Clinical Outcome Controversy in Helicobacter pylori Infection

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ABSTRACT

H. pylori infection can manifest as intestinal and extraintestinal disease. In this review, we summarize several factors that cause differences in clinical manifestations of H. pylori infection. Host inflammatory response and bacterial virulence are key in determining the pattern of acid secretion and gastritis. The acid level factor that has a greater effect, not H. pylori infection itself. Gastritis predominant in the gastric in the initial phase will produce higher acid and trigger gastroesophageal reflux disease (GERD). H. pylori is also the cause of gastric adenocarcinoma. Different vacA genotypes are related to the risk of clinical manifestations such as peptic ulcer or gastric cancer. However, there is variance prevalence in some countries which can be explained through a combination of several factors including age at infection, virulence factors of H. pylori, host genetic profile, and environmental factors. Besides, important differences were found at a locus in CagA H. pylori which resulted in differences in clinical outcomes in the form of gastritis or MALT lymphoma. H. pylori infection alone is not enough to trigger idiopathic thrombocytopenic purpura (ITP). Additional triggers are needed to obtain an anti-platelet autoimmune response at ITP associated with H. pylori. Therefore, the difference in clinical manifestations of H. pylori infection remains controversial. H. pylori is not only a single cause, but the host and environmental factors also contribute to producing different responses.

Keywords: H. pylori, clinical manifestations, intestinal and extraintestinal disease

ABSTRAK

Infeksi H. pylori dapat bermanifestasi sebagai penyakit usus dan ekstraintestinal. Dalam ulasan ini, kami merangkum beberapa faktor yang menyebabkan perbedaan dalam manifestasi klinis infeksi H. pylori. Respon inflamasi host dan virulensi bakteri adalah kunci dalam menentukan pola sekresi asam dan gastritis. Faktor kadar asam yang memiliki efek lebih besar, bukan infeksi H. pylori itu sendiri. Gastritis yang dominan di lambung pada fase awal akan menghasilkan asam yang lebih tinggi dan memicu gastroesophageal reflux disease (GERD). H. pylori juga merupakan penyebab adenokarsinoma lambung. Genotipe vacA yang berbeda berkaitan dengan risiko manifestasi klinis seperti tukak lambung atau kanker lambung. Namun, ada prevalensi varians di beberapa negara yang dapat dijelaskan melalui kombinasi beberapa faktor termasuk usia saat terinfeksi, faktor virulensi H. pylori, profil genetik inang, dan faktor lingkungan. Selain itu, perbedaan penting ditemukan di lokus di CagA H. pylori yang menghasilkan perbedaan dalam hasil klinis dalam bentuk gastritis atau limfoma MALT. Infeksi H. pylori saja tidak cukup untuk memicu idiopathic thrombocytopenic purpura (ITP). Pemicu tambahan diperlukan
H. pylori infection can manifest as intestinal and extraintestinal disease. Intestinal diseases consist of peptic ulcer, chronic gastritis, gastroesophageal reflux disease (GERD), mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer; whereas extraintestinal diseases are related to cardiopulmonary, hematologic, metabolic, neurological and dermatological systems, also autoimmune diseases including idiopathic thrombocytopenic purpura (ITP).\(^5\)

Interestingly, epidemiological data show that there are contrasts in the clinical manifestations of H. pylori. One of the controversies is that some patients suffer from duodenal ulcer, while some others experience gastric ulcer. In addition, some patients suffer from gastroesophageal reflux disease (GERD), gastric cancer, MALT lymphoma and ITP, but others do not. In this review we summarize several factors that cause differences in clinical manifestations of H. pylori infection.

### INTRODUCTION

*Helicobacter pylori* is a gram-negative spiral bacterium and include as the class I carcinogenic agent.\(^1\,^2\) *H. pylori* colonizes in the gastric almost 50% of the world’s human population throughout their lives if not treated. The prevalence of *H. pylori* infection is between 30-50% in developed countries and between 85-95% in developing countries.\(^3\) Indonesia is reported to have a low prevalence of *H. pylori* infection compared to other countries in Asia. A study of 267 patients with symptoms of dyspepsia on five major islands in Indonesia found that the prevalence of *H. pylori* infection was only 22.1%.\(^4\)

*H. pylori* infection can manifest as intestinal and extraintestinal disease. Intestinal diseases consist of duodenal and gastric ulcer. Although the incidence tends to decrease, duodenal ulcer is estimated to occur in 3.5%, while gastric ulcer is estimated 2.4%. Duodenal ulcer is usually diagnosed in men and young age, whereas gastric ulcer occurs more often in older patients without any gender bias.\(^7\) The typical pattern of pain in duodenal ulcers is that pain occurs 90 minutes to 3 hours after eating and often disappears with antacids or food (hunger pain food relief), whereas pain in gastric ulcers is often triggered by food.\(^7\) *H. pylori* infection is related with an increased risk of peptic ulcer 3 to 4 fold and people infected with *H. pylori* will experience peptic ulcer is about 10-15% of.\(^8\)

Duodenal ulcer initiated by *H. pylori* arises due to the presence of non-atrophic corpus gastritis and antral-predominant gastritis. Antral inflammation causes a decrease in somatostatin production which causes a negative feedback effect on gastrin production and results in hypergastrinemia (Figure 1A). The mechanism of decreased somatostatin secretion may include three potential mechanisms. First, antral *H. pylori* gastritis can change the function of gastrin and D cells through local production of specific cytokines. *H. pylori* infection causes severe antral gastritis through mucosal infiltration with acute and chronic inflammatory cells. Second, cytokines are induced by inflammation and/or production of N-methyl histamine, a selective H3 receptor agonist, by *H. pylori*. Gastrin, in turn, stimulates histamine secretion from Enterochromaffin-like/ECL which leads to an increase in acid secretion. Third, *H. pylori* increases the mucosal surface pH based on high urease activity and ammonia synthesis. Low antral pH is an important physiological stimulus for the synthesis and release of antral somatostatin.\(^8\) So therefore, *H. pylori* should not be able to colonize the normal duodenum because it is inhibited by bile, can colonize due to the presence of gastric metaplasia that causes inflammation and ulceration.\(^7,^9\)

In gastric ulcer, acid hypersecretion lasts about 8 weeks and is caused by an increase in parietal cell mass and hypergastrinemia-induced ECL causing the gastric to respond with inflammation by reducing somatostatin levels, thereby releasing inhibition of G cells and parietal cells to maximize gastric acid output. Over time, predominant corpus gastritis in chronically infected patients reduces the amount of acid and causes atrophy of the glands of the specks with loss of parietal cells. Resulting irreversible achlorhydria and is associated with gastric ulcers (Figure 1B). The
The process of peptic ulcers is generally observed in the transition zone between the antrum and the corpus in the minor curvatura, which may be related to severe colonization and due to marked inflammation and epithelial damage and to ulceration. It is not clear why *H. pylori*-induced inflammation has a predominant pattern of pan-gastritis or corpus in some people, but antral predominance in others. One possibility is that it occurs similar to autoimmune gastritis caused by an immune effector with specificity for proton pump ATPase in the gastric. Interestingly, the involvement of acidity is supported by the observation that long-term gastric acid inhibition can result in a shift from antral-predominant to corpus-predominant inflammation.\textsuperscript{7,8}

Genetic polymorphisms in conjunction to bacteria and/or environmental factors. Duodenal ulcer is related with high acid secretion and high antral inflammation (A). Gastric ulcer related with pan gastritis or corporeal gastritis and decreased or normal acid secretion (B).\textsuperscript{8}

Host inflammatory response and bacterial virulence are key in determining the pattern of acid secretion and gastritis. East Asian CagA-positive strains can mainly induce corpus pangastritis or predominant gastritis with hypochlorhidria.\textsuperscript{9} Likewise strains with long intact dupA are related with an increased risk of gastric ulcer. Whereas patients infected with *oipA* strains, 12-bp *cagA* insertions, *vacA* d1 and *dupA* have a significant increased risk of duodenal ulcer (Table 1).\textsuperscript{8} Hosts with the *IL-1B-511* T/T allele had a significantly duodenal ulcer, whereas *IL-10-592-A/A* had a significantly higher frequency in gastric ulcer patients.\textsuperscript{8}

**Table 1. Outline of the relationship between host genetic polymorphism, bacterial virulence genes and peptic ulcer**\textsuperscript{8}

| Gen                  | Region          | Gastric ulcer | Duodenal ulcer |
|----------------------|-----------------|---------------|----------------|
| Host factors         |                 |               |                |
| TNF- A-238 G/A       | Western         | ↑             | ↑              |
| TNF- A-308 G/A       | Western         | ↑             | ↑              |
| TNF- A-857 T/T       | Western         | ↑             | ↑              |
| TNF- A-863 A carriers| Asian           | ↑             | ↑              |
| TNF- A-1031 C carriers| Asian         | ↑             | ↑              |
| IL-1B-31 C/C         | Asian           | ↑             | ↑              |
| IL-1B-511 T/T        | Asian           | ↑             | ↑              |
| IL-1B-31 C/C         | Asian           | ↑             | ↑              |
| IL-1 -RN2*2*         | Asian           | ↑             | ↑              |
| IL-6-572 G/G         | Asian           | ↑             | ↑              |
| IL-8-251 A/A         | Asian           | ↑             | ↑              |
| IL-10-819 T carriers | South American  | ↑             | ↑              |
| IL-10-592 A/A        | Asian           | ↑             | ↑              |
| CYP2C19 URM          | Western         | ↑             | ↑              |
| CYP2C19 RM           | Asian           | ↑             | ↑              |
| PSCA rs2 294008 C carriers | Asian   | ↑             | ↑              |
| Bacterial virulence  |                 |               |                |
| *oipA*               | Asia and Western| ↑             | ↑              |
| *babA*               | Western         | ↑             | ↑              |
| *cagA*               | Asian and Western| ↑         | ↑              |
| 12-bp insertion *cagA* | Asian         | ↑             | ↑              |
| *cagA* type Asia Timur | Asian         | ↑             | ↑              |
| *vacA* s1m1          | Asian and Western| ↑         | ↑              |
| *vacA* d1            | Asian and Western| ↑         | ↑              |
| *vacA* d1            | Asian           | ↑             | ↑              |
| *dupA*               | Asian           | ↑             | ↑              |
| intact long type *dupA* | Asian         | ↑             | ↑              |
| *iceA1*              | Asian and Western| ↑         | ↑              |
| TNF: tumour necrosis factor; IL: interleukin; CagA: cytotoxin-associated gene A; *oipA*: outer inflammatory protein A; *dupA*: duodenal ulcer promoting gene A; URM: ultra-rapid metabolizers; RM: rapid metabolizers, *vacA*: vacuolating cytotoxin gene A

**Gastroesophageal Reflux Disease (GERD) and non GERD**

GERD is a condition in which there is gastric reflux that expose the contents of the gastric to the esophageal squamous epithelium. Reflux disease is characterized...
Interesting, \textit{H. pylori} infection is lower in developed countries such as North America, Western Europe and Australia, while GERD and its complications are more common in these countries. In contrast, the frequency of \textit{H. pylori} infection is higher in developing countries such as South America, Eastern Europe, Africa, China and India while GERD and its severity are lower in these countries.\textsuperscript{11}

The existence of the negative correlation between the prevalence of GERD with \textit{H. pylori} infection raises the suspicion that \textit{H. pylori} has a protective effect to prevent the occurrence of GERD. It is also supported that patients with \textit{H. pylori}-positive peptic ulcers are more likely to develop GERD than patients with \textit{H. pylori}-negative gastric ulcers.\textsuperscript{12} But after further analysis, the acid level factor that has a greater effect, not \textit{H. pylori} infection itself. Gastritis predominant in the gastric in the initial phase will produce higher acid and trigger GERD. Whereas gastritis with antrum predominance has lower acid levels, thus, the risk of GERD is lower.\textsuperscript{10}

The genetic polymorphisms of IL-1B and IL-1RN are inversely proportional to the risk of GERD in \textit{H. pylori}-infected subjects because their specific genotypes are related to gastric cancer, hypochlorhidria and corpus atrophy.\textsuperscript{9,11} Thus, these specific genotypes, including the IL-1RN-1, IL-1B-511-T, and IL-1B-31-C allele, can be considered protective against GERD. Specifically, subjects with IL-1B-511 T alleles were emphasized in the presence of \textit{H. pylori} infection due to high gastric mucosal IL-1 \( \beta \) levels. However, other researchers have reported conflicting results that the IL-1B-511-T allele is related with reflux oesophagitis.\textsuperscript{9,11} A few genetic risk factors for GERD, including polymorphisms in the G-protein beta 3 (GNB3) subunit, glutathione S-transferase P1, IL-10, CYP2C19, DNA repair genes and cyclin D1, may be involved. The interaction between the virulence of \textit{H. pylori} infection and genetic factors may be the cause for the low prevalence of GERD in Asian states.\textsuperscript{9,11}

\textbf{Gastric Cancer and Non Gastric Cancer}

\textit{H. pylori} is the cause of gastric adenocarcinoma. Gastric adenocarcinoma is divided into intestinal and diffuse subtypes. The sequence of pathological changes leading to intestinal type cancer starting with chronic gastritis, followed by gastric atrophy and continues to intestinal metaplasia, dysplasia, and finally carcinoma.\textsuperscript{13} There were 21,000 new cases of gastric cancer in the United States and 10,570 Americans died in 2010.\textsuperscript{1}

Interestingly, there is a population infected with \textit{H. pylori} in Africa by 91\%, but has a very low prevalence of gastric cancer. Similar patterns are reported in South Asian countries such as India and Bangladesh. In contrast, in East Asian countries such as Japan, China and Korea; there is a positive relationship between the prevalence of gastric cancer and \textit{H. pylori} infection. This variance can be explained through a combination of several factors including age at infection, virulence factors of \textit{H. pylori} (Table 2), host genetic profile and environmental factors.\textsuperscript{14}

CagA protein is injected into the host cell via T4SS. In both humans and animals, CagA expression is related to the host's inflammatory response and increases the risk of developing mucosal ulcer and atrophy. The presence of CagA-positive increases the risk of developing gastric cancer by about 2-fold. Whereas gastritis, peptic ulcer and gastric cancer also occur in CagA-negative \textit{H. pylori} infection. It can be explained that infection with CagA-positive strains is associated with increased IL-8 production. In vitro experiments also showed epithelial cells infected with CagA-positive \textit{H. pylori} producing elongation and spread of epithelial cells, referred to as the 'hummingbird phenotype'. In vivo studies of a number of different experiments in experimental animals have shown that CagA-positive infection is associated with increased gastric mucosal inflammation.\textsuperscript{2}

The CagA protein subtype is based on the presence of the Glu-Pro-Ile-Tyr-Ala motif (EPIYA). Variations in amino acid sequences consist of EPIYA motifs that identify 4 subtypes, namely APIYA-A, APIYA-B, EPIYA-C and EPIYA-D followed by CagA which are separated into Western-types (ABC, ABCC, ABCCC) or East-Asian type (ABD). East-Asian-type CagA showed stronger in vitro affinity ties to the Src homology 2 domain from Src homology 2 containing protein-thyrosine phosphatase (SHP2) as well as a better ability to induce the hummingbird phenotype compared to Western-type CagA. Both types are associated with greater mucosal inflammation than CagA-negative infections. \textit{H. pylori} East-Asian type CagA is also associated with greater mucosal inflammation than infection with Western-type CagA.\textsuperscript{2} Thus, patients infected with \textit{H. pylori} CagA positive and East-Asian type CagA tend to have a higher risk of developing gastric cancer than the negative one.

VacA was recognized as vacuolating cytotoxin, functioning vacuation of epithelial cells in vitro. VacA have multiple functions, including initiation of infection, lymphocyte modulation, changing
membrane permeability in mammalian epithelial cells. Different vacA genotypes are related with the risk of clinical manifestations such as peptic ulcer or gastric cancer. Genes are divided into two types based on differences in the signal and middle regions (ie types tipe s’ and m’). The vacA s1m1 genotype is related with the most cytotoxic strain and is associated with an increased risk of gastric cancer. This is supported by the relationship between the vacA s1m1 genotype and peptic ulcer or gastric carcinoma in the Middle East, Latin America, and several African states. Studies in Spain report that strains of vacA s1 and m1 tend to develop preneoplastic gastric lesions. In the Portuguese population, s1m1 is related with an increased risk of gastric carcinoma. The outer inflammatory protein (OipA) is associated with increased inflammation and involves the production of IL-8 in the gastric mucosa via interplay with AP-1, nuclear factor-kappaB (NF-κB) transcription factors and ISRE-like elements. OipA’s ability to increase NF-κB activity is an independent PAI cag. A study shows that oipA 'on' shows a significant relationship with an increased risk of peptic ulcer and gastric cancer. The representation of the antigen-binding adhesin (BabA) blood group, which adheres to monofucosilat ABO and diphosylate (Lewisb) can be thought of as BabA blood group, which adheres to monofucosilat (BabA) and is turned to carcinogens. The amount of salivary nitrates and nitrites is positively associated with the high prevalence of gastric cancer in endemic areas in other states.

Mucosa-associated Lymphoid Tissue (MALT) Lymphoma and non MALT Lymphoma

Primary gastric lymphoma is the most common extranodal site of non-Hodgkin’s lymphoma and ranges from 30% to 40% of all extranodal lymphomas. It also represents 4% to 20% of all non-Hodgkin’s lymphomas and about 5% of primary gastric neoplasms. The frequent histological subtype in primary gastric lymphoma is marginal B cell zone lymphoma of MALT lymphoma. The incidence of development of primary gastric lymphoma is 2-3 times higher in men than women. Clinical manifestations vary from nausea, vomiting, dyspepsia, epigastric pain to massive bleeding, chronic gastric bleeding with iron deficiency anemia, pyloric stenosis, and weight loss.

MALT gastric lymphoma is very strongly related with H. pylori infection. During H. pylori infection, normal B cells are transformed into malignant clones through three translocations of chromosomes t (11; 18) (q21; q21), t (1; 14) (p22; q32) and t (14; 18) (q32; q21), results in the activation of kappa B nuclear factor (NF-κB), which acts in inflammation, apoptosis and immunity. Studies show that t (11; 18) (q21; q21) is found more frequently in patients with a CagA-positive H. pylori strain that determines occurrence of MALT lymphoma. However, conventional cagA and vacA genotypes did not show a significant difference between gastric cancer and MALT lymphoma. Further analysis of complete sequences of protein from CagA and VacA could recognize four loci in CagA, and three loci in VacA that could potentially cause MALT lymphoma or gastric cancer in the long term. Important differences were found at a locus in CagA H. pylori which resulted in differences in clinical outcomes in the form of gastritis or MALT lymphoma. In addition, a locus was found in VacA which caused a difference between gastritis and gastric cancer.

Table 2. Putative virulence factors that may be associated with clinical manifestations

| Gene or region | Protein | H. pylori virulence genes type |
|---------------|---------|-------------------------------|
|               |         | High virulent | Less virulent |
| cag PAI       | CagA    | Complete | Incomplete or absent |
| cagA          | CagA dan T4SS | Positive | Negative |
| vacA          | VacA    | East-Asian type CagA | Western-type CagA |
| babA          | BabA    | Multiple repeats (e.g. ABCC, ABCCC, ABBB) | Single repeat |
| oipA          | OipA    | s1, m1, i1, d1 forms | s2, m2, c2, d2 forms |
|               |         | Present | Absent |
|               |         | On | Off |

CagA: cytotoxin-associated gene A; oipA: outer inflammatory protein A
Other studies show patients with MALT lymphoma have a high prevalence of Human Leucocyte Antigen (HLA)-DQA1*0103, HLA-DQB1*0601 and R702W mutations in the NOD2/CARD15 gene.\textsuperscript{17}

**Idiopathic thrombocytopenic purpura (ITP) and non ITP**

ITP is defined as an autoimmune disorder characterized by immunologic destruction of normal platelets. \textit{H. pylori} infection is a secondary cause of ITP\textsuperscript{19,20}. The prevalence of \textit{H. pylori} infection in patients with ITP is higher than healthy individuals of the same age group and gender.\textsuperscript{19} At least 70\% of cases diagnosed in childhood will heal fully within six months, even no treatment. One third of the remaining chronic cases will fully recover during the follow-up period, another third will only finish with mild thrombocytopenia. Thrombocytopenia purpura is usually prolonged in adults and the chance of complete remission is 20-40.\textsuperscript{21}

Several authors have looked for differences in hereditary factors in ITP patients with or without \textit{H. pylori} infection. Several studies examined HLA-DQB1 and DRB1 alleles in Italian patients with ITP and found that \textit{H. pylori}-positive patients had higher DRB1*11 frequencies, DRB1*14, and DQB1*03, and lower DRB1*03 frequencies, compared with \textit{H. pylori}-negative patients. Nevertheless, several studies unsuccessfully to find an relationship between \textit{H. pylori} infection and HLA-DQB1 or DRB1 alleles in Japanese patients with ITP. Gene polymorphisms in the IL-1β are related with \textit{H. pylori} infection in patients diagnosed before 50 years old.\textsuperscript{19,22} In addition, there were no differences in serum IL-2, IL-4, or IL-6 levels in patients with and without \textit{H. pylori} infection. Serum chemokine levels, including monocyte chemoattractant protein-1, are regulated in the activation of T cells that are normally expressed and secreted, and epithelial cell-derived neutrophil attractant-78, are significantly higher in patients with \textit{H. pylori} infection compared to negative, although this increase in chemokine levels was also monitored in individuals who had digestive disorders associated with \textit{H. pylori} but did not have ITP.\textsuperscript{19}

One interesting hypothesis is the theory of molecular mimicry with the production of cross-reactive antibodies that respond on \textit{H. pylori} components and platelet surface antigens. Several studies have shown that eluted platelets in \textit{H. pylori}-infected ITP patients recognize CagA protein in immunoblots, but unrecognized in non-ITP-infected \textit{H. pylori} patients.\textsuperscript{23} One study even reported that monoclonal antibodies produced for \textit{H. pylori} urease B respond with GP IIb/IIIa expressed on the platelet surface.\textsuperscript{24} In other potential mechanism, \textit{H. pylori} infection can change the balance of Fcy receptors from monocytes/macrophages and lead the formation of autoantibodies. A study represented that the expression of FcyRII B in circulating monocytes was downregulated in ITP patients infected with \textit{H. pylori}. Therefore, \textit{H. pylori} can change the balance of Fcy receptors from monocytes/macrophages through downregulation of FcyRII B receptor inhibitors.\textsuperscript{19,25} In addition, some strains of \textit{H. pylori} cause platelet aggregation that depends on the interaction of von Willebrand factor and IgG antibodies for \textit{H. pylori} with the appropriate receptors, GP Ib and FcyRII A, on platelets. In this model, anti-\textit{H. pylori} antibodies can operate on platelets by binding to \textit{H. pylori}, von Willebrand factor, and GP Ib, such as anti-platelet autoantibodies. \textit{H. pylori} infection alone is not enough to trigger ITP. Additional triggers are needed to obtain an anti-platelet autoimmune response at ITP associated with \textit{H. pylori}.\textsuperscript{19}

Several studies reported an association in 1998 that there was a significant increase in platelets in ITP patients after eradication of \textit{H. pylori}.\textsuperscript{19,22} This effect is present in the next few reports and is summarized in a systematic review of 24 observational studies and 1 control study involving 1,555 patients. Several studies have found that 50\% of adults have an increased platelet response after \textit{H. pylori} eradication therapy, especially in those with mild ITP. A systematic review of 11 controlled studies obtained platelet count responses in 51\% of patients infected with \textit{H. pylori} versus an 8.8\% increase in platelets in negative control \textit{H. pylori}, which further strengthened the causal relationship. In a follow-up study 8 years after eradication therapy, no recurrence occurred.\textsuperscript{19}

**CONCLUSION**

The difference in clinical manifestations of \textit{H. pylori} infection remains controversial. \textit{H. pylori} is not only a single cause, but host and environmental factors also contribute to produce different responses.

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