



## Incidence, Forms of Transmission and Management of Resistant H. Pylori Infections

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### ABSTRACT

Introduction : H. pylori (HP) has flagellum-mediated motility, survives in the acidic stomach environment and binds to host receptors by adhesions, causing tissue damage through the release of toxin, which contributes to its colonization. Risk factors for adults include age, low socioeconomic status, certain eating habits, family crowding and living in a rural environment. Objectives: To carry out a literature review on the management of H. Pylori infections, its obstacles and challenges. Methodology: After pre-selecting the articles, a research protocol was created, which clearly illustrated the aim of the study, the data collection process and the criteria involved in including the articles. Therefore, 23 articles were selected for this review. Results and discussions: physicians recommended testing for and treating H. pylori in cases of peptic ulcer disease, and about half of the participants reported being first-degree relatives of gastric cancer patients for H. pylori testing, with evidence that eradicating H. pylori reduces the risks of both peptic ulcer disease and gastric cancer. Conclusions: Based on the facts mentioned in the results and during the discussion, it was concluded that H. pylori infection is very common in the world and can lead to the development of gastric and neoplastic diseases if it is not eradicated. We also found a relationship between the infection and certain risk factors, showing a higher prevalence in places where these factors are present. In addition, it was concluded that EDA, endoscopic biopsy, urinary test, 13C-UBT and hematological parameters are suitable methods for making the diagnosis.

**Key- words:** H. Pylori; acidic stomach environment; gastric cancer patients for H. Pylori.

### INTRODUCTION

Helicobacter pylori (H. pylori) is a gram-negative bacterium, a common infectious pathogen that inhabits the gastric mucosa in about 40-50% of the world's population, leading to a global public health problem (HAFIZ, et al.,2021).

H. pylori (HP) has flagellum-mediated motility, survives in the acidic stomach environment and binds to host receptors by adhesions, causing tissue damage through the release of toxin, which contributes to its colonization (HAILE; TIMERGA, 2021).

Risk factors for adults include age, low socioeconomic status, certain eating habits, family crowding and living in a rural environment (LORENZO, et al., 2019).

According to Lim et al. (2018), the lower prevalence of HP infection in developed countries than in developing countries has been attributed to better hygiene and living conditions, which reduce the spread of the bacteria.

HP was the first recognized bacterial carcinogen, and has been etiologically investigated for its association with gastritis, peptic ulcer, gastric adenocarcinoma and primary gastric lymphoma (NEGASH et al., 2018).

*Helicobacter pylori* has been identified as a primary causative factor of gastric cancer, with almost 90% of cases of non-cardiac gastric cancers attributable to HP infection (LIU, et al., 2019).

This carcinogenic process is initiated and promulgated by HP, starting with chronic active gastritis that evolves into chronic atrophic gastritis, intestinal metaplasia and dysplasia that finally evolves into invasive carcinoma (MUHSEN, et al., 2019).

However, according to Matsumura et al. (2021), eradication therapy against HP infection, which is defined as a carcinogen, has been recommended for the prevention of gastric cancer.

Therefore, this literature review seeks to understand the obstacles to achieving HP eradication therapy and analyze whether such conduct is beneficial for the prevention of diseases of the gastrointestinal system.

## GENERAL OBJECTIVE

To carry out a literature review on the management of *H. Pylori* infections, its obstacles and challenges.

## METHODOLOGY

A search strategy was developed based on the evaluation of an objective on the subject in question, which forms the basis of the study.

The search descriptors were selected from the Descriptors in Health Sciences (DeCS) website and then combined with the Boolean operator "AND".

The databases used for the search were PubMed and the Virtual Health Library (VHL), which evaluated cross-sectional, cohort and case-control studies in Portuguese, English and Spanish.

The inclusion criteria were cross-sectional studies that were freely available and focused on the management of *H. Pylori* infections, their obstacles and challenges.

After pre-selecting the articles, a research protocol was created, which clearly illustrated the aim of the study, the data collection process and the criteria involved in including the articles. Therefore, 23 articles were selected for this review.

## RESULTS AND DISCUSSION

### 1 Incidence of H. PYPORI

A worldwide study selected 1748 articles from 111 countries were eligible for analysis. The crude global prevalence of *H. pylori* decreased from 52.6% before 1990 to 43.9% in adults between 2015 and 2022, but remained at 35.1% in children and adolescents between 2015 and 2022 (HAILE; TIMERGA, 2023).

Secular trend and multivariate regression analyses showed that the global prevalence of *H. pylori* has decreased by 15.9% over the last 3 decades in adults, but not in children and adolescents (FIGURE 1).

A significant reduction in the prevalence of *H. pylori* in adults was observed in the Western Pacific, Southeast Asia and Africa regions. However, there was no significant reduction in the prevalence of *H. pylori* in children and adolescents in any of the World Health Organization regions. The incidence of gastric cancer has decreased worldwide and in several countries where the prevalence of *H. pylori* infection has decreased (HAILE; TIMERGA, 2023)

### Global prevalence of *Helicobacter pylori* infection and incidence of gastric cancer between 1980 and 2022

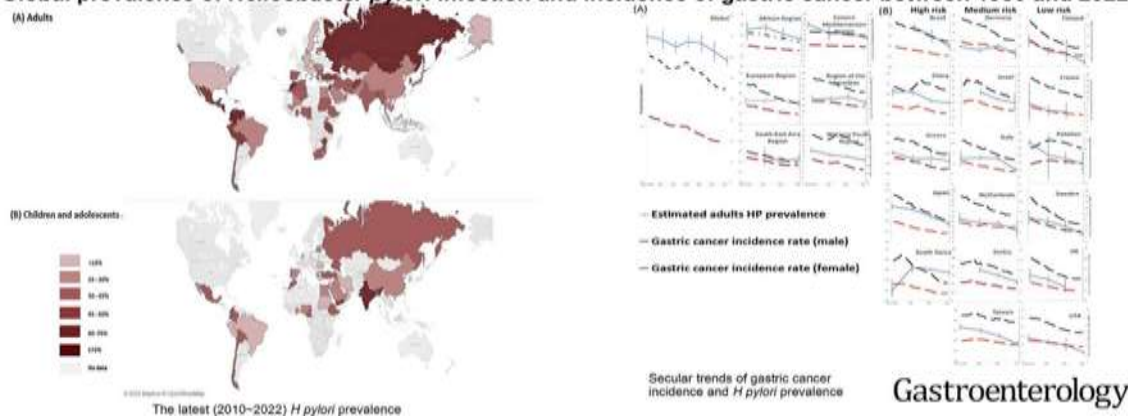


Figure 1. choropleth map of the global prevalence of HP. Certain regions are enlarged to better visualize smaller countries. The interactive online global map showing the prevalence of HP can be found in the following. Source: (HAILE; TIMERGA, 2023).

The prevalence of *H. pylori* infection in humans is correlated with socioeconomic status and age. Low socioeconomic status predisposes to infection; in fact, the prevalence among middle-aged adults is over 80% in many developing countries; on the contrary, in industrialized countries, about 50% of people over 60 are infected, while 20% under 40 are infected (NEGASH et al., 2018).

Gastric cancer is the fifth most common malignant neoplasm in the world (after lung, breast, colorectal and prostate cancers). Worldwide, it is estimated that in 2012, around one million (952,000) new cases and 723,000 deaths occurred due to this disease (NEGASH et al., 2018).

HP is responsible for 7% of new cancer cases and 9% of all cancer deaths worldwide. The distribution map of gastric cancer incidence (FIGURE 2) in men shows great variation between geographical regions, with the highest rates observed in Asia, Central and South America and Eastern Europe (HAILE; TIMERGA, 2023).

The distribution pattern for women is almost identical to that for men, although female rates are generally around half of male rates.

More than 70% of new gastric cancer cases in 2021 occurred in less developed regions of the world, with Asia contributing around 72% of the global burden and almost half of the world's cases occurring in China (HAILE; TIMERGA, 2023).

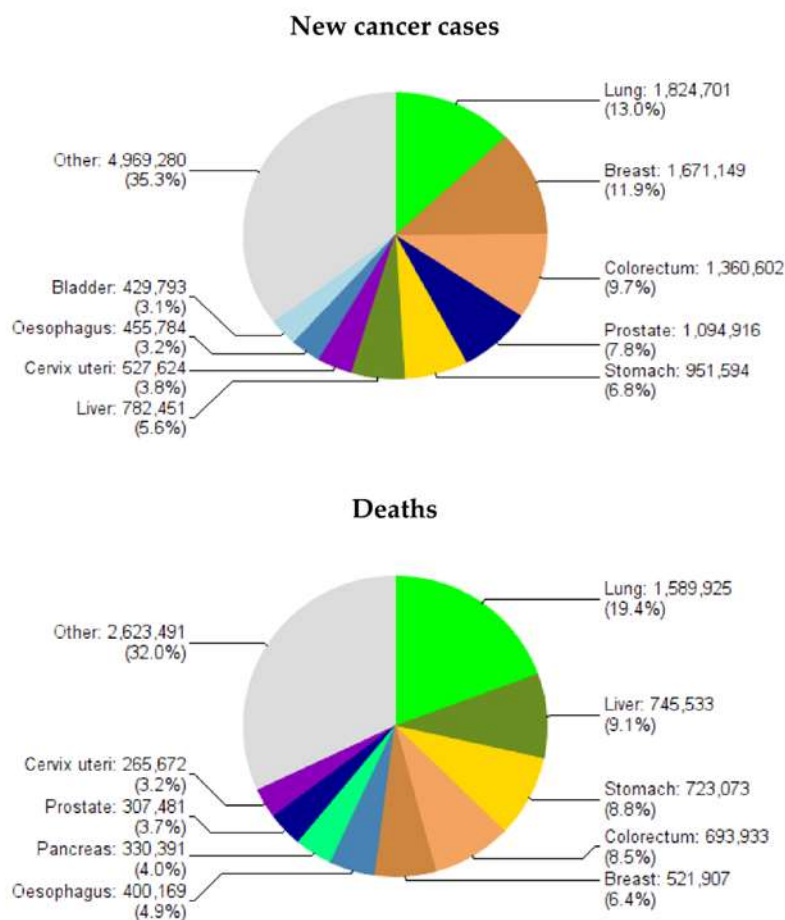


Figure 2: Estimated frequency of new cancer cases and deaths worldwide in 2021, for both sexes. Source: (HAILE; TIMERGA, 2023).

According to the study by Lim et al. (2018), there has been a downward trend in the seroprevalence of *Helicobacter pylori* infection and an increase in the putative eradication rate of *Helicobacter pylori*. Suggesting that the factors underlying this increase in eradication therapy may not be due to an increase in the incidence of *Helicobacter pylori*-related diseases, but rather due to easier access to medical information and medical services and/or changes over time in the guidelines that define the target population for *Helicobacter pylori* eradication therapy, such as older people, average levels of education, average levels of income and males.

The study by Ryoo et al. (2020) explains that patients with *Helicobacter pylori* infection had a higher risk of developing advanced colorectal neoplasia, which was strongly associated with histological positivity and not serological positivity, due to its false positivity.

In patients with current infection, serum biomarker levels remained high, while in those who were not infected or who had the disease in the past, serological biomarkers decreased significantly up to two years after eradication, continuing to decline slowly over time. It can therefore be concluded that patients with long-term eradication become serologically and histologically uninfected (FUKUDA, et al.; 2022).

The infected patient's hematological picture is linked to iron consumption by *H. pylori*, iron depletion due to absorption secondary to chronic gastritis, iron loss due to gastritis and hemorrhagic peptic ulcers, and iron and vitamin B12 deficiency secondary to chronic and atrophic gastritis. In addition, high RDW indicates impaired erythropoiesis, which reflects chronic inflammation and micronutrient deficiency, both significant signs of *H. pylori* infection, which result in erythrocyte size variation (HAILE; TIMERGA, 2021).

Therefore, the hematological parameters: Hemoglobin concentration, RBC count, HCT and VCM and RDW should be considered for proper diagnosis and treatment of patients infected with *H. pylori*, and eradication of this microorganism from infected patients (LIU, et al., 2019).

In the metabolic findings, hyperglycemia was associated with a 1.7-fold increased risk of gastric cancer, indicating that it is a cofactor that increases the risk of gastric cancer in the presence of *H. pylori* infection. In the subgroup analysis by *H. pylori* status, this association occurs only in the *H. pylori* positive population with an OR of 1.98. Leading to a 3.23-fold increased risk of gastric cancer (LIU, et al., 2019).

Majima et al. (2019) explain that the presence of map-like redness and absence of regular arrangement of collecting venules in the remaining fundic gland are risk factors for gastric cancer, even after successful eradication of *Helicobacter pylori* and that, with linked color images, redness is more likely to be identified than with white light, and that mucosal atrophy and intestinal metaplasia are not independent risk factors for the detection of gastric cancer after successful eradication of *H. pylori*.

Furthermore, in the study by Matsumura et al. (2021), color light imaging showed early gastric cancer surrounded by redness mapping with a large color difference and better visibility than white light imaging.

In Na'amnih et al. (2020), 85% of physicians recommended testing for and treating *H. pylori* in cases of peptic ulcer disease, and about half of the participants reported being first-degree relatives of gastric cancer patients for *H. pylori* testing, with evidence that eradicating *H. pylori* reduces the risks of both peptic ulcer disease and gastric cancer.

Nam et al. (2020) also explain that persistent *Helicobacter pylori* infection increases the risk of pathologies or neoplasms compared to those who have eradicated the disease. The justification for the persistent disease causing regenerative atypia may be due to damage to the gastric epithelial cells produced by the body itself in response to *Helicobacter pylori*. This can subsequently lead to a neoplastic lesion, which is why the eradication of *H. pylori* is so important, in order to prevent the pathology from proliferating and even regressing.

According to Lai et al. (2022), the risk of venous thromboembolism (VTE) compared to those who had initial eradication and late eradication, the risk is higher in those who had late eradication of *Helicobacter pylori*, in both sexes and the risk is significantly higher in women, older age and with comorbidities, showing that early eradication is beneficial both for reducing the risk of EVT and for others and for the progression of the disease in the pathological process in the gastric mucosa with the occurrence of cancer and peptic ulcer disease.

1. standard dose proton pump inhibitor (PPI) + amoxicillin 1.0 g + clarithromycin 500 mg twice a day for 7 days.
2. PPI in standard dose, once a day + clarithromycin 500 mg twice a day + furazolidone 200 mg twice a day, for 7 days.
3. Standard dose PPI, once a day + furazolidone 200 mg three times a day + tetracycline hydrochloride 500 mg four times a day, for 7 days.

After the failure of one of the initial treatments proposed above by the Consensus, two more treatment attempts are recommended, lasting between 10 and 14 days, without repeating or extending the initial regimen. The regimens to be used depend on the initial treatment (HAILE; TIMERGA, 2021).

According to Kusano et al. (2017), either PPI + amoxicillin + clarithromycin or PPI + furazolidone + clarithromycin was used:

#### **First option**

Full-dose PPI + bismuth salt 240 mg + furazolidone 200 mg + amoxicillin 1.0 g (can be replaced by doxycycline 100 mg), given twice a day for 10 or 14 days.

#### **Second option**

IBP (full dose) bid + levofloxacin 500 mg uid + amoxicillin 1.0 g bid for 10 days, or IBP in full dose + levofloxacin 500mg + furazolidone 400 mg, given as a single daily dose for 10 days.

If the initial regimen was PPI + furazolidone + tetracycline:

#### **First option**

Full-dose PPI + amoxicillin 1.0 g + clarithromycin 500 mg, given twice a day for 7 days.

#### **Second option**

Full-dose PPI + bismuth salt 240 mg + furazolidone 200 mg + amoxicillin 1.0 g (can be replaced by doxycycline 100 mg), given twice a day for 10 or 14 days.

Although most therapeutic studies for Hp using bismuth salts recommend its use 3 or 4 times a day, the Consensus, based on recent observations, opted for regimens using it only twice a day, in order to simplify the therapeutic regimen and increase adherence to treatment. Based on various international

studies and even in the absence of national studies, the consensus recommends using the combination of levofloxacin, amoxicillin and PPIs as a second-choice retreatment therapy. The recommendation to use the combination of levofloxacin, furazolidone and PPI in a single daily dose was based on a national pilot study with excellent initial results. The Consensus also recommended a national multicenter study to validate the regimens suggested here (NEGASH et al., 2018; LIU, et al., 2019).

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## CONCLUSION

Based on the facts mentioned in the results and during the discussion, it was concluded that *H. pylori* infection is very common in the world and can lead to the development of gastric and neoplastic diseases if it is not eradicated.

We also found a relationship between the infection and certain risk factors, showing a higher prevalence in places where these factors are present. In addition, it was concluded that EDA, endoscopic biopsy, urinary test, 13C-UBT and hematological parameters are suitable methods for making the diagnosis.

This highlights the importance of analyzing the patient's profile and needs in order to decide which diagnostic or screening method is most suitable and will be most effective in each situation.

Furthermore, therapy is an obstacle to eradicating *H. pylori*, with a high rate of resistance to some of the drugs used in the treatment regimen.

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