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REVIEW ARTICLE

The role of *Helicobacter pylori* in functional dyspepsia

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Abstract

We present a narrative review that analyzes the role of *Helicobacter pylori* infection in the pathophysiology of functional dyspepsia, showing the most current evidence on this relationship. The importance of diagnosing and treating the infection when found in these patients is emphasized, using appropriate non-invasive diagnostic tests and selecting the most suitable therapeutic regimen, recognizing that *H. pylori* eradication only achieves remission or improvement of symptoms in a subgroup of patients. This review presents the current challenges in the treatment of the bacterium, particularly in relation to increasing antibiotic resistance and its clinical impact, and discusses some of the options that could increase eradication rates in patients, highlighting the relevance of susceptibility-based treatments. Finally, the importance of confirming the success of eradication treatment after its completion is emphasized.

Keywords: *Helicobacter pylori*. Functional dyspepsia. Pathophysiology. Eradication. Resistance. Susceptibility.

Papel de Helicobacter pylori *en la dispepsia funcional*

Resumen

Presentamos una revisión narrativa que analiza el papel que desempeña la infección por *Helicobacter pylori* en la fisiopatología de la dispepsia funcional, mostrando la evidencia más actual sobre esta relación. Se destaca la importancia de diagnosticar y tratar la infección cuando se encuentre en estos pacientes, utilizando las pruebas diagnósticas no invasivas apropiadas y seleccionando el esquema terapéutico más adecuado, reconociendo que la erradicación de *H. pylori* solo logra la remisión o la mejoría de la sintomatología en un subgrupo de pacientes. Esta revisión presenta los desafíos actuales en el tratamiento de la bacteria, en particular en relación con la creciente resistencia a los antibióticos y su impacto clínico, y se discuten algunas de las opciones que podrían incrementar las tasas de erradicación en los pacientes, destacando la relevancia de los tratamientos basados en las sensibilidades. Finalmente, se destaca la importancia de confirmar el éxito del tratamiento de erradicación posterior a su realización.

Palabras clave: *Helicobacter pylori*. Dispepsia funcional. Fisiopatología. Erradicación. Resistencia. Sensibilidad.

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Relationship between *Helicobacter pylori* infection and functional dyspepsia: current evidence

Helicobacter pylori is a bacterium recognized as a Group 1 carcinogen. Infection by this microorganism is associated with common gastrointestinal diseases, such as chronic gastritis, acid-peptic disease, functional dyspepsia, and, more importantly, although less frequently, gastric cancer. It is a flagellated, G ram-negative bacillus with a high infection rate that primarily colonizes the gastric epithelium and represents the most common chronic bacterial infection worldwide. Transmission of this bacterium can occur directly from person to person, or indirectly from an infected person to their environment, with transmission through contaminated water or food, which contributes to the high infection rate[1,2]. Various studies report prevalences ranging from 7% to 87%, depending on geographic region, age, and socioeconomic factors; the global incidence is more than 40%, with higher prevalence in developing countries[3,4]. Mexico, like most Latin American countries, has a high prevalence of *H. pylori* infection. The national mean seroprevalence of patients with the infection is estimated to be approximately 66%[5]. The high prevalence of *H. pylori* is primarily associated with low socioeconomic status, overcrowding and overpopulation conditions, and deficiency o f sanitation and public services[6]. In the last decade, the prevalence of *H. pylori* has decreased due to improvements in sanitary and socioeconomic conditions; however, a uniform and global reduction has not been achieved, with this accomplishment being more evident in developed regions and countries[7,8].

Functional dyspepsia (FD) is a gastrointestinal disorder that affects 8.4% of the global population[9]. It represents one of the main disorders of gut-brain interaction. According to the Rome IV criteria, the diagnosis is established by one or more of the following positive symptoms: early satiation, postprandial fullness, and epigastric pain or burning; all of this, after ruling out organic causes that explain them. The symptoms must be present for at least the last 3 months (one or more times per week), with symptom onset ≥ 6 months[10]. Dyspepsia may have an organic etiology; therefore, to consider it functional, symptoms must be thoroughly investigated through different laboratory and imaging studies, including endoscopy, according to the clinical characteristics and risk factors presented by the patient, in order to exclude other causes. Before conducting this investigation, a definitive d iagnosis o f F D cannot be established, and the condition must be treated as uninvestigated dyspepsia[11].

The exact incidence of FD in Mexico is poorly understood. In a study that included more than 8,000 patients from Latin America who completed an internet-based questionnaire using the Rome IV criteria, a prevalence of FD ranging from 6.59% to 10.6% was observed, with a predominance in women[12].

The pathophysiology of FD is multifactorial and complex. Various dietary, infectious, inflammatory, allergic, psychological, and even genetic factors are involved. These etiological factors can cause dysfunction in gastrointestinal motility, primarily delayed gastric emptying, increased visceral hypersensitivity, enhanced immune system responses, alterations in the intestinal microbiome, increased epithelial permeability, and alterations in acid sensitivity in the stomach and duodenum, as well as nervous system dysfunction and psychological disorders[11,13]. Among the infectious factors, FD is frequently associated with *H. pylori* infection. The high prevalence of both conditions means they frequently coexist[11]. The rate of patients with FD and concomitant *H. pylori* infection reaches 40-70%, which supports the idea that chronic gastritis generated as a consequence of *H. pylori* colonization may be the cause of dyspeptic symptoms in these patients[13].

There are other debatable aspects regarding the definition that are important to consider. To date, controversy still persists as to whether a person with dyspepsia and *H. pylori* can be considered as having FD or whether this infection should be considered an organic cause of dyspepsia and, therefore, is a diagnosis of exclusion based on the original definition of FD.

The 2015 Kyoto Consensus states that, given the lack of clarity regarding whether dyspeptic symptoms can be attributed solely to *H. pylori* infection, in patients with suspected FD, the infection should be treated and the patient monitored for 6-12 months. When eradication leads to symptom improvement, the dyspepsia will be considered to have been caused by the infection, in which case the term “functional dyspepsia” will be ruled out and it will be considered a specific disease termed “*H. pylori*-associated dyspepsia,” whose symptoms can be attributed to “*H. pylori*-induced gastritis.” Cases in which symptoms do not improve despite eradication are considered FD[14]. The Rome IV Consensus proposes a similar criterion, stating that *H. pylori* is a probable cause of dyspeptic symptoms in patients with a diagnosis suggestive of FD, establishing that this diagnosis can be confirmed once the infected patient

has received eradication treatment and there is no symptom improvement despite having achieved bacterial elimination[10]. Finally, the Maastricht VI Consensus is the most specific in this regard by determining that the diagnosis of FD requires that *H. pylori* infection be ruled out[15].

Proposed mechanisms for *Helicobacter pylori* in functional dyspepsia

Determining whether the coexistence of *H. pylori* and FD represents an association or true causality has been the subject of investigation. Some studies have considered that *H. pylori* infection may cause an alteration in the immune response of patients with FD, demonstrating that it produces an increase in the number of intraepithelial CD3+ and CD8+ lymphocytes, mast cells, and eosinophils in the duodenum in patients positive for this infection[16].

It has been considered that *H. pylori* infection may also cause gastrointestinal symptoms through alterations in the gastric and intestinal microbiota, generating a proinflammatory effect primarily in the stomach and duodenum, which promotes alterations in the epithelial barrier and consequently bacterial translocation and colonization by other bacteria. *H. pylori* infection affects the Th1-type immune response related to immunoglobulin G2, as well as the production of cytokines such as interleukins 1 and 17, and Reg III, and through the production of reactive oxygen species and N-nitrosamines[17].

Impairment of acid secretion appears to be another mechanism involved. It is known that, depending on the gastric segment colonized by *H. pylori*, an increase or decrease in gastric acidity may occur, which determines the symptoms and type of damage generated by *H. pylori*, and may also favor dyspeptic symptoms through alterations in the secretion of glucagon-like peptide-1, somatostatin, and gastrin, which, by decreasing acid secretion in the stomach, promotes delayed gastric emptying, in addition to increasing dysbiosis[18].

Eradication therapy: does it improve symptoms in all patients?

Studies have been conducted to determine whether *H. pylori* eradication can improve symptoms in patients with FD, with heterogeneous results. This may be due to different factors, such as the diversity in the criteria used to define treatment response, the lack of evidence that this infection is a causative agent of the symptoms in all cases, and the follow-up time used to determine symptom persistence.

The HEROES randomized clinical trial included 404 patients, of whom 201 were assigned to eradication treatment and 203 to the control group. Symptomatic response was evaluated, defined as an improvement of at least 50% measured objectively using a global symptom and quality of life questionnaire. 49% of the eradication group and 36.5% of the control group achieved at least 50% symptomatic improvement at 12 months ($p = 0.01$), with a number needed to treat (NNT) of 8[19].

Although most clinical trials and meta-analyses show some benefit from *H. pylori* eradication in patients with FD, not all have demonstrated improvement. For example, Padole et al.[20] conducted a single-center study in New Delhi that included 202 patients with FD who were positive for *H. pylori*, dividing them into two groups of 101 patients each: one group that received eradication treatment and another that received only symptomatic treatment. The 7-point Global Overall Symptom Scale (GOS) was used to assess the severity of dyspepsia symptoms, and treatment response was defined as complete remission of symptoms or improvement determined by GOS < 2, or a decrease of 2 points from the baseline symptom score. This study demonstrated complete remission of symptoms in 40% of patients treated for *H. pylori* infection, with no statistically significant difference in symptom improvement[20]. It should be noted that there was a loss to follow-up of more than 20% of patients in each group, which may explain the lack of response to eradication.

In order to obtain more robust scientific evidence to determine the efficacy of *H. pylori* eradication on symptom improvement in patients with FD, systematic reviews and meta-analyses addressing this issue have been conducted. Ford et al.[21] performed a meta-analysis that analyzed 29 randomized clinical trials from May 2015 to 2022, with a total of 6,781 patients with FD who were positive for *H. pylori*. This meta-analysis demonstrated that, compared with controls, eradication is superior for achieving symptom control, with a relative risk (RR) for symptom cure of 0.91 (95% confidence interval [95% CI]: 0.88-0.94) and a number needed to treat (NNT) of 14 (95% CI: 11-21) and with an RR for symptom improvement of 0.84 (95% CI: 0.78-0.91) and an NNT of 9 (95% CI: 7-17). The authors conclude that improvement in dyspeptic symptoms was observed in these patients 1 year after eradication treatment. These results proved to be more favorable for patients in whom eradication had been confirmed than for patients

in whom *H. pylori* had not been eradicated, although the benefit is modest. It is also worth mentioning that a higher incidence of adverse effects was observed compared with the group without eradication[21]. Another meta-analysis, conducted by Du et al.[22], of 25 randomized clinical trials (n = 5,555 patients), demonstrated that *H. pylori* eradication achieves symptomatic improvement at long-term follow-up (≥ 1 year), but not at short-term follow-up (< 1 year).

To evaluate the mechanism by which *H. pylori* eradication is associated with symptom improvement in a subgroup of patients with FD, but not in all of them, Kim et al.[23] conducted a meta-analysis of 16 randomized clinical trials and found that metronidazole-based treatments for 14 days were associated with greater symptomatic improvement than those based on clarithromycin. The authors consider that a possible explanation is that the treatment not only eliminates the bacteria but also corrects the gastric and intestinal dysbiosis associated with *H. pylori*-related dyspepsia; therefore, further controlled studies are needed to corroborate this hypothesis[23].

Although not all clinical studies clearly demonstrate the benefit of treating *H. pylori* infection in patients with FD, based on the evidence from the highest quality clinical studies, such as those included in the aforementioned meta-analyses, we can conclude that, while the benefits of bacterial eradication in patients with FD appear to be modest, it is a therapeutic strategy that can modify the natural course of the disease in responders, although the symptomatic response may take up to 1 year. Additionally, the benefit should be considered not only in terms of resolution or improvement of dyspeptic symptoms but also with regard to the reduction in the risk of developing complications such as peptic ulcer and gastric cancer.

Strategies in the era of antibiotic resistance

There are various strategies to prevent the development of increased antibiotic resistance, among which the following stand out:

- Utilize appropriate diagnostic tests to establish the diagnosis of *H. pylori* infection.
- Administer treatments with scientific evidence, considering regionally validated regimens and guided, whenever possible, by antibiotic susceptibility testing.
- To confirm the eradication of *H. pylori* following treatment.

There are established indications for providing eradication treatment for *H. pylori*, one of which is uninvestigated dyspepsia in patients without risk factors for organic disease (younger than 55 years, without evidence of upper gastrointestinal bleeding, iron deficiency anemia, weight loss, dysphagia, persistent vomiting, thrombocytopenia, or family history of gastric cancer)[11,15,24-26], as well as in patients with FD[11,15,24]. In uninvestigated dyspepsia without risk factors, the "test and treat" strategy for *H. pylori* before considering performing an endoscopy or providing antisecretory treatment is considered a cost-effective measure[11,15,24,25]. In the absence of alarm features, the risk of a patient presenting clinically significant lesions, precursor lesions of gastric cancer, or cancer is very low. A meta-analysis conducted by Nasseri-Moghaddam et al.[27], which included 15 randomized clinical trials (n = 41,763 participants), showed that more than 85% of endoscopies in patients with uninvestigated dyspepsia without alarm features were normal. The main finding was erosive esophagitis, followed by peptic ulcer, highlighting that the finding of cancer was less than 0.4%[27].

It is important to emphasize that to implement this "test and treat" strategy, it is essential to select a non-invasive test with high sensitivity and specificity in order to confirm the presence of *H. pylori*. The diagnostic approach for these patients can be performed using the urea breath test with labeled urea or the monoclonal antibody test in stool. The urea breath test is relatively low cost and generally available; its specificity is 96% and its sensitivity is 93%. The detection of monoclonal antibodies against *H. pylori* antigens in stool by ELISA (Enzyme-Linked ImmunoSorbent Assay) has a sensitivity of 94% and a specificity of 97%. Although there is no advantage of one test over the other, the monoclonal antibody test in stool may have lower patient adherence, and its availability in Mexico tends to be limited; therefore, the urea breath test is preferred[28,29]. A common error is to use the serological test, which detects antibodies against bacterial antigens, as a basis for treatment. It is important to emphasize that this serological test is not capable of determining whether the infection is active or whether the patient was simply exposed; therefore, it should not be used as a diagnostic test, and even less does it justify administering treatment based on this test[30].

Numerous national and international clinical guidelines establish the recommended treatment regimens to achieve successful therapy that accomplishes bacterial eradication. In addition to the relevance of the antibiotic employed, it has been determined that the

type of acid inhibitor is equally relevant. An increasing number of clinical studies demonstrate the advantage of using a new class of acid suppressors, known as potassium-competitive acid blockers (PCABs), as a replacement for proton pump inhibitors (PPIs) in these treatment regimens, as they have proven to be an ideal therapeutic option due to their high effectiveness and safety; therefore, they should be considered according to their availability and cost in each region.

The following presents the evidence supporting the different recommended regimens[11,15,24,31-33]:

- Bismuth-based quadruple therapy: consists of bismuth, metronidazole, tetracycline, and a PPI for 14 days. Due to the limited availability of oral tetracycline in Mexico, an alternative regimen that substitutes tetracycline with doxycycline is frequently used. This regimen is the treatment of choice due to its high eradication rates. The efficacy of bismuth-based therapy is attributed to the bactericidal properties of bismuth, and its effect is not attenuated by clarithromycin or metronidazole resistance[25,34]. The American College of Gastroenterology guidelines recommend a variant of this therapy as empirical first- or second-line treatment; this variant is known as optimized bismuth-based quadruple therapy and is based on using higher doses of the drugs to achieve greater eradication rates[24]. One of the advantages of this regimen is that it can be used in patients with known allergy to penicillin and its derivatives.
- Quadruple non-bismuth or concomitant therapy: this regimen consists of a PPI with clarithromycin, amoxicillin, and metronidazole administered simultaneously for 14 days. It has the disadvantage that it cannot be used in patients with penicillin allergy. It achieves acceptable eradication rates even in regions with clarithromycin resistance close to or slightly above 15-20%. In a meta-analysis that included six studies and 1,810 patients, which compared the efficacy of bismuth-based quadruple therapy versus concomitant therapy, no statistically significant differences were found between the two regimens[35].
- Triple therapy with levofloxacin: this therapy has gradually reduced its effectiveness in achieving eradication due to increasing rates of fluoroquinolone resistance. For this reason, its use is not recommended in empirical treatments and should be reserved for cases with demonstrated sensitivity to levofloxacin. The addition of bismuth may be considered to increase the eradication rate. The use of this regimen has been decreasing due to increasing resistance; therefore, its use is limited to cases where no other therapy is available. No guideline indicates its use as first-line treatment[36]. Its use is only suggested when susceptibility testing confirms that *H. pylori* is sensitive to levofloxacin[24]. Recently, the possibility of using other quinolones as an alternative to levofloxacin has been investigated; thus, the use of sitafloxacin, a fourth-generation fluoroquinolone, has been studied due to its bactericidal properties and higher minimum concentration levels, which maintain its effectiveness despite failure of treatment with third-generation quinolones[37]. The addition of bismuth may also be considered to increase the eradication rate.
- Triple therapy with rifabutin: combines the use of a PPI, amoxicillin, and rifabutin. The addition of bismuth may be considered to increase the eradication rate. Rifabutin is associated with good eradication rates and low resistance (less than 1%); however, its use is restricted in many countries due to its adverse effects (such as myelotoxicity), as well as to prevent resistance in other bacteria, since it is an indispensable antibiotic for the treatment of tuberculosis and for treating *Mycobacterium avium* in patients with human immunodeficiency virus infection. No studies are available comparing this regimen with others; therefore, although it is considered a good alternative, its use is not recommended as first-line therapy[24].
- Dual therapy with high-dose amoxicillin: initially, the use of a dual regimen combining high-dose PPIs (at least double dose) with high-dose amoxicillin (at least 1 g every 8 hours) was promoted; however, clinical guidelines have recently recommended the use of PCABs instead of high-dose PPIs. In studies comparing dual therapy with PCABs (vonoprazan and amoxicillin) versus bismuth-based quadruple therapy, the dual therapy with PCABs was not found to be inferior; therefore, this treatment may represent an alternative in patients for whom bismuth-based quadruple therapy is not feasible[38,39].
- Conventional triple therapy with PPI, amoxicillin, and clarithromycin: currently, the clarithromycin-based triple therapy regimen is no longer recommended in Mexico because, due to the high rate of clarithromycin resistance, its eradication rate falls well below acceptable levels. Clarithromycin and metronidazole resistance are the most relevant factors for triple therapy failure, particularly in Latin America. In a study conducted in the United States and Europe, clarithromycin resistance reaches up to 22.2%[25,36].
- Conventional triple therapy with PCAB, amoxicillin, and clarithromycin: in some countries, clinical studies

have been conducted showing that replacing the PPI with a PCAB may increase the effectiveness of the combination with amoxicillin and clarithromycin in 14-day regimens; however, sufficient evidence is not available in most countries. In a meta-analysis that included seven studies and 1,168 patients in Asia, triple therapy with PCAB was compared to triple therapy with PPI, and the results favored P-CAB therapy[40].

In any of the treatment regimens, substitution of the PPI with a PCAB may be considered. The new treatment regimens with PCAB plus amoxicillin (dual PCAB) or triple PCAB, which include PCAB, clarithromycin, and amoxicillin, have represented an advance in eradication therapy[24]. The use of PCABs is based on the increased potency and effect of acid suppression, which is key to the action of antibiotics, since a pH > 6 increases the stability, bioavailability, and efficacy of these drugs, in addition to inhibiting bacterial replication[40].

Regarding the optimal duration of treatment, 10-day and 14-day regimens have been compared. In a non-randomized study conducted at Brown University in the United States of America, the records of 1,101 patients with confirmed *H. pylori* infection who were prescribed different treatment regimens with varying durations were analyzed[36]. It was found that 14-day bismuth-based quadruple therapy achieved an eradication rate of 87%, whereas when the same therapy was used for 10 days, it decreased to 77%[36]. With this evidence, which has been replicated in various clinical studies, current guidelines suggest 14-day treatment over 10-day treatment.

Another question that has emerged in recent years is whether changes in the gut microbiota due to antibiotic use in eradication regimens may influence the evolution and prognosis of patients. For this reason, studies have been conducted to determine whether supplementation with probiotics can influence the microenvironment, thereby aiding eradication and symptom improvement[17,41,42]. A meta-analysis that included 1,620 patients undergoing different eradication therapies demonstrated that changes in the microbiota resulting from antibiotics used as part of eradication regimens are minimal and transitory[43].

Currently, the treatment of *H. pylori* infection in patients with FD still poses several clinical challenges:

- There is no universally accepted therapeutic regimen.
- There is an increase in resistance to various antibiotics used as part of treatment regimens, which compromises their effectiveness and is associated with eradication rates below the recommended threshold (≥ 90%) to consider empirical treatment as effective.
- Antibiotic resistance and treatment regimens vary according to region and country, and the evidence from clinical guidelines is not always applicable everywhere.
- Evidence from clinical trials (e.g., on in vitro antibiotic resistance) cannot always be extrapolated, as it is not necessarily reproducible in clinical practice.

Therefore, careful use of the most effective empirical regimens is required to avoid generating resistance. We must also ensure therapeutic adherence in patients receiving a treatment regimen. It is important to consider each patient's context in order to select the regimen that best adapts according to their availability, resistance index, allergies, greater adherence, and even cost, with the aim of guaranteeing eradication, since failure to achieve this can generate an increase in the incidence of complications.

Clinical guidelines make a distinction between treatment regimens for patients receiving a therapeutic regimen for the first time and treatment regimens for patients who have already received and experienced failure with previous treatments. Table 1 presents in a synthesized manner the recommended treatment regimens and the clinical context in which they may be useful.

In Mexico, antibiotic resistance has been one of the major health problems; this poses a significant challenge for the treatment of *H. pylori* infection and its complications, although more studies are needed to establish the specific resistances in our country in order to determine the best treatment. The resistance rates of *H. pylori* to various antibiotics are high. The LEGACy consortium study by Medel et al.[44] reported that, in Mexico, resistance to clarithromycin is 12%, to metronidazole 58.6%, and to amoxicillin 1.8%, and the *CYP2C19* polymorphism for rapid metabolizers has a prevalence of 14.3%[44]. A more recent study based on molecular next-generation sequencing tests reported the following *H. pylori* resistance rates in Mexico: to clarithromycin 15.8%, to fluoroquinolone 60.5%, to metronidazole 18.4%, to amoxicillin 10.5%, and to rifabutin 2.6%. When the *H. pylori* resistance rate to one or more antibiotics was analyzed, it was 71.1%; to two or more antibiotics, it was 29%; and to three or more antibiotics, it was 2.6%[45].

It is recommended to avoid empirical treatments with clarithromycin (except for concomitant therapy), as well as those including levofloxacin, since resistance to these antibiotics has increased significantly in our

Table 1. Proposed eradication regimens for *Helicobacter pylori* infection[11,15,24,31-33]

Outline	Dose	First line	First-line therapy in penicillin allergy	Second-line	
				Empirical	Antibiotic susceptibility testing
Optimized bismuth-based quadruple therapy	PPI 1× 2 Tetracycline 500 mg 1 × 4 Metronidazole 500 mg 1 × 3-4 Bismuth 120-300 mg 1 × 2-4	Recommended	Recommended	Suggested	Suggested
Bismuth-free quadruple therapy or concomitant therapy	PPI 1 × 2 Clarithromycin 500 mg 1 × 2 Amoxicillin 1 g 1 × 2 or 1 × 3 Metronidazole 500 mg 1 × 2 or 1 × 3	Suggested	Not due to allergy	Suggested	
Levofloxacin-based triple therapy	PPI 1 × 2 Levofloxacin 500 mg 1 × 1 Amoxicillin 1 g 1 × 2 or 1 × 3	No	Not due to allergy		Suggested
Triple therapy with rifabutin	PPI 1 × 2 Rifabutin 150 mg 1 × 2 or 50 mg 1 × 3 Amoxicillin 1 g 1 × 2 or 1 × 3	Suggested	Not due to allergy	Suggested	Suggested
Dual therapy with high-dose amoxicillin or dual PCAB therapy	PPI 1 × 2 or PPI 1 × 3 Amoxicillin 1 g 1 × 3	Suggested	Not due to allergy	Suggested	
Triple PPI-based therapy	PPI 1 × 2 Clarithromycin 500 mg 1 × 2 Amoxicillin 1 g 1 × 2		Not due to allergy		Suggested
Conventional triple therapy	PPI 1 × 2 Clarithromycin 500 mg 1 × 2 Amoxicillin 1 g 1 × 2	Not recommended	Not recommended	Not recommended	Not recommended

PPI: proton pump inhibitor; PCAB: potassium-competitive acid blocker.

country, which may result in low eradication rates. The empirical eradication regimens without the need for antibiotic susceptibility testing that are recommended as first-line therapy are bismuth-based quadruple therapy and non-bismuth quadruple therapy or concomitant therapy. Other regimens that have been suggested as empirical alternatives when the aforementioned are not available are therapy with potassium-competitive acid blocker plus high-dose amoxicillin (dual PCAB) and triple therapy with rifabutin (scarcely available in Mexico). Another option that has recently been evaluated in some countries is triple therapy with amoxicillin, clarithromycin, and dual PCAB, but in Mexico, there is no evidence of its effectiveness.

In Latin America, until recently, there were few updated studies regarding antibiotic resistance. High rates of resistance to clarithromycin, levofloxacin, and metronidazole have been reported, whereas resistance to amoxicillin and tetracyclines is low. There is an increasing number of cases of combined resistance to two or more antibiotics (e.g., metronidazole and clarithromycin)[46,47]. Therefore, in Mexico, it has been established that in regions where clarithromycin resistance exceeds 15%, bismuth-based quadruple therapy is recommended instead of triple therapy, unless antimicrobial susceptibility studies or an antibiogram is available to detect bacterial sensitivity. For amoxicillin and tetracycline, low resistance levels (<2%) are reported; thus, their use in triple therapy and bismuth-based quadruple therapy remains a good option in most countries[46].

In recent years, a project has been implemented that seeks to create national databases, such as the Mexican Registry of *Helicobacter pylori* (Hp-MexReg), regional databases such as the Latin American Registry of *Helicobacter pylori* (Hp-LatamReg), and continental databases such as the European Registry of *Helicobacter pylori* (Hp-EuReg), and a World Registry of *Helicobacter pylori* (WorldHpReg). These databases compile information regarding patients infected with *H. pylori* to enable the study of the epidemiology of the bacillus and to determine the efficacy and safety of

Table 2. Mechanisms of *Helicobacter pylori* resistance to different antibiotics[46]

Antibiotic	Resistance mechanisms
Clarithromycin	Mutations in the 23S ribosomal ribonucleic acid gene
Levofloxacin	Mutations in gyrA
Metronidazole	Decreased nitroreductase activity
Amoxicillin	Mutations in PBP1A and absence of PBP4
Tetracyclines	Mutations in 16S ribosomal ribonucleic acid

different therapeutic regimens, provide data on bacterial resistance patterns, and determine treatment accessibility, with the aim of identifying the best eradication regimens in each location. The Hp-MexReg project is a multicenter national registry that compiles information on treatment indications and diagnostic tests used by gastroenterologists in Mexico. This type of project opens the door to better knowledge that allows for the promotion of the best treatment options for patients.

In 2017, the World Health Organization declared *H. pylori* as one of the "12 priority pathogens" due to its increasing antibiotic resistance[47]. Currently, it is recommended that only those regimens demonstrating an eradication rate of ≥ 90% be used empirically. As is known, different antibiotic regimens exist for the treatment of *H. pylori* infection; however, antibiotic resistance is increasingly frequent, which has limited the utility of most first-line regimens.

Eradication failure is multifactorial, and its causes can be divided into those related to the host (e.g., smoking, age, diabetes, obesity, dysbiosis, prior antibiotic exposure, *CYP2C19* gene polymorphisms that modify PPI metabolism, and treatment adherence), to the healthcare system (use of empirical regimens with low eradication rates or non-validated empirical regimens), or to the bacterium. Bacterial resistance is the main cause of failure and the greatest challenge we face as clinicians[46].

Resistance mechanisms encompass changes in the amino acids of proteins that bind to the antibiotic, adjustments in transport systems or membrane permeability that limit uptake, increased activity of oxygen scavengers, as well as alterations in the activity of enzymes involved in drug metabolism by bacteria[48]. Antibiotic resistance develops through point mutations in genes. Table 2 shows some of the most relevant mutations that have been associated with resistance to different antibiotics[46].

Whenever possible, the goal should be to provide eradication treatment for *H. pylori* based on the susceptibility of the bacterium. Undoubtedly, the use of susceptibility testing and modern molecular methods will enable guided selection of treatments; this option is currently ideal and will be of vital importance in the years to come. Susceptibility testing allows for the determination of bacterial phenotypes and genotypes. Different types of tests exist, such as culture with antimicrobial susceptibility testing, molecular methods for the detection of mutations through polymerase chain reaction (PCR), and next-generation sequencing tests[46]. These techniques will enable the use of personalized medicine instead of employing empirical therapies. Molecular tests are the most sensitive and specific for detecting the infection; among these, the most widely used in our setting is PCR, which allows for the evaluation of pathogenic genes and those specific for antimicrobial resistance, with a sensitivity of 98% and a specificity of 100%. PCR is considered by some guidelines as the reference method[30].

Finally, it is also important to mention that, in all patients undergoing eradication therapy, this must be confirmed at least 4 weeks after completion of antibiotic treatment and at least 2 weeks after discontinuation of the PPI[11,24]. This confirmation can be performed using noninvasive tests (urea breath test or stool antigen test for *H. pylori*). The relevance of confirming post-treatment eradication lies in the fact that persistence of the infection increases the incidence of complications, as well as the persistence of dyspeptic symptoms. An observational study that included 371,813 United States veterans with confirmed eradication of the infection demonstrated a decrease in the risk of developing gastric cancer, with a hazard ratio of 0.24 (95% CI: 0.15-0.42), compared to those in whom eradication was not confirmed[49].

Conclusions

The diagnostic and therapeutic approach to FD is a challenge. It remains unclear whether *H. pylori*-associated dyspepsia is an etiological factor for FD or whether it is a completely independent condition. Some pathophysiological mechanisms have been considered to be involved, but not all are known, nor is the way in which they interact. Eradication therapy has been shown to improve or eliminate symptoms in a subgroup of patients. The response of FD symptoms is not

immediate, even in cases where symptom remission is achieved; therefore, close follow-up after treatment is required before it can be considered successful. Finally, given the increasing antibiotic resistance, the eradication therapeutic regimen must be carefully selected, using those that achieve the highest response rates in the region, and treatment should be guided by susceptibility testing whenever possible, as well as confirming treatment success.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments have been conducted on human subjects or animals for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor does it require ethical approval. The SAGER guidelines do not apply.

Statement on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for the writing of this manuscript.

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