Management Studies, Jan.-Feb. 2025, Vol. 13, No. 1, 24-30
doi: 10.17265/2328-2185/2025.01.003

Atrophic Gastritis: A Critical Precancerous Lesion

XING Lina, ZHANG Xiyang, MUGE Cheli
Ordos Central Hospital, Ordos, P.R. China
Inner Mongolia University of Science and Technology, Baotou, P.R. China
CAO Ruizhen
Ordos Central Hospital, Ordos, P.R. China

AG (atrophic gastritis) is characterized by precancerous lesions associated with gastric cancer and can cause serious adverse health effects. The high incidence coupled with a low diagnosis rate and the mediocre effectiveness of clinical treatment raises concerns. This article reviews the pathologic features, clinical manifestations, and treatment progress of AG.

Keywords: atrophic gastritis, pathologic features, treatment progress

Introduction

AG emerges as a digestive system ailment characterized of the loss of gastric mucosal glands, leading to diminished secretion of gastric acid and pepsinogen, ultimately reducing digestive function. AG is typically divided into two subtypes: one predominantly involving the gastric antrum due to Hp (helicobacter pylori) infection, and the other primarily affecting the gastric body owing to autoimmune causes, that is, AIG (autoimmune atrophic gastritis). The early manifestations of AG are often nonspecific, with most patients experiencing epigastric pain or abdominal distension, and some exhibiting acid reflux. In the progressive stage of AG, it can manifest as anemia and other symptoms typically associated with nutrient deficiencies (Neumann, Coss, Rugge, & Genta, 2013). Therefore, the early diagnosis and treatment of AG is of vital importance.

Hp Infection-Mediated AG

One subtype of chronic AG is primarily instigated by Hp infection, resulting in atrophy of the gastric antrum. Studies have demonstrated that Hp-mediated AG involves the expression of C-X-C motif chemokine ligands (Neumann et al., 2013; Malfertheiner, Camargo, El-Omar, Liou, Peek, Schulz, Smith, & Suerbaum, 2023), which can accelerate the aging of gastric epithelial cells (Q. Cai, Shi, Yuan, Peng, Ou, Zhou, Li, Su, Lin, S. Cai, He, & Xu, 2021). The process driving this expression may be ascribed to the release of inflammation-related factors, including interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha, due to Hp infection. This process leads to damage and aging of the gastric mucosal epithelium, and the aging, in turn, induces DNA damage and activation

XING Lina, Department of Gastroenterology, Ordos Central Hospital, Ordos, Inner Mongolia 017000; Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, P.R. China.
ZHANG Xiyang, Department of Gastroenterology, Ordos Central Hospital, Ordos, Inner Mongolia 017000; Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, P.R. China.
MUGE Cheli, Department of Gastroenterology, Ordos Central Hospital, Ordos, Inner Mongolia 017000; Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, P.R. China.
CAO Ruizhen, Department of Gastroenterology, Ordos Central Hospital, Ordos, Inner Mongolia 017000, P.R. China.

of proto-oncogenes, thereby contributing to tumor development. Studies indicate an increase in aging cells in IM (intestinal metaplasia**)** cells but a decrease in aging cells in gastric cancer. However, the presence of aging cells in atrophic mucosa has not been reported. Research findings reveal that mice infected with Hp exhibited reduced aging and atrophy of the gastric mucosa when administered a CXCR2 inhibitor (Guo, Zhang, Gerhard, Gao, Mejias-Luque, Zhang, Vieth, Ma, Bajbouj, Suchanek, Liu, Ulm, Quante, Li, Zhou, Schmid, Classen, Li, You, & Pan, 2020), suggesting that Hp infection induces cell aging, mediates gastric mucosal atrophy, and leads to AG. Hp positive can cause dysbiosis of the gastrointestinal microbiota, potentially contributing to the progression from late-stage AG to gastric cancer (Miranti, Stolzenberg-Solomon, Weinstein, Selhub, Männistö, Taylor, Freedman, Albanes, Abnet, & Murphy, 2017). MicroRNAs (miRNAs) are small non-coding molecules that mediate various biochemical reactions. Studies have identified significant dysregulation of has-miR-215-3p/5p and has-miR-934 in gastric cancer patients infected with Hp (Guo et al., 2020). Consequently, the intricate cascade reactions involved in the process by which Hp mediates AG and its advancement to gastric cancer, along with the associated genetic changes, are crucial. Thus, we infer that dysbiosis in the gastrointestinal microbiota and genetic mutations linked to Hp are fundamental factors contributing to the occurrence of gastric cancer, representing potential targets for future research.

Regarding the Impact on AG of Hp Eradication

Since 1978, the World Health Organization has classified CAG (chronic AG) as a precancerous lesion of gastric cancer. The progression of gastric cancer involves stages such as Hp infection, CAG, and eventually gastric cancer. Early gastric cancer refers to cancer localized to the submucosa or submucosal layer of the stomach, with or without lymph node metastasis. Atrophy of gastric glands can advance to newly developed gastric cancer. Treating patients with Hp infection can result in a reduction in the synchronous occurrence of gastric cancer, indicating that eradication therapy for Hp in early gastric cancer patients can effectively prevent synchronous gastric cancer (Cai et al., 2021; Sung, Coker, Chu, Szeto, Luk, Lau, & Yu, 2020; Guo et al., 2020; Miranti et al., 2017; Choi, Kook, Y. I. Kim, Cho, Lee, C. G. Kim, Park, & Nam, 2018). In 2020, the Taipei Consensus also recommended early screening for Hp of susceptible populations in high-incidence areas for gastric cancer, followed by early treatment, to reduce the incidence of AG-intestinal metaplasia-gastric cancer. This approach is effective not only for young individuals but also for those aged 50 and above, with eradication therapy best administered before atrophy and metaplasia occur (Liou et al., 2020). In a study by Sung et al. (2020), it was discovered that after one year of eradication therapy for 295 patients with Hp infection, inflammation in both the gastric antrum and corpus decreased substantially for the average patient. However, analysis of bacterial biodiversity in their bodies revealed that biodiversity did not tend to increase further. Beneficial bacteria, such as *Lactobacillus*, were depleted in precancerous GA (gastric atrophy) after Hp eradication (Sung et al., 2020). Therefore, it can be inferred that while eradicating Hp can alleviate inflammation, it may also impact the growth and interactions of other bacteria. Besides Hp, other bacteria such as *Acinetobacter lwoffii*, *S. anginosus*, *Ralstonia*, *Erwinia*, and *Prevotella*, which become enriched, can promote inflammation in the stomach and the development of gastric cancer.

Overview of AIG

AIG represents another subtype of AG, with a prevalence in the general population ranging from 0.1% to 1%-2%. However, studies suggest a higher prevalence in females and the elderly, approximately 2%-3%, with

young women aged 35-44 exhibiting a higher incidence than older women (Song, Held, Sandin, Rautelin, Eliasson, Söderberg, Hallmans, Engstrand, Nyrén, & Ye, 1990). The pathology of AIG involves the destruction of gastric wall cells, resulting in a decrease in intrinsic factor and subsequently reducing gastric acid secretion. The diminished gastric acid initiates a negative feedback loop in the regulation of serum gastrin, leading to increased serum gastrin secretion and causing a state of hypergastrinemia, which, in turn, leads to ECL (enterochromaffin-like) cell hyperplasia (Hall & Appelman, 2019). The reduction in gastric acid also impedes the absorption of iron and vitamin B12, and AIG patients are typically diagnosed with iron-deficiency anemia or pernicious anemia (macrocytic anemia) (Shah, Piazuelo, Kuipers, & Li, 2021). Further research reveals that the decrease in gastric acid is a consequence of autoimmune reactions targeting H+/K+ ATPase, the main cell responsible for acid secretion. Self-reactive T cells recognize H+/K+ ATPase on parietal cells, leading to the activation of T cell-dependent B cells and subsequent production of PCA (parietal cell antibodies) (Rustgi, Bijlani, & Shah, 2021). Although H^+/K^+ ATPase is the primary target of PCA, many AG patients exhibit antibodies for intrinsic factor and $H+/K^+$ ATPase. While anti-H^+/K^+ ATPase antibodies lack specificity, when combined with anemia, the presence of intrinsic factor antibodies can be considered diagnostic evidence for pernicious anemia (Hall & Appelman, 2019).

Symptoms of AIG

Patients with AIG commonly present with iron-deficiency anemia and pernicious anemia. Iron-deficiency anemia may stem from the destruction of the gastric mucosa, resulting in reduced absorption of iron ions due to decreased gastric acid. Furthermore, a lack of iron reserves in the body can contribute to iron deficiency. Consequently, iron-deficiency anemia typically manifests in the early stages of autoimmune AG, particularly in young women (Rodriguez-Castro, Franceschi, Noto, Miraglia, Nouvenne, Leandro, Meschi, De' Angelis, & Di Mario, 2018). Pernicious anemia is characterized by a deficiency of vitamin B12, a crucial cofactor in the body's metabolism that facilitates the conversion of methionine to homocysteine. Despite the abundance of vitamin B12 in the body, deficiency can occur due to insufficient B12 intake. Symptoms of pernicious anemia encompass general manifestations of anemia, such as fatigue, palpitations, and exertion-induced shortness of breath. Neurological symptoms may also manifest, including cognitive impairment, emotional apathy, depression, abnormal sensations like numbness in the hands and feet (termed "glove-and-stocking syndrome"), distal tingling, coldness, swelling, or the sensation of external pressure. Other potential manifestations include spastic paralysis, sensory ataxia, visual or auditory impairments, an unstable gait, urinary system disorders, and changes in tendon and reflex responses. The specific neurological damage resulting from vitamin B12 deficiency is referred to as "funicular myelosis" (Rodriguez-Castro et al., 2018). Beyond deficiencies in iron and vitamin B12, AIG patients may also lack other nutrients such as vitamin C, vitamin D, and folic acid. Vitamin C absorption may be compromised in patients with chronic atrophic AG due to the elimination of ascorbic acid in the gastric mucosa caused by elevated pH and bacterial overgrowth (Cavalcoli, Zilli, Conte, & Massironi, 2017). Some patients may exhibit symptoms of gastric adenocarcinoma or gastric neuroendocrine tumors at the time of AIG diagnosis. Concurrent thyroid disorders, type 1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus, among other autoimmune diseases, are frequently observed in AIG patients (Arango, Perricone, Kivity, Cipriano, Ceccarelli, Valesini, & Shoenfeld, 2017). AIG is commonly associated with thyroid diseases, particularly thyroiditis (Xu, W. Wang, Zhu, Lin, Ma, Zhu, Zhao, Nie, Cai, Li, W. Fang, Li, N. Wang, Chen, Peng, H. Fang, & Shen, 2020). Patients with type 1 diabetes (T1DM) face an increased risk of developing AG, warranting iron

and vitamin B12 supplementation for confirmed autoimmune disease patients, regardless of the presence of anemia. A study identified greater microbial diversity in the stomach of female patients with autoimmune AG compared to male patients (Pivetta, Dottori, Fontana, Cingolani, Ligato, Dilaghi, Milani, Ventura, Borro, Esposito, Annibale, & Lahner, 2023). Considering autoimmune AG as a precancerous lesion, despite the incidence of gastric cancer being approximately twice as high in men as in women, prompts exploration into whether interactions among stomach microbes play a role in promoting or inhibiting the progression of AG to gastric cancer.

Diagnosis of AIG

The diagnosis of AIG lacks an optimal treatment, and its serological diagnostic specificity is not high. PCA, while considered highly sensitive markers, may also be detected in a minority of normal individuals and those with other autoimmune diseases. As the condition progresses and gastric mucosal atrophy worsens, PCA may decrease. Due to the destruction of gastric wall cells, the secretion of gastric protease I (PG I) and gastric protease II (PG II) decreases. The ratio of PG I to PG II can assist in the diagnosis of gastric atrophy (Rugge, Meggio, Pennelli, Piscioli, Giacomelli, De Pretis, & Graham, 2007). In comparison to serology, endoscopic examination is more accurate, but early manifestations may still be undetectable. Early-stage endoscopic features include thinning of the mucosa, flattening of rugae, loss of gastric folds, pale mucosa, and prominent vessels visible through the thinned mucosa. Small lesions, such as hyperplastic and pseudopolyps, NETs (neuroendocrine tumors), and even adenomas or adenocarcinomas, may be present. The presence of intestinal metaplasia enhances the clarity of endoscopic features. Gastric intestinal metaplasia often exhibits a tubulovillous pattern and a light blue crest sign (Shah et al., 2021). The severity of atrophy is typically staged using the OLGA (Operative Link for Gastritis Assessment) and OLGIM (Operative Link for Gastric Intestinal Metaplasia) staging systems (Rugge et al., 2007; Capelle, de Vries, Haringsma, Ter Borg, de Vries, Bruno, van Dekken, Meijer, van Grieken, & Kuipers, 2010). On histopathology, AIG is generally divided into three stages: early, atrophic, and end-stage. In the early stage, characterized as the non-atrophic phase, there is invasion of inflammatory cells into the parietal cells, represented by lymphocyte and plasma cell infiltration. As the disease progresses into the atrophic phase, features include the destruction of oxyntic glands. The end-stage is characterized by severe atrophy of oxyntic mucosa (Miceli, Vanoli, Lenti, Klersy, Di Stefano, Luinetti, Caccia Dominioni, Pisati, Staiani, Gentile, Capuano, Arpa, Paulli, Corazza, & Di Sabatino, 2019). Combining measurements of gastric protease, gastric hormone, anti-Hp antibodies, and PCA is crucial for diagnosing AG, as proposed by Zagari, Rabitti, Greenwood, Eusebi, Vestito, and Bazzoli (2017). Therefore, for patients highly suspected of having chronic AG, serological testing, including gastric protease/gastrin and anti-Hp antibodies, should be conducted first to confirm the presence of AG. Subsequently, PCA or endoscopic testing can be performed to confirm the diagnosis of autoimmune AG. Finally, personalized treatment can be administered based on the test results.

Treatment of Autoimmune AG (AIG)

In the context of treating AG, as discussed previously, the eradication of Hp is deemed essential. Additionally, proton pump inhibitors (PPIs), acid suppressants, and gastric mucosal protective drugs constitute the main medications for managing chronic AG (CAG). However, Xu et al.'s (2023) research demonstrated that experimental rabbits treated with MSCs (mesenchymal stem cells) experienced a recovery in the number of gastric glands in the gastric mucosa after 60 days of treatment (Q. Xu, Liu, Meng, Zhao, Men, Lan, & H. Xu,

2023) (MSCs are a type of cell derived from bone marrow (BM-MSCs), umbilical cord (UC-MSCs), or adipose tissue (AD-MSCs) (Choi et al., 2018) with antioxidative, immunosuppressive, and tissue repair functions). This suggests that submucosal injection of MSCs may contribute to repairing the gastric mucosa in AG, potentially slowing down the progression from AG to intestinal metaplasia and gastric cancer. Several Chinese scientists have identified treatments with significant efficacy in addressing chronic AG. For instance, the WEN (Weierning tablet) has demonstrated the ability to reduce serum levels of IL-1β and mRNA expression of IL-6, IL-8, IL-10, TNF-α, and γ-IFN in gastric tissues. WEN alleviates inflammation in the stomach, protects the gastric mucosa, maintains its barrier function, reverses intestinal metaplasia, and delays the progression from AG to intestinal metaplasia and gastric cancer (Han, Li, Wang, Lai, Zhou, Niu, Su, Lv, Zhang, Gao, Huang, & Lou, 2023). QHY (GHY, QHY), another traditional Chinese medicine, studied by Huang, S. Li, He, C. Lin, Sun, M. Li, Zheng, Xu, P. Lin, and Ke (2021), was found to promote the growth and reproduction of lactobacilli in the stomach, counteracting the decrease in biodiversity caused by antibiotics. Lactobacilli, as probiotics, can enhance the microbial environment in the gastrointestinal tract and have a protective effect on the gastric mucosa. Although the specific molecular process is not yet clear, it is presumed that GHY slows down the progression of AG by regulating the gut microbiota. A study conducted by the German Cancer Research Center (Weise et al., 2020) reported that the survival rate of patients with gastric cancer combined with autoimmune AG is better than that of patients with gastric cancer alone. Consequently, for patients already diagnosed with autoimmune AG, early monitoring and follow-up for gastric cancer can play a pivotal role in preventing its progression and improving survival rates.

Conclusion and Future Perspectives

AG, whether mediated by Hp or autoimmune processes, entails the expression of various molecules in its pathology. The transition from AG to gastric cancer involves intricate changes. Early eradication therapy for Hp in patients with chronic AG significantly improves survival rates. For individuals diagnosed with autoimmune diseases such as thyroid diseases, lupus, type 1 diabetes, etc., comprehensive serological testing, including antibodies against parietal cells, serum gastrin, and other markers, or electronic gastroscopy can aid in identifying AG. Early prevention and monitoring for gastric cancer can then be initiated, enhancing the survival rates of these individuals. In addition to these measures, patients with chronic AG can explore personalized treatments that combine traditional Chinese medicine and Western medicine. Scholars are increasingly discovering that traditional Chinese medicine can ameliorate symptoms, reverse intestinal metaplasia, and delay progression to gastric cancer in AG. This finding holds global significance for AG patients. In the future, utilizing traditional Chinese medicine as a vital regulator of AG may prove to be the most effective strategy.

References

Arango, M. T., Perricone, C., Kivity, S., Cipriano, E., Ceccarelli, F., Valesini, G., & Shoenfeld, Y. (2017). HLA-DRB1 the notorious gene in the mosaic of autoimmunity. *Immunol Res.*, *65*(1), 82-98.

Cai, Q., Shi, P., Yuan, Y., Peng, J., Ou, X., Zhou, W., Li, J., Su, T., Lin, L., Cai, S., He, Y., & Xu, J. (2021). Inflammation-associated senescence promotes helicobacter pylori-induced atrophic gastritis. *Cell Mol Gastroenterol Hepatol*, *11*(3), 857-880.

Capelle, L. G., de Vries, A. C., Haringsma, J., Ter Borg, F., de Vries, R. A., Bruno, M. J., van Dekken, H., Meijer, J., van Grieken, N. C., & Kuipers, E. J. (2010). The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis. *Gastrointestinal Endoscopy*, *71*(7), 1150-1158.

Cavalcoli, F., Zilli, A., Conte, D., & Massironi, S. (2017). Micronutrient deficiencies in patients with chronic atrophic autoimmune gastritis: A review. *World J. Gastroenterol*, *23*(4), 563-572.

Choi, I. J., Kook, M. C., Kim, Y. I., Cho, S. J., Lee, J. Y., Kim, C. G., Park, B., & Nam, B. H. (2018). *Helicobacter pylori* therapy for the prevention of metachronous gastric cancer. *The New England Journal of Medicine, 378*(12), 1085-1095.

Guo, Y., Zhang, Y., Gerhard, M., Gao, J. J., Mejias-Luque, R., Zhang, L., Vieth, M., Ma, J. L., Bajbouj, M., Suchanek, S., Liu, W. D., Ulm, K., Quante, M., Li, Z. X., Zhou, T., Schmid, R., Classen, M., Li, W. Q., You, W. C., & Pan, K. F. (2020). Effect of *Helicobacter pylori* on gastrointestinal microbiota: A population-based study in Linqu, a high-risk area of gastric cancer. *Gut, 69*(9), 1598-1607.

Hall, S. N., & Appelman, H. D. (2019). Autoimmune gastritis. *Arch Pathol Lab Med., 143*(11), 1327-1331.

Han, L., Li, T., Wang, Y., Lai, W., Zhou, H., Niu, Z., Su, J., Lv, G., Zhang, G., Gao, J., Huang, J., & Lou, Z. (2023). Weierning, a Chinese patent medicine, improves chronic atrophic gastritis with intestinal metaplasia. *J. Ethnopharmacol, 309*, 116345.

Huang, M., Li, S., He, Y., Lin, C., Sun, Y., Li, M., Zheng, R., Xu, R., Lin, P., & Ke, X. (2021). Modulation of gastrointestinal bacterial in chronic atrophic gastritis model rats by Chinese and west medicine intervention. *Microb Cell Fact., 20*(1), 31.

Lenti, M. V., Rugge, M., Lahner, E., Miceli, E., Toh, B. H., Genta, R. M., De Block, C., Hershko, C., & Di Sabatino, A. (2020). Autoimmune gastritis. *Nat. Rev. Dis. Primers., 6*(1), 56.

Liou, J. M., Malfertheiner, P., Lee, Y. C., Sheu, B. S., Sugano, K., Cheng, H. C., Yeoh, K. G., Hsu, P. I., Goh, K. L., Mahachai, V., Gotoda, T., Chang, W. L., Chen, M. J., Chiang, T. H., Chen, C. C., Wu, C. Y., Leow, A. H., Wu, J. Y., Wu, D. C., Hong, T. C., Lu, H., Yamaoka, Y., Megraud, F., Chan, F. K. L., Sung, J. J., Lin, J. T., Graham, D. Y., Wu, M. S., & El-Omar, E. M. (2020). Asian Pacific alliance on helicobacter and microbiota (APAHAM). Screening and eradication of *Helicobacter pylori* for gastric cancer prevention: The Taipei global consensus. *Gut, 69*(12), 2093-2112.

Liu, L. H., Han, B., Tao, J., Zhang, K., Wang, X. K., & Wang, W. Y. (2023) .The effect of *Saccharomyces boulardii* supplementation on *Helicobacter pylori* eradication in children: A systematic review and meta-analysis of Randomized controlled trials. *BMC Infect Dis., 23*(1), 878.

Malfertheiner, P., Camargo, M. C., El-Omar, E., Liou, J. M., Peek, R., Schulz, C., Smith, S. I., & Suerbaum, S. (2023). *Helicobacter pylori* infection. *Nat. Rev. Dis. Primers., 9*(1), 19.

Miceli, E., Vanoli, A., Lenti, M. V., Klersy, C., Di Stefano, M., Luinetti, O., Caccia Dominioni, C., Pisati, M., Staiani, M., Gentile, A., Capuano, F., Arpa, G., Paulli, M., Corazza, G. R., & Di Sabatino, A. (2019). Natural history of autoimmune atrophic gastritis: A prospective, single centre, long-term experience. *Alimentary Pharmacology & Therapeutics, 50*(11-12), 1172-1180.

Miranti, E. H., Stolzenberg-Solomon, R., Weinstein, S. J., Selhub, J., Männistö, S., Taylor, P. R., Freedman, N. D., Albanes, D., Abnet, C. C., & Murphy, G. (2017). Low vitamin B_{12} increases risk of gastric cancer: A prospective study of one-carbon metabolism nutrients and risk of upper gastrointestinal tract cancer. *Int. J. Cancer, 141*(6), 1120-1129.

Neumann, W. L., Coss, E., Rugge, M., & Genta, R. M. (2013). Autoimmune atrophic gastritis—Pathogenesis, pathology and management. *Nat. Rev. Gastroenterol Hepatol, 10*(9), 529-541.

Pivetta, G., Dottori, L., Fontana, F., Cingolani, S., Ligato, I., Dilaghi, E., Milani, C., Ventura, M., Borro, M., Esposito, G., Annibale, B., & Lahner, E. (2023). Gastric microbiota gender differences in subjects with healthy stomachs and autoimmune atrophic gastritis. *Microorganisms, 11*(8), 1938.

Rodriguez-Castro, K. I., Franceschi, M., Noto, A., Miraglia, C., Nouvenne, A., Leandro, G., Meschi, T., De'Angelis, G. L., & Di Mario, F. (2018). Clinical manifestations of chronic atrophic gastritis. *Acta Biomed., 89*(8-S), 88-92.

Rugge, M., Meggio, A., Pennelli, G., Piscioli, F., Giacomelli, L., De Pretis, G., & Graham, D. Y. (2007). Gastritis staging in clinical practice: The OLGA staging system. *Gut, 56*(5), 631-636.

Rustgi, S. D., Bijlani, P., & Shah, S. C. (2021). Autoimmune gastritis, with or without pernicious anemia: Epidemiology, risk factors, and clinical management. *Therap Adv. Gastroenterol, 14*, 17562848211038771.

Shah, S. C., Piazuelo, M. B., Kuipers, E. J., & Li, D. (2021). AGA clinical practice update on the diagnosis and management of atrophic gastritis: Expert review. *Gastroenterology, 161*(4), 1325-1332.

Song, H., Held, M., Sandin, S., Rautelin, H., Eliasson, M., Söderberg, S., Hallmans, G., Engstrand, L., Nyrén, O., & Ye, W. (2015). Increase in the prevalence of atrophic gastritis among adults age 35 to 44 years old in northern Sweden between 1990 and 2009. *Clin Gastroenterol Hepatol., 13*(9), 1592-1600.

Sung, J. J. Y., Coker, O. O., Chu, E., Szeto, C. H., Luk, S. T. Y., Lau, H. C. H., & Yu, J. (2020). Gastric microbes associated with gastric inflammation, atrophy and intestinal metaplasia 1 year after *Helicobacter pylori* eradication. *Gut, 69*(9), 1572-1580.

Varkalaite, G., Vaitkeviciute, E., Inciuraite, R., Salteniene, V., Juzenas, S., Petkevicius, V., Gudaityte, R., Mickevicius, A., Link, A., Kupcinskas, L., Leja, M., Kupcinskas, J., & Skieceviciene, J. (2022). Atrophic gastritis and gastric cancer tissue miRNome analysis reveals hsa-miR-129-1 and hsa-miR-196a as potential early diagnostic biomarkers. *World J. Gastroenterol, 28*(6), 653-663.

Weise, F., Vieth, M., Reinhold, D., Haybaeck, J., Goni, E., Lippert, H., Ridwelski, K., Lingohr, P., Schildberg, C., Vassos, N., Kruschewski, M., Krasniuk, I., Grimminger, P. P., Waidmann, O., Peitz, U., Veits, L., Kreuser, N., Lang, H., Bruns, C., Moehler, M., Lordick, F., Gockel, I., Schumacher, J., Malfertheiner, P., & Venerito, M. (2020). Gastric cancer in autoimmune gastritis: A case-control study from the German centers of the staR project on gastric cancer research. *United European Gastroenterol J.*, *8*(2), 175-184.

Xu, Q., Liu, M., Meng, R., Zhao, Q., Men, X., Lan, Y., & Xu, H. (2023). Therapeutic effects and potential mechanisms of endoscopic submucosal injection of mesenchymal stem cells on chronic atrophic gastritis. *Sci, Rep.*, *13*(1), 20745. doi:10.1038/s41598-023-48088-3

Xu, R., Wang, W., Zhu, B., Lin, X., Ma, D., Zhu, L., Zhao, Q., Nie, Y., Cai, X., Li, Q., Fang, W., Li, H., Wang, N., Chen, Y., Peng, C., Fang, H., & Shen, L. (2020). Disease characteristics and treatment patterns of Chinese patients with metastatic colorectal cancer: A retrospective study using medical records from China. *BMC Cancer*, *20*(1), 131.

Zagari, R. M., Rabitti, S., Greenwood, D. C., Eusebi, L. H., Vestito, A., & Bazzoli, F. (2017). Systematic review with meta-analysis: Diagnostic performance of the combination of pepsinogen, gastrin-17 and anti-Helicobacter pylori antibodies serum assays for the diagnosis of atrophic gastritis. *Aliment Pharmacol Ther.*, *46*(7), 657-667.