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Helicobacter Pylori Infection in Peptic Ulcer Disease

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1. Introduction

1.1 Background

Helicobacter pylori infection is one of the most common bacterial infections worldwide.[1,2] Nearly 50% of the world's population is affected.[3] Though the prevalence of this infection appears to be decreasing in many parts of the world, H. pylori remains an important factor linked to the development of peptic ulcer disease, gastric malignancy and dyspeptic symptoms.[4] Majority of H. pylori infected persons remain asymptomatic. Approximately 10-15% of the infected persons develop associated illnesses, 1 to 10% developing peptic ulcer disease, 0.1 to 3% developing gastric cancer and less than 0.01% developing gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

There are several lines of evidence implicating H. Pylori in the development of gastric and duodenal ulcers.

1. H. Pylori is found in most patients who have peptic ulcers in absence of NSAID use.
2. Presence of H. Pylori is a risk factor for the development of ulcer.
3. Eradication of H. Pylori significantly reduces the recurrence of gastric and duodenal ulcers.
4. Treatment of H. Pylori infection leads to more rapid and reliable ulcer healing than does treatment with anti-secretory therapy alone.[15,21]

Early studies have estimated the rate of H. Pylori infection in patients with duodenal ulcer to be as high as 90% and in gastric ulcer to be as high as 70 to 90%.[5,6,7,29] Despite the decreasing prevalence of H. Pylori infection in developed countries, it is still an important factor in the aetiology of non-iatrogenic peptic ulcer disease. Up to 80% of duodenal ulcers and 70% of gastric ulcers are associated with H. Pylori infection. Several studies have shown that a pre- existing H. Pylori infection increases the risk for developing peptic ulcer disease.[8,9,10,11] In one study, 11% of patients with H. Pylori gastritis developed peptic ulcer disease compared to 1% of persons without gastritis.[10] Eradication of H. Pylori infection significantly reduces the recurrence of gastric and duodenal ulcers.[12,13,14,21] One study reviewed the relationship between H. Pylori eradication and reduced recurrence of duodenal and gastric ulcers. Ulcer recurrence was significantly less common among H. Pylori cured patients versus non-cured patients (6% versus 67% for patients with duodenal ulcers; 4% versus 59% for patients with gastric ulcers).[12]

H. Pylori has also been linked to the development of idiopathic thrombocytopenic purpura, ischemic heart disease and cerebrovascular accident. However, if confounding factors are taken into consideration, the strength of these associations is reduced.[16, 17, 221]

2. Bacteriology

Helicobacter pylori is a unipolar, multiflagellate, spiral shaped, microaerophilic, gram negative bacterium.[18] The bacterium was first isolated by Marshall and Warren in 1983 from gastroscopy biopsy specimens, which they described as a new species related to the genus Campylobacter.[18] The new genus Helicobacter was first published in October 1989. At least 22 species are now included in this genus, the majority of which colonise mammalian stomachs or intestines.

Helicobacter pylori is a slow growing bacterium. It can be cultured on non-selective agar media, such as blood agar, chocolate agar or on selective agar media, such as Skirrows media incubated in a humidified, micro-aerobic (5% oxygen) atmosphere at 35 to 37 degree centigrade for three to seven days.[19] Small, translucent circular colonies form and organisms are identified as Helicobacter pylori based on typical cellular morphology and positive results for oxidase, catalase and urease tests.

Under stress and nutritional deprivation, H. Pylori undergoes a morphological transformation from spiral bacilli to inactive coccoids.[19] H. Pylori cell wall enzyme Ami A, a peptidoglycan hydrolase, is involved in this morphologic transition.[20] Coccoid forms may be indicative of a dormant state. Coccoid forms may enable the organism to survive outside the human host in faeces or in water.

3. Epidemiology

Helicobacter pylori is one of the most common bacterial infections worldwide. At least 50% of the world's population is infected. The prevalence of H. Pylori infection in a community is related to three factors: 1. Rate of acquisition of infection, i.e. the incidence 2. the rate of loss of the infection 3. the prolonged prevalence of the bacterium in the gastro-duodenal mucosa between infection and eradication. [Prevalence is directly related to incidence and duration of illness].[2] Acute H. Pylori infection invariably passes undetected. Thus, the incidence of infection is determined indirectly from epidemiological studies. The incidence of H. Pylori infection is estimated to be approximately 0.5% per year in adults of developed countries. This incidence has been decreasing over time. However, the incidence of H. Pylori infection continues to be high in developing countries (3% to 10% per year).[25]

The infection is usually acquired in the first few years of life. Once acquired, infection persists indefinitely unless treated. In developing countries, the majority of children become infected during childhood and chronic infection continues during adulthood.[2,26] By age 1 year, approximately 20% are infected and by age 10 years, 50% are infected.[26] The prevalence of H. Pylori infection may be as high as 80% in adults.[30,31] However, in developed countries, such as, the United States, evidence of infection is rare before age 10, but increases to 10% between 18 and 30 years of age and to 50% in those older than age 60.[2] The higher prevalence in older age groups is thought to reflect a cohort effect related to poorer living conditions of children in previous decades. Within any age group, H. Pylori infection is more common in non-Hispanic blacks and Hispanics compared to the white population, which may be related to socioeconomic factors.[27, 28]

Important risk factors for H. Pylori infection are socioeconomic status and living conditions during childhood. Lower socioeconomic status and poor living conditions during childhood have been associated with higher risk of acquiring H. Pylori infection.[38,39,40,41] There may also be genetic susceptibility to H. Pylori infection.[42,43] Twin studies support hereditary susceptibility to infection, but this has not been proven. Individuals of certain ethnic groups including Hispanics and blacks have a higher rate of infection than Caucasians, which are not entirely explained by differences in socioeconomic status.[44]

4. Helicobacter pylori transmission

The mode of transmission of H. Pylori infection is poorly known.[1,45] Various modes of transmission have been suggested, such as person-to-person, water-borne, food-borne and zoonotic transmission.[45,46,47,48,49,50,51,52,53,54] The transmission of H. Pylori seems to be direct from person-to-person via faecal-oral or oral-oral routes.[45,46] Certain epidemiological studies have suggested water-borne and food-borne transmissions.[51,52,53,54] Zoonotic transmission has also been suggested based on isolation of H. Pylori from primates, domestic cats and sheep. [47,48,49]

Person-to person transmission is supported by the increased prevalence of infection among family members of patients with H. Pylori and among institutionalized patients. Isolation of genetically identical strains of H. Pylori from infected members of the same family and in patients in a chronic care facility further support this hypothesis.[32,33,34,35,36,37] Faecal-oral transmission is a possibility as H. Pylori has been cultured from faeces[54,55] and the organism seems to survive in water in non-culturable forms[50,51,52] (detected by PCR techniques). There is some indirect, but scarce evidence for oral-oral transmission.[45] H. Pylori has been identified in dental plaques[56], but it is unknown if this location can serve as a reservoir. Gastro-oral route of transmission through vomitus has also been suggested based on presence of bacteria in gastric secretions.[57,58]

Studies employing microbiological techniques have demonstrated that Helicobacter pylori is present in water and other environmental samples all over the world. Epidemiological studies have shown that water source and exposures related to water supply, including factors related to sewage disposal and exposure to animals, are risk factors for infection.[51] Children who swim in rivers, streams, pools, drink stream water or consume raw vegetables are more likely to be infected.[53] H. Pylori has also been detected in various food samples. So it has been hypothesised that food or water may be a reservoir in H. Pylori transmission.

Iatrogenic transmission has also been documented after the use of inadequately disinfected endoscopes and endoscopic accessories.[58]

5. Patho-physiology

5.1 Patho-physiology of gastric ulcers

Up to 70% of gastric ulcers are associated with H. Pylori infection. Three types of gastric ulcers have been described. Type I ulcers occur in the body of the stomach and are not related to other gastro-duodenal disease. Type II ulcers also occur in the body of the stomach and are associated with a duodenal ulcer scar or active ulcer. Type III ulcers occur in the immediate pre-pyloric area. Type II and III ulcers are associated with higher levels of gastric acid secretion as seen in patients with duodenal ulcers, but type I ulcers tend to be associated with normal or low levels of gastric acid secretion. Role of H. Pylori in these

different types of gastric ulcer is not known. Gastric acid secretion may not be the most important factor in the development of gastric ulcers as gastric ulcers have been seen in the presence of achlorhydria.[59] It has also been observed that basal and stimulated gastric acid secretion is within normal limits in groups of patients with gastric ulcers

5.2 Patho-physiology of duodenal ulcers

The mechanism by which Helicobacter pylori predisposes to duodenal ulcer is unclear. The pathogenesis of duodenal ulcer appears to be multi-factorial, involving an imbalance between "damaging" (e.g. acid, pepsin) and "protecting" (e.g. mucus, mucosal barrier, bicarbonate production, blood flow, cellular regeneration) factors.[60]The bacterium seems to affect different aspects of gastric and intestinal mucosal physiology that may contribute to development of ulcer disease. Disturbances in gastric acid secretion, gastric metaplasia, host inflammatory and immune response and down-regulation of various mucosal defence factors may contribute to ulcer formation. Various bacterial, host and environmental factors may also have a role in the pathogenesis of duodenal ulcer.

5.2.1 Disturbances in gastric acid secretion

Gastric acid secretion is elevated in patients with duodenal ulcers.[61,70] Helicobacter pylori infection can alter acid secretion in both directions. Acid secretion decreases temporarily during acute infection and may dwindle later if H. Pylori causes gastric atrophy.[63] In patients with duodenal ulcers, H. Pylori produces inflammation of non-acid secreting antral region of the stomach, whereas the more proximal acid-secreting fundic mucosa is relatively spared.[70,71] This may explain the increased gastric acid secretion in patients with duodenal ulcers. When compared to H. Pylori negative subjects, patients with duodenal ulcers have elevated basal acid output, peak acid output, fasting and meal-stimulated gastrin concentrations.[61,62,70]

H. Pylori infection is thought to change the physiological control of acid secretion. H. Pylori infection has been found to decrease the local expression of the inhibitory peptide somatostatin[63] and to increase the release of the acid-stimulating hormone, gastrin.[62,70] Hypergastrinemia, in addition to decreased inhibitory somatostatin, may be responsible for the increased gastric acid secretion. Hypergastrinemia may result from a decrease in the inhibitory peptide somatostatin.[64] Bacterial factors that inhibit somatostatin release have not been recognised, although TNF-alpha induced by H. Pylori infection may play a role in inhibiting somatostatin release.[65] In patients with H. Pylori infected duodenal ulcers, there is an exaggerate response to stimulation by gastrin.[61,70,71] This may be due to increased parietal cell mass in patients with duodenal ulcers[60,66,71] (Duodenal ulcer patients have approximately twice the normal parietal cell mass). But it is unclear whether or not this is due to H. Pylori infection.[67] Increased parietal cell mass may be due to trophic effects of hypergastrinemia over time or it may be related to host factors.

5.2.2 Gastric metaplasia

Elevated gastric acid secretion increases the duodenal acid load, which damages the duodenal mucosa, causing ulceration and gastric metaplasia. Gastric metaplasia occurs in the duodenum in response to acidic PH (when PH is less than 2.5).[68] Metaplastic gastric epithelium allows H. Pylori to colonise the duodenal mucosa, where it produces an acute inflammatory response. Colonization of these areas of gastric metaplasia by H. Pylori may significantly increase the risk of ulceration.[69]

However, gastric metaplasia is found in most, but not all patients with duodenal ulcers.[72,73,74] Gastric metaplasia can also be commonly found in the duodenum of healthy persons.[73,74,75] Studies have found a similar prevalence of gastric metaplasia among patients with duodenal ulcers and non ulcer dyspepsia.[76] Therefore, the role of gastric metaplasia in the pathogenesis of duodenal ulcer disease is unclear.

5.2.3 Host immune and inflammatory response

Host immune system responds to H. Pylori infection by production of inflammatory cytokines, such as interleukin(IL)-1, IL-6, tumor necrosis factor alpha, IL-8. These inflammatory cytokines may have a role in the development of duodenal ulcer.

5.2.4 Down-regulation of mucosal defence factors

i. Mucus- Mucus is a protective coat overlying the intestinal mucosa. Helicobacter pylori produces proteolytic enzymes that degrade this mucus layer, thus exposing the underlying mucosa to damaging effects of acid.[77]
ii. Bicarbonate- Most patients with duodenal ulcers have impaired proximal duodenal mucosal bicarbonate secretion. Impaired bicarbonate secretion in patients with duodenal ulcers could be caused by a cellular and/or physiological regulatory transport defect possibly related to H. Pylori infection as eradication of the infection normalises proximal mucosal bicarbonate secretion.[78]
iii. Cellular regeneration- Epidermal growth factor (EGF) and transforming growth factor-alpha(TGF-alpha) are potent gastric acid inhibitors and stimuli of mucosal growth and protection. H. Pylori may contribute to ulcerogenesis by affecting these factors for cellular regeneration as eradication of H. Pylori infection has shown to increase mucosal content and expression of TGF-alpha, EGF and EGF receptor (EGFr).[79]
iv. Blood flow- Thrombotic occlusion of surface capillaries is promoted by a bacterial platelet activating factor. Circulating platelet aggregates and activated platelets were detected in patients with H. Pylori infection. Platelet activation and aggregation may contribute to microvascular dysfunction.[84] This may play a role in producing mucosal damage and ulcer.

5.2.5 Other contributing factors

i. Bacterial factors- Various bacterial factors, such as the bacterial strain may play role in the pathogenesis of duodenal ulcer. For example, Strains with the cytotoxin-associated gene A(cag A) are associated with duodenal ulcer. Approximately 95% of patients with duodenal ulcers have cag A+ strains compared to 65% of infected patients without ulcers.[80]
ii. A specific Helicobacter pylori gene, duodenal ulcer promoting gene (dupA) is associated with an increased risk of duodenal ulcer. One study found that dup A was present in 42% of patients with duodenal ulcer versus 21% of patients with gastritis (adjusted odds ratio[OR]=3.1, 95% confidence interval; CI-1.7-5.7).[81] Its presence was also associated with more intense antral neutrophil infiltration and interleukin-8 levels and was a marker for protection against gastric atrophy, intestinal metaplasia, and gastric cancer.[81,82]
iii. Host factors- Host factors may be important in the development of duodenal ulcer. For example, patients with Helicobacter pylori who develop duodenal ulcer have higher

parietal cell mass or sensitivity to gastrin than Helicobacter pylori infected healthy persons.[60,66,71]

iv. Environmental factors, such as NSAID use and smoking may also increase the risk of duodenal ulcer in patients with Helicobacter pylori infection.[83]

5.3 Pathogenesis of H. Pylori-induced peptic ulcer disease

H. pylori causes three major gastric morphologic changes.[87] The extent and distribution of H. Pylori-induced gastritis ultimately determine the clinical outcome. The commonest morphologic change is the "simple or benign gastritis", characterized by mild pangastritis with little disruption of gastric acid secretion. This form of gastritis is commonly seen in asymptomatic people with no serious gastrointestinal disease. Up to 15 % of infected subjects develop an antral-predominant gastritis with relative sparing of the acid producing corpus mucosa. Subjects with antral-predominant gastritis have high antral inflammatory scores, high gastrin levels, relatively healthy corpus mucosa and very high acid output.[70] These abnormalities lead to the development of peptic ulcers, particularly duodenal and a large proportion of pre-pyloric ulcers. Up to 1% of infected subjects develop a corpus predominant pattern of gastritis, gastric atrophy and hypo- or achlorhydria.[85] These abnormalities develop as a direct result of the chronic inflammation induced by the infection and increase the risk of gastric cancer.

It is believed that the complex interplay between the host and the bacterium determines the disease outcome. Various bacterial factors have been described which aid in the colonisation of the gastric mucosa and subsequent modulation of the host's immune response. Studies have investigated the impact of these bacterial factors on inflammation and disease outcome. Role of bacterial factors for disease outcome remains limited, with most "virulent" strains being found in asymptomatic subjects.[86] Therefore, the variation in the host's inflammatory and immune response to infection may play a key role in determining the disease outcome. Nonetheless, the bacterium is required to initiate the host's response.

5.3.1 Bacterial factors

i. Colonisation/ Bacterial attachment

H. pylori is very sensitive to acid and it dies rapidly in the acidic PH found in the gastric lumen. Bacterial motility, urease and its ability to adhere to gastric epithelium are the factors that allow it to survive in the acidic environment.[87]

Various changes are observed in H. Pylori expression of genes following exposure to low PH. There is an increase in the expression of genes encoding proteins involved in the motility apparatus as well as genes encoding urease and proteins associated with the optimal function of the urease.[88] These observations suggest that the bacterial genes are turned on in the gastric mucosa.

H. pylori is capable of swimming freely within the mucus gel by utilising its polar flagella. It seems that the bacterium is able to sense and respond to PH gradients by swimming away from the acidic PH.[89] This allows the bacterium to swim away from the acidic PH in the gastric lumen to the close proximity of gastric epithelium, where the PH is near normal. In this environment, it enjoys the same cytoprotective mechanism as the gastric epithelium.

Other remarkable feature of H. Pylori is its ability to produce large amounts of cytosolic and cell surface associated **urease**. The urease produced by H. Pylori functions optimally at 2 different PH values, 7.2 and 3.[91]Cell-surface associated urease hydrolyses gastric luminal

urea to ammonia that helps neutralise gastric acid and form a protective cloud around the bacterium.[92] Within H. Pylori's urease gene cluster, there is a specific gene, Ure I, which encodes for a PH dependent urea channel.[22] The urea channel allows movement of urea from gastric lumen into the cytoplasm. The metabolism of urea by the cytosolic urease generates ammonia ions, which buffer hydrogen ions as they reach the cytoplasm of the organism.[93,94]

H. pylori infects gastric type epithelium to which it adheres closely. **Adherence** of the bacterium to the gastric epithelium is an important virulence factor and is necessary for the induction of pro-inflammatory responses. Adhesion to gastric epithelium may be beneficial to the bacterium in many ways. It may protect the bacterium against the mechanical clearance. Adhesion may promote invasion and persistence. The bacterium may use the cell surface as a site of replication. Increased inflammation and cellular damage caused by adhesion may release nutrients for H. Pylori. Adhesion also plays a major role in the delivery of toxins such as, Cag A and Vac A to host epithelial cell.[87]

Approximately 20% of H. Pylori in the stomach are found attached to the surfaces of mucus epithelial cells.[90] Adhesion is mediated by specific interactions between bacterial adhesin(s) and host receptor(s).[23,24] Over 30 genes in H. Pylori genomes are dedicated to the expression of outer membrane proteins (OMPs). Several of these OMPs have been classified as adhesins. Best described adhesins are BabA, Oip A and SabA. The leb-binding adhesin, BabA mediates binding to fucosylated Lewis b(Leb b) histo-blood group antigen on gastric epithelial cell.[95] Epidemiological studies also provide evidence in support of interaction between Leb and Bab A. For example, Strains of H. Pylori with BabA2 genotype are associated with inflammation, duodenal ulcer and gastric cancer.[96,97] Outer membrane protein (Oip A) coded by HPO638 gene may act as adhesins as well as promote inflammation by inducing IL-8 production.[98] However, their receptors have not yet been characterized. Sialic acid-binding adhesin (SabA) mediates binding to sialyl-dimeric-Lewix X glycosphingolipid in gastric epithelial cell.[99] Many strains of H. Pylori express a vacuolating cytotoxin Vac A, which may serve as a ligand for bacterial attachment. Although the majority of the Vac A is secreted, some may remain on the surface of the bacteria and serve as a ligand for bacterial attachment to epithelial cells, via an interaction with protein tyrosine phosphatases.[100] The Alp A and Alp B proteins have also been described as as adhesins in vitro.[101] However, there is a marked heterogeneity in H. Pylori adhesion system.[102] No individual adhesin is necessary for attachment to the gastric mucosa. Expression of adhesins is diverse between strains and variable within a single strain over time and these mechanisms of variability and adaptation are controlled at the genetic level by on/off switching of adhesin gene expression, gene inactivation or recombination.[87,102,103,104,105]

Le antigens expressed by host cells may serve as the major receptor for bacterial binding.[106,107] Bab A mediates binding to Leb receptor on host cell. However, there may be other host molecules besides Le antigens that can bind H. Pylori as it has been seen that the binding of H. Pylori to epithelial cells freshly isolated from human gastric biopsy specimens is unaffected by the expression of Le antigen[108] and individuals who do not express Leb can clearly be infected with H. Pylori.[109] One such host molecule may be class II major histocompatibility (MHC) molecule expressed on the surface of gastric epithelial cell.[110] H. Pylori can bind to class II MHC molecules on the surface of gastric epithelial cells and induce apoptosis.[111] A family of pathogen-associated molecular pattern receptors, the Toll-like receptors(TLRs) have also been examined for their role in binding of H. Pylori to the

host epithelial cells. 11 TLRs have been described.[86] Each one appears to have a different specificity for various bacterial molecules.[112] These receptors may bind bacterial products and thereby, enhance both bacterial binding and signalling. For example, TLR5 binds bacterial flagellins[113], TLR4 binds bacterial lipopolysaccharide(LPS).[114,115] The gastric trefoil protein TFF1, predominantly expressed in the gastric mucosa and the gastric mucus may serve as another receptor for H. Pylori.[116] A host cell glycosylphosphatidylinositol(GPI)-anchored glycoprotein, DAF has also been described as a potential receptor for binding H. Pylori.[117]

ii. Virulence factors

H. pylori induced gastritis and damage to the gastric mucosa is probably secondary to immune recognition of the bacteria and damage from various bacterial products.[87] Various bacterial products have been described as "toxins" based on biological activity.

Vac A

Many strains of H. Pylori express a pore forming cytotoxin, Vac A.[118] Vac A has been shown to cause cell injury in vitro and gastric tissue damage in vivo.[23,120,121] However for Vac A to cause cell damage, it must be secreted from the bacteria and delivered in an active form to host cell membranes where it assembles into pores that allow the leakage of chloride ions.[122] The Vac A gene shows a considerable genetic diversity. The activities of different alleles of the toxin vary in their toxicity. For example, strains harbouring s1 types of Vac A are highly associated with ulcers and gastric cancer.[123] M1 types of Vac A are also associated with ulcers.[123] Although the majority of Vac A is secreted, some remain associated with the bacterial cell surface. The Vac A molecules that remain on the surface of the bacteria are functional and delivered to host cells by direct contact between adhered bacteria and the host cell membrane.[124] As described earlier, Vac A on the surface of the bacteria may also serve as a ligand for bacterial attachment via an interaction with protein tyrosine phosphatases.

Several toxigenic properties of Vac A have been described that may contribute to the development of the disease.[125,126] Vac A may lead to vacuolation of epithelial cells, probably through its effect on endosomal maturation.[87] Vac A also induces apoptosis of host cells, probably through the activation of pro-apoptotic signalling molecules[127] and pore formation in mitochondrial membranes.[128] Vac A may disrupt the barrier function of tight junctions, leading to the leakage of ions and small molecules, such as iron, sugars and amino acids.[129] Vac A was also found to be a powerful inhibitor of T-cell activation in vitro.[130]

Cag A and the cag Pathogenicity island (Cag PAI)

Cag A is an important virulence factor associated with H. Pylori. It was initially thought to be the most important virulence factor as patients with antibodies against this protein showed higher rates of peptic ulcer disease[119] and gastric cancer. [131,132,133] Cag A positive strains have also been associated with increased inflammation[134], cell proliferation[135] and gastric metaplasia.[136] However, 30 to 60% of patients infected with CagA + strains do not develop any significant disease.[80] Therefore, Cag A may not be the most important virulence factor.

Cag A is a 128 to 140 kd protein, that can activate a number of signalling mechanisms and thus, affect the structure, differentiation and behaviour of epithelial cells.[87] Cag A is translocated into the host cell by the type 4 secretion system(TFSS). Genes within the cag pathogenicity island(PAI) encode proteins for the type 4 secretion apparatus(TFSS), also

referred to as Cag E.[125,137] These genes are co-transcribed and are genetically linked to Cag A.[120] TFSS allows bacterial macromolecules, such as Cag A, peptidoglycan to be translocated into the host cell.[125,137] The intact cag PAI of H. Pylori plays an important role in the pathogenesis of gastritis.[125,137,138] For example, Mutations of H. Pylori cag region were associated with decreased gastric mucosal inflammation in vivo and reduced activation of IL-8 or apoptosis in vitro.[139] It is believed that cag PAI results in the activation of nuclear factor(NF-kb) and AP-1, which in turn, regulate the expression of a wide variety of pro-inflammatory cytokines.[140,141] Cag PAI may collaborate with other bacterial factors, such as Oip A to enhance IL-8 production.[142] Bacterial peptidoglycan may also leak into the cell through the TFSS, resulting in the activation of Nod-1 mediated inflammatory response.[143]
Once inside the host cell, Cag A is tyrosine phosphorylated by host Src kinases.[144] Src kinases are normally involved in controlling basic cytoskeletal process, cell proliferation and differentiation. After its tyrosine phosphorylation, it interacts with a number of host proteins, triggering growth receptor-like signalling. Through these signal transduction events, Cag A affects the proliferative activities, adhesion and cytoskeletal organisation of epithelial cells.[87,145,146,147] Cag A also perturbs cell cycle control.[148] Cag A may also have a phosphorylation independent effect on gene transcription.[149] Independently of tyrosine phosphorylation, Cag A can form complexes with several junction proteins such as Zo-1, JAM and E-cadherin and can perturb the assembly and function of both the tight junction and the adherens junctions.[150,151] Phenotypically, this leads to the deregulation of epithelial cell-cell adhesion and loss of epithelial polarity.[152] Cag A, independent of cag TFSS, can activate the nuclear factor, NF-kb leading to activation of pro-inflammatory signal and IL-8 secretion.[140,141] Cag A may also induce DNA damage and apoptosis of gastric epithelial cells via oxidative stress.[171]

Other virulence factors

Most persons infected with H. Pylori strains that produce Vac A and possess Cag A genotype nonetheless remain asymptomatic, suggesting that additional virulence factors are important in virulence. Several other H. Pylori virulence factors, such as ice A, Bab A2, Oip A have been described.[153,154,155,156,157] For example, "induced by contact with epithelium" ice A has been linked to peptic ulcers and increased mucosal concentrations of IL-8.[153,154,155] H. Pylori strains with "blood group antigen binding adhesin" Bab A2 genotype are associated with inflammation, duodenal ulcer and gastric cancer[156]. Oip A has been associated with duodenal ulcers.[157] However, the importance of these virulence factors in the life of H. Pylori is poorly understood.

iii. Mechanism of persistence

In order to colonise the human stomach, H. Pylori must overcome the physical and chemical barriers as well as innate and adaptive immune responses that are triggered in the stomach by its presence.[87] H. Pylori urease functions mainly as a protective buffering enzyme against gastric acidity. Several bacterial factors including catalase and urease antagonise innate host immune responses.[158] H. Pylori may decrease the expression of the antibacterial molecule secretory leukocyte protease inhibitor.[159] H. Pylori produces an enzyme, arginase that inhibits nitric oxide production and may favour bacterial survival.[160] Virulent strains of H. Pylori may alter mucus production[161] and phagocytosis.[162] A number of H. Pylori factors may actually contribute to reduce inflammation or recognition by the immune system. Molecular mimicry may be an important mechanism employed by the bacterium to evade recognition by the host immune system. For example, H. Pylori flagellar proteins have

evolved to avoid being recognised by toll-like receptors.[163] H. Pylori lipopolysaccharides mimic host molecules such as Lewis antigens.[164] H. Pylori virulence factors elicit both pro-inflammatory cytokines such as INF-gamma, TNF-alpha and anti-inflammatory cytokines, such as IL-4, !L-10 and transforming growth factor-beta. These anti-inflammatory cytokines may impair immune responses and may favour persistence.[86] However, these anti-inflammatory cytokines, IL-4, IL-10 and TGF-b are not expressed to the same levels as pro-inflammatory cytokines.[165,166,167,182] Hence, it has been hypothesized that H. Pylori induces a robust, but specific form of chronic inflammation that is ineffective in clearing the infection while avoiding forms of inflammation that would eliminate it.[87] This may be due to inappropriate T-cell responses or a lack of coordination in T-cell responses required for immunity.[86] A number of host polymorphisms may also lead to variations in the immune response.[87]

5.3.2 Role of host response in H. Pylori induced disease

As described earlier, the host response to H. Pylori infection is an important component in the pathogenesis of gastro-duodenal disease. H. Pylori induce chronic inflammation in the gastric mucosa, mediated by an array of pro- and anti-inflammatory cytokines. Heterogeneity in the regions of genome that control the magnitude of inflammation is thought to determine an individual's ultimate clinical outcome. For example, genetic polymorphisms in the regions controlling IL-1 beta were associated with an increased incidence of hypochlorhydria, gastric cancer and decreased occurrence of duodenal ulcer.[168,169] Il-1 beta has a profound pro-inflammatory effect and it is also a powerful acid inhibitor.[170] The pro-inflammatory genotypes of TNF-alpha, IL-8 and IL-10 were associated with the development of gastric cancer.[168]

i. Epithelial cell response to H. Pylori infection

The epithelial cell response to H. Pylori infection is determined by several variables: bacterial virulence factors, the signalling linked to specific receptors that recognise the bacterial components and the local effects of hormones, neurotransmitters, immune/inflammatory cytokines and stromal factors.[86] These responses include changes in epithelial cell morphology[175], increased epithelial cell proliferation[176], increased rates of epithelial cell death via apoptosis[177], disruption of the tight junctional complexes150, the production of inflammatory cytokines[137] and induction of numerous genes, most importantly genes involved in the regulation of the immune/inflammatory responses, epithelial cell turn over including apoptosis and proliferation and those affecting physiological properties in the stomach.[178,179,180,181] The expression of these genes in epithelial cells is modulated by transcription factors that are controlled by a series of signalling mechanisms. For example, nuclear factor kb(NF-kb) and AP-1 regulate the expression of pro-inflammatory cytokines and cellular adhesion molecules in response to infection.[182,183] These transcription factors are controlled by several signalling mechanisms including mitogen-activated protein kinases(MAPKs).[138,184] The MAPK cascades regulate several cell functions including proliferation, inflammatory responses and cell survival. ERK and P38 MAPK pathways regulate IL-8 production in gastric epithelial cells.[185,186] ERK and P38 also regulate the expression of other inflammatory response genes. Specific bacterial products as described earlier activate different transcription factors, which collaborate to enhance IL-8 production.[86] Interleukin-8 and related peptides in chemokine family secreted by gastric epithelial cells recruit and activate neutrophils and macrophages.

ii. Host responses in the lamina propria

Although H. Pylori resides predominantly in the gastric lumen, it induces a robust inflammatory and immune response. The magnitude of the host inflammatory response cannot be explained solely based upon the host epithelial cell responses to the bacterium. Significant amounts of bacterial product may leak around epithelial cells and reach the lamina propria, where it can activate phagocytes, including macrophages and neutrophils.[86] Disruption of epithelial tight junctions may enhance bacterial antigen delivery to the lamina propria. Several studies have demonstrated the ability of H. Pylori to invade gastric epithelial cells in vitro and in vivo.[172,173] Transmission electron microscopy and immunogold detection have shown H. Pylori to be in direct contact with immune cells of the lamina propria in the majority of cases of gastritis.[174] Engulfment of H. Pylori infected epithelial cells by phagocytes may be one of the mechanisms by which H. Pylori can activate the host immune response.[187]

Several bacterial products have been shown to trigger immune response within the lamina propria. A broad array of cytokines is released in the lamina propria in response to intact bacteria or bacterial factors. One such bacterial factor is H. Pylori neutrophil-activating protein, a 150 kilodalton protein, which promotes neutrophil adhesion to endothelial cells and stimulates chemotaxis of monocytes and neutrophils.[188] Bacterial urease can induce he production of IL-6 and TNF-alpha by macrophages.[189] Heat shock protein 60 induces the production of IL-6.[190] Intact bacteria can induce the production of chemokines that recruit T-cells[191] as well as IL-12[192] and IL-18[193], that favour the selection of Th1 cell. Increased IL-1, IL-6, IL-8 and TNF-alpha in response to H. Pylori infection recruit and activate monocytes and neutrophils. Release of neutrophil mediators may in turn, disrupt epithelial cells and contribute to ulcer formation.

iii. Gastric T-cell responses

Bacterial activation of epithelial cells, monocytes, macrophages and neutrophils leads to a T-helper cell type of adaptive response.[194,195] Different T-helper cell subsets emerge in response to infection with characteristic cytokine production. In H. Pylori infection, T-cell response is predominantly of T-helper cell 1(Th1) type.[138,196] Th1 cells promote cell-mediated immune responses, mainly through the production of INF-gamma and TNF-alpha while Th2 cells promote humoral immunity through the production of cytokines, such as IL-4, IL-5, IL-10 and IL-13. Previously, it was thought that the gastric mucosa is pre-conditioned to favour Th1 cell development.[165,192,197] One possible hypothesis is that H. Pylori selectively blocks Th2 development by interfering with STAT6 activation by IL-4.[198] IL-12 and IL-18 induced in response to infection may positively select for the Th1 response.[86] Activated Th1 cells produce INF-gamma and TNF-alpha which increase the expression of many pro-inflammatory genes in the epithelium including IL-8.[182] These cytokines also enhance bacterial binding[110] and may contribute to increased bacterial load.[199] Th1 cells may induce epithelial cell death through Fas-Fas L interactions.[200] In summary, Th1 activation may contribute to more severe inflammation and mucosal damage. However, Th1 type of T-cell response is a type of cell-mediated immunity against the control of intracellular pathogens.[196] It is unlikely to be effective against H. Pylori which is largely an extracellular pathogen. Hence, Th1 cell activation may produce inflammation, but not effective one which would clear the infection. In addition to Th1 cells, a subset of anti-inflammatory T-cells may be activated by H. Pylori infection. These cells may impair excessive inflammation which would otherwise lead to the clearance of the organism.[86]

iv. Gastric B-cell responses

Gastric T-cells can modulate B-cell responses, leading to the production of specific antibodies to a variety of H. Pylori antigens. During infection with H. Pylori, Ig G, Ig A and Ig M types of antibodies can be detected.[201,202] The role of these antibodies in the disease is poorly understood. Ig G class of antibody can activate complement and may contribute to immune-complex mediated inflammation.[203] In addition to producing antigen-specific antibodies, B-cells have also been shown to produce auto-reactive antibodies, that may be pathogenic.[204,205]

6. Indications for H. pylori testing

H. pylori is a common worldwide infection. The vast majority of patients with H. Pylori infection do not develop clinically significant gastroduodenal disease. Therefore, routine testing for H. Pylori is not recommended. When to test a patient for H. Pylori infection is an important question for a clinician. Guidelines from the American college of Gastroenterology [ACG] and the European Helicobacter study group [EHSG] have been published to assist clinicians in making this decision.

ACG recommendations[206]

Testing for H. Pylori should only be performed if the clinician plans to offer treatment for positive results.
Testing is indicated in patients with

1. Active peptic ulcer disease(gastric or duodenal ulcer)
2. Confirmed history of peptic ulcer disease(not previously treated for H. Pylori)
3. Gastric MALT lymphoma(low grade)
4. After endoscopic resection of early gastric cancer
5. Uninvestigated dyspepsia(depending upon H. Pylori prevalence)

The test-and-treat strategy for H. Pylori infection is a proven management strategy for patients with uninvestigated dyspepsia who are under the age of 55 yr and have no "alarm features" (bleeding, anaemia, early satiety, unexplained weight loss, progressive dysphagia, odynophagia, recurrent vomiting, family history of GI cancer, previous esophagogastric malignancy)
Deciding which test to use in which situation relies heavily upon whether a patient requires evaluation with upper endoscopy and an understanding of the strengths, weaknesses, and costs of the individual test.

EHSG recommendations[207]

Testing is indicated in patients with

1. Gastroduodenal diseases such as peptic ulcer disease and low grade gastric MALT lymphoma
2. Atrophic gastritis
3. First degree relatives of patients with gastric cancer
4. Unexplained iron deficiency anaemia
5. Chronic Idiopathic thrombocytopenic purpura (ITP)

The test-and-treat strategy using a non-invasive test is recommended in adult patients with persistent dyspepsia under the age of 45 and no "alarm symptoms".
Testing is not recommended in GORD. However, testing should be considered in patients on long-term maintenance therapy with PPIs.

Testing should be considered in patients who are naive NSIADs users.
Testing should be considered in patients who are long-term aspirin users who bleed.
Children with recurrent abdominal pain, who have a positive family history of peptic ulcer and gastric cancer should be tested for H. Pylori after exclusion of other causes.

Duodenal and gastric ulcer

Testing for H. Pylori is indicated in patients with confirmed gastric or duodenal ulcers. As described earlier, H. Pylori has been established as a major risk factor for both duodenal and gastric ulcers. H. Pylori eradication has also shown to reduce the recurrence of peptic ulcer disease. Therefore, both ACG and EHSG recommend testing patients with peptic ulcer disease for H. Pylori.

Gastroduodenal bleeding

A meta-analysis performed by Sharma et al showed that H. Pylori treatment decreased recurrent ulcer bleeding by 17% and 4% compared with ulcer healing treatment alone (bismuth, ranitidine or omeprazole) or ulcer healing treatment followed by maintenance therapy respectively.[208] Another study performed in Taiwanese patients with a history of ulcer bleeding showed that maintenance acid suppression was not routinely necessary to prevent ulcer recurrence after successful H. Pylori cure and ulcer healing.[209] Therefore, patients with a bleeding duodenal or gastric ulcer should be treated for H. Pylori.

Uninvestigated dyspepsia

The Cochrane Systematic review confirmed that there is a small benefit of eradicating H. Pylori in patients with non-ulcer dyspepsia.[210] Eradication of H. Pylori may also reduce the incidence of peptic ulcer in patients with ulcer-like functional dyspepsia.[211] Therefore, the test-and-treat strategy is recommended in patients with uninvestigated dyspepsia who are under the age of 55 yrs or 45 yrs (depending upon the specific set of guidelines) and have no "alarm features". However, this strategy has been criticised. In a placebo-controlled trial of empirical treatment involving 294 patients with uninvestigated dyspepsia and a positive H. Pylori breath test, the 1-year rate of symptom resolution was 50% in those receiving H. Pylori eradication therapy, as compared with 36% of those receiving placebo (p=0.02)[212]; 7 patients would need to receive eradication therapy for 1 patient to have a benefit. This suggests that most patients treated with the test-and-treat strategy would incur the inconvenience, costs and potential side-effects of therapy without a benefit.

Long-term maintenance therapy with PPIs

EHSG suggests H. Pylori testing in patients on long-term maintenance therapy with PPIs. Patients who are infected with H. Pylori and maintained on a PPI may be at risk for the development of atrophic gastritis.[213]However, the findings have not been confirmed in other studies.[214]

Persons using NSAIDS or Aspirin

EHSG suggests H. Pylori testing in patients who are naive NSAIDs users. A meta-analysis of five studies including 939 patients showed that H. Pylori eradication was associated with a reduced incidence of peptic ulcer in patients taking NSAIDs(OR 0.43, 95% CI 0.20-0.93). Sub-analyses demonstrated that risk reduction was evident in NSAID-naive individuals, but not for those previously taking NSAIDs.[215,219]

Iron-deficiency anaemia

EHSG recommends H. Pylori testing and eradication in patients with unexplained iron deficiency anaemia. There is emerging evidence to suggest that eradication of H. Pylori can improve iron deficiency anaemia[216,217], but the available data do not prove cause and effect.

Chronic ITP

EHSG recommends H. Pylori testing and eradication in patients with chronic ITP. The available data support an association between H. Pylori infection and ITP.[218] Studies have also shown that there is a significant increase in platelet count in patients with ITP after H. Pylori eradication.[220,222,223,224]

Prevention of gastric cancer

ACG recommends H. Pylori testing after endoscopic resection of early gastric cancer. EHSG recommends H. Pylori testing and eradication in first-degree relatives of patients with gastric cancer. Whether H. Pylori eradication reduces the risk of developing gastric cancer is unknown. H. Pylori eradication may protect against the progression of premalignant gastric lesions.[225,226] H. Pylori eradication may decrease the risk of developing cancer in individuals without precancerous lesions from high risk populations.[227] However, this may not apply to low-risk populations.

7. Diagnostic tests for H. pylori infection

Diagnostic tests for H. Pylori can be divided into endoscopic and non-endoscopic tests. Various diagnostic tests for H. Pylori infection are shown in Table 1-2. All the methods currently available for the detection of H. Pylori have their advantages and disadvantages regarding sensitivity, specificity, convenience, cost and immediacy. Choosing among these tests depends upon the clinical circumstance, the pre-test probability of infection, the accuracy of the tests, the availability and the relative costs.

General recommendations from ACG

When endoscopy is indicated, the test of first choice is the rapid urease test (RUT) in patients who have not been on a PPI within 1-2 week or an antibiotic or bismuth within 4 week of endoscopy.

For patients who have been taking a PPI, antibiotics or bismuth, it is appropriate to obtain biopsies from the gastric body and antrum for histology with or without RUT or plan testing with Urea breath test(UBT) or faecal antigen test(FAT) at a later date after withholding the offending agents for an appropriate period of time.

Culture or PCR is not routinely recommended.

UBTs and faecal antigen tests provide reliable means of identifying active H. Pylori infection before antibiotic therapy.

In the setting of acute upper GI bleeding, a positive RUT indicates the presence of active H. Pylori infection, whereas a negative RUT and/or histology should be confirmed with another test. An antibody test provides a reasonably sensitive testing option. Alternatively, patient can undergo a UBT or FAT at a later date after withholding medications that can negatively affect the sensitivity of these tests for an appropriate period of time.

Antibody testing for H. Pylori is appropriate in patients with uninvestigated dyspepsia in regions where the prevalence of H. Pylori infection is high. In low prevalence populations

(prevalence less than 20%), antibody tests should be avoided altogether or positive results should be confirmed with a test that identifies active infection, such as UBT or FAT prior to initiating eradication therapy.

Tests	Advantages	Disadvantages
Non- Endoscopic		
1.Urea Breath Test (13_C & 14_C)	• Rapid, inexpensive and identifies active infection. • Excellent PPV regardless of H. Pylori prevalence. • Useful after H. Pylori therapy.	• False negative results may be observed in patients who are taking PPIs, bismuth or antibiotics. • May not be available consistently.
2.Serological Test or Antibody Test	• Widely available. • Least expensive test. • Excellent NPV.	• The PPV is greatly influenced by the prevalence of H. pylori infection. Not recommended for confirming eradication as positive results may reflect past rather than current infection.
3. Fecal Antigen Test	• Identifies active H. pylori infection. • High positive and negative predictive values. • Useful before and after H. Pylori treatment.	• Collecting stool may be unpleasant to patients. • False negative results may be observed in patients who are taking PPIs, bismuth or antibiotics. • Polyclonal test less well validated.
Endoscopic		
1.Rapid Urease Testing	• Rapid, inexpensive and accurate in properly selected patients.	• False negative results may be observed in patients who are taking PPIs, bismuth or antibiotics.

2.Histological assessment	• High sensitivity and specificity.	• Expensive. • Requires trained personnel.
3. Culture	• Excellent specificity. • Allows determination of antibiotic sensitivities.	• Sensitivity variable. • Requires infrastructure and trained personnel. • Expensive, time consuming, difficult to perform and not widely available.
4. Polymerase Chain Reaction	• High sensitivity and specificity. • Provides opportunity to test for antibiotic sensitivity.	• False positive results may be due to contamination, homologous DNA sequences among various species, non-specific amplifications. • False negative results may be due to reaction failure. • Methodology not standardized across laboratories. • Not widely available.

Table 1.

Test	**Sensitivity**	**Specificity**
Non-Endoscopic Tests		
1.Urea Breath Test	90%-96%	88%-98%
2.Antibody Test	88%-94%	74%-88%
3.Fecal Antigen Test	86%-96%	92%-97%
Endoscopic Tests		
1.Rapid Urease Test	88%-95%	95%-100%
2.Histology	93%-96%	98%-99%
3.Culture	80%-98%	100%
4.Polymerase Chain Reaction	>95%	>95%

Table 2.

Confirmation of eradication is indicated in any patients with an H. Pylori-associated ulcer, persistent dyspeptic symptoms despite the test-and-treat strategy, H. Pylori-associated MALT lymphoma and in individuals who have undergone resection of early gastric cancer. If testing to prove eradication were performed in the setting of endoscopy, histology or the combination of histology and RUT would be appropriate.

UBT is the most reliable non-endoscopic test to document eradication of H. Pylori infection. The monoclonal FAT provides another non-endoscopic means of establishing H. Pylori cure. Testing to prove H. Pylori cure appears to be most accurate if performed at least 4 wk after the completion of antibiotic therapy.

7.1 Endoscopic diagnostic tests

Currently available biopsy-based diagnostic methods for H. Pylori infection are the rapid urease test, histology, culture and polymerase chain reaction (PCR).

7.1.1 Rapid Urease test (RUT)

Rapid Urease tests depend on the activity of bacterial urease. Endoscopic biopsy specimens are placed into an agar gel or on a reaction strip containing urea, a buffering agent and a PH sensitive dye. If H. Pylori is present, its urease cleaves urea to liberate ammonia and bicarbonate, leading to an increase in the PH and change in the colour of the dye. CLO test, Hp Fast, HUT-test, Pyloritek and Pronto Dry are some of the commercially available RUT kits. The overall performance of these tests is comparable.[228,229]

Although RUTs are rapid, inexpensive and easy to perform, their sensitivity is reduced under certain circumstances. The tests may produce a false negative result in patients with active or recent bleeding from the upper gastrointestinal tract when gastric contents are contaminated with blood.[230,231,232] Furthermore, these tests may give a false negative result in patients who have recently been taking proton pump inhibitors (PPIs), H2-receptor antagonists (H2RAs), antibiotics, or bismuth containing compounds.[228]In these patients, the RUT is usually combined with other endoscopic or non-endoscopic tests to determine the presence or absence of the infection. It is also recommended to obtain biopsies from two sites, the body of the gastric angularis and greater curvature of the antrum.[233] This may increase the sensitivity of the test. An alternative is to withhold the offending agents, such as PPIs or antibiotics for an appropriate period of time prior to endoscopy. The duration of the deleterious effects of medications on the sensitivity of the RUT is unknown. However, based on data from UBT, it is probably reasonable to withhold a PPI for 1-2 weeks and bismuth and antibiotics for four weeks prior to the RUT.[234,235]

7.1.2 Histology

Histological testing of gastric biopsy specimens is another method of diagnosing H. Pylori infection. A significant advantage of histology over other diagnostic tests is the ability to evaluate for pathological changes associated with H. Pylori infection, such as gastritis, atrophy, intestinal metaplasia and malignancy.[236]The presence of type B chronic gastritis (non-atrophic diffuse antral gastritis or atrophic pangastritis) may be used as a surrogate marker for the infection when organisms are not detected whereas the absence of chronic gastritis may be used as a marker for the absence of infection. However, the sensitivity of histology is affected by several factors, such as the site, number and size of gastric biopsies, method of staining, level of training of the examining pathologist and use of medications, such as bismuth, antibiotics and PPIs. It is therefore recommended to obtain a minimum of three biopsies, one from the greater curvature of the corpus, one from the greater curvature of the antrum and one from the angularis to maximize the diagnostic yield of histology.[237]

7.1.3 Brush cytology

Brush cytology may be used as an alternative to histology for the diagnosis of H. Pylori infection, especially in patients who have an increased risk of bleeding following forces biopsy. Data with endoscopic brush cytology are encouraging, with reported sensitivity and specificity of more than 95%.[238]

7.1.4 Culture

Bacterial culture is highly specific method for detecting active H. Pylori infection. In addition to identifying infection, it permits testing for sensitivity to anti-microbial agents.[239] However, bacterial culture is relatively insensitive[240,241] and seldom performed in routine clinical practise. Not all hospital laboratories have necessary expertise or resources available to offer routine culturing. Furthermore, culturing H. Pylori is difficult, time consuming and expensive.

Culture and sensitivity testing may be useful in patients with refractory disease since the incidence of resistance is very high in this subgroup.

7.1.5 Polymerase chain reaction (PCR)

Detection of H. Pylori by PCR is based on the amplification of a target DNA sequence in the bacterial genome. The use of PCR for the detection of H. Pylori from environmental samples is well documented.[269,270] PCR can also be used to detect H. Pylori in biopsy specimens.[261,262,265] In fact, PCR may be more sensitive than other biopsy-based diagnostic techniques in diagnosing H. Pylori infection.[264,265] PCR testing may be more sensitive than other biopsy based tests in detecting H. Pylori infection in patients who are taking PPIs, H2 RAs, antibiotics or bismuth containing compounds.[263] The testing is also highly specific and allows testing for antibiotic sensitivities.[266,267,268]

Although PCR has many advantages, its clinical use is limited due to its tendency towards false positive and false negative results. False positives can result from clinical or laboratory contamination, carry over contaminations and most importantly, similarities between the primer binding regions of H. Pylori and other organisms especially at the 3′ ends. False negatives can result from low number of target organisms, the presence of a specific PCR inhibitor, degenerated target DNA, and polymorphisms in the primer binding regions, especially at the 3′ ends, that prevent the amplification of the target DNA. Furthermore, the test is not widely available and the methodology is not standardized across laboratories.

Newer PCR techniques, such as multiplex PCR assays may reduce false positive and false negative results and thereby improve the accuracy of the test. For example, TZAM HP multiplex PCR assay amplifies 10 DNA fragments from 5 DNA regions in the genome of H. Pylori at the same time. Amplifying more than one DNA region increases the sensitivity because the probability of amplifying several selected DNA regions is much higher than the chance of amplifying only one region. It also increases the specificity because probing different loci at the same time more accurately distinguishes one pathogen from another.[265]

7.2 Non-endoscopic diagnostic tests

Currently available non-endoscopic diagnostic tests for H. Pylori infection are urea breath test (UBT), antibody test and fecal antigen test (FAT).

7.2.1 Urea breat test (UBT)

The urea breath test, like the RUT, depends on the activity of bacterial urease. The test involves the ingestion of urea, labelled with either the non-radioactive isotope ^{13}C or the radioactive isotope ^{14}C, which is converted to labelled carbon dioxide by the bacterial urease. The labelled carbon dioxide can then be measured in expired air.[242,243,244] Although the dose of radiation exposure in ^{14}C UBT is small, the ^{13}C UBT is preferred in children and women of child bearing potential.[242,243]

The UBT has excellent sensitivity and specificity[242,243] therefore, it is considered to be the most reliable test to document H. Pylori infection. It can be used to screen for infection as well as to confirm eradication after H. Pylori treatment.[244,245,246,247] However, UBTs may produce a false negative result in patients who are taking PPIs, bismuth or antibiotics. It is currently recommended to withhold bismuth and antibiotics for at least 28 days and a PPI for 7-14 days prior to UBT to reduce false negative results.[234,235,248] It is unknown whether H2RAs affect the sensitivity of the UBT[249], although these drugs are generally stopped for 24-48 hours before the UBT.

A urease blood test, using a 13 C- bicarbonate assay also reliably detects active H. Pylori infection before and after treatment. In the presence of H. Pylori, the ingestion of a 13 C-urea rich meal results in the production of labelled bicarbonate, which can be measured in serum.[250,251]

7.2.2 Serological test or antibody test

Antibody testing is based upon the detection of H. Pylori specific Ig G antibodies in serum, whole blood or urine. Antibodies to H. Pylori can be quantitatively assessed using laboratory-based ELISA and latex agglutination techniques or qualitatively assessed using office-based serological kits.

Antibody testing is cheap, widely available and easy to perform. However, there are several factors limiting its usefulness in clinical practice. The test is less accurate when compared with other diagnostic tests.[252] The test has high sensitivity (88-94%), but variable specificity (74-88%) with accuracy ranging from 83 to 98%. In general, office based serological kits are less accurate than laboratory-based quantitative tests. The PPV of the test is greatly influenced by the prevalence of H. Pylori infection.[253] In a population with low prevalence of H. Pylori infection, a positive antibody test is more likely to be a false positive test. Finally, serological tests are unreliable indicators of H. pylori status in patients who have received treatment for the infection.[254]Although antibody titres fall in most patients after successful eradication, the rate and extent of the decline are highly variable and unpredictable.

7.2.3 Fecal antigen test (FAT)

H. pylori infection can be diagnosed by identifying H. Pylori specific antigens in the stool by enzyme immunoassay with the use of polyclonal or monoclonal anti-H. Pylori antibodies.[255,256] The FAT is a reliable test to diagnose H. Pylori infection as well as to confirm eradication after treatment and can be used interchangeably with the UBT. Both polyclonal and monoclonal tests have excellent sensitivity, specificity, positive and negative predictive values for diagnosing infection before treatment.[255] However, in the post-treatment setting, only the monoclonal test appears to have sensitivity, specificity and predictive values of greater than 90%. The polyclonal test appears to have less satisfactory sensitivity and positive predictive value.[255] Therefore, in the post-treatment setting, the monoclonal FAT is more reliable than the polyclonal test. The FAT may be effective in confirming eradication as early as 14 days after treatment[257] but, the general recommendation is to perform the test more than 4 weeks after treatment.[255]

The FAT has its own disadvantages. Like the UBT, the FAT may produce a false negative result in patients who are taking PPIs, antibiotics or bismuth.[258,259] To reduce false negative results, it is generally recommended to withhold bismuth and antibiotics for at least 4 weeks

and a PPI for 2 weeks prior to the FAT. The FAT may produce a false positive result in patients with acute upper gastrointestinal bleeding.[231,260] This may be due to cross-reactivity with blood products. Furthermore, the process of stool collection may be unpleasant to patients.

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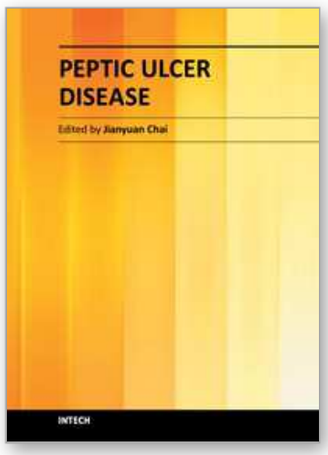

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Peptic ulcer disease is one of the most common chronic infections in human population. Despite centuries of study, it still troubles a lot of people, especially in the third world countries, and it can lead to other more serious complications such as cancers or even to death sometimes. This book is a snapshot of the current view of peptic ulcer disease. It includes 5 sections and 25 chapters contributed by researchers from 15 countries spread out in Africa, Asia, Europe, North America and South America. It covers the causes of the disease, epidemiology, pathophysiology, molecular-cellular mechanisms, clinical care, and alternative medicine. Each chapter provides a unique view. The book is not only for professionals, but also suitable for regular readers at all levels.

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