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Review: Treatment of Helicobacter pylori infection

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ABSTRACT

Helicobacter pylori (H. pylori) is strongly associated with a wide spectrum of gastrointestinal diseases, such as duodenal or gastric ulcers and gastric cancer. Currently, the main treatment of H. pylori infection involves the use of a combination of antimicrobial agents such as amoxicillin, metronidazole and clarithromycin and proton pump inhibitors (PPIs). In many guidelines, triple therapy consisting of two antibiotics (amoxicillin/metronidazole and clarithromycin) and a PPI is used as the first treatment line. Unfortunately, the increased resistance of H. pylori to clarithromycin and metronidazole adversely affect the effectiveness of triple therapy and reduces the eradication rates to an unacceptable level. Several regimens have been proposed to replace standard triple therapy such as bismuth-containing quadruple therapy, sequential therapy, concomitant therapy, hybrid therapy and levofloxacin-based therapy. Many regimens are used as rescue therapy based on what was previously used in the treatment such as bismuth quadruple therapy, rifabutin triple therapy and levofloxacin-based therapies. However, due to the bacterial resistance to antibiotics that can limit the applicability of such regimens and because the resistance to amoxicillin is very low, high-dose dual therapy (HDDT) consisting of amoxicillin and a PPI has been proposed as an effective and safe first-line or rescue therapy.

Keywords*: H. pylori infection, Triple, Concomitant, Sequential, High dose dual therapy.*
Running title: *Treatment of H. Pylori*

INTRODUCTION

Helicobacter pylori *(H. pylori)*, formerly named Campylobacter pyloridis, was first identified, isolated and cultured by Marshall and Warren **(Marshall and Warren 1984)**. *H. pylori* is a spiral, rod shaped, microaerophilic, gram-negative bacterium that has flagella at one end for mobility**(McColl 2010)**. The route of transmission of *H. pylori* from individual to another individual is not yet fully known but faecal–oral route, iatrogenic route, and oral to oral route is the most likely path for *H. pylori* infection **(Brown 2000)**. More than 50% of the world's population is infected with *H. pylori*. The prevalence of infection with *H. pylori* in developing countries may exceed 90% **(Mentis, Lehours et al. 2015)**. Infection with *H. pylori* is associated with a number of gastrointestinal diseases, such as gastric inflammation, duodenal or gastric ulcers, gastric cancer and gastric mucosa-associated lymphoid-tissue (MALT) lymphoma **(McColl 2010)**. In 1994, the International Agency for Research on Cancer has classified *H. pylori* as group 1 carcinogen. Several guidelines have been developed for treatment of *H. pylori* infection **(Yang, Lu et al. 2014).**

Pathophysiology of *H. pylori*:

The *H. pylori* is not an acidophile so, upon the entry to stomach it secretes urease enzyme, which converts urea to ammonia and carbon

dioxide, thus raising the pH of the stomach. Then the *H. pylori* moves through the mucus layer towards the epithelial cells of the stomach using its flagella. *H. pylori* then adheres to epithelial cells using many proteins like: BabA, BabB, SabA, and OipA. *H. Pylori* secrets CagA protein into the stomach cell that cause a morphological change in the cells and activates the inflammatory cells causing epithelial cell damage. It secrets also VacA toxin that induces massive vacuolization and apoptosis of epithelial cells **(Sgouras, Trang et al. 2015).**

Treatment of *H. pylori* infection:

H. pylori infection is typically treated with combinations of 2–4 antibiotics with antisecretory agents, taken concomitantly or sequentially, for periods from 3 to 14 days; however, there is no treatment regimen guarantees eradication of *H. pylori* infection in 100% of patients **(Chey, Leontiadis et al. 2017).** The main antisecretory agents used are proton pump inhibitors (PPIs) and there are many antibiotics that have been used to treat *H. pylori* infection, including amoxicillin, clarithromycin, metronidazole, levofloxacin and bismuth-containing compounds, **(Yang, Lu et al. 2014).** Different combinations of these drugs have been shown to be effective with various efficacy rates of eradication and tolerability **(Yang, Lu et al. 2014).** However, higher treatment failure rate for *H. pylori* infection increases significantly due to the rapid emergence of the antibiotic-resistant strains of *H. pylori* and due to poor adherence to treatment by patients **(Graham and Fischbach 2010).** Because of these factors, the effectiveness of treatment have been reduced to unacceptable levels (less than 80%) in several geographic regions; thus, new treatment regimens have recently been validated and used to replace triple therapy **(Garza-González, Perez-Perez et al. 2014).**

Frist line treatments:

Careful attention must be paid to choosing the most appropriate first-line eradication treatment as first-line therapy, offers the greatest likelihood of treatment success **(Chey, Leontiadis et al. 2017).** The American College of Gastroenterology (ACG) launched a list of available first-line treatment options (shown in table 1) **(Chey, Leontiadis et al. 2017).**

Figure (1) summarizes ACG guidelines to choose the best therapy for an individual patient **(Chey, Leontiadis et al. 2017).**

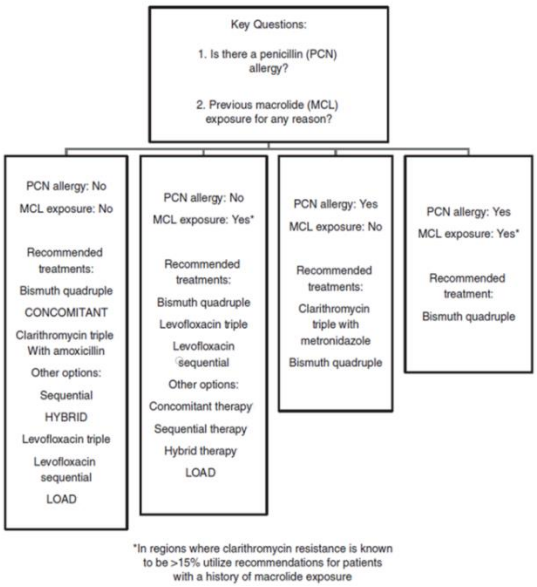


Figure (1): Selection of a first-line H. pylori treatment regimen (Chey, Leontiadis et al. 2017).

Triple therapy:

H. pylori triple therapy is recommended in many guidelines as first-line therapy **(Chey, Leontiadis et al. 2017).** This therapy is taken for 7 to 14 days and consists of a PPI (omeprazole 20 mg BID, lansoprazole 30 mg BID, pantoprazole 40 mg BID, rabeprazole 20 mg BID, or esomeprazole 40 mg QD), amoxicillin (or in case of patients with an allergy to penicillin, metronidazole is used as an alternative to amoxicillin) & clarithromycin **(Garza-González, Perez-Perez et al. 2014).** The duration of therapy is debatable. Four meta-analyses were conducted and resulted in very similar results, that is, the 10-day treatment improves the eradication rate by 4% and treatment for 14 days improves the rate of eradication by 5-6%, compared with treatment for 7 **days (Calvet, Garcia et al. 2000, Ford and Moayyedi 2003, Fuccio, Minardi et al. 2007, Flores, Salvana et al. 2010)**.

Unfortunately, for many years now, meta-analyses have stated that the efficacy of the clarithromycin triple therapy has been decreased over time, corresponding with the increase in clarithromycin resistance.

Table 1. Recommended first-line therapies for H pylori infection (Chey, Leontiadis et al. 2017).

Regimen	Drugs (doses)	Dosing frequency	Duration
Triple therapy	PPI (standard or double dose) Clarithromycin (500 mg) Amoxicillin (1 gram) or Metronidazole (500 mg TID)	BID BID BID	14
Bismuth quadruple	PPI (standard dose) Bismuth subcitrate (120–300 mg) or subsalicylate (300 mg) Tetracycline (500 mg) Metronidazole (250–500 mg)	BID QID QID QID (250) TID to QID (500)	10–14
Sequential	PPI (standard dose) +Amoxicillin (1 grm) PPI, Clarithromycin (500 mg) + Nitroimidazole	BID BID	5-7 5-7
Concomitant	PPI (standard dose) Clarithromycin (500 mg) Amoxicillin (1 gram) Nitroimidazole (500 mg)	BID	10-14
Hybrid	PPI (standard dose) + Amox (1 grm) PPI, Amox, Clarithromycin (500 mg), Nitroimidazole (500 mg)	BID BID	7 7
Levofloxacin triple	PPI (standard dose) Levofloxacin (500 mg) Amox (1 gram)	BID QD BID	10-14
Levofloxacin sequential	PPI (standard or double dose)+Amox (1 grm) PPI, Amox, Levofloxacin (500 mg QD), Nitroimidazole (500 mg)	BID BID	5-7 5-7
LOAD	Levofloxacin (250 mg) PPI (double dose) Nitazoxanide (500 mg) Doxycycline (100 mg)	QD QD BID QD	7-10

BID, twice daily; PPI, proton pump inhibitor; TID, three times daily; QD, once daily; QID, four times daily
LOAD: levofloxacin, omeprazole, nitazoxanide (Alinia) and doxycycline.

An eradication rate for clarithromycin triple therapy below 80% has repeatedly been reported in several meta-analyses and systematic reviews in several countries which is below what should be achieved for an infectious disease **(Graham and Fischbach 2010).** There are many explanations for the lack of effectiveness of triple therapy: high gastric acidity, poor compliance, high bacterial load, the type of strains, and the last and most important one is increasing resistance of bacteria to clarithromycin **(Malfertheiner, Megraud et al. 2012).** Several studies have showed that point mutations that occur in the peptidyltransferase region encoded in domain V of 23S rRNA are responsible for clarithromycin resistance, in particular, two major mutations: A2142G and A2143G**(Yang, Lu et al. 2014, Abadi 2017)**. Metronidazole is activated in the cytosol of the microorganism by nitroreductase, inactivation of these nitroreductases by mutations contributes to development of resistance **(Francesco, Zullo et al. 2011).** The effectiveness of triple therapy is highly dependent on the PPI used, thus increasing the dose of PPI was one of the attempts made to increase the effectiveness of treatment **(Malfertheiner, Megraud et al. 2012).**A meta-analysis demonstrated that increasing the PPI dose resulted in an increase in eradication rate from 6% to 10% **(Villoria 2008)**. The cytochrome P450 (CYP450)2C19 and multidrug resistance gene (MDR) polymorphisms greatly influence PPI function. A recent meta-analysis study showed that CYP2C19 rapid metabolizer patients had a lower cure rate. Also, patients with the MDR T／T genotype had a lower cure rate than patients with the T/C and C/C genotypes **(Furuta, Sugimoto et al. 2007).**

Quadruple therapy:

Bismuth-containing quadruple therapy is recommended as first line empirical treatment in areas with high resistance to clarithromycin **(Malfertheiner, Megraud et al. 2012).** This is because quadruple therapy is not affected by resistance to clarithromycin as in case with triple therapy. Furthermore, although resistance to metronidazole affects the effectiveness of quadruple therapy, it is not as profound as the effect of clarithromycin resistance on the effectiveness of triple therapy **(Venerito, Krieger et al. 2013).** Also, it is advised to use quadruple therapy as a first line of treatment in the case that the patient has been treated before using macrolides for any reason **(Chey, Leontiadis et al. 2017).** A meta-analysis included studies from all over the world showing that quadruple therapy is similar to clarithromycin triple therapy in efficacy, tolerability and compliance **(Luther, Higgins et al. 2010)**. Treatment duration is recommended to be from 10 to14 days **(Chey, Leontiadis et al. 2017).**

Sequential therapy:

Sequential treatment consists of a combination of a PPI and amoxicillin for first 5 days, followed by a PPI, clarithromycin, and a nitroimidazole: tinidazole for an extra 5 days. A systematic review and meta-analysis included 46 studies that compared sequential therapy with other established and new treatment regimens revealed that the overall eradication rate of sequential therapy was 84.3%. Sequential treatment was betterthan7 days triple therapy. And it was only marginally superior to 10 days triple therapy. But it was not superior to 14 days triple therapy **(Gatta, Vakil et al. 2013).** Also, there is no significant differences in the tolerability and compliance between sequential therapy and clarithromycin triple therapy **(Li, Threapleton et al. 2015)**. A large study found that areas with high resistance to clarithromycin have reduced eradication rates with sequential therapy, although to a lesser extent than with triple therapy **(Liou, Chen et al. 2013).** A 10-day sequential treatment seems to be an alternative to 14 day clarithromycin triple therapy **(Chey, Leontiadis et al. 2017).**

Concomitant therapy:

Concomitant therapy involves the concurrent administration of 3 antibiotics (amoxicillin, clarithromycin, and a nitroimidazole: tinidazole or metronidazole) with PPI given together for 3 to 10 days **(Treiber, Ammon et al. 1998).** There is a meta-analysis comprising 19 controlled trials found that a mean cure rate of 88% occurred when using a concomitant therapy **(Gisbert and Calvet 2012).** The results of randomized controlled trials comparing concomitant therapy (481 patients) with triple therapy (503 patients),revealed that concomitant therapy achieving a cure rate of 90%, while triple therapy achieved a cure rate of 78% **(Gisbert and Calvet 2012).**A meta-analysis of 6 studies of concomitant therapy with over 2000 patients revealed no differences between the effectiveness of the 10-day sequential therapy and concomitant therapy for 5–10 days **(Gatta, Vakil et al. 2013).** Concomitant therapy is used as an alternative to sequential treatment in areas where the resistance to clarithromycin is more than 20% and quadruple therapy is not available **(Garza-González, Perez-Perez et al. 2014).** The side effects of concomitant therapy are high, as 30.9% of patients report at least one side effect. But in general, these effects are mild, and treatment can be continued despite these effects **(De Francesco, Giorgio et al. 2010).**

Hybrid therapy:

Hybrid therapy consists of two steps: using amoxicillin and a PPI for 7 days, followed by using amoxicillin, clarithromycin, PPI and a nitroimidazole for another 7 days **(Hsu, Wu et al. 2011).** There is a meta-analysis for six randomized controlled trials which evaluated

hybrid therapy versus sequential and/or concomitant therapy and when data from the hybrid treatment arms were collected the intention to treat eradication rate was 88.6% **(Wang, Wang et al. 2015).** This result was confirmed by two other meta-analyses, where the eradication rate in one of them was 89% **(Li, Threapleton et al. 2015),** and in the other it was 86.6% **(He, Deng et al. 2015).** Hybrid therapy has proven to be more effective than the 7-day triple therapy (89% for hybrid therapy vs. 73% for triple therapy) **(Li, Threapleton et al. 2015).** It also shows that there is no significant differences between hybrid, concomitant or sequential, therapies in efficacy, tolerability or compliance **(He, Deng et al. 2015, Wang, Wang et al. 2015).**

Levofloxacin-based therapies:

Levofloxacin belongs to fluoroquinolone class of antibiotics which has antibacterial effect against Gram-positive and Gram-negative bacteria including *H. pylori* and has been used in the first line and rescue regimens **(Chey, Leontiadis et al. 2017).** Levofloxacin was used as a first line treatment in three types of regimens: (1) triple therapy: Levofloxacin along with amoxicillin and a PPI (2) modified sequential therapy: a PPI and amoxicillin for 5–7 days followed by levofloxacin, a nitroimidazole and a PPI 5–7 days (3) quadruple therapy (LOAD): 7 or 10 days of levofloxacin, a PPI (omeprazole), nitazoxanide (Alinia) and doxycycline **(Chey, Leontiadis et al. 2017).** A meta-analysis which included seven studies revealed that eradication rate of 7 days levofloxacin triple therapy is similar to clarithromycin triple therapy for 7 days (79% vs. 81% respectively) **(Peedikayil, Alsohaibani et al. 2014).** In Another network meta-analysis, 10–14 days of levofloxacin triple therapy has been shown to outperform 7 days clarithromycin triple therapy, the pooled eradication rate of levofloxacin triple therapy was also superior than 10-14 days of clarithromycin triple therapy, but the tolerability of levofloxacin triple therapy was similar to clarithromycin triple therapy **(Li, Threapleton et al. 2015).**

In the modified sequential therapy, Levofloxacin and ciprofloxacin also have been utilized **(Chey, Leontiadis et al. 2017).** A meta-analysis of six trials that includes 738 treatment-naive *H. pylori* infected patients compared the efficiency of 10-14 days of flouroquinolone sequential therapy versus 7-14 days of clarithromycin triple therapy or 10 days of standard sequential therapy. The levofloxacin sequential therapy was superior to clarithromycin triple therapy (83.6% vs. 64%) and standard sequential therapy (87.4% vs. 78.9%). The tolerability and patient compliance was similar between groups **(Kale-Pradhan, Mihaescu et al. 2015).**

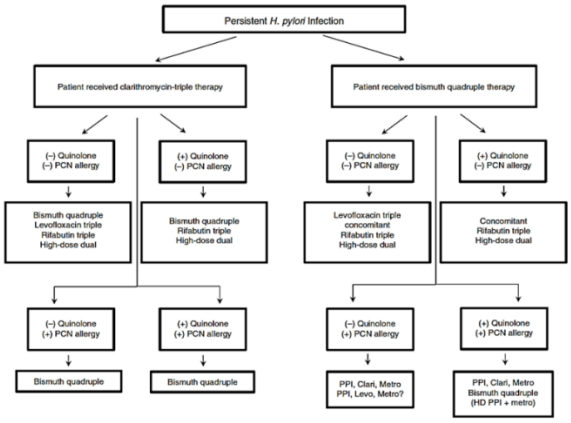
In an open-label, randomized trial that was performed in the United States and included 270 patients, the eradication rate resulting from using the LOAD for a period of 7 or10 days was 89% and 90% compared to 73% when using a course of amoxicillin, clarithromycin and lansoprazole for 10-days **(Basu, Rayapudi et al. 2011).**

Salvage therapy:

The choice of treatment for the patient with persistent *H. pylori* infection after the failure of the first treatment line is widespread and facing gastroenterologists a lot, the most important factor for the success of treatment of *H. pylori* is the sensitivity or resistance of *H. pylori* to the antibiotics used, bacterial resistance to an antibiotic is closely related to the use of this antibiotic previously, either for treating *H. pylori* or other infections. This should be noted when using clarithromycin, fluoroquinolones and rifabutin (an antibiotic that is not used in a first line of treatment) which should not be reused, because bacterial resistance to them cannot be overcome by increasing the dose, increasing the duration of treatment, or frequency of administration. Because amoxicillin and tetracycline resistance are rare,

even after they have been used previously, they can be reused again **(Chey, Leontiadis et al. 2017).**

Figure (2) shows ACG Guidelines to choose the best salvage therapy for *H. pylori* patient.



(–) Quinolone = No previous quinolone exposure, (+) Qui Previous quinolone exposure, (–) PCN allergy = No penicillin al PCN allergy = Penicillin allergy, PPI = proton pump inhibitor clarithromycin, Levo = levofloxacin, Metro =metronidazole, H dose.

Figure 2.Selection of a rescue therapy for persistent H. pylori (Chey, Leontiadis et al. 2017).

PAST AND FUTURE USE OF HIGH DOSE DUAL THERAPY (HDDT):

The high resistance rate of *H. pylori* against clarithromycin and metronidazole can adversely affect the efficacy of any regimens containing these drugs. Conversely, primary resistance to amoxicillin is very low worldwide, and secondary resistance to it is also rare. Therefore, it is advisable to use amoxicillin in the treatment of *H. pylori* infection **(Yang, Lin et al. 2015).** In 1989 the dual therapy consisting of amoxicillin and a PPI (omeprazole) was investigated for the first time and it showed higher eradication rate than treatment with either amoxicillin or PPI alone **(Unge, Gad et al. 1989).** When a typical dual therapy which consists of a standard dose of Amoxicillin (2 gram or less per day) and a PPI was used, the efficacy was found to be unacceptable compared with triple therapies. However, the administration of a high dose dual therapy which consists of Amoxicillin (more than 2 grams per day) and PPI more than twice daily for 14 days, has been reported to have better efficacy (i.e, more than 90%) compared with typical dual therapy **(Gao, Zhou et al. 2016).** In 1995, high-dose dual therapy, which consisted of omeprazole 40 mg and amoxicillin 750 mg, was used three times daily, and it achieved high eradication rates exceeding 90% **(Bayerdörffer, Miehlke et al. 1995).** It has also been shown that high-dose dual therapy improves the impact of CYP2C19genotype. As there is a study that evaluated the effect of the use of rabeprazole (10 mg) and amoxicillin (500 mg) four times per day on the eradication rate in patients with different CYP2C19genotypes, it was found that the rate of eradication has reached 100% in the extensive and intermediate metabolizer patients **(Furuta, Shirai et al. 2001).**

The amoxicillin antibiotic depends on time in its bactericidal effect, therefore, the strategy for this regimen is not to increase the maximum concentration but rather to increase the duration of exposure. Thus, to obtain the maximum effect, it is preferable to give small and more frequent doses of amoxicillin rather than to give large and less frequent doses (e.g., 500 mg four times daily) **(Yang, Lu et al. 2014).** Amoxicillin is more stable at a high degree of intragastric PH (> 5.5). Also, the bacteria are reproducible and so become susceptible to amoxicillin when the pH of the stomach is high to more than 6. Therefore, the success of the action of amoxicillin is highly dependent on the PH **(Safavi, Sabourian et al. 2016).** Therefore, the principle of this regimen is to increase the dose of PPI greater than the standard doses or administer the PPI at shorter intervals to keep high intragastric PH and thereby maintain the stability and effectiveness of amoxicillin **(Gao, Zhou et al. 2016).** Studies on high-dose dual therapy have shown different eradication rates and more studies are needed to clarify the discrepancies in the eradication rates. Table (2) illustrates some of the studies done on this treatment and its results. Table (3) shows a comparison between HDDT & other treatments regarding the efficacy and side effects.

Table 2. different regimens of high dose dual therapy for Helicobacter pylori infection

Author	role	Regimen	Pt.n	ITT	PP
Bayerdörffer et al **(Bayerdörffer, Miehlke et al. 1995)**	1st	OME 40 mg and AMO 750 mg tid for 14 d	139	89.0%	90.6%
Miehlke et al **(Miehlke, Kirsch et al. 2003)**	2nd	OME 40 mg and AMO 750 mg qid for 14 d	41	75.6%	83.8%
Shirai et al **(Shirai, Sugimoto et al. 2007)**	2nd	RAB 10 mg and AMO 500 mg qid	66	90.9%	93.8%
Graham et al **(Graham, Javed et al. 2010)**	1st	ESO 40 mg and AMO 750 mg tid for 7 d	36	72.2%	74.2%
Kim et al **(Kim, Jung et al. 2012)**	1st	LAN 30 mg and AMO 750 mg *tid* for 14 d	104	67.3%	78.4%
Goh et al **(Goh, Manikam et al. 2012)**	2nd	RAB 20 mg and AMO 1 g tid for 14 d	149	71.8%	75.4%
Zullo et al **(Zullo, Ridola et al. 2015)**	1st	ESO 40 mg and AMO1 g tid for 10 d	56	87.5%	
J. C. Yang et al **(Yang, Lin et al. 2015)**	1st 2nd	RAB 20 mg and AMO 750 mg qid for 14 d RAB 20 mg and AMO 750 mg qid for 14 d	150 56	95.3% 89.3%	96.6% 89.3 %

Pt.n: patients number; ITT: Intention-to-treat; PP: Per-protocol; OME: Omeprazole; AMO: Amoxicillin; RAB: Rabeprazole; ESO: Esomeprazole; LAN: Lansoprazole; tid: Three times daily; qid: Four times daily; 1st: First-line treatment; 2nd: Rescue treatment

Finally, there are no studies done on Egyptian patients using HDDT. Results from other studies indicate that it could be the the treatment of choice in the Egyptian hospitals being the one that avoids the using of clarithromycin with high potential growing resistance among the Egyptian patients.

Nanoparticle Based Treatment Approaches

Nanoparticles (NP) are small materials ranging in size from 1 to 1000 nm and characterizes by large surface area and small dimension. There are many types of NPs such as metal NPs and polymeric NPs.The advantages of using NPs are to increase the therapeutic effect of the drugs and to control the release of active substances. In recent years, there is increasing interest in studies on the drug nanoparticle systems against *H.Pylori* **(Safarov, Kiran et al. 2019).**

Metallic Nanoparticles:

There are several studies on the use of bismuth, zinc, gold and especially silver nanoparticles in the treatment of *H. Pylori*. Metallic nanoparticles are an alternative for the treatment of multi-drug resistant bacteria by direct communication with the bacterial cell wall, inducing adaptive and innate immune responses, generation of reactive oxygen species, inhibition of biofilm formation and stimulation of intracellular effects **(Baptista, McCusker et al. 2018).**

Gold nanoparticles:

Gold nanoparticles with average sizes of 7 nm and 55 nm showed antibacterial activity against *H.Pylori*strains **(Gopinath, Priyadarshini et al. 2019).**

Zinc oxide (ZnO) nanoparticles:

ZnO nanoparticles with sizes of 3-7 nm caused membrane damage of H.pylori. Synergies with antibiotics also were observed. It showed antibacterial effect on metronidazole resistant *H.pylori* strains **(Chakraborti, Bhattacharya et al. 2013).**

Silver (Ag) nanoparticles:

- **Ag Np:** sized between 5-60 nm showed activity against *H.pylori* and was validated with standard antibiotics amoxicillin. It provides biofilm inhibition **(Safarov, Kiran et al. 2019).**

Ag Np: in the size of 20 nm exhibited anti-bacterial and anti-biofilm activity against *H. pylori* by formation of Reactive Oxygen Species (ROS) **(Safarov, Kiran et al. 2019).**

drug delivery systems against

Table 3. Table 3. Comparison between high dose dual therapy and other treatment regimens

Author	groups	Regimen	Eradication rate	Efficacy Side effect
J. Yang et al **(Yang, Zhang et al. 2019)**	HDDT Control	E 20mg qid, A 750 mg qid × 14 d E 20 mg bid, B 220 mg bid, A 1g bid, C 500 mg bid × 14d (bismuth-containing quadruple therapy)	87.9% 89.7%	**EF**: Similar **S:E:** HDDT is safer
WC Tai et al **(Tai, Liang et al. 2019)**	HDDT Control	E 40mg tid, A 750 mg qid × 14d E 40mg bid, C 500 mg bid, A 1g bid, M 500 mg bid × 7d (non bismuth-containing quadruple therapy)	91.7% 87.5%	**E.F:** HDDT is more effective **S.E:** HDDT is safer
J. C. Yang et al. **(Yang, Lin et al. 2015)**	HDDT Control Control	R 20 mg qid, A 750 mg qid x 14 d R 20 mg bid, A 1g bid x 5 d followed by R 20 mg bid, M 500 mg bid, C 500 mg bid x 5 d (sequential therapy) R 20 mg bid. A 1 g bid, C 500 mg bid x 7 d (triple therapy)	95.3% 85.3% 80.7%	**E.F:** HDDT is more effective than others **S.E:** Similar

E: esomeprazole; A: amoxicillin; B: bismuth; C: clarithromycin; M: metronidazole; R: rabeprazole; d: days; qid: four times a day; bid: twice daily; E.F: efficacy; S.E: side effects

- **Toxicodendronvernicifluum (Tv-AgNP):** in the size between 2-40 nm displayed potential antibacterial, and anti-proliferative activities by inducing the ROS, oxidative stress, DNA division in bacterial cells **(Safarov, Kiran et al. 2019).**

Bismuth nanoparticles:

Bismuth Np in size of 9.2 nm exhibited a comparable anti-*H. Pylori* activities to the clinically used drug, colloidal bismuth subcitrate**(Safarov, Kiran et al. 2019).**

Polymeric Nanoparticles:

Drug and therapeutic molecules can be directly encapsulated with polymeric nanoparticles or covalently conjugated to the surface of the nanoparticles **(Gao, Thamphiwatana et al. 2014)**.

Examples:

- **Poly lactic-co-glycolic acid (PLGA**) nanoparticles: provide low water solubility of drugs such as clarithromycin to reach the target region. clarithromycin loaded PLGA nanoparticles was synthesized and showed activity against *H.pylori*.**(Lotfipour, Valizadeh et al. 2016)**.
- **Polyalkylcyanoacrylate (PECA)** nanoparticles: have mucoadhesive properties and this feature provides opportunities for the development of *H.Pylori***(Fontana, Licciardi et al. 2001).**
- **gliadin nanoparticles:** has natural polymer and mucoadhesive properties and this is advantageous for the development of nanoparticular drug delivery systems against *H. pylori* **(Umamaheshwari and Jain 2003).**
- **Cellulose:** clarithromycin encapsulated into ethylcellulose nanoparticles and showed a high activity against *H.pylori***(Pan-In, Banlunara et al. 2014)**.

Targeting nanoparticles:

Here, modifications are made to the surface of NPs by adding organic groups surface atoms or targeting receptors to make sure that nanoparticles which carry the drug enter and bind to the target areas **(Safarov, Kiran et al. 2019).**

Example:

- The acidic condition of the stomach is a major barrier to the degradation of H.Pylori antimicrobial drugs in the infected region. For this purpose, pH-sensitive urea modified UCCs-2-PLGA nanoparticles containing urea-mediated targeted drug delivery system have been developed **(Safarov, Kiran et al. 2019).**

Membrane coated nanoparticles:

Here, the membranes were used to coat the surfaces of polymeric nanoparticles. The

membranes derived from various tissues, allowing membrane coated nanoparticles to bind to mucosal tissues and enabling the transport of drugs in a targeted way **(Safarov, Kiran et al. 2019).**

Example:

Clarithromycin was encapsulated into PLGA nanoparticles and adenocarcinoma gastric epithelial cell membrane has used to cover the surface of these nanoparticles and the use of the drug alone was compared to this met hod. And it was found that the therapeutic effects of the membrane coated NPs were higher than other formulations **(Safarov, Kiran et al. 2019).**

CONCLUSION:

The first or second line of treatment of *H. pylori* infection consists mainly of combinations of antimicrobial agents and antisecretory agents. Generally, the success of the treatment depends on many factors, but the most important one is the bacterial resistance to antibiotics. Among the antibiotics frequently used to treat H. *pylori*, resistance to amoxicillin is low. Dual therapy consisting of amoxicillin and a PPI achieved different eradication rates, and its efficacy could be improved by adjusting the dose and dose frequency. There is many successful studies on the drug nanoparticle systems to treat *H.Pylori* infection.

REFERENCES

Abadi, A. T. B. (2017). Resistance to clarithromycin and gastroenterologist's persistence roles in nomination for Helicobacter pylori as high priority pathogen by World Health Organization. World journal of gastroenterology 23(35): 6379-6384.

Baptista, P. V., M. P. McCusker, A. Carvalho, D. A. Ferreira, N. M. Mohan, M. Martins and A. R. Fernandes (2018). Nano-Strategies to Fight Multidrug Resistant Bacteria-"A Battle of the Titans". Frontiers in microbiology 9: 1441-1441.

Basu, P. P., K. Rayapudi, T. Pacana, N. J. Shah, N. Krishnaswamy and M. Flynn (2011). A randomized study comparing levofloxacin, omeprazole, nitazoxanide, and doxycycline versus triple therapy for the eradication of Helicobacter pylori. Am J Gastroenterol 106(11): 1970-1975.

Bayerdörffer, E., S. Miehlke, G. A. Mannes, A. Sommer, W. Höchter, J. Weingart, W. Heldwein, H. Klann, T. Simon, W. Schmitt and et al. (1995). Double-blind trial of omeprazole and amoxicillin to cure Helicobacter pylori infection in patients with duodenal ulcers. Gastroenterology 108(5): 1412-1417.

Brown, L. M. (2000). Helicobacter pylori: epidemiology and routes of transmission. Epidemiol Rev 22(2): 283-297.

Calvet, X., N. Garcia, T. Lopez, J. P. Gisbert, E. Gene and M. Roque (2000). A meta-analysis of short versus long therapy with a proton pump inhibitor, clarithromycin and either metronidazole or amoxycillin for treating Helicobacter pylori infection. Aliment Pharmacol Ther 14(5): 603-609.

Chakraborti, S., S. Bhattacharya, R. Chowdhury and P. Chakrabarti (2013). The molecular basis of inactivation of metronidazole-resistant Helicobacter pylori using polyethyleneimine functionalized zinc oxide nanoparticles. PLoS One 8(8): e70776.

Chey, W. D., G. I. Leontiadis, C. W. Howden and S. F. Moss (2017). ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. Am J Gastroenterol 112(2): 212-239.

De Francesco, V., F. Giorgio, C. Hassan, G. Manes, L. Vannella, C. Panella,

E. Ierardi and A. Zullo (2010). Worldwide H. pylori antibiotic resistance: a systematic review. J Gastrointestin Liver Dis 19(4): 409-414.

Flores, H. B., A. Salvana, E. L. R. Ang, N. I. Estanislao, M. E. Velasquez, J. Ong, E. R. Nolasco, M. L. Daez and V. Banez (2010). M1138 Duration of Proton-Pump Inhibitor-Based Triple Therapy for Helicobacter pylori Eradication: A Meta-Analysis. Gastroenterology 138(5): S-340.

Fontana, G., M. Licciardi, S. Mansueto, D. Schillaci and G. Giammona (2001). Amoxicillin-loaded polyethylcyanoacrylate nanoparticles: influence of PEG coating on the particle size, drug release rate and phagocytic uptake. Biomaterials. 22(21): 2857-2865.

Ford, A. and P. Moayyedi (2003). How can the current strategies for Helicobacter pylori eradication therapy be improved? Can J Gastroenterol 17 Suppl B: 36b-40b.

Francesco, V. D., A. Zullo, C. Hassan, F. Giorgio, R. Rosania and E. Ierardi (2011). Mechanisms of Helicobacter pylori antibiotic resistance: An updated appraisal. World journal of gastrointestinal pathophysiology 2(3): 35-41

Fuccio, L., M. E. Minardi, R. M. Zagari, D. Grilli, N. Magrini and F. Bazzoli (2007). Meta-analysis: duration of first-line proton-pump inhibitor based triple therapy for Helicobacter pylori eradication. Ann Intern Med 147(8): 553-562.

Furuta, T., N. Shirai, M. Takashima, F. Xiao, H. Hanai, K. Nakagawa, H. Sugimura, K. Ohashi and T. Ishizaki (2001). Effects of genotypic differences in CYP2C19 status on cure rates for Helicobacter pylori infection by dual therapy with rabeprazole plus amoxicillin. Pharmacogenetics 11(4): 341-348.

Furuta, T., M. Sugimoto, N. Shirai, F. Matsushita, H. Nakajima, J. Kumagai, K. Senoo, C. Kodaira, M. Nishino, M. Yamade, M. Ikuma, H. Watanabe, K. Umemura, T. Ishizaki and A. Hishida (2007). Effect of MDR1 C3435T polymorphism on cure rates of Helicobacter pylori infection by triple therapy with lansoprazole, amoxicillin and clarithromycin in relation to CYP 2C19 genotypes and 23S rRNA genotypes of H. pylori. Aliment Pharmacol Ther 26(5): 693-703.

Gao, C. P., Z. Zhou, J. Z. Wang, S. X. Han, L. P. Li and H. Lu (2016). Efficacy and safety of high-dose dual therapy for Helicobacter pylori rescue therapy: A systematic review and meta-analysis. J Dig Dis 17(12): 811-819.

Garza-González, E., G. I. Perez-Perez, H. J. Maldonado-Garza and F. J. Bosques-Padilla (2014). A review of Helicobacter pylori diagnosis, treatment, and methods to detect eradication. World journal of gastroenterology 20(6): 1438-1449.

Gatta, L., N. Vakil, D. Vaira and C. J. B. Scarpignato (2013). Global eradication rates for Helicobacter pylori infection: systematic review and meta-analysis of sequential therapy. 347: f4587.

Gisbert, J. P. and X. Calvet (2012). Update on non-bismuth quadruple (concomitant) therapy for eradication of Helicobacter pylori. Clinical and experimental gastroenterology 5: 23-34.

Gao, W., S. Thamphiwatana, P. Angsantikul and L. Zhang (2014). Nanoparticle approaches against bacterial infections. Wiley interdisciplinary reviews. Nanomedicine and nanobiotechnology 6(6): 532-547.

Goh, K. L., J. Manikam and C. S. Qua (2012). High-dose rabeprazole-

amoxicillin dual therapy and rabeprazole triple therapy with amoxicillin and levofloxacin for 2 weeks as first and second line rescue therapies for Helicobacter pylori treatment failures. Aliment Pharmacol Ther 35(9): 1097-1102.

Gopinath, V., S. Priyadarshini, D. MubarakAli, M. F. Loke, N. Thajuddin, N. S. Alharbi, T. Yadavalli, M. Alagiri and J. J. A. j. o. c. Vadivelu (2019). Anti-Helicobacter pylori, cytotoxicity and catalytic activity of biosynthesized gold nanoparticles: Multifaceted application. Arabian journal of chemistry. 12(1): 33-40.

Graham, D. Y. and L. Fischbach (2010). Helicobacter pylori treatment in the era of increasing antibiotic resistance. Gut 59(8): 1143-1153.

Graham, D. Y., S. U. Javed, S. Keihanian, S. Abudayyeh and A. R. Opekun (2010). Dual proton pump inhibitor plus amoxicillin as an empiric anti-H. pylori therapy: studies from the United States. J Gastroenterol 45(8): 816-820.

He, L., T. Deng and H. Luo (2015). Meta-analysis of sequential, concomitant and hybrid therapy for Helicobacter pylori eradication. Intern Med 54(7): 703-710.

Hsu, P.-I., D.-C. Wu, J.-Y. Wu and D. Y. Graham (2011). Modified sequential Helicobacter pylori therapy: proton pump inhibitor and amoxicillin for 14 days with clarithromycin and metronidazole added as a quadruple (hybrid) therapy for the final 7 days. Helicobacter 16(2): 139-145.

Kale-Pradhan, P. B., A. Mihaescu and S. M. Wilhelm (2015). Fluoroquinolone Sequential Therapy for Helicobacter pylori: A Meta-analysis. Pharmacotherapy 35(8): 719-730.

Kim, S. Y., S. W. Jung, J. H. Kim, J. S. Koo, H. J. Yim, J. J. Park, H. J. Chun, S. W. Lee and J. H. Choi (2012). Effectiveness of three times daily lansoprazole/amoxicillin dual therapy for Helicobacter pylori infection in Korea. Br J Clin Pharmacol 73(1): 140-143.

Li, B.-Z., D. E. Threapleton, J.-Y. Wang, J.-M. Xu, J.-Q. Yuan, C. Zhang, P. Li, Q.-L. Ye, B. Guo and C. J. b. Mao (2015). Comparative effectiveness and tolerance of treatments for Helicobacter pylori: systematic review and network meta-analysis. 351: h4052.

Liou, J. M., C. C. Chen, M. J. Chen, C. C. Chen, C. Y. Chang, Y. J. Fang, J. Y. Lee, S. J. Hsu, J. C. Luo, W. H. Chang, Y. C. Hsu, C. H. Tseng, P. H. Tseng, H. P. Wang, U. C. Yang, C. T. Shun, J. T. Lin, Y. C. Lee and M. S. Wu (2013). Sequential versus triple therapy for the first-line treatment of Helicobacter pylori: a multicentre, open-label, randomised trial. Lancet 381(9862): 205-213.

Lotfipour, F., H. Valizadeh, M. Milani, N. Bahrami and R. Ghotaslou (2016). Study of Antimicrobial Effects of Clarithromycin Loaded PLGA Nanoparticles against Clinical Strains of Helicobacter pylori. Drug Res (Stuttg). 66(1): 41-45.

Luther, J., P. D. Higgins, P. S. Schoenfeld, P. Moayyedi, N. Vakil and W. D. Chey (2010). Empiric quadruple vs. triple therapy for primary treatment of Helicobacter pylori infection: Systematic review and meta-analysis of efficacy and tolerability. Am J Gastroenterol 105(1): 65-73.

Malfertheiner, P., F. Megraud, C. A. O'Morain, J. Atherton, A. T. Axon, F. Bazzoli, G. F. Gensini, J. P. Gisbert, D. Y. Graham, T. Rokkas, E. M. El-Omar and E. J. Kuipers (2012). Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. Gut 61(5): 646-664.

Marshall, B. J. and J. R. Warren (1984). Unidentified curved bacilli in the stomach of

patients with gastritis and peptic ulceration. Lancet 1(8390): 1311-1315.

McColl, K. E. (2010). Clinical practice. Helicobacter pylori infection. N Engl J Med 362(17): 1597-1604.

Mentis, A., P. Lehours and F. Mégraud (2015). Epidemiology and Diagnosis of Helicobacter pylori infection. Helicobacter 20 Suppl 1: 1-7.

Miehlke, S., C. Kirsch, W. Schneider-Brachert, C. Haferland, M. Neumeyer, E. Bästlein, J. Papke, E. Jacobs, M. Vieth, M. Stolte, N. Lehn and E. Bayerdörffer (2003). A prospective, randomized study of quadruple therapy and high-dose dual therapy for treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin. Helicobacter 8(4): 310-319.

Pan-In, P., W. Banlunara, N. Chaichanawongsaroj and S. Wanichwecharungruang (2014). Ethyl cellulose nanoparticles: clarithomycin encapsulation and eradication of H. pylori. Carbohydr Polym. 109: 22-27.

Peedikayil, M. C., F. I. Alsohaibani and A. H. Alkhenizan (2014). Levofloxacin-based first-line therapy versus standard first-line therapy for Helicobacter pylori eradication: meta-analysis of randomized controlled trials. PLoS One 9(1): e85620.

Safarov, T., B. Kiran, M. Bagirova, A. M. Allahverdiyev and E. S. Abamor (2019). An overview of nanotechnology-based treatment approaches against Helicobacter Pylori. Expert Rev Anti Infect Ther 17(10): 829-840.

Safavi, M., R. Sabourian and A. Foroumadi (2016). Treatment of Helicobacter pylori infection: Current and future insights. World J Clin Cases 4(1): 5-19.

Sgouras, D. N., T. T. H. Trang and Y. Yamaoka (2015). Pathogenesis of Helicobacter pylori Infection. Helicobacter 1(01): 8-16.

S**hirai, N., M. Sugimoto, C. Kodaira, M. Nishino, M. Ikuma, M. Kajimura, K. Ohashi, T. Ishizaki, A. Hishida and T. Furuta (2007).** Dual therapy with high doses of rabeprazole and amoxicillin versus triple therapy with rabeprazole, amoxicillin, and metronidazole as a rescue regimen for Helicobacter pylori infection after the standard triple therapy. Eur J Clin Pharmacol 63(8): 743-749.

Tai, W. C., C. M. Liang, C. M. Kuo, P. Y. Huang, C. K. Wu, S. C. Yang, Y. H. Kuo, M. T. Lin, C. H. Lee, C. N. Hsu, K. L. Wu, T. H. Hu and S. K. Chuah (2019). A 14 day esomeprazole- and amoxicillin-containing high-dose dual therapy regimen achieves a high eradication rate as first-line anti-Helicobacter pylori treatment in Taiwan: a prospective randomized trial. J Antimicrob Chemother 74(6): 1718-1724.

Treiber, G., S. Ammon, E. Schneider and U. Klotz (1998). Amoxicillin/metronidazole/omeprazole/clarithromycin: a new, short quadruple therapy for Helicobacter pylori eradication. Helicobacter 3(1): 54-58.

Umamaheshwari, R. B. and N. K. Jain (2003). Receptor mediated targeting of lectin conjugated gliadin nanoparticles in the treatment of Helicobacter pylori. J Drug Target 11(7): 415-423

Unge, P., A. Gad, H. Gnarpe and J. Olsson (1989). Does omeprazole improve antimicrobial therapy directed towards gastric Campylobacter pylori in patients with antral gastritis? A pilot study. Scand J Gastroenterol Suppl 167: 49-54.

Venerito, M., T. Krieger, T. Ecker, G. Leandro and P. Malfertheiner (2013). Meta-analysis of bismuth quadruple therapy versus clarithromycin triple therapy for empiric primary treatment of

Helicobacter pylori infection. Digestion 88(1): 33-45.

Villoria, A. (2008). [Acid-related diseases: are higher doses of proton pump inhibitors more effective in the treatment of Helicobacter pylori infection?]. Gastroenterol Hepatol 31(8): 546-547.

Wang, B., Y. H. Wang, Z. F. Lv, H. F. Xiong, H. Wang, Y. Yang and Y. Xie (2015). Review: efficacy and safety of hybrid therapy for Helicobacter pylori infection: a systematic review and meta-analysis. Helicobacter 20(2): 79-88.

Yang, J. C., C. J. Lin, H. L. Wang, J. D. Chen, J. Y. Kao, C. T. Shun, C. W. Lu, B. R. Lin, M. J. Shieh, M. C. Chang, Y. T. Chang, S. C. Wei, L. C. Lin, W. C. Yeh, J. S. Kuo, C. C. Tung, Y. L. Leong, T. H. Wang and J. M. Wong (2015). High-dose dual therapy is superior to standard first-line or rescue therapy for Helicobacter pylori infection. Clin Gastroenterol Hepatol 13(5): 895-905.e895.

Yang, J. C., C. W. Lu and C. J. Lin (2014). Treatment of Helicobacter pylori infection: current status and future concepts. World J Gastroenterol 20(18): 5283-5293.

Yang, J., Y. Zhang, L. Fan, Y. J. Zhu, T. Y. Wang, X. W. Wang, D. F. Chen and C. H. Lan (2019). Eradication Efficacy of Modified Dual Therapy Compared with Bismuth-Containing Quadruple Therapy as a First-Line Treatment of Helicobacter pylori. Am J Gastroenterol 114(3): 437-445.

Zullo, A., L. Ridola, V. D. Francesco, L. Gatta, C. Hassan, D. Alvaro, A. Bellesia, G. de Nucci and G. Manes (2015). High-dose esomeprazole and amoxicillin dual therapy for first-line Helicobacter pylori eradication: a proof of concept study. Ann Gastroenterol 28(4): 448-451.

علاج عدوى بكتيريا الهليكوباكتر بيلوري

قسم الممارسة الصيدلية- كليه الصيدلة- جامعه الزقازيق- مصر

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ترتبط بكتيريا الهليكوباكتر بيلوري ارتباطًا وثيقًا بطائفة واسعة من أمراض الجهاز الهضمي ، مثل قرحة الأمعاء أو المعدة وكذلك سرطان المعدة. في الوقت الحالي ، يتم علاج بكتيريا الهيلكوباكتر بيلوري باستخدام مجموعة من المضادات الحيوية في نفس الوقت مثل الأموكسيسيلين وميترونيدازول وكلاريثروميسين ومثبطات مضخة البروتون. يستخدم العلاج الثلاثي بشكل كبير كخط علاج أول ويتكون من المضاد الحيوي الأموكسيسيلين أو الميترونيدازول بالإضافة الى المضاد الحيوي الكلاريثروميسين ومثبط مضخة البروتون. ولكن للأسف، فإن مقاومة بكتيريا الهيليكوباكتر بيلوري للكلاريثروميسين والميترونيدازول أثرت سلبا على فعالية العلاج الثلاثي وتسببت في تقليل معدلات الشفاء الى مستويات غير مقبولة. تم اقتراح العديد من أنظمة العلاج لتحل محل العلاج الثلاثي مثل العلاج الرباعي الذي يحتوي على البزموت، والعلاج المتسلسل ، والعلاج المصاحب ، والعلاج الهجين والعلاج القائم على الليفوفلوكساسين. يتم استخدام العديد من الأنظمة كعلاج إنقاذي استنادًا إلى ما تم استخدامه سابقًا في العلاج الأولي مثل العلاج الرباعي والعلاج الثلاثي الذي يحتوي على الريفابوتين والعلاجات القائمة على الليفوفلوكساسين. ولكن بسبب مقاومة البكتيريا للمضادات الحيوية والتي يمكن أن تحد من قابلية تطبيق هذه الأنظمة ولأن مقاومة البكتيريا للأموكسيسيلين منخفضة جدًا ، فقد تم اقتراح استخدام العلاج الثنائي والذي يتكون من جرعة عالية من الأموكسيسيلين و مثبط مضخة البروتون كخط علاج أولي و فعال وآمن أو كعلاج إنقاذي.