REVIEW ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Helicobacter pylori Infection: Diagnosis and Therapy

Darius Hartanto[1,2]

[1]*Faculty of Medicine, North Sumatera University, Medan, Indonesia,* [2]*Medical Doctor of Sathya Sai Primary Clinic, Jakarta, Indonesia*

Submission: 24-01-2021 Revision: 25-02-2021 Publication: 01-04-2021

ABSTRACT

Helicobacter pylori (H. pylori) is a spiral shape gram-negative bacillus and have flagella for motility in mucus environment. *H. pylori* is microaerophilic organism, slow growing and requires complex growth media in vitro. *H. pylori* infecting more than 50% populations in worldwide. Prevalence of *H. pylori* infection is higher in developing countries compared to developed one, and indicates that socioeconomic and living standard may play a major role in the distribution. This study aims to provide an overview of how to diagnose and manage *Helicobacter pylori* infection. This study reviewed various sources then reviewed as a literature review. The most successful regimens are triple and quadruple combinations, which consist of a PPI and two or three antibiotics for 7 – 14 days. Patient's compliance and the use of drug to which strain of *H. pylori* has not acquired resistance are the most important factors in successful *H. pylori* treatment.

Key words: *Helicobacter pylori*; microaerophilic; antibiotics

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v12i4.34506

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a spiral shape gram-negative bacillus and have flagella for motility in mucus environment. *H. pylori* is microaerophilic organism, slow growing and requires complex growth media in vitro.[1] *H. pylori* also a part of primary causes for upper gastrointestinal diseases such as dyspepsia, heartburn, gastroesophageal reflux disease, peptic ulcer, and malignancy.[2]

H. pylori infecting more than 50% populations in worldwide. Prevalence of *H. pylori* infection is higher in developing countries compared to developed one, and indicates that socioeconomic and living standard may play a major role in the distribution.[2] *H. pylori* was stated as definite carcinogen of gastric cancer by International Agency for Reasearch on Cancer (IARC) in 1994. This pathogen can cause superficial gastritis, atrophic gastritis, intestinal metaplasia and dysplasia, which can lead to cancer.[3]

PATHOPHYSIOLOGY

Colonization

H. pylori colonization in host gastric environments require special mechanism. After reaching the stomach, *H. pylori* uses the aid of the flagellum to swim in the stomach contents until it reaches the gastric mucosa. *H. pylori* mobility also takes advantage of chemotaxis activity in response to various molecules such as mucin, sodium bicarbonate, urea, sodium chloride, and some specific amino acids. There are about 10 *H. pylori* genes that are associated with reception, signal transmission, and processing of chemotaxis stimuli. There are several chemoreceptors namely T1pA, B, C, and D, Che A kinase, and various protein couplings. This protein is important in bacterial colonization.[4]

Address for Correspondence:
Dr. Darius Hartanto, Tanjung Duren Raya Street No. 101 C, Jakarta, Indonesia, 11520. **Mobile No:** +6285773608233.
E-mail: darius_hartanto@hotmail.com

Nickel (nickel transition metal) is an important metal for *H. pylori* because it functions as a cofactor of the urease and hydrogenase enzymes.[4] Urease hydrolyzes urea to carbon dioxide and ammonia so that bacteria can survive in an acidic environment. Enzyme activity is regulated by pH-gated urea channels (Ure-I) which open in low pH and close the urea flow when pH is neutral.[5] The hydrogenase enzyme facilitates *H. pylori* to uses hydrogen molecules as a source of energy for its metabolism.[4]

Adhesin molecules and gastric surface receptors are also important in the interactions between bacteria and the host. One of the adhesive molecules is BabA (Blood group antigen binding adhesin A) which binds specifically to the Lewis H-1 antigen. Bacteria with high BabA expression are more virulent and can cause duodenal ulcers and gastric adenocarcinoma (Table 1).[4]

CagA

CagA pathogenicity island (Cag-PAI) is a group of genes encoding the Type IV secretion system.[4] Some of these genes play a role in translocation of CagA into host cells. In epithelial cells, CagA phosphorylation occurs and binds to SHP-2 tyrosine phosphatase, causing a cellular growth factor-like response and cytokine production by the host cell.[5] CagA pathogenicity islands are present in 40 - 60% of *H. pylori* strains and are associated with peptic ulcer formation and gastric cancer.[6]

Non-CagA Virulence Factors

VacA protein plays a role in the pathogenicity of *H. pylori* and is present in almost all strains of bacteria. VacA stimulates the formation of acidic vacuoles in the cytoplasm of gastric epithelial cells. This causes instability of the mitochondrial integrity, cytoplasmic membrane, and endomembranous structures, so that the cell collapses.[4]

The DupA protein causes the bacteria to become more resistant to high acids and promotes IL-8 formation in the antrum mucosa. IL-8 can cause mucosal inflammation and polymorphonuclear cell infiltration, thus playing a role in gastritis and duodenal ulcers.[4]

OipA outer membrane protein plays a role in adhesion and increases IL-8 production. The GGT enzyme produced by *H. pylori* plays a role in the formation of reactive oxygen species (ROS), causing apoptosis and cell necrosis. This enzyme also inhibits T cell proliferation and dendritic cell differentiation.[4]

Host genetic and environmental factor

Genetic polymorphisms lead to enhanced activation of innate immune response, includes polymorphisms in cytokine genes or genes for encoding the bacterial recognition proteins (Toll-like receptors). Smoking can increase the risk of gastric carcinoma and duodenal ulcers in patients with *H. pylori* infection. High salt and preserved foods diet can also increase the risk for cancer, whereas high vitamin C and antioxidant diet can act as protective agent.[1]

Based on Figure 2 sequenced by the number, (1) VacA protein play multiple roles of cellular processes in chronic *H. pylori* colonization. (2) Secreted VacA can initiate a proinflammatory response by binding to a cell membrane receptor, (3) directly taken up to the cell and trafficked to the mitochondria and cause apotosis, (4) taken up by pinocytosis and induce vacuolization, (5) causing nutrient leakage to extracellular space by formin a membrane channel, or (6) passing through the tight junction and inhibit activation and proliferation of T-cell.[7]

CLINICAL MANISFESTATION

Clinical manifestations are widely vary from asymptomatic, functional dyspepsia, peptic ulcer and gastric cancer.[5] Basically, all patients with *H. pylori* colonization have abnormal histologic gastritis, but around 10-15% develop an associated disease such as peptic ulcer, gastric adenocarcinoma, or gastric lymphoma.[1]

Gastritis

Colonization of *H. pylori* in the first week may be associated with acute gastritis with nonspecific dyspepsia symptoms such as a stomach fullness, nausea and vomiting.[6]

Table 1: H. pylori adhesion molecules[4]

BabA	Specific binding to the b and H-1 Lewis antigens from the surface of the gastric epithelial cells
SabA	Binding to Lex, which is upregulated in gastric epithelial cells by *H. pylori* after initial colonization mediated by BabA. Also allows the adherence of the bacterium to laminin, an extracellular matrix protein
AlpA and AlpB	Mediation of adherence to gastric mucosal cells and promotion of inflammatory intracellular signaling cascades (might induce IL-8 and IL-6)
OipA	Adhesion to the gastric mucosa cells and promotion of proinflammatory environment (associated with IL-8 increase, mucosal damage and duodenal ulcer)
HopQ	Interaction with CEACAM family proteins of gastric mucosal cells, allowing CagA translocation. Might inhibits the activity of natural killer cells and T cells
HopZ	Interaction with undetermined receptors, promoting adhesion to gastric cells

H. pylori: Helicobacter pylori; CagA: Cytotoxin associated antigen A; IL: Interleukin; BabA: Binding adhesin A; OipA: Outer inflammatory protein.

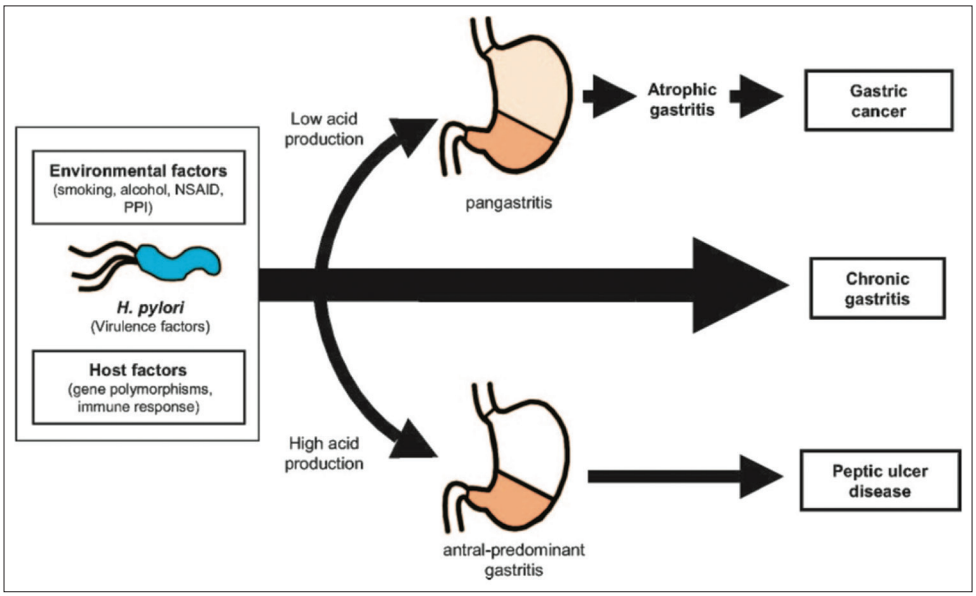

Figure 1: *H. pylori* and disease outcome[7]

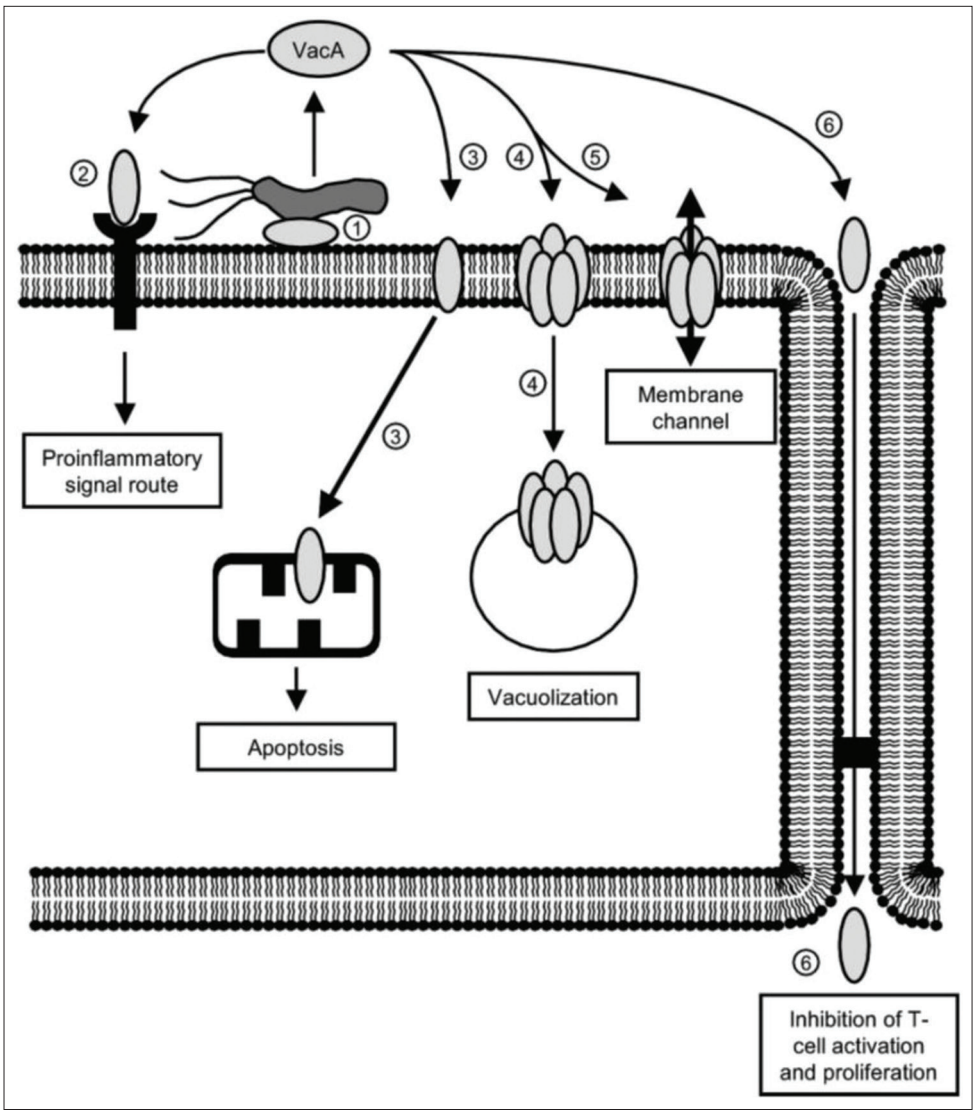

Figure 2: *H. pylori* VacA protein pathway[7]

Table 2: Treatment regimens proposed for the management of Helicobacter Pylori[9]

Treatment	Asia-Pasific Region	Developing Countries	Europe	United States
First-Line	Triple therapy (PPI+CLA+AMO/MET) BIS-based quadruple therapy (PPI+BIS+MET+TET)	Triple therapy (PPI+CLA+AMO/FUR) Quadruple therapy (PPI+CLA+AMO+BIS/MET or PPI+BIS + MET+TET)	Triple therapy (PPI-CLA-containing regimen) BIS-based quadruple therapy (for high clarithromycin resistance) Sequential therapy (for high clarithromycin resistance)	Triple therapy (PPI+CLA+AMO/MET) BIS-based quadruple therapy (BIS+MET+TET+RAN) Sequential therapy (PPI + AMO and PPI+CLA+TIM)
Second-Line	BIS-based quadruple therapy (PPI+BIS+MET+TET) LEV-based triple therapy (PPI+LEV+AMO) RIF-based triple therapy (PPI+RIF+AMO)	Sequential therapy (PPI+AMO and PPI+CLA+NIT) BIS-based quadruple therapy (PPI+BIS+TET+MET/FUR) LEV-based triple therapy: (PPI+LEV + BIS/FUR/AMO)	BIS-based quadruple therapy LEV-based triple therapy	BIS-based quadruple therapy (PPI+TET+BIS+MET) LEV-based triple therapy (PPI+AMO+LEV)
Third-Line	RIF-based triple therapy (PPI+RIF+AMO)	LEV-based or FUR-based triple therapy (PPI+AMO+LEV/RIF or PPI+FUR + LEV)	Guided by antimicrobial susceptibility testing	

AMO: Amoxicillin; BIS: Bismuth; CLA: Clarithromycin; FUR: Furazolidone; LEV: Levofloxacin; MET: Metronidazole; NIT: Nitronidazole; RAN: Ranitidine; RIF: Rifabutin; TET: Tetracycline; TIM: Timidazole; PPI: Proton pump inhibitor.

Functional dyspepsia

Some patients with functional dyspepsia have colonization of *H. pylori*. Research shows that eradication of *H. pylori* can improve symptoms, but it is not known whether the patient actually had a peptic ulcer that already remitted on endoscopy or if it was functional dyspepsia that responded to *H. pylori* therapy.[1]

Peptic ulcer

About 20% of individuals who tested positive for *H. pylori* infection can develop peptic ulcer disease. Ulcers can be associated with bleeding and perforation of the intestine, and in some cases stricture formation occurs. Ulcers can be duodenal ulcers and gastric ulcers.[6]

Gastric cancer

H. pylori can initiate chronic cell proliferation and promote mutagenic processes in the presence of carcinogenic substances. Only 1-2% of patients infected with *H. pylori* develop gastric carcinoma.[6] *H. pylori* colonization is a risk factor for distal (noncardial) gastric adenocarcinoma.[1]

Mucosa-associated lymphoid tissue (MALT) lymphoma

Normal gastric mucosa contains no lymphoid follicles, but in all individuals who are positive for *H. pylori*, there are lymphocytes in the gastric mucosa. In rare cases, MALT B-cell lymphoma is formed.[6]

Menetrier's disease

Menetrier's disease or hypertrophic gastropathy is a rare condition with an unknown etiology. Most cases are associated with *H. pylori* infection, and *H. pylori* eradication may improve symptoms.[6]

DIAGNOSIS

Non-endoscopic testing

Urea breath test (UBT)

UBT has the highest accuracy among all of other noninvasive test.[7] UBT is requires patient to ingest wether non-radioactive ^{13}C or radioactive carbon ^{14}C. Urea will be breaks down by urease that produced by the bacteria and releasing the labeled carbon dioxide which can be measured by exhaled air. Antibiotics and bismuth need to be avoided for at least one month prior, and 7-14 days prior for PPI.[8]

H. pylori antibodies in blood, saliva, and urine

IgG antibodies of H pylory usually are generally detectable around 21 ays after infection and can remain positive after eradication.[8] Some publication shows that IgG antibodies level tested using ELISA shows higher sensitivity and specificity in saliva by 85% and 82% respectively than in serum by 71% and 79% respectively.[7]

Stool antigen test (SAT)

SAT identifies *H. pylori* antigen in stool using immunologic techniques (polyclonal antibody directly against the *H. pylori*). SAT can be used for screening and confirming eradication (8 weeks after complete therapy). Avoid using of PPI 14 days prior is needed to minimize the chance of obtaining false negative.[8]

Endoscopic testing

Biopsy urease test (BUT)

BUT is the most convenient biopsy-based test, using one or two biopsy specimens and placed in a gel containing urea and an indicator. *H. pylori* will alter the pH and therefore changes the color, which occurs within minutes but can up to 24 hours.[1]

Histology

Histology testing using gastric biopsy has a high sensitivity and specificity exceeding 95%. Combining gastric body and antral biopsies will increase the detection rate of *H. pylori*.[8] This test uses a special stain (Modified Giemsa or silve stain) for optimal visualization of the organism.[1]

Bacterial culture and PCR

Culture test may be insensitive because the difficulty of *H. pylori* isolation, although its specificity approaches 100%. *H. pylori* can be identified by its typical appearance using Gram's stains.[1,8] PCR is a DNA amplification technique to identify *H. pylori* using target DNA sequence. PCR able to detect *H. pylori* not identified on histology test, with sensitivity greater than 90%. This both methods are not widely available and rarely used.[8]

TREATMENT

The most successful regimens are triple and quadruple combinations, which consist of a PPI and two or three antibiotics for 7 – 14 days. Patient's compliance and the use of drug to which strain of *H. pylori* has not acquired resistance are the most important factors in successful *H. pylori* treatment (Table 2).[1]

Combination of a PPI and two antibiotics (Clarithromycin and Amoxicillin/Metronidazole) is the first line regimen for *H. pylori* infection treatment. The efficacy of standard triple therapy is decreasing and in some areas the eradication rate in below 80%. Maastricht IV/Florence Consensus Report has recommended the use of bismuth containing quadruple therapy as first line in areas with 15-20% resistance rate of Clarithromycin. Due to bismuth side effect, some countries are not using bismuth, but a non-bismuth-quadruple therapy as the recommended alternative first line therapy.[9]

REFERENCES

1. Atherton, J.C., Blaser, M.J. Helicobacter pylori Infections. In : 19th Edition Harrison's Principles of Internal Medicine. USA: *Mc Graw Hill Education* 2015; p1038-1042.
2. Rana R, Wang SL, Li J, Wang YX, Rao QR, and Yang CQ. Helicobacter pylori Infection: A Recent Approach to diagnosis and management. Journal of Biomedicine. 2017; 2:45-56.
   https://doi.org/10.7150/jbm.17612
3. Seta T, Takahashi Y, Noguchi Y, Shikata S, Sakai T, Sakai K, et al. Effectiveness of Helicobacter pylori eradication in the prevention of primary gastric cancer in healthy asymptomatic people: A systematic review and meta-analysis comparing risk ratio with risk difference. PLoS ONE. 2017; 12(8):e0183321
   https://doi.org/10.1371/journal.pone.0183321
4. Brito BBD, Silva FAFD, Soares AS, Pereira VA, Santos MLC, Sampaio MM, et al. Pathogenesis and Clinical Management of Helicobacter pylori gastric infection. World J Gastroenterol. 2019; 25(37): 5578-5589.
   https://doi.org/10.3748/wjg.v25.i37.5578
5. Rani AA and Fauzi A. Infeksi Helicobacter pylori dan Penyakit Gastroduodenal. In: Setiati, S., et al. Buku Ajar Ilmu Penyakit Dalam Edisi Keenam. Jakarta: Interna Publishing 2014; p1772-1779.
6. Hoed CMD and Kuipers EJ. Helicobacter pylori infection. In: Magil AJ, Solomon, T, Ryan ET. (eds.) Hunter's Tropical Medicine and Emerging Infectious Disease 9th ed. London: *Saunders Elsevier;* 2013. p 428-441.
7. Kusters JG, Vliet AHMV and Kuipers EJ. Pathogenesis of Helicobater pylori infection. Clinical Microbiology Reviews 2006; 19(3):449-490.
   https://doi.org/10.1128/CMR.00054-05
8. Skrebinska S, Megraud F and Bessede E. Diagnosis of Helicobacter pylori Infection. Helicobacter. 2018; 23(Suppl. 1):e12515.
   https://doi.org/10.1111/hel.12515
9. Wong U and McLean LP. Diagnosis and management of Helicobacter Pylori. J Clin Gastroenterol Treat. 2016; 2:015. https://doi.org/10.23937/2469-584X/1510015
10. Yang JC, Lu CW and Lin CJ. Treatment of Helicobacter pylori infection: Current Status and future Concepts. World J Gastroenterol. 2014; 20(18):5283-5293.
    https://doi.org/10.3748/wjg.v20.i18.5283

Author's contribution:
DH - Conceptualized and designed the study, literature search, prepared first draft of the manuscript, critical revision of the manuscript.

Work attributed to:
Faculty of Medicine, North Sumatera University, Medan, Indonesia

Orcid ID:
Dr. Darius Hartanto - https://orcid.org/0000-0001-5158-0971

Source of Funding: None, **Conflict of Interest:** None.