

Pharmacological therapy used in the elimination of *Helicobacter pylori* infection: A review

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Received: July 13, 2014

Peer-review started: July 13, 2014

First decision: August 6, 2014

Revised: August 16, 2014

Accepted: September 18, 2014

Article in press: September 19, 2014

Published online: January 7, 2015

Abstract

The optimal therapy for *Helicobacter pylori* (*H. pylori*) infection should combine a high cure rate and a short treatment duration with a favorable side-effect profile and should maintain a low cost. Several strategies have been proposed to increase the *H. pylori* eradication rate, including the extension of the treatment duration to 14 d, the use of a four-drug regimen (quadruple, sequential, and concomitant treatments), and the use of novel antibiotics, such as levofloxacin. However, triple therapy remains the most widely accepted first-line treatment regimen in Brazil and the United States

and throughout Europe. Because this therapy is limited by resistance to clarithromycin, other therapeutic regimens have been investigated worldwide. This review describes the current literature involving studies directly comparing these different therapies and their efficacies.

Key words: Clarithromycin resistant; *Helicobacter pylori*; Peptic ulcers; Triple therapy; Treatment

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Core tip: *Helicobacter pylori* is a bacterium that is commonly found in the stomach and is capable of causing a number of digestive problems, including ulcers and stomach cancer. Over the past few years, the efficacy of conventional therapy has decreased. However, new therapies are not commonly accepted as first-line treatments in some countries because of a lack of national validation studies. This review aimed to report studies demonstrating the effectiveness of different non-conventional therapies and comparing them with conventional triple therapy.

dos Santos AA, Carvalho AA. Pharmacological therapy used in the elimination of *Helicobacter pylori* infection: A review. *World J Gastroenterol* 2015; 21(1): 139-154 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i1/139.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i1.139>

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium found on the luminal surface of the gastric epithelium. The bacterium induces chronic inflammation of the underlying mucosa and typically infects the stomach in the first few years of life. It was isolated for the first time

by J. Barry Robin Warren and Marshall^[1]. The majority of patients (up to 85%) with *H. pylori* infection do not develop any clinically significant complications^[2,3]. However, since its discovery in 1983, infection with this microorganism has been associated with the pathogenesis of various gastrointestinal diseases, such as duodenal and gastric ulcers, gastritis, gastric cancer and mucosa-associated lymphoid tissue, a lymphoma of the stomach. The World Health Organization classified *H. pylori* as a group I carcinogen with an attributable risk of gastric cancer of 50%-60%^[1-4]. Therefore, it is recommended that all patients with peptic ulcers be tested for *H. pylori* infection^[3].

The first-line choice of treatment for *H. pylori* infection in the United States and Europe consists of a conventional triple therapy, in which a proton pump inhibitor (PPI), clarithromycin and amoxicillin are administered for 7-14 d^[5-7]. Conventional triple therapy is also recommended as a first-line therapy by Asian-Pacific and Brazilian consensus groups^[8,9]. However, over the past few years, the efficacy of conventional triple therapy has decreased, with eradication rates of less than 80%^[10,11]. Decreased eradication rates are due primarily to increased bacterial resistance to clarithromycin, indicating the need for new first-line treatments. However, new therapies are not commonly accepted as first-line treatments in some countries because of a lack of national validation studies and a lack of studies of clarithromycin resistance. This review aimed to report studies demonstrating the effectiveness of different therapies and comparing them with conventional triple therapy.

RESEARCH

Search strategy and study selection

This review was developed according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement guidelines. We searched the medical literature using Medline (2008 to Aug 2014), Science Direct (2008 to Aug 2014), and Scielo (2008 to Aug 2014). We identified eligible studies using different combinations of the search terms "*Helicobacter pylori*", "*H. pylori*", "eradication" and "treatment". We only analyzed papers written in English, Portuguese and Spanish. Two investigators (AAS and AAC) evaluated the abstracts of the papers, which were identified as appropriate by the initial search, independently and in a blinded manner. Papers written in foreign languages were translated when necessary. In addition, we contacted authors to obtain unpublished data from their studies when necessary.

Data extraction

Two investigators assessed the articles independently using pre-designed data extraction forms. Disagreements between investigators were resolved by discussions with another investigator. Data regarding eradication were evaluated based on an intention-to-treat analysis. In

addition, the following clinical data were extracted for each trial: country of origin, type of publication (article, abstract), type of therapy, use of different drugs, duration of comparative eradication treatment, and effectiveness. Review articles, theses, dissertations, letters to the editor and commentaries were excluded. Fifty-five articles were included in this review.

Quantitative data of the articles used in this review are described in Table 1.

TRIPLE THERAPY

Over the last two decades, the recommended first-line treatment for the eradication of *H. pylori* has been the standard triple therapy, comprising a PPI, amoxicillin and clarithromycin or metronidazole^[11,12]. In African patients, the success rate of the triple therapy is 80%-90%^[13]. However, the effectiveness of this traditional system, which was initially 90%, has progressively decreased in many parts of the world and is currently 57%-73%^[11]. We were able to confirm that the eradication rate of *H. pylori* infection after standard triple therapy is decreasing worldwide^[14].

The 3rd Brazilian Consensus on *H. pylori* recommend conventional triple therapy as the primary treatment option. This regimen consists of the administration of one PPI at the standard dose, 1 g amoxicillin and 0.5 g clarithromycin twice daily for 7 d. The recommendations by consensus groups of a 7-d treatment are supported by increased patient adherence and reduced financial costs. In addition, similar rates of efficacy, safety and patient compliance are observed with both one week and two weeks of triple-therapy treatments^[9,15,16]. However, there have been proposals suggesting variations in this triple therapy, including the use of metronidazole^[17], moxifloxacin^[18], azithromycin^[19] or levofloxacin^[20-26] instead of clarithromycin when patient resistance to clarithromycin occurs.

A prospective study was performed at the Hospital of Lidice, Venezuela from October 2010 to October 2011 of two groups of patients presenting with dyspeptic symptoms who underwent upper gastrointestinal endoscopy and whose biopsies were positive for infection with *H. pylori*^[11]. The group evaluated the efficacy of triple therapy with PPI, levofloxacin and amoxicillin in the eradication of *H. pylori* compared with the conventional triple therapy. They observed that the eradication rate of the triple therapy with levofloxacin was superior to the same therapy with clarithromycin^[11]. Another prospectively randomized, parallel-group, comparative, multicenter study carried out at two centers in the Kingdom of Saudi Arabia (Al Noor Hospital in Makkah and Al Ameen Polyclinic in Al Kharj) and the National Liver Institute in Egypt evaluated the eradication rate, tolerability, and patient compliance of levofloxacin, clarithromycin and esomeprazole-combined triple therapy for *H. pylori* eradication^[25]. The patients in group 1 received 500 mg clarithromycin twice daily, 1000 mg amoxicillin twice daily,

Table 1 Quantitative data summary

Therapy	Drug protocols	Experimental design	Side effects (% or number of patients)	Eradication rate	Compliance	Statistical significance	Ref.
Triple Therapy	Rabeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg twice daily for 7 or 10 d	Randomized, controlled trial carried out at the Gastroenterology Unit of The Lagos State University Teaching Hospital, Ikeja, Nigeria, from June 2012 to August 2013	No adverse effects were reported	7 d: 88.9% (UBT) 10 d: 86.2% (UBT)	Compliance was 100%	The 10-d treatment showed no significant advantage over the 7-d treatment	Onyekwere <i>et al</i> ^[16]
Triple Therapy	Esomeprazole regimen: esomeprazole 20 mg, clarithromycin 400 mg, and amoxicillin 750 mg for the first 7 d, with all drugs given twice daily Lansoprazole regimen: lansoprazole 30 mg, clarithromycin 400 mg, and amoxicillin 750 mg for the first 7 d, with all drugs given twice daily	Multicenter, randomized, open-label, non-inferiority trial performed at 20 hospitals with Osaka Gut Forum from May 2012 to February 2013 in Japan Samples: 268 patients equally divided between regimens	Esomeprazole regimen: Diarrhea (36.7%), Bitter taste (16.12%), Nausea (1%), Vomiting (3.2%), Eruption (3.2%), Fatigue (1%), Appetite loss (3.2%), Thirst (2.1%), Belching (1%), Bad breath (1%), Sore throat (1%), Joint pain (1%), Chest discomfort (2.1%), Floating (1%), Abdominal wind (1%), and Constipation (1%). Lansoprazole regimen: Diarrhea (41.31%), Bitter taste (16.12%), Nausea (1%), Eruption (3.2%), Headache (2%), Appetite loss (1%), Stomatitis (1%), Chelitis (2.1%), Leg edema (1%), Abdominal wind (1%), Constipation (1%), and Pruritus ani (1%)	Group A: 69.4% (ITT), 76.9% (PT) Group B: 73.9% (ITT), 79.8% (PT)	Compliance of all patients except for 3 patients (50%, 79%, 86%) was 100% in the PP population and was excellent based on all patients' medication diaries	Esomeprazole showed non-inferiority and safety in a 7-d triple therapy treatment for the eradication of <i>H. pylori</i> compared with lansoprazole	Nishida <i>et al</i> ^[27]
Triple Therapy	Group A: levofloxacin, 500 mg b.i.d., amoxicillin/clavulanate, 875 mg/125 mg b.i.d., and rabeprazole, 20 mg b.i.d. for 7 d Group B: clarithromycin, 500 mg b.i.d., amoxicillin, 1000 mg b.i.d., and rabeprazole, 20 mg b.i.d. for seven days	Single-center, prospective study performed between December 2007 and December 2009 in Taiwan	Group A: Abdominal pain (2), Flatulency/abdominal fullness (1), Loose stool/diarrhea (3), Nausea/hiccough (4), Vomiting (2), Change in appetite (2), and Insomnia (1) Group B: Abdominal pain (2), Flatulency/abdominal fullness (3), Loose stool/diarrhea (1), Nausea/hiccough (4), and Change in appetite (4)	Group A: 78.1% (ITT), 80.9% (PT) Group B: 57.5% (ITT), 61.8% (PT)	Group A: Lost to follow-up (<i>n</i> = 3) (lost contact, <i>n</i> = 1, withdrew, <i>n</i> = 2). Protocol violation <i>n</i> = 2) (received amoxicillin/clavulanate from ENT doctor before follow-up, <i>n</i> = 1, follow-up < 3 wk, <i>n</i> = 1 Group B: Lost to follow-up (<i>n</i> = 4), (withdrew, <i>n</i> = 4), Protocol violation (<i>n</i> = 1) (follow-up < 3 wk, <i>n</i> = 1)	Triple therapy with levofloxacin provided improved <i>H. pylori</i> eradication efficacy when compared with the standard triple therapy in eastern Taiwan	Chen <i>et al</i> ^[26]
Triple Therapy	Group A: triple therapy with clarithromycin for 10 d Group B: triple therapy with levofloxacin for 10 d	Prospective study performed from October 2010 to October 2011 at the Hospital of Lídice, Venezuela Samples: 81 patients, 42 in Group A, and 39 in Group B	Group A: Nausea and Diarrhea (20.33%) Group B: Nausea and Diarrhea (8.4%)	Group A: 66.66% Group B: 94.87% determination of <i>H. pylori</i> was performed using hematoxylin and eosin (HE) and Giemsa (when HE negative)	Not described	Treatment with levofloxacin was more effective than conventional triple therapy	Dib <i>et al</i> ^[11]

Triple Therapy	Esomeprazole, amoxicillin and clarithromycin for either 7 d or 14 d	Prospective, randomized, comparative trial of 7-d and 14-d triple therapy regimens conducted at the Aga Khan University Hospital, Nairobi Samples: 120 patients, 60 in the 7-d group, and 60 in the 14-d group	Headache, Nausea, Vomiting, Diarrhea, Loss of appetite, Taste disturbance, Abdominal pain and Rash. 17 (34%) were affected in the 7-d group, and 25 (53.2%) were affected in the 14-d group	7 d: 76.7% (ITT) and 92% (PP). 14 d: 73.3% (ITT) and 93.6% (PP)	Compliance was found to be inadequate (intake of < 90% of total tablets) in 1 patient (1.02%). Compliance was good in 97 (98.98%) of the participants	No significant difference between 7- and 14-d triple therapy regimens	Sokwala <i>et al.</i> ^[15]
Triple Therapy	Rabeprazole group: rabeprazole 10 mg b.i.d., amoxicillin 750 mg b.i.d., and metronidazole 250 mg b.i.d (7 d) Lafutidine group: lafutidine 10 mg t.i.d., amoxicillin 750 mg b.i.d., and metronidazole 250 mg b.i.d (7 d)	Prospective, randomized, comparative trial of 7-d second-line amoxicillin- and metronidazole-containing triple therapy study performed at the University of Toyama, Toyama, Japan. Samples: 52 patients, 26 in the rabeprazole group, and 26 in the lafutidine group	Rabeprazole group: Soft stool (3), Diarrhea (1), and Flatus (1). Lafutidine group: Soft stool (2), Diarrhea (1), and Abdominal bloating (1)	96.2% (ITT and PP) for both groups	All patients completed treatments according to the protocols, and the rate of compliance was 100%	The treatments with both the H2-receptor antagonist lafutidine and the PPI rabeprazole together with clarithromycin and metronidazole were similarly safe and effective in the eradication of <i>H. pylori</i> after the failure of clarithromycin-based regimens	Kudo <i>et al.</i> ^[17]
Triple Therapy	Lansoprazole 30 mg, amoxicillin 1000 mg and moxifloxacin 400 mg for 7 d or 10 d	Prospective, randomized, comparative trial of 10-d vs 7-d moxifloxacin-based therapy conducted at Clinical Hospital Sveti Duh, Zagreb, Croatia. Samples: 150 patients divided equally into both groups	7-d group: Epigastric discomfort (3), Nausea/vomiting (2), Diarrhea (3), Constipation (1), Headache (1), and Skin rash (1). 10-d group: Pruritus (2), Metallic taste (2), Epigastric discomfort (4), Nausea/vomiting (3), Diarrhea (5), and Headache (2)	7 d: 76% (ITT) and 84% (PP) 10 d: 84% (ITT) and 90% (PP)	All patients were included in the ITT analysis. 12 patients (8%) did not complete the study for one of the following reasons: loss to follow-up (<i>n</i> = 1), refusal to go under a second endoscopy (<i>n</i> = 3), adverse effects leading to the discontinuation of treatment (<i>n</i> = 5), taking disapproved medication (<i>n</i> = 2) and taking less than 80% of the prescribed medicines (<i>n</i> = 1). Those patients were excluded from the PP analysis	Moxifloxacin-based treatment is an effective and safe option compared to standard triple regimens due to the increased prevalence of clarithromycin resistance observed in the standard regimens	Bago <i>et al.</i> ^[18]
Triple Therapy	Group 1: levofloxacin 500 mg o.d., amoxicillin 1 g b.i.d and proton pump inhibitor b.i.d. for 10 d Group 2: levofloxacin 500 mg b.i.d., amoxicillin 1 g b.i.d. and proton pump inhibitor b.i.d. for 10 d	Single-center, randomized, open-label trial carried out in Ankara, Turkey Samples: 110 patients equally divided into two groups	Not described	Group 1: 60% Group 2: 72.7%	All patients completed the study	The efficacy of the triple therapy containing levofloxacin was not within the acceptable limits for first-line <i>H. pylori</i> eradication	Seven <i>et al.</i> ^[20]

Triple Therapy	Group 1: clarithromycin 500 mg twice daily, amoxicillin 1000 mg twice daily, and esomeprazole 20 mg twice daily for 7 d Group 2: levofloxacin 500 mg once daily, amoxicillin 1000 mg twice daily, and esomeprazole 20 mg twice daily for 7 d Group 3: levofloxacin 500 mg once daily, clarithromycin 500 mg twice daily, and esomeprazole 20 mg twice daily for 7 d	Prospective, randomized, parallel-group, comparative, multicenter study carried out at 2 centers in the Kingdom of Saudi Arabia (Al Noor Hospital in Makkah and Al Ameen Polyclinic in Al Kharij) and the National Liver Institute in Egypt between November 2006 and May 2009 Samples: 450 patients equally distributed into groups	Group 1: Nausea (38), Taste disturbance (16), Diarrhea (30), Headache (16), and Abdominal pain (32) Group 2: Nausea (34), Taste disturbance (14), Diarrhea (28), Headache (16), and Abdominal pain (28) Group 3: Nausea (33), Taste disturbance (18), Diarrhea (22), Headache (17), and Abdominal pain (26)	Group 1: 78.6% (ITT), 81.3% (PP) Group 2: 84.7% (ITT), 86.7% (PP) Group 3: 90.6% (ITT), 93.7% (PP)	Of these 450 patients, 14 were excluded from the per protocol analysis: 3 due to poor compliance, 2 who had taken their breath test less than 42 d after the completion of treatment, and 9 who had not attended visit 3	The combined levofloxacin, clarithromycin and esomeprazole-based regimen as a first-line triple therapy for <i>H. pylori</i> eradication can allow for a more significant eradication rate with similar safety compared with the classic triple therapy	Assem <i>et al.</i> ^[25]
Triple Therapy	Group 1: 20 mg omeprazole, 1 g amoxicillin, and 500 mg clarithromycin twice daily for 2 wk Group 2 (with vitamin C): 20 mg omeprazole, 1 g amoxicillin, 250 mg clarithromycin and 250 mg vitamin C twice daily for 2 wk	Prospective, randomized, controlled study conducted in Iran. Samples: 214 patients, 100 in Group 1, and 114 in Group 2	Not described	Group 1: 89% Group 2 (with vitamin C): 86.8%	Not described	Adding vitamin C might reduce the needed dosage of clarithromycin for the eradication of <i>H. pylori</i>	Kaboli <i>et al.</i> ^[24]
Triple Therapy	Group 1: amoxicillin 500 mg b.i.d., metronidazole 500 mg b.i.d., bismuth 240 mg b.i.d. and omeprazole 20 mg b.i.d. Group 2 (with vitamin C): amoxicillin 500 mg b.i.d., metronidazole 500 mg b.i.d., bismuth 240 mg b.i.d. and omeprazole 20 mg b.i.d. and vitamin C 500 mg/d	Randomized, controlled clinical trial performed at Taleghani Research Center of Gastroenterology and Liver Disease in Iran Samples: 312 patients, 162 in Group 1, and 150 in Group 2	Nausea, Loose stool, and Headache for both groups	Group 1: 48.8% (ITT), 56.4% (PP) Group 2: 78% (ITT), 83% (PP)	Twenty-two patients from group 1 did not terminate the course of treatment due to non-compliance and minor side effects. Nine patients from group 2 were excluded from the per-protocol analysis due to the discontinuation of treatment for minor side effects. In total, 141 patients completed the treatment course	Adding vitamin C to the <i>H. pylori</i> treatment regimen of amoxicillin, metronidazole and bismuth can significantly increase the <i>H. pylori</i> eradication rate	Zojaji <i>et al.</i> ^[33]
Triple Therapy	Rabeprazole 20 mg b.i.d., clarithromycin 500 mg b.i.d., and amoxicillin 1 g b.i.d. for 7 d, for 10 d or for 14 d	Prospective, randomized, controlled study performed at 2 endoscopic centers in Greece Samples: 307 patients equally divided between the groups	Not described	7 d: 74.5% 10 d: 90.2% 14 d: 76% ¹ Campylobacter-like organism (CLO) test and histology	Not described	Both 10- and 14-d rabeprazole-based triple regimens reached eradication rates of above the threshold of 80% on an intention-to-treat basis	Karatapanis <i>et al.</i> ^[40]

Triple Therapy	Levofloxacin group: levofloxacin 500 mg, esomeprazole 40 mg and clarithromycin 500 mg once daily Amoxicillin group: amoxicillin 1 g, esomeprazole 40 mg, and clarithromycin 500 mg twice daily	Prospective, randomized, open-label trial performed at the Keelung Chang-Gung Memorial Hospital in Taiwan. Samples: 189 patients, 90 in the levofloxacin group, and 99 in the amoxicillin group	Levofloxacin group: Taste distortion (3), Diarrhea (1), Dizziness (1), Headache (2), and Abdominal pain (1). Amoxicillin group: Diarrhea (1), Headache (1), Abdominal pain (2), Skin rash (4), and Taste distortion (4)	Levofloxacin groups: 78.9% (ITT), 83.5% (PP) Amoxicillin groups: 74.8% (ITT), 86% (PP)	Levofloxacin group: all patients completed the 7-d course of eradication therapy, but one became pregnant during the study period, one expired due to hepatocellular carcinoma, and three were lost to follow-up. Amoxicillin group: six failed to take all of the 7-d eradication drugs (four with skin allergies and two with intolerances to all drugs). The remaining seven patients were lost to follow-up	The efficacy and tolerability of once-daily levofloxacin-containing triple therapy were equal to those of the standard twice-daily triple therapy	Chen <i>et al</i> ^[21]
Triple Therapy	MTL regimen: moxifloxacin 400 mg once daily, tetracycline 500 mg four times a day, lansoprazole 30 mg twice daily and bismuth subcitrate at double dose of 300 mg twice daily for 14 d	Single-center, prospective, open-label study performed at the Gastroenterology Department of the Ankara Education and Research Hospital in Turkey in 2012. Sample: 74 patients	Darkening of stool (38.9%), Nausea (33.8%), Metallic taste (29.2%), Headache (18.4%), Vomiting (15.3%), Itching (12.3%), Abdominal pain (9.2%), Diarrhea (6.1%), Skin rash (6.1%), and Constipation (4.6%)	82.1% (ITT and PP)	Drug compliance was 98.6%	The addition of bismuth to the MTL regimen as a 2-wk course achieved a 82.1% eradication rate with relatively mild side effects	Ergül <i>et al</i> ^[23]
Sequential Therapy	Lansoprazole 30 mg b.i.d. and amoxicillin 1000 mg b.i.d. for the first five days followed by lansoprazole 30 mg b.i.d. and levofloxacin 500 mg b.i.d. for the remaining five days	Prospective, open-label study conducted at the Gastroenterology Outpatient Clinic in Turkey Sample: 40 patients	Nausea and Metallic Taste (8.4%)	67.5% (ITT), 71% (PP)	Thirty-eight patients completed the study	Levofloxacin-based sequential therapy had less efficacy	Güzelbulut <i>et al</i> ^[21]
Sequential Therapy	Group A: pantoprazole 40 mg b.i.d. and amoxicillin 1 g b.i.d. for 5 d followed by pantoprazole 40 mg b.i.d., tetracycline 500 mg q.i.d., and metronidazole 500 mg t.i.d. for the remaining 9 d Group B: pantoprazole 40 mg b.i.d. and amoxicillin 1 g b.i.d. for 5 d, followed by pantoprazole 40 mg b.i.d., tetracycline 500 mg q.i.d., metronidazole 500 mg t.i.d., and amoxicillin 1 g b.i.d. for the remaining 9 d	Prospective, randomized, controlled study performed at Haydarpas, a Numune Education and Research Hospital, Gastroenterology Outpatient Clinic, Istanbul, Turkey between January 2009 and April 2009. Sample: 112 patients equally divided onto the groups	Group A: Diarrhea (2), Nausea (2), and Abdominal discomfort (4) Group B: Diarrhea (3), Nausea (2), and Abdominal discomfort (2)	Group A: 82.1% (ITT), 83.6% (PP) Group B: 78.57% (ITT), 81.48% (PP)	None of the patients discontinued the therapy because of adverse effects	Extended duration of amoxicillin treatment during the entire tetracycline-containing sequential therapy period did not improve the <i>H. pylori</i> eradication rate	Cetinkaya <i>et al</i> ^[39]

Sequential Therapy	Pantoprazole 40 mg b.i.d. (30 minutes before meals for 14 d), colloidal bismuth subcitrate, 300 mg (equivalent to Bi2O3 120 mg) (two tablets at 1 hour before breakfast and dinner for 14 d), amoxicillin, 1 g b.i.d. (from day 1 to day 7), tetracycline 500 mg q.i.d. (an hour after meals and at bedtime from day 8 to day 14 with ample amounts of water), and metronidazole, 500 mg t.i.d. (after meals from day 8 to day 14)	Prospective, randomized, controlled study carried out at four medical centers in different geographic regions of Turkey. Sample: 142 patients equally divided into the groups	Diarrhea (1), Vaginal discharge (1), Facial swelling (1), Nausea/vomiting (1), Numbness of face and hands (1), Fever and Epigastric pain (1)	80.98% (ITT), 92% (PP)	Compliance was satisfactory (11 patients, four women and seven men, were unavailable for follow-up)	The 14-d modified sequential treatment, including bismuth, achieved significantly high eradication rates in patients with <i>H. pylori</i> infection, with five compliant patients and minor side effects	Uygun <i>et al</i> ^[41]
Sequential Therapy	A standard dosage of proton pump inhibitor (PPI) and amoxicillin 1 g for the first 5 d (both twice daily) followed by a standard dosage of PPI, levofloxacin 500 mg and tetracycline 500 mg for the remaining 5 d (all given twice daily) plus a standard dosage of PPI once daily every day for an additional 4 wk	Prospective study performed at a primary gastroenterological center located in South Italy [Servizio di Gastroenterologia Territoriale, ASI BAT, Andria (BT)]	Twenty-nine patients (24.37%) showed side effects. Two (1.68%) experienced severe side effects (vomiting, diarrhea, and abdominal pain) and withdrew from the study. The additional 27 patients (22.69%) experienced some side effects but completed the study	67.23% (ITT), 68.38% (PP)	One-hundred and one patients (84.87%) were fully compliant	A 10-d sequential triple therapy containing amoxicillin, levofloxacin and tetracycline seems to be effective and safe in curing resistant <i>H. pylori</i> infection	Tursi <i>et al</i> ^[42]
Quadruple Therapy	Group A (quadruple therapy with doxycycline): esomeprazole 20 mg b.i.d., bismuth potassium citrate 220 mg b.i.d., amoxicillin 1 g b.i.d. and doxycycline 100 mg b.i.d. for ten days Group B (quadruple therapy): esomeprazole 20 mg b.i.d., bismuth potassium citrate 220 mg b.i.d., metronidazole 400 mg b.i.d. and tetracycline 750 mg q. 6 h for ten days	An open-label, controlled study conducted from April 2010 to March 2011 in China Sample: 85 patients, 43 in Group A, and 42 in Group B	Group A: Nausea (2), Diarrhea (1), Headache (2), Abdominal pain (2), and Anorexia (2). Group B: Nausea (5), Diarrhea (2), Headache (2), Abdominal pain (5), Anorexia (4), Constipation (1), and Dizziness (1)	Group A: 67.4% (ITT), 72.5% (PP) Group B: 59.5% (ITT), 64.1% (PP)	Compliance was 100%	Quadruple therapy containing doxycycline is as effective as routine quadruple therapy for <i>H. pylori</i> eradication	Wang <i>et al</i> ^[43]
Quadruple Therapy	Group A: quadruple therapy with metronidazole, metronidazole 500 mg b.i.d., amoxicillin 1 g b.i.d., omeprazole 20 mg b.i.d. and bismuth 240 mg b.i.d. Group B: quadruple therapy with azithromycin, azithromycin 500 mg once daily for 1 wk and amoxicillin 1 g b.i.d., omeprazole 20 mg b.i.d. and bismuth 240 mg b.i.d. for 2 wk	Double-blind, randomized clinical trial conducted at Rasoule-Akram Hospital, Iran, in 2006 Sample: 60 patients equally divided between the groups	Not described	Group A: 68% (UBT) Group B: 69% (UBT)	Group A: five patients discontinued treatment because of the side effects of the treatment. Group B: one patient discontinued treatment because of the side effects of the treatment	No significant difference was observed between the two quadruple-therapy regimens that were tested	Agah <i>et al</i> ^[43]

Quadruple Therapy	Group A: quadruple therapy (2 wk): azithromycin 500 mg twice daily for 6 d and omeprazole 20 mg, amoxicillin 1 g, and bismuth 240 mg, all given twice daily for 2 wk Group B: quadruple therapy (3 g azithromycin for 1 wk), azithromycin 500 mg twice daily for 3 d and omeprazole 20 mg, amoxicillin 1 g, and bismuth 240 mg, all given twice daily for 1 wk Group C: quadruple therapy (1.5 g azithromycin for 1 wk): azithromycin 250 mg twice daily for 3 d and omeprazole 20 mg, amoxicillin 1 g, and bismuth 240 mg, all given twice daily for 1 wk	Prospective, open-label, randomized study performed in Iran Sample: 84 patients, 31 in Group A, 28 in Group B and 25 in Group C	The frequencies of drug side effects were as follows: Group A: 19.23% Group B: 7.6% Group C: 0%	Group A: 92% (UBT) Group B: 88.46% (UBT) Group C: 80% (UBT)	Not described	One-week quadruple regimens of 3 g azithromycin may be more favorable for <i>H. pylori</i> eradication	Rogha <i>et al</i> ^[35]
Sequential Therapy with Triple Therapy	Sequential therapy group (14 d): esomeprazole 40 mg b.i.d. and amoxicillin 1 g b.i.d. for the first week followed by esomeprazole 40 mg b.i.d., levofloxacin 500 mg q.d. and metronidazole 500 mg t.i.d. for the second week Triple therapy group (2 wk): esomeprazole 40 mg b.i.d., amoxicillin 1 g b.i.d. and clarithromycin 500 mg b.i.d	Prospective, randomized, parallel-arm trial conducted at an outpatient center in academic medical center in Turkey Sample: 150 patients equally divided among the groups	Twenty-two (14.6%) patients reported side effects, such as nausea (7), metallic taste (6), diarrhea (5), abdominal pain (4), vomiting (2) and rash (1). One patient in the sequential group stopped treatment because of severe nausea, vomiting and abdominal pain during the second week of treatment	Sequential therapy group: 90.2% (ITT) Triple therapy group: 50.7% (ITT)	Seventy-two patients in the sequential therapy group and 67 patients in the triple therapy group completed their regimens and were included in the per-protocol population	Both regimens were similarly well tolerated, and the side effects were comparable	Polat <i>et al</i> ^[36]
Sequential Therapy with Triple Therapy	Standard triple therapy: rabeprazole 20 mg, amoxicillin 1.0 g and clarithromycin 500 mg twice daily for 7 d, 10 d or 14 d Sequential treatment: amoxicillin 1.0 g and rabeprazole 20 mg twice daily for the first 5 d followed by rabeprazole 20 mg, clarithromycin 500 mg and tinidazole 500 mg twice daily for the remaining 5 d (10 d total)	Prospective, open-label study performed from March 2008 to August 2011 at the Korea University Anam Hospital Sample: 460 patients equally divided among the groups	Triple therapy (7 d): Taste alteration (1), Loose stools (3), Abdominal distention (2), Nausea/vomiting (2), and Epigastric discomfort (3). Triple therapy (10 d): Taste alteration (1), Loose stools (3), Abdominal distention (3), Nausea/vomiting (4), Epigastric discomfort (2), and Itching (1). Triple therapy (14 d): Taste alteration (1), Loose stools (2), Abdominal distention (3), Nausea/vomiting (3), Epigastric discomfort (3), and Itching (3). Sequential therapy: Taste alteration (1), Loose stools (3), Abdominal distention (3), Nausea/vomiting (4), Epigastric discomfort (3), and Itching (1)	Triple therapy (7 d): 70.4% (UBT) Triple therapy (10 d): 74.7% (UBT) Triple therapy (14 d): 80% (UBT) Sequential therapy (14 d): 75.6% (UBT)	The compliance was greater than 95% for all groups	No significant differences between the 10-d sequential eradication therapy for <i>H. pylori</i> and any duration of the standard triple treatments were observed in the Korean patients	Choi <i>et al</i> ^[43]

Sequential Therapy with Quadruple Therapy	Quadruple therapy: esomeprazole 40 mg, amoxicillin 1 g, levofloxacin 500 mg and tinidazole 500 mg, all given twice daily for 5 consecutive days. Sequential therapy: esomeprazole 40 mg twice daily and amoxicillin 1 g twice daily for 5 d followed by esomeprazole 40 mg, levofloxacin 500 mg and tinidazole 500 mg, all given twice daily for 5 additional days	Prospective, randomized, controlled study performed between January and December 2011 in Italy. Sample: 468 patients. Each group consisted of 90 patients	Quadruple therapy: Diarrhea (9), Epigastric pain (6), Nausea (6), Vomiting (5), Glossitis (7), Bad taste/taste alteration (25), Headache (4), Itching (5), and Skin rash (5). Sequential therapy: Diarrhea (7), Epigastric pain (7), Nausea (5), Vomiting (3), Glossitis (6), Bad taste/taste alteration (24), Headache (3), Itching (2), and Skin rash (2)	Quadruple therapy: 92.2% (ITT), 95% (PP) Sequential therapy: 93.3% (ITT), 95.5% (PP)	Discontinuation of therapy: quadruple therapy: 4 patients (4.4%) Sequential therapy: 2 patients (2.2%)	Five days of levofloxacin-containing quadruple concomitant therapy was effective, safe, and less costly in eradicating <i>H. pylori</i> infection compared with 10 d of levofloxacin-containing sequential therapy	Federico <i>et al.</i> ^[50]
Sequential Therapy with Quadruple Therapy	Sequential therapy: esomeprazole 20 mg twice daily and amoxicillin 1 g twice daily for the first 5 d followed by esomeprazole 20 mg twice daily, clarithromycin 500 mg twice daily and metronidazole 400 mg four times daily for the subsequent 5 d Quadruple therapy: esomeprazole 20 mg twice daily, bismuth subcitrate 120 mg four times daily, tetracycline 500 mg four times daily and metronidazole 400 mg four times daily for a total of 10 d	Prospective, open-label, randomized, crossover study performed at the Department of Medicine, Queen Mary Hospital, Hong Kong, China. Sample: 357 patients. 179 in the sequential therapy group, and 178 in the quadruple therapy group	Sequential therapy: Nausea (1), Vomiting (2), Increased stool frequency (1), Abdominal pain (1), Skin rash (4), Taste disturbance (3), Dizziness (1), and Headache (1). Quadruple therapy: Nausea (6), Vomiting (4), Increased stool frequency (3), Abdominal pain (3), Skin rash (4), Taste disturbance (2), Dizziness (3), Headache (2), Insomnia (1), and Fatigue (1)	Sequential therapy: 89.4% (ITT), 95.2 (PP) Quadruple therapy: 92.7% (ITT), 98.9% (PP)	Sequential therapy: 92.7% and quadruple therapy: 91.6%	Both sequential therapy and modified bismuth containing quadruple therapy were highly effective as first-line therapies in eradicating <i>H. pylori</i> in Hong Kong Chinese patients with a low frequency of adverse events	Liu <i>et al.</i> ^[55]
Sequential Therapy with Concomitant Therapy and Triple Therapy	Sequential therapy: pantoprazole 40 mg twice daily and amoxicillin 1 g twice daily for 5 d followed by pantoprazole 40 mg, clarithromycin 500 mg and metronidazole 500 mg, all given twice daily for an additional 5 d Concomitant treatment: pantoprazole 40 mg, clarithromycin 500 mg, amoxicillin 1 g and metronidazole 500 mg, all given twice daily for 7 d Triple therapy: pantoprazole 40 mg, clarithromycin 500 mg, and amoxicillin 1 g, all given twice daily for 7 d	Open-label, randomized trial conducted at the Kaohsiung Veterans General Hospital in Taiwan Sample: 306 patients equally divided among groups	Sequential therapy: Constipation (1), Taste perversion (2), Headache (1), Anorexia (1), Nausea (5), Vomiting (5), Fatigue (1), and Others (1). Concomitant therapy: Abdominal pain (1), Diarrhea (1), Taste perversion (4), Headache (5), Anorexia (1), Nausea (7), Vomiting (7), and Others (3). Triple therapy: Constipation (1), Diarrhea (3), Taste perversion (1), Nausea (3), Vomiting (4), Skin rash (1), and Others (1)	Sequential therapy: 89.2% (ITT), 90% (PP) Concomitant therapy: 94.1% (ITT), 94.1% (PP) Triple therapy: 81.6% (ITT), 82.2% (PP)	All groups displayed similar compliance rates: triple therapy: 99.0% sequential therapy: 98.0%, concomitant therapy: 100%	Concomitant therapy is superior to standard triple therapy for <i>H. pylori</i> eradication and is less complex than sequential therapy because the drugs are not changed halfway through the treatment course	Hsu <i>et al.</i> ^[54]

Quadruple Therapy with Triple Therapy	Group A: quadruple therapy; omeprazole 20 mg, metronidazole 500 mg, amoxicillin 1 g and bismuth subcitrate 240 mg, all given twice daily for 14 d Group B: triple therapy with penbactam; omeprazole 20 mg, clarithromycin 500 mg and penbactam 750 mg, all given twice daily for 14 d Group C: triple therapy; omeprazole 20 mg, clarithromycin 500 mg and amoxicillin 1 g, all given twice daily for 14 d	A prospective double-blind, randomized clinical trial conducted at Taleghani Hospital in Tehran, Iran, from March 2007 to September 2011. Sample: 110 patients equally divided among each group	Group A: Dyspepsia (13), Diarrhea (8), Nausea (14), Abdominal pain (9), Stool abnormality (14), Dizziness (4), Headache (6), Cough (2), Bad taste (3), and Metallic taste (15) Group B: Dyspepsia (10), Diarrhea (6), Nausea (10), Abdominal pain (6), Stool abnormality (8), Dizziness (2), Headache (3), Cough (1), Bad taste (35), and Metallic taste (2) Group C: Dyspepsia (12), Diarrhea (14), Nausea (11), Abdominal pain (11), Stool abnormality (7), Dizziness (2), Headache (8), Cough (2), Bad taste (37), and Metallic taste (5)	Group A: 87% (UBT) Group B: 90.8% (UBT) Group C: 56% (UBT)	Not described	Seyedmajidi <i>et al</i> ^[46] Two-week quadruple therapy showed a lower eradication rate compared to common triple treatment schedules when used as the first-line eradication treatment for <i>H. pylori</i> infection in Iranian population
Quadruple Therapy with Triple Therapy	Group A: quadruple therapy; omeprazole 20 mg, metronidazole 500 mg, amoxicillin 1 g and bismuth subcitrate 240 mg for 14 d Group B: triple therapy with penbactam; omeprazole 20 mg, clarithromycin 500 mg and penbactam 750 mg Group C: triple therapy; omeprazole 20 mg, clarithromycin 500 mg and amoxicillin 1 g, all given twice daily	A prospective, double-blind, randomized clinical trial carried out at Taleghani Hospital in Tehran from March 2006 to September 2008 Sample: 330 patients, 110 in each group	Group A: Dyspepsia (13), Diarrhea (8), Nausea (14), Abdominal pain (9), Stool abnormality (14), Dizziness (4), Headache (6), Cough (2), Bad taste (3), and Metallic taste (15) Group B: Dyspepsia (10), Diarrhea (6), Nausea (10), Abdominal pain (8), Stool abnormality (2), Dizziness (3), Headache (1), Cough (1), Bad taste (35), and Metallic taste (2) Group C: Dyspepsia (12), Diarrhea (14), Nausea (11), Abdominal pain (11), Stool abnormality (7), Dizziness (2), Headache (8), Cough (2), Bad taste (37), and Metallic taste (5)	Group A: 87% (UBT) Group B: 88.8% (UBT) Group C: 56% (UBT)	Not described	Seyedmajidi <i>et al</i> ^[47] Two-week quadruple therapy showed a lower eradication rate compared to the common triple treatment schedules when used as the first-line eradication treatment for <i>H. pylori</i> infection in the Iranian population
Quadruple Therapy with Triple Therapy	Quadruple therapy: esomeprazole 20 mg, clarithromycin 0.5 g, amoxicillin 1.0 g, and bismuth potassium citrate 220 mg for 7 d Triple therapy: esomeprazole 20 mg, clarithromycin 0.5 g and amoxicillin 1.0 g for 7 d	Prospective, open-label, randomized study Sample: 136 patients divided equally between the groups	Not described	Quadruple therapy: 82.09% (ITT), 88.71% (PP) Triple therapy: 66.67% (ITT), 73.02% (PP)	Not described	Xu <i>et al</i> ^[48] Compared to the standard triple therapy regimen, the bismuth-containing quadruple therapy regimen has a higher eradication rate and is more cost effective than the triple therapy
Quadruple Therapy with Triple Therapy	Triple therapy: proton pump inhibitor, amoxicillin 1,000 mg b.i.d., and clarithromycin 500 mg b.i.d. Quadruple therapy: proton pump inhibitor 12/h, metronidazole 500 mg t.i.d., tetracycline 500 mg q.i.d., and bismuth 300 mg q.i.d	Prospective, open-label study performed in Korea from 2001 to 2007 Sample: 4688 patients; 4198 in the triple therapy group, and 490 in the quadruple therapy group	Not described	UBT analyses: Triple therapy: 2001: 81.3%, 2002: 83.7% 2003: 80.1% 2004: 80.7% 2005: 82.0% 2006: 75.9% 2007: 77.5% Quadruple therapy: 2001: 77.3%, 2002: 86.2%, 2003: 95.6%, 2004: 95.9%, 2005: 89.6%, 2006: 83.2%, 2007: 86.4%	Not described	Chung <i>et al</i> ^[49] The eradication rate of the first-line therapy (triple therapy) has decreased over the last 7 yr, while that of the second-line therapy (quadruple therapy) has remained the same

Quadruple Therapy with Triple Therapy	Triple therapy: rabeprazole 20 mg o.d., levofloxacin 500 mg o.d., and amoxicillin 1 g b.i.d. (4 tablets/d) for 7 d. Quadruple therapy: rabeprazole 20 mg, clarithromycin 500 mg, tinidazole 500 mg and bovine lactoferrin 200 mg, all given twice daily (10 tablets/d) for 7 d	Prospective, open-label, randomized, multicenter Italian study involving five hospitals (one northern, two central, two southern) Sample: 144 patients; 72 in the triple therapy group, and 72 in the quadruple therapy group	Triple therapy: eight (11.3%) patients presented with side effects, including diarrhea (2), abdominal pain (2), glossitis (2), pruritus (1), and vomiting (1). Quadruple therapy: seven (10.3%) patients presented with side effects, including diarrhea (3), abdominal pain (2), and taste disturbance (2)	Triple therapy: 68.1% (ITT), 68.2% (PP) Quadruple therapy: 72.2% (ITT), 76.5% (PP)	The reported compliance to the therapy was excellent in all groups, but one patient in the triple therapy group stopped the treatment after 6 d	The <i>H. pylori</i> eradication rates following both quadruple therapy with lactoferrin and low-dose, triple therapy with levofloxacin were low	Zullo <i>et al.</i> ^[4]
Quadruple Therapy with Triple Therapy	Triple therapy: pantoprazole 40 mg b.i.d., amoxicillin, 1.0 g b.i.d. and clarithromycin 500 mg b.i.d. for 7 d. Quadruple therapy: pantoprazole 40 mg b.i.d., colloidal bismuth subcitrate, 220 mg b.i.d., metronidazole 400 mg t.i.d., and tetracycline 750 mg b.i.d. for 10 d	Single-center, randomized, open, parallel, controlled study performed at the Emergency Department, Renji Hospital, Shanghai Jiaotong University from 2008 to 2009 in China Sample: 170 patients; 85 in the triple therapy group, and 85 in the quadruple therapy group	Triple therapy (60%): Bitter taste, nausea, poor appetite, vomiting, drug eruption Quadruple therapy (42.3%): Bitter taste, nausea, poor appetite, diarrhea, vomiting, drug eruption	Triple therapy: 63.5% (ITT), 65.1% (PP) Quadruple therapy: 89.4% (ITT), 91.6% (PP)	All patients completed the study	The quadruple therapy was more effective than the triple therapy	Zheng <i>et al.</i> ^[23]
Quadruple Therapy with Triple Therapy	Triple therapy: PPI b.i.d., clarithromycin 500 mg b.i.d., and amoxicillin 1 g b.i.d. for 1 wk Quadruple therapy: esomeprazole 20 mg b.i.d., tripotassium dicitrate bismuthate 300 mg q.i.d. (three tabs at 30 minutes before meals and one tab at 2 hours after dinner), metronidazole 500 mg t.i.d., and tetracycline 500 mg q.i.d. for 2 wk	Prospective, open-label, randomized study performed at the Seoul National University Bundang Hospital (SNUBH) in Korea from April 2003 to April 2009. Sample: 227 patients equally divided between the groups	Triple therapy: Nausea/vomiting (4), Epigastric soreness or pain (6), Bloating or dyspepsia (5), Weakness or dizziness (1), Regurgitation symptoms (2), and Anorexia (1) Quadruple therapy: Diarrhea (4), Neuromyopathy (2), Nausea/vomiting (22), Epigastric soreness or pain (12), Bloating or dyspepsia (5), Weakness or dizziness (5), Regurgitation symptoms (1), and Anorexia (1)	Triple therapy: 64.3% (ITT), 77.2% (PP) Quadruple therapy: 82.6% (ITT), 93.6% (PP)	Group A: 2 patients discontinued the treatment due to adverse events Group B: 9 patients discontinued the treatment due to adverse events	Two-week bismuth-containing quadruple therapy was more effective than the 1-wk treatment in Korean patients	Lee <i>et al.</i> ^[53]

¹Method used for the detection of *H. pylori*.

and 20 mg esomeprazole twice daily for 7 d (CAF); the patients in group 2 received 500 mg levofloxacin once daily, 1000 mg amoxicillin twice daily, and 20 mg esomeprazole twice daily for 7 d; and the patients in group 3 received 500 mg levofloxacin once daily, 500 mg clarithromycin twice daily, and 20 mg esomeprazole twice daily for 7 d (1CE). No further treatment was given, and instructions regarding treatment adherence were provided to each patient. The eradication of *H. pylori* was successful in 136/150 (90.6%) of the patients in group 3, in 127/150 (84.7%) of the patients in group 2 and in 118/150 (78.6%) of the patients in group 1.

In a multicenter, randomized, open-label, non-inferiority trial performed at 20 hospitals with lansoprazole using a 7-d triple therapy for the eradication of *H. pylori*. In this study, *et al.*^[27] revealed that esomeprazole shows greater non-inferiority and safety compared with lansoprazole using a 7-d triple therapy for the eradication of *H. pylori*. In this study, 268 patients (≥ 20 years of age) with *H. pylori* infection from 20 hospitals in Japan were randomly allocated to receive esomeprazole therapy (20 mg esomeprazole, 400 mg clarithromycin, and 750 mg amoxicillin for the first 7 d, with all drugs administered twice daily) or lansoprazole therapy (30 mg lansoprazole, 400 mg amoxicillin, and 750 mg amoxicillin for the first 7 d, with all drugs administered twice daily). Intention-to-treat (ITT) analysis showed eradication rates of 69.4% (95%CI: 61.2%-76.6%) for the esomeprazole therapy and 73.9% (95%CI: 65.9%-80.6%) for the lansoprazole therapy. The per-protocol (PP) eradication rate was 76.9% (95%CI: 68.6%-83.5%) for the esomeprazole therapy and 79.8% (95%CI: 71.9%-86.0%) for the lansoprazole therapy. Comparisons of the two therapies showed non-inferiority (ITT, $P = 0.4982$; PP, $P = 0.6423$) in both the ITT and PP analyses^[27].

Although triple therapy remains the most widely used and recommended treatment regimen throughout the world, its effectiveness depend primarily on the rate of

clarithromycin resistance, and it is not recommended in areas where these rates are higher than 20% in the population^[9,27-31]. To evaluate the use of a lower dose of clarithromycin, Kaboli *et al.*^[32] performed a clinical assay using vitamin C as an adjuvant treatment. This group demonstrated that vitamin C may allow for the reduction of the necessary dosage of clarithromycin in the eradication of *H. pylori*. Similarly, Zojaji *et al.*^[33] demonstrated that the addition of vitamin C to the *H. pylori* treatment regimen of amoxicillin, metronidazole and bismuth could significantly increase the *H. pylori* eradication rate.

The prevalence of clarithromycin resistance in *H. pylori* has been evaluated in Recife, which is a city in northeastern Brazil^[34]. From January 2006 to December 2007, 114 gastric biopsy samples positive for *H. pylori* at the time of culture were directly assayed by polymerase chain reaction (PCR) to detect the most frequent point mutations involved in clarithromycin resistance. Based on the results of the PCR, which detected three specimens with the *H. pylori*-resistant genotype, primary clarithromycin resistance was found in 15 (16.5%) patients. This prevalence has also been reported in southeastern Brazil, 16% in São Paulo, and 17.3 % in Belo Horizonte^[34]. In Colombia, Trespalacios *et al.*^[35] demonstrated resistance to triple therapy with metronidazole, clarithromycin and amoxicillin by the E-test method. Genomic DNA was extracted, and the *vacA* and *cagA* allelic variants were identified by PCR. Metronidazole resistance was observed in 81.01% of the patients (95%CI: 70.3%-88.6%), amoxicillin resistance in 38% (95%CI: 0%-8.6%), and clarithromycin resistance in 17.72% (95%CI: 10.37-28.29)^[33]. Clarithromycin resistance was demonstrated in 47.5% of patients with dyspepsia at the Endoscopy Unit of the Department of Gastroenterology, Duzce University, Medical Faculty Hospital, Konuralp/Duzce, Turkey^[35]. These findings demonstrate the need for new therapies in populations in which there is resistance to clarithromycin.

SEQUENTIAL THERAPY

Sequential therapy was introduced in Italy in 2000. This regimen is a simple 10-d dual therapy that includes a PPI plus 1 g amoxicillin, which are both administered twice daily for the first 5 d, after which patients undergo triple therapy, which includes a PPI, 500 mg clarithromycin, and tinidazole (all drugs are administered twice daily) for the remaining 5 d. In general, this regimen represents a novel therapeutic approach based on different combinations of available antibiotics^[14,15,17].

As demonstrated by some studies, one advantage of the sequential treatment is that its efficacy appears to be less affected by clarithromycin resistance compared with that of the triple therapy^[36]; for this reason, this type of therapy has the potential to become the standard first-line treatment for *H. pylori* infection^[37-42].

Various trials have compared the efficacies of

sequential therapies with that of the standard triple therapy in curing *H. pylori* infection. In Taiwan, a multicenter, open-label, randomized study performed at gastroenterology clinics at six studies demonstrated that the use of 30 mg lansoprazole and 1 g amoxicillin for the first 5 d followed by 30 mg lansoprazole, 500 mg clarithromycin, and 500 mg metronidazole for an additional 5 d and the use of 14 d of 30 mg lansoprazole and 1 g amoxicillin for the first 7 d followed by 30 mg lansoprazole, 500 mg clarithromycin, and 500 mg metronidazole for an additional 7 d have the same efficacies compared with that of 14 d of standard triple therapy (30 mg lansoprazole, 1 g amoxicillin, and 500 mg clarithromycin)^[37].

However, at an outpatient center of an academic medical center in Turkey, patients were treated with 40 mg esomeprazole and 1 g amoxicillin for the first week followed by 40 mg esomeprazole, 500 mg levofloxacin and 500 mg metronidazole for the second week, and the results were compared with those obtained from patients treated with standard triple therapy (40 mg esomeprazole, 1 g amoxicillin and 500 mg clarithromycin) for 2 wk. This study revealed that the *H. pylori* eradication rate per protocol was 90% in the sequential treatment group versus 57% in the standard treatment group; this difference was statistically significant ($P < 0.000$)^[38]. Another study performed in Turkey compared the effects of 14 d of an amoxicillin treatment (40 mg pantoprazole and 1 g amoxicillin for 5 d followed by 40 mg pantoprazole, 500 mg tetracycline, 500 mg metronidazole, and 1 g amoxicillin for the remaining 9 d) and 5 d of an alternative amoxicillin treatment (40 mg pantoprazole and 1 g amoxicillin for 5 d followed by 40 mg pantoprazole and 500 mg tetracycline) administered during tetracycline-containing sequential *H. pylori* therapy on the eradication rate. This group showed that an extended duration of amoxicillin administration during the entire tetracycline-containing sequential therapy period did not improve the *H. pylori* eradication rate, which may indicate that sequential therapy using 5 d of amoxicillin is an acceptable first-line therapy option for the eradication of *H. pylori* in the Turkish population^[39].

Also in Turkey, the efficacy of a modified sequential therapy with bismuth subcitrate as a first-line therapy was demonstrated. The patients received 40 mg pantoprazole for 14 d, 4: 300 mg colloidal bismuth subcitrate tablets per d (two tablets before breakfast and dinner for 14 d), 1 g amoxicillin (for the first 7 d), 500 mg tetracycline (for the second 7 d) and 500 mg metronidazole (for the second 7 d)^[41]. When compliance was observed, the results were satisfactory, and the side effects were minimal; all of the side effects could be reversed and resolved after the cessation of the related treatment^[41].

When the treatment times were compared, similar results were observed^[37,42,43]. As described above, in Taiwan, there was no difference between standard triple therapy and a 10-d sequential treatment using 30 mg lansoprazole and 1 g amoxicillin for the first 5 or 7 d followed by 30 mg lansoprazole, 500 mg clarithromycin,

and 500 mg metronidazole for an additional 5 or 7 d^[37]. Furthermore, when we compared the efficacies of 14-d (40 mg pantoprazole and 1 g amoxicillin for 5 d followed by 40 mg pantoprazole, 500 mg tetracycline, 500 mg metronidazole, and 1 g amoxicillin for the remaining 9 d) and 5-d (40 mg pantoprazole and 1 g amoxicillin for 5 d followed by 40 mg pantoprazole, 500 mg tetracycline, and 500 mg metronidazole for the remaining 9 d) amoxicillin treatments we observed no difference, which indicates that sequential therapy using 5 d of amoxicillin treatment is an acceptable first-line option for the eradication of *H. pylori* in Turkish patients^[42]. In Korean patients, a different comparison was made. The 10-d sequential treatment (1.0 g amoxicillin and 20 mg rabeprazole twice daily for the first 5 d followed by 20 mg rabeprazole, 500 mg clarithromycin and 500 mg tinidazole twice daily for the remaining 5 d) was compared with (1) standard triple therapy (20 mg rabeprazole, 1.0 g amoxicillin and 500 mg clarithromycin twice daily) for 7 d; (2) standard triple therapy for 10 d; and (3) standard triple therapy for 14 d. No significant differences between the 10-d sequential eradication therapy for *H. pylori* and any duration of the standard triple treatment tested (7-, 10- and 14-d regimens) were observed in these patients^[43].

Collectively, these results suggest that the sequential treatment may be used as the standard first-line treatment for infection with *H. pylori* in Taiwanese^[34,35], Turkish^[36,38-42] and Greek^[37] patients. Moreover, the 14-d sequential therapy combined with bismuth has been shown to achieve high eradication rates in Turkish patients infected with *H. pylori*^[38].

QUADRUPLE THERAPY

A significant number of patients remain infected despite several consecutive standard treatment regimens. Increased resistance to clarithromycin and metronidazole has been reported as the main cause of the decreased success rates of *H. pylori* eradication therapies, and several studies have reported intention-to-treat eradication rates of less than 80%^[41,42]. Because of the non-satisfactory results observed with PPI-based triple regimens, the uses of second-line therapies have increased, including the use of bismuth-containing quadruple therapy (PPI, bismuth citrate, tetracycline, and metronidazole). This therapy comprises a PPI, tetracycline or amoxicillin and doxycycline, metronidazole and a bismuth salt^[9]. Although many studies have reported the efficacy of quadruple therapy, those performed on the Iranian population have demonstrated a lower eradication rate compared with those achieved using the common triple-treatment regimens^[43,44]. These studies compared a 14-d quadruple therapy comprising 20 mg omeprazole, 500 mg metronidazole, 1 g amoxicillin, and 240 mg bismuth subcitrate (twice daily) with a 14-d triple regimen.

In contrast to these findings, an additional study performed on the Iranian population demonstrated that a bismuth-containing quadruple regimen (20 mg

esomeprazole, 0.5 g clarithromycin, 1.0 g amoxicillin, and 220 mg bismuth potassium citrate for 7 d) achieved a very high eradication rate compared with those observed using classical triple therapies^[45]. In addition, in the Chinese population, the efficacy of a quadruple therapy containing doxycycline (20 mg esomeprazole, 220 mg bismuth potassium citrate, 1 g amoxicillin and 100 mg doxycycline, all b.i.d. for ten d) or tetracycline (20 mg esomeprazole b.i.d., 220 mg bismuth potassium citrate b.i.d., 400 mg metronidazole b.i.d. and 750 mg tetracycline q.i.d. every 6 h for ten d) was demonstrated^[46].

The main adverse effects of the 4-drug regimen observed in the clinical trials were black stool, nausea, headache and dizziness. However, the safety of these drugs during pregnancy is still unknown^[47].

Our comparison of the efficacies of the different quadruple-therapy protocols with the treatment period, produced contrasting results. A Korean study involved 227 patients with persistent *H. pylori* infection that had been previously treated with first-line PPI-clarithromycin-amoxicillin triple therapy, who were randomized to 1-week (112 patients) and 2-week (115 patients) quadruple therapies with 300 mg tripotassium dicitrate bismuthate q.i.d., 500 mg metronidazole t.i.d., 500 mg tetracycline q.i.d. and 20 mg esomeprazole b.i.d. This study demonstrated that the two-week bismuth-containing quadruple therapy was more effective than the 1-week treatment and should be considered as a second-line treatment^[48-51]. However, Agah *et al.*^[52] (2009) compared the efficacies of two quadruple-therapy regimens for *H. pylori* eradication in patients with dyspepsia; one included azithromycin, and the other included metronidazole. The first group of patients received 500 mg metronidazole b.i.d, 1 g amoxicillin b.i.d, 20 mg omeprazole b.i.d, and 240 mg bismuth b.i.d, and the second group received 500 mg azithromycin once daily for 1 wk and 1 g amoxicillin b.i.d, 20 mg omeprazole b.i.d, and 240 mg bismuth b.i.d for 2 wk. No significant differences were observed between the two quadruple-therapy regimens that were evaluated^[49]. However, Rogha *et al.*^[53] (2009) demonstrated that one-week quadruple regimens involving 3 d of azithromycin treatment (500 mg azithromycin twice daily for 3 d and 20 mg omeprazole, 1 g amoxicillin, and 240 mg bismuth all twice daily for 1 wk) might be more favorable for *H. pylori* eradication compared with a two-week quadruple-therapy regimen (500 mg azithromycin twice daily for 6 d and 20 mg omeprazole, 1 g amoxicillin, 240 mg bismuth all twice daily for 2 wk)^[50].

Furthermore, a novel non-bismuth quadruple therapy, the concomitant therapy, has been proven successful in the presence of clarithromycin resistance. It is a 4-drug regimen containing a PPI, clarithromycin, amoxicillin and metronidazole, which are all administered for the entire duration of therapy. It is less complex than sequential therapy and has excellent potential for replacing standard triple therapy as the first-line treatment for *H. pylori* infection, particularly in regions with high levels of clarithromycin resistance^[54]. In a prospective, randomized,

controlled study performed by Hsu *et al.*^[54] conducted at the Kaohsiung Veterans General Hospital in Taiwan, concomitant therapy was shown to be superior to triple therapy for *H. pylori* eradication and less complex than sequential therapy. Similarly, Liu *et al.*^[55] showed that both sequential therapy and modified bismuth-containing quadruple therapy were highly effective in Hong Kong Chinese patients.

CONCLUSION

Studies of new drug therapies for the eradication of *H. pylori* have shown improved efficacies compared with that of standard triple therapy, which is mainly limited by clarithromycin resistance. Therefore, further research on clarithromycin resistance in patients worldwide is essential to ensure for the development of adequate treatments because treatments using this antibiotic have been proven to be effective in some regions of the world. Further validation studies of different treatment method in addition to resistance studies are essential for providing clinicians with a greater range of options for the eradication of *H. pylori*.

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P- Reviewer: Luo HS, Suarez J **S- Editor:** Qi Y **L- Editor:** A
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ISSN 1007-9327



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