Review Article

Hybrid Therapy Regimen for *Helicobacter Pylori* Eradication

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Abstract

Objective: *Helicobacter pylori* (*H. pylori*) eradication remains a challenge with increasing antibiotic resistance. Hybrid therapy has attracted widespread attention because of initial report with good efficacy and safety. However, many issues on hybrid therapy are still unclear such as the eradication efficacy, safety, compliance, influencing factors, correlation with antibiotic resistance, and comparison with other regimens. Therefore, a comprehensive review on the evidence of hybrid therapy for *H. pylori* infection was conducted.

Data Sources: The data used in this review were mainly from PubMed articles published in English up to September 30, 2015, searching by the terms of "*Helicobacter pylori*" or "*H. pylori*", and "hybrid".

Study Selection: Clinical research articles were selected mainly according to their level of relevance to this topic.

Results: Totally, 1871 patients of 12 studies received hybrid therapy. The eradication rates were 77.6–97.4% in intention-to-treat and 82.6–99.1% in per-protocol analyses. Compliance was 93.3–100.0%, overall adverse effects rate was 14.5–67.5%, and discontinued medication rate due to adverse effects was 0–6.7%. *H. pylori* culture and sensitivity test were performed only in 13.3% patients. Pooled analysis showed that the eradication rates with dual clarithromycin and metronidazole susceptible, isolated metronidazole or clarithromycin resistance, and dual clarithromycin and metronidazole resistance were 98.5%, 97.6%, 92.9%, and 80.0%, respectively. Overall, the efficacy, compliance, and safety of hybrid therapy were similar with sequential or concomitant therapy. However, hybrid therapy might be superior to sequential therapy in Asians.

Conclusions: Hybrid therapy showed wide differences in the efficacy but consistently good compliance and safety across different regions. Dual clarithromycin and metronidazole resistance were the key factor to efficacy. Hybrid therapy was similar to sequential or concomitant therapy in the efficacy, safety, and compliance.

Key words: Antibiotic; *Helicobacter pylori*; Resistance; Therapy

Introduction

Due to the rising antibiotic resistance, empiric therapy for *Helicobacter pylori* (*H. pylori*) infection has become increasingly ineffective.[1-5] Therefore, eradication regimens with good efficacy, safety, and compliance are imperative. Hybrid therapy that was proposed by Hsu *et al*.[6] in 2011 has attracted widespread attention because of excellent efficacy and safety profile.

Hybrid therapy has been studied only for four years with few relevant reviews, and comprehensive and clear understanding of the therapy is still limited. The efficacy, adverse effects, compliance, influencing factors, relationship with antibiotic resistance, comparison with other regimens, and the role of proton pump inhibitor (PPI) in hybrid therapy need to be systematically explored.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.179803

Medication Scheme and Mechanism

Hybrid therapy was divided into two stages: dual therapy (PPI and amoxicillin) and quadruple therapy (PPI, amoxicillin, clarithromycin, and metronidazole/tinidazole) with a routine course of 14 days (7 days + 7 days). The usual drug dosage was PPI standard dosage, amoxicillin 1 g, clarithromycin 0.5 g, and metronidazole/tinidazole 0.5 g all

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Received: 30-12-2015 **Edited by:** Ning-Ning Wang

How to cite this article: Song ZQ, Liu J, Zhou LY. Hybrid Therapy Regimen for *Helicobacter Pylori* Eradication. Chin Med J 2016;129:992-9.

given twice daily.[4,6,7] Minor adjustments in hybrid regimen in some studies included increase in PPI dosage (double standard dosage)[6,8-12] and administration frequency of metronidazole (three times daily)[13] and decrease in administration time (3 days + 7 days,[12] 5 days + 7 days,[12] and 5 days + 5 days)[13-15] [Table 1].

Sequential, concomitant, and hybrid therapies belong to nonbismuth quadruple therapy.[4,20] Hybrid therapy represents the combination of the other two therapies: dual therapy in the first stage is similar to sequential therapy and quadruple therapy in the second stage is similar to concomitant therapy. The origin of hybrid therapy is based on the optimization process of sequential therapy: administration time prolonged from 10 days to 14 days and amoxicillin added in the second stage.[4,6,7,20]

The mechanism of hybrid therapy is similar to sequential therapy. In addition, to the larger number of antibiotics to which *H. pylori* is exposed compared with standard triple therapy, the improved efficacy of hybrid therapy may be due to the sequential administration. The marked reduction in bacterial load and prevention of bacterial transmembrane efflux channels associated with amoxicillin pretreatment results in altered susceptibility of the organisms and improved efficacy of subsequent clarithromycin and tinidazole.[21-23] However, additional evidence is needed to establish this theory.

Literature Retrieval

A PubMed search was conducted up to September 30, 2015. Relevant studies were identified using the following terms: "*Helicobacter pylori*" or "*H. pylori*", and "hybrid". The search was restricted to human subjects and publications in English language. All references were retrieved. Additional studies were identified using a manual search of references. All the clinical studies, meta-analyses, and systemic reviews relevant to hybrid therapy were included. Two independent reviewers extracted the data from the selected studies using standardized data extraction forms. Disagreements were resolved by consensus. We performed pooled analyses to the data from the clinical studies in the eradication rate, compliance, overall rate of adverse effects, rate of discontinued medication due to adverse effects, relationship between antibiotic resistance and eradication rate, and role of PPIs. As shown in Table 1, we reviewed a total of 1871 patients in 15 groups (all adult patients and in first-line treatment, sample size 70–241 cases) from 12 studies (all open-label randomized control trials) from five regions (Taiwan, China; Iran; Korea; Spain; Italy).

In this study, sequential regimen included dual drug therapy (PPI and amoxicillin 1 g) for 5–7 days, followed by triple drug therapy (PPI, clarithromycin 0.5 g and metronidazole/tinidazole 0.5 g) for another 5–7 days all given twice daily. The concomitant regimen included quadruple drug therapy for 5–14 days including PPI, amoxicillin (1 g), clarithromycin (0.5 g), and metronidazole/tinidazole (0.5 g) all given twice daily.

Eradication Rate

The eradication rate of hybrid therapy was 77.6–97.4% in intention-to-treat (ITT) analysis and 82.6–99.1% in per-protocol (PP) analysis. Pooled analysis showed that the eradication rate was 85.1% (ITT) and 91.2% (PP) [Table 1].

According to the eradication efficacy grading of *H. pylori* infection recommended by Prof. Graham,[24] as shown in Table 2, the eradication efficacies distribution of hybrid therapy varied widely across different regions and populations, which might be related to different backgrounds of antibiotic resistance.

Compliance

The compliance of hybrid therapy was 93.3–100%. Pooled analysis showed that the compliance was 96.6% [Table 1].

Safety

The overall rate of adverse effects of hybrid therapy was 14.5–67.5%. Pooled analysis showed that the overall rate was 32.9% [Table 1]. The common adverse effects included taste distortion, abdominal pain/discomfort, nausea, vomiting, diarrhea, dizziness, headache, and so on, most of which were mild or moderate (not or partially interfering with daily activities) and less severe (markedly disturbing daily activities and resulting in discontinuation of eradication therapy). The rate of discontinued medication due to adverse effects was 0–6.7% and pooled analysis showed that the rate was 2.5% [Table 1]. Overall, the safety of hybrid therapy was good.

Relationship of Antibiotic Resistance and Eradication Efficacy

H. pylori culture and antibiotic sensitivity test were performed in the patients of six treatment groups with hybrid therapy from four studies (three from Taiwan, China[6,8,12] and one from Spain/Italy).[10] The relationship between antibiotic resistance and efficacy was analyzed in 248 patients, accounting for only 13.3% of 1871 patients with hybrid therapy.

The rates of background antibiotic resistance were amoxicillin 0–1.8%, clarithromycin 7.0–23.5%, metronidazole 30.4–56.1%, and dual clarithromycin and metronidazole 4.3–8.9%. Pooled analysis showed that the eradication rates of susceptible to both clarithromycin and metronidazole, isolated metronidazole resistance, isolated clarithromycin resistance, and dual clarithromycin and metronidazole resistance were 98.5%, 97.6%, 92.9%, and 80.0%, respectively (amoxicillin resistance was not included because of very small number) [Table 3].

When isolated resistance to clarithromycin or metronidazole was present, the eradication efficacy of hybrid therapy still remained good. Only under dual clarithromycin and metronidazole resistance, the efficacy was decreased significantly, suggesting that dual clarithromycin and

Table 1: Summary of the published articles of HT for *Helicobacter pylori* eradication

First author, year	Region	Centers (*n*)	Cases (*n*)	Study type	Control groups	Duration of HT (d)	Regimens of HT	Cure rate of ITT (%)	Cure rate of PP (%)	Compliance (%)	Overall rate of adverse effects (%)	Discontinued medication due to adverse effects (%)
Hsu, 2011[6,16]	Taiwan, China	3	117	RCT	14d ST	7 + 7	E 40 mg A 1 g C 0.5 g M 0.5 g	97.4	99.1	94.9	14.5	4.3
Sardarian, 2013[17]	Iran	1	210	RCT	10d ST	7 + 7	P 40 mg A 1 g C 0.5 g T 0.5 g	89.5	92.9	96.7	28.1	1.4
Molina-Infante, 2013[10]	Spain/ Italy	4	171	RCT	14d CT	7 + 7	O 40 mg A 1 g C 0.5 g M/T 0.5 g	90.0	92.0	98.8	47.0	2.4
Zullo, 2013[18]	Italy	3	90	RCT	10d ST 5d CT	7 + 7	O 20 mg A 1g C 0.5 g T 0.5 g	80.0	85.7	93.3	24.4	6.7
Oh, 2014[11]	Korea	1	90	RCT	14d ST	7 + 7	R 20 mg A 1 g C 0.5 g M 0.5 g	81.1	85.9	97.7	33.7	3.5
De Francesco, 2014[19]	Italy	1	110	RCT	10d ST 5d CT 14d CT	7 + 7	O 20 mg A 1 g C 0.5 g T 0.5 g	82.7	95.8	NR	22.7	6.4
Wu, 2014[12]	Taiwan, China	3	77	RCT	12d HT 14d HT	3 + 7	E 40 mg A 1 g C 0.5 g M 0.5 g	81.8	95.0	94.0	14.7	NR
Wu, 2014[12]	Taiwan, China	3	73	RCT	10d HT 14d HT	5 + 7	E 40 mg A 1 g C 0.5 g M 0.5 g	86.3	95.1	97.0	17.1	NR
Wu, 2014[12]	Taiwan, China	3	70	RCT	10d HT 12d HT	7 + 7	E 40 mg A 1 g C 0.5 g M 0.5 g	85.7	93.4	95.6	17.6	NR
Cuadrado-Lavín, 2015[13]	Spain	3	120	RCT	10d TT 10d CT	5 + 5	O 20 mg A 1 g C 0.5 g M 0.5 g*	90.8	93.9	98.3	67.5	1.7
Metanat, 2015[15]	Iran	1	134	RCT	14d HT	5 + 5	P 40 mg A 1 g C 0.5 g T 0.5 g	77.6	83.9	96.3	38.1	3.0
Metanat, 2015[15]	Iran	1	136	RCT	10d HT	7 + 7	P 40 mg A 1 g C 0.5 g T 0.5 g	86.0	92.9	95.6	38.2	3.7
Heo, 2015[14]	Korea	6	241	RCT	10d CT	5 + 5	E 20 mg A 1 g C 0.5 g M 0.5 g	78.8	89.6	95.0	NR	0
Chen, 2015[8]	Taiwan, China	1	88	RCT	10d ST	7 + 7	R 20 mg A 1 g C 0.5 g M 0.5 g	92.0	96.4	97.7	59.1	2.3
Hwang, 2015[9]	Korea	1	144	RCT	14d MBST	7 + 7	R 20 mg A 1 g C 0.5 g M 0.5 g	79.2	82.6	100	19.6	0
Pooled-data analysis			1871					85.1 (1592/1870)	91.2 (1554/1704)	96.6 (1648/1706)	32.9 (529/1610)	2.5 (41/1612)

*Three times a day, and the others twice a day. A: Amoxicillin; C: Clarithromycin; CT: Concomitant therapy; E: Esomeprazole; HT: Hybrid therapy; M: Metronidazole; MBST: Moxifloxacin-containing sequential therapy; NR: Not reported; O: Omeprazole; P: Pantoprazole; R: Rabeprazole; RCT: Randomized controlled trial; ST: Sequential therapy; T: Tinidazole; TT: Triple therapy; PP: Per-protocol; ITT: Intention-to-treat; d: Days.

metronidazole resistance played a key role in the treatment failure of hybrid therapy. The differences of cure rates in hybrid therapy across different regions and populations mainly depended on the ratio of the patients with dual clarithromycin and metronidazole resistance, which was consistent with the results of studies in sequential therapy and concomitant therapy.[25,26]

Up to date, only a small number of patients from few studies received *H. pylori* culture and antibiotic sensitivity test. The relevant data were mostly from the regions and populations with low antibiotic resistance rate. Therefore, the number of patients with isolated clarithromycin resistance ($n = 14$) and dual clarithromycin and metronidazole resistance ($n = 15$) was small, and estimation of eradication rates in these small subpopulations of resistant patients was subject to random error. Therefore, it was necessary to perform more studies, especially in the area of high antibiotic resistance. Accumulation of cases with antibiotic resistance will be very helpful to accurately evaluate the role of antibiotic resistance on the efficacy of hybrid therapy.

Table 2: Effectiveness grading of the published articles of hybrid therapy for *Helicobacter pylori* eradication

Cure rate (intention-to-treat)	Studies (*n*)	Cure rate (per-protocol)	Studies (*n*)
Grade A: Excellent (≥95%)	1	Grade A: Excellent (≥95%)	5
Grade B: Good (90-95%)	3	Grade B: Good (90-95%)	5
Grade C: Acceptable (85-89%)	4	Grade C: Poor (85-89%)	3
Grade D: Poor (81-84%)	3	Grade F: Unacceptable (≤85%)	2
Grade F: Unacceptable (≤80%)	4	NR	NR

NR: Not reported.

Comparison with Other Regimens

Sequential therapy

Hybrid therapy ($n = 705$ in six treatment groups) and sequential therapy ($n = 714$ in six treatment groups) were compared in six studies (two in Taiwan, China and Italy, respectively, and one in Iran and Korea, respectively) as shown in Table 4.

The studies from Taiwan, China[6,8,16] and Iran[17] showed that the eradication rates of hybrid therapy were significantly superior to sequential therapy. In the two studies from Italy,[18,19] the absolute efficacy of sequential therapy was higher but not significantly different than that of hybrid therapy. However, similar efficacy was found in the report from Korea.[11] Pooled analysis showed that the eradication rates of hybrid therapy were 87.8% (ITT) and 93.0% (PP), and those of sequential therapy were 83.8% (ITT) and 86.6% (PP). Overall, in Asian patients, the efficacy of hybrid therapy seems to be superior to that of sequential therapy; while in Italy, sequential therapy may be more appropriate.

The compliance and safety profile were not significantly different between hybrid therapy and sequential therapy in all six studies.[6,8,11,16-19] Pooled analysis showed that the compliance, overall rate of adverse effects, and the rate of discontinued medication because of adverse effects were 96.1%, 29.1%, and 3.7%, respectively, for hybrid therapy, and 97.5%, 29.9%, and 2.0%, respectively, for sequential therapy.

Concomitant therapy

Hybrid therapy ($n = 732$ in five treatment groups) and concomitant therapy ($n = 840$ in six treatment groups) were compared in five studies (two in Italy and one in Italy/Spain, Spain, and Korea, respectively) as shown in Table 5.

Table 3: Antibiotic resistance and eradication efficacies of hybrid therapy for *Helicobacter pylori* eradication

First author, year	Region	Cases (*n*)	Duration (d)	Cure rate of ITT (%)	Cure rate of PP (%)	Susceptibility test (*n*)	Antibiotic resistance rate (%)				Cure rate of subgroups (% (*n*/*n*))			
							AMO	CLA	MET	CLA and MET	Neither CLA-R or MET-R	Isolated MET-R	Isolated CLA-R	Dual CLA-R and MET-R
Hsu, 2011[6]	Taiwan, China	117	7 + 7	97.4	99.1	57	1.8	7.0	56.1	7.0	100 (25/25)	100 (28/28)	0 (0/0)	100 (4/4)
Molina-Infante, 2013[10]	Spain/ Italy	171	7 + 7	90.0	92.0	34	0	23.5	33.0	8.8	100 (18/18)	87.5 (7/8)	100 (5/5)	33.3 (1/3)
Wu, 2014[12]	Taiwan, China	77	3 + 7	81.8	95.0	29	0	9.8	30.4	4.3	100 (21/21)	100 (4/4)	50 (1/2)	100 (2/2)
Wu, 2014[12]	Taiwan, China	73	5 + 7	86.3	95.1	34	0	9.8	30.4	4.3	100 (19/19)	100 (12/12)	100 (2/2)	0 (0/1)
Wu, 2014[12]	Taiwan, China	70	7 + 7	85.7	93.4	29	0	9.8	30.4	4.3	100 (19/19)	100 (8/8)	100 (1/1)	100 (1/1)
Chen, 2015[8]	Taiwan, China	88	7 + 7	92.0	96.4	65	0	15.3	37.9	8.9	94.3 (33/35)	95.5 (21/22)	100 (4/4)	100 (4/4)
Pooled-data analysis		596				248					98.5 (135/137)	97.6 (80/82)	92.9 (13/14)	80.0 (12/15)

AMO: Amoxicillin; CLA: Clarithromycin; ITT: Intention-to-treat; MET: Metronidazole; PP: Per-protocol; R: Resistance; d: Days.

Table 4: Comparison of HT and sequential therapy in the eradication of *Helicobacter pylori*

First author, year	Region	Centers (*n*)	Duration	Cases (*n*)	Cure rate of ITT (%)	Cure rate of PP (%)	Compliance (%)	Overall rate of adverse effects (%)	Discontinued medication due to adverse effects (%)
Hsu, 2011[6,16]	Taiwan, China	3	14d HT	117	97.4	99.1*	94.9	14.5	4.3
			14d ST	123	91.9	93.9	95.9	21.1	3.3
Sardarian, 2013[17]	Iran	1	14d HT	210	89.5*	92.9*	96.7	28.1	1.4
			10d ST	210	76.7	79.9	98.6	24.8	0.5
Zullo, 2013[18]	Italy	3	14d HT	90	80.0	85.7	93.3	24.4	6.7
			10d ST	90	91.1	92.1	98.9	18.9	1.1
Oh, 2014[11]	Korea	1	14d HT	90	81.1	85.9	97.7	33.7	3.5
			14d ST	94	79.8	82.0	95.7	39.8	3.2
De Francesco, 2014[19]	Italy	1	14d HT	110	82.7	95.8	NR	22.7	6.4
			10d ST	110	90.0	94.3	NR	19.1	2.7
Chen, 2015[8]	Taiwan, China	1	14d HT	88	92.0*	96.4*	97.7	59.1	2.3
			10d ST	87	78.2	81.9	97.6	69.0	2.3
Pooled-data analysis			HT	705	87.8 (619/705)	93.0 (608/654)	96.1 (566/589)	29.1 (204/701)	3.7 (26/701)
			ST	714	83.8 (598/714)	86.6 (589/680)	97.5 (586/601)	29.9 (213/713)	2.0 (14/713)

*P<0.05: HT versus ST. CT: Concomitant therapy; HT: Hybrid therapy; ITT: Intention-to-treat; NR: Not reported; PP: Per-protocol; ST: Sequential therapy; d: Days.

Table 5: Comparison of HT and CT in the eradication of *Helicobacter pylori*

First author, year	Region	Center (*n*)	Duration	Cases (*n*)	Cure rate of ITT (%)	Cure rate of PP (%)	Compliance (%)	Overall rate of adverse effects (%)	Discontinued medication due to adverse effects (*n*)
Molina-Infante, 2013[10]	Spain/ Italy	4	14d HT	171	90.0	92.0	98.8	47.0	2.4
			14d CT	172	91.8	96.2	95.2	56.0	6.0
Zullo, 2013[18]	Italy	3	14d HT	90	80.0	85.7	93.3	24.4	6.7
			5d CT	90	85.6	91.7	93.3	30.0	6.7
De Francesco, 2014[19]	Italy	1	14d HT	110	82.7	95.8*	NR	22.7	6.4
			5d CT	110	78.2	85.1	NR	24.5	5.5
			14d CT	110	86.4	95.0	NR	26.4	7.3
Cuadrado-Lavín, 2015[13]	Spain	3	10d HT	120	90.8	93.9	98.3	67.5	1.7
			10d CT	120	89.9	90.3	96.7	65.8	5.0
Heo, 2015[14]	Korea	6	10d HT	241	78.8	89.6	95.0	NR	0†
			10d CT	238	78.6	89.9	90.1	NR	3.2
Pooled-data analysis			HT	732	84.1 (615/731)	91.4 (602/659)	96.5 (577/598)	42.4 (207/488)	2.7 (19/703)
			CT	840	84.6 (708/837)	91.5 (686/750)	93.3 (559/599)	42.8 (255/596)	5.3 (43/818)

*P<0.05: 14d HT versus 5d CT; †P<0.05: 10d HT versus 10d CT. CT: Concomitant therapy; HT: Hybrid therapy; ITT: Intention-to-treat; NR: Not reported; PP: Per-protocol; ST: Sequential therapy; TT: Triple therapy; d: Days.

In a study from Italy,[19] in PP analysis, the eradication rate of 14-day hybrid therapy was significantly superior to that of 5-day concomitant therapy (no significant difference in ITT analysis). However, in another study from Italy,[18] no significant difference was found between 14-day hybrid therapy and 5-day concomitant therapy. The study from Spain/Italy[10] revealed that the eradication rate in PP analysis of 14-day hybrid therapy was lower than that of 14-day concomitant therapy, but with a borderline significant difference (P = 0.07), while there was no significant difference in ITT analysis. In the other two studies,[13,14] similar efficacies were found between hybrid therapy and concomitant therapy. Pooled analysis showed that the eradication rates were 84.1% (ITT) and 91.4% (PP) for hybrid therapy and 84.6% (ITT) and 91.5% (PP) for concomitant therapy. Overall, the eradication efficacies of hybrid therapy and concomitant therapy were similar.

Two studies demonstrated that the compliance of hybrid therapy was higher than that of concomitant therapy, but with a borderline significant difference (Spain/Italy, P = 0.05,[10] and Korea, P = 0.051).[14] Similar results on compliance were reported in another two studies (Italy[18] and Spain).[13] The study from Spain/Italy[10] showed that the overall rate of adverse effects of hybrid therapy was lower than that of concomitant therapy with a borderline significant difference (P = 0.06); while similar results were shown in another three studies (two from Italy[18,19] and one

from Spain).[13] A report from Korea[14] suggested that the rate of discontinued medication because of adverse effects was significantly lower than that of concomitant therapy, while not significantly different in other studies.[10,13,18,19] Pooled analysis showed that the compliance, overall rate of adverse effects, and the rate of discontinued medication because of adverse effects were 96.5%, 42.4%, and 2.7%, respectively, for hybrid therapy, and 93.3%, 42.8%, and 5.3%, respectively, for concomitant therapy. Overall, the safety of hybrid therapy seems to be a little better than concomitant therapy.

Standard triple therapy

A study from Spain[13] compared 10-day hybrid therapy and 10-day standard triple therapy (n = 60, omeprazole, amoxicillin, and clarithromycin). The eradication rate of hybrid therapy was significantly higher than that of standard triple therapy (ITT, 90.8% vs. 70.0%, P = 0.002; PP, 93.9% vs. 72.4%, P = 0.001). The compliance of the two regimens was both good (98.5% vs. 99.6%), while the overall rate of adverse effects of hybrid therapy was significantly higher (67.5% vs. 45.0%, P = 0.012).

Other regimens

A study from Korea[9] compared 14-day hybrid therapy and 14-day modified sequential therapy containing moxifloxacin (n = 140, rabeprazole and amoxicillin for 7 days followed by rabeprazole, metronidazole, and 400 mg moxifloxacin once daily for 7 days). The cure efficacy of hybrid therapy was significantly lower than that of modified sequential therapy (ITT, 79.2% vs. 91.4%, P = 0.013; PP, 82.6% vs. 94.1%, P = 0.003). The compliance of the two regimens was both 100%, while the overall rate of adverse effects of hybrid therapy was significantly higher (19.6% vs. 11.8%, P = 0.019).

Related meta-analyses

All the three meta-analyses on hybrid therapy were published from China. Wang *et al*.[27] and He *et al*.[28] reported no significant difference in the eradication rate (ITT analysis and PP analysis), compliance and side effects rate between either hybrid therapy and sequential therapy or concomitant therapy. Li *et al*.[29] also reported similar results in their network meta-analysis of comparative effectiveness and tolerance of treatments for *H. pylori* infection. However, Hsu *et al*.[30] reported that hybrid therapy was more effective than sequential therapy in the non-Italian population (relative risk: 1.09, 95% confidence interval: 1.01–1.18) but less so in the Italian population (relative risk: 0.90, 95% confidence interval: 0.83–0.98).

Factors Influencing Eradication Efficacy

A total of five studies analyzed the potential risk factors on the eradication efficacy of hybrid therapy.

Antibiotic resistance

Two studies from Taiwan, China[6,8] explored the influence of antibiotic resistance on the eradication rates. Neither the studies found that antibiotic resistance was an independent risk factor for the treatment failure of hybrid therapy, probably due to the too small sample size of enrolled patients with antibiotic resistance.

Compliance

Four studies (two from Taiwan, China,[6,8] one from Spain/Italy[10] and Korea,[14] respectively) explored the influence of compliance on eradication rate. However, only the study from Spain/Italy[10] showed that compliance was an independent risk factor for the treatment failure of hybrid therapy (compliance > 80%: odds ratio: 12.5, 95% confidence interval: 3.1–52, P = 0.001), and no evident influence was found in the other three studies.

Other potential factors

In the studies of Hsu *et al*.[6] (age, gender, smoking, alcohol drinking, coffee, tea, nonsteroid anti-inflammation drugs, comorbidity, endoscopic findings, and side effects), Molina-Infante *et al*.[10] (age, gender, area, smoking, comorbidity, types of dyspepsia, and side effects), Oh *et al*.[11] (age, gender, body mass index, smoking, alcohol drinking, diabetes, endoscopic findings, and *H. pylori* bacterial density), Heo *et al*.[14] (age, gender, smoking, endoscopic findings, and *H. pylori* bacterial density), and Chen *et al*.[8] (smoking, alcohol drinking, types of dyspepsia, and *H. pylori* bacterial density), no independent risk factor for the treatment failure of hybrid therapy was found.

Shortening Therapy Duration

Metanat *et al*.[15] from Iran compared the eradication rate, compliance and safety between 10-day (5 days + 5 days) and 14-day (7 days + 7 days) hybrid therapy, and found no significant difference in compliance and safety, but the eradication efficacy of 10-day hybrid therapy was significantly lower than that of 14-day hybrid therapy (ITT, 77.6% vs. 83.9%, P = 0.17; PP, 86.0% vs. 92.9%, P < 0.01). Therefore, the authors concluded that 10-day hybrid regimen could not achieve acceptable eradication rate, however, 14-day hybrid regimen seems to be an acceptable option for *H. pylori* eradication in Iran.

Wu *et al*.[12] from Taiwan, China compared the eradication rate, compliance and safety among 10-day (3 days + 7 days), 12-day (5 days + 7 days), and 14-day (7 days + 7 days) hybrid therapy, and demonstrated no significant difference among them (ITT, 81.8% vs. 86.3% vs. 85.8%; PP, 95.0% vs. 95.1% vs. 93.4%). This study suggested that in regions of moderate to low clarithromycin and/or metronidazole resistance, it may be feasible to shorten hybrid therapy to 10 or 12 days.

Heo *et al*.[14] from Korea and Cuadrado-Lavín *et al*.[13] from Spain evaluated the eradication rates of 10-day (5 days + 5 days) hybrid therapy: 78.8% (ITT) and 89.6% (PP) in Korea, and 90.8% (ITT) and 93.9% (PP) in Spain. Nevertheless, both the two studies failed to compare 14-day hybrid therapy.

Thus, the marked regional differences across studies may be associated with different levels and patterns of antibiotic resistance, which need to be investigated further to establish the optimal duration of hybrid therapy.

Role of Proton Pump Inhibitors

Different PPIs have been used in hybrid therapy. Eradication was achieved in 86.7% (425/490, ITT) and 92.1% (421/457, PP) patients following the omeprazole-containing regimen (four studies),[10,13,18,19] in 85.2% (409/480, ITT) and 90.4% (404/447, PP) patients with pantoprazole (two studies),[15,17] in 83.2% (268/322, ITT) and 87.3% (268/307, PP) patients with rabeprazole (three studies),[8,9,11] and in 84.8% (490/578, ITT) and 93.5% (461/493, PP) patients with esomeprazole (three studies).[6,12,14] No data with lansoprazole are available.

Eradication was achieved in 87.0% (721/829, ITT) and 91.7% (698/761, PP) patients who received high PPI dosage (double dose, in six studies),[6,8-12] and in 83.7% (871/1041, ITT) and 90.8% (856/943, PP) patients who received standard PPI dosage (six studies).[13-15,17-19]

No study has compared the different dosages and types of PPIs in hybrid therapy.

Limitations

There are still some issues needed further exploration about hybrid therapy. Studies in areas with high antibiotic resistance were lacking. The small number of patients with antibiotic resistance, especially dual clarithromycin and metronidazole resistance, leads to an unclear relationship between the eradication efficacy of hybrid therapy and antibiotic resistance. Furthermore, the optimal duration of hybrid therapy and dosage of PPIs were also unclear. Studies determining the influencing factors for the eradication success of hybrid therapy were less, and some factors were yet not evaluated such as cytochrome P450 isoenzyme 2C19 gene polymorphism.[31-33] Up to now, few studies have ever explored the cost implications of hybrid therapy. Among the studies reviewed, there were differences in patient enrollment, *H. pylori* detection methods, medication administration (therapy duration, dosage, frequency, and relationship with food intake), and the rates of background antibiotic resistance, which further intensified the analytical challenges.

Conclusions

There are significant differences in the cure rates of hybrid therapy in different regions and populations with consistently good compliance and safety. The limited results show that dual resistance to clarithromycin and metronidazole is the key factor compromising the eradication efficacy of hybrid therapy. The eradication efficacy, compliance, and safety of hybrid therapy are similar to those of sequential and concomitant therapies. In the future, the eradication efficacy in regions with high antibiotic resistance, the relationship between eradication rate and antibiotic resistance and the cost implications of hybrid therapy are worthy of further investigation.

Financial support and sponsorship

This study was supported by grants from the National Science and Technology Pillar Program during the Twelfth 5-year Plan Period (No. 2012BAI06B02), the Capital Health Research and Development of Special (No. 2011-4032-02), and Key Laboratory for *Helicobacter pylori* Infection and Upper Gastrointestinal Diseases in Beijing (No. BZ0371).

Conflicts of interest

There are no conflicts of interest.

References

1. Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. Gut 2010;59:1143-53. doi: 10.1136/gut.2009.192757.
2. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, *et al.* Management of *Helicobacter pylori* infection – The Maastricht IV/Florence Consensus Report. Gut 2012;61:646-64. doi: 10.1136/gutjnl-2012-302084.
3. Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, *et al. Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut 2013;62:34-42. doi: 10.1136/gutjnl-2012-302254.
4. Molina-Infante J, Gisbert JP. Optimizing clarithromycin-containing therapy for *Helicobacter pylori* in the era of antibiotic resistance. World J Gastroenterol 2014;20:10338-47. doi: 10.3748/wjg.v20.i30.10338.
5. Song Z, Zhang J, He L, Chen M, Hou X, Li Z, *et al.* Prospective multi-region study on primary antibiotic resistance of *Helicobacter pylori* strains isolated from Chinese patients. Dig Liver Dis 2014;46:1077-81. doi: 10.1016/j.dld.2014.08.038.
6. 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* 2011;16:139-45. doi: 10.1111/j.1523-5378.2011.00828.x.
7. Graham DY, Lee YC, Wu MS. Rational *Helicobacter pylori* therapy: Evidence-based medicine rather than medicine-based evidence. Clin Gastroenterol Hepatol 2014;12:177-86.e3. doi: 10.1016/j.cgh.2013.05.028.
8. Chen KY, Lin TJ, Lin CL, Lee HC, Wang CK, Wu DC. Hybrid vs sequential therapy for eradication of *Helicobacter pylori* in Taiwan: A prospective randomized trial. World J Gastroenterol 2015;21:10435-42. doi: 10.3748/wjg.v21.i36.10435.
9. Hwang JJ, Lee DH, Yoon H, Shin CM, Park YS, Kim N. Efficacy of moxifloxacin-based sequential and hybrid therapy for first-line *Helicobacter pylori* eradication. World J Gastroenterol 2015;21:10234-41. doi: 10.3748/wjg.v21.i35.10234.
10. Molina-Infante J, Romano M, Fernandez-Bermejo M, Federico A, Gravina AG, Pozzati L, *et al.* Optimized nonbismuth quadruple therapies cure most patients with *Helicobacter pylori* infection in populations with high rates of antibiotic resistance. Gastroenterology 2013;145:121-8.e1. doi: 10.1053/j.gastro.2013.03.050.
11. Oh DH, Lee DH, Kang KK, Park YS, Shin CM, Kim N, *et al.* Efficacy of hybrid therapy as first-line regimen for *Helicobacter pylori* infection compared with sequential therapy. J Gastroenterol Hepatol 2014;29:1171-6. doi: 10.1111/jgh.12518.
12. Wu JY, Hsu PI, Wu DC, Graham DY, Wang WM. Feasibility of shortening 14-day hybrid therapy while maintaining an excellent *Helicobacter pylori* eradication rate. *Helicobacter* 2014;19:207-13. doi: 10.1111/hel.12113.
13. Cuadrado-Lavín A, Salcines-Caviedes JR, Diaz-Perez A, Carrascosa MF, Ochagavía M, Fernandez-Forcelledo JL, *et al.* First-line eradication rates comparing two shortened non-bismuth

quadruple regimens against *Helicobacter pylori*: An open-label, randomized, multicentre clinical trial. J Antimicrob Chemother 2015;70:2376-81. doi: 10.1093/jac/dkv089.
14. Heo J, Jeon SW, Jung JT, Kwon JG, Lee DW, Kim HS, *et al.* Concomitant and hybrid therapy for *Helicobacter pylori* infection: A randomized clinical trial. J Gastroenterol Hepatol 2015;30:1361-6. doi: 10.1111/jgh.12983.
15. Metanat HA, Valizadeh SM, Fakheri H, Maleki I, Taghvaei T, Hosseini V, *et al.* Comparison between 10- and 14-day hybrid regimens for *Helicobacter pylori* eradication: A randomized clinical trial. *Helicobacter* 2015;20:299-304. doi: 10.1111/hel.12202.
16. Hsu PI, Wu DC, Wu JY, Graham DY. Is there a benefit to extending the duration of *Helicobacter pylori* sequential therapy to 14 days? *Helicobacter* 2011;16:146-52. doi: 10.1111/j.1523-5378.2011.00829.x.
17. 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* 2013;18:129-34. doi: 10.1111/hel.12017.
18. Zullo A, Scaccianoce G, De Francesco V, Ruggiero V, D'Ambrosio P, Castorani L, *et al.* Concomitant, sequential, and hybrid therapy for *H. pylori* eradication: A pilot study. Clin Res Hepatol Gastroenterol 2013;37:647-50. doi: 10.1016/j.clinre.2013.04.003.
19. 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 2014;63(Pt 5):748-52. doi: 10.1099/jmm.0.072322-0.
20. Rimbara E, Fischbach LA, Graham DY. Optimal therapy for *Helicobacter pylori* infections. Nat Rev Gastroenterol Hepatol 2011;8:79-88. doi: 10.1038/nrgastro.2010.210.
21. Gisbert JP, Calvet X, O'Connor JP, Mégraud F, O'Morain CA. The sequential therapy regimen for *Helicobacter pylori* eradication. Expert Opin Pharmacother 2010;11:905-18. doi: 10.1517/14656561003657152.
22. Vaira D, Zullo A, Hassan C, Fiorini G, Vakil N. Sequential therapy for *Helicobacter pylori* eradication: The time is now! Therap Adv Gastroenterol 2009;2:317-22. doi: 10.1177/1756283X09343326.
23. Zullo A, De Francesco V, Hassan C, Morini S, Vaira D. The sequential therapy regimen for *Helicobacter pylori* eradication: A pooled-data analysis. Gut 2007;56:1353-7. doi: 10.1136/gut.2007.125658.
24. Graham DY, Lu H, Yamaoka Y. A report card to grade *Helicobacter pylori* therapy. *Helicobacter* 2007;12:275-8. doi: 10.1111/j.1523-5378.2007.00518.x.
25. Zhou L, Zhang J, Chen M, Hou X, Li Z, Song Z, *et al.* A comparative study of sequential therapy and standard triple therapy for *Helicobacter pylori* infection: A randomized multicenter trial. Am J Gastroenterol 2014;109:535-41. doi: 10.1038/ajg.2014.26.
26. Zhou L, Zhang J, Song Z, He L, Li Y, Qian J, *et al.* Tailored versus triple plus bismuth or concomitant therapy as initial *Helicobacter pylori* treatment: A randomized trial. *Helicobacter* 2016;21:91-99. doi: 10.1111/hel.12242.
27. Wang B, Wang YH, Lv ZF, Xiong HF, Wang H, Yang Y, *et al.* Review: Efficacy and safety of hybrid therapy for *Helicobacter pylori* infection: A systematic review and meta-analysis. *Helicobacter* 2015;20:79-88. doi: 10.1111/hel.12180.
28. He L, Deng T, Luo H. Meta-analysis of sequential, concomitant and hybrid therapy for *Helicobacter pylori* eradication. Intern Med 2015;54:703-10. doi: 10.2169/internalmedicine.54.3442.
29. Li BZ, Threapleton DE, Wang JY, Xu JM, Yuan JQ, Zhang C, *et al.* Comparative effectiveness and tolerance of treatments for *Helicobacter pylori*: Systematic review and network meta-analysis. BMJ 2015;351:h4052. doi: 10.1136/bmj.h4052.
30. Hsu PI, Lin PC, Graham DY. Hybrid therapy for *Helicobacter pylori* infection: A systemic review and meta-analysis. World J Gastroenterol 2015;21:12954-62. doi: 10.3748/wjg.v21.i45.12954.
31. Furuta T, Graham DY. Pharmacologic aspects of eradication therapy for *Helicobacter pylori* Infection. Gastroenterol Clin North Am 2010;39:465-80. doi: 10.1016/j.gtc.2010.08.007.
32. Furuta T, Shirai N, Kodaira M, Sugimoto M, Nogaki A, Kuriyama S, *et al.* Pharmacogenomics-based tailored versus standard therapeutic regimen for eradication of *H. pylori*. Clin Pharmacol Ther 2007;81:521-8. doi: 10.1038/sj.clpt.6100043.
33. Yang JC, Lin CJ. CYP2C19 genotypes in the pharmacokinetics/pharmacodynamics of proton pump inhibitor-based therapy of *Helicobacter pylori* infection. Expert Opin Drug Metab Toxicol 2010;6:29-41. doi: 10.1517/17425250903386251.