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REVIEW

Sequential versus concomitant therapy for treatment of *Helicobacter pylori* infection: an updated systematic review and meta-analysis

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Abstract

Background Sequential and concomitant therapies are two innovative therapies for *Helicobacter pylori* (*H. pylori*) eradication. However, the comparative efficacy and safety of these treatments are controversial. Therefore, we aimed to conduct an updated systematic review and meta-analysis of studies that compared these two treatments.

Methods A search of PubMed, Embase, the Cochrane Library, and Web of Science was carried out. Randomized controlled trials (RCTs) that compared sequential with concomitant therapies were selected for meta-analysis.

Results Twenty RCTs were included in the analysis. The eradication rate of 10-day sequential therapy was superior to that of 5-day concomitant therapy (82.09 versus 77.79%, relative risk (RR) 1.052 (95% confidence interval (CI) 1.004–1.103), $P = 0.035$)), similar to that of 7-day concomitant therapy (82.40 versus 86.99%, RR 0.959 (95% CI 0.874–1.053), $P = 0.382$), and inferior to that of 10-day concomitant therapy (78.39 versus 83.32%, RR 0.945 (95% CI 0.907–0.984, $P = 0.006$); the occurrence of diarrhea was higher in 10-day concomitant therapy than that in 10-day sequential therapy. Compared with the eradication rate of sequential therapy, that of concomitant therapy was higher in metronidazole-resistant strains (RR 0.912 (95% CI 0.844–0.986, $P = 0.020$)) and strains resistant to metronidazole and clarithromycin (RR 0.542 (95% CI 0.308–0.956, $P = 0.035$)).

Conclusion The efficacy of concomitant therapy was duration dependent, and 10-day concomitant therapy was superior to 10-day sequential therapy. Compared to sequential therapy, concomitant therapy was more efficacious for metronidazole-resistant strains and metronidazole plus clarithromycin-resistant strains. However, diarrhea was more frequent with concomitant therapy than with sequential therapy.

Keywords *Helicobacter pylori* · Sequential · Concomitant · Duration dependent · Non-bismuth · Metronidazole and clarithromycin

Introduction

Helicobacter pylori (*H. pylori*) is a global human pathogen that plays important roles in certain gastrointestinal diseases, such as peptic ulcers, chronic gastritis, gastric cancer, and gastric malignant disease [1–3]. *H. pylori* infection remains one of the most common human infections worldwide, particularly in developing countries [4, 5]. In the previous decade, the most widely recommended approach for eradicating *H. pylori* was the standard triple therapy consisting of a proton pump inhibitor (PPI), amoxicillin, and clarithromycin or metronidazole [6, 7]. Unfortunately, the high success rates initially reported for conventional triple therapy have been eroded by the increasing prevalence of antibiotic resistance. Currently, the success of triple therapy has decreased to 80% or less in most countries [8, 9].

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These data have led to the pursuit of strategies to improve *H. pylori* treatment efficacy. One recent innovation postulated as an alternative to standard triple therapy is sequential treatment, which was introduced in Italy by Zullo et al. [10] and consists of a 5-day induction phase with amoxicillin and a PPI, immediately followed by 5 days of triple therapy (metronidazole, clarithromycin, and PPI). Studies have also recommended tinidazole or other antibiotics instead of metronidazole [11], and several studies support the sequential treatment strategy as a standard first-line treatment for *H. pylori* infection [12–14].

Another therapeutic innovation for the treatment of *H. pylori* infection is concomitant therapy. In 1998, investigators from Germany and Japan proposed a short-term, 4-drug regimen (a PPI, clarithromycin, metronidazole, and amoxicillin) to be administered concomitantly as a non-sequential, 3-antibiotic, non-bismuth-containing quadruple therapy [15, 16]. This treatment paradigm has recently reappeared, with a prolonged 10-day or longer duration, as a valid, simple, and widely available first-line treatment option [17, 18].

Several studies have focused on the efficacy and safety of these two therapies; however, their results are controversial. Three meta-analyses showed similar efficacies for sequential and concomitant therapies [19–21], whereas the Maastricht V/Florence Consensus Report insists that concomitant therapy should be the preferred non-bismuth quadruple therapy and is the most effective in overcoming antibiotic resistance because the efficacy of concomitant therapy is duration dependent [22]. These three meta-analyses were published in 2013 and 2015, and less than 10 studies were employed in their analyses. Regarding analyses between different therapy durations, there are fewer studies providing reliable results for their conclusions. To further explore the efficacies of concomitant and sequential therapies, we present an updated systematic review and meta-analysis of the evidence published to date regarding the potential efficacy and safety of these two therapies.

Methods

The systematic review and meta-analysis were performed following the recommendations of the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement [23].

Information sources

We searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science (until February 2017).

Search terms

The search strategy was not limited by language, and the search terms included *H. pylori*, sequential, concomitant, and non-bismuth quadruple. The search terms used in the PubMed database were as follows: (*Helicobacter pylori* or *H. pylori*) and sequential and (concomitant or "non-bismuth quadruple").

Study selection

Articles eligible for inclusion in the meta-analysis met the following inclusion criteria: (1) randomized controlled trials (RCTs) published as full texts; (2) articles that included at least two branches of treatment consisting of (i) concomitant therapy and (ii) sequential therapy; (3) studies in which *H. pylori* infection was determined using one or more of the standard detection methods (urea breath tests (UBT), rapid urease test (RUT), histology, bacterial culture or fecal antigen testing); (4) studies in which the *H. pylori* eradication rate was determined at least 4 weeks after the completion of the eradication regimen; (5) studies in which the eradication rate was obtainable; and (6) studies in which the patients were naïve to therapy.

Data collection process

Two independent reviewers (W-YH and Z-RL) extracted the data from the selected studies; a third investigator resolved disagreements (W-B).

Data items

The following data were extracted into a predefined data extraction form (Tables 1, 2, and 3): the author and published year, country of the trial, eradication regimens, duration of treatments, test used to confirm persistent infection prior to study enrollment and the eradication of infection after the completion of treatment, number of patients in each treatment arm by intention-to-treat analysis (ITT) and per-protocol (PP) analysis, number of patients with successful eradication determined by ITT and PP analyses, number of strains with primary resistance to antibiotics, number of patients with eradicated infections of resistant strains, number of patients who experienced adverse effects, and compliance rates of the two therapies.

Risk of bias in individual studies

The risk of bias was evaluated by two independent reviewers (W-YH and Z-RL) according to the risk of bias assessment tool developed by the Cochrane Collaboration [44]. The criteria referred to the characteristics of studies that may be related to random sequence generation, allocation concealment, performance bias (blinding of participants and personnel), detection bias (blinding of the outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting). Each criterion was scored as yes (Y), no (N), or unclear (U), where "yes" indicated a low risk of bias, "no" indicated a high risk of bias, and "unclear"

Table 1 Characteristics of the studies included

Author-year	Country	Sequential therapy	Duration (days)	Concomitant therapy	Duration (days)	*H. pylori* infection initial diagnosis/re-checking
Greenberg, ER-2011 [24]	American	L'A, L'CM	10	L'ACM	5	UBT/UBT
Federico, A-2012 [25]	Italy	EA, ELT	10	EALT	5	(UBT/(RUT, histology))/UBT
ZUllo, A-2013 [26]	Italy	OA, OCT	10	OACT	5	RUT/UBT
De Francesco, V-2014 [27]	Italy	OA, OCT	10	OACT	5/14	(RUT and histology)/UBT
Hsu, PI-2014 [28]	Taiwan	PA, PCM	10	PACM	7	(RUT, histology and/or culture)/(RUT, history, and culture)
Lee, HJ-2015 [29]	Korea	RA, RCM	10	RACM	7	Histology/UBT
Tepes, B-2016 [30]	Slovenia	EA, ECM	10	RACM	7	(UBT, RUT, histology, and culture)/UBT
Wu, DC-2010 [31]	Taiwan	EA, ECM	10	EACM	10	(Histology, culture, and RUT)/(RUT, histology, and culture)
Huang, YK-2012 [32]	China	L'A, L'CM	10	L'ACM	10	(RUT and histology, or culture)/UBT
McNicholl, AG-2014 [33]	Spain	OA, OCM	10	OACM	10	UBT, histology, RUT or bacterial culture/(UBT or histology)
Ang, TL-2015 [34]	Singapore	P'A, P'CM	10	P'ACM	10	(RUT, UBT, or histology)/UBT
Gungor, G-2015 [35]	Turkey	PA, PTM	10	PATM	10	(UBT, stool antigen test, RUT or histology)/UBT
Apostolopoulos, P-2016 [36]	Greece	PA, PCM	10	PCAM	10	(UBT, RUT, histology)/UBT
Basyigit, S-2016 [37]	Turkey	PA, RLM	10	RACM	10	Histology/UBT
Chung, JW-2016 [38]	Korea	PA, PMC	10	PAMC	10	Histology/UBT
Das, R-2016 [39]	India	OA, OCM	10	OCAM	10	(RUT and histology)/RUT
Georgopoulos, SD-2016 [40]	Greece	EA, ECM	10	EACM	10	(RUT and/or histology)/(UBT, histology)
Kefeli, A-2016 [41]	Turkey	PA, RCM	10	RACM	10	Histology/UBT
Park, SM-2016 [42]	Korea	PA, PCM	10/14	PACM	10/14	(Histology or RUT)/(UBT, RUT or histology)
Lim, JH-2013 [43]	Korea	RA,RCM	14	RACM	14	(RUT or histology)/RUT

E esomeprazole, *A* amoxicillin, *C* clarithromycin, *M* metronidazole, *L* levofloxacin, *O* omeprazole, *T* tinidazole, *R* rabeprazole, *L'* Lansoprazole, *P'* (PPI), *P* pantoprazole, *RUT* rapid urease test, *UBT* urea breath test

Table 2 Result and bias of randomized controlled trials

Author-year	Seq ITT eradicated (total)	Seq PP eradicated (total)	con ITT eradicated (total)	con PP eradicated (total)	Side effects of Seq (con)	Diarrhea of seq (con)	Compliance of Seq (con)	Risk of bias assessment
Greenberg, ER-2011 [24]	372 (486)	–	360	–	–	–	468 (471)	Y-N-N-N-Y-Y
Federico, A-2012 [25]	84 (90)	84 (88)	83 (90)	83 (86)	–	7 (9)	–	Y-Y-N-Y-Y-Y
Zullo, A-2013 [26]	82 (90)	82 (89)	77 (90)	77 (84)	17 (27)	6 (4)	84 (89)	Y-N-N-N-Y-U
De Francesco, V-2014 [27]	99 (110)	99 (105)	86/95 (110/110)	86/95 (101/100)	21 (27/29)	11 (11/16)	–	Y-N-N-N-Y-U
Hsu, PI-2014 [28]	91 (102)	90 (100)	96 (102)	96 (102)	91 (14)	0 (1)	102 (102)	Y-N-N-N-Y-Y
Lee, HJ-2015 [29]	119 (170)	119 (141)	135 (170)	135 (143)	70 (69)	0 (0)	–	Y-N-N-N-Y-U
Tepes, B-2016 [30]	113 (120)	113 (117)	110 (120)	110 (117)	24 (30)	14 (28)	–	Y-Y-N-N-Y-U
Wu, DC-2010 [31]	108 (117)	108 (116)	107 (115)	107 (115)	36 (31)	2 (3)	112 (113)	Y-Y-N-N-Y-U
Huang, YK-2012 [32]	68 (85)	64 (75)	74 (84)	70 (74)	54 (52)	7 (4)	81 (79)	Y-N-N-N-Y-U
McNicholl, AG-2014 [33]	138 (170)	119 (139)	146 (168)	125 (137)	92 (160)	24 (43)	147 (145)	Y-Y-N-Y-Y-U
Ang, TL-2015 [34]	130 (154)	128 (136)	125 (153)	125 (131)	–	–	–	Y-N-N-N-Y-U
Gungor, G-2015 [35]	71 (100)	71 (88)	72 (100)	72 (86)	11 (17)	3 (2)	97 (98)	N-N-N-N-Y-U
Apostolopoulos, P-2015 [36]	129 (182)	125 (160)	154 (182)	154 (170)	164 (205)	22 (56)	175 (181)	N-N-N-N-Y-U
Basyigit, S-20016 [37]	53 (75)	53 (73)	98 (127)	98 (126)	–	–	73 (126)	N-N-N-N-Y-U
Chung, JW-2016 [38]	120 (170)	119 (133)	137 (176)	135 (143)	55 (69)	–	169 (176)	Y-N-N-N-Y-U
Das, R-2016 [39]	25 (35)	25 (29)	27 (33)	27 (30)	–	–	29 (30)	Y-Y-N-N-Y-Y
Georgopoulos, SD-2016 [40]	140 (178)	140 (169)	156 (175)	156 (167)	115 (115)	12 (14)	176 (173)	Y-N-N-N-Y-Y
Kefeli, A-2016 [41]	113 (130)	113 (119)	113 (130)	113 (118)	51 (52)	–	119 (118)	Y-N-N-N-Y-U
Park, SM-2016 [42]	66/62 (85/84)	64/61 (70/67)	65/67 (86/86)	65/66 (68/67)	23/33 (23/27)	6/9 (7/8)	72/71 (77/73)	Y-N-N-N-Y-Y
Lim, JH-2013 [43]	65 (86)	63 (82)	63 (78)	61 (75)	34 (36)	8 (9)	82 (75)	Y-N-N-N-Y-Y

Risk of bias was evaluated for six criteria in order: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Each criterion was scored as yes (Y), no (N), or unclear (U), yes indicates a low risk of bias, no indicates a high risk of bias, and unclear indicates an uncertain risk of bias

seq sequential therapy, *con* concomitant therapy, – unavailable

Table 3 Effect of antibiotic resistance on *H. pylori* eradicate

	Sequential therapy succeed (*N*)	Sequential therapy failure (*N*)	Sequential therapy eradication rate (%)	Concomitant therapy succeed (*N*)	Concomitant therapy failure (*N*)	Concomitant therapy eradication rates (%)
Federico, A-2012 [25]						
Cla^r	10	0	100.0	8	0	100.0
Met^r	10	1	90.9	9	1	90.0
Cla^r Met^r	4	0	100.0	3	0	100.0
Lev^r	2	1	66.7	2	1	66.7
Huang, YK-2012 [32]						
Cla^r	3	2	60.0	3	0	100.0
Met^r	14	4	77.8	16	0	100.0
Lev^r	1	0	100.0	3	0	100.0
Amo^r	0	1	0	1	0	100.0
Cla^r Met^r	2	2	50.0	2	0	100.0
Hsu, PI-2014 [28]						
Cla^s Met^r	10	1	90.9	18	0	100.0
Cla^r Met^s	2	1	66.7	2	0	100.0
Cla^r Met^r	1	1	50.0	2	1	66.7
Georgopoulos, SD-2016 [40]						
Cla^s Met^r	31	8	79.5	38	1	97.4
Cla^r Met^s	26	5	83.9	25	3	89.3
Cla^r Met^r	4	7	36.4	9	3	75.0
Tepes, B-2016 [30]						
Cla^r	6	3	66.7	13	2	86.7
Met^r	28	3	90.3	29	2	93.5
Wu, DC-2010 [31]						
Cla^r	4	3	57.1	3	1	75.0
Met^r	27	3	90.0	24	2	92.3
Lev^r	10	2	83.3	5	0	100.0
Amo^r	0	0	–	1	0	100.0
Cla^r Met^r	1	2	33.3	3	1	75.0

Cla clarithromycin, *Met* metronidazole, *Lev* levofloxacin, *Amo* amoxicillin, *s* susceptible, *r* resistant

indicated an uncertain risk of bias. A third investigator (W-B) resolved disagreements.

Summary measurements

Data analysis was performed using Stata meta-analysis software, version 12.0 (StataCorp LP, College Station, TX). The relative risks (RRs) were presented with 95% confidence intervals (CIs) and were calculated based on a random-effects model as described by Mantel-Haenszel. *P* values less than 0.05 were considered statistically significant.

Synthesis of results

The primary study outcome for the meta-analysis was the eradication rate of sequential therapy compared with that of concomitant therapy, and the secondary end points were the adverse effects of and compliance with sequential therapy compared with those for concomitant therapy. The study end points were calculated using ITT and PP analyses. We estimated the degree of heterogeneity among the trial results using χ^2 statistics (with *P* values less than 0.10 considered significant) and the I^2 test (25, 50, and 75% represented low, moderate, and high heterogeneity, respectively).

Sensitivity analysis

Sensitivity was analyzed using Stata meta-analysis software. The stability of the results was evaluated by removing articles with high heterogeneity and reporting bias, as these articles may substantially affect the results.

Risk of bias across studies

The presence of publication bias was assessed using Egger's test; *P* values less than 0.10 were considered significant.

Results

Selection of studies

The literature search yielded 591 studies, which were reviewed with full text and/or abstracts. Among these studies, duplication checking was performed using the software "NoteExpress, standard version 3.0" (Beijing, China), according to the publication year, title of the article, and the name of the author. After the first step of the duplicate article elimination, 286 records remained. We subsequently checked the abstracts or full texts of these records, and only clinical investigations that included at least two branches of treatment consisting of (i) concomitant therapy and (ii) sequential therapy were included. After this process, 25 records remained. Among these articles, two studies were excluded because of data repetition [45, 46], one study was excluded because of the lack of raw data [47], one study was excluded because the method used to detect *H. pylori* infection was obscure [48], and one study was excluded because it did not conform to an RCT [49]. Finally, 20 RCTs met the inclusion criteria and were included for further analysis. A flowchart of the multistep exclusion process is presented in Fig. 1.

Study characteristics

Twenty studies were used after rigorous filtering. Of these studies, nine studies evaluated the eradication rate by comparing sequential therapy with concomitant therapy [49]; six studies compared the efficacies of triple, sequential, and concomitant therapies [24, 28–30, 34, 38]; and two studies compared the efficacies of hybrid, sequential, and concomitant therapies [26, 27]. Two studies compared bismuth-containing quadruple therapy, sequential therapy, and concomitant therapy [37, 41]. One study compared five different regimens [35]. Considering the objective of our meta-analysis, the data that compared sequential therapy with concomitant therapy were analyzed. Of all studies, 18 studies performed 10-day sequential therapies, and 2 studies performed 14-day sequential therapies; however, the duration of concomitant therapy varied among these articles. To reduce the heterogeneity of the meta-analysis, we did not pool the result of concomitant therapies with different durations. A total of 5697 patients were randomized to the two groups (Table 1).

Risk of bias within studies

Among these 20 studies, all studies were published as full-text publications with methodological details reported. Seventeen studies reported methods for sequence generation. Five studies described methods for allocation concealment. None of the studies described methods for blinding of the participants. Three of the studies provided methods for blinding of the outcome assessment. None of the studies provided incomplete outcome data. In addition, seven studies had a low risk of reporting bias (Table 2).

Synthesis of results

10-day sequential versus 5-day concomitant therapy

Primary outcome: *H. pylori* eradication rates We identified four studies that compared the efficacy of concomitant therapy with sequential therapy in *H. pylori* eradication, which reported data from 1555 participants (776 participants who underwent sequential therapy and 779 participants who underwent concomitant therapy). There was low heterogeneity among these studies (P = 0.344; I^2 = 9.9%). The meta-analysis showed that the eradication rate of 5-day concomitant therapy was lower than that of 10-day sequential therapy when pooled as ITT data, the relative risk (RR) was 1.052 (95% CI 1.004–1.103, P = 0.035) (Fig. 2a), and the eradication rates were 82.09% for sequential therapy and 77.79% for concomitant therapy (four RCTs). However, when calculating the PP data, the pooled RR was 1.027 (95% CI 0.957–1.101, P = 0.463), and the eradication rates were 93.97% for sequential therapy and 90.77% for concomitant therapy (3 RCTs).

Risk of bias across studies Egger's test (P = 0.197) suggested that there were no significant biases across the studies.

10-day sequential versus 7-day concomitant therapy

Primary outcome: *H. pylori* eradication rates We identified three studies that compared the efficacy of concomitant therapy with sequential therapy in *H. pylori* eradication, which reported data from 784 participants (392 participants who underwent sequential therapy and 392 participants who underwent concomitant therapy). There was a moderate heterogeneity among these studies (P = 0.040; I^2 = 69.0%). The meta-analysis showed that the eradication rate of 7-day concomitant therapy was not inferior to that of 10-day sequential therapy when pooled as ITT data, the RR was 0.959 (95% CI 0.874–1.053, P = 0.382) (Fig. 2b), and the eradication rates were 82.40% for sequential therapy and 86.99% for concomitant therapy (three RCTs). When calculating the PP data, the pooled RR was 0.997 (95% CI 0.928–1.071, P = 0.930) and the eradication rates were 93.55% for sequential therapy and 94.06% for concomitant therapy (two RCTs).

Risk of bias across studies Egger's test (P = 0.129) suggested there were no significant biases across the studies.

Secondary outcome: side effects Data on adverse events were available for three trials. There was low heterogeneity among these studies (P = 0.424; I^2 = 0.0%). There were no significant

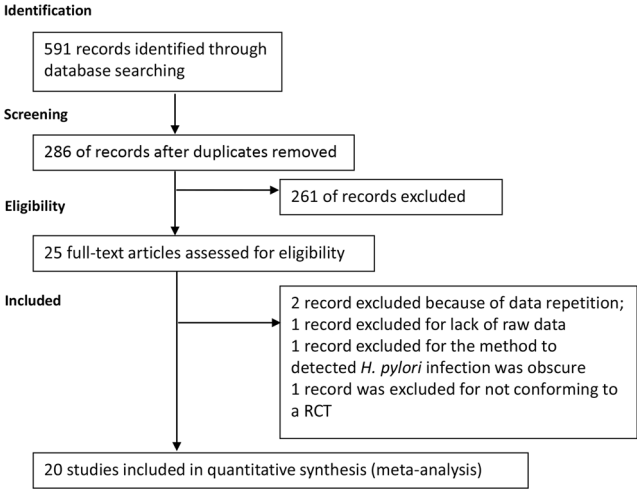

Fig. 1 Flowchart of study selection for inclusion in meta-analysis

differences in the occurrence of side effects between sequential therapy and concomitant therapy. The ITT pooled RR was 0.931 (95% CI 0.785–1.106, $P = 0.417$) (three RCTs).

10-day sequential versus 10-day concomitant therapy

Primary outcome: *H. pylori* eradication rates We identified 12 studies that compared the efficacy of concomitant therapy with sequential therapy in *H. pylori* eradication, which reported data from 3010 participants (1481 participants who underwent sequential therapy and 1529 participants who underwent concomitant therapy). There was moderate heterogeneity among these studies ($P = 0.157$; $I^2 = 29.5\%$). The meta-analysis showed that the eradication rate of 10-day concomitant therapy was superior to that of 10-day sequential therapy when pooled as ITT data, the RR was 0.945 (95% CI 0.907–0.984, $P = 0.006$) (12 RCTs) (Fig. 2c), and the eradication rates were 78.39% for sequential therapy and 83.32% for concomitant therapy. When calculating the PP data, the pooled RR was 0.950 (95% CI 0.922–0.979, $P = 0.001$) (12 RCTs), and the eradication rates were 86.38% for sequential therapy and 91.36% for concomitant therapy.

Risk of bias across studies Egger's test ($P = 0.513$) suggested there were no significant biases across the studies.

Sensitivity analysis Regarding the sensitivity analysis, the outcome was stable.

Secondary outcome: side effects and compliance Data on adverse events were available from eight of the included trials; these trials reported data from 1957 participants (1035 participants who received sequential therapy and 1034 participants who received concomitant therapy). There was low heterogeneity among these studies ($P = 0.683$; $I^2 = 0\%$). There were no significant differences in the occurrence of side effects between sequential therapy and concomitant therapy. The ITT pooled RR was 0.942 (95% CI 0.863–1.030, $P = 0.189$) (eight RCTs) (Fig. 3a). When considering severe side effects, the pooled RR was 0.597 (95% CI 0.328–1.087, $P = 0.091$). Regarding the sensitivity analysis, the outcome was stable. In addition, we analyzed side effects, such as abdominal pain, diarrhea, bloating, nausea, vomiting, anorexia, dizziness, bitter taste, headache, and general weakness, between the two therapies. Only the occurrence of diarrhea was higher for the concomitant therapy than that for sequential therapy, with an ITT pooled RR of 0.606 (95% CI 0.444–0.827, $P = 0.002$) (eight RCTs) (Fig. 3b); the other side effects were not significantly different between the two treatments.

Data on compliance were available from 11 of the 12 trials. There was low heterogeneity among these studies ($P = 0.487$; $I^2 = 0.00\%$). No significant differences in compliance were identified between the sequential and concomitant therapies, and the pooled RR was 0.994 (95% CI 0982–1.006) (Fig. 3c).

Sequential versus 14-day concomitant therapy

We identified three studies that compared the efficacy of concomitant therapy with sequential therapy in *H. pylori* eradication, which reported data from 554 participants (280 participants who underwent sequential therapy and 274 participants who underwent concomitant therapy). Among these three studies, one study compared 10-day sequential therapy versus 14-day concomitant therapy and two studies compared 14-day sequential therapy versus 14-day concomitant therapy. Ten-day sequential therapy did not significantly differ from 14-day concomitant therapy. When we pooled 14-day sequential therapy versus 14-day concomitant therapy, there was low heterogeneity among these studies ($P = 0.918$; $I^2 = 0.0\%$). The meta-analysis showed that the eradication rate of 14-day concomitant therapy was similar to that of 14-day sequential therapy, the RR was 0.941 (95% CI 0.837–1.058, $P = 0.311$) (Fig. 2d), and the eradication rates were 74.71% for sequential therapy and 79.27% for concomitant therapy. When calculating the PP data, the pooled RR was 0.962 (95% CI 0.897–1.031, $P = 0.270$), and the eradication rates were 93.02% for sequential therapy and 96.41% for concomitant therapy (two RCTs).

Ability to overcome antibiotic resistance Seven studies provided data to investigate the role of primary resistance in the eradication of *H. pylori* infection, whereas one study did not analyze treatment outcome stratified according to antibiotic resistance profiles and treatment arms [50]. Six studies were included in the analysis, and the data are summarized in Table 3. When comparing the eradication rate of metronidazole-resistant strains, the results showed that the eradication rate of concomitant therapy was superior to that of sequential therapy, 85.71 versus 95.71%, respectively, RR 0.912 (95% CI 0.844–0.986, $P = 0.020$) (Fig. 4a). Regarding

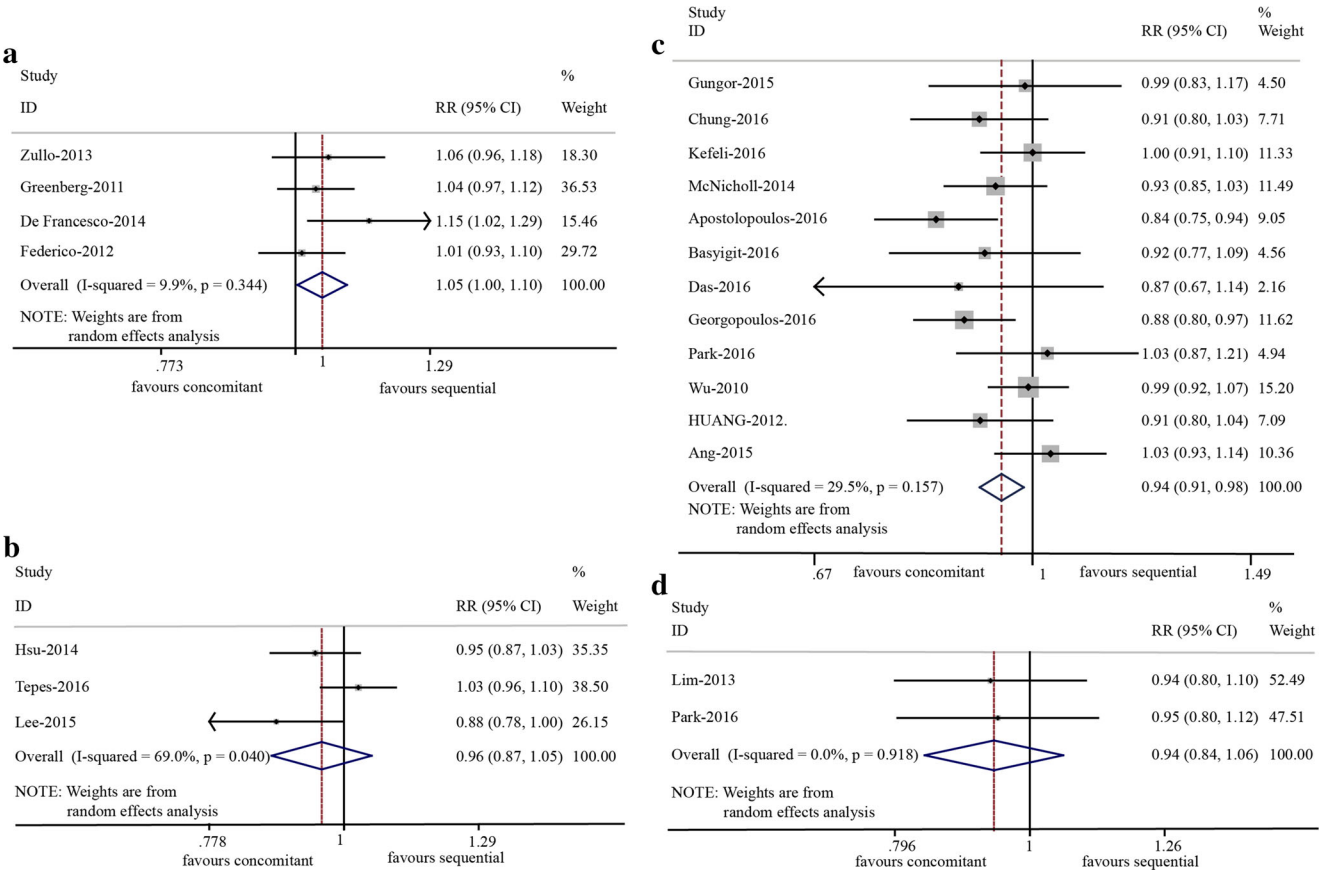

Fig. 2 *Helicobacter pylori* eradication rates of sequential therapy versus concomitant therapy. **a** Ten-day sequential therapy versus 5-day concomitant therapy. **b** Ten-day sequential therapy versus 7-day concomitant therapy. **c** Ten-day sequential therapy versus Ten-day concomitant therapy. **d** Fourteen-day sequential therapy versus 14-day concomitant therapy

the eradication rates of clarithromycin-resistant strains, the eradication rates of the two therapies were similar, 74.55 versus 88.46%, respectively, RR 0.886 (95% CI 0.745–1.055, $P = 0.174$) (Fig. 4b). When considering the eradication rates of clarithromycin and metronidazole dual-resistant strains, the data showed that the eradication rate of concomitant therapy was superior to that of sequential therapy, 50.00 versus 79.17%, respectively, RR 0.542 (95% CI 0.308–0.956, $P = 0.035$) (Fig. 4c).

Discussion

Sequential therapy was proposed by Italian investigators in 2000 [10]. This regimen has been postulated to replace standard triple therapy, particularly in patients with dual resistance (clarithromycin and imidazole), precluding the use of standard triple therapy [3, 51]. Studies have also suggested that a long duration of amoxicillin administration would decrease the bacterial load and disrupt the efflux pump, thereby preventing clarithromycin resistance [52]. In concomitant therapy, four drugs (a PPI and three antibiotics) are administered together. This regimen is implemented as a first-line therapy when high clarithromycin resistance is present and bismuth is not locally available [51]. Compared with sequential therapy, concomitant therapy appears to reduce the complexity of the regimen [53].

This meta-analysis provides evidence of the safety and efficacy of sequential therapy versus concomitant therapy for *H. pylori* infection. The main findings of this study were that the eradication rate of 10-day sequential therapy was superior to that of 5-day concomitant therapy, similar to that of 7-day concomitant therapy, and inferior to that of 10-day concomitant therapy, which indicates a duration-dependent efficacy of concomitant therapy. A different result was obtained when comparing sequential therapy with 14-day concomitant therapy. The similar eradication rates of the two treatments may be a result of the increased duration of both therapies, according to Yeo et al. [54]. Fourteen-day sequential therapy has a higher eradication rate than sequential therapy at a duration ≤ 10 days (OR = 1.84, 95% CI 1.17–2.29); thus, prolonging the duration from 10 days to 14 days may improve the eradication rate of sequential therapy more than concomitant therapy.

When we compared the safety and compliance of 10-day sequential therapy with 10-day concomitant therapy, there were no significant differences regarding the total number of side effects; however, the occurrence of diarrhea was higher in

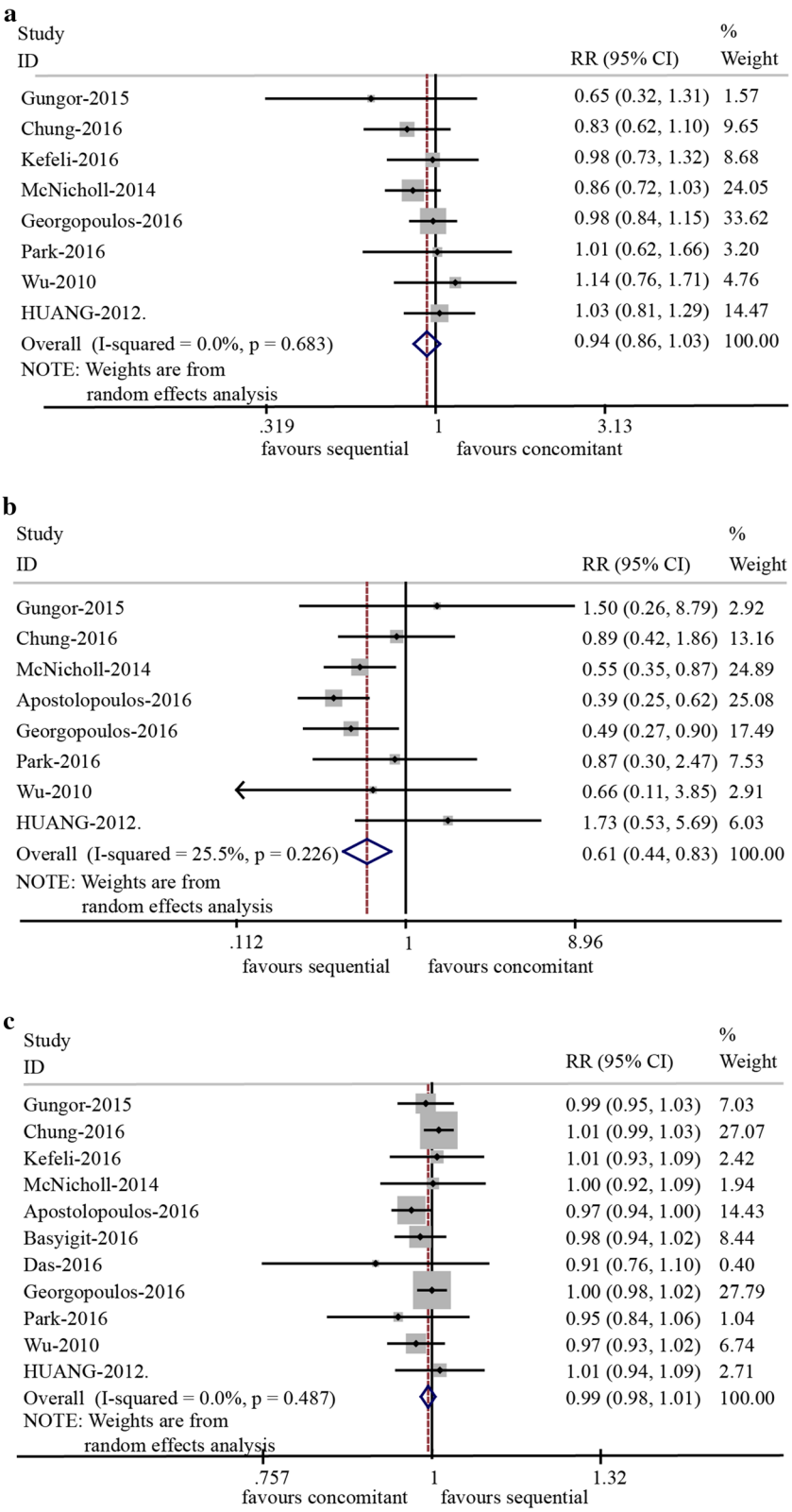

Fig. 3 Side effects and compliance of 10-day sequential therapy versus 10-day concomitant therapy. **a** Total side effects of 10-day sequential therapy versus 10-day concomitant therapy. **b** Occurrence of diarrhea in 10-day sequential therapy versus 10-day concomitant therapy. **c** Compliance of 10-day sequential therapy versus 10-day concomitant therapy

concomitant therapy than in sequential therapy. This phenomenon may be a result of the use of three antibiotics administered together, which influence the microbiota in the gut; a normal microbiota environment is important to degrade undigested carbohydrates to short-chained fatty acids and protect the host from harm caused by conditional pathogenic bacteria

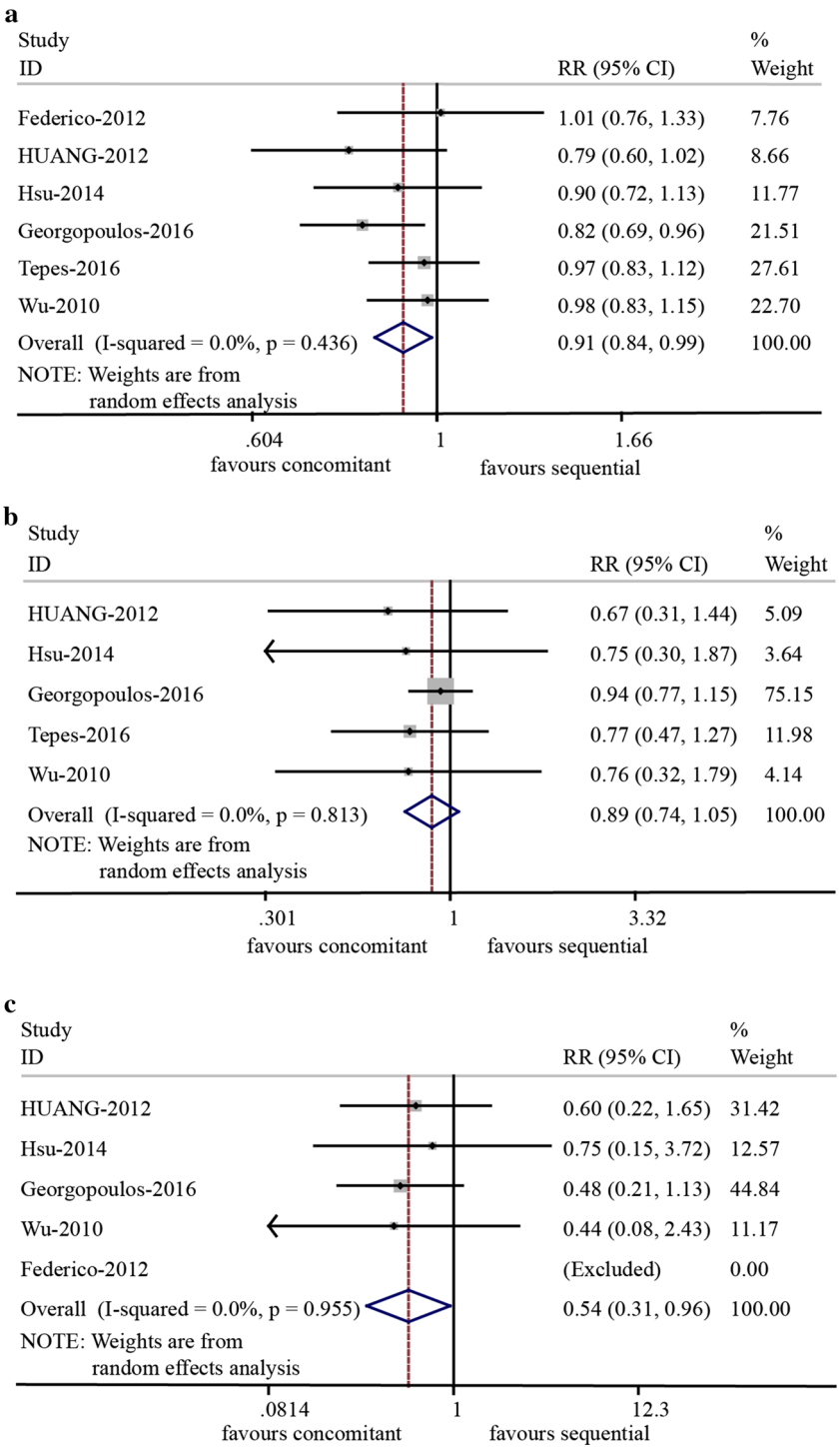

Fig. 4 *Helicobacter pylori* eradication rates of antibiotic-resistant strains compared for sequential therapy and concomitant therapy. **a** *H. pylori* eradication rates of metronidazole-resistant strains compared for sequential therapy and concomitant therapy. **b** *H. pylori* eradication rates of clarithromycin-resistant strains compared for sequential therapy and concomitant therapy. **c** *H. pylori* eradication rates of metronidazole and clarithromycin-resistant strains compared for sequential therapy and concomitant therapy

in the gut [55]. The compliance was similar between these two regimens. We did not compare the safety and compliance of sequential therapy with 5-day or 14-day concomitant therapy because of the limited data available to perform the analysis.

Besides, previous research has demonstrated that combining three antibiotics in concomitant therapy may more effectively overcome antibiotic resistance [56], and the Maastricht V/Florence Consensus Report suggests that concomitant therapy is the most effective approach in overcoming antibiotic resistance. We also identified positive evidence to support this viewpoint in the current study. When compared with sequential therapy, concomitant therapy was less affected by metronidazole resistance and dual resistance (metronidazole and clarithromycin resistance). Regarding clarithromycin resistance, although there were no significant differences between the two therapies, the results showed that the

eradication rates of the two therapies were 74.9 versus 89.2%, respectively, RR 0.854 (95% CI 0.709–1.028), which is an approximately 15% difference (a clinically relevant difference), with a marginal statistical significance; this finding strongly suggests a low statistical power as a result of a small sample size. To increase the sample size, we pooled the data from 7-day concomitant therapy, which would increase the heterogeneity of the results; however, concomitant therapy continued to exhibit a superior result to sequential therapy.

Conclusion

The efficacy of concomitant therapy was duration dependent, and 10-day concomitant therapy was superior to 10-day sequential therapy. Compared to sequential therapy, concomitant therapy was more effective for metronidazole- and dual clarithromycin and metronidazole-resistant strains. However, diarrhea was more frequent with concomitant therapy than with sequential therapy.

Author contributions Yong Xie designed the concept. Youhua Wang and Rulin Zhao acquired the data. Youhua Wang and Rulin Zhao performed the analysis and interpretation of the data. You-hua Wang drafted the manuscript. Ben Wang, Qiaoyun Zhao, Zhen Li, Liya Zhu-ge, and Wenzhu Yin provided a critical revision of the manuscript for important intellectual content. Youhua Wang and Ben Wang performed the statistical analysis, and Yong Xie provided study supervision.

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Compliance with ethical standards

Conflict of interest All authors approved the final version of the manuscript and declare no conflict of interest. This study was not funded by the pharmaceutical industry.

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