Dear editors,

Enclosed is our revised manuscript entitled "Helicobacter pylori intragastric colonization and migration: endoscopic manifestations and potential mechanisms" (Manuscript ID: 85676) by Wang et al. Thank you and the reviewers for the valuable comments and suggestions. We hope this revision will meet your final approval for publication in *World Journal of Gastroenterology*.

According to the comments, we have made several changes in the revised manuscript, which are highlighted in red. Appended to this letter is our point-by-point responses to the comments. The comments are reproduced, and our responses are provided immediately afterward.

Reviewers' Comments:

Reviewer #1:

1. H. pylori causes beside gastric cancer, most importantly, peptic ulcer!!! this is not mentioned in the introduction.

We are grateful for the comment. We revised the text in the "INTRODUCTION" section as follows: "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 500,000 deaths per year".

2. Colonization of the bacteria on the surface of gastric mucosa is a continuous process lasting for decades. Its separation into acute and chronic phase seems to me artificial and it must substantiated by the authors the reasons for it.

We apologize for the unclear description in the article. The reasons we separated the infection into acute and chronic phases are as follows: (1) As mentioned in Correa's review, gastric mucosal lesions caused by *H. pylori*

infection may slowly develop before *H. pylori* eradication treatment. We described the endoscopic manifestations and mechanisms in the "ACUTE INFECTION" and "CHRONIC GASTRITIS" sections, respectively, to better illustrate the development. This does not mean that we believe the colonization by the bacteria is a discontinuous process. (2) In an artificial ingestion study, Marshall et al. described the endoscopic and histological features of acute *H. pylori* infection, which are different from those of chronic gastritis observed in most adult patients who were infected during early life. (3) The initial colonization is a unique process, and its mechanisms have been comprehensively studied. The interaction between the host and the bacterium occurs before typical endoscopic findings, such as nodularity, diffuse redness, and spotty redness, appear. Therefore, we described the mechanisms of initial colonization before the "CHRONIC GASTRITIS" section. (4) According to the "point of no return" theory, patients can gain more benefits from early *H. pylori* eradication. Therefore, describing this process from the perspective of lesion progression is more beneficial for doctors to understand and apply this information in clinical practice.

We revised the text in the "INTRODUCTION" section as follows: "The highly motile pathogen *H. pylori* usually infects young children and initiates acute infection that lasts for only a few weeks and chronic inflammation that can last for the lifetime of the host. Its ability to swim in the gastric mucus and colonize the stomach enables it to survive in the hostile gastric environment and leads to various endoscopic and histological features as gastric mucosal lesions progress".

We revised the text in the "ACUTE INFECTION" section as follows: "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".

3. Although the purpose of the work is presentation of background bacteriologic and biochemical/immunologic mechanism of infection and endoscopic changes, it is not presented in tabular form which mechanism lead to which endoscopic change (eryrthema, nodularity,m etc).

Thank you for your comment.

We added Table 1 in the review as follows:

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]

We revised the text in the "CHRONIC GASTRITIS" section as follows: "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".

We revised the text in the "Early Stage of H. pylori Infection" section as follows: "Nodularity is characterized by a miliary pattern resembling "gooseflesh" in the gastric mucosa on endoscopy and follicular lymphoid hyperplasia with intraepithelial lymphocytosis on histological examination. Okamura et al. 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 immune response, which is more likely to occur in children".

We revised the text in the "Corpus Inflammation" section as follows: "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. Diffuse redness, defined as uniform redness with continuous expansion observed in nonatrophic mucosa mainly in the corpus, and mucosal swelling, defined as the presence of swelling of the gastric area in the fundic gland and/or thick, uneven gastric mucosa in the pyloric gland, correlate predominantly with the degree of neutrophilic and mononuclear cell infiltration caused by *H. pylori* infection. Spotty redness comprises multiple spotted small flat erythema, commonly observed in the upper corpus and fornix, but its mechanism remains unclear. An enlarged fold is defined as a fold with a width of 5 mm or more in the greater curvature of the corpus, which is not flattened or only partially flattened by stomach insufflation. 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".

We revised the text in the "Atrophy and Intestinal Metaplasia" section as follows: "Gastric gland replacement by connective tissue or inflammatory cells is referred to as atrophy. 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. A recent study showed a new mechanism of *H. pylori*–induced atrophy through C-X-C motif chemokine receptor 2 (CXCR2)-mediated cellular senescence. However, in general, the pathogenetic mechanisms that trigger atrophy are still debated.

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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. Pathologically, metaplasia refers to gland replacement by a different type of epithelium in a tissue where it is not normally found".

We added a paragraph in the "Atrophy and Intestinal Metaplasia" section as follows: "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. It is a small yellowish or yellowish-white plaque-like or nodular lesion characterized by the accumulation of lipids, including cholesterol, neutral fat, low-density lipoprotein, and low-density oxidized lipoprotein, in histiocytic foam cells. However, the etiopathogenesis is also unclear".

4. MIgration of H pylori into duodenum and causing duodenal metaplasia is not mentioned.

Thank you for your comment. We added a paragraph in the "INTRAGASTRIC MIGRATION" section as follows: "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. 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. 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. 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. Liu and Wright 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. 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, the amount of *H. pylori* in the duodenal bulb might be related to the extent of gastric metaplasia in the duodenal bulb, and the presence of DGM significantly decreased after *H. pylori* eradication. However, some researchers have suggested that DGM is associated with high acid output in the stomach rather than gastric *H. pylori* infection".

Reviewer #2:

This is a well-organized review article.

We are grateful for your approval.

Yours sincerely,

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