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REVIEW

Treatment of *Helicobacter pylori* infection: Current and future insights

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Abstract

Helicobacter pylori (*H. pylori*) is an important major cause of peptic ulcer disease and gastric malignancies such as mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma worldwide. *H. pylori* treatment still remains a challenge, since many determinants for successful therapy are involved such as individual primary or secondary antibiotics resistance, mucosal drug concentration, patient compliance, side-effect profile and cost. While no new drug has been developed, current therapy still relies on different mixture of known antibiotics and anti-secretory agents. A standard triple therapy consisting of two antibiotics and a proton-pump inhibitor proposed as the first-line regimen. Bismuth-containing quadruple treatment, sequential treatment or a non-bismuth quadruple treatment (concomitant) are also an alternative therapy. Levofloxacin containing triple treatment are recommended as rescue treatment for infection of *H. pylori* after defeat of first-line therapy. The rapid acquisition of antibiotic resistance reduces the effectiveness of any regimens involving these remedies. Therefore, adding probiotic to the medications, developing anti-*H. pylori* photodynamic or phytomedicine therapy, and achieving a successful *H. pylori* vaccine may have the promising to present synergistic or additive consequence against *H. pylori*, because each of them exert different effects.

Key words: *Helicobacter pylori*; Therapeutic regimens; Probiotics; Photodynamic; Phytomedicine

Core tip: This article aimed to provides a review of

current therapeutic options and the efficacy of some recent regiments. Also, essential need to new therapeutic agents such as probiotics, phytomedicine, photodynamic therapy and protective vaccine are described.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is spiral in shape with a flagellum, gram-negative, micro aerophilic bacterium which colonizes in the human gastric mucosa, and the infection may last for decades. It is thought *H. pylori* infection to be the most common bacterial infection, and influence approximately 50%-75% of the population all over the world[1]. *H. pylori* is the main reason for the upper gastrointestinal diseases, including peptic ulcer disease (gastric and duodenal), chronic gastritis, gastric cancer and gastric mucosal-associated lymphoid tissue lymphoma[2].

Along with upper gastrointestinal tract problems, *H. pylori* caused chronic and low-grade inflammation in the gastric mucosa that could lead to some metabolic disorders. *H. pylori* infection may be correlated with insulin resistance, increased total and low density lipoprotein cholesterol and decrease of high density lipoprotein in infected peoples[3]. Also, *H. pylori* has a critical role in the other extragastric diseases such as chronic urticaria[4].

Although a variety of treatment regimens have been proposed for the eradication of *H. pylori* in order to achieve more effective eradication resistance[5]. In recent years, regimens that utilize proton-pump inhibitors (PPIs) in combination with several antibiotics such as amoxicillin plus clarithromycin or metronidazole have been considered as the first-line treatment for *H. pylori* infection[6]. PPI-based triple therapy has been described to be losing its efficacy for *H. pylori*, with eradication cure rates as low as 50% to 70%, due to high rates of antibiotic resistance, high rates of antibiotic-associated side effects and low compliance[5]. Decreased eradication rate has led to the development and use of new first-line treatment[4,7]. In some countries, new first-line treatments are not accepted because of a lack of national validation studies and a lack of studies of clarithromycin resistance[7].

The Maastricht Ⅳ/Florence Consensus Report recommended the bismuth-containing quadruple therapy as an alternative for first-line empirical treatment in areas with the clarithromycin resistance over 15%-20%. If this regimen is not available sequential therapy or a non-bismuth quadruple therapy (the so-called "concomitant" treatment) is recommended[8]. After failure of a PPI-clarithromycin-containing treatment for *H. pylori* infection, either a bismuth-containing quadruple therapy or levofloxacin-based triple therapy is recommended as second-line treatment or rescue therapy[8,9].

In patients with penicillin allergy, for a first-line treatment, the bismuth containing quadruple therapy appear to be a better choice than a PPI-clarithromycin-metronidazole combination regimen[10]. As a rescue regimen, a levofloxacin containing regimen together with a clarithromycin and PPI represents a second-line treatment in the presence of penicillin allergy[8,10].

The Maastricht Ⅳ/Florence Consensus Report recommended the use of antimicrobial susceptibility testing (culture-guided therapy), after the failure of second-line treatment[8]. However, culture-guided third-line therapy has been advised, but if antimicrobial sensitivity data are not available, an empirical triple or quadruple therapy can be recommended as third-line regimens[11].

As such, during the last 30 years that the *H. pylori* was identified, there have been numerous therapeutic regimens suggested but a unique most effective and least harmful therapeutic regimen to cure *H. pylori* infection in all reported colonized individuals is still lacking[12].

THERAPEUTIC OPTIONS

Antimicrobial agents

Despite the number of studies, the optimal treatment for *H. pylori* infection has not been found and routine clinical treatments are usually triple or quadruple antibiotic therapies[13].

Prevalence of antibiotic resistance to various antimicrobials varies in different geographical regions, and is associated with the consumption of antibiotics in those areas[14]. The most commonly used antibiotics are imidazole (metronidazole or tinidazol), macrolide (clarithromycin or azithromycin), tetracycline, amoxicillin, rifabutin and furazolidon[9,15]. Bismuth, a heavy metal with anti-*H. pylori* activity is used in bismuth-based quadruple therapy and seems almost totally maintains high eradication rates, independent of antibiotic resistance[16,17].

A survey of antibiotic resistance to the four commonly used antibiotics against *H. pylori* in Vietnam from July 2012 to January 2014 showed that 42.4% were resistant to clarithromycin, 41.3% to levofloxacin, 76.1% to metronidazole, and 1.1% to amoxicillin[18].

A cross-sectional study with collection of gastric biopsies in the United States from 2009 through 2013 showed the prevalence of *H. pylori* resistance to levofloxacin was 31.3%, to metronidazole it was 20.3%, to clarithromycin it was 16.4%, and to tetracycline it was 0.8%. No isolate exhibited amoxicillin resistance, but clarithromycin resistance increased from 9.1% in 2009-2010 to 24.2% in 2011-2013[19].

Results on antibiotic resistance in two time, the first time period (2000) and the second period (2010)

in Greece revealed during the first time period 30% and 0% of patients were infected with clarithromycin or quinolone-resistant strains but, in the second time period (2010), the resistance rate to clarythromycin or quinolone increased to 42% and 5.3%, respectively[20].

A systematic review of literatures on *H. pylori* antibiotic resistance carried out in Iran within the time span of 1997 to 2013. The incidance of *H. pylori* resistance to various antibiotics, including metronidazole, clarithromycin, furazolidone, amoxicillin, tetracycline, ciprofloxacin, levofloxacin was 61.6%, 22.4%, 21.6%, 16.0%, 12.2%, 21.0% and 5.3%, respectively[21]. Compared the results from different countries showed prevalence of *H. pylori* resistance to various antibiotics is not the same and may be changed in time even in the same population.

Overwhelming evidence indicates that in order to determine an appropriate antibiotic in drug regimen against *H. pylori* infections, information on antibiotic susceptibility of the bacterium within different geographical areas of world is required.

Antisecretory agents-PPI

H. pylori treatment involves combination of antimicrobial and anti-secretory agents for 7 to 14 d. PPIs inhibit the parietal cell H^+/K^+ adenosine triphosphatase (ATPase), the enzyme of canalicular membrane of gastric parietal cells which is responsible for the last step in gastric acid secretion[22,23]. Inhibition of this enzyme is more efficient than H2-receptor antagonists in suppressing gastric acid secretion[24].

At low pH, gastric PPIs as acid-activated pro drug transform to a spiro intermediate of dihydrobenzimidazole, then undergoes aromatization to a sulfenic acid followed by dehydration to form a tetracyclic sulfonamide[25]. PPIs bind to different cysteines in the α subunit of the H^+/K^+ ATPase and inhibits the enzyme[26,27].

PPI with anti-secretory effect declines the acid production from stomach, which allows the tissues damaged by the infection to heal. PPI can also make acid-labile antibiotics more stable by elevation of the gastric pH, and also may alter luminal concentrations of antibiotics by transporting of antibiotics from plasma to gastric juices and elevating the success rate of eradication[28,29].

The differences in pharmacokinetics for example elimination half-life, bioavailability and metabolism of currently available PPIs may translate into differences in clinical outcomes[30]. All PPIs have good oral bioavailability and all PPIs except tenatoprazole undergo hepatic metabolism *via* the CYP isoforms CYP2C19 and CYP3A4, therefore with the elimination half-lives ranging from 1 to 1.5 h have the short elimination rate[31,22]. Genetic polymorphism in CYP2C19 plays an important role in the metabolism of individual PPIs to different amounts, thereby affecting therapeutic effectiveness[32].

Several studies have produced conflicting data on eradication rates of *H. pylori* among CYP2C19 genotypes taking PPI based regimens[33]. Some examples of the CYP2C19 pathway's relative impact on the PPI metabolism have been demonstrated. The lansoprazole-based or omeprazole-based triple therapies were affected by CYP2C19 genotype status, whereas esomeprazole-based or rabeprazole-based triple therapies were not[30,33,34]. The dosage and duration of treatment of PPIs for adults correspond to those that are able to suppress gastric acid secretion. Long-term omeprazole therapy in *H. pylori* positive patients induced changes in mucosal inflammation and glandular atrophy[35]. Hyper gastrinemia induced by PPI administration and corpus atrophic gastritis in patients with *H. pylori* infection might promote the development of gastric cancer[36].

THERAPEUTIC REGIMENS

Dual therapy

Dual treatments including a PPI with either clarithromycin or amoxicillin or metronidazole were popular during the previous decades. Dual therapy is now obsolete due to lack of efficacy of clarithromycin and metronidazole[37]. On the contrary, worldwide primary and secondary resistance to amoxicillin of *H. pylori* is generally low and rare respectively, although it is a usual medication in standard triple therapy and therefore it is suitable for use in the dual therapy of *H. pylori* infection[9].

Amoxicillin is effective at high (> 5.5) pH environments. According to some controversial data, PPI in standard doses wouldn't be able in rapid metabolizers to achieved enough pH inhibition for effective antibiotic activity in mucus of gastric, determining lower eradication rates after therapy with regimens containing standard dose of PPI[38,39].

Several studies assumed that there is direct and indirect demonstration which stated high-dose PPI, above the common standards, could ameliorate *H. pylori* treatment cure rates. The general idea in the back of high-dose PPI plus amoxicillin treatment is to overcoming resistance by altering the environment in which dormant *H. pylori* settled, thus inciting the bacteria to get in the replicative state and become sensitive to the antibiotics[40,41]. In spite of the advantage of the low resistance rate to amoxicillin and theoretical advantages of high-dose PPI, it has been shown that the efficacy of high dose dual treatment is vary in different reports[9].

A number of recently different regiments for the *H. pylori* treatments are described in Table 1.

An open-label, prospective, single-center pilot study evaluated the effectiveness of amoxicillin plus high-dose PPI dual therapy for *H. pylori* eradication. The intention-to-treat (ITT) cure was achieved in 72.2% and in per protocol (PP) 74.2%, respectively[42].

In an open-labelled and single-center prospective study, the overall success at eradication of *H. pylori* by two planned consecutive rescue therapies was tested.

Table 1 Numbers of different regimens for *Helicobacter pylori* infection treatments

Regimens	Patients (*n*)	Eradication rate	Conclusion	Ref.
High dose dual therapies				
Amoxicillin 750 mg and esomeprazole 40 mg every 8 h for 14 d	36	The ITT cure was achieved in 72.2% (95%CI: 56%-84%) and PP cure achieved in 74.2% (95%CI: 56%-87%)	However, the regimen was not sufficient to eradicate 90% *H. pylori* but, the result was positive in that dual therapy with the doses tested here was at least as successful as empiric triple therapy with a PPI, amoxicillin, and clarithromycin	[42]
Amoxicillin 1 g t.d.s. and rabeprazole 20 mg t.d.s. for 2 wk	149	Eradication success PP and ITT was 75.4% (95%CI: 68.3%-82.4%) and 71.8% (95%CI: 64.6%-79.0%), respectively.	Eradication success of 75% on PP analysis as a first rescue therapy including 2-wk high dose PPI-amoxicillin dual therapy was achieved. Following these patients by a second rescue therapy with PPI triple therapy were highly successful in achieving eradication rate (> 90%) in *H. pylori* treatment failures	[43]
Amoxicillin 1 g b.i.d. and omeprazole 20 mg q.i.d. for 14 d	74	Eradication rate of 81.1% in the dual therapy group *vs* 63.8% in the triple therapy group was achieved	Dual therapy is more effective, cost-effective and is less risky in terms of side effects compared to standard triple therapy in patients with dyspepsia	[44]
Amoxicillin 1 g and dexlansoprazole 120 mg each twice a day at approximately 12-h intervals for 14 d	13	PP and ITT treatment success were both 53.8% (95%CI: 25%-80%)	However compliance was 100% and reported side effects were mild and none interrupted therapy but dexlansoprazole, despite being administered at high dose, failed to achieve an intragastric milieu in treatment-native patients	[41]
Amoxicillin 750 mg and rabeprazole 20 mg, 4 times/d for 14 d	150	In the ITT analysis, *H. pylori* was eradicated in 95.3% of treatment-naïve patients (95%CI: 91.9-98.8%) and in 89.3% of treatment-experienced patients (95%CI: 80.9%-97.6%)	High-dose dual therapy is superior to standard regimens as empirical first-line or rescue therapy for *H. pylori* infection with similar safety profiles and tolerability	[45]
Triple therapies				
Amoxicillin 1 g and metronidazole 500 mg both three times a day plus esomeprazole 40 mg twice a day	136	Eradicationrates were 82.4% (95%CI: 74.7%-88.1%) by ITT analysis and 88.2% (95%CI: 81.2%-92.8) by PP analysis.	Cure rates of the combination of esomeprazole, amoxicillin and metronidazole are high and the treatment was well tolerated	[47]
Amoxicillin 1 g twice daily, levofloxacin, 500 mg, once daily and esomeprazole 20 mg twice daily for 7 d	345	ITT analysis eradication rates 78.1% (95%CI: 69.4%-85.3%), 78.3% (95%CI: 69.6%-85.4%), and 82.8% (95%CI: 74.6%-89.1%) for tripletherapy, standard sequential therapyand levofloxacin-containing sequential therapyre spectively and PP analysis eradication rates were 80.9% (95%CI: 72.3%-87.8%), 82.6% (95%CI: 74.1%-89.2%), and 86.5% (95%CI: 78.7%-92.2%), respectively, for the three therapies	Standard sequential therapy and 7-d levofloxacin triple therapy produced unacceptably therapeutic efficacy in China. Only levofloxacin-containing sequential therapy achieved borderline acceptable result	[48]
Amoxicillin 50 mg/kg per day, q.d.s., nifuratel 30 mg/kg per day, q.d.s. and bismuthsubcitrate 8 mg/kg per day, q.d.s. for 10 d	73	PP and ITT treatment success were both 86% (95%CI: 76.6%-93.2%)	The combination of nifuratel, bismuth subcitrate, and amoxicillin was a tolerable and effective regimen for *H. pylori* eradication	[49]
Amoxicillin 1 g, clarithromycin 500 mg and rabeprazole 20 mg all twice daily for 10 d in comparison with half dose	115	Eradication rates were 77.6% (95%CI: 66.9%-88.3%) in the standard dose *vs* half dose 77.2% (95%CI: 66.3%-88.1%) on ITT analysis. PP eradication rates were 78.9% (95%CI: 68.4%-85.9%) and 81.5% (95%CI: 71.1%-91.8%) respectively	A half-dose 10-d regimen is equally effective but cheaper and better tolerated than its standard-dose regimen	[50]
Amoxicillin 1 g, clarithromycin 500 mg plus either omeprazole 20 mg or esomeprazole 40 mg twice daily for 1 wk	200	For patients classified as homologous extensive metabolizers, the PP *H. pylori* eradication rate was significantly higher in the esomeprazole group than in the omeprazole group (93% *vs* 76%, $P < 0.05$)	Only for extensive metabolizers esomeprazole 40 mg twice daily for triple therapy improve the *H. pylori* eradication compared to omeprazole-based therapy	[51]
Amoxicillin 1 g, clarithromycin 500 mg and lansoprazole 30 mg, all taken twice a day for 14 d	1463	Comparing effectiveness of standard 14-d regimen of triple therapy with that of the four-drug regimens given concomitantly or sequentially therapy showed the eradication rate with standard therapy was 82.2%, and concomitant therapy (73.6%) and finally by sequential therapy (76.5%)	Neither four-drug regimen was significantly better than standard triple therapy in any of the seven sites of Latin America	[52]

Quadruple therapies				
Tetracycline 500 mg q.d.s., levofloxacin 500 mg o.d. esomeprazole 40 mg b.d and tripotassium dicitratobismuthate 120 mg q.d.s.	24	The eradication rates according to ITT and PP analysis were both 95.8% (95%CI: 87.8%-103.8%)	The 10-d quadruple therapy achieves a very high eradication rate for *H. pylori* infection after failure of sequential therapy	[56]
Amoxicillin 1 g b.d., esomeprazole 40 mg b.d., levofloxacin 500 mg o.d. and bismuth 240 mg b.d. for 14 d	200	PP and ITT eradication rates were 91.1% (95%CI: 87%-95%) and 90% (95%CI: 86%-94%)	14-d bismuth - and levofloxacin-containing quadruple therapy is effective second-line therapy in patients whose sequential or concomitant therapies have failed	[10]
lansoprazole (30 mg twice daily) and bismuth potassium citrate (220 mg twice daily), along with 500 mg tetracycline and 400 mg metronidazole 4 times daily (LBTM), 500 mg tetracycline and 100 mg furazolidone 3 times daily (LBTF), 1000 mg amoxicillin 3 times and 500 mg tetracycline 4 times daily (LBAT), or 1000 mg amoxicillin and 100 mg furazolidone 3 times daily (LBAF)	424	PP rates of eradication were greater than 90%for all regimens: 93.1% for LBTM (95%CI: 88.1%-98.0%), 96.1% for LBTF (95%CI: 92.4%-99.8%), 94.6% for LBAT (95%CI: 90.0%-99.2%), and 99.0% for LBAF (95%CI: 97.0%-100%). The ITT response rates were 87.9% for LBTM (95%CI: 81.7%-94.0%), 91.7% for LBTF (95%CI: 87.1%-96.3%), 83.8% for LBAT (95%CI: 76.8%-90.9%), and 95.2% for LBAF (95%CI: 91.1%-99.3%)	Four bismuth-containing quadruple therapies achieved greater than 90% eradication of *H. pylori* in patients who did not respond to previous treatment, including patients with metronidazole resistance	[57]
Amoxycillin 1000 mg, ranitidine 300 mg and bismuth subcitrate 240 mg b.d., with either furazolidone 200 mg b.d. (RABF), or metronidazole 500 mg b.d. (RABM) for 2 wk	106	ITT eradication rates were 75% and 55% (P = 0.03) and per protocol eradication rates were 82% and 56% (P = 0.006) in the RABF and RABM groups, respectively	Quadruple therapy containing furazolidone, instead of metronidazole, results in a significantly higher *H. pylori* eradication rate in Iranian duodenal ulcer patients	[60]
Tetracycline hydrochloride 375 mg, metronidazole 375 mg and bismuth subcitrate potassium 420 mg q.d.s., and omeprazole 20 mg b.d. for 10 d	64	Eradication rates ranged from 93.2% to 93.8% in the ITT population, and from 94.7% to 95.0% in the PP population	A quadruple regimen of bismuth, metronidazole and tetracycline plus omeprazole produces a high eradication rate in subjects previously failing *H. pylori* eradication regimens	[61]
Tetracycline 500 mg q.d.s., esomeprazole 40 mg b.d. and bismuth subcitrate 300 mg q.d.s. plus either levofloxacin 500 mg once daily or metronidazole 500 mg q.d.s. for 10 d	150	ITT analysis revealed that both groups showed similar eradication rates. levofloxacin group, 78.9% (95%CI: 69.7%-88.1%) and metronidazole group, 79.7% (95%CI: 70.5%-88.7%)	The 10-d bismuth quadruple therapies with high-dose metronidazole or levofloxacin were effective even in areas with high resistance. These two therapies were equally safe and tolerated	[62]
Amoxicillin 1 gram, clarithromycin 500 mg, metronidazole 500 mg esomeprazole 40 mg given twice a day for 10 d	232	ITT analysis demonstrated similar eradication rates for sequential 92.3%; (95%CI: 87.5%-97.1%) and concomitant therapy 93.0% (95%CI: 88.3%-97.7%). PP eradication results were similar for sequential 93.1%; (95%CI: 90.7%-95.5%) and concomitant therapy 93.0% (95%CI: 88.3%-97.7%)	Sequential or concomitant therapy with a PPI, amoxicillin, clarithromycin, and an imidazole agent are equally effective and safe for eradication of *H. pylori* infection. Concomitant therapy may be more suitable for patients with dual resistance to antibiotics.	[67]
Amoxicillin 1 g and omeprazole 40 mg twice daily for 14 d, clarithromycin 500 mg and nitroimidazole 500 mg twice daily (for the final 7 d) Concomitant therapy: Same 4 drugs taken concurrently, twice daily for 14 d	343	In PP analysis, rates of eradication for hybrid and concomitant therapies were 92% and 96.1%, respectively. In ITT analysis, rates were 90% and 91.7% respectively	Optimized non bismuth quadruple hybrid and concomitant therapies cured more than 90% of patients with *H. pylori* infections in areas of high clarithromycin and metronidazole resistance	[68]
Sequential therapy				
Amoxycillin 1 g b.d. plus omeprazole 20 mg b.d. for the first 5 d, followed by clarithromycin 500 mg b.d. tinidazole 500 mg b.d. and omeprazole 20 mg b.d., for the remaining 5 d	52	The eradication rate was 98% (95%CI: 94.3%-100%) with ITT analysis	The 5 plus 5 d therapy as sequential therapy achieved sufficient eradication rate	[70]
Amoxicillin plus omeprazole for 5 d, followed by omeprazole plus clarithromycin plus tinidazole for another 5 d	78	*H. pylori* eradication was achieved in 36 children receiving sequential treatment 97.3% (95%CI: 86.2%-99.5%) and 28 children receiving triple therapy 75.7% (95%CI: 59.8%-86.7%)	10-d sequential treatment achieves a higher eradication rate than standard triple therapy	[71]

Amoxicillin 1000 mg b.i.d. and pantoprazole 40 mg b.i.d. for the first 5 d, followed by pantoprazole 40 mg b.i.d., clarithromycin 500 mg b.i.d. and metronidazole 500 mg b.i.d. in the remaining 5 d	175	Comparison of standard triple therapy with a sequential schema represented two treatment groups did not differ with regard to *H. pylori* eradication rate for both ITT population (63.9% *vs* 71.4% for standard and sequential therapy respectively, $P = 0.278$) and per protocol population (65.9% *vs* 74.1% for standard and sequential therapy respectively, $P = 0.248$)	In the present study, the two treatments resulted in similar rates of eradication, and both treatments were relatively ineffective	[72]
Amoxicillin 1 g and lansoprazole 30 mg for the first 7 d or 5 d, followed by lansoprazole 30 mg, clarithromycin 500 mg, and metronidazole 500 mg for another 7 d or 5 d	900	The eradication rate was 90.7% (95%CI: 87.4%-94.0%) in the 14 d, 87.0% (95%CI: 83.2-90.8) in the 10 d group, and 82.3% (95%CI: 78.0-86.6) in the triple therapy 14-d group	This study support to the use of sequential treatment as the standard first-line treatment for *H. pylori* infection	[76]
Amoxicillin 1 g plus omeprazole 20 mg for the first 5 d, followed by 20 mg of omeprazole, 500 mg of clarithromycin, 500 mg of metronidazole, for the remaining 5 d	158	Comparing 10 d-sequential therapy with PPI-based triple therapy revealed eradication rate for 10 d-sequential therapy was 77.9% (60/77) by ITT and 85.7% (60/70) by PP analysis, but eradication rates in PPI-based triple therapy were 71.6% (58/81) and 76.6% (58/76) by ITT and PP analysis, respectively	The 10-d sequential therapy regimen failed to achieve significantly higher eradication rates than PPI-based triple therapy	[77]
Amoxicillin 1 g b.d. plus PPI b.d. for the first 5 d, followed by a PPI b.d. clarithromycin 500 mg b.d. and metronidazole 500 mg b.d. for the next 5 d	139	The ITT eradication rate was 84.2% (95%CI: 77%-90%) and the PP cure rate 90.7% (95%CI: 84%-95%)	Sequential treatment seems highly effective for eradicating *H. pylori*	[75]
Amoxicillin 1 g plus omeprazole 20 mg followed by 5 d omeprazole 20 mg, clarithromycin 500 mg and tinidazole 500 mg or followed by 5 d omeprazole 20 mg, levofloxacin 250 mg and tinidazole 500 mg or followed by 5 d omeprazole 20 mg, levofloxacin 500 mg and tinidazole 500 mg twice daily	375	Eradication rates in the ITT analyses were 80.8% (95%CI: 72.8%-87.3%) with clarithromycin sequential therapy, 96.0% (95%CI: 90.9%-98.7%) with levofloxacin-250 sequential therapy, and 96.8% (95%CI: 92.0%-99.1%) with levofloxacin-500 sequential therapy	Levofloxacin-containing sequential therapy is more effective, equally safe and cost-saving compared to a clarithromycin-containing sequential therapy	[79]

ITT: Intention-to-treat; CI: Confidence interval; PP: Per protocol; *H. pylori*: *Helicobacter pylori*; PPI: Proton-pump inhibitor; t.d.s.: Ter die sum endum; b.i.d.: Bis in die; q.i.d.: Quater in die; q.d.s.: Quater die sum endum; b.d.: Twice daily.

The first rescue therapy including high-dose PPI dual therapy with amoxicillin or rabeprazole for 2 wk was highly tolerable and the PP and ITT success rate was 75.4% and 71.8% which was less than the second rescue therapy with amoxicillin and rabeprazole and levofloxacin[43].

In the study of Ince *et al*[44], dual therapy containing high-dose PPI (omeprazole) and amoxicillin was more cost-effective, successful and safe compared to standard triple therapy in patients with dyspepsia.

A prospective, open-label pilot study of *H. pylori* eradication revealed that 2-wk dual regimen of twice a day high-dose long acting lansoprazole plus amoxicillin treatment success was not acceptable[41].

Based on a large-scale multihospital trial study, high-dose dual therapy containing rabeprazole and amoxicillin is superior to standard regimens as sequential therapy or triple therapy for *H. pylori* infection, with similar safety profiles and tolerability[45].

If the theory, that consistently high intra gastric pH is required to reliably achieve more than 90% *H. pylori* eradication, the some mentioned studies results do not confirmed this theory. It seems many regiments were not sufficient to eradicate *H. pylori*.

Triple therapy

Triple *H. pylori* therapy comprising a PPI, amoxicillin and clarithromycin is used as the firstline therapy. Clarithromycin or metronidazole resistance has been related to a reduction of success rates, making it a significant reason leading to treatment failure of *H. pylori*[46]. The other factors such as rapid metabolism of PPIs by CYP2C19, poor patient compliance, high acidity of stomach and bacterial load seem to be the main causes of eradication failure[33,42]. One hundred and thirty-six patients enrolled in the study of 10-d triple therapy comprising esomeprazole plus amoxicillin and metronidazole. Cure rates of patients were 82.4% by ITT analysis and 88.2% by PP analysis[47].

Based on several available clinical trials, it seems that a quinolone-based triple therapy will be operative as the first-line therapy in *H. pylori* infection[11]. The use of levofloxacin as an alternative of clarithromycin in triple and sequential therapies has been investigated by Qian *et al*[48] 7-d levofloxacin based triple therapy (levofloxacin, amoxicillin, esomeprazole) generated unsatisfactorily therapeutic efficiency, only levofloxacin-containing sequential therapy reached adequate outcome.

The effectiveness of a triple bismuth-consisting regimen along with amoxicillin and nifuratel used for eradication of *H. pylori* in patients were evaluated. The results of this study revealed the therapy containing bismuth subcitrate, amoxicillin and nifuratel yielded a success rate of 86% in childhood[49].

Standard dose (amoxicillin 1 g, clarithromycin 500 mg and rabeprazole 20 mg, all two times per day for 10 d) *vs* half dose regimen in therapy of *H. pylori* infected subjects was equally efficient and better tolerated[50].

The results of triple therapy containing clarithromycin, amoxicillin and esomeprazole 40 mg or omeprazole 20 mg in different genotypes of CYP2C19 showed that esomeprazole containing regimen increased eradication rate in comparison with the triple therapy based on omeprazole in extensive metabolizers of CYP2C19. Regardless to genotyping of CYP2C19 the *H. pylori*, eradication rates remained similarly comparable among the omeprazole and the esomeprazole group[51].

One thousand four hundred and sixty-three *H. pylori* infected participated in a study to compare 10-d sequential, 14-d triple and 5-d concomitant therapies. The best eradication efficacy has been reported by standard 14-d triple therapy followed by sequential 10-d therapy[52].

Quadruple therapy

Quadruple therapy comprising bismuth subcitrate, PPI, metronidazole and tetracycline has been accepted better than standard triple therapy in several studies[53-55]. Ten-days quadruple therapy containing bismuthate dicitrate, esomeprazole, levofloxacin and tetracycline showed success rate of 95.8% after the failure of sequential therapy. This regimen could be used as a good choice in high clarithromycin resistance areas[56]. In a similar study 14-d therapy with esomeprazole, amoxicillin, levofloxacin, and bismuth achieved more than 90% eradiation rate after the failed sequential or concomitant therapies[10].

Four hundred and twenty-four patients (96.8% metronidazole resistance) did not respond to standard therapies treated by lansoprazole, bismuth potassium citrate plus (tetracycline and metronidazole or tetracycline and furazolidone or amoxicillin and tetracycline or amoxicillin and furazolidone) which all bismuth-containing quadruple therapies reached higher than 90% success rate[57].

The efficiency of quadruple *H. pylori* therapy has been confirmed as the first-line regimen in a randomized trial. During this study, 14-d quadruple therapy was compared with 7-d standard therapy. Fourteen-days quadruple therapy comprising bismuth, PPI, amoxicillin and clarithromycin exhibited acceptable success rate and could be prescribed as the first line therapy[58].

An open alabel, randomized, phase 3 trial compared 10-d quadruple therapy with 7-d standard therapy in 440 patients. The quadruple therapy produced higher success rates (80%) in comparison with standard triple therapy (55%). Quadruple therapy could be accepted as the first line of treatment because of increased incidence of clarithromycin-resistant. In addition, quadruple therapy showed higher eradication rate but comparable side effects with standard therapy[59].

One hundred and six Iranian duodenal ulcer patients participated in the study of furazolidone in comparison with metronidazole during a quadruple therapy for eradication of *H. pylori* infection. In furazolidone group eradication rate was 75% and 82% (in ITT and PP analysis) but in metronidazole group 55% and 56% respectively[60].

Sixty-four patients who failed previous clarithromycin, amoxicillin and omeprazole, (standard triple treatment) eradication treatment were treated for 10 d with tetracycline, bismuth subcitrate potassium and metronidazole four times per day and omeprazole two times per day. According to results, *H. pylori* eradication rates were between 93.2% to 95.0%[61].

One hundred and fifty patients in high resistance area were enrolled in a study to evaluate levofloxacin-containing quadruple therapy or high dose metronidazole plus bismuth subcitrate, esomeprazole, and tetracycline. Eradication rates were similar in both groups. Thus, metronidazole is a good choice because it is cheaper and more feasible[62].

Concomitant quadruple therapy is a non-bismuth quadruple based therapy comprising omeprazole, metronidazole, amoxicillin, and clarithromycin during 5 to 7 d[63,64]. The consequence of a meta-analysis of several randomized trials exhibited that concomitant quadruple therapy has been better than standard triple therapy[65] in addition, another meta-analysis of 2070 patients also confirmed this result[66].

Resistance to both metronidazole and clarithromycin considerably influence sequential therapy but did not affect the success rate of concomitant quadruple therapy. In addition, concomitant regimen has been confirmed to be safe and similarly active like sequential therapy in eradication of *H. pylori*[67]. In an area that 23.5% of subjects had clarithromycin resistant *H. pylori* strains, (33% resistant to metronidazole and 8.8% resistant to both drugs), the efficacy of 2 different optimized nonbismuth quadruple regimens was compared. According to the results, concomitant quadruple therapy with omeprazole, amoxicillin, clarithromycin and nitro imidazole two times a day for 14 d showed more than 90% cure rate of *H. pylori*[68].

Sequential therapy

An Italian innovation in the quadruple therapy leads to sequential therapy comprising dual therapy for 5 d with amoxicillin and PPI and 5 more days with tinidazole, clarithromycin and PPI[69]. This regimen was studied among 52 patients suffering from *H. pylori* infection and eradication rate around 98% was achieved with ITT analysis[70]. The other study which assessed the success rate of treatment by sequential therapy in compare with standard triple therapy showed that 10-d sequential therapy was better than standard triple therapy in children, that is confirmed by the researches done on adults[71].

A retrospective study compared eradication treatment in subjects that underwent triple treatment consisting of clarithromycin, PPI and amoxicillin or sequential treatment involving a clarithromycin, PPI and amoxicillin, and metronidazole in a high anti-microbial resistance setting. Eradication rate of *H. pylori* was comparable between the two treatment groups[72].

Two recently meta-analysis studies established above mentioned data, according to Jafri *et al*[73], review *H. pylori* treatment in 2747 patients. Success rates were 93.4% in sequential regimen where as 76.9% in common triple therapy.

The influence of different factors on success rate of *H. pylori* eradication assessed using two therapy regimens (sequential and triple therapy) for equal 10-d period of study. The data suggested that traditional factors such as smoking and *CagA* gene change efficacy of triple therapies but did not affect sequential therapy[74].

Ten-days sequential regime consisted of amoxicillin plus a PPI for 5 d, was continued by clarithromycin, metronidazole and a PPI for more 5 d demonstrated higher efficacy of triple therapy[75]. In another study 900 patients were examined for sequential therapy comprising amoxicillin and lansoprazole for 7 d continued by metronidazole, lansoprazole, and clarithromycin *vs* standard triple therapy. In the outcome, success rate was 90.7% in sequential therapy but 82.3% in triple therapy[76].

Cure rate of the sequential therapy was altered based on the type of used nitro imidazole, on the other hand, a therapy program with metronidazole provided results which were not as good as tinidazole[69]. Certainly, the results of Choi *et al*[77], study showed that *H. pylori* eradication rate was 77.9% of subjects treated by a metronidazole-based 10-d sequential regimen[77] compared to the results of the other study which indicated 97.4% of treatment by a tinidazole-based regimen. Eradication rate was 84.2% in the other metronidazole-based sequential therapy which was less than tinidazole-based therapy[75]. Most likely, such occurrence is because of longer half-life of tinidazole *vs* metronidazole[78].

In high clarithromycin resistance areas, clarithromycin substitution by levofloxacin has been investigated. Levofloxacin sequential therapy showed eradication rate more than 96% in comparison with 80.8% clarithromycin sequential therapy[79]. Levofloxacin-based sequential regimen is better than usual triple therapy as the first line in the sites with high incidence of resistance to clarithromycin[80].

Recently a retrospective study has been done among subjects that underwent triple treatment consisting of clarithromycin, amoxicillin and a PPI or sequential treatment involving amoxicillin, a PPI, clarithromycin, and metronidazole eradication treatment in a high anti-microbial resistance setting. The *H. pylori* eradication rate was not statistically different between the 2 treatment groups[72].

FUTURE PERSPECTIVES

Overuse of antibiotics and accumulation of point mutations in the *H. pylori* DNA is intended as the main cause of the increase in antibiotic resistance[81].

In the present, the recommendation of antibiotics for two weeks or high-dose PPI are commonly associated with the development of undesirable side effects and complaints during anti-*H. pylori* therapy[82].

A large number of *H. pylori* eradication reports from different geographic areas are indicating conflicting results and a treatment regimen may be extremely efficient in one geographic area and deliver unsatisfactory results in another[83]. In 2010, An *H. pylori* strain was isolated from a 31-year-old woman with gastric cancer that was resistant to all seven antibiotics that were tested: Clarithromycin, metronidazole, amoxicillin, tetracycline, furazolidone, erythromycin and ciprofloxacin[84]. Finding new molecules for treatment of *H. pylori* infection is a part of ongoing research programs[85-92].

Therefore, the development of a new and alternative treatment regimen for the eradication of *H. pylori* which also reduces the frequency of adverse effects would be an invaluable advancement.

PROBIOTICS

The probiotics, live microorganisms mostly within *Lactobacillus, Bifido bacterium* and *Saccharomyces* genus which, when administered in sufficient amounts, exert a health benefit on the host beyond inherent basic nutrition[93,94].

Current interest in probiotic effectiveness against *H. pylori* and its activity in reducing bacterial colonization and decreasing gastric inflammation have been stimulated because it provides a large-scale and low-cost alternate solution to prevent or decrease *H. pylori* colonization[94-97].

A number of mechanisms have been anticipated for probiotic efficacy against *H. pylori*. Probiotic bacteria can modulate *H. pylori* activity by either immunological (*e.g.*, increment of serum IgA and reduction in cytokine profiles such as IL-6) or non-immunological mechanisms (antagonism and competition with potential pathogens[97-100].

The studies those using probiotics alone, showed

only partial improvement in probiotics efficacy against *H. pylori,* while administration of probiotics with eradication regiments lead to increase in efficacy and/or reduction of side effects[98,101,102].

However, conflicting data have been obtained with probiotics treatment[101]. Addition of yogurt to PPI-based triple therapy improved the eradication rate but side effects were the same to that in the control group with standard triple therapy[103].

The effect of probiotic supplementation on *H. pylori* eradication and side effects which was conducted on May 2014 showed that specific strains of probiotics supplementation can improve rates of eradication specially when antibiotic therapies are relatively inefficient. This meta-analysis observed no significant decrease of side effects so that, noticeable heterogeneity was observed for the overall occurrence of adverse events[104].

In another study addition of bovine lactoferrin leads to increase in the eradication rate of *H. pylori*, and probiotics reduced the side effects of antibiotic therapy in the standard triple treatment[105]. Dajani *et al*[106], designed a study to evaluate the effect of adding the probiotic *Bifidus infantis* to triple therapy or pretreatment by probiotic before triple therapy. They showed pretreatment with 2 wk of *B. infantis* before standard triple therapy increased the eradication rate to 90.5% in compare with triple therapy plus probiotic (83%) and triple therapy alone (68.9%)[106].

The effectiveness of probiotics in a standard triple *H. pylori* therapy which analyzed in a systematic review and meta-analysis study suggests that supplementation of a standard triple therapy regimen with probiotics improved the *H. pylori* eradication rates specially in Asian patients and the prevalence of total side effects[15].

The other meta-analysis, by Lv *et al*[107], in 2015 compared the probiotics as adjuvant agents of anti-*H. pylori* standard triple therapy regimens with placebo or no treatment. It was concluded that supplementing triple *H. pylori* therapy regimens with probiotic can enhance eradication rates and reduce the adverse events occurred during eradication treatment. Administration of probiotic before or subsequent to eradication treatment for a duration of > 2 wk probably improve the eradication efficacy[107]. Probiotic pretreatment plus quadruple therapy can decrease *H. pylori* loads despite antimicrobial resistance, thus increasing the treatment efficacy of quadruple therapy in the *H. pylori* eradication[108].

A randomized, prospective, double-blind, placebo controlled study corresponding to 100 *H. pylori*-positive naive patients demonstrated *Lactobacillus reuteri* combination alone is capable of exerting an inhibitory activity against *H. pylori*, and when administered with eradication therapy, it increases eradication rates by about 9% and cause a significant reduction in antibiotic related adverse events[109].

The use of probiotics, as adjuvant therapy, appears promising for the current *H. pylori* eradication treatment, in order to reduce the frequency of antibiotic induced side-effects, though it still requires optimization[110,111].

HERBAL COMPOUNDS

In recent years, a number of studies have suggested that phytomedicine has a complementary function in *H. pylori* treatment, and *H. pylori* infection can be prevented through the use of inexpensive, safe and non-toxic anti-*H. pylori* formulations from medicinal plants. Many plant extracts, partially purified reactions and natural compounds with the anti-*H. pylori* activity has been reported[3,112-114]. Some bioactive compounds from medicinal plants with anti-*H.pylpri* activity include carvacrol[115], polyphenolic catechins[116], tannins[113], cinnamaldehyde, eugenol[117], quercetin[118], licoricidin, licoisoflavone B[119], Berberine, sanguinarine, chelerythrine, protopine, β-hydrastine[120], mastic[121,122], plumbagin[123] protocatechuic acid[124].

Concerning the reducing power of plant extracts on antibiotic resistance, the anti-mutagenic properties of some plant extracts on the incidence of mutations conferring resistance to clarithromycin in *H. pylori* was evaluated. The results of this study showed the considerable efficacy of *Mirtus communis*, *Teucrium polium* extracts in prohibiting antibiotic resistance. This may be more beneficial if the medicinal plants in combination with present antibiotic regimens are used to develop more effective eradication regimens[125]. However, mode of action, potential cytotoxicity and benefits of herbal medicine are complex, incomplete and confusing[126]. Further evaluation of pharmacokinetics for those products in animals and the design of precise clinical trials of promising herbal products should be addressed in future investigations.

PHOTODYNAMIC THERAPY

Photodynamic inactivation of microorganisms is on the basis of the combination of a dye known as a sensitizer or photo sensitiser and harmless visible light of an appropriate wavelength to generate the triplet excited state ($^3O_2$) of the dye molecules which, in turn, may react with molecular oxygen which lead to production of different cytotoxic reactive oxygen species such as superoxide radical-anion ($O_2^{\bullet -}$) and singlet molecular oxygen ($^1O_2$)[127,128].

Recently, some *in vitro*[129-131] and *in vivo*[132,133] studies to develop anti-*H. pylori* photodynamic therapy for the eradication of *H. pylori* were successful[128].

In an *in vitro* study, a photosensitizer such as Chlorin e6 (Ce6) as a natural product reduced from chlorophyll, was used to achieve an optimal irradiation conditions like initial Ce6-concentration, incubation time, light intensity and exposure time for an effective inactivation of *H. pylori*. Photodynamic inactivation of *H. pylori* using Ce6 shows that the exposure time of irradiation, followed by the light intensity and the concentration of Ce6 were the major cause of strains inactivation[130].

Hamblin *et al*[131] demonstrated multiple strains of *H. pylori* are killed *in vitro* by photodynamic action upon illumination.

H. pylori is sensitive to inactivation by blue light which may represent a novel therapy approach especially in patients with failed standard antibiotic therapy. Blue light phototherapy produces a rapid decline of bacterial numbers in endoscopically delivered blue light in the gastric antrum of the 10 patients who were positive for the *H. pylori*[133].

Based on a controlled, prospective pilot trial study, intra-gastric violet light phototherapy is safe and feasible and may demonstrate a new approach for *H. pylori* eradication, particularly in patients who have failed therapy with standard antibiotic regiments[132].

Choi *et al*[129] applied endoscopic white light and methylene blue dye to show impressive antibacterial effect against *H. pylori*. The primary mechanism of the bactericidal effect has been shown to be oxidative DNA damage of *H. pylori*[129].

In vitro photodynamic therapy against *H. pylori* using endoscopic light (NBI and conventional white light), with low or high concentration of protoporphyrin Ⅸ as a photosensitizer revealed the bactericidal activities are very efficient and the main mechanism of this photodynamic therapy involves damage to the cell membrane[134].

According to the results, it is necessary to perform *in vivo* photodynamic therapy using animal model of disease and indicate the limitations and effectiveness of this novel technique. Also the cost, side effects and ease of administration should be also taken into account and develop new photosensitizer materials to improve the antibacterial activity or using light of a wavelength specific to the photosensitizer instead of light of a broad wavelength spectrum[127,129].

VACCINE

All known gastric *H. pylori* species are urease positive that catalyze the hydrolysis of urea. UreB is the relatively conserve urease activity unit and It has very strong antigenicity and is the critical for the bacterial survival and colonization under acidic condition of the stomach. UreI, a *H. pylori* urea channel protein, is a key factor for bacterial colonization in acidic mammalian stomach[135]. In a research, a multi-epitope vaccine was designed by coupling two antigenic fragments (UreB and UreI) of *H. pylori* and cholera toxin B subunit (CTB), resulting considerable protection effects against *H. pylori* challenge in BALB/c mice[136].

Both intramuscular injection and oral administration of multi-epitope antigen, UreI and UreB, with CTB had immune protective effect against *H. pylori* challenge, and oral administration had the higher infection protection rate against *H. pylori*[135].

Several other *H. pylori* proteins have already been reported as effective vaccine antigens such as cytotoxin-associated gene A, vacuolating cytotoxin A (Vac A)[137] heat-shock proteins[138], neutrophil-activating protein[139], surface-localized protein HpaA[140] and so on. It is probable a combination of some mentioned antigens with each other or with a suitable adjuvant may induce a protective effect through vaccination[140,141].

Recently, a reverse vaccinology approach was employed to predict the potential vaccine candidates against *H. pylori* and search novel antigens using computational methods or bioinformatics. In this study, 5 antigenic epitopes including adhesion protein babA, sabA, omp16, iron (Ⅲ) dicitrate transport protein fecA and vacuolating cytotoxin vacA have been prioritized as potential vaccine candidates against *H. pylori* infections[142].

Therapeutic antibodies present valuable tools in targeting a wide range of enteric diseases and pathogens during the years[143]. A recent study by den Hoed *et al*[144] has shown monotherapy with bovine antibody-based oral immunotherapy is well tolerated, but does not significantly reduce intragastric *H. pylori* density in humans[144].

The generation and application of virus-like particles and nanobeads with a surface adsorbed antigen that can elicit strong T and B cell immune responses would be as a useful tool for the development of vaccines[145]. The development of safe and effective vaccine against *H. pylori* infection becomes particularly important.

CONCLUSION

The use of antibiotics as first-line therapies may be appropriate if they are selected based on country-wide studies of the local and regional antimicrobial resistance patterns. Development of alternative antibiotics for the eradication of *H. pylori* would be an invaluable advancement, although it takes number of years before to evaluate these potentially interesting molecules in humans.

Adjuvant therapy with probiotics is recommended due to immunomodulation, stimulation of mucin production and inhibition of colonization and survival of *H. pylori*. On the other hand, potential options such as medicinal plants, Photodynamic therapy and vaccine are still in the experimental phase.

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