Meta-Analysis of Sequential, Concomitant and Hybrid Therapy for *Helicobacter pylori* Eradication

Lei He, Tao Deng and Hesheng Luo

Abstract

Objective To compare the efficacy of sequential therapy, concomitant therapy and hybrid therapy for the treatment of *Helicobacter pylori* (*H. pylori*) infection.

Methods PubMed, Web of Science, Medline, Embase, the Cochrane Central Register of Controlled Trials and CNKI were searched up to the end of May 10, 2014 in order to identify all randomized controlled trials (RCTs) reporting the effects of sequential therapy, concomitant therapy and hybrid therapy on *H. pylori* eradication. The relative risk (RR) of eradicating *H. pylori* infection after sequential therapy compared with concomitant therapy or hybrid therapy was pooled. The eradication rates were considered both on an intention-to-treat (ITT) and per-protocol (PP) basis.

Results A total of 10 RCTs involving 3,501 patients were included. The pooled data suggested that the differences between the three groups were not statistically significant (ITT analysis: sequential therapy vs. concomitant therapy: RR=1.01, 95%confidence interval (CI): 0.97-1.04, sequential therapy vs. hybrid therapy: RR=1.02, 95%CI: 0.85-1.22, concomitant therapy vs. hybrid therapy: RR=1.03, 95%CI: 0.97-1.08; PP analysis: sequential therapy vs. concomitant therapy: RR=1.00, 95%CI: 0.96-1.03, sequential therapy vs. hybrid therapy: RR=0.97, 95%CI: 0.86-1.09, concomitant therapy vs. hybrid therapy: RR=1.01, 95%CI: 0.93-1.10). In the ITT and PP analyses, the overall eradication rates were 84.3% (95%CI: 79.1-89.4) and 86.4% (95%CI: 81.7-91.0) for the sequential therapy group, 86.7% (95%CI: 81.0-92.3) and 89.8% (95%CI: 85.1-94.5) for the concomitant therapy group and 86.6% (95%CI: 82.3-91.0) and 92.7% (95%CI: 90.5-94.9) for the hybrid therapy group, respectively. There were no significant differences among these therapies in terms of the rate of side effects.

Conclusion The pooled evidence suggests that sequential therapy, concomitant therapy and hybrid therapy are similar with respect to the treatment of *H. pylori* infection.

Key words: eradication, *Helicobacter pylori*, sequential therapy, concomitant therapy, hybrid therapy, meta-analysis

(Intern Med 54: 703-710, 2015)

(DOI: 10.2169/internalmedicine.54.3442)

Introduction

Helicobacter pylori (*H. pylori*) infection is present in at least 50% of the world's human population and is well recognized to be the main cause of gastritis, peptic ulcers and gastric cancer (1). Currently, the most often recommended treatment for the eradication of *H. pylori* remains triple therapy [a proton pump inhibitor (PPI) and clarithromycin with either amoxicillin or metronidazole] (2, 3). However, with

the increasing rate of *H. pylori* resistance to antibiotics in most countries, the eradication rate of *H. pylori* achieved with triple therapy is currently decreasing to an unacceptable level ($\leq 80\%$) (4, 5). Therefore, several regimens have been proposed as alternative first-line treatments for *H. pylori* infection, including sequential, concomitant and hybrid regimens.

Sequential therapy, which consists of the administration of a PPI and amoxicillin for the first five days followed by a PPI, clarithromycin and tinidazole for the remaining five

days, was pioneered in Italy in 2000 (6). The superiority of this therapy over standard triple therapy has been widely documented (7). Meanwhile, concomitant therapy, first introduced in 1998 (8, 9), is now being reconsidered as a first-line *H. pylori* eradication therapy (10). The concomitant regimen includes quadruple therapy with standard triple therapy (PPI, clarithromycin, amoxicillin) plus metronidazole or tinidazole. The duration of treatment is not standardized and various durations, ranging widely from three to 14 days, have been proposed. However, various studies have demonstrated the high (>90%) efficacy of concomitant therapy, even when administered for only five days (11). Hybrid therapy combines the sequential and concomitant therapy regimens with seven days of dual therapy (PPI and amoxicillin) followed by seven days of quadruple therapy (a PPI, amoxicillin, clarithromycin and metronidazole) (12). Some studies have reported the seven-day plus seven-day hybrid therapy to achieve high eradication rates (12, 13).

Recently, several studies have examined the efficacy of these therapies for *H. pylori* eradication (14-24). However, there is currently no consensus regarding the optimal strategy. Therefore, we conducted a meta-analysis of published data in order to evaluate the efficacy and safety of sequential, concomitant and hybrid therapy regimens for use in *H. pylori* eradication.

Materials and Methods

Search strategy

A literature search was conducted using PubMed, Web of Science, Medline, Embase, the Cochrane Central Register of Controlled Trials and CNKI up to May 10, 2014 without language restrictions. Relevant studies were identified using the following terms: “*Helicobacter pylori* or *H. pylori*,” “eradication,” “sequential therapy,” “concomitant therapy” and “hybrid therapy.” The search was restricted to human subjects. Additional studies were identified using a hand search of references of original and review articles as well as international conferences on this topic, primarily including Asian Pacific Digestive Week, United European Gastroenterology Week and American Gastroenterological Association Digestive Disease Week.

Inclusion criteria

Studies were included if they met the following criteria: 1) randomized controlled trials (RCTs) comparing the efficacy of sequential therapy, concomitant therapy or hybrid therapy for *H. pylori* eradication, 2) sequential therapy regimens consisting of a PPI plus amoxicillin for the first phase of treatment followed by a PPI, clarithromycin and tinidazole (or metronidazole) for the next phase, 3) concomitant therapy regimens consisting of a PPI, amoxicillin, clarithromycin and tinidazole (or metronidazole), 4) hybrid therapy regimens consisting of a PPI and amoxicillin for seven days followed by a PPI, amoxicillin, clarithromycin and tinida-

zole (or metronidazole) for seven days, 5) the patients had not received previous treatment for *H. pylori* infection, 6) the patients were confirmed to have *H. pylori* infection and eradication was subsequently verified according to at least one of the following methods: a rapid urease test (RUT), *H. pylori* culture, histology or urea breath test (UBT).

Data extraction

Two investigators (He L., Deng T.) independently extracted the data and reached a consensus for all items. If the investigators generated different results, they checked the data again and had a discussion in order to reach an agreement. If they were unable to reach an agreement, an expert (Luo H.S.) was invited to join the discussion. The data extracted from the selected articles included the first author's name, year of publication, country of origin, baseline characteristic of the patients, details of *H. pylori* eradication therapy (dosage and duration), methods of diagnosing infection and confirming eradication and incidence of side effects.

Quality assessment

The quality of the included studies was assessed according to the Jadad scale (25). In this scale, the scores range from 1 to 5, with a higher score indicating higher quality. The scores are determined based on the method of randomization, level of blinding, concealment of allocation and use of complete accounting of all randomized patients. We considered RCTs with a score greater than 3 to be of high quality.

Outcome measurements

The primary outcome of this study was the relative risk (RR) of eradication rates of the sequential therapy, concomitant therapy and hybrid therapy regimens. The secondary outcome was the RR of adverse events of the sequential therapy, concomitant therapy and hybrid therapy regimens. The eradication rates were considered both on an intention-to-treat (ITT) and per-protocol (PP) basis.

Statistical analysis

A meta-analysis was performed using the Cochrane Collaboration RevMan 5.2 (The Nordic Cochrane Center, Copenhagen, Denmark) and STATA package version 12.0 (Stata, College Station, USA). The analyses were carried out by calculating the pooled estimates of the primary and secondary endpoints. The χ^2 -test-based Q statistic test was performed to assess the between-study heterogeneity (26). We also quantified the effect heterogeneity according to the I^2 test. For significant Q tests ($p < 0.05$) or $I^2 > 50\%$ values indicating heterogeneity across the studies, the random effects model was used (27); otherwise, the fixed effects model was used (28). An analysis of sensitivity was performed to evaluate the stability of the results. Finally, potential publication bias was investigated using Begg's funnel plot and Egger's regression test (29, 30). A p value of < 0.05 was regarded as

being statistically significant.

Results

Study characteristics

According to the search strategy, a total of 153 citations were identified. A total of 11 RCTs (14-24) were selected based on the inclusion criteria and subjected to a further examination. We excluded one study (24) because the authors used levofloxacin rather than clarithromycin as concomitant therapy. Therefore, 10 RCTs (14-23) with 3,501 patients were included in the meta-analysis. The characteristics of the selected studies are summarized in Table. Of the 10 eligible studies, five RCTs (14, 17, 18, 21, 22) were conducted in Asia, four RCTs (15, 19, 20, 23) were performed in Europe and one study (16) was carried out in Latin America; all studies were published in English (nine full-text articles and one abstract). A quality assessment of the included studies was performed using the Jadad score. No trials met all quality measurements; however, all scores were greater than 3, thus indicating high quality.

Quantitative data synthesis

Primary outcome

Sequential therapy vs. concomitant therapy

Eight studies (14-19, 22, 23) compared sequential therapy with concomitant therapy. In all, 1,220 patients were treated with sequential therapy and 1,321 patients were treated with concomitant therapy. The ITT eradication rate was 85.2% [95%confidence interval (CI): 79.8-90.7] for sequential therapy and 86.0% (95%CI: 79.6-92.4) for concomitant therapy, the PP eradication rate was 87.3% (95%CI: 82.4-92.2) for sequential therapy and 88.8% (95%CI: 83.9-93.6) for concomitant therapy. Significant heterogeneity was present for all pooled eradication rates, and the random effects model was used. The pooled RR of the ITT eradication rates was 1.01 (95%CI: 0.97-1.04, $p=0.75$) with the fixed effects model (Fig. 1A). The pooled RR of the PP eradication rates was 1.00 (95%CI: 0.96-1.03, $p=0.92$) with the fixed effects model (Fig. 2A).

In the subgroup analyses based on the duration of concomitant therapy (5, 10, 14 days), four studies compared sequential therapy with concomitant therapy administered for 10 days, and the pooled RR with the fixed effects model of the ITT and PP eradication rates was 0.95 (95%CI: 0.91-1.00, $p=0.03$) and 0.95 (95%CI: 0.91-1.00, $p=0.05$), respectively. Meanwhile, three studies compared sequential therapy with concomitant therapy administered for five days, and the pooled RR with the fixed effects model of the ITT and PP eradication rates was 1.06 (95%CI: 1.00-1.12, $p=0.03$) and 1.04 (95%CI: 0.99-1.09, $p=0.13$), respectively, and two studies compared sequential therapy with concomitant therapy administered for 14 days and the pooled RR with the fixed effects model of the ITT and PP eradication rates was 1.00 (95%CI: 0.92-1.09, $p=0.97$) and 0.97 (95%CI: 0.90-1.05, $p=$

0.48), respectively.

Regarding antibiotic resistance, two studies (17, 22) reported available data, and the pooled results showed the efficacy of sequential therapy and concomitant therapy for the antibiotic-resistant strains to be comparable.

Sequential therapy vs. hybrid therapy

Three studies (15, 21, 23) compared sequential therapy with hybrid therapy. In all, 410 patients were treated with sequential therapy and 410 patients were treated with hybrid therapy. The ITT eradication rate was 85.9% (95%CI: 76.9-95.0) for sequential therapy and 84.9% (95%CI: 78.8-91.0) for hybrid therapy, and the PP eradication rate was 88.8% (95%CI: 80.2-97.4) for sequential therapy and 92.2% (95%CI: 87.7-96.8) for hybrid therapy. Significant heterogeneity existed for all of the pooled eradication rates, and the random effects model was used. The pooled RR of the ITT eradication rates was 1.02 (95%CI: 0.85-1.22, $p=0.86$) with the random effects model (Fig. 1B), while the pooled RR of the PP eradication rates was 0.97 (95%CI: 0.86-1.09, $p=0.57$) with the random effects model (Fig. 2B).

Concomitant therapy vs. hybrid therapy

Three studies (15, 20, 23) compared concomitant therapy with hybrid therapy. In total, 480 patients were treated with concomitant therapy and 370 patients were treated with hybrid therapy. The ITT eradication rate was 86.7% (95%CI: 80.4-93.0) for concomitant therapy and 84.9% (95%CI: 78.5-91.3) for hybrid therapy, and the PP eradication rate was 92.9% (95%CI: 88.7-97.1) for concomitant therapy and 92.0% (95%CI: 87.2-96.8) for hybrid therapy. Significant heterogeneity existed for all of the pooled eradication rates, and the random effects model was used. The pooled RR of the ITT eradication rates was 1.03 (95%CI: 0.97-1.08, $p=0.37$) with the fixed effects model (Fig. 1C), and the pooled RR of PP eradication rates was 1.01 (95%CI: 0.93-1.10, $p=0.78$) with the random effects model (Fig. 2C).

Secondary outcome

Six studies (15, 17-19, 22, 23) reported available data for the side effects of sequential therapy and concomitant therapy, and the pooled RR for developing side effects with the fixed effects model was 0.98 (95%CI: 0.87-1.10, $p=0.73$) (Fig. 3A). Regarding, sequential therapy vs. hybrid therapy and concomitant therapy vs. hybrid therapy, data for therapy-related side effects were available in all studies. The pooled RR with the fixed effects model was 0.98 (95%CI: 0.87-1.10, $p=0.73$) and 0.98 (95%CI: 0.87-1.10, $p=0.73$), respectively (Fig. 3B, C). These results indicate the absence of significant differences between the three therapies in terms of side effects.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the potential publication bias in the available literature. The shape of the funnel plots did not reveal any evidence of

Table. Characteristics of Studies Included in the Meta-Analysis

Reference	Year	Country	Patients	No. of patients	Test for confirming infection	Follow-up (weeks)	Test for confirming eradication	Regimen	Concomitant therapy	Hybrid therapy	Jadad score
14	2013	Singapore	PUD+NUD +GERD	153	UBT, RUT, Histology	4	UBT	PPI+A 1g, bid, 5d; PPI+C 500mg, M 400mg, bid, 5d	PPI+A+C+M, bid, 10d	-	3
15	2014	Italy	PUD+NUD	440	RUT, Histology	6-8	¹³ C-UBT	O 20mg+A 1g, bid, 5d; O+C 500mg+T 500mg, bid, 5d	O+A+C+T, bid, 5d or 14d	O+A, bid, 7d O+A+C+T, bid, 7d	4
16	2011	Latin American	NR	975	UBT	6-8	UBT	L 30mg+A 1g, bid, 5d; L+C 500mg, M 500mg, bid, 5d	L+A+C+M, bid, 5d	-	4
17	2012	China	PUD+Gastritis	169	RUT, Histology, Culture	12	UBT	L 30mg+A 1g, bid, 5d; L+C 500mg, M 500mg, bid, 5d	L+A+C+M, bid, 10d	-	4
18	2013	South Korea	PUD+Gastritis	164	RUT, Histology	4	¹³ C-UBT	R 20mg+A 1g, bid, 7d; R+C 500mg, M 500mg, bid, 7d	R+A+C+M, bid, 14d	-	4
19	2014	Spain	PUD+NUD	338	¹³ C-UBT, RUT, Histology, Culture	4	¹³ C-UBT, Histology	O 20mg+A 1g, bid, 5d; O+C 500mg, M 500mg, bid, 5d	O+A+C+M, bid, 10d	-	3
20	2013	Italy, Spain	PUD+NUD +Others	340	¹³ C-UBT, RUT, Histology, Culture	8	¹³ C-UBT	-	O 40mg+A 1g+C 500mg+N 500mg, bid, 14d	O+A, bid, 7d O+A+C+N, bid, 7d	4
21	2012	Iran	PUD+ gastric/ duodenal erosions	420	UBT, Histology	8	UBT	P 40mg+A 1g, bid, 5d P+C 500mg+T 500mg, bid, 5d	-	P+A, bid, 7d P+A+C+T, bid, 7d	3
22	2010	Taiwan (China)	PUD+Gastritis +Others	232	RUT, Histology, Culture	6	UBT, RUT, Histology, Culture	E 40mg+A 1g, bid, 5d; E+C 500mg, M 500mg, bid, 5d	E+A+C+M, bid, 10d	-	3
23	2013	Italy	NUD	270	RUT, Histology	6	¹³ C-UBT	O 20mg+A 1g, bid, 5d; O+C 500mg, T 500mg, bid, 5d	O+A+C+T, bid, 5d	O+A, bid, 7d O+A+C+T, bid, 7d	4

PUD: peptic ulcer disease, NUD: non-ulcer dyspepsia, GERD: gastroesophageal reflux disease, UBT: urea breath test, RUT: rapid urease test, A: amoxicillin, C: clarithromycin, M: metronidazole, T: tinidazole, N: nitroimidazole, PPI: proton pump inhibitor, O: omeprazole, E: esomeprazole, L: lansoprazole, R: rabeprazole, P: pantoprazole, NR: not reported

A

B

C

Figure 1. Forest plots comparing the different therapies in terms of the eradication rates in the ITT analysis. A: sequential therapy vs. concomitant therapy; B: sequential therapy vs. hybrid therapy; C: concomitant therapy vs. hybrid therapy.

asymmetry (Fig. 4). Egger's test also showed no statistical significance for the evaluation of publication bias (ITT: $p=0.560$, PP: $p=0.071$).

Discussion

As the efficacy of standard triple therapy does not reach the acceptable threshold of an eradication rate of 80% in most contexts, new strategies must be sought (4). To date, several therapies, including sequential, concomitant and hybrid therapy regimens, have been reported to be effective treatments for *H. pylori* infection. Moreover, many previous meta-analyses have suggested that sequential therapy is superior to triple therapy for achieving *H. pylori* eradication (7, 31, 32), and a meta-analysis conducted by Essa et al. found concomitant therapy to be better than triple therapy for this purpose (33). However, among these three therapies, there are no specific recommendations for treatment choices for *H. pylori* infection.

In this study, we included 10 studies involving 3,501 patients to assess the efficacy and safety of sequential, concomitant and hybrid therapy regimens for *H. pylori* eradication. The results showed that the differences in *H. pylori*

eradication rates were not statistically significant among the three groups and the therapies achieved equivalent rates, above 80%, in both the ITT and PP analyses. Regarding the comparison of sequential therapy vs. concomitant therapy, when the analysis was stratified according to the duration of concomitant therapy, we found the sequential therapy regimen to not be superior to the 5-, 10- and 14-day concomitant therapy regimens in terms of the eradication rate. As the ideal eradication regimen for *H. pylori* infection requires an ITT eradication rate of at least 90%, our results (sequential therapy: 84.3%, 95%CI: 79.1-89.4; concomitant therapy: 86.7%, 95%CI: 81.0-92.3; hybrid therapy: 86.6%, 95%CI: 82.3-91.0) are somewhat disappointing. The suboptimal eradication rates achieved with these regimens may be explained by geographical variation in the antibiotic resistance of *H. pylori*, presence of multiple strains of infection, side effects and individual patient factors, such as compliance with treatment, type of gastritis, CYP2C19 polymorphisms (affecting PPI metabolism), smoking and body mass index. The global rate of antibiotic resistance of *H. pylori* has been reported to 17.2% for clarithromycin and 26.7% for metronidazole (34). In Italy, the dual resistance rate of clarithromycin and metronidazole has been reported to be only 3.5-

A

B

C

Figure 2. Forest plots comparing the different therapies in terms of eradication rates in the PP analysis. A: sequential therapy vs. concomitant therapy; B: sequential therapy vs. hybrid therapy; C: concomitant therapy vs. hybrid therapy.

4.3% (35). In contrast, the dual resistance rates for these antibiotics are relatively high in Asian countries [China: 20.5% (36)]. In the current study, two studies (17, 22) reported available data for antibiotic resistance, and the pooled results showed the efficacy of sequential therapy and concomitant therapy for the antibiotic-resistant strains to be comparable. However, due to the limited data, it is necessary to be very cautious when generalizing the results of this analysis, and more studies are needed.

Since the three therapies for *H. pylori* eradication were found to be equally effective in this study, the therapeutic cost should be considered. As is well known, the cost of sequential therapy is cheaper than that of 10- or 14-day concomitant or 14-day hybrid therapy. For example, in Iran, the price of the whole course of therapy with the mentioned hybrid and sequential regimens is 30.37 and 20.55 US dollars, respectively. Similarly, in South Korea, the total cost of the 14-day sequential and 10- or 14-day concomitant regimens is approximately 50, 52 and 73 US dollars per patient, respectively. In addition, the overall number of tablets administered for sequential therapy is distinctly lower than that of both the 10- and 14-day concomitant and 14-day hybrid regimens. Therefore, it is questionable to require patients to take more drugs in order to achieve the same result. How-

ever, the complicated dosing of the sequential therapy regimen, a mid-course change in drugs may result in poor compliance. With regard to side effects, although the reported pooled prevalence is somewhat different among studies, the present results indicated that there are no differences between the three therapies.

Some limitations of this meta-analysis should be addressed. First, the quality of the included RCTs was relatively low, as no trials met all quality measurements, which may have influenced the results. Second, the duration of sequential therapy and concomitant therapy was not uniform among the RCTs. The duration of sequential therapy ranged from 10 to 14 days among the studies, while that of concomitant therapy ranged from 5 to 10 to 14 days. Third, the use of various PPIs and nitroimidazole medications and the diversity of the regimes may have produced a small amount of bias.

In conclusion, this meta-analysis showed that the efficacy of sequential therapy, concomitant therapy and hybrid therapy is similar with respect to the treatment of *H. pylori* infection. The concomitant therapy regimen is less complex than that of the sequential therapy and hybrid therapy regimens. Therefore, compliance with concomitant therapy may be better in clinical practice, whereas sequential therapy has

A

B

C

Figure 3. Forest plots comparing the different therapies in terms of side effects. A: sequential therapy vs. concomitant therapy; B: sequential therapy vs. hybrid therapy; C: concomitant therapy vs. hybrid therapy.

Figure 4. Begg's funnel plot for publication bias (ITT: sequential therapy vs. concomitant therapy).

a benefit in terms of cost.

The authors state that they have no Conflict of Interest (COI).

References

- McColl KE. Clinical practice. *Helicobacter pylori* infection. N Engl J Med **362**: 1597-1604, 2010.
- Malferteiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection: the Maastricht IV/Florence Consensus Report. Gut **61**: 646-664, 2012.
- Fock KM, Katelaris P, Sugano K, et al. Second Asia-Pacific Consensus Guidelines for *Helicobacter pylori* infection. J Gastroenterol Hepatol **24**: 1587-1600, 2009.
- Gisbert JP, Calvet X. Review article: the effectiveness of standard triple therapy for *Helicobacter pylori* has not changed over the last decade, but it is not good enough. Aliment Pharmacol Ther **34**: 1255-1268, 2011.
- Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. Gut **59**: 1143-1153, 2010.
- Zullo A, Rinaldi V, Winn S, et al. A new highly effective short-term therapy schedule for *Helicobacter pylori* eradication. Aliment Pharmacol Ther **14**: 715-718, 2000.
- Gatta L, Vakil N, Leandro G, Di Mario F, Vaira D. Sequential therapy or triple therapy for *Helicobacter pylori* infection: systematic review and meta-analysis of randomized controlled trials in adults and children. Am J Gastroenterol **104**: 3069-3079, 2009.
- Treiber G, Ammon S, Schneider E, Klotz U. Amoxicillin, metronidazole, omeprazole, clarithromycin: a new, short quadruple therapy for *Helicobacter pylori* eradication. Helicobacter **3**: 54-58, 1998.
- Okada M, Oki K, Shirota T, et al. A new quadruple therapy for the eradication of *Helicobacter pylori*. Effect of pretreatment with omeprazole on the cure rate. J Gastroenterol **33**: 640-645, 1998.
- Gisbert JP, Calvet X. Update on non-bismuth quadruple (concomitant) therapy for eradication of *Helicobacter pylori*. Clin Exp Gastroenterol **5**: 23-34, 2012.
- Treiber G, Wittig J, Ammon S, Walker S, van Doorn LJ, Klotz U. Clinical outcome and influencing factors of a new short-term quadruple therapy for *Helicobacter pylori* eradication: a random-

- ized controlled trial (MACLOR study). Arch Intern Med **162**: 153-160, 2002.
12. Hsu PI, Wu DC, Wu JY, Graham DY. Modified sequential *Helicobacter pylori* therapy: proton pump inhibitor and amoxicillin for 14 days with clarithromycin and metronidazole added as a quadruple (hybrid) therapy for the final 7 days. Helicobacter **16**: 139-145, 2011.
 13. Molina-Infante J, Romano M, Fernandez-Bermejo M, et al. 14-day, high-dose acid suppression, non-bismuth quadruple therapies (hybrid vs. concomitant) for *Helicobacter pylori* infection: a randomized trial [abstract]. Gastroenterology **144**: S-53, 2013.
 14. Ang TL, Fock KM, Ang D. A randomized controlled trial of triple therapy versus sequential therapy versus concomitant therapy as first line treatment for *H. pylori* Infection [abstract]. Gastroenterology **144**: S-53, 2013.
 15. De Francesco V, Hassan C, Ridola L, Giorgio F, Ierardi E, Zullo A. Sequential, concomitant and hybrid first-line therapies for *Helicobacter pylori* eradication: a prospective randomized study. J Med Microbiol **63**: 748-752, 2014.
 16. Greenberg ER, Anderson GL, Morgan DR, et al. 14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomized trial. Lancet **378**: 507-514, 2011.
 17. Huang YK, Wu MC, Wang SS, et al. Lansoprazole-based sequential and concomitant therapy for the first-line *Helicobacter pylori* eradication. J Dig Dis **13**: 232-238, 2012.
 18. Lim JH, Lee DH, Choi C, et al. Clinical outcomes of two-week sequential and concomitant therapies for *Helicobacter pylori* eradication: a randomized pilot study. Helicobacter **18**: 180-186, 2013.
 19. McNicholl AG, Marin AC, Molina-Infante J, et al. Randomised clinical trial comparing sequential and concomitant therapies for *Helicobacter pylori* eradication in routine clinical practice. Gut **63**: 244-249, 2014.
 20. Molina-Infante J, Romano M, Fernandez-Bermejo M, et al. Optimized nonbismuth quadruple therapies cure most patients with *Helicobacter pylori* infection in populations with high rates of antibiotic resistance. Gastroenterology **145**: 121-128.e1, 2013.
 21. Sardarian H, Fakheri H, Hosseini V, Taghvaei T, Maleki I, Mokhtare M. Comparison of hybrid and sequential therapies for *Helicobacter pylori* eradication in Iran: a prospective randomized trial. Helicobacter **18**: 129-134, 2013.
 22. Wu DC, Hsu PI, Wu JY, et al. Sequential and concomitant therapy with four drugs is equally effective for eradication of *H. pylori* infection. Clin Gastroenterol Hepatol **8**: 36-41, 2010.
 23. Zullo A, Scaccianoce G, De Francesco V, et al. Concomitant, sequential, and hybrid therapy for *H. pylori* eradication: a pilot study. Clin Res Hepatol Gastroenterol **37**: 647-650, 2013.
 24. Federico A, Nardone G, Gravina AG, et al. Efficacy of 5-day levofloxacin-containing concomitant therapy in eradication of *Helicobacter pylori* infection. Gastroenterology **143**: 55-61, 2012.
 25. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials **17**: 1-12, 1996.
 26. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med **127**: 820-826, 1997.
 27. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials **7**: 177-188, 1986.
 28. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst **22**: 719-748, 1959.
 29. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics **50**: 1088-1101, 1994.
 30. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ **315**: 629-634, 1997.
 31. Jafri NS, Hornung CA, Howden CW. Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment. Ann Intern Med **148**: 923-931, 2008.
 32. Yoon H, Lee DH, Kim N, et al. Meta-analysis: is sequential therapy superior to standard triple therapy for *Helicobacter pylori* infection in Asian adults? J Gastroenterol Hepatol **28**: 1801-1809, 2013.
 33. Essa AS, Kramer JR, Graham DY, Treiber G. Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing "concomitant therapy" versus triple therapy for *Helicobacter pylori* eradication. Helicobacter **14**: 109-118, 2009.
 34. De Francesco V, Giorgio F, Hassan C, et al. Worldwide *H. pylori* antibiotic resistance: a systematic review. J Gastrointest Liver Dis **19**: 409-414, 2010.
 35. Zullo A, Perna F, Hassan C, et al. Primary antibiotic resistance in *Helicobacter pylori* strains isolated in northern and central Italy. Aliment Pharmacol Ther **25**: 1429-1434, 2007.
 36. Su P, Li Y, Li H, et al. Antibiotic resistance of *Helicobacter pylori* isolated in the Southeast Coastal Region of China. Helicobacter **18**: 274-279, 2013.