Clinical and Endoscopic Features in *Helicobacter Pylori* Infection: Literature Review

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ABSTRACT

Helicobacter pylori is a common infection worldwide and can cause functional dyspepsia, gastritis, and peptic ulcers, leading to gastric cancer. The very diverse clinical outcomes and symptoms of this infection are difficult to distinguish from one another. Endoscopy is one of the methods used to detect Helicobacter pylori infection. Still, it has various endoscopic features, has the possibility of false-negative results, and requires skill to get the maximum results.

This study found that infection can cause various clinical manifestations due to different virulence factors of Helicobacter pylori bacteria. In functional dyspepsia, the patient's most common symptoms are epigastric pain, nausea, and vomiting. In gastritis, Helicobacter pylori infection often causes chronic gastritis with topographic features of pangastritis, and endoscopic features that are usually found are redness, swelling, and regular arrangement of collecting venules (RAC). The most common symptom in peptic ulcers is pain that occurs after eating or at night, and this infection can cause duodenal and gastric ulcers. Currently, the relationship between Helicobacter pylori infection and gastroesophageal reflux disease (GERD) is controversial. In gastric cancer, the most common symptoms are weight loss and repeated vomiting. This infection is more likely to causes intestinal-type gastric cancer.

Keywords: *Helicobacter pylori, clinical outcomes, endoscopic features*

ABSTRAK

Infeksi Helicobacter pylori merupakan infeksi yang sering terjadi di seluruh dunia dan dapat menyebabkan fungsional dispepsia, gastritis, ulkus peptikum, dan dapat menyebabkan kanker lambung. Gambaran klinis yang dihasilkan oleh infeksi bakteri ini sangat beragam sehingga sulit dibedakan antar satu dan yang lainnya. Endoskopi merupakan salah satu metode yang digunakan untuk mendeteksi infeksi Helicobacter pylori, namun memiliki gambaran endoskopi yang beragam, memiliki kemungkinan hasil negatif palsu dan dibutuhkan ahli yang terampil untuk mendapatkan hasil yang maksimal.

Ditemukan gambaran klinis yang beragam akibat perbedaan faktor virulensi dari bakteri Helicobacter pylori. Pada fungsional dispepsia, ditemukan gejala yang paling sering dialami penderita yaitu nyeri epigastrium, mual, dan muntah. Pada gastritis, infeksi Helicobacter pylori sering menyebabkan gastritis kronis dengan gambaran topografi pangastritis dan gambaran endoskopi kemerahan, pembengkakan, dan regular arrangement of collecting venules (RAC). Pada ulkus peptikum, gejala yang sering ditemukan adalah nyeri yang terjadi

setelah makan atau pada malam hari, infeksi ini dapat menyebabkan ulkus duodenum, dan ulkus lambung. Saat ini, hubungan antara infeksi Helicobacter pylori dengan gastroesophageal reflux disease (GERD) masih kontroversial. Pada kanker lambung, gejala yang paling sering terjadi yaitu penurunan berat badan dan muntah berulang. Infeksi ini menyebabkan intestinal-type kanker lambung.

Kata kunci: *Helicobacter pylori, clinical outcomes, endoscopic features*

INTRODUCTION

H.pylori is a gram-negative bacteria, spiral-shaped, and first discovered in 1982 by Warren and Marshall.[1–3] *H.pylori* infection is currently the most common cause of chronic infection in humans. It is estimated to occur in more than 50% of the world's population, with a higher prevalence in developing countries.[4,5] *H.pylori* colonize and damage gastric mucous, leading to inflammation, and is known to be a major risk factor for peptic ulcer, atrophy, and dysplasia, and can eventually lead to gastric malignancy.[4,6,7] These bacteria colonize and damage gastric mucous, cause inflammation, and are a major risk factor for peptic ulcers, atrophy, and dysplasia, leading to gastric cancer.[4,6,7] Most people who are infected are asymptomatic.[8] However, over a long period, *H. pylori* infection can increase the risk of developing multiple clinical outcomes.[9] The clinical outcomes caused by these bacteria depend on the host's genetic factors, virulence factors in the *H. pylori* strain, and environmental factors.[10,11]

Identification of these bacteria is needed so that treatment can be given as soon as possible.[7] The diagnostic test options available for *H. pylori* infection are divided into invasive tests that include endoscopy, histology, culture, rapid urease test, and non-invasive tests, such as urea breath test, stool antigen sets, and serologic.[12,13] These diagnostic options depend on clinical manifestations, "alarm symptoms" such as vomiting, bleeding, weight loss, or age over 45 years.[14,15]

FUNCTIONAL DYSPEPSIA

Rome IV defines functional dyspepsia (FD) as a syndrome with one or more of the following symptoms: bothersome postprandial fullness, early satiety, epigastric pain, and epigastric burning without structural disease based on the results of endoscopic examination. Symptoms must occur during the last three months, with at least six months of onset.[16,17] *H.pylori* infection may cause dyspepsia symptoms through several mechanisms, such as changes in gastric acid secretion, persistent and active inflammation of the gastric mucosa, and changes in gastroduodenal mucosa. *H. pylori* causes an increase in gastrin, decrease in somatostatin, and ghrelin, which causes disturbances in acid secretion, hunger, and gastrointestinal motility.[18]

The most common symptoms experienced in dyspepsia patients is epigastric pain. The pain is probably caused by hypersecretion of stomach acid.[18–23] Patients with positive *H. pylori* complained of fullness, early satiety, epigastric pain or burning, nausea, persistent or occasional vomiting, loss of appetite, and frequent burping..[19–23] Also, based on Koitche Mabeku LB et al, abdominal distention and nausea or vomiting showed a significant positive result of *H. pylori* infection.[23] These bacteria cause gastrointestinal motility disturbance leading to a redistribution of food in the stomach's distal portion and causing the stomach to be overloaded, resulting in early satiety.[24] Besides, slowing gastric emptying is thought to have implications for the appearance of symptoms such as nausea, vomiting, and abdominal fullness.[24] The Leeds Dyspepsia Questionnaire (LDQ) assessment can be used to measure dyspepsia's presence and severity, namely assessing epigastric pain, retrosternal pain, regurgitation, nausea, vomiting, satiety, and dysphagia.[20] In a study by Faintuch et al, an endoscopic examination was carried out in patients who experienced persistent epigastric burning for more than three months, six months of onset, normal endoscopy was found in 56 patients (20%), indicating functional dyspepsia.[17] In a study conducted on patients with dyspepsia, the most common virulence factor in these patients was *cagA*.[25]

The possible cause of functional dyspepsia is multifactorial, and the role of *H. pylori* in functional dyspepsia is still abe controverted.[8,15,26] In several studies, *H. pylori* eradication provides a small but statistically significant benefit in reducing dyspepsia symptoms.[5,18] Study conducted with meta-analysis, eradication of *H. pylori* works effectively in about 10% of patients with functional dyspepsia.[19] An upper gastrointestinal endoscopy is an option for investigating patients older than 40 years old with dyspepsia and those with "alarm symptoms" to diagnose ulcers and other macroscopic disorders such as malignancies.[22,27]

GASTRITIS

Gastritis is inflammation due to the injury of the stomach mucosal lining.[8] *H. pylori* will infect and cause acute gastritis, which can heal by itself, characterized by dyspepsia or nausea.[8,15,28] Acute phase of gastritis in humans rarely been the focus of research because the cases reported in the literature are few.[29] However, most *H. pylori* infections will progress to chronic, active gastritis.[6,28,30] Based on a study conducted in Brazil, patients with positive *H. pylori* are found mostly in chronic gastritis.[31]

Different chronic gastritis patterns can affect clinical outcomes, including antral-predominant, corpus-predominant, or diffuse (pangastritis or multifocal gastritis).[8,15,28,32] Antral-predominant gastritis occurs when infection and inflammatory reactions occur only in the antrum.[28,32,33] Gastric acid secretion in antral-predominant gastritis is normal or slightly increased. This is because the *H. pylori* bacteria can hydrolyze urea and create a high gastric pH resulting in decreased somatostatin secretion and increased gastrin secretion. Antral-predominant gastritis can develop into a duodenal ulcer.[15,28,32,34,35] Diffuse (pangastritis) is a condition when inflammation extends proximal to the stomach and involves the stomach's body and fundus.[32] Patients with diffuse gastritis are usually characterized by impaired gastric secretion, causing *H. pylori* to colonize the stomach's corpus.[15,34] Diffuse gastritis can develop into hypochlorhydria, which contributes to gastric malignancy.[8,32,34] Hypochlorhydria occurs due to *H.pylori* product, and the inflammatory reaction inhibits gastric parietal cells from secreting gastric acid. Prolonged inhibition of acid secretion, loss of the ability to secrete acid due to chronic inflammation, leading to gastric atrophy resulting in gastric malignancy.[35]

In a study conducted by Carabotti et al, the most common chronic gastritis topography was pangastritis, which occurred 63.9% (98/154) than 36.4% (56/154) of antral gastritis.[32] In a recent study by Idowu et al, 2019, pangastritis was found in 76.9% (180/444) of positive *H.pylori* infection, *cagA* was the virulence factor of *H.pylori* bacteria which was mostly found in patients with pangastritis 76.5% (111/444).[36] The *cagA* gene causes gastritis, *vacA,* and *babA* gene significantly cause chronic inflammation of the gastric mucosa.[10,37]

The most common endoscopic features found in acute *H.pylori* infection are hemorrhagic spots on the fundus and the stomach's upper body, nodular gastritis, and hypertrophic gastric rugae.[38] Nodular gastritis is described as a small, round, yellowish nodule.[38] The endoscopic classification for chronic gastritis has been widely proposed, but the integrated classification is still not accepted worldwide.[39] The Sydney System classification assesses the antrum, angulus, lesser and greater curvature of the lower gastric body, greater curvature of the upper gastric body, and cardia.

Table 1. The definition and characteristics of the endoscopic features based on the Sydney system classification[39,40]

Endoscopic features	Definition
Diffuse redness	Redness occurs uniformly involving
Absent	the entire mucosa of the fundic gland
present	Light orange/yellow to white mucosa redness
Spotty redness	Multiple, spotty, minor redness of fundic gland mucosa
Red streak	Longitudinal red streaks in the antrum and corpus
Patchy redness	Localized redness of various sizes
Enlarge fold	Enlargement of the mucosal fold, about 5mm in diameter
Mucosal edema	Fundic gland mucosa soft, thick, and enlarged
	The pylorus gland mucosa is smooth and convexo-concave
Nodular change	Protrusion 2-3mm uniformly at the gastric angle towards the antrum
Regular arrangement of collecting venules (RAC)	Regular red spots like starfish can be seen on the fundus of the mucosa.
Fundic gland polyposis	Polyps of various sizes on the mucosa of the fundus gland
Erosion	
Flat type	Grayish mucosal defects of various sizes
Raised type	Mucosal elevation, whitish in the center
Hemorrhagic erosion	Erosion with bleeding
Bleeding spot	Red or dark blackish ecchymotic spots

Several studies found endoscopic features in *H.pylori* infection with diffuse redness, spotty redness, enlarged gastric folds, RAC, and mucosal swelling.[39,40] A study conducted by Hassan et al, 2020, found endoscopic features in gastritis patients are redness, erosion, mucosal nodularity, ulcers, and antral-predominant gastritis pattern more often seen.[41] Inflammatory reactions and active or healing ulcers, causing endoscopic features such as mucosal atrophy, swelling, spotty redness or red streak, and erosions.[42]

PEPTIC ULCER DISEASE

Peptic ulcer disease is damage to the gastric or duodenal mucosa that penetrates the muscularis mucosa.[43] *H.pylori* infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs) or a combination of the two are the leading causes of peptic ulcers in developing countries.[12,27,44,45] *H.pylori* infection has been shown to cause duodenal ulcers and about two-thirds of causing gastric ulcers.[14,45] *H.pylori* with *cagA, vacA,* and *babA* positive strain pose a significant risk from developing peptic ulcers,

especially duodenal ulcers.[10,46–49] Meanwhile, gastric ulcers are related to the *iceA1* and *iceA2* genes.[10,50] *H.pylori* with *cagA* and *vacA* is localized to the cell mitochondria, causing vacuole formation, damage to the gastric barrier, and pepsin capable of causing cell death and clinical symptoms.[46,51]

The most common symptoms are epigastric pain, bloating, nausea, early satiety, abdominal fullness.[12] Pain is often described as burning or gnawing, and is usually food-related, occurs 1-3 hours after a meal or at night. The pain may be relieved by food.[27] In a cohort study conducted by Feder et al, 2018, the clinical characteristics of peptic ulcer disease were gastrointestinal bleeding (53%), pain (32%).[52]

Endoscopy with biopsy is required in patients with peptic ulcers to determine the location and benign or malignant etiology.[12] Research by Feder et al, as many as 97 patients (64%) patients had gastric ulcers, 36 patients (24%) had duodenal ulcers, and 17 patients (11%) had gastric and duodenal ulcers.[52] In a study conducted by Vinagre et al, found that endoscopy results with gastric ulcers were 17% (78/442), and duodenal ulcers were 22% (96/442).[53] Another study conducted by Faintuch et al, showed that endoscopy results with gastric ulcers were 12 patients (4%) and duodenal ulcers were 26 patients (9%).[17]

Complications from peptic ulcer disease are perforation, penetration, gastric tract obstruction, and ulcer bleeding, causing hematemesis and melena, chronic bleeding, and anemia.[12,27] Perforation is a severe and fatal complication of peptic ulcer disease.[54] Peptic ulcer disease is the main cause of upper gastrointestinal tract bleeding.[44,45] Without proper treatment, peptic ulcer disease is a chronic disease that recurs easily and causes morbidity and mortality due to pain, bleeding, and perforation.[14]

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is the most common gastrointestinal condition in the population.[55,56] The relationship between GERD and *H.pylori* is still controversial.[26,43,57] Most of the studies conducted showed negative results between the relationship between *H.pylori* and GERD.[43] In several studies, it is stated that *H.pylori* infection can protect against GERD.[5,58] Individuals with GERD may experience improvement of GERD symptoms after eradication of *H.pylori* infection due to slowly reducing gastric acid secretion.[5] However, based on eight randomized trials, it is indicated that *H.pylori* eradication did not have a substantial effect on newly-emerging GERD or worsening existing symptoms.[26] Based on a study conducted in 2018, there was no relation between GERD and this infection. Still, GERD is a disease determined due to several factors and mechanisms, such as smoking, alcohol consumption, and lifestyle.[55] Further research is needed regarding these risk factors and their relationship between *H.pylori* infection and GERD.[55]

GASTRIC CANCER

In 2012, gastric cancer was the fifth most common malignancy worldwide and was the third most common cause of cancer death worldwide. In other studies, gastric cancer is the second leading cause of cancer death.[8,29] Colonization of *H.pylori* bacteria is the most significant and important risk factor for gastric malignancy development.[29,59,60] Gastric adenocarcinoma can be classified into intestinal-type and diffuse-type.[15,61] Intestinal-type adenocarcinoma is more common, has been well studied, and *H.pylori* infection can cause chronic gastritis, atrophy, intestinal metaplasia, dysplasia, and cause intestinal-type gastric cancer.[8,15,60,61] However, gastric malignancies development depends on *H.pylori* virulence factors, genetic hosts, dietary factors, micronutrients, and gastrointestinal microbiota.[14]

H.pylori bacteria, which carry the *cagA* gene, cause more severe inflammation, and the disease can progress to atrophic gastritis and malignancy.[50,62] Also, based on a study conducted by Bartpho et al, 2020, found that 64 patients (91%) with gastric cancer had the *babA2* gene, the *oipA* gen was found in 64 patients (91%), and *vacA* in 42 patients (60%).[37] *BabA* binds to Lewis (Le^b) antibodies present in red blood cells and certain epithelial cells. This binding causes dsDNA (double-stranded DNA) breakdown of host cells and gene mutations, contributing to gastric cancer.[15] Research by Farzi *et al.,* 2018, the *oipA* gene was found in patients suffering from more severe diseases, including gastric cancer.[49] *OipA* causes increased production of IL-8, leading to cell proliferation, angiogenesis, and metastasis, thus contributing to carcinogenesis.[15,63]

Based on the study conducted by Sheikh et al, 2018, gastric cancer's most common symptoms are abdominal pain, weight loss, epigastric pain, and vomit.[64] Another study found upper gastrointestinal malignancy in 14 (6.7%) patients over 40 years of age, with dyspepsia symptoms.[22] Also, patients with new symptoms or "alarm symptoms" (vomit, iron deficiency

anemia, bleeding, weight loss, or dysphagia) indicate immediate endoscopic examination.[8,62]

A congress held in Kyoto in 2013 developed the Kyoto classification for endoscopic findings. The purpose of this classification is to assess the state of gastric mucosa, which may be at risk for developing gastric cancer. In this classification, an assessment of atrophy, intestinal metaplasia, gastric fold enlargement, and nodularity, redness with or without RAC may be related to *H.pylori* infection status, which may contribute to the risk of gastric cancer.[65] Gastric atrophy is considered the final stage of chronic gastritis characterized by loss of glands in the gastric mucosa, causing a decrease in gastric secretion, and is a precancerous condition.[8,59] On endoscopy examination, gastric atrophy can be seen as transparent blood vessels or yellowish blood vessels. Intestinal metaplasia was seen on endoscopy as grayish-white mucosa with an uneven surface and patchy redness.[38,65]

CONCLUSION

H.pylori infection can cause various clinical manifestations due to different virulence factors of *H.pylori* bacteria. It also causes ongoing clinical manifestations, starting from functional dyspepsia, gastritis, peptic ulcers, GERD, and gastric cancer. This infection most commonly develops into chronic gastritis, and the most common symptoms are epigastric pain, nausea, and vomiting.

Diagnosis of this infection is needed to be done as soon as possible. A proper diagnosis is required to detect *H.pylori* infection to prevent and assess the risk of gastric malignancy. The endoscopic features often found in patients with *Helicobacter pylori* are redness, swelling, and RAC. It is currently working to harmonize the worldwide accepted assessment of gastritis's macroscopic features.

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