# PATHOPHYSIOLOGY OF GASTRITIS AND CORRELATION WITH *H. PYLORI*: AN IN-DEPTH INVESTIGATION AND ITS CLINICAL IMPLICATIONS

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## ABSTRACT

Gastritis is an inflammation of the gastric mucosa that can be triggered by several factors, such as prolonged use of some medications, smoking, and infection by the bacterium Helicobacter pylori (HP). The prevalence of this infection encompasses approximately half of the world population, and although its relationship with gastritis has not been fully elucidated, it is known that bacterial virulence, the host's immune system, and environmental influences interact to constitute a complex mechanism that establishes different gastritis phenotypes. These different phenotypes can be distinguished in chronicity, severity, late diagnosis, response or refractoriness to treatment, and clinical complications. This literature review aims to explore the pathophysiology of Helicobacter pylori-associated

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gastritis and its clinical implications, in order to provide a comprehensive understanding of this condition and its implications for medical practice, addressing its association with peptic ulcers, gastric cancer, and anemia, as well as reviewing available therapeutic options against this infection. To this end, 154 articles were identified, and of these, 18 were selected for this study based on the inclusion and exclusion criteria adopted. Thus, the potentiating action of H. pylori in the development of some gastroenterological diseases was observed, as seen in the increase in the genetic expression of PREX2, found in cancer cells, and in the endoscopic findings of antral nodularity, both due to this bacterium, which allows us to conclude the close relationship of gastritis with clinical implications of intense severity and in the long term.

**Keywords:** Gastritis. Pathophysiology. *Helicobacter pylori*.

## INTRODUCTION

Gastritis is an inflammation of the stomach lining that can be triggered by a variety of factors, including long-term use of some medications, excessive alcohol consumption, smoking, autoimmunity, and especially infection with the bacterium Helicobacter pylori (HP). This infection affects approximately half of the world's population, and although the exact relationship between H. pylori and gastritis is not yet fully understood, socioeconomic, environmental, and cultural factors are thought to exert a significant influence, while genetic predisposition plays a less prominent role (DDINE et al.; 2012).

The pathophysiology of H. pylori infection involves complex bacterial virulence mechanisms, interactions with the host immune system, and environmental influences, culminating in different gastritis phenotypes, which, in turn, can evolve into various gastroduodenal conditions. H. pylori infection often establishes itself in childhood and persists throughout life if left untreated, leading to chronic gastritis. This condition can progress to serious complications, including peptic ulcer disease, gastric cancer, and lymphomas of mucosa-associated lymphoid tissue. (MALFERTHEINER et al.; 2023).

Chronic and aggressive inflammation in gastritis can lead to progressive destruction of the gastric mucosa over years and decades, resulting in the condition known as atrophic gastritis. This continuous deterioration can eventually cause dysfunctions in the stomach mucosa. In advanced stages, atrophic gastritis can result in a significant reduction in stomach acid production, leading to hypochlorhydria or even complete achlorhydria. These conditions, particularly when severe, pose a substantial and independent risk for the development of gastric cancer. In addition, an acid-poor stomach and severe forms of atrophic gastritis can interfere with the absorption of crucial vitamins such as vitamin B12, as well as essential micronutrients such as iron, calcium, magnesium, and zinc, as well as affect the effectiveness of the diet and certain medications (SIPPONEN; MAAROOS; 2015).

Currently, there is a wide range of tests available to diagnose H. pylori infection. Among the non-invasive methods are the breath test with 13C labeled urea (13C-UBT), the fecal antigen test (SAT) and the serological test. On the other hand, invasive techniques such as endoscopy, histology, culture, urease test or rapid urease test (RUT) and polymerase chain reaction (PCR) offer greater specificity for diagnosis, although they are invasive procedures. The choice of method of diagnosing infection often depends on the clinical information required, local availability, and the cost of individual tests. (SUN et al.; 2023).

Treatment to eliminate H. pylori infection not only relieves gastrointestinal symptoms but also reduces the risk of gastric cancer. The current therapeutic approach advocates the

eradication of H. pylori with a combination of two antibiotics and a proton pump inhibitor, forming the triple therapy. In some situations, a fourth drug, bismuth salicylate, is included, resulting in quadruple therapy. Although success rates in eliminating the bacterium range from 70% to 95%, these rates have decreased due to increased antibiotic resistance (LIANG et al.; 2022).

Based on this premise, the present study aims to develop a literature review, with the objective of describing the pathophysiology of gastritis, exploring its correlation with H. pylori infection, presenting the different diagnostic methods, including advantages and disadvantages, and discussing therapeutic approaches and possible complications in order to broaden the understanding of the main etiological factors of gastritis, to facilitate clinical reasoning, workup, therapy and prevention of this condition and its implications.

## THEORETICAL FRAMEWORK

Regarding the diagnosis of Helicobacter pylori infection, Nevoa et al. (2017), described that the Polymerase Chain Reaction (PCR) test showed a higher detection rate (82.35%) compared to the rapid urease test (TRU), highlighting advantages such as sensitivity and specificity, but stressed the need for care in interpreting the results, especially due to the possibility of false-positive results.

The results described by RIBEIRO et al. (2016) point to gastritis as the most common pathology in PH+ (78.34%). However, comparatively, the percentile of disproportion favorable to the HP- group (73.63%) was not statistically significant. Pointing out that gastritis remains highly incident regardless of the presence of H. pylori.

## METHODOLOGY

The methodology of this study is a systematic review of the literature, conducted through the search for scientific articles on the pathophysiology of gastritis and its correlation with the bacterium Helicobacter pylori, following six steps: definition of the study question; establishment of inclusion and exclusion criteria; definition of the information to be extracted from the identified and selected articles; information analysis; interpretation of the results; and presentation of the review.

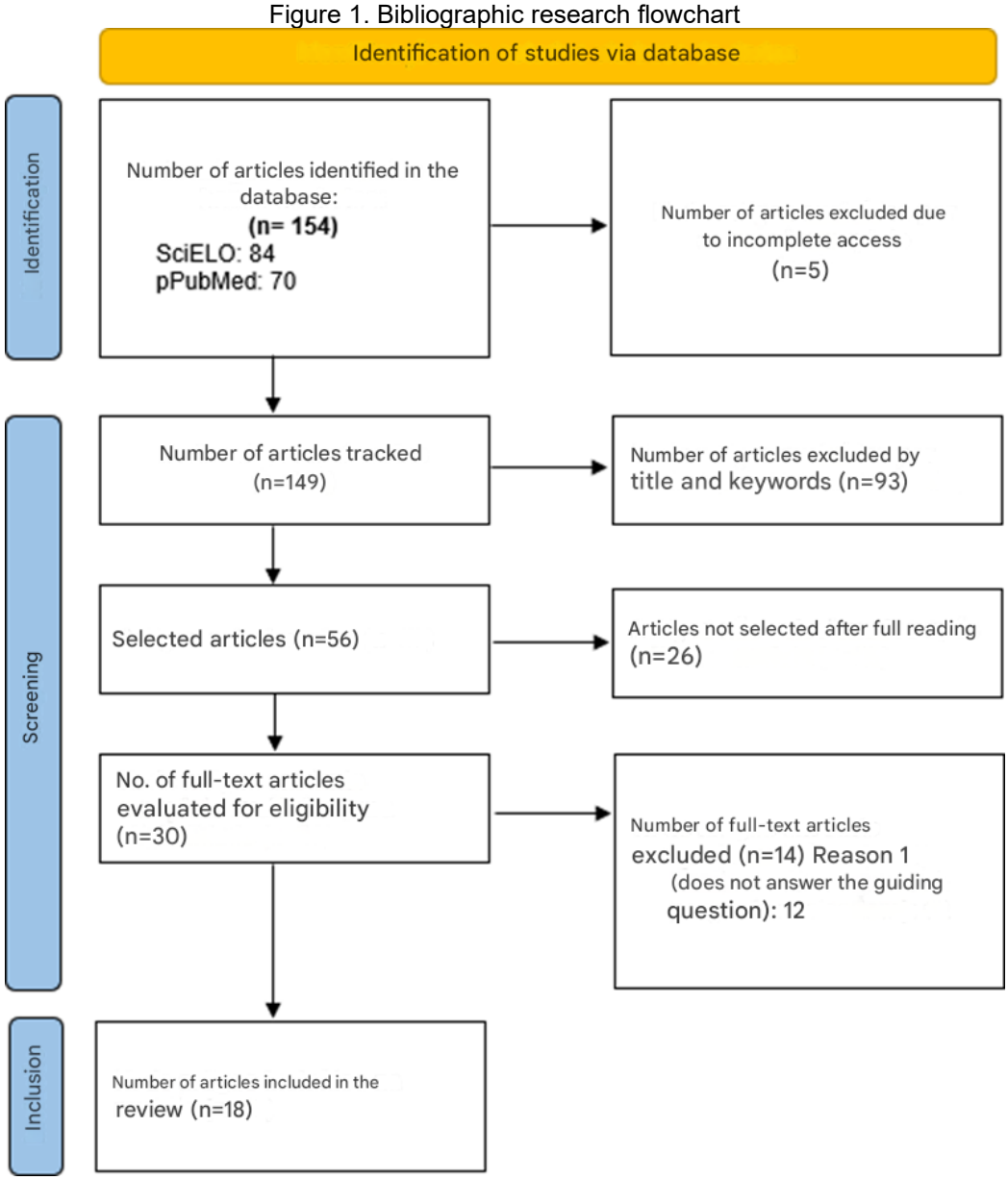
Data collection was guided by the following guiding question: "How does Helicobacter pylori infection contribute to the pathophysiology of gastritis and what are the main clinical implications of this correlation?" The formulation of the research question used the acronym PICo, which refers to Population, Intervention and Context, as detailed below: P = gastritis; I = H. pylori infection; Co = clinical implications.

The search was conducted in the Electronic Databases Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed) and Scientific Electronic Library Online (SciELO). The controlled terms of the Health Sciences Descriptors (DeCS) and the Medical Subject Headings (MeSH) were used.

The keywords used were: "gastritis", "pathophysiology" and "Helicobacter pylori". The Boolean operators "AND" and "OR" were used in order to find the largest number of references. The searches were carried out by two different researchers, who evaluated the articles independently and together to verify whether they met the inclusion criteria. Any disagreement was resolved by consensus among the researchers.

For the selection of studies, the following steps were followed: the first consisted of screening the database using the descriptors (n=154) and incomplete access articles (n=5) were excluded. The second stage consisted of reading titles and abstracts, 93 articles were excluded, and 56 studies were selected in full, published in Portuguese and English, dated between 2014 and 2024. After full reading evaluating the full text for eligibility, they were excluded (n=26). Articles that did not answer the guiding question were excluded (n=12). Finally, in the last stage, 18 articles were considered relevant and included in the analysis of this study. The research was translated into the description of the results, reported in the flowchart of Figure 1.

Figure 1. Bibliographic research flowchart




Source: Prepared by the authors following PRISMA guidelines

## RESULTS AND DISCUSSIONS

It was observed that H. pylori infection can be triggered by several different mechanisms, including medication, external, autoimmune, and organic-metabolic factors, and its correlation with chronic inflammation of the stomach, the main organ affected by this pathology, is undeniable. In view of this range of causalities caused by gastritis, the present study brought several diagnostic methods and therapeutic approaches presented by the selected studies.

Among the 56 articles included in this literature review, from academic platforms, PubMed and SCIELO, 18 were selected because they were able to address the topic effectively. Chart 1 shows the authors and the year of publication of the selected articles.

Table 1. Findings

| Autor | Ano |
|---|---|
| WEN, Zhengwei *et al.* | 2014 |
| CAMILO, Sílvia Maria Perrone *et al.* | 2015 |
| GOMES, Alexandre *et al.* | 2016 |
| RIBEIRO, Irma Cláudia Saboya *et al.* | 2016 |
| NEVOA, Jéssica C. *et al.* | 2017 |
| GÖNEN, Sevim *et al.* | 2017 |
| VINAGRE, Ruth Maria Dias Ferreira *et al.* | 2018 |
| RODRIGUES, Michele Fernandes *et al.* | 2019 |
| MATTAR, Rejane *et al.* | 2020 |
| SANTOS, Maria Luísa Cordeiro *et al.* | 2020 |
| COELHO, Maria Clara Freitas *et al.* | 2021 |
| OLIVEIRA, Ana Karoline Silva *et al.* | 2021 |
| HEDAYATI, Manouchehr Ahmadi *et al.* | 2021 |
| MLADENOVA, Irena. | 2021 |
| MIWA, Hiroto *et al.* | 2022 |
| FERRARI, Fangio; OGATA, Daniel Cury; ME | 2023 |
| ALANLI, Recep *et al.* | 2023 |
| VINAGRE, Ruth Maria Dias Ferreira et al. | 2023 |

Source: Prepared by the authors

Regarding morphological changes at endoscopy, the study described by Gomes et al. (2016) showed that the endoscopic findings most associated with H. pylori infection were nodularity in the antrum, elevated erosions, and mosaic enanthema in the gastric body. The most representative form of gastritis caused by this bacterium is characterized by the presence of nodularity in the antral mucosa, whereas elevated erosions and mosaic mucosa in the gastric body are suggestive, but not specific, of infection.

Although gastritis has different causes (e.g., inappropriate diet, smoking, alcoholism, medications, H. pylori infection), including idiopathic ones, the importance of H. pylori is due to the clinical implications that infection by this bacterium can trigger. This microorganism has the ability to increase the body's gastrin levels. In this sense, the PREX2 protein — whose expression plays a role in cell migration, cell proliferation and apoptosis, found in some cancer cells — was the target of research by Hedayati et al. who, through gastric antral biopsy evaluations, attested that PREX2 gene expression increased in patients with H. pylori infection. In patients with gastritis associated with HP+, the increase was 2.38, and in those with gastric cancer associated with HP+, the increase was 2.27 times the incidence of patients without the infection. Therefore, gastric cancer more than doubles its prevalence in the HP+ population.

Nevertheless, Hedayati et al. (2021) showed that H. pylori infection, with the specific genotypes vacA, s1m1, and sabB, may be correlated with an increase in the expression of

the PREX2 gene in patients with gastritis and gastric cancer, which suggests that not all strains of this bacterium lead to complications and malignant lesions of the stomach. Therefore, studies that deepen the genetic content of this compatibility and allow a better understanding of the etiopathogenesis and future diagnostic criteria are urgent.

Also regarding the risk of patients with gastritis and chronic PH+ developing gastric cancer, the study by Coelho et al. (2021) indicated that the association of the histopathological classifications Operative Link for Gastritis Assessment (OLGA) and Operative link for Gastric Intestinal Metaplasia (OLGIM) obtained greater accuracy used together, rather than separately, to identify gastric atrophy and premalignant lesions, This allows for greater and earlier identification of this high-risk group for the development of gastric neoplasia.

However, the surveys by Ferrari et al. (2023) demonstrated that in the analysis of biopsy and the OLGA and OLGIM criteria, the presence of HP+ only showed relevance associated with age over 50 years. Therefore, PH positivity was an important factor for gastric atrophy only when correlated with another independent risk factor, which demonstrates that the clinical implications of H. pylori should be traced in association with other risk factors for gastric disorders, such as age.

Also according to Oliveira et al. (2021), there was no significant association between the presence of the cagA gene and the severity of gastric lesions. In addition, phylogenetic analysis of H. pylori strains showed no differences in phylogenetic distribution between severe and non-severe diseases. Thus, although the cagA gene is prevalent among H. pylori isolates, it does not represent a marker of gastric lesion severity.

Vinagre et al. (2018) discuss local inflammation in H. pylori infection, which occurs due to the infiltration of specific neutrophils and lymphocytes into the gastric mucosa, as well as increased cytokine production. These H. pylori-induced immunoregulatory and proinflammatory cytokines may influence the nature of the local response of T10 and T15 cells. Stimulation of helper T lymphocytes (CD4+) is observed during the specific immune response, which leads the immune response to both the Th1 and Th2 profiles. However, the cell-mediated response (Th1) predominates, and most CD4+ cell clones, which are specific against H. pylori, secrete interferon gamma (IFN-γ) in response to antigenic stimulation, indicating the Th1 phenotype of the immune response.

According to Gonen et al. (2017), HLA-B*51 was the most frequently found antigen in pediatric patients with PH+ (40%), which suggests a genetic component in the pathophysiology and autoimmune response to this bacterium. However, the gastric panel tracing - which analyzes the combination of several genes, including gastrin 17 (G-17),

pepsinogens I and II (PGI and PGII), and the anti-Helicobacter pylori antibody - did not show high diagnostic sensitivity for atrophic gastritis, according to the findings of Matter et al. (2020).

However, even though the immunological and histopathological findings, individually, make it difficult to establish a unique association of HP+ with atrophic gastritis and neoplasms, statistically, the prevalence of H. pylori continues to demonstrate high clinical relevance. Thus, studies such as Rodrigues et al. (2019) point to a 2.5 times higher prevalence of atrophy (17.6 vs 6.9%) and 1.3 times higher metaplasia (17.7 vs 13.3%) compared to HP- patients.

In addition, the studies by Santos et al. (2020) concluded that there is no need for tissue damage and hemorrhagic processes for the appearance of anemia due to H. pylori infection, and that anemia resulting from infection by this bacterium is directly related to growth disorders in children and adolescents. Therefore, it is essential to screen groups of children with unexplained anemia and growth disorders who present clinical symptoms suggestive of H. pylori infection, so that, if necessary, they can be submitted to eradication of this infectious agent.

The presence of antral gastritis due to PH is related to the development of duodenal ulcers. This happens because this bacterium causes degeneration and injury of epithelial cells, due to the inflammatory response mediated by neutrophils, lymphocytes, plasma cells and macrophages. According to Mladenova et al. (2021), in patients with DUP, VacA s1 is an important marker of virulence and patients carrying these strains are more likely to develop ulcers, being useful as an excellent marker for H. pylori virulence.

It is worth mentioning that Sia et al. (2023) present that, contrary to the epidemiology of the general population, bariatric patients with Roux-en-Y gastric bypass (RYGB) infected with H. pylori not only reduced their incidence of gastritis, but also presented it as a protective factor against jejunal erosions. According to the studies, no effects of PH infection on weight loss were found in individuals undergoing Roux-en-Y Gastric Bypass (RYGB). In fact, the highest incidence of gastritis was observed in individuals with PH infection prior to surgery. In addition, new-onset PH infection after RYGB was a protective factor against jejunal erosions.

Regarding treatment, it is important to emphasize that "dyspepsia accompanied by H. pylori infection should be treated as H. pylori-associated dyspepsia" Miwa et al. (2022). For the first-line treatment of gastritis, proton pump inhibitors (PPIs), histamine type 2 receptor antagonists (H2RAs), acetylcholinesterase inhibitor (AChE), rikkunshito (herbal medication of Japanese origin) and lifestyle changes, such as quitting smoking and

consuming less fatty foods - it is necessary that the treatment be individualized, seeking specific improvements possible for each person. In addition to the gold standard management, it has been observed that dopamine receptor antagonist drugs, serotonin-4 receptor agonists, tricyclic antidepressants, and anxiolytics form a second line of treatment for dyspeptic symptoms. In addition, cognitive behavioral therapies have been shown to be a complementary therapy of great effectiveness in reducing symptoms.

Thus, it remains extremely important to efficiently treat Helicobacter pylori in order to prevent gastric complications. In the recent context, treatment regimens for H. pylori are being updated and constantly researched, especially with the increase in resistance to drugs such as metronidazole and levofloxacin. However, widely known regimens continue to be effective, such as amoxicillin, metronidazole, bismuth subcitrate, and pantoprazole (AMBP) and new regimens, such as amoxicillin, gemifloxacin, and pantoprazole (AGP), emerge as treatment alternatives with a good response, according to the study by Alanli et al (2023). This study also concluded that therapy with gemifloxacin may be a more effective option for the eradication of H. pylori when compared to bismuth-containing treatment. This is because treatment with gemifloxacin had greater patient adherence, and fewer adverse effects, in addition to shorter treatment time, with fewer pills when compared to bismuth.

Furthermore, it is worth noting that, according to Camilo et al. (2015), there is no relationship between the chronic use of proton pump inhibitors and Helicobacter pylori infection or other histopathological or endoscopic alterations.

## CONCLUSION

In the course of this study, the relationship between gastritis and Helicobacter pylori and its implication in several pathologies, such as gastric cancer, anemia, gastric and duodenal peptic ulcers, is perceived. Thus, it is essential to carry out the early diagnosis of H. pylori through tests, which range from breath test with marked urea, fecal, serology, to endoscopy. After confirming the presence of Helicobacter pylori, it is essential to establish appropriate pharmacological and non-pharmacological treatment in order to treat the infection in question and jointly prevent the diseases associated with it, as evidenced in this study.

In view of this study, it was possible to analyze the potentiating action of H. pylori with regard to gastroenterological diseases. An increase in gene expression, genotypes and specific antigens was observed when interacting with the physiological, immunological and anatohistological changes caused by the presence of this bacterium. Thus, PH-positive patients had an increase in the PREX2 gene, which is associated with cancer in the

gastrointestinal tract. The genotype VacA s1m1 and sabB associated with PH was presented, in addition to being a precipitating factor for gastric cancer, as the greatest marker of greater probability for the development of duodenal ulcers.

It is concluded that the main purpose of the current review is to expose the pathophysiology of gastritis and its correlation with the bacterium H. Pilory, based on a review of literature between the years 2014 and 2024. Most of these studies are observational or clinical trials, being the best references we have on the subject, with publications made on the "SCIELO" and "PubMed" platforms. The current knowledge on this subject is unique for physicians, especially gastroenterologists, as it seeks to understand the main consequences and causes of the disease, evaluating risk factors and treatments. However, it is not possible to define exactly the relationship between the mechanism of H. pylori and the severity of the implications of gastritis, as well as the increase in its incidence. That said, it is essential to develop more evidence and studies for a greater understanding and diagnostic and prognostic direction of gastritis, its pathophysiology and connection with Helicobacter pylori.

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