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REVIEW

Helicobacter pylori intragastric colonization and migration: Endoscopic manifestations and potential mechanisms

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Abstract

After being ingested and entering the human stomach, *Helicobacter pylori* (*H. pylori*) adopts several effective strategies to adhere to and colonize the gastric mucosa and move to different regions of the stomach to obtain more nutrients and escape from the harsher environments of the stomach, leading to acute infection and chronic gastritis, which is the basis of malignant gastric tumors. The endoscopic manifestations and pathological features of *H. pylori* infection are diverse and vary with the duration of infection. In this review, we describe the endoscopic manifestations of each stage of *H. pylori* gastritis and then reveal the potential mechanisms of bacterial intragastric colonization and migration from the perspective of endoscopists to provide direction for future research on the effective therapy and management of *H. pylori* infection.

Key Words: *Helicobacter pylori*; Colonization; Endoscopy; Gastritis; Infection

Core Tip: *Helicobacter pylori* (*H. pylori*) adopts several effective strategies to adhere to and colonize the gastric mucosa and move to different regions of the stomach, leading to acute infection and chronic gastritis that can be observed through endoscopy. Herein, we describe the endoscopic manifestations of each stage of *H. pylori* gastritis and then discuss the potential mechanisms of bacterial intragastric colonization and migration from the perspective of endoscopists to provide direction for future research on the effective therapy and management of *H. pylori* infection.

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INTRODUCTION

More than half of the world's population is estimated to be infected by the gram-negative, flagellated, spiral-shaped bacterium *Helicobacter pylori* (*H. pylori*)[1]. The bacterium has received intensive attention because *H. pylori* infection is closely associated with the development of peptic ulcers, mucosa-associated lymphoid tissue lymphoma and gastric cancer (GC), resulting in at least 500000 deaths per year[2-4]. The slow carcinogenic process is known as Correa's cascade [5]: At first, gastritis occurs in all infected individuals[2], and then a series of intermediate stages (characterized by precancerous lesions), including atrophy, intestinal metaplasia (IM) and dysplasia, may slowly develop, and eventually, 1%-3% of infected patients develop gastric malignant tumors[6].

All gastric mucosal lesions that occur after *H. pylori* infection can be observed by skilled endoscopists through upper gastrointestinal endoscopy. Based on the Kyoto classification of gastritis, endoscopic features, such as nodularity, diffuse redness, spotty redness, mucosal swelling, enlarged folds, xanthoma, atrophy and IM, are helpful in diagnosing *H. pylori* gastritis[7]. Atrophy can be endoscopically identified with high confidence by applying the Kimura-Takemoto classification[8], while IM and dysplasia can be diagnosed more accurately with advanced image-enhanced endoscopy (IEE) [9].

The highly motile pathogen *H. pylori* usually infects young children[3] and initiates acute infection that lasts for only a few weeks[10,11] and chronic inflammation that can last for the lifetime of the host[12]. Its ability to swim in the gastric mucus and colonize the stomach enables it to survive in the hostile gastric environment[13] and leads to various endoscopic and histological features as gastric mucosal lesions progress[14]. Many articles and reviews have reported the underlying mechanisms, but few have linked endoscopic features to mechanisms. Therefore, in the following sections, we describe the endoscopic manifestations of each stage of *H. pylori* gastritis and summarize the process and potential mechanisms of intragastric colonization by *H. pylori* and its migration.

ACUTE INFECTION

Acute *H. pylori* infection only lasts for a few weeks[10,11] and has been rarely observed or reported in recent decades. The endoscopic manifestation of gastric erythema and a gaping pylorus[10,11] is always featureless. Although the gastric mucosa does not appear damaged at this stage, initial colonization of the mucosa is the basis of a series of lesions, such as atrophic gastritis, peptic ulcer and even gastric carcinoma.

The prevalence of *H. pylori* infection is high, but colonization by this microbe is not easy. Multiple spontaneous eradication events may occur before colonization, leading to acute infection[15]. Sophisticated strategies have been adopted by *H. pylori* that have enabled it to adapt to and survive in the hostile gastric environment.

When *H. pylori* is ingested by adults, it is almost completely destroyed in the gastric acid, while it is easier to survive in the stomach of children younger than the age of five, both in developing and developed countries[3]. Bucker *et al*[3] simulated the pH changes of the postprandial stage in babies, young children and adults and suggested that the bacteria were easiest to reach the mucus layer in young children, whose feature of postprandial gastric condition is moderate food-induced pH elevation and slow reacidification.

During the process of slow reacidification, the urease enzyme is believed to play a key role in bacterial survival and adhesion. Urea is degraded by the urease enzyme, which buffers the cytoplasm and periplasm[16]. This confers many benefits. First, *H. pylori* prefers to live in an environment with elevated pH. A recent study[17] showed that *H. pylori* does not escape from phosphate buffer solutions of pH 6.6 and 7.0. Second, intracellular urease could also increase membrane potential, thereby allowing protein synthesis at a low pH[18]. Third, mucosal viscosity highly depends on acidity[19]. At a less acidic pH, the mucus is less gel-like, which enables *H. pylori* to more easily move through the mucus layer[20]. Fourth, trefoil factor 1 (TFF1) is a member of the trefoil peptide family of proteins and is coexpressed with Mucin-5AC (MUC5AC), a gel-forming mucin that is predominantly secreted and expressed by gastric surface epithelial cells in the stomach[21]. The optimum pH for bacterial binding to TFF1, which thereby promotes colonization, was found to be 5.0-6.0[22]. In addition, urea and bicarbonate were considered to have a chemotactic effect on *H. pylori in vitro*[23], but research by Schreiber *et al*[13] shows that neither the urea/ammonium gradient nor the bicarbonate/CO_2 gradient are essential for the orientation of *H. pylori in vivo*.

However, this does not mean that a neutral or alkaline environment is suitable for *H. pylori*. Previous studies have shown that *H. pylori* is sensitive to alkaline conditions[24], and its growth is limited at neutral pH[25]. To prevent lethal alkalinization of the cytoplasm, *H. pylori* utilizes a proton-gated channel, UreI, which regulates the uptake of urea[26] and only functions in conditions of an acidic pH; thus, the transport of urea into the bacterial cell does not occur at a neutral pH[24]. Therefore, *H. pylori* prefers a weakly acidic environment.

The epithelial surface of the stomach is covered with an approximately 300 μm thick layer of secreted mucus, which mainly consists of mucins Mucin 6 (MUC6) and MUC5AC[27]. MUC6 exists in each layer of the mucus gel, while MUC5AC is mainly present on the surface and bottom. The increase in the viscosity of gastric mucus gel is due to this natural stratification of mucins[28]. While protecting gastric epithelial cells, the mucus layer also plays an important role in the colonization process. The pH is approximately neutral at the epithelium and very acidic (pH 1-2) close to the lumen [21], resulting in a mucus pH gradient that can be used by *H. pylori* for precise spatial orientation[13]. The membrane-bound chemoreceptor TlpA of *H. pylori* detects and mediates repulsion from environments with a lower pH, and the cytoplasmic chemoreceptor TlpD mediates both attraction to higher pH environments and repulsion from lower pH environments[17,29]. Under this chemotactic effect, *H. pylori* penetrates the gastric mucus quickly and reaches the narrow region within 25 μm of the gastric epithelial surface with the help of its two to six sheathed unipolar flagella and helical shape[30,31].

After approaching the lower mucus layer, the majority of *H. pylori* swim in gastric mucus, while others directly adhere to epithelial cells[13,31]. Although it is considered a noninvasive gastric pathogen to date[19], *H. pylori* can indeed bind to, invade, be internalized into and proliferate in gastric epithelial cells[27,32]. The invasiveness of *H. pylori* may partially depend on the strain. Research by Camorlinga-Ponce *et al*[33] showed that CagA-negative bacteria adhered to the surface of the apical epithelium, while CagA-positive bacteria were identified in the intercellular spaces or the immediate vicinity of epithelial cells. Sigal *et al*[34] found a subgroup of *H. pylori* associated with cells deep in the antral glands. These microbes can promote gland hyperplasia by inducing stem cell proliferation and expansion and altering gene expression of stem cells[34].

H. pylori adheres to epithelial cells mainly by outer membrane proteins (OMPs). Blood group antigen-binding adhesion (BabA) and sialic acid-binding adhesion (SabA) are important OMPs[19,27]. Lewis antigens are common in normal, infected and inflamed gastric mucosa[35,36]. BabA can identify and bind to Lewis b antigen[35], while SabA can bind to the antigens Lewis a and Lewis X[36], and its expression can quickly respond to the changes in the stomach or different areas of the stomach, enabling the bacteria to adapt to host's immune responses and varied microenvironments to maintain long-term colonization and infection[37]. In addition to BabA and SabA, other surface proteins, such as AlpA, AlpB, DupA, outer inflammatory protein A (OipA) and HopZ, are considered related to adhesion, but none of them has been shown to be essential to adhesive mechanisms[38]. After *H. pylori* adheres to epithelial cells, the Cag type IV secretion system (T4SS) promotes CagA translocation into host cells, resulting in changes in cell shape, disruption of cell□cell junctions, altered cell polarity and cell adhesion, increased cell motility and cell migration, increased cell proliferation, β-catenin activation, and epithelial-mesenchymal transition[39]. Some bacteria are internalized into the cytoplasm of gastric epithelial cells through endocytosis within 45 minutes of bacterial attachment to the cell surface[32]. *H. pylori* can replicate and proliferate in epithelial cells[40], escape the immune response, and exit cells to colonize and infect cells again when the external environment is suitable for survival[27].

In an artificial ingestion study[10], histological examination during the acute phase of *H. pylori* infection showed many polymorphonuclear neutrophil leucocytes (PMNs) in the lamina propria and on the surface of the mucosa and an absence of intracellular mucus. Spiral bacilli adhered to the surface and glandular epithelium as well as among PMNs in the mucus[10]. Zhao *et al*[41] proposed a novel staging strategy according to the depth and degree of gastric mucosal injury induced by *H. pylori* infection and the progression of lesions. Stage I means the bacteria were present in the mucus layer, stage IIA refers to the specific adhesion to and selective destruction of gastric epithelial cells, and stage IIB refers to the degeneration and shedding of surface mucus cells[41]. It seems that stages I and II are consistent with the pathological characteristics of acute *H. pylori* infection.

CHRONIC GASTRITIS

Cases of *H. pylori* gastritis that are observed by doctors usually involve chronic gastritis that has lasted for years[42]. Chronic gastritis has various endoscopic findings, among which nodularity, diffuse redness, spotty redness, xanthoma, mucosal swelling, enlarged folds, atrophy, and IM are common in *H. pylori*-infected gastric mucosa[43,44] (Figure 1). Considering the severity and progression of chronic *H. pylori* gastritis, we discuss endoscopic manifestations and potential mechanisms from the following three aspects: (1) Early stage of *H. pylori* infection; (2) corpus inflammation; and (3) atrophy and intestinal metaplasia, which are summarized in Table 1.

Early stage of H. pylori infection

Nodular gastritis is considered a feature of an early stage of *H. pylori* infection in adults and is more common in children, with an incidence of 32.9% to 85%[45,46]. It appears more frequently in the antral mucosa than in the corpus mucosa[47]. Nodularity is characterized by a miliary pattern resembling "gooseflesh" in the gastric mucosa on endoscopy[46] and follicular lymphoid hyperplasia with intraepithelial lymphocytosis on histological examination[47]. Okamura *et al*[48] further demonstrated that superficially located, enlarged hyperplastic lymphoid follicles corresponded to nodular and/or granular lesions, and the percentage of MECA-79 high endothelial venule (HEV)-like vessels was greater in areas with gooseflesh-like lesions in nodules than in normal gastric mucosa. The pathogenesis of nodular gastritis may involve a Th2

Table 1 The mechanisms of common endoscopic features

Endoscopic features	Mechanisms
Nodularity	Follicular lymphoid hyperplasia with intraepithelial lymphocytosis[47]; Superficially located, enlarged hyperplastic lymphoid follicles [48]; Increased numbers of MECA-79 HEV-like vessels[48]; Th2 immune response[49]
Diffuse redness	Infiltration of neutrophils and monocytes[44,58]
Spotty redness	Unclear
Mucosal swelling	Infiltration by neutrophils and monocytes[44]
Enlarged folds	Tumor necrosis factor-alpha gene polymorphism[64]; Genome wide hypomethylation and regional hypermethylation[65,66]; Stimulation of epithelial cell proliferation and inhibition of acid secretion induced by interleukin 1 beta and hepatocyte growth factor [61,62]; Inhibition of acid secretion caused by morphological changes in parietal cells[63]
Xanthoma	Unclear
Atrophy	Cellular injury inflicted by *Helicobacter pylori* or mediated by inflammation or apoptosis[77]; Th1 immune response[78]; C-X-C motif chemokine receptor 2-mediated cellular senescence[79]
Intestinal metaplasia	Death of parietal cells and reprograming of chief cells[82]

immune response, which is more likely to occur in children[49,50].

Early colonization usually occurs in the gastric antrum, and early inflammation is always more serious in the gastric antrum, which is consistent with endoscopic findings. Animal research suggested that the wild-type *H. pylori* strain mostly colonized the antrum and the transition zone between the antrum and corpus rather than the corpus[31,34]. Rolig *et al*[51] demonstrated that inflammation was worse in the antrum than in the corpus in mice infected with wild-type *H. pylori* strains. This may be associated with the particularity of antral glands and chemotaxis of the bacterium.

It is well known that the corpus is populated by oxyntic glands containing many acid-secreting parietal cells that promote acidic conditions in the stomach. In contrast, the antrum, which is defined by the presence of gastrin-expressing G cells, mainly comprises the pyloric or antral glands containing MUC6-expressing deep mucous cells, G cells, D cells, enterochromaffin cells and foveolar surface mucous cells[52]. Interestingly, oxyntic glands also exist in the human gastric antrum, but the proportion of parietal cells and chief parietal cells is significantly less than that in corpus glands[53]. The effects of parietal cells in the antrum on *H. pylori* colonization remains unclear. However, generally, the weaker acidic environment of the antrum provides the bacteria with more opportunities to survive and colonize.

The chemotaxis system of *H. pylori* includes three membrane-bound chemoreceptors, including TlpA, TlpB, and TlpC; one cytoplasmic chemoreceptor, TlpD[29]; three core signaling complex proteins, including CheW, CheA and CheY[54,55]; and auxiliary chemotaxis proteins containing CheV-type coupling proteins (CheV1, CheV2, and CheV3), CheZ phosphatase and ChePep[56]. The role of pH sensing in chemotaxis has been mentioned above. In addition, a study by Rolig *et al*[51] shows that chemotaxis is required for *H. pylori* to swim to and achieve normal bacterial loads in the antrum and transition zone. The number of nonchemotactic mutant (Che-) *H. pylori* strains at this site was found to increase more slowly than that of the wild-type strains. TlpD plays a major role in this process. Therefore, chemotaxis may be necessary for *H. pylori* to locate or to maintain colonization of the antrum.

Corpus inflammation

Previous clinical studies focused on the relationship between endoscopic findings and *H. pylori* infection and demonstrated that diffuse redness, spotty redness, mucosal swelling and enlarged folds under endoscopy are associated with *H. pylori* infection[14,46]. Diffuse redness, defined as uniform redness with continuous expansion involving the nonatrophic mucosa in the region of fundic gland, and mucosal swelling, defined as swollen gastric mucosa in the region of fundic gland or thick, uneven mucosa in the region of pyloric gland, correlate predominantly with the degree of neutrophilic and mononuclear cell infiltration caused by *H. pylori* infection[44,57-59]. Spotty redness comprises multiple spotted small flat erythema, commonly observed in the upper corpus and fornix[44], but its mechanism remains unclear. An enlarged fold is defined as a fold with a width of 5 mm or more in the gastric greater curvature, which is not or only partially flattened by air insufflation[60]. Stimulation of epithelial cell proliferation, inhibition of acid secretion, tumor necrosis factor-alpha gene polymorphism, genome-wide hypomethylation and regional hypermethylation may play a role in the generation of enlarged folds caused by bacterial infection[61-66]. We describe another perspective: these endoscopic features that are mainly observed in the corpus indicate the existence of corpus inflammation, the development of gastric mucosal lesions, and a later stage of *H. pylori* infection that differs from the early stage and mainly manifests as antral inflammation.

H. pylori can survive in and colonize the harsh conditions of the corpus that are promoted by oxyntic glands. This has been indicated by previous studies. *H. pylori* was identified in the corpus in 83% of patients with a previous diagnosis of intestinal metaplasia and known *H. pylori* infection[67]. Biopsies taken from the corpus are conducive to an accurate histologic diagnosis and assessment of *H. pylori* infection[68,69]. Combined antrum and corpus biopsies can lead to a significantly better success rate of *H. pylori* culture than single antrum biopsy[4].

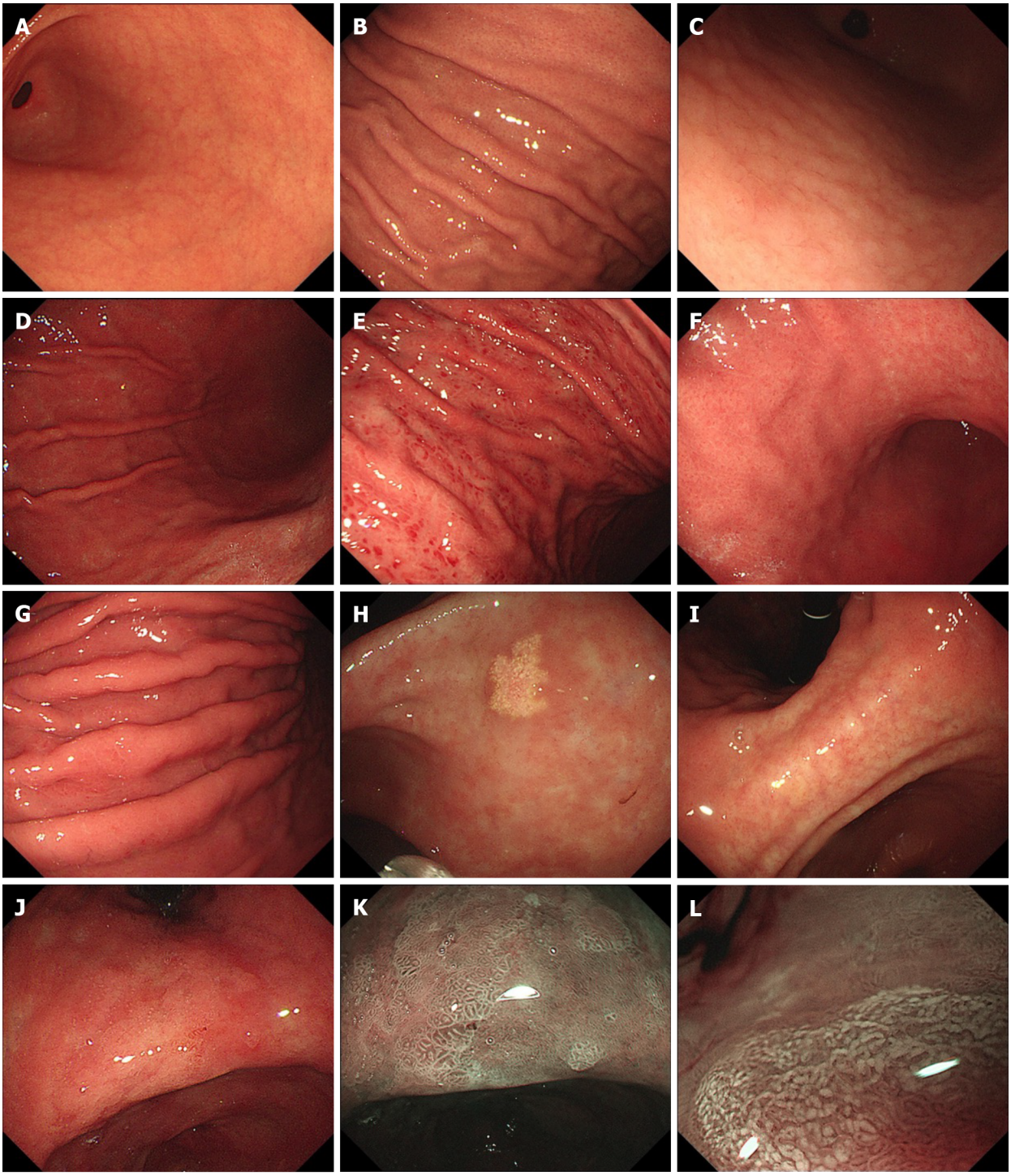

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Figure 1 Endoscopic features without and with *Helicobacter pylori* infection. A: Antrum without *Helicobacter pylori* infection; B: Corpus without *Helicobacter pylori* infection; C: Nodularity; D: Diffuse redness; E: Spotty redness; F: Mucosal swelling; G: Enlarged folds; H: Xanthoma; I: Atrophy; J: Intestinal metaplasia; K: Light-blue crest; L: White opaque substance.

H. pylori also reaches the corpus under the guidance of chemotaxis, but afterward, chemotaxis is not needed for *H. pylori* populations to increase[51]. It is likely that the spontaneous eradication of the bacteria is almost impossible at this stage. However, to live, proliferate and induce chronic infection, bacteria need to acquire nutrients and escape immune reactions in addition to adapting to acidic environments, as mentioned above. Due to the low permeability of the mucosal layer, essential nutrients (for example, Fe^{3+}) for ingested microorganisms are scarce in the stomach[70]. Following the successful colonization of gastric epithelial cells, *H. pylori* induces immune cells that cause cell damage to shed nutrients onto the surface of the gastric mucosa for survival[71]. However, *H. pylori* needs to take measures to protect itself from host immunity. Sophisticated mechanisms participate in the response to innate immunity; these mechanisms include: (1) The induction of mitochondrial-dependent apoptosis in macrophages; (2) the defense against NO products available in the gastric microniche through production of peroxiredoxin by the AhpC gene; and (3) the reduction of NO or O_2^- radicals

by arginase due to substrate competition; responses to adaptive immunity, which have been elaborated in a previous review, include: (1) The binding of the VacA toxin to an unknown surface ligand in T cells, which results in actin rearrangement and then inhibition of cell proliferation; (2) The promotion of vacuoles in host cells, which leads to apoptosis by an anion-selective channel formed by the VacA toxin; and (3) VacA binding to mitochondria, which activates the associated apoptotic pathway[19]. In addition, *H. pylori* can be internalized into epithelial cells through endocytosis[32]. Long-term exposure to VacA during chronic infection causes the formation of immature autophagosomes, resulting in a failure to clear the bacteria[72].

In the novel pathological staging strategy mentioned above[41], stage III, the laminar lesion stage, may be consistent with the early stage of gastric antrum and corpus inflammation. Stage III is subdivided into: (1) Stage IIIA: Infiltration of inflammatory cells and vacuolar-like degeneration; (2) stage IIIB: The development of mucous neck cell hyperplasia, glandular hyperplasia and heteroplasia, and serrated structures; (3) stage IIIC: Mucosal ulcers develop; and (4) stage IIID: Histologically diffuse lymphocyte proliferation occurs, and many lymphatic follicles of varying sizes are present.

Atrophy and intestinal metaplasia

In the absence of treatment, the inflammation and immune response caused by *H. pylori* infection may lead to atrophic gastritis[73], which is defined as the loss of gastric glands, with or without metaplasia[74]. This process takes several years in humans[75]. Early *H. pylori* eradication should be considered for preventing GC development prior to the appearance of atrophy or metaplasia because the benefits of *H. pylori* eradication diminish after the gastric IM stage is reached, which is referred to as the "point of no return"[76].

Gastric gland replacement by connective tissue or inflammatory cells is referred to as atrophy[73,74]. Previous studies have reported that atrophy may be related to the Th1 immune response and cellular injury, which is directly inflicted by the bacteria or mediated by inflammation or apoptosis[77,78]. A recent study showed a new mechanism of *H. pylori* –induced atrophy through C-X-C motif chemokine receptor 2 (CXCR2)-mediated cellular senescence[79]. However, in general, the pathogenetic mechanisms that trigger atrophy are still debated.

Color changes (yellowish pale) in the mucosa, mucosal thinning and visible vascular patterns are typical endoscopic atrophic features[80]. In 1966, Kimura and Takemoto described the appearance of an "atrophic transitional zone" in patients with gastritis for the first time, which was subsequently known as the endoscopic atrophic border[8]. The differences in mucosal color and the visibility of capillary networks are remarkable between the two sides of the endoscopic atrophic border[81]. The degree of atrophy can be divided into 6 types based on the location of the endoscopic atrophic border. Endoscopic atrophic findings that are only visible in the antrum are referred to as closed type C-1. In closed types C-2 and C-3, atrophy can be observed in the angulus and the lesser curvature of the corpus. In open type O-1, the atrophic border lies between the lesser curvature and the anterior wall; in type O-2, it lies within the anterior wall; and in type O-3, the endoscopic atrophic area is widely spread within the border between the anterior wall and the greater curvature[81].

When deep damage to the gastric mucosa occurs, acid-secreting parietal cells die, and pepsin-secreting chief cells are reprogrammed into mucin-secreting, wound-healing cells to reduce endogenous production of caustic substances; this response to injury is known as metaplasia[82]. Pathologically, metaplasia refers to gland replacement by a different type of epithelium in a tissue where it is not normally found[74,83]. The characteristics of mucus secretion were used to discriminate metaplastic lineages[83]. Pseudopyloric metaplasia is defined as the presence of MUC6- and trefoil factor 2 (TFF2)-expressing cells at the base of corpus glands with a morphology more characteristic of mucus-producing deep antral glands[84]. IM refers to the presence of Mucin2 (MUC2)/trefoil factor 3 (TFF3)-expressing intestinal-type goblet cells in the stomach[85]. IM can be divided into two types: (1) Incomplete IM, which may be found in either the superficial or foveolar epithelium and in the glands and is characterized by secretive columnar cells that secrete mucin into the apical cytoplasm and the presence of goblet cells; and (2) complete IM, which is characterized by columnar absorptive cells without mucin secretion and the presence of goblet cells[86]. Both incomplete and complete IM can be subdivided into small intestinal type and colonic type (Table 2).

An ash-colored flat nodular change has been considered a typical endoscopic finding of IM since the last century[80]. With the development of endoscopic technology, advanced IEE, including narrow band imaging (NBI) endoscopy, has been used as a more accurate IM diagnostic tool than traditional white light endoscopy[9]. Various markers are related to gastric IM[87]. Light-blue crest (LBC) (Figure 1K), a light blue line observed on the surface of gastric mucosal epithelium, is the earliest mentioned IEE finding[88]. Combining the findings of white opaque substance (WOS) (Figure 1L), white mucosal epithelium observed under IEE, and LBC improves the sensitivity of diagnosing IM[89]. Through systematic review and meta-analysis, the diagnostic sensitivity and specificity of LBC were found to be 0.79 [95% confidence interval (CI): 0.76-0.81] and 0.95 (95%CI: 0.94-0.96), respectively. The sensitivities of the groove type (GT) and marginal turbid band (MTB) were 0.49 (95%CI: 0.43-0.54) and 0.47 (95%CI: 0.40-0.53), respectively, and the specificities were 0.92 (95%CI, 0.89-0.94) and 0.92 (95%CI: 0.89-0.95)[87], respectively. In addition, researchers derived a classification for endoscopic grading of gastric IM (EGGIM) using IEE, which permits immediate grading of intestinal metaplasia without biopsies and is beneficial for GC risk stratification[90].

In addition, gastric xanthoma is a common endoscopic finding in patients with *H. pylori* infection and may serve as a warning endoscopic sign for advanced atrophic gastritis, intestinal metaplasia and GC[91-93]. It is a small yellowish or yellowish-white plaque-like or nodular lesion characterized by the accumulation of lipids, containing cholesterol, low-density oxidized lipoprotein, low-density lipoprotein and neutral fat, in histiocytic foam cells[93,94]. However, the etiopathogenesis is also unclear.

Table 2 Intestinal metaplasia with different mucin secretion

Cells	Incomplete intestinal metaplasia		Complete intestinal metaplasia	
	Small intestinal type	Colonic type	Small intestinal type	Colonic type
Columnar cells	Neutral and scanty sialomucins	Sulpho- and scanty sialomucins	No mucin secretion	No mucin secretion
Goblet cells	Sialomucins	sialomucins	Neutral and sialomucins	Sulpho- and sialomucins

INTRAGASTRIC MIGRATION

H. pylori has shared a coevolutionary history with humans for more than 60000 years[41,95]. Human migration has led to the global distribution of the bacterium from East Africa to other continents[19]. In addition to geographical migration, *H. pylori* has the ability to move between different regions of the stomach.

The motility of *H. pylori* provided by its flagella and helical shape is the basis of intragastric migration. The bacterium possesses two to six sheathed unipolar flagella[96]. The sheath, which consists of both proteins and lipopolysaccharide, protects the flagellar filaments from gastric acid[97]. Expression of the two major flagellar proteins, FlaA and FlaB, is required for full motility of the bacteria[21]. An efficient screw-like movement resulting from the characteristic helical shape of *H. pylori* also provides an advantage for penetrating the gastric mucus layer[98]. Any mutation in the genes associated with bacterial morphology, such as Ccrp89, Ccrp58, Ccrp1142 and Ccrp1143, can lead to a deficiency in bacterial shape and motility[99].

The chemotaxis system of *H. pylori* is necessary for intragastric migration. Chemotactic signals sensed by chemoreceptors are transmitted to the histidine kinase CheA through the coupling protein CheW or CheV1[100]. Repellents activate CheA autophosphorylation, and CheY is subsequently phosphorylated *via* histidine-to-aspartate phosphorelay [101]. Phosphorylated CheY interacts with the flagellar motor, causing it to rotate clockwise and the bacteria to reverse or change direction[56]. Alternatively, the bacteria swim straight because chemicals perceived as attractants squelch CheA autophosphorylation[56]. As described above, the ability of chemoreceptors to sense pH guides the bacteria to the surface of the gastric epithelium. It has been suggested that different regions of the stomach contain unique chemotactic signals [51]. The gastric antrum is usually the first colonized area because of its weaker acidic environment but not due to chemotaxis. The chemotactic signals produced by the antrum or transition zone play an important role in the increase in *H. pylori* numbers that occurs from 14 h to 1 wk after colonization[51]. Chemotaxis is also required when *H. pylori* migrates to the corpus from the antrum but is not needed for the increase in bacterial populations after the initial colonization of the corpus[27]. In addition, *H. pylori* can swim toward injured epithelia[102].

H. pylori can simultaneously survive in the antrum and the corpus in general. However, when atrophy occurs, an environment that is unfavorable to the growth of *H. pylori* develops, and the bacteria can only be found in a small percentage of endoscopic biopsy specimens[103]. Research has revealed that atrophy in the corpus manifests as a continuous sheet of pseudopyloric metaplasia and forms an advancing histologically atrophic front, the presence of which is similar to the spread of antral mucosa toward the corpus and is faster in the lesser curvature[104]. This pattern is the same as the endoscopic atrophic border described by Kimura and Takemoto[8]. This may indicate that the suitable region in which *H. pylori* survives shrinks as the atrophic front advances and is well discriminated by the endoscopic atrophic border.

In addition, *H. pylori* can migrate to the duodenum and colonize the duodenal gastric metaplasia (DGM) with a bacterial density 100-fold lower than that in the antrum[105,106]. DGM is characterized by the metaplastic replacement of normal duodenal epithelial cells with cells displaying a phenotype similar to that of mucus-secreting cells of the gastric mucosa[107]. It is frequently found in patients with duodenal ulcers with a prevalence of 72 to 90% and is associated with the chronicity and recurrence of duodenal ulcer disease[108-110]. The exact pathogenesis of DGM remains unclear. It is speculated that a high acid burden in the duodenum caused by increased gastrin secretion and the inflammatory damage to duodenal mucosa induced by bacterial cytotoxin may lead to the development of DGM in patients with *H. pylori* infection[109]. Liu and Wright[111] considered that metaplastic cells originate from Brunner's gland duct epithelium or basal buds growing out of the crypts of Lieberkühn and migrate in straight lines. However, Shaoul *et al*[112] suggested that DGM develops from goblet cells that simultaneously express gastric antigens, MUC5AC and TFF1, and intestinal antigen, MUC2 core antigen, migrate upward and transform to foveolar-like cells at the site of early metaplastic patches. Published results about the association between *H. pylori* infection and DGM are also conflicting. Some studies reported that *H. pylori* infection was one of the independent risk factors for DGM[113], the amount of *H. pylori* in the duodenal bulb might be related to the extent of gastric metaplasia in the duodenal bulb[114], and the presence of DGM significantly decreased after *H. pylori* eradication[109]. However, some researchers have suggested that DGM is associated with high acid output in the stomach rather than gastric *H. pylori* infection[115-117].

CARDIA

The endoscopic characteristics of the cardia have received little attention in previous studies. In recent years, cardiac nodularity, which involves the appearance of miliary nodules or scattered small whitish circular colorations within 2 cm of the esophagogastric junction, has been proposed by researchers[46,118].

Cardia glands lack chief cells and parietal cells, and have similar characteristics to the pyloric glands[53]. The cardiac and pyloric glands secrete mucus and bicarbonate and are involved in the defense of the gastric epithelium[46]. In addition, both of them secrete MUC6 and pepsinogen II rather than pepsinogen I[46]. Unlike the fundic glands, the similarity of the cardiac and pyloric glands may lead to the appearance of cardiac nodularity.

Nodularity can be observed more frequently in the stomach of children and improves gradually with age[119,120]. Reportedly, the eradication of *H. pylori* in patients with antral nodularity could effectively prevent diffuse-type GC[119]. A study by Nishikawa *et al*[119] suggested that compared with patients without cardiac nodularity, patients with cardiac nodularity were significantly younger and had lower IM scores. Therefore, cardiac nodularity may also be a feature of the early stage of *H. pylori* infection, but further research is needed to analyze its clinicopathological importance.

CONCLUSION

H. pylori infection has received worldwide attention for decades. In this review, we described the process of intragastric colonization by *H. pylori* and its migration and tried to identify a link between endoscopic manifestations and potential mechanisms. Upper gastrointestinal endoscopy and pathological examination of biopsy specimens are useful tools for diagnosing *H. pylori*-induced gastritis and estimating the risk of *H. pylori*-induced GC. In addition to animal models, exploring the mechanisms of *H. pylori* infection requires biopsy sampling. However, extensive study is needed to evaluate the association between endoscopic manifestations and mechanisms.

FOOTNOTES

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