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Helicobacter Pylori role in Peptic Ulcer

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ABSTRACT

Helicobacter pylori were commonly found in the stomach. Patient infected with these bacteria had no problems. Problems are developed in many patient like peptic or duodenal ulcer; because the peptic ulcers causes no symptoms or may causes discomfort or pain the upper part of the abdomen, abdominal flatness, vomiting, feel full when eating small meals, anorexia, dark stools, nausea. Bleeding ulcers may cause decreased in blood count. H. pylori can be diagnosis in blood specimen, breath test, stool, or biopsy for invasive test, and PCR, and ELISA technique for non-invasive test. Testing of H. pylori is recommend for diagnosed peptic (stomach or duodenal) ulcer, for ulcer heal and lowering the recurrent risk of ulcer, and lowering the bleeding. Several methods were used to diagnose H. pylori in the biopsy by using rapid urease test. The ideal temperature for growth was 37C°.

Key words: *Helicobacter pylori*, Urease activity, Peptic ulcer

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INTRODUCTION

Helicobacter pylori represent the risk factor of active chronic gastritis and are associated with peptic, gastric ulcer, and non-ulcer dyspepsia [1], and is the main risk of gastric cancer, and adenocarcinoma [2,3]. Nearly 50% of the world's populations are infected with *H. pylori*. *Helicobacter pylori* represent the first bacterial infections in the world with a significant morbidity and mortality. Their prevalence varies dependent on geography, ethnicity, living conditions, and age. Peptic ulcer is a worldwide disease. Many methods are available for detection of *H. pylori* from which invasive methods for biopsy sample collection by endoscope for and non-invasive methods not required endoscopy. *H. pylori* contain Lipopolysaccharide (LPS) on their outer membrane [4,5] is an important molecule in the structure and function of the outer membrane and serves as toxic effectiveness [6]. *H. pylori* are gram negative bacteria, spiral in shape with unipolar sheathed flagella (4-8) and terminal lumps, microaerophilic, their dimintions are 3 µm long and 0.5 µm diameter [7,8], the spiral shape of the bacteria and their flagella allow it from motile in the mucus of the gastric juice. *H. pylori* first named Compylobacter pyloridis and then for reason related to the provisions of the Latin designation was changed to *Campylobacter pylori* and last to *Helicobacter pylori* due to differences in ultrastructure like presence of sheathed flagella with terminal lumps, sequences of rRNA, differences in cellular fatty acids, enzymatic capacity and growth requirements [9]. *H. pylori* has the ability to changed their shaped from spiral to coccid shaped within 1-2 hrs at room temperature, and this shaped haven't any form of virulence [10,11]. Human gastric mucosa represents the main host for *H. pylori* infection. Apparently all *H. pylori* strains are isolated from biopsy samples, and also transiently present in gastric juice, saliva, and stool [12]. *H. pylori* is isolated from domastic cats [13,14], this increased the role of domastic animals in transmission of the disease to human.

H. pylori is endemic in the cardiac portion, body, and antrum of the stomach and may exist under the mucus layer close to the epithelial cells, and sometimes may invade the bloodstream [15,16]. *H. pylori* have many features enable it to resist the harsh environment for the stomach. They

has the ability for production huge amount of urease enzyme, where the latter has the ability to hydrolyzed urea to bicarbonate and ammonium ions for allows the bacteria to pass through the barrier of gastric acid to protective mucous layer. Ammonium ions worked as buffer in the bacterial environment to neutralized hydrogen ions to facilitate adaptation with gastric juice [17,18]. Other studies explained the importance of urease enzyme in bacterial colonization [19,20]. *H. pylori* has the ability to produce 15% from urease enzyme proteins, this enables used this enzymes as clinical test in *H. pylori* diagnosis as CLO (Campylobacter like organism) test by detect bacterial infection in gastric biopsy, and urea breath test (UBT) by using radio isotopic (C14 or C13) as non-invasive test for detection of *H. pylori* infection [19,21]. *H. pylori* has prominent flagella enables them from penetration mucus layer of the stomach and their infection is acquired early in life in economically poor communities. *H. pylori* infection causes chronic inflammation in the mucosa of the stomach and the infected patients don't show any significant clinical symptoms. *H. pylori* infection is associated with upper gastrointestinal diseases development. Where, 1–10% of peptic ulcers are related with *H. pylori* infections, and these inflammations are located within antral region (non–acid secreting) of the stomach, cause released gastrin hormone, cause excess secretion of acid from fundic region of the stomach result in ulceration of the duodenal mucosa [22,23]. So treatment of *H. pylori* infection leads to cure in 80% of patients. Chronic infections lead to gastric cancers [24], this risk is increased when the infection is dominant in the mucosa of both antral and fundic region; then lead to atrophy of the mucosa and intestinal metaplasia [25].

Non-steroidal anti-inflammatory drugs is one of many drugs caused damage to gastroduodenal mucosa [26], many studies explained the relationship between the infection with *H. Pylori* and both idiopathic thrombocytopenic purpura and deficiency idiopathic iron anemia [27]. *H. pylori* has the ability to produce hydrogenase enzyme used for hydrogen molecule (H2) oxidation secreted by gut bacteria for energy production, also have the ability for products oxidase, catalase, and urease enzymes, biofilm formation, coccal transformation (non-cultural form); both spiral and coccid forms of *H. pylori* is favored for survival and be factors for epidemiology, the coccid form has the ability for adherence to gastric mucosa in vitro [8,28].

H. pylori has lipopolysaccharide (LPS) in their outer membrane and cholesterol glucosides. *H. pylori* are highly motile according to their own of flagella (4-8 lophotrichous flagella). Characteristic the sheathed flagellar filaments for Helicobacter are composed from two copoly merized flagellins, FlaA and FlaB [8].

Virulence factor for H. pylori

Cytotoxic associated gene Antigen (CagA)

This gene represents the indicator for the most risk strains for peptic ulcer and gastric cancer [29-31]. Cag A produces by 60% strains of *H. pylori* and linked strongly with a duodenal ulcer and these strains of *H. pylori* considered the most dangerous in peptic ulcer and gastric cancer [31,32].

Vacuolating cytotoxin gene A (VacA)

Vac A is the most important gene in *H. pylori* that produce protein causing vacuolation in the epithelial cells of the stomach. This pathogenic protein causes pores in the gastric epithelial cells membrane and allowing the urea and negative ions to exit [33,34] and this induces *H. pylori* infection by urea hydrolysis with urease enzyme activity, protecting the bacteria from the acidity of the stomach and thus leading to changes in cytoskeletal of the cell, apoptosis, and suppression of cell division in the stomach [35,36].

During colonization by H. pylori, it stimulates releasing variety cytokines, from which: IL-1, IL-8, and tumor necrosis factor-α (TNF-α) [37]. Molecular mimicry was found between *H. pylori* and antigens of the host in patients infected with H. pylori. *H. pylori* have a role in path of genetic in characterization of diseases by abnormal releasing of cytokines or induction of immunity [38].

Urease enzyme

H. pylori has the ability to transport and growth in harsh environment conditions as in the human stomach, possesses the ability to produce huge amount of urease enzyme, and their ability to hydrolyzed the urea to CO2 and ammonia, ammonia work as a buffer in the vicinity of

bacterial growth and neutralized the hydrogen ions [20]. *H. pylori* produce 15% of urease enzyme proteins, used in clinical diagnosis of infection by *H. pylori* by detection the presence of bacteria in the clinical specimen [39], like urea breath test using radioactive isotopes C13 or C14 [21].

Pathophysiology

Owning the bacterium to spiral form and the flagella allowing the bacteria to motile in mucus layer and gastric juice. Hydrolysis of urea in the gastric juice by urease enzyme produces bicarbonate and ammonium ions this form protected space around the bacteria allowing it from passage the barrier of the gastric acidity and reached mucous layer, then the ammonia ions releases from urea hydrolysis increases the PH of the stomach to reach 7 [17,40]. Aerobic cells depleted for alpha keto-glutarate, represent essential substrate for tricarboxylic acid cycle (TCA) in the cell. Present the ammonia ions in huge amount causes formation of vacuoles as same as exposes the cells to Vaculating A toxin for *H. pylori* [41,42]. In the mucus layer, *H. pylori* has the ability to attaches to the phospholipids layer of the host cell membrane as phosphatidyl ethanolamine, sialylated glycoproteins, and Lewis antigens B in blood group O [43]. During their attaches to the mucus layer, they secrets chemicals like soluble proteases enzyme and phospholipase enzyme, these two enzymes have harmful effects on the mucus layer and underlying layer. Increased moisturized during *H. pylori* infection in the mucus layer occurs due to phospholipid lysis [44,45].

Duodenal ulcer promoting gene A (dupA) another virulence associated with *H. pylori* in many populations from previous reports included 2,358 patients appeared positive with dupA gene [46]. *H. pylori* cause increases the level of gastrin which in turn increases secretion of gastric acid causing duodenal ulcer. Eradicate of *H. pylori* decrease hypergastrinemia and those indicated infections with *H. pylori* [47]. Deficient Somatostatin in the antrum part of the stomach found in patients with H. pylori, and all somatostatin related function from immunoreactivity, D cells are decreases in *H. pylori* patients [48]. Parietal cells mass are increases during *H. pylori* infection due to genetic predisposition or alteration in the function of G-cell (gastrin cell) or D-cell (somatostatin-producing cell), this large parietal mass leads to increases the acidity of the stomach and causes gastric metaplasia in the duodenum of some patients infected with H. pylori. Antral gastritis caused by *H. pylori* has prerequisite for colonization, duodenal metaplasia which leads to duodenitis, and then duodenal ulcer [49].

Laboratory diagnosis

There are several methods for detection the infection with H. pylori, from which advantages, disadvantages, and limitations. Endoscopy is first way for detection. Diagnostic method that depends on biopsy sample such as histological examination, culture on a properate media, PCR, RUT, previously tests requires the tissue sample (biopsy) that collected during endoscopy. The other tests, UBT, serology test, and detection antigen of bacteria in the stool (SAT), these tests not depend on biopsy samples so it's not requires endoscope.

Invasive methods

Histopathological test and microscope

Histological test is the standard method for diagnosed and collect information on the mucosa layer of the stomach like the presence of inflammation and determine their severity, intestinal metaplasia, glandular atrophy, dysplasia, and neoplasia. In this test depend on biopsies are taken from the antrum and pyloric regions of the stomach and combined with other biopsy are taken from corpus region of the stomach for *H pylori* diagnosis during the infection in patients with dyspepsia on acid suppression therapy [50].

Culture

Biopsy samples are specific for *H. pylori* culturing where there's no commensal bacterial flora was suspected (gastric acid reduction increases overabundance of commensal bacteria flora). Taken samples from the gastric juice other than biopsy are less invasive, and can be used for culturing but less sensitivity than when biopsy specimens are used [51].

Polymerase chain reaction (PCR)

Small samples were used for *H. pylori* diagnosis by PCR technique where few bacteria are present in the sample. This technique can be applied on invasive and non-invasive methods and not required to any processing or special transport; and this technique is fast and precise and can

be used to diagnose diverse bacterial genotypes for this reason used in epidemiological studies. But disadvantage of this technique is detection segments of DNA for dead bacteria in the mucosa layer of the stomach after treatment and lead to false-positive results [51].

Rapid urease test (RUT)

This test used to determined *H. pylori* ability in production huge amount of urea as a result of diagnosis of infection. Biopsy collected by endoscopy is place in media contain urea and pH indicator. Presence of urease enzyme, the urea was brake down to CO2 and NH3, the ammonia ions changes the color of media by pH indicator. Reading of urease enzyme activity is during the first minutes of the test and the maximum reading is 24 hrs, depend on the amount of bacterial numbers in biopsy sample. This test is inexpensive, give the result through the first time, available, and specific from which we can know the presence or absent bacteria in the biopsy.

Urea breath test depend on *H. pylori* ability in producing urease enzyme although many others microbiota in oropharynx produces urease enzyme when is swallowing in saliva, and denature rapidly in the stomach due to high acidity. So this test may give false-negative results due to lowing activity of urease enzyme caused through gives of antibiotics, gives of bismuth compounds, or gives proton pump inhibitors (PPIs) [52].

Noninvasive methods (not requiring endoscope) for detection *H. pylori* include

Serological test

Serological test includes several techniques for detection antibodies formed against H. pylori, of which enzyme immunoassay (EIA) test; this technique based on detection of IgG, with high sensitivity and specificity 60% to 100% respectively. Factors that give importance for evaluation quality of this test in active infection are the prevalence of infection (recent or past infection), aggravation of geography, and population's characteristics. Validity of this test is necessary. Serological tests that contain mixtures of complex antigen for various strains appear with high sensitivity [53].

Stool antigen test (SAT)

Stool antigen test is an enzyme immunoassay technique used for detection the bacterial antigens in the stool samples. This test is active for detection *H. pylori* infection and then determines active treatment. Stool specimen is store in room temperature for 24 or 72 h at 4°C, more time in the refrigerated; this test is exposed to low sensitivity within 2 to 3day. Many factors effects on the results of this test are: digestive disorders, treatment with PPI, and appeared bleeding ulcer [54].

Urea breathing test (C13-UBT)

Urea breath test depend on ingested labeled urea (C13 or C14) after 2h from ingestion, then exhaled breath is collected in closed tube and examined labeled CO2 concentration, high concentration means the presence of *H. pylori* due to urease activity.

PEPTIC ULCER TREATMENT

The therapeutic regimens that uses in treatment of *H. pylori* infection are: triple therapy is the initial treatment is used, including proton pump inhibitors (PPI), clarithromycin antibiotic and amoxicillin antibiotic (or metronidazole used when the patients have allergy with penicillin [55].

First-line therapy

Initial treatment varying in different regions, according to resistance of microbes to antibiotics and availability of it. International guidelines [56] recommend used the triple therapy (PPI + clarithromycin + amoxicillin – all b.i.d.). Resistant of clarithromycin and metronidazole is the cause in decreasing the efficiency of triple therapy where it rang from 72% to 78% lower than the 80% is the minimum eradicated rate expected for an infectious disease [57].

Second-line therapy

This line of therapy remaining unclear; the current guidelines of the Maastricht-IV suggested the treatment with quadruple therapy that containing bismuth or triple therapy containing levofloxacin after failure the treatment that containing PPI with clarithromycin [58]. You can nutritionally prevented stomach ulcers and help yourself healing, instead of reliev the symptoms [59].

Natural remedies that help treat the peptic ulcer

Probiotics

Acidophilus and Bifidus bacteria (Beneficial bacteria) slow the growing of *H. pylori* in six weeks [59,60] and can also killed it. Probiotics can also reduce the side effects and improve

the affectivity of conventional treatment, Recommended take a high-strength probiotic providing 10 billion CFUs daily a week before antibiotic therapy, and for three months after antibiotic therapy. (Probiotics are graded by the number of colony forming units (CFUs)) [60].

Oregano

Oregano one of the best natural agents uses against H. pylori, by inhibit the production ability of *H. pylori* to chemicals that neutralize acidity in their vicinity, allow them to survive, so it is effective natural antibiotic. Can be present in capsules or tinctures, taken 15–45mg a day [61].

Deglycyrrhised liquorice root (DGL)

Deglycyrrhised liquorice root causes suppress the growing of *H. pylori* and repaired and strengthened the epithelial lining of the stomach. Taken 500mg–1,500mg a day, must be taken liquid form of DGL, since liquorice can be raised blood pressure if be taken for long term [62].

Mastic gum

Mastic gum is uses in the traditional medicine in Greek for thousands of years for gastrointestinal disorders, from whom the peptic ulcer. In 2012 Greek Researchers found that mastic gum did not eradicated H. pylori, but reduced their numbers [63].

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