REVIEW ARTICLE

Treatment of *Helicobacter pylori* Infection: A Review

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Abstract

Helicobacter pylori is a particular bacterium that has evolved to survive in the acidic environment of the human stomach. Currently, no single antibiotic can treat the infection, so multiple medications are needed for treatment. Two antibiotics given more than a few times each day for seven to fourteen days, together with acid-suppressing medications, are the standard recommended treatments. The purpose of this review was to conclude the treatment of *H.pylori* infection. Without standard triple therapy, which consists of amoxicillin, clarithromycin, and PPI for the first five days, followed by PPI, clarithromycin, and tinidazole for the final five days, is the most frequently used course of treatment for clarithromycin-resistant *H. pylori* infections. Moreover, One of the first therapeutic regimens for the removal of *H. pylori* infection included bismuth-based therapy (bismuth salts, metronidazole, and tetracycline, each four times daily for two weeks with PPI), but the number of tablets taken daily and the associated mild side effects can have a negative effect on tolerance and compliance. Therefore, it is usually kept as a second-line treatment. Finally, rescue therapy (PPIs, Levofloxacin, and amoxicillin twice daily for 10 days) is a recently suggested treatment for *H. pylori* infection. This combination can cure about 80% of patients with *H. pylori* infection who have already tried one or more earlier treatments but failed.

Keywords: *Helicobacter pylori*, Treatment, Infection.

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Introduction

Helicobacter pylori is a unique bacterium well adapted to survive in the acidic environment of the human stomach. Their many unipolar flagella and helical shape enable them to readily glide over the gastrointestinal mucosa, shielding them from the acidic environment of the stomach.[1] *H. pylori* bacteria overproduce the urease enzyme, which Hydrolyzes urea into alkaline ammonia and carbon dioxide. As a result, the pH of the *H. pylori* bacteria's microenvironment can be further controlled. For clinical diagnostic tests of infection, urea breath testing and fast urea biopsy testing are used. *H. pylori* grow slowly and require particular media as well as a controlled microaerophilic environment, making their cultivation challenging.

When *H. pylori* enters a human host, they recognizes and fastens to a number of gastrointestinal epithelium surface receptors, leading to long-term mucosal colonization, interfering with cellular function, inducing potent local inflammatory and systemic immune responses, and altering the physiology of gastric acid secretion.[2] The clinical outcome and manifestation of *H. pylori* infection include gastric ulcer, duodenal ulcers, gastric mucosal-associated lymphoid tissue lymphoma (MALToma), and stomach adenocarcinoma; however, the majority of infected individuals remain asymptomatic for life even with chronic histologic gastritis.[1, 3] It is uncertain what variables determine why some people recover from illness while others do not, but environmental factors, host genetics, and bacterial factors undoubtedly impact clinical results.[4,5] Research into the epidemiology, pathogenesis, management, and prevention of *H. pylori* infection and associated clinical conditions and gastric cancer are still being driven by the enormous prevalence of infection worldwide, especially in less developed nations and the enormous health and financial burden of ulcer disease. There has also been increased awareness of the bacteria since Drs. Robin Warren and Barry Marshall were awarded the 2005 Nobel Prize in Physiology or Medicine.[3]

Since no *H. pylori*-specific or standalone medicines can treat the infection, eradicating the bug required a cocktail of medications. Two antibiotics given more than a few times each day for seven to fourteen days, together with an anti-acid secretory medication, make up the recommended treatment plan.[6,7] Reduced efficacy frequently follows attempts to streamline treatment regimens or cut treatment duration. Because taking many prescriptions can be challenging and small medication-related side effects are frequently seen, adherence can be a challenge. The fact that antibiotic-resistant germs are more common than previously thought may be connected to the fact that treatment success rates differ between nations and possibly even between regions within nations.[7,8] Despite these issues, there are still cures for more than 75% of *H. pylori* infections.[6,9]

After recovery, annual adult reinfection is infrequent in wealthy nations, where it may be less than 1%. Greater reinfection rates have been reported, although in these

instances, the original infection spontaneously resurfaces because antibiotic treatment failed to successfully treat it.[10] Children and adults who live in places where *H. pylori* is prevalent have greater rates of reinfection, especially after the initial infection has cleared on its own.[11]

Literature Review

Commonly used treatment regimens are precise in Table 1.[9,12] Two antibiotics: amoxicillin (1 g BID), clarithromycin (500 mg BID) and a Proton pump inhibitor (e.g., Lansoprazole 30 mg BID, omeprazole 20 mg BID, pantoprazole 40 mg BID, rabeprazole 20 BID, esomeprazole 40 mg BID) for 7 to 14 days are the combination of Triple therapy, for now this regimen is the greatest common original treatment for *H. pylori* infection. Moreover, more than 80% of infections are cured by this regimen, especially when the microorganisms were clarithromycin-sensitive and the duration of treatment was longer (14 or 10 days *versus* 7 days). Metronidazole (500 mg BID) can be replaced for amoxicillin or clarithromycin, but only in individuals with penicillin allergy or macrolide intolerance since metronidazole resistance is common, and will reduce the success rate of treatment.[6,7]

A 10-day consecutive regimen (PPI and amoxicillin 1 g BID for the first 5 days, followed by PPI, clarithromycin 500 mg BID, and tinidazole 500 mg BID for the remaining 5 days) improved overall eradication rates compared with standard PPI triple therapy (89 *vs*. 77%), But it's especially effective against clarithromycin resistant bacteria (89 *vs*. 29%).[13] Pooled analyzes of studies evaluating sequential therapy have demonstrated superior efficacy of sequential therapy, especially against macrolide-resistant strains.[14] While maximum knowledge with this treatment is limited to Mediterranean countries, such results are encouraging. However, no reason to suppose different effects in other regions.[6,13] Although used more than a decade ago, a dual therapy regimen containing of a single antibiotic (amoxicillin or clarithromycin) and a PPI is no longer suggested as annihilation rates are meaningfully lower than with a three-drug regimen.[13]

Bsalts QID, tetracycline 500 mg QID and metronidazole 500 QID, with daily acid-suppressive drug (usually a daily PPI) for two weeks is called Bismuth-based therapy, in fact, it was the first treatment used to treat *H. pylori*. While it is still effective (over 80% annihilation rate), The number of daily tablets and the related common slight side effects can harmfully impact tolerability and compliance. Therefore, it is generally reserved as a second-line or retreatment option in the United States.[6,12,13] Combination capsules containing metronidazole 125 mg, bismuth sub citrate 140 mg and tetracycline 125 mg are available in the US and Canada, make simpler bismuth-based therapy. In a comparative study, *H. pylori* eradication rates were comparable in patients treated with three combination capsules four times daily and a twice-daily PPI for 10 days compared to patients treated with traditional PPI triple therapy (88 *vs*. 83%).[15] Short-term treatment (1 to 7 days) of bismuth has been evaluated,[16] but long-term treatment of persistent infection has not been demonstrated, so short-term treatment cannot be recommended.[17]

The first treatment for *H. pylori* infection fails in 25% of patients due to several factors, including antibiotic-resistant infection, poor adherence, and patient demographics. These demographics may include younger age, smoking, prior antibiotic use, and underlying medical conditions such as functional dyspepsia and gastric ulcer.[8,18] A review of different retreatment Therapies (Table 2) informed annihilation rates of PPI dual treatments, PPI triple treatments, ranitidine-bismuth citrate-based triple therapy, and bismuth-based therapy was 46, 70, 80, and 76%, respectively.[18] No longer available ranitidine bismuth citrate in the United States while during retreatment two new antibiotics were used, the infection healed more easily than when only one new antibiotic was used. A rescue therapy consists of a PPI, levofloxacin 250 mg BID, and amoxicillin 1 g BID for 10 days. The infection can

Table 1: The first-line Treatment of *H. pylori* Infection

Treatment Regimen	*Eradication rate (%)*	*Duration (days)*	*Comments*
PPI† plus clarithromycin 500 mg BID plus amoxicillin 1000 mg BID	70–85	10–14	Resistant to macrolide can impact the eradication rate
PPI † Plus clarithromycin 500 mg BID plus metronidazole 500 mg BID	70–85	10–14	Suitable for those who are allergic to penicillin
PPI † plus amoxicillin 1000 mg BID followed by PPI † Plus clarithromycin 500 mg BID plus tinidazole 500 mg BID	90	5	Shows high efficacy despite clarithromycin resistance
Bismuth subsalicylate 525 mg QID plus metronidazole 500 mg QID plus tetracycline 500 mg QID plus PPI † or H2RA (twice daily)	75–90	10–14	Cheap; consider in Persons allergic to penicillin or clarithromycin suspect resistance

Note. The U.S. Food and Drug Administration (FDA) currently not approved all of these regimens. †Lansoprazole 30 mg per day , pantoprazole 40 mg per day , rabeprazole 20 mg per day, omeprazole 40 mg per day , esomeprazole 40 mg per day , dexlansoprazole 60 mg per day H2RA, histamine H2-receptor antagonist; PPI, proton pump inhibitors.[6,9]

eliminate in up to 80% of patients who have failed one or more previous treatment attempts. However, there are few adequate studies showing that the combination of a PPI and amoxicillin 1 g BID plus rifabutin 300 mg daily for 10 days is 85% effective as retreatment. The positivity rate appeared to be lower at rifabutin doses below 150. Effective retreatment with furazolidone instead of metronidazole has also been described, however, furazolidone is no longer commercially available in the United States.[19]

As a preliminary management for *H. pylori*, a 10 to 14-days course of standard PPI triple therapy (PPI, amoxicillin, and clarithromycin) is suggested, as previously stated, but a 10-day sequential regimen may provide an appropriate substitute. Special caution should be exercised if a clarithromycin-resistant infection is doubted (see below). If the infection continues after treatment, the bacteria may become resistant to clarithromycin. Therefore, a 14-day retreatment should be performed with one of the previously mentioned triple PPIs comprising different drug combinations or bismuth-based therapy. Consequent courses of treatment should also include different combinations of antibiotics, if necessary, to reduce the impact of acquired antimicrobial resistance. Although selecting treatment based on antibiotic susceptibility testing may improve outcomes with subsequent treatment, it is generally not recommended.[20]

Table 2 shows other indications for eradication of *H. pylori*. Once the source of GI bleeding is identified and ruled out, eradication of infection is helpful in several extra gastric disorders, including B12 deficiency and iron deficiency anemia. Platelet counts improve and may normalize after eradication therapy in patients with idiopathic thrombocytopenic purpura; Unknown mechanism.[21]

Around the world, primary resistance of antibiotics with *H. pylori* is commonly varies.[7,18,24] In the U.S., metronidazole resistance was detectable in up to 40% of stains, compared with approximately 11% for clarithromycin resistance. Resistance to tetracycline and amoxicillin is uncommon, typically less than 1%.[18,25] In the United States, resistance to clarithromycin and metronidazole rises with age as well as is more common in women than men but resistance with clarithromycin is more common in the Atlantic Ocean and Northeast regions of the country. Moreover, resistance to metronidazole is more common in Hispanics and Asians [26].

Table 2: Indications for *H. pylori* eradication in *H. pylori*-positive patients[21-23]

Definite indications	• Peptic ulcer
	• Positive *H. pylori*, dyspepsia, family history of extranodal gastric cancer
	• Aforementioned resection for gastric cancer
	• NSAID used for Long-term otherwise low-dose aspirin users
	• PPI user more than 1 year
	• marginal-zone lymphomas of MALT types
	• Additional gastric complaints:
	  • Deficiency of Unexplained vitamin B12
	  • Purpura Idiopathic thrombocytopenic
	  • Anemia due to Iron deficiency

Not specified	• Disease of Gastro-esophageal reflux • Gastric cancer risk factors with Asymptomatic people

Triple PPI regimens is significantly affected by antibiotic resistance meaningfully but is less important in bismuth-based regimens.[24] Bacterial point mutations that prevent decrease of metronidazole to its active metabolite are responsible for the drug resistance.[24] Resistance against metronidazole seems to be a relative state that can be overcome in most cases by increasing the dose (500 mg) or by combining metronidazole with bismuth preparations but clarithromycin resistance seems to be an absolute condition that cannot be easily overcome by increasing the macrolide dose. One of three bacterial point mutations (A2143G, A2142G, and A2142C) within the conserved loop of the ribosomal RNA 23S strand interferes with ribosomal macrolide binding and causes clarithromycin resistance.[24] The A2143G mutation seems to have the major negative effect on treatment and may be a major cause of failure of PPI triple therapy. Specific mutations cannot be detected clinically, so if clarithromycin resistance is suspected or definite by culture, non-macrolide or sequential therapy is a suitable treatment choice. Table 3 Summarize the rescue treatment of persistent infection.

Table 3: Persistent *H. pylori* infection rescue treatment

Treatment Routine	*Eradication rate (%)*	*Duration (days)*	*Remarks*
525 mg, Bismuth subsalicylate metronidazole plus QID Tetracycline plus 500 mg QID PPI† or H2RA (twice daily) 500 mg plus QID	70	14	Two weeks of treatment appear necessary with full dose of metronidazole
Amoxicillin 1000 mg plus PPI† levofloxacin 250-500 mg BID plus BID	57–91	10–14	Limited data
amoxicillin 1000 mg plus PI † rifabutin 150 mg BID plus BID	60–80	14	Costly; adverse hematologic events and drug interactions possible. Limited data

*Note U.S. Food and Drug Administration (FDA) not currently approved all these regimens.
†Lansoprazole 30 mg per day , pantoprazole 40 mg per day , rabeprazole 20 mg per day, omeprazole 40 mg per day , esomeprazole 40 mg per day , dexlansoprazole 60 mg per day H2RA, histamine H2-receptor antagonist; PPI, proton pump inhibitor.[6,9,17]

Failed eradication attempts often lead to secondary antibiotic resistance.[7] Therefore, we can hypothesize that, when metronidazole or clarithromycin -having regimens are ineffective, definite resistance develops, which affects subsequent treatment options.[18,24]

Treatment-related side effects may occur in up to 50% of patients receiving one of the previous treatment regimens, but these effects are usually mild and do not require treatment discontinuation. Some common side effects include taste changes, gastrointestinal (GI) discomfort with metronidazole and clarithromycin, and allergic reactions and diarrhea with amoxicillin. It is worth noting that tetracyclines should not be used in children and pregnant women. Side effects of *H. pylori* treatment have recently been extensively reviewed elsewhere.[9,18]

Conclusion

Until now, there is no antibiotic that can eliminate the *H. pylori* infection in a single form, so for the treatment of *H. pylori*, a combination of two antibiotics is often used, which should continue for 7 to 14 days with ant secretory i.e. PPI for 4 to 6 weeks.

The most commonly used regimen for treatment is standard triple therapy (amoxicillin 1gm BID plus clarithromycin 500 mg BID plus PPI). This regimen causes the eradication of infection in about 80 percent of patients, especially if the infection is clarithromycin-sensitive. In this regimen, metronidazole can be added, especially if *H.pylori* infection is clarithromycin resistant, if the patient is allergic to penicillin, metronidazole can be given instead of amoxicillin.

The 10-day regimen (PPI and amoxicillin 1 g BID for the first 5 days, then PPI, clarithromycin 500 mg, and tinidazole 500 mg BID for the remaining 5 days) increased Compared with standard PPI triple therapy, the overall eradication rate was higher (89 *vs.* 77%), but it was particularly effective against clarithromycin-resistant bacteria (89 *vs.* 29%).

Bismuth-based therapy (bismuth salts, Metronidazole 500 mg and Tetracycline 500 mg each four times a day) for two weeks with PPI. It was one of the first therapeutic regimens to treat *H. pylori* infection. Although it remains effective (more than 80% eradication rate), the number of tablets taken per day and the related common slight side effects can negatively impact tolerance and compliance. Therefore, it is usually kept as a second-line or retreatment option.

Rescue therapy (PPIs, Levofloxacin, and amoxicillin twice daily for 10 days) has recently been recommended for H. *pylori* infection. This combination can eradicate *H. pylori* infection in nearly 80% of patients who have failed one or more previous treatment efforts.

Source of Support

Nil.

Conflict of Interest

None.

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