somatostatin hormone, which is released by the D- cells within the mucosa of antrum. The D-cells lies near to the G cells and they release somatostatin and it exerts the paracrine inhibitory control on the production and release of the gastrin hormone. Some studies determined that the deficiency of antral somatostatin produced more amount of gastrin hormone. (Graham *et al.* 1993; Kaneko *et al.* 1992; Moss *et al.* 1992; Queiroz *et al.*1993; Sumii *et al.* 1994;) [22, 30].

Effects of body gastritis on production of acid: In some individuals, *Helicobacter pylori* also effect the mucosa layer of body. Reduction of gastric acid production takes place in those individuals which having body gastritis orachlorhydria (Yasunaga *et al.* 1994; El-Omar *et al.* 1997) [62]. *Helicobacter pylori* eradication decreases acid production. Body-predominant gastritis impairs parietal cell function and produces Hypochlorhydria and increased risk of gastric cancer. Bacterial strain plays important role in causing gastritis. Cag $^{+}$ strains are more virulent and the risk of development of ulcers in the duodenum and gastric cancer are more in those individuals in which the Cag^{+} strains are found. Cag^{+} strain rises the risk of duodenal ulcerslinked with body gastritis. *Helicobacter pylori* infection causing a condition i.e. hypochlorhydria in those individuals who are suffering from body gastritis. Di*et al*.so plays an important role. More salt intake increases the risk of gastric cancer.

D.U: duodenal ulcer Gastric
Ca: gastric cancer

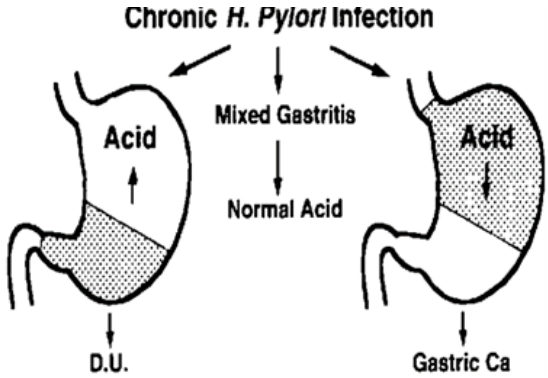

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Fig 2: Showing different response of *H. pylori* infection and showing the factors which affecting their response.

Role of *Helicobacter pylori* in acid hypersecretion in the pathophysiology of duodenal ulcer diseases: Due to more acid secretion duodenal acid load increased (Hamlet and Olbe, 1996) [24]. *Helicobacter pylori* infection decreases the production of bicarbonate ions in the duodenum and this bicarbonate ion will decreases the resistance of bacteria from increased level of acid in the stomach (Hogan *et al.* 1996) [27]. Due to more acid, damage of duodenal mucosa occurs and formation of gastric metaplasia with in duodenum takes place (Khulusi *et al.* 1996) [31].

Helicobacter pylori are able to colonise in duodenum due to presence of similar mucosal layer which is present in the stomach. Due to damage of duodenal mucosa, ulceration develops.

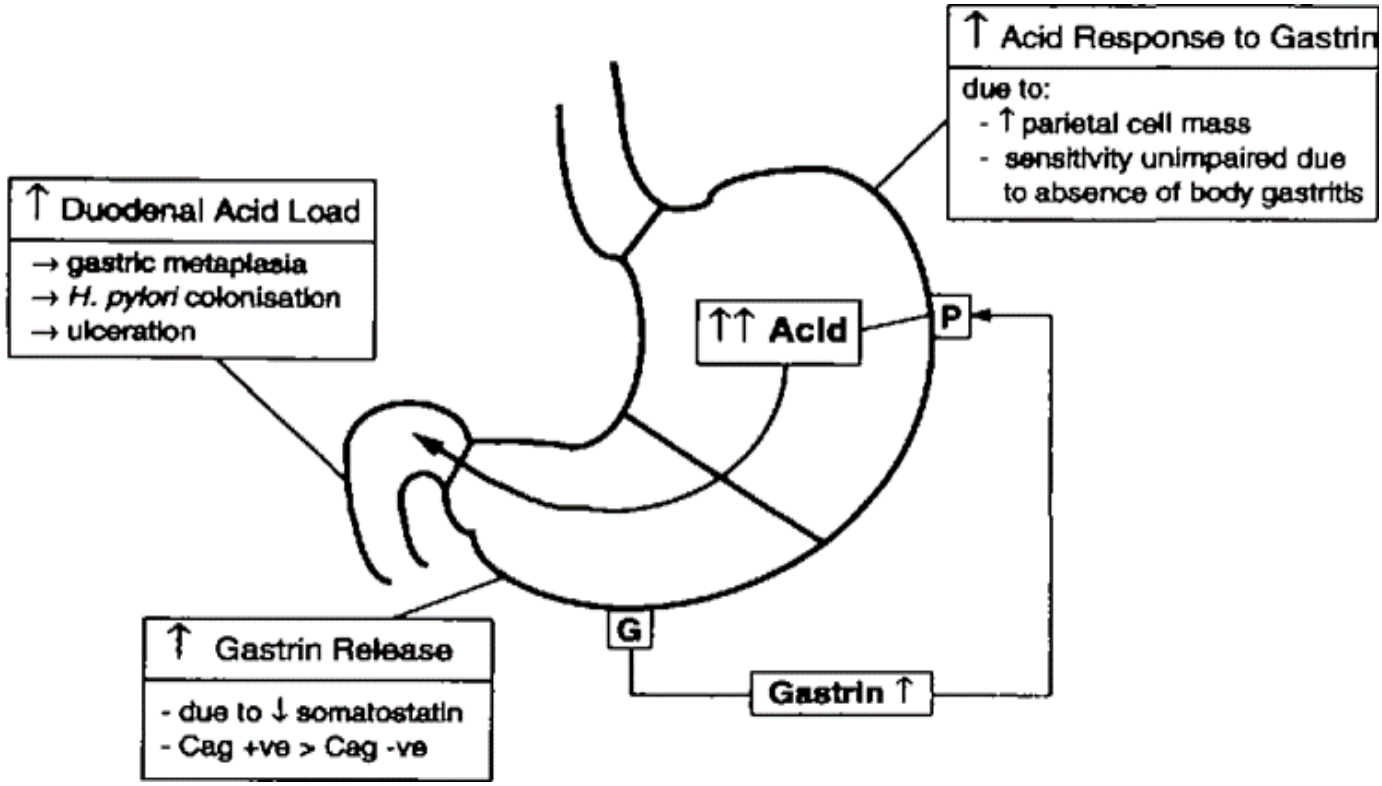

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Fig 3: Sequence of events by which H. pyloro-infection of natural mucosa leads to duodenal in some subjects. F= fastrin producing cell, P = parietral cell

Species	Primary mammalian host	Pathology	Animal model
Gastric *Helicobacter* spp.			
H. pylori	Human, primate	Gastritis, peptic ulcer disease, gastric adenocarcinoma, MALT lymphoma	Mouse, Mongolian gerbil, guinea pig, gnotobiotic piglet
H. felis	Cat, dog, mouse	Gastritis in natural host; may cause peptic ulcers or gastric adenocarcinoma in mouse	Mouse
H. mustelae	Ferret	Gastritis, peptic ulcer disease, gastric adenocarcinoma, MALT lymphoma	None
H. acinonychis	Cheetah, tiger, other big cats	Gastritis, peptic ulcer disease	Mouse
H. heilmannii	Human, dog, cat, monkey, cheetah, rat	Gastritis, dyspeptic symptoms, MALT lymphoma	Mouse
Enterohepatic *Helicobacter* spp.			
H. hepaticus	Mouse, other rodents	Proliferative typhlocolitis, hepatitis, hepatocellular carcinoma	None

***Source*:** https://d3i71xaburhd42.cloudfront.net/23c53c0d3514422b5da9b0abee211b37ebeb76e4/3-Table1-1.png

Morphology: It is a gram -negative bacteria, helical shaped & it consists flagella. It is a microaerophilic bacterium. *Helicobacter pylori* bacterium is 2.5 - 5.0 um long and 0.5 - 1.0 um wide and 4 - 6 unipolar sheathed flagella(O'Toole *et al.*2000), which play role in movement of bacterium. Evolution of several mechanism takes place in bacteria to increase their survivability rate in the acidic environment of stomach and their capacity of causing infection also increases.

Cell envelope, outer membrane and lipopolysaccharide: *Helicobacter pylori* bacteria cell envelope composition is similar to gram positive bacteria. This bacterium consists outer & inner membrane, peptidoglycan layer. *Helicobacter pylori* outer membrane phospholipid moiety consists of cholesterol glucosides (Gisbert *et al.* 2004; Bukholm *et al.* 2004; Tannaes *et al.* 2005). During clinical isolation, *Helicobacter pylori* produce high molecular weight LPS(smooth) with an O-antigen but during *in vivo* condition the bacteria may convert to rough LPS variants, rough LPS lacks the O-side chain (Walsh *et al.* 1997., Moran *et al.* 2002). The O- side chain may be fucosylated and imitate Lewis blood group antigen, promoting molecular mimicry of host antigen and associated immune evasion (Appelmelk *et al.* 1997) [3]. *Helicobacter pylori* LPS shows phase variation through length variation of poly (C) tracts in the gene which encodes α-1,3 fructosyltransferases and repeats of poly (C) tracts and poly (TAA) in the gene which encodes for α-1,2 fucosyltransferase (Wang *et al.* 2001). The phase variation in LPS provide heterogenecity to the population and due to this *Helicobacter pylori* adapt itself in the varying environment of stomach (Tannaes *et al.* 2001; Tannaes *et al.* 2005; Moran *et al.* 2002).

Genome and plasmid: genome size of *Helicobacter pylori* is from 1.6 -1.73 mbP (Tomb *et al.* 1997; Marais *et al.* 1999; Doig *et al.* 1999; Berg *et al.* 1997; de Jonge *et al.* 2004).*Helicobacter pylori* contain plasmid. Size of plasmid is 1.5-23.3 kb but virulence factors are not present in the plasmid.

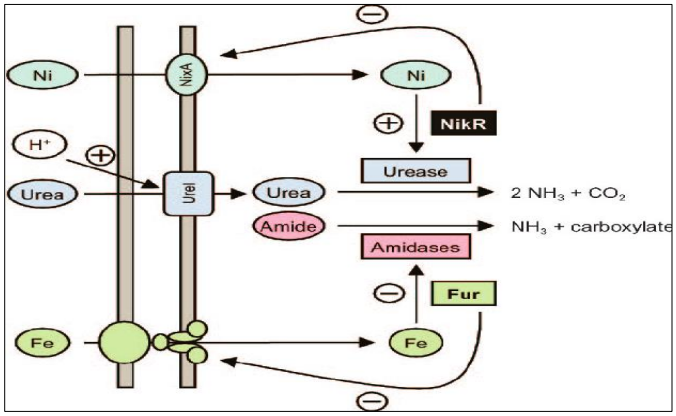
Metabolism: *Helicobacter pylori* has narrow host rangebut the duration of infection is long lasting. Several biosynthetic pathways are absent in *Helicobacter pylori* which are responsible for survivability of bacteria. Biosynthetic pathways for amino acids production are absent in *Helicobacter pylori*. Genomic and biochemical information both are showing that *Helicobacter pylori* only catabolize sugar, other sugar cannot be catabolize by *Helicobacter pylori* (Berg *et al.* 1997; Nedenskov, P., 1994)

Respiration and oxidative stress defence: It is microaerophilic bacteria, it not able to survive in more oxygen concentration, but required only two percent of oxygen because oxygen used as terminal electron receptors in bacteria (Mendz *et al.* 1997). *Helicobacter pylori* not able to utilize another electron acceptor, like Nitrate or Formate (Smith *et al.* 1995).In human hosts, due to active immune response oxidative stress arises. To overcome from this condition, *Helicobacter pylori* expresses several components which are stress resistance like superoxide dismutase (Seyler *et al.* 2001; Ernst *et al.* 2005; Barnard *et al.* 2004) and the peroxide stress defence(Harris *et al.* 2003; Olczak *et al.* 2003).

Nitrogen metabolism: Two major source of nitrogen is ammonia and urea in the gastric environmental. Ammonia is an Acid resistant component and it is a main component of nitrogen metabolism (Stingl *et al.* 2000). Urease enzyme produced ammonia from urea and in urease enzyme Nickel is present that have 12 UreA and 12 UreB subunits. Both subunits are coded by the UreA and UreB gene (Sung *et al.* 2001). Urease gene cluster in *Helicobacter pylori* also contains UreAB genes which are coding the UreIEFGH proteins.

UreIEFGH protein function is assembly of subunit and it helps the Nickel to incorporate in the active sites of urease enzyme (Cussac *et al.* 1992; Mobley *et al.* 1995) [8]. In *Helicobacter pylori*, transcription of urease gene cluster takes place from 2 promoters, 1 is the upstream of the UreA gene & other is in the intergenic region (Akada *et al.* 2000) between UreB and UreI (P ureI).

For the urease activity urea is required because urea acts as substrate. Ure1 is the H^+ gated urea channel which helps in Transportation of urea in the cell. Surplus amount of ammonia is removed by an enzyme i.e. Glutamate synthetase enzyme.



***Source*:**https://www.researchgate.net/profile/Johannes_Kusters/publication/6938890/figure/fig1/AS:277827069988864@1443250543020/Schematic-representation-of-the-relationships-between-acid-resistance-urease-activity.png

Metal metabolism: Metal are very essential for metabolism in all organism. Several metals acts as cofactor of enzymes; catalyse basic function such as electron transport chain, redox reaction and they are very important to maintain the osmotic pressure of the cell.

Nickel: Nickel is the cofactor of urease and hydrogenase and these enzymes are essential colonization factors. Some nickel transporter identified in *Helicobacter pylori*. The NixA protein (HP1077) is located in the cytoplasmic membrane and it is 37KDa protein and this protein have high affinity for Nickel (Mobley *et al.* 1995; Fulkerson *et al.* 1998).Second nickel transporter system encoded by the abcCD locus (Hendricks *et al.* 1997). Third transporter system is Dpp dipeptide permease.

Iron: In gastric mucosa main source of iron are lactoferrin, heme compounds released from damage tissue. *Helicobacter pylori* genome encodes 11 proteins which play role in iron transportation (van Vliet *et al.* 2001; Tomb *et al.* 1997; Alm *et al.* 1999) [56, 2]. In acidic, microaerobic gastric environment, it was thought that ferrous iron (Fe^{2+}) is the main form of free iron and this is transported via the (Worst *et al.* 1998) FeoB protein (HP0687) by *Helicobacter pylori*. Helicobacter pylori have free ferric reductase activity. This enzyme convertsFe^{3+} to Fe^{2+}& it is transported by the FeoB system.

Copper: Copper play an important role in the formation of (Rensing *et al.* 2003) [49] reactive oxygen species (ROS). *Helicobacter pylori* have various proteins which involved in copper export like CopA (HP1073) and $CopA_2$ (HP1503), p-type ATPase and crdA (HP1365) copper resistant determinant. CopP acts as copper Chaperones (Megraud and F., 1995; Taylor *et al.* 1996; Beier *et al.* 1997; Bayle *et al.* 1998) [20].

Prevalence and geographical distribution: Prevalence of *Helicobacter pylori* shows large geographical variations. More than eighty percent of the population is infected by *Helicobacter pylori* in developing countries, even at young ages (Rothenbacher *et al.* 2004) [47]. In western countries, the popularity of *Helicobacter pylori* infection is more. The infection rate of *Helicobacter pylori* rapidly increases during first five year of life and always remains high, this indicates that the chances of bacterial infection is more during childhood. In the western world the chances of new *Helicobacter pylori* infections in the adults is less than 0.5% per year (Kuipers *et al.* 1995; Parsonnet *et al.* 1997).

Transmission of bacteria: *Helicobacter pylori* transmit from one individual to another individual via faecal to oral route, oral to oral route, by contaminated water and food**.**
During *in vivo* conditions various factors of pylori acts as both virulence and maintenance factors:

Induction of gastric inflammation: When an individual infected with *Helicobacter pylori*, the histological picture of mucosal layer changes immediately and gastritis is identified by a greater number of uninuclear cells, predominantly lymphocytes, plasma cells and macrophages, lymphoid follicles with germinal centre. *In vivo* for the survivability of *Helicobacter pylori* inflammation is playing an important role. (Blaser and M J 1996) [61].

Interleukin-8: It is a potent inflammatory mediator which activates neutrophils. *Helicobacter pylori* strain have ability to induce IL-8 secretion from gastric carcinoma cells *in vitro* (Crabtree *et al.* 1995; Huang *et al.* 1995; Sharma *et al.* 1995) [7]. Wild type strain i.e. $VacA^{+}CagA^{+}$produce more IL-8 as compare to wild type $VacA^{-}CagA^{-}$ strains (Crabtree *et al.* 1995; Sharma *et al.* 1995) [7].

Neutrophil adherence: It is a 150K-Da protein& it increases the neutrophil expression & increases association of neutrophil with endothelial cells (Hachem *et al.* 1995).

Platelet- Activating factor: It is a potent ulcerogenic agent. Under basal conditions gastric mucosal cells produced lyso-PAF (Sobhani *et al.* 1996) and it has ability to stimulate the gastric acid secretion. *Helicobacter pylori* have ability to convert Lyso-PAF (non-ulcerogenic precursor).Due to synthesis of Lyso-PAF, *Helicobacter pylori* cause mucosal injury by producing more gastric acid.

Lipopolysaccharide (LPS): Bacteria contain LPS and it cause disruption of gastric mucous layer of stomach. The interaction between mucin and its mucosal receptor is interrupt by the Lipopolysaccharide. LPS has low proinflammatory activity (Morgan and A. P.,1996; Muotiala *et al.* 1993). On the polysaccharide side chain Lewis antigen is expressed (Wirth *et al.* 1996; Appelmelk *et al.* 1996; Aspinall *et al.* 1996) [60, 61, 3] which is coherent with LPS molecules.

Urease: *Helicobacter pylori* have a very potent enzyme i.e. urease and it play an important role in inflammatory cytokine production & activation of mononuclear phagocyte (Harris *et al.* 1996). For human gastric epithelial cells urease activity is harmful (Smooth *et al.* 1990). This urease enzyme function as both colonization (maintenance) factor and a virulence factor.

Disruption of the gastric mucosal barrier: *in vitro* *Helicobacter pylori* can inhibit the mucus cell (Micots *et al.* 1993).

Phospholipase: A phospholipid rich layer found on the apical surface of the mucous cell which is harmed by the bacteria (Mauch *et al.* 1993). Phospholipases C and A2expressed by *Helicobacter pylori* bacteria they induce more changes in phospholipid layer *in vitro* conditions (Weitkamp *et al.* 1993).

The effect of phospholipase A2 and C expressed by bacteria is inhibited by bismuth salts (Ottlecz *et al.* 1993).

Mucinase: the activity of mucinase enzyme disrupts the gastric mucosal barriers if this activity expressed *in vivo* condition.

Vacuolating cytotoxin: *Helicobacter pylori* produce vacuolating cytotoxin *in vitro* (Leunk *et al.* 1988). In eukaryotic cells this vacuolating cytotoxin induces the acidic vacuoles in the cytoplasm.

Reactive oxygen species: In the living organisms body (*in vivo* conditions) *Helicobacter pylori* are able to induce the production of reactive oxygen species in gastric mucosa. There is a positive interaction between the amount of reactive oxygen species present, the infective load of *Helicobacter pylori*, and the extent of gastric mucosal injury (Davies *et al.* 1994). Ascorbic acid helps in production of reactive oxygen species in human gastric mucosa (Drake *et al.* 1996).

Inducible Nitric oxide synthase: Nitric oxide synthase cause tissue injury. *In vivo*, (Patel *et al.* 1994) bacterium stimulates the activity of nitric oxide synthase enzyme.

Apoptosis: *Helicobacter pylori* activates the programmed cell death of gastric epithelial cells (Mannick *et al.*1996; Wirth *et al.* 1997) & cause damaging of oxidative DNA in infected human gastric mucosa(Baik *et al.* 1996). Migration and proliferation of gastric epithelial cells (Ricci *et al.* 1996) prevents by *Helicobacter pylori.*

Altered gastric homeostasis: *H. Pylori* infection induced the gastrin hormone expression i.e. acid-stimulating hormone and supress the activity of Somatostatin (Calam and J., 1995) hormone i.e. acid inhibitory hormone.
*A*cid-secretory study has determined that *Helicobacter pylori* rises the acid level in duodenum under some conditions and decreases production of acid under some other conditions (Chen *et al.* 1994; Sumii *et al.* 1994).
When omeprazole is used to supress acid production, the presence of *Helicobacter pylori* in antrum and corpus is different this produce the movement of bacteria from antrum to the corpus (Logan *et al.* 1995).Some factors are helping in survivability of *Helicobacter pylori* in the stomach: -

Motility: motility is a colonization factor. Mainly, *Helicobacter pylori* has 2 – 6 polar &s heathed flagella. These flagella encode by the 2 genes i.e. flaA and flab (Josenhans *et al.* 1995; Suerbaum *et al.* 1993). These genes have been cloned and both genes are very important for motility and colonization in gnotobiotic piglets.

Urease: *Helicobacter pylori* produces urease enzyme. The molecular weight of urease is 540KDa and it is a hexameric molecule containing Nickle and urease have 2 subunits (urea [30KDa] and ureB[62KDa]) and molar ratio is 1:1 (Dunn *et al.*1991; Dunn *et al.* 1990; Mobley *et al.* 1990). In gastric lumen neutral environment is produced by the urease enzyme activity which protects the bacteria from acidic environment. On the outer membrane of *Helicobacter pylori* urease enzyme is associated.Within the cytoplasm urease activity is also determined. Divalent cations like Ca^{2+} and $Mg^{2+}$are very essential in stabilization of linkage between urease enzyme and bacterial surface (Gower *et al.* 1994) and some other cations inhibits the activity of enzyme urease. For the activity of recombinant *Helicobacter pylori* urease a high affinity (Garner *et al.* 1995) [39] Nickel transport protein (NixA) required.

Catalase and superoxide dismutase: Catalase and superoxide dismutase are linked to the surface of *Helicobacter pylori* and provides resistance from killing by polymorphonuclear leukocytes (Odenbriet *et al.* 1996; Spiegelhalder *et al.* 1993).

Heat shock protein homologs: Heat shock protein homologs of *Helicobacter pylori* are encoded by highly conserved sequence of gene. This conservation suggests that the function of protein is affected when any modification occurs in the sequence of gene. On the basis of structural similarity, Heat shock protein homologs acts as molecular chaperone for urease enzyme. Bicistronic operon has 2 parts hspA-hspB, which has been cloned and sequenced (Suerbaum *et al.* 1994). Expression of both heat shock proteins i.e.hspA and hspBwith *Helicobacter pylori* urease rises the urease enzyme activity.

P-type ATPase: It is considered that the ATPase is the main target of the bactericidal action of proton pump inhibitor,like omeprazole, (Mobely *et al.* 1995) Iansoprazole on *Helicobacter pylori*. Those mutants were viable in which this gene is absent;on the minimal inhibitory concentration of Omeprazole inactivation of ATPase gene had no effect. It is find out that the ATPase is not targetedby the bactericidal action of Omeprazole (Hiratsuka *et al.* 1995).

Siderophores (iron scavenging proteins): Iron is very important for development & metabolism of bacteria, but studies on iron acquisition in *Helicobacter pylori* had yielded adverse results. It is reported by Husson *et al*. that under the iron-limiting conditions *Helicobacter pylori* do not able to produce siderophores. Illingworth *et al*. noticed the siderophores production but not able to find the binding of lactoferrin with *Helicobacter pylori* proteins. Thus, it is not determine that how *Helicobacter pylori* obtain iron for its development& metabolism.

Symptoms of Helicobacter pylori infection: Pain in the chest or upper abdomen, indigestion, sharp and sudden pain, heartburn, nausea, vomiting, passing excessive amount of gas, blood in vomiting and in fecael material, weight loss, poor appetite, fatigue, paleness and black stools, weakness, hole in the stomach wall, stomach cancer, gastrointestinal bleeding ulcers etc.

Diagnosis

Table 1 Diagnostic tests for the detection of *H. pylori* infection (2,15-17)

Test	Sensitivity	Specificity	Advantages	Disadvantages
Noninvasive				
Serology	76-84	79-90	Widely available, inexpensive	Positive result may reflect previous rather than current infection, not useful after treatment
Urea breath test	>95	>95	High negative and positive predictive values, useful before and after treatment	False-negative results possible in the presence of PPIs or with recent use of antibiotics of bismuth preparations, considerable resources and personnel required to perform test
Stool antigen test	96	97	High negative and positive predictive values, useful before and after treatment	Process of stool collection may be distasteful to patient, false-negative results possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations
Invasive				
Histology	95	99	Excellent sensitivity and specificity, especially with special and immune stains, provides additional information about gastric mucosa	Expensive (endoscopy and histopathology costs), interobserver variability, accuracy affected by PPI and antibiotics use, requires trained personnel
Rapid urease test	90	93	Rapid results, accurate in patients not using PPIs or antibiotics, no added histopathology cost	Requires endoscopy, less accurate after treatment or in patients using PPIs
Culture	58.1	100	Specificity 100%, allows antibiotics sensitivity testing	Variable sensitivity; requires trained staff and properly equipped facilities, expensive

PPI, proton pump inhibitor; *H. pylori*, *Helicobacter pylori*.

***Source*:**http://atm.amegroups.com/article/viewFile/5094/6269/30050

Treatment: Various antibiotics like Clarithromycin (Biaxin), Amoxicillin or Metronidazole are widely used in killing the*Helicobacter pylori* bacterium. In various countries Dual therapies are used widely but it is replaced by triple therapies. From last two decades, triple therapies are used for the treatment of *Helicobacter pylori* infection (Papastergiou *et al*. 2014), triple therapies using proton pump inhibitor or ranitidine bismuth citrate, combined with 2 antibiotics such as clarithromycin and amoxicillin. Quadruple therapies is the combination of proton pump inhibitor and bismuth compounds with 2 antibiotics. Some drugs are most widely used for the *Helicobacter pylori* eradication therapy like tetracycline, amoxicillin, imidazoles and macrolides (clarithromycin, azithromycin) etc.

During the nineteen centuries, the standard triple therapy was used for the treatment of *Helicobacter pylori* infections. This bacterium is resistant to those antibiotics which are used in therapies like clarithromycin and due to this the efficacy of standard triple therapies decreases (Malfertheiner *et al*. 2002). In different countries the popularity of *H. pylori* resistance to clarithromycin varies such as sixteen percent in japan and 1.7 - 23.4% in Europe (Elitsur *et al*. 2006; Horiki *et al*. 2012; Koletzko *et al*. 2006). *H. pylori*becomes resistant to Metronidazole antibiotics which are used in the triple therapies (Malfertheiner *et al*. 2002). It is estimated that the popularity of *H. pylori* to metronidazole is seventeen percent to fourty four percent in Europe & America,respectively (Ogata *et al*.2013; De Francesco *et al*.2010). On the basis of these publications, standard triple therapies are not more used.

Future prospects for prevention of *Helicobacter pylori* associated gastroduodenal diseases: Development of new strategies for treatment of H. pylori associated gastroduodenal disease is the main research goal.

Understanding epidemiology: understanding the epidemiology, particularly transmission of bacteria, is the major improvement in the control of many infections in developing countries. According to some researchers H. pylori is transmit through feceal-oral, while other support the concept of spread via regurgitated gastric contents. Infection is appear more in childhood and it correlates with crowded living conditions. By maintain hygenicity and improvement in living conditions, will decrease the infection.

Antimicrobial therapy: *H. pylori* can be treated with antimicrobial agents. Currently for eradiction of *H. pylori* triple therapy is used. Triple therapy is 2 weeks of treatment with bismuth subcitrate, tetracyclin or amoxicillin and metronidazole. But bacteria have made themselves resistant to antibiotics used in triple therapies. complete eradication of H. pylori will be possible, when Antibiotics used in triple and quadruple therapies can be replaced by other antibiotics. The alternative in the future will be the proton pump inhibitor omeprazole and a single antibiotic, e.g: - amoxicillin or clarithromycin.

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References

1. Akada JK, Shirai M, Takeuchi H *et al*. Identification of the urease operon in *Helicobacter pylori* and its control by mRNA decay in response to pH. Mol. Microbiol. 2000; 36:1071–1084.
2. Alm RA, Ling LS, Moir DT *et al*. Genomic-sequence comparison of two unrelated isolates of the human gastric

pathogen *Helicobacterpylori*. Nature. 1999; 397:176–180.
3. Appelmelk BJ, Simoons-Smit I *et al*. Potential role of molecular mimicry between *Helicobacterpylori* lipopolysaccharide and host Lewis blood group antigens in autoimmunity. Infect. Immun. 1996; 64:2031–2040.
4. Aspinall GO, Monteiro MA. Lipopolysaccharides of A *Helicobacterpylori* strains P466 and MO19: structures of the O antigen and core oligosaccharide regions. Biochemistry. 1996; 35:2498–2504.
5. Berg DE, Hoffman PS *et al*. The *Helicobacterpylori* genome sequence: genetic factors for long life in the gastric mucosa. Trends Microbiol. 1997; 5:468–474.
6. Bruce E Dunn, Hartley Cohen, Martin J Blaser. *Helicobacterpylori*. Clinical Microbiology Reviews, 1997, 10(4).
7. Crabtree JE, Covacci A *et al*. *Helicobacterpylori* induced interleukin-8 expression in gastric epithelial cells is associated with cagA positive phenotype J Clin. Pathol. 1995; 48:41–45.
8. Cussac V, Ferrero RL *et al*. Expression of *Helicobacterpylori* urease genes in *Escherichiacoli* grown under nitrogen-limiting conditions. J Bacteriol. 1992; 174:2466–2473.
9. Dailidiene D, Dailide G *et al*. *Helicobacteracinonychis*: genetic and rodent infection studies of a *Helicobacterpylori*-like gastric pathogen of cheetahs and other big cats. J Bacteriol. 2004; 186:356–365.
10. Dixon MF. IV *Helicobacterpylori* and peptic ulceration: histopathological aspects. J Gastroentrol Hepatol. 1991; 6:125-30.
11. Doig P, de Jonge BL *et al*. *Helicobacterpylori* physiology predicted from genomic comparison of two strains. Microbiol. Mol. Biol. Rev. 1999; 63:675–707.
12. Eaton KA, Dewhirst FE. *Helicobacteracinonyx* sp. nov., isolated from cheetahs with gastritis. Int. J. Syst. Bacteriol. 1993; 43:99–106.
13. El-Omar E, Penman ID, Ardill JES *et al*. *Helicobacter pylori* infection lowers gastrin mediated acid secretion by two thirds in patients with duodenal ulcer disease. Gastroenterology. 1995; 109:681-91.
14. Ernst PB, Gold BD. The disease spectrum of *Helicobacter pylori*: the immunopathogenesis of gastroduodenal ulcer and gastric cancer. Annu. Rev. Microbiol. 2000; 54:615-640.
15. Evans DJ, Jr, Evans DG *et al*. A sensitive and specific serologic test for detection of *Campylobacterpylori* infection. Gastroenterology. 1989; 96:1004–1008.
16. Fox JG. The non *H. pylori helicobacters*: their expanding role in gastrointestinal and systemic diseases Gut. 2002; 50:273-283.
17. Fox JG, Cabot EB. Gastric colonization by *Campylobacterpylori* subsp. mustelae in ferrets. Infect. Immun. 1988; 56:2994–2996.
18. Fox JG, Edrise BM *et al*. *Campylobacter*-like organisms isolated from gastric mucosa of ferrets. Am. J Vet. Res. 1986; 47:236–239.
19. Fulkerson JF, Garner RM *et al*. Conserved residues and motifs in the NixA protein of *Helicobacterpylori* are critical for the high affinity transport of nickel ions. J Biol. Chem. 1998; 273:235–241.
20. Ge Taylor DE. *Helicobacterpylori* genes hpcopA and hpcopP constitute a cop operon involved in copper export. FEMS Microbiol. Lett. 1996; 145:181–188.
21. Goodwin CS, Armstrong JA *et al*. Transfer of *Campylobacterpylori* and *Campylobactermustelae* to *Helicobacter* gen. nov. as *Helicobacterpylori* comb. Nov. and *Helicobactermustelae* comb. Nov., respectively. Int. J Syst. Bacteriol. 1989; 39:397-405.
22. Graham DY, GO MF, Lew GM *et al*. *Helicobacterpylori* infection and exaggerated gastrin release. Effects of inflammation and progastrin processing. Scand J Gastroenterol. 1993-1997; 34:757-61.
23. Gueneau P, Loiseaux-De Goer S. *Helicobacter*: molecular phylogeny and the origin of gastric colonization in the genus. Infect. Genet. Evol. 2002; 1:215–223.
24. Hamlet A, Olbe L. The influence of *Helicobacterpylori* on postprandial duodenal acid load and duodenal bulb pH in humans. Gastroenterology. 1996; 111:391-400.
25. Haque M, Hirai Y *et al*. Lipid profile of Helicobacter spp.: presence of cholesteryl glucoside as a characteristic feature. J. Bacteriol. 1996; 178:2065–2070.
26. Hendricks JK, Mobley HL. *Helicobacterpylori* ABC transporter: effect of allelic exchange mutagenesis on urease activity. J Bacteriol. 1997; 179:5892–5902.
27. Hogan DL, Rapier RC, Dreilinger A *et al*. Duodenal bicarbonate secretion: eradication of *Helicobacterpylori* and duodenal structure and function in humans. Gastroenterology. 1996; 110:705-16.
28. Johannes G Kusters, Arnoud HM van Vliet, Ernst J Kuipers. Pathogenesis of *Helicobacterpylori* Infection. Clinical Microbiology Reviews. 2006, 19(3). https://doi.org/10.1128/CMR.0054-05
29. Josenhans C, Ferrero RL *et al*. Cloning and allelic exchange mutagenesis of two flagellin genes of *Helicobacterfelis*. Mol. Microbiol. 1999; 33:350–362.
30. Kaneko H, Nakada K, Mitusma T *et al*. *Helicobacter Pylori* infection induces a decrease in immunoreactive-somatostatin concentrations of human stomach. Dig Dis Sci. 1992; 37:409-16.
31. Khulusi S, Badve S, Patel P *et al*. Pathogenesis of gastric metaplasia of the human duodenum: role of *Helicobacterpylori*, gastric acid, and ulceration. Gastroloenterology. 1996; 110:452-8.
32. Kuiper's, EJ, Pena AS *et al*. Seroconversion for *Helicobacterpylori*. Lancet. 1993; 342:328–331.
33. Labigne A, Cussac V, Courcoux P. Shuttle cloning and nucleotide sequences of *Helicobacterpylori* genes responsible for urease activity. J Bacteriol. 1991; 173:1920–1931.
34. Lee A, Hazell SL. Isolation of a spiral-shaped bacterium from the cat stomach. Infect. Immun. 1988; 56:2843-2850.
35. Leunk RD, Johnson PT *et al*. Cytotoxic activity in broth-culture filtrates of *Campylobacterpylori*. J Med. Microbiol. 1988; 26:93–99.
36. Marais A, Mendz GL *et al*. Metabolism and genetics of *Helicobacterpylori*: the genome era. Microbiol. Mol. Biol. Rev. 1999; 63:642–674.
37. Melchers K, Herrmann L *et al*. Properties and function of the Ptypeion pumps cloned from *Helicobacter pylori*. Acta Physiol. Scand. Suppl. 1998; 643:123–135.
38. Mendz GL, Shepley AJ, Hazell SL *et al*. Purine metabolism and the microaerophily of *Helicobacter pylori*. Arch. Microbiol. 1997; 168:448–456.
39. Mobley HL, Garner RM, Bauerfeind P. *Helicobacterpylori* nickel-transport gene nixA: synthesis of catalytically active urease in *Escherichiacoli*

independent of growth conditions. Mol. Microbiol. 1995; 16:97–109.
40. Mobley HL, Island MD, Hausinger RP. Molecular biology of microbial ureases. Microbiol. Rev. 1995; 59:451–480.
41. Munson L, Nesbit JW, Meltzer DG *et al*. Diseases of captive cheetahs (*Acinonyx jubatus* jubatus) in South Africa: a 20-year retrospective survey. J Zoo Wildl. Med. 1999; 30:342–347.
42. Nagata K, Satoh H *et al*. Potent inhibitory action of the gastric proton pump inhibitor lansoprazole against urease activity of *Helicobacterpylori*: unique action selective for H. pylori cells. Antimicrob. Agents Chemother. 1993; 37:769–774.
43. Nakamura H, Yoshiyama H *et al*. Urease plays an important role in the chemotactic motility of *Helicobacterpylori* in a viscous environment. Infect. Immun. 1998; 66:4832–4837.
44. Nedenskov P. Nutritional requirements for growth of *Helicobacterpylori*. Appl. Environ. Microbiol. 1994; 60:3450–3453.
45. Parsonnet J. The incidence of *Helicobacterpylori* infection. Aliment. Pharmacol. Ther. 1995; 9(2):45–51.
46. Pel PK. Diseases of the stomach. De Erven Bohn, Amsterdam, The Netherlands (In Dutch), 1899.
47. Perez-Perez GI, Rothenbacher D, Brenner H. Epidemiology of *Helicobacterpylori* infection. *Helicobacter*. 2004; 9(1):1–6.
48. Phadnis SH, Parlow MH *et al*. Surface localization of *Helicobacterpylori* urease and a heat shock protein homolog requires bacterial autolysis. Infect. Immun. 1996; 64:905–912.
49. Rensing C, Grass G. *Escherichia* coli mechanisms of copper homeostasis in a changing environment. FEMS Microbiol. Rev. 2003; 27:197–213.
50. Schreiber S, Bucker R *et al*. Rapid loss of motility of *Helicobacter pylori* in the gastric lumen *in vivo*. Infect. Immun. 2005; 73:1584–1589.
51. Schreiber S, Konradt M *et al*. The spatial orientation of *Helicobacter pylori* in the gastric mucus. Proc. Natl. Acad. Sci. USA. 2004; 101:5024–5029.
52. Solnick JV. Clinical significance of *Helicobacter* species other than *Helicobacter pylori*. Clin. Infect. Dis. 2003; 36:349–354.
53. Solnick JV, O'Rourke J, Lee A *et al*. An uncultured gastric spiral organism is a newly identified *Helicobacter* in humans. J Infect. Dis. 1993; 168:379–385.
54. Solnick JV, Schauer DB. Emergence of diverse *Helicobacter* species in the pathogenesis of gastric and enterohepatic diseases. Clin. Microbiol. Rev. 2001; 14:59–97.
55. Stingl K, Altendorf K, Bakker EP. Acid survival of Helicobacter Helicobacter pylori: how does urease activity trigger cytoplasmic pH homeostasis? Trends Microbiol. 2002; 10:70–74.
56. Tomb JF, White O *et al*. The complete genome sequence of the gastric pathogen Helicobacter pylori. Nature. 1997; 388:539–547.
57. Velayudhan J, Hughes NJ, McColm AA *et al*. Iron acquisition and virulence in Helicobacter pylori: a major role for FeoB, a high-affinity ferrous iron transporter. Mol. Microbiol. 2000; 37:274–286.
58. Vliet van AHM, Kuipers EJ *et al*. Nickel-responsive induction of urease expression in Helicobacter pylori is mediated at the transcriptional level. Infect. Immun. 2001; 69:4891–4897.
59. Wilson KT, Ramanujam KS *et al*. Helicobacter pylori stimulates inducible nitric oxide synthase expression and activity in a murine macrophage cell line. Gastroenterology. 1996; 111:1524–1533.
60. Wirth HP, Yang MQ *et al*. Expression of the human cell surface glycoconjugates Lewis X and Lewis Y by Helicobacter pylori isolates is related to cagA status. Infect. Immun. 1996; 64:4598–4605.
61. Wirth HP, Yang MQ, Karita M, Blaser MJ. Expression of the human cell surface glycoconjugates Lewis X and Lewis Y by Helicobacter pylori isolates is related to cag A status. Infect. Immun. 1996; 64:4598–4605.
62. Yasunaga Y, Shinomura Y, Kanayama S *et al*. Improved fold width and increased acid secretion after eradication of the organism in Helicobacter pylori associated enlarged fold gastritis. Gut. 1994; 35:1571-4
63. Yoshiyama H, Nakazawa T. Unique mechanism of Helicobacter pylori for colonizing the gastric mucus. Microbes Infect. 2000; 2:55–60.