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Review Article

DIAGNOSIS AND TREATMENT OF HELICOBACTER PYLORI INFECTION: A REVIEW

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ABSTRACT

Helicobacter pylori remain a prevalent, worldwide, chronic infection. Though the prevalence of this infection appears to be decreasing in many parts of the world, H. pylori remains an important factor linked to the development of peptic ulcer disease, gastric malignancy and dyspeptic symptoms. Whether to test for *H. pylori* in patients with functional dyspepsia, Gastroesophageal reflux disease, patients taking nonsteroidal anti-inflammatory drugs, with iron deficiency anemia, or who are at greater risk of developing gastric cancer remains controversial. *H. pylori* can be diagnosed by endoscopic or Nonendoscopic methods. A variety of factors including the need for endoscopy, pretest probability of infection, local availability, and an understanding of the performance characteristics and cost of the individual tests influences choice of evaluation in a given patient. Testing to prove eradication should be performed in patients who receive treatment of *H. pylori* for peptic ulcer disease, individuals with persistent dyspeptic symptoms despite the test-and-treat strategy, those with *H.pylori*-associated MALT lymphoma, and individuals who have undergone resection of early gastric cancer. Recent studies suggest that eradication rates achieved by first-line treatment with a proton pump inhibitor (PPI), clarithromycin, and amoxicillin have decreased to 70–85%, in part due to increasing clarithromycin resistance. Eradication rates may also be lower with 7 *versus* 14-day regimens. Bismuth-containing quadruple regimens for 7–14 days are another first-line treatment option. Sequential therapy for 10 days has shown promise in Europe but requires validation in North America. The most commonly used salvage regimen in patients with persistent *H.pylori* is bismuth quadruple therapy. Recent data suggest that a PPI, Levofloxacin, and amoxicillin for 10 days is more effective and better tolerated than bismuth quadruple therapy for persistent *H. pylori* infection, though this needs to be validated in the United States.

INTRODUCTION

Helicobacter pylori (H. Pylori) remain one of the most common worldwide human infections and are associated with a number of important upper gastrointestinal (GI) conditions including chronic gastritis, peptic ulcer disease, and gastric malignancy. The prevalence of H. pylori is closely tied to socioeconomic conditions and accordingly, this infection is more common in developing countries than in developed countries such as the United States [1]. Regardless, it has been estimated that 30–40% of the U.S. population is infected with H. pylori [2]. The vast majority of individuals acquire this infection during childhood. Based upon this observation and the fact that H. pylori infection rates in children are decreasing, in coming years.

Indications for diagnosing and treating H. pylori infection:

Recommendation:

- Testing for H. pylori infection is indicated in patients with active peptic ulcer disease, a past history of documented peptic ulcer, or gastric MALT lymphoma.
- The test-and-treat strategy for H. pylori infection is a proven management strategy for patients with uninvestigated dyspepsia who are under the age of 55 yr and have no “alarm features” (bleeding, anemia, early satiety, unexplained weight loss, progressive dysphasia, odynophagia, recurrent vomiting, family history of GI cancer, previous esophagogastric malignancy).

Although the majority of those infected remain clinically silent, there are a number of well-established clinical conditions that have been associated with H. pylori infection. The indications for the diagnosis and treatment of H. pylori infection are listed in table 1.

Duodenal and gastric ulcer:

There is a clear link between H. pylori infection and the pathogenesis of peptic ulcer disease (PUD) [3]. Given the overwhelming evidence supporting this relationship, few would question the clinical and economic merits of H. pylori eradication in a patient with PUD. The H. pylori eradication therapy yielded superior healing rates for duodenal ulcer but not gastric ulcer compared with short courses of ulcer healing medications such as histamine-2 receptor antagonists (H2RAs) or proton pump inhibitors (PPIs). The study found that H. pylori eradication was superior to no treatment in preventing duodenal and gastric ulcer recurrence. *H. pylori* eradication was also superior to maintenance therapy with acid suppressive medications in preventing gastric ulcer but not duodenal ulcer recurrence [4].

Following are the indication of diagnosis and treatment of H.pylori infection.
1.Established:
-Active peptic ulcer disease (Gastric or duodenal ulcers).
-Confirmed history of peptic ulcer disease (Previously not treated for H.pylori).
-Gastric MLT lymphoma.
- After endoscopic resection of early gastric cancers.
-Uninvestigated Dyspepsia.
2.Controversial:
-Nonulcer dyspepsia.
- Gastroesophageal reflux disease.
-Person using nonsteroidal anti-inflammatory drugs.
-Unexplained Iron deficiency anaemia.
-population at higher risk of gastric cancers.

Table 1: Indication of Diagnosis and treatment of H.pylori

Gastro duodenal Bleeding:

The H. pylori treatment decreased recurrent bleeding by 17% and 4% compared with ulcer healing treatment alone (bismuth 120 mg q.i.d to ulcer healing, ranitidine 300 mgq.h.s. for 16 wk or omeprazole 20 mg q.d. for 2 wk) or ulcer healing treatment followed by maintenance therapy (ranitidine150–300 mg q.h.s. or omeprazole 20 mg q.d. for 12–24 months), respectively [5].

Gastric MALT Lymphoma:

For localized gastric MALT lymphoma, *H. pylori* treatment achieves tumor regression in 60–90% of patients [6]. The *H. pylori* eradication provides durable remission in patients with low-grade MALT lymphoma with recurrence rates of 3–13% over 5 yr of follow up (12–14). *H. pylori* eradication led to complete remission in 64% [7]. Amongst patients with complete remission following *H. pylori* cure, relapse rates were 0% for high-grade MALT lymphoma after a median follow-up of more than 5 yr.

Uninvestigated Dyspepsia:

The test-and-treat strategy provides an evidence-based management strategy for patients with uninvestigated dyspepsia who are under the age of 55 year and have no alarm features.

Benefit of eradicating h. pylori infection:

- The patients with functional dyspepsia will experience clinical benefit following H. pylori eradication.
- There is no clear evidence to support that eradicating H. pylori infection consistently worsens or improves GERD symptoms.
- H. pylori and NSAIDs are independent risk factors for the development of PUD. Therefore, regardless of whether or not a patient is taking an NSAID, all patients with a peptic ulcer should be tested and when infected, treated for H. pylori.

- The available data support an association between H. pylori infection and iron deficiency but do not prove cause and effect.
- Though there is some evidence to suggest that curing H. pylori may prevent progression of intestinal metaplasia to gastric adenocarcinoma.

Functional Dyspepsia (FD):

The eradicating H. pylori infection is of clinical and economic benefit in patients with dyspeptic symptoms who have undergone a negative structural evaluation remains controversial, whereas some studies observed a beneficial effect [8], others have failed to confirm such benefits [9].

Eradicating H. pylori in patients with FD may offer benefits beyond symptom improvement. Studies have reported that peptic ulcers develop in 1–14% of patients with FD when followed over extended periods [10]. The H. pylori eradication reduced the 1 yr incidence of peptic ulcer in patients with ulcer-like functional dyspepsia but not in those with dysmotility-like or unclassifiable FD [10].

Gastro esophageal Reflux Disease (GERD):

The relationship between H. pylori infection and GERD remains incompletely defined. It is known that H. pylori infection results in different levels of severity and patterns of gastric inflammation in different individuals. Patient has abnormal lower esophageal sphincter function or esophageal clearance mechanisms, which would predispose to a greater risk of GERD, undoubtedly also affects outcomes. A recent study found that antral predominant gastritis was the most common *H. pylori* associated phenotype in functional dyspepsia patients from western countries and that eradication therapy in this subgroup of patients led to overall improvements in heartburn and regurgitation at 1 year of follow-up [11].

Some investigators have suggested that *H. pylori* status is inversely related to the likelihood of suffering with GERD [12]. The available evidence does not support an association between *H. pylori* eradication and the development of reflux oesophagitis or worsening of heart burn in patients with a duodenal ulcer. The *H. pylori* eradication was not associated with a worsening of symptoms in those with preexisting GERD. The esophageal acid exposure, the severity of erosive oesophagitis, and efficacy of proton pump inhibit or therapy is similar in GERD patients with and without *H. pylori* infection [13]. Therefore, it is reasonable to conclude that therapy for *H. pylori* should not be withheld related to concerns of creating or worsening GERD.

Persons Using Nonsteroidal Anti-inflammatory Drugs (NSAIDs) or Aspirin:

The interaction between *H. pylori* infection and NSAIDs in the pathogenesis of PUD remains controversial. The *H. pylori* infection and nonselective NSAID use are independent risk factors for the development of peptic ulcer and ulcer bleeding. The risk factors are at least additive and possibly synergistic for the development of peptic ulcer and ulcer bleeding [14]. The H. pylori eradication was associated with a reduced incidence of peptic ulcer in patients taking NSAIDs. *H. pylori* eradication may reduce the risk of PUD; it does not eliminate the risk of ulcer development or complications in those using an NSAID.

At present all patients with an ulcer should be tested for *H. pylori* regardless of whether or not he/she is taking an NSAID or aspirin [15]. In patients already taking an NSAID, *H. pylori* eradication appears to be less

effective than PPI therapy in reducing the risk of peptic ulcer recurrence or ulcer bleeding. On the other hand, there is evidence to suggest that recurrent ulcer bleeding in persons using low-dose aspirin is similar 6 months after *H. pylori* eradication or with PPI therapy. For patients with a history of an ulcer complication who require subsequent therapy with an NSAID or aspirin, H. pylori eradication alone may not be a sufficient risk reduction strategy. Co-therapy with a PPI in such patients at high risk for recurrence of an ulcer complication has been recommended [15].

Iron Deficiency Anemia:

A number of studies have suggested a potential association between unexplained iron deficiency anemia and H. pylori infection. The explanation most commonly offered for this relationship is based upon the development of *H. pylori* associated chronic pan gastritis with resultant achlorhydria and reduced ascorbic acid secretion leading to reduced intestinal iron absorption. Other potential explanations for an association between iron deficiency and *H. pylori* include occult blood loss from erosive gastritis and sequestration and utilization of iron by the organism.

H. *pylori* infection was an independent risk factor for iron deficiency anemia [16]. There is emerging evidence to suggest that eradication of H. pylori can improve iron deficiency anemia [17]. The available data support an association between H. pylori infection and iron deficiency but do not prove cause and effect.

Prevention of Gastric Cancer:

The H. pylori infection can reduce the risk of developing gastric adenocarcinoma remains unknown [18]. The H. pylori eradication was protective against progression of premalignant gastric lesions in their Chinese population study. Patients treated for H. pylori were 13.7 % less likely to experience progression of preneoplastic gastric lesions. There was an absolute reduction in gastric cancer incidence in subjects who received H. pylori eradication therapy when compared with placebo. However, in a subgroup of H. pylori carriers without precancerous lesions at index endoscopy, the incidence of gastric cancer was significantly lower in subjects receiving eradication therapy than in those receiving placebo. This study supports the possibility that H. pylori eradication may reduce the risk of developing gastric cancer in individuals without precancerous lesions from high-risk populations.

A recent international working group reviewed the literature addressing this topic. The majority of the scientific taskforce favored testing and treating H. pylori in first-degree relatives of gastric cancer patients. The task force also endorsed the evaluation of the chemo preventive benefits for gastric malignancy with a more general screen and treat strategy in populations with a high incidence of *H. pylori*-associated diseases [18].

DIAGNOSIS OF H. PYLORI INFECTION:

- Testing for H. pylori should only be performed if the clinician plans to offer treatment for positive results.
- Deciding which test to use in which situation relies heavily upon whether a patient requires evaluation with upper endoscopy and an understanding of the strengths, weaknesses, and costs of the individual tests.

The methods of diagnostic testing for *H. pylori* can be divided into those that do and those that do not require endoscopy. Table 2 provides a list of the available diagnostic tests for H. pylori. There is no single test that can be considered the gold standard for the diagnosis of H. pylori.

Following are the Diagnostic test available for the diagnosis of H.pylori:
1.Endoscopic Testing:
•Histology.
•Rapid urease testing.
•Culture.
•Polymerase chain reaction.
2. Nonendoscopic Testing:
•Antibody Testing.
•Urea breath Tests.
•Fecal antigen Test.

Table 2: Diagnostic testing for Helicobacter pylori

Endoscopic Diagnostic Tests:

- In patients who have not been on a PPI within 1–2 week or an antibiotic or bismuth within 4 week of endoscopy, the rapid urease test (RUT) provides an accurate, inexpensive means of identifying H. pylori.
- For patients who have been taking a PPI, antibiotics, or bismuth, endoscopic testing for H. pylori should include biopsies from the gastric body and antrum for histology with or without rapid urease testing.
- Though culture or polymerase chain reaction (PCR) are the primary means by which antibiotic sensitivities can be determined, neither is widely available and therefore, cannot be routinely recommended.

There are presently four biopsy-based diagnostic methods for H. pylori infections. These include the RUT, histology, culture, and PCR.

Rapid Urease Testing (RUT):

The RUT identifies active *H. pylori* infection through the organism's urease activity. Gastric biopsies are obtained and placed into an agar gel or on a reaction strip containing urea, a buffer, and a pH-sensitive indicator. In the presence of H. pylori urease, urea is metabolized to ammonia and bicarbonate leading to a pH increase in the microenvironment of the organism. A change in color of the pH sensitive indicator signifies the presence of active infection. Commercially available kits yield results in 1–24 h.

Medications that reduce the density and/or urease activity of *H. pylori,* such as bismuth-containing compounds, antibiotics, or PPIs, can decrease the sensitivity of the RUT by up to25% [19]. Though controversial, acute ulcer bleeding at the time of testing may decrease the sensitivity and negative predictive value of the RUT [20]. As a result of the patchy distribution of *H. pylori* infection after antibiotics or PPIs, it is recommended that biopsies for the RUT be obtained from two sites, the body at the gastric anglularis and greater curvature of the antrum [21]. The simplicity, low cost, and relatively rapid results make the RUT a practical and cost effective means of testing for *H. pylori* in patients not taking antibiotics, bismuth, or PPIs who

require upper endoscopy. Unfortunately, the usefulness of the RUT in routine clinical practice has been compromised by the widespread use of PPIs as an empiric treatment for upper GI symptoms. More commonly, the RUT is combined with other endoscopic or non endoscopic modalities to establish the presence or absence of this infection.

To identification of H. pylori's urease activity, it is reasonable to suggest that PPIs should be withheld for 1–2 week before performance of the RUT. In situations where a patient has not taken a PPI for a period of 1–2 wk before their procedure, the sensitivity of the RUT is likely sufficient to justify its use as a single test for *H. pylori*.

Histology:

Histology has been considered by some to be the gold standard for detection of *H. pylori* [22]. Unfortunately, histology is an imperfect gold standard as the detection of *H. pylori* relies upon a number of issues including the site, number and size of gastric biopsies, method of staining, and the level of experience of the examining pathologist [22]. A significant advantage of histology over other diagnostic methods is the ability to evaluate for pathologic changes associated with H. pylori infection such as inflammation, atrophy, intestinal metaplasia, and malignancy [23].

As the prevalence and density of H. pylori varies throughout the stomach, particularly in the face of medications that may reduce the density of *H. pylori*, multiple biopsies are needed for accurate diagnosis. It is therefore recommended that a minimum of three biopsies be obtained, one from the anglularis, one from the greater curvature of the corpus, and one from the greater curvature of the antrum, to maximize the diagnostic yield of histology [22]. Similar to the RUT, the sensitivity of histology is significantly affected by the use of medications such as bismuth, antibiotics, and PPIs. Although widely available and capable of achieving sensitivity and specificity of >95%, the cost and need for properly trained personnel are limitations of histology in clinical practice.

Culture:

Culture is another highly specific method for identifying active H. pylori infection. Conceptually, culture is attractive because it not only provides a means by which to identify infection, but also allows characterization of antimicrobial sensitivities [24]. Unfortunately, culture is not as sensitive as RUT or histology [25]. Furthermore, culturing techniques for *H. pylori* are demanding and costly and as a consequence, only available in a limited number of clinical laboratories. Non culture-based means of determining antibiotic resistance are being developed but have not been adequately standardized and are not widely available.

Polymerase Chain Reaction:

PCR is a DNA amplification technique that utilizes the rapid production of multiple copies of a target DNA sequence to identify *H. pylori*. This testing method is highly specific and may be more sensitive than other biopsy-based diagnostic techniques. A recent study found that PCR was able to detect H. pylori in approximately 20% of gastric biopsies with chronic gastritis but no identifiable organisms by histology [26]. PCR also provides a means of identifying mutation associated with antimicrobial resistance [27]. Although

presently restricted to the research arena, this method may someday provide a practical, reproducible method for antibiotic sensitivity testing, organism typing, and organism virulence testing.

Nonendoscopic Diagnostic Tests:

- Antibody testing is inexpensive and widely available but poor PPV in populations with a low prevalence of H. pylori infection limits its usefulness in clinical practice.
- The UBTs and fecal antigen tests provide reliable means of identifying active H. pylori infection before antibiotic therapy.
- The UBT is the most reliable non endoscopic test to document eradication of H. pylori infection.
- The monoclonal fecal antigen test provides another non endoscopic means of establishing H. pylori cure after antibiotic treatment.
- Testing to prove H. pylori eradication appears to be most accurate if performed at least 4 wk after the completion of antibiotic therapy.

There are currently three Nonendoscopic diagnostic testing methods for *H. pylori* infection. Antibody testing identifies an immunological reaction to the infection while the non endoscopic urease tests and fecal antigen test identify the presence of active *H. pylori* infection.

Antibody Tests:

Antibody testing relies upon the detection of IgG antibodies specific to *H. pylori* in serum, whole blood, or urine. IgG antibodies to *H. pylori* typically become present approximately 21 days after infection and can remain present long after eradication [28]. Antibodies to *H. pylori* can be quantitatively assessed using enzyme-linked immunosorbent assay (ELISA) and latex agglutination techniques or qualitatively assessed using office-based kits. The advantages of the antibody tests are their low cost, widespread availability, and rapid results. Unfortunately, several factors limit the usefulness of antibody testing in clinical practice.

Urea Breath Tests:

The UBT, like the RUT, identifies active *H. pylori* infection by way of the organism's urease activity. In the presence of H. pylori, the ingestion of urea, labeled with the non radioactive isotope 13C or the radioactive isotope 14C, results in production of labeled CO2, which can be quantities in expired breath [29]. Although the amount of radiation in the 14C UBT is less than daily background radiation exposure, the 13C test is preferred in children and pregnant females. Overall, the performance characteristics of both tests are similar with sensitivity and specificity typically exceeding 95% in most studies [30]. Test reproducibility has been found to be excellent. The UBT also provides an accurate means of post treatment testing [31]. Most tests utilize a citrate test meal (50–75 mg), which is administered before the labeled urea. A urease blood test, which relies upon the detection of labeled bicarbonate in a blood sample, also reliably identifies active *H. pylori* infection before and after treatment. As the non endoscopic urease tests rely upon the identification of H. pylori's robust urease activity, test sensitivity is decreased by medications that reduce organism density or urease activity, including bismuth containing compounds, antibiotics, and PPIs. It is currently recommended that bismuth and antibiotics

be withheld for at least 28 days and a PPI for 7–14 days prior to the UBT. Antacids do not appear to affect the accuracy of the UBT.

Fecal Antigen Test (FAT):

The fecal antigen test (FAT) identifies *H. pylori* antigen in the stool by enzyme immunoassay with the use of polyclonal anti-H.pylori antibody. Recently, a stool test utilizing a monoclonal anti-H pylori antibody has been evaluated [32]. As both tests detect bacterial antigen(s) suggestive of ongoing infection, they can be used to screen for infection and as a means of establishing cure following therapy.

Recent studies indicate that the FAT may be effective in confirming eradication as early as 14 days after treatment [33]. However, there is evidence to suggest that the FAT should be done more than 4 wk and perhaps as long as 8–12 wk after treatment of *H. pylori* [32].

Similar to the UBT, the sensitivity of the FAT is affected by the recent use of bismuth compounds, antibiotics and PPIs [34]. Recent studies also suggest that the specificity of the FAT is reduced in the setting of bleeding PUD and, for this reason, should not be the sole diagnostic test employed in this setting.

FAT can be used interchangeably with the UBT to identify H. pylori before antibiotic therapy. The polyclonal FAT has been less well validated than the UBT in the post treatment setting. Compared with the polyclonal test, the monoclonal FAT appears to provide a more reliable means of proving *H. pylori* eradication.

H. *PYLORI* TESTING IN CLINICAL PRACTICE:

Testing When There Is a Need for Endoscopy:

If endoscopy is necessary based upon the patient's clinical presentation, biopsy-based endoscopic tests are most appropriate. Provided the patient has not been on recent bismuth, antibiotics, or a PPI, the RUT offers the desirable combination of accuracy and low cost. If there are mucosal abnormalities identified at the time of endoscopy, which require further histological evaluation, biopsies should be obtained for histology. Unfortunately, most patients referred for upper endoscopy are taking acid-suppressive agents such as a PPI or H_2RA or have recently received drugs that can suppress H. pylori (antibiotics or bismuth). In such patients, it is appropriate to obtain biopsies for histology with or without RUT or plan testing with a UBT or FAT at a later date after with holding the offending agents for an appropriate period of time.

Testing in Patients with Uninvestigated Dyspepsia:

Primary care providers are frequently asked to evaluate and treat patients with uninvestigated dyspepsia. The test and-treat strategy for *H. pylori* has been endorsed for the management of uninvestigated dyspepsia by a number of organizations, including the American Gastroenterological Association and the American College of Gastroenterology. For a detailed discussion regarding H. pylori testing in patients with uninvestigated dyspepsia, the reader is referred to these recent publications. Both document semphasize that in regions where the prevalence of *H.pylori* infection is high, such as urban areas or communities with large immigrant populations, the PPV of antibody testing is reasonably good and therefore provides an acceptable means of screening for *H. pylori* infection. However, in regions where *H.* pylori prevalence is low, the PPV of antibody testing is poor.

Testing to Prove Eradication after Antibiotic Therapy:

All patients treated for H. pylori infection would undergo testing to prove eradication of the infection. Unfortunately, universal post treatment testing is neither practical nor cost-effective. The accepted indications for testing to prove eradication after antibiotic therapy, largely based upon expert consensus, have broadened to include:

- Any patient with an H. pylori-associated ulcer.
- Individuals with persistent dyspeptic symptoms despite the test-and-treat strategy.
- Those with H. pylori-associated MALT lymphoma.
- Individuals who have undergone resection of early gastric cancer.

When confirmation of eradication is necessary, testing should generally be performed no sooner than 4 wk after the completion of treatment. Because of its high cost, endoscopic tests should only be used if endoscopy is clinically indicated for other reasons. If testing to prove eradication were performed in the setting of endoscopy, most would advocate using histology or the combination of histology and RUT as RUT alone has reduced sensitivity in the post treatment setting [35]. When endoscopic follow-up is UN necessary, testing to prove eradication of *H. pylori* infection is best accomplished with the UBT. The FAT provides an alternative means of establishing eradication though, as has already been discussed, the timing and reliability of this test have not been as clearly demonstrated as for the UBT. Because antibody tests can remain positive for prolonged periods following successful cure of *H. pylori* infection, they should be avoided in the post treatment setting. If antibody testing is performed in the post treatment setting, only a negative result is reliable. A positive result should be confirmed with a UBT or FAT before offering antibiotic therapy for presumed persistent infection.

TREATMENT OF H. PYLORI INFECTION:

Primary Treatment of H. pylori Infection:

- The recommended primary therapies for H. pylori infection include: a PPI, clarithromycin, and amoxicillin, or metronidazole (clarithromycin-based triple therapy) for 14 days or a PPI or H_2RA, bismuth, metronidazole and tetracycline (bismuth quadruple therapy) for 10–14 days.
- Sequential therapy consisting of a PPI and amoxicillin for 5 days followed by a PPI, clarithromycin, and tinidazole for an additional 5 days may provide an alternative to clarithromycin-based triple or bismuth quadruple therapy but requires validation within the United States before it can be recommended as a first-line therapy.

The first course of therapy offers the greatest likelihood of eradicating H. pylori infection. Subsequent treatment trials, particularly if the same antibiotics are utilize or if the patient has been previously exposed to any antibiotics contained in the treatment regimen, are less likely to achieve a successful outcome. As such, it is important to only use treatment regimens for which there is evidence of proven effectiveness [36].

In the United States, the recommended primary therapies for *H. pylori* infection include: a PPI, clarithromycin, and amoxicillin or metronidazole (clarithromycin-based triple therapy) or a PPI orH_2RA, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy). Details regarding these regimens can

be found **in** Table 3**.** When given at the recommended doses, most recent studies report intention-to-treat (ITT) eradication rates in the range of 70–80% [37]. The international guidelines have recommended treatment durations of at least7 days, treatment durations of 10–14 days have typically been employed in the United States.

The recommend a 14-day course of clarithromycin triple therapy, eradication rates have typically been 80% or less with shorter durations of therapy. Treatment durations of less than 7 days are clearly associated with reduced eradication rates and are not recommended. The recent meta-analysis of 13 studies suggests that b.i.d. dosing of a PPI in clarithromycin-based triple regimens is more effective than q.d. dosing [38]. The H_2RA can be substituted if a patient cannot tolerate a PPI [39].

Following are the regimen for eradication of Helicobacter pylori infection.		
1.Standard dose:	**Duration**	**Eradication rate**
• PPI (Esomeprazole) –q.d	10-14 days	70-80 %
•Clarithromycin 500 mg b.i.d	10-14 days	
•Amoxicillin 1000 mg b.i.d	10-14 days	
Or -Standard dose PPI b.i.d + Clarithromycin 500 mg b.i.d +metronidazole 500 mg b.i.d- 14 days.		
2. Tab Bismuth subsalicylate 525 mg q.i.d	10-14 days	75-90 %
Tab metronidazole 250 mg q.i.d	10-14 days	
Tab Tetracycline 500 mg q.i.d	10-14 days	
Tab Ranitidine 150 mg b.i.d	10-14 days	
Or PPI+ Amoxicillin 1 g b.i.d followed by	5 days	> 90 %
PPI+ Clarithromycin 500 mg + Tinidazole 500 b.i.d	5 days	

Table 3: First line regimens for Helicobacter Pylori Eradication

PPI= Proton Pump inhibitors. q.d= once daily. b.i.d= twice daily. q.i.d= Four time daily

Bismuth quadruple therapy has been advocated as a primary therapy for *H. pylori*. Bismuth quadruple therapy offers eradication rates that are similar to clarithromycin triple therapy. Although minor side effects with bismuth-based quadruple therapy occur commonly, the frequency of moderate or severe side effects is no greater than with clarithromycin-based triple therapy.

It seems reasonable to consider a PPI, clarithromycin, and amoxicillin in patients who have not previously received clarithromycin and who are not allergic to penicillin. For patients allergic to penicillin, metronidazole can be substituted for amoxicillin. Bismuth quadruple therapy should be favored in those allergic to penicillin or in those who have previously been treated with a macrolide antibiotic. Unfortunately, eradication rates yielded by clarithromycin based triple therapy or bismuth-based quadruple therapy are less than 85% and may be decreasing. As such, alternative primary therapies are necessary.

The eradication rates exceeding 90% with a novel sequential therapy consisting of a PPI and amoxicillin for 5 days followed by a PPI, clarithromycin, and tinidazole for an additional 5 days. Whether metronidazole or other imidazoles can be used in place of tinidazole has not yet been established. This regimen

has achieved eradication rates superior to clarithromycin-based triple therapy and was well tolerated in children, adults, and elderly patients infected with H. pylori [40]. Further sequential therapy may be superior to clarithromycin triple therapy in patients with clarithromycin-resistant *H. pylori* strains.

Predictors of H. pylori Treatment Outcome:

The most important predictors of treatment failure following anti-H.pylori therapy include poor compliance and antibiotic resistance. There is limited evidence to suggest that smoking, alcohol consumption, and diet may also adversely affect the likelihood of successful eradication [41]. Patients should also be informed of the most commonly reported treatment-related side effects. While mild side effects are very common with any of the recommended H. pylori treatment regimens, significant side effects are reported in only 5–20% [42]. The most commonly reported side effects with the PPIs include headache and diarrhea, occurring in upto 10% of patients. To optimize their effects on gastric acid secretion, PPIs should be taken 30–60 minutes before eating. The most frequent side effects reported with clarithromycin include GI upset, diarrhea, and altered taste. Common side effects associated with amoxicillin include GI upset, headache, and diarrhea. Side effects of metronidazole tend to be dose related and include a metallic taste in the mouth, dyspepsia, and a disulfiram-like reaction with alcohol consumption. Common side effects of tetracycline include GI upset and photosensitivity. This antibiotic should not be used in children under 8 yr of age because of possible tooth discoloration. Finally, bismuth compounds have been associated with darkening of the tongue and stool, nausea, and GI upset [43].Informed patients are less likely to be alarmed when side effects that they are aware of occur and, consequently, less likely to needlessly stop their treatment.

Antibiotic resistance must also be carefully considered when choosing amongst the various anti-H.pylori treatment regimens. The antibiotic resistance rates amongst *H. pylori* strains of 37% for metronidazole, 10% for clarithromycin, 3.9% for both antibiotics, and 1.4% for amoxicillin [44]. Recent data suggest that bacterial and host factors also influence treatment outcomes.

Salvage Therapy for Persistent H. pylori Infection:

- In patients with persistent H. pylori infection, every effort should be made to avoid antibiotics that have been previously taken by the patient.
- Bismuth-based quadruple therapy for 7–14 days is an accepted salvage therapy.
- Levofloxacin-based triple therapy for 10 days is another option in patients with persistent infection, which requires validation in the United States.

When faced with a patient who has failed an initial course of therapy for H. pylori, the clinician should avoid using antibiotics employed in previous treatment regimens. Because of the expense and lack of availability, culture and antibiotic sensitivity testing are typically not performed unless a patient has failed at least 2 courses of therapy. Even in this circumstance, the usefulness of such testing is arguable as there is no evidence to suggest that choosing a salvage regimen based upon an understanding of the patient's previous antibiotic exposure is any less successful than choosing an antibiotic regimen based upon the results of

antimicrobial sensitivity testing. Recommendations regarding salvage therapy regimens are provided in Table 4.

Regimen	Duration	Eradication rates
1.Bismuth quadruple therapy:		
•PPI q.d + Tetracycline+ pepto Bismol + metronidazole q.i.d	7 days	68 %
2.Levofloxacin triple therapy:		
•PPI + Amoxicillin 1 g b.i.d + Levofloxacin 500 mg q.d	10 days	87 %

Table 4: Salvage therapy for persistent H.pylori infection

PPI= Proton pump inhibitors. q.d= Daily. q.i.d= Four time daily. b.i.d= Twice daily

If a patient with persistent infection has not been previously treated with clarithromycin, triple therapy with a PPI, clarithromycin, and amoxicillin or metronidazole can be considered. Unfortunately, most patients are initially treated with a clarithromycin-containing regimen. In such circumstances, the most frequently used "rescue" or "salvage" therapy is bismuth quadruple therapy consisting of a PPI, tetracycline, metronidazole, and bismuth [45]. The salvage regimen is widely available, inexpensive, and relatively effective. The average eradication rates of 76% (range 60–100%) for quadruple therapy when used as second-line therapy [46]. The disadvantages of bismuth based quadruple therapy include the large daily pill count (potentially exceeding 18 pills), dosing frequency (typically four times daily), and frequent side effects. In the hopes of addressing some of these issues, a simplified twice-daily regimen was recently evaluated and reported to yield an eradication rate of over 90% in patients who had received at least 2 previous courses of antibiotic therapy [47].

A In a recent study from Australia, 137 patients who had failed therapy with omeprazole, clarithromycin, and amoxicillin were treated with a 12-day course of rifabutin 150 mg, pantoprazole 80 mg, and amoxicillin 1 g or 1.5 g daily. The overall eradication rate was 91% and the presence of clarithromycin or metronidazole resistance did not influence the likelihood of treatment success [48]. The most common side effects with rifabutin include rash and gastrointestinal complaints including nausea, vomiting, dyspepsia, and diarrhea. Rifabutin has been associated with rare but potentially serious myelotoxicity and ocular toxicity [49, 50]. Patients should be warned about the possibility of red discoloration of urine while taking rifabutin.

Furazolidone, an antibiotic commonly used to treat giardia, cholera, and bacterial enteritis has been evaluated as an alternative to clarithromycin, metronidazole, or amoxicillin for persistent *H. pylori* infection. Available studies utilizing Furazolidone have yielded widely variable eradication rates, ranging from 52% to 90% [51]. Side effects including nausea, vomiting, headache, and malaise occur in up to a third of patients. Less frequent side effects include hypersensitivity, hypotension, a disulfiram-like reaction to alcohol, and mild, reversible hemolytic anemia [52].

Levofloxacin is a fluoroquinolone antibiotic with *in vitro* activity against H. pylori. Levofloxacin-based triple therapy (PPI, Levofloxacin, and amoxicillin) has recently been studied as a second- and third-line therapy in patients with persistent H. pylori infection. In general, the available clinical trials have involved relatively

small numbers of patients and demonstrated variable eradication rates, ranging from 63% to 94% [53, 54]. The 10-day regimen of Levofloxacin-based triple therapy yielded superior eradication and was associated with fewer side effects than a 7-day course of bismuth-based quadruple therapy. Summary eradication rates for Levofloxacin-based triple therapy and bismuth-based quadruple therapy were 87% and 68% respectively [53].

A recent study from Italy found that using rabeprazole, Levofloxacin, and tinidazole in place of amoxicillin yielded an ITT eradication rate of 84% [55].

CONCLUSIONS

The use of both bismuth and non bismuth quadruple therapies as first-line alternatives to standard triple therapy in regions of high clarithromycin resistance. In addition to serving as a first-line alternative, bismuth quadruple therapy may be used as a second-line treatment, but it is limited by its availability in some countries. Levofloxacin-based regimens appear to be useful as a rescue therapy. The emerging problem of Levofloxacin resistance remains an issue, but there is hope that newer generation quinolone, such as sitafloxacin, moxifloxacin and gemifloxacin, May partially overcome this problem [9]. Rifabutin offers a promising alternative if Levofloxacin resistance is detected. Treatment duration is a key factor in H. pylori eradication success, with studies demonstrating that increasing the treatment duration improves the efficacy of standard triple therapy, bismuth quadruple therapy, sequential therapy, concomitant therapy and Levofloxacin-based therapy. Treatment on the basis of antimicrobial susceptibility testing is to improve eradication rates of both first-line and rescue therapies. The cost-effectiveness of tailoring first-line therapy has been questioned; however, it is thought to be economically viable, particularly in areas where clarithromycin resistance is known to be high.

Abbreviations:

GERD: Gastroesophageal Reflux disease.

PPI: Protons pump Inhibitors.

IIT: Intention to treat.

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