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Is short-term therapy really sufficient to eradicate *Helicobacter pylori* infection?*

Ning ZHOU, Wei-xing CHEN, Wei ZHANG, Lan LI, Xi JIN, You-ming LI†‡

(*Department of Gastroenterology, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China*)

†E-mail: zlym@zju.edu.cn

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Abstract: Objective: The aim of our study was to perform a systematic review and meta-analysis of the efficacy of short-term protocols for *Helicobacter pylori* eradication and to review the safety and adverse profiles of these eradication protocols. Methods: Literatures were located through electronic searches by PubMed, Medline, ISI Web of Knowledge, and Cochrane Library using the relevant terms. Abstracts of important meetings were searched manually in some journal supplements. Additional bibliographies were identified from the reference lists of identified studies. Three independent reviewers systemically identified randomized controlled trials (RCTs) comparing short-duration protocols vs. 7-d proton pump inhibitor (PPI)-based triple protocols, as well as studies reporting eradication rates of short-duration protocols for *H. pylori*. Summary effect size was calculated as relative risk (RR) and 95% confidence intervals (CI) using Review Manager 4.2, and $P<0.05$ was defined as statistically significant in all analyses. Results: Among 90 abstracts retrieved, 15 studies were analyzed, including a total of 30 treatment regimens with 1856 subjects. Mean intention-to-treat (ITT) cure rates of 63.2% and 81.3% were achieved with short-term protocols and 7-d PPI-containing protocols, respectively. Per-protocol (PP)-based overall cure rates were 66.6% and 86.1%, respectively. Short-term therapy was inferior to 7-d triple regimen ($P<0.00001$). After sub-analysis, however, comparing the effects of ≥3-d protocols and 7-d triple protocols, the cumulative ITT RR was 0.95 ($P=0.26$), and PP RR was 0.95 ($P=0.10$), without significant heterogeneity. Moreover, slightly fewer adverse-effects were found in short-term protocols. Conclusions: Although more economical, short-duration protocols are inferior to 7-d PPI-based triple protocols with regarding to eradication rate of *H. pylori*. Protocols of more than 3 d, however, may be equivalent to 7-d protocols.

Key words: *Helicobacter pylori*, Eradication therapy, Short-term, Meta-analysis, Adverse effects
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1 Introduction

When developing a treatment plan for eradication of *Helicobacter pylori*, efficacy, expenditure, adherence, and adverse reactions are all taken into considerations. Short-duration therapy, lasting less than one week, has the advantages of simplicity, lower expense, better patients' compliance, and fewer side effects (Zheng *et al*., 2005). However, is it sufficient to adequately resolve *H. pylori* infection? To our knowledge, there has been little systematic analysis of the efficacy of short-term therapies for *H. pylori* eradication (Treiber, 2000). Although great progress has been made, there is no definitive treatment for permanent *H. pylori* eradication as the constant mutation of bacterial stains. The ideal scheme should be simple, prompt, long-lasting, economical, well-tolerated, and harmless, with low drug resistance. With the wide use of antibiotics in the treatment of *H. pylori* infection and other infectious diseases, antibiotic resistance is increasing, resulting in a declining

‡ Corresponding author
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cure rate in most clinic settings. A substantial proportion of patients fail with the classical anti-*H. pylori* protocol consisting of a proton pump inhibitor (PPI) and two antimicrobial agents (Kim *et al*., 2007). The potential adverse effects of more extensive protocols and treatment-related costs are increasing, while patients' compliance is decreasing. Various novel therapies have been therefore considered, including shortening the duration to less than one week. Theoretically, short-term therapy for eradicating *H. pylori* infection can offer advantages in costs, compliance, reduced adverse effects, and less drug resistance, as compared to sophisticated 7-d protocols. However, there is no consensus on the efficacy of shorter protocols. It has been 10 years since the introduction of short-term protocols for the eradication of *H. pylori* infection (Treiber, 2000). Are short-term protocols really sufficient to eradicate *H. pylori* infection? Here, we explore the feasibility of this therapy by systematic analysis, and conduct head-to-head comparisons of adverse effects of short-term protocols and 7-d triple protocols.

2 Materials and methods

2.1 Selection of studies

For literature up to May 2009, PubMed, Medline, ISI Web of Knowledge, and Cochrane Library were used as search engines, using the following terms: 'ultrashort', 'short-term', 'short-duration', 'therapy', 'treatment', '*Helicobacter pylori*', '*H. pylori*', 'Hp', '*Campylobacter pylori*', 'one-day', '1-day', 'two-day', '2-day', 'weekend', 'six-day', '6-day', etc. Boolean operators (AND, OR) were also used in succession to narrow and widen the search (Jafri *et al*., 2008). We searched the abstracts of important meetings and relevant articles from the reference list by hand. Abstracts of the 'grey' and 'fugitive' literatures were also retrieved and scrutinized to minimize the publication bias.

2.2 Eligibility criteria

Original randomized controlled trials (RCTs) and studies reporting eradication rates of short-duration (lasting less than one week) regimens for *H. pylori* published in English and Chinese languages were reviewed. The search was limited to adult studies (age >18 years). The other inclusion criteria were as follows: (1) RCTs conducted to compare short-duration (range 1–6 d) protocols (study group) with 7-d PPI-based triple protocols (control group); (2) *H. pylori* positivity and elimination documented by routine confirmatory examinations (urea breath test, stool antigen test, gastric mucosal biopsy for histology, rapid urease test, or culture) (Fuccio *et al*., 2007), with reassessment performed at least four weeks after completion of therapy; (3) ITT and PP reports that were complete or could be calculated by sufficient data.

Studies were excluded if one of the following settings was met: (1) pediatric studies; (2) duplicate, review, case, or incomplete data, sequential or intensified therapy; (3) studies with intravenous medication; (4) subjects who had active ulcer bleeding, regularly took any one of the PPI or H2-receptor antagonist (H2RA) during the 15- or 7-d period preceding the study, respectively, or antibiotics and bismuth up to four weeks before (Savarino *et al*., 1999); (5) similar drugs taken during the course of therapy or in the four-week period after stopping treatment, except antacids for symptom relief, or PPI for ulcer healing (Savarino *et al*., 1999); (6) previous *H. pylori* eradication; (7) total duration of antibiotic therapy in study group exceeding 6 d; (8) unusual use of PPI-containing triple protocols.

2.3 Data extraction

Three reviewers independently assessed both trial eligibility and quality, and extracted data on eradication. For each trial, data were extracted in a predefined form, including author, year of publication, country, method of RCT, blind or not, allocation concealment, number of included participants, underlying diseases, methods of determining and reassessment of *H. pylori* status, quality scoring, exact methods of therapy, mean age, male/female ratio, eradication rates, adverse effects, and compliance (Gisbert and Morena, 2006).

2.4 Quality assessment

The quality of the studies was assessed using the score proposed by Jadad *et al*. (1996) based on three items: (1) randomization; (2) double blinding; and (3) description of withdrawals and dropouts. Points are awarded if: the study was described as randomized

(+1); the means of carrying out randomization was described and appropriate (+1); the study was described as double-blind (+1); the means of double-blind was described and appropriate (+1); and there was a description of withdrawals giving number and reason in both groups (+1) (Canter *et al*., 2007).

Two assessors marked the quality of studies independently. Discrepancies in the interpretation were resolved by consensus (Gisbert *et al*., 2005).

2.5 Statistical analysis

Pooled eradication rates and relative risk (RR) with 95% confidence interval (CI) were calculated using Cochrane software Review Manager 4.2 provided by the Cochrane Collaboration, Oxford, UK. $P<0.05$ was considered statistically significant. The test for heterogeneity was analyzed by Cochrane's χ^2-test (Wang *et al*., 2007), and when the Higgins I^2 statistic was ≤50%, which determines the percentage of total variation across studies due to heterogeneity (Wang *et al*., 2009), the fixed effect model was used to pool studies; otherwise, the random effect model was used. $P<0.10$ was considered to be significant for heterogeneity between studies (Li *et al*., 2008).

When three or more study arms in a same trial were encountered, the similar pairs were extracted after the comparison of one short-term arm with one 7-d arm separately.

3 Results

3.1 Description of the studies

Of all 338 generated studies, 95.6% were excluded after title screening and reviewing of abstracts and full-text articles. A total of 15 RCTs (33 study arms) satisfied the criteria of our review (Fig. 1). They came from studies conducted in eight regions from six countries (Table 1). To make paired comparison convenient, one matched study arm was omitted from Wong *et al*. (2001a)'s, Pieramico *et al*. (1998)'s, and Yang *et al*. (2003)'s trials, respectively.

Characteristics of the 15 studies comparing *H. pylori* eradication efficacy with short-term (1–6 d) protocols vs. that with 7-d PPI-based triple protocols are summarized in Tables 1 and 2. Definition of compliance was taking 80%–85% of the study medication.

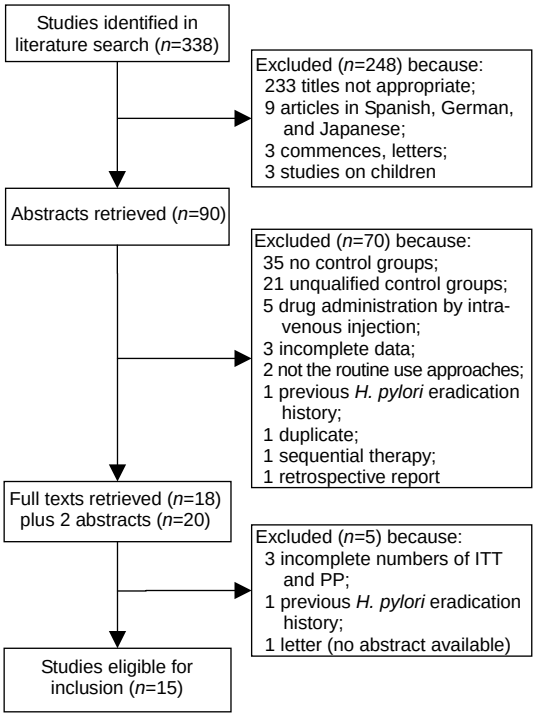


Fig. 1 Flow diagram of assessment of studies identified in the systematic review

There were five trials excluded after full-text reading, including one letter written by Scuderi *et al*. (2000) (because no abstract available, we read the full article) and one abstract searched manually (Grimley *et al*., 1999; Scuderi *et al*., 2000; Nagahara *et al*., 2001; Vakil *et al*., 2002; Malekzadeh *et al*., 2003).

3.2 Adverse events and compliance

Because of incomplete data, we did not perform a meta-analysis comparing the occurrence of adverse events and drop-outs between study groups and controls, but we did head-to-head comparisons of the adverse effects (Table 2). Most of them were short-lasting and self-limiting without serious symptoms. The major adverse effects were loose stools/diarrhea, metallic taste/bitter taste, fatigue, nausea, vomiting, headache, dizziness, stomatitis, oral ulcers, skin rush, pharyngeal oedema, and short-lasting increase of liver enzymes, with mild to moderate intensities. The reasons for dropping out were not typically related to adverse effects. Rare toxicity episodes were reported.

Three of the included trials reported significant differences in total adverse-effects occurring among different study arms. A significant reduction of adverse effects was observed with the use of a shorter

Table 1 Characteristics of included randomized, controlled trials

Study	Origin	RCT method	Blind	Allocation concealment	Total cases (*n*)	Underlying diseases
Zhang *et al*., 2006	China	Cluster sampling	No	NM	396	Healthy
Huo *et al*., 2006	China	NM	No	NM	60	NM
Zheng *et al*., 2005	China	NM	No	NM	80	NUD
Lara *et al*., 2003	USA	NM	No	NM	160	Dyspepsia
Wermeille *et al*., 1999	Switzerland	NM	No	NM	34	GU/DU/gastritis/duodenitis
Wong *et al*., 2001a	Hong Kong, China	Computer-generated	Single	Sealed envelope	116	DU/GU/erosion/normal
Wong *et al*., 2001b	Hong Kong, China	NM	Single	Sealed envelope	118	DU
Pieramico *et al*., 1998	Italy	NM	NM	NM	67	NM
Gambaro *et al*., 2003	Italy	Computer-generated	No	NM	128	PU/NUD
Giannini *et al*., 2006	Italy	Computer-generated	No	NM	169	GU/DU/chronic gastritis
Yang *et al*., 2003	Taiwan, China	NM	No	NM	46	Active DU/GU
Isomoto *et al*., 2000	Japan	NM	NM	Sealed envelope	139	DU/GU/NUD
Wang *et al*., 2004	China	NM	NM	NM	95	DU/GU/erosive gastritis
Trevisani *et al*., 1998	Italy	NM	No	NM	160	GU/DU/gastritis
Treiber *et al*., 1998	Germany	NM	No	NM	88	DU/GU/erosive gastritis

Study	Test for confirming infection	Verification of eradication	Time of reassess	Jadad score
Zhang *et al*., 2006	13C-UBT	13C-UBT	6 weeks	2
Huo *et al*., 2006	Histology or RUT	Histology, RUT, and 14C-UBT (6 months)	≥5 weeks	2
Zheng *et al*., 2005	Histology and RUT	13C-UBT	≥4 weeks	2
Lara *et al*., 2003	14C-UBT	14C-UBT	5 weeks	2
Wermeille *et al*., 1999	RUT	13C-UBT	6–8 weeks	2
Wong *et al*., 2001a	CLO and histology	CLO and histology	6 weeks	3
Wong *et al*., 2001b	13C-UBT+at least one of CLO, histology, and culture	13C-UBT, CLO, histology, and culture	6 weeks	2
Pieramico *et al*., 1998	Histology, RUT, and culture	Histology, RUT, and culture	4–8 weeks	1
Gambaro *et al*., 2003	Two of CLO, histology, and 13C-UBT	13C-UBT	28–32 d	3
Giannini *et al*., 2006	Histology	13C-UBT	≥4 weeks	3
Yang *et al*., 2003	CLO, culture, and 13C-UBT	CLO, culture, and 13C-UBT	8 weeks	2
Isomoto *et al*., 2000	At least two of serology, CLO, and histology	Serology, CLO, and histology	≥4 weeks	2
Wang *et al*., 2004	Histology, RUT, and 14C-UBT	Histology and 14C-UBT	28 d	2
Trevisani *et al*., 1998	RUT and histology	RUT and histology	≥1 month	2
Treiber *et al*., 1998	RUT and 13C-UBT	13C-UBT	≥4 weeks	2

RCT: randomized controlled trial; NM: not mentioned; NUD: non-ulcer dyspepsia; GU: gastric ulcer; DU: duodenal ulcer; PU: peptic ulcer; UBT: urea breath test; RUT: rapid urease test; CLO: campylobacter-like organism test

Table 2 Head-to-head comparison of side effects of short-term and 7-d triple therapies

Study	Percentage of side effects (%)		Level of significance	Study	Percentage of side effects (%)		Level of significance
	<7 d	7 d			<7 d	7 d	
Zhang *et al*., 2006				Wong *et al*., 2001a	45.0	47.0	NS
Skin rash	0.9	5.4	P=0.013	Wong *et al*., 2001b*	79.0	78.0	NS
Abdominal bloating	6.6	12.8	P=0.035	Pieramico *et al*., 1998	14.0	15.0	NS
Stool discoloration	33.2	9.5	P<0.001	Gambaro *et al*., 2003	19.0	21.7	NS
Huo *et al*., 2006	13.3	13.3	NS	Giannini *et al*., 2006	13.0	29.0	P=0.022
Zheng *et al*., 2005	7.9	17.9	NS	Yang *et al*., 2003	21.7	13.0	NS
Lara *et al*., 2003				Isomoto *et al*., 2000	20.0	20.3	NS
Experienced at least one side effect	30.0	37.0	NS	Wang *et al*., 2004	8.9	38.0	P<0.001
Wermeille *et al*., 1999				Trevisani *et al*., 1998	1.3	2.6	NS
Slight discomfort	86.6	42.1	P=0.021	Treiber *et al*., 1998	41.5	26.5	NS
No side-effects	6.7	47.3	P=0.027				

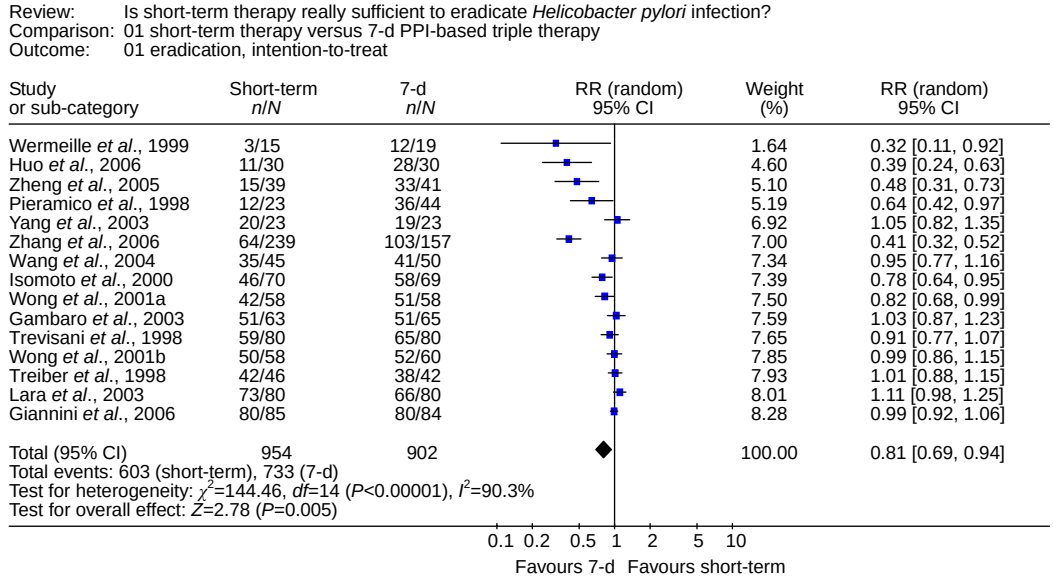
NS: no significance. * By shortening the duration of treatment by 4 d (2.59 d for short-term therapies vs. 6.15 d for 7-d triple therapies, P<0.001), the day number with side-effects was reduced by an average of 3.5 d per patient in this study

protocol in studies conducted by Wong *et al*. (2001b). It was reported that the mean duration of all adverse effects was significantly shorter in the 3-d RAC (rabeprazole, amoxicillin, and clarithromycin) group when compared to the 7-d RAC group (2.8 d vs. 6.0 d, $P<0.001$) (Wong *et al*., 2001a).

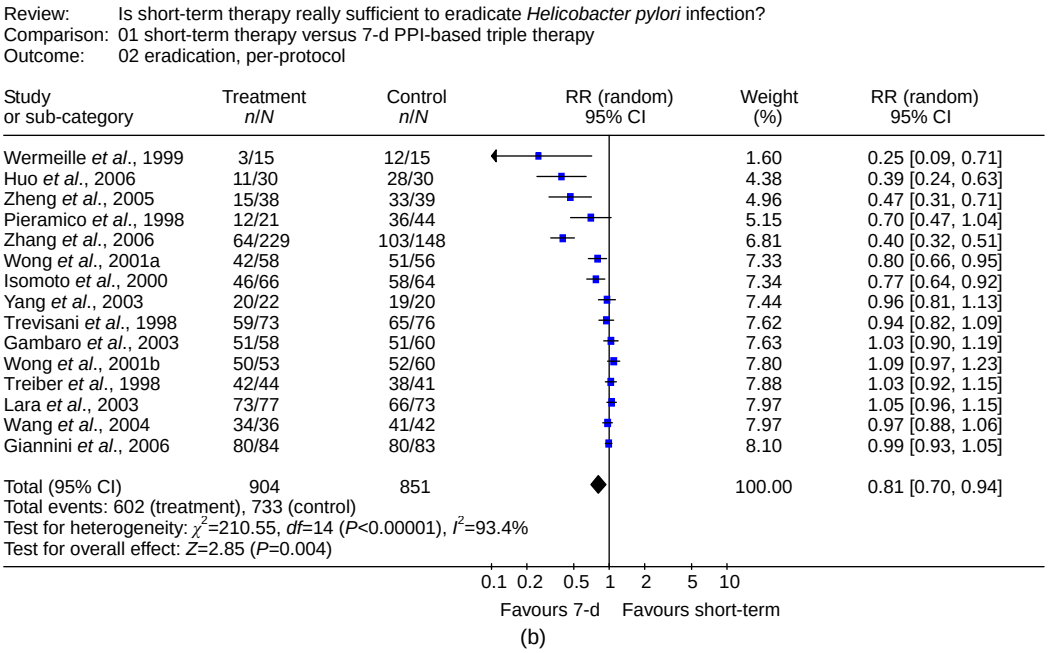
3.3 Summary estimates

As shown in Figs. 2–4, the overall *H. pylori* eradication rates by ITT analysis were 63.2% (603/954) in short-term protocols, and 81.3% (733/902) in 7-d PPI-based triple protocols, respectively; and by PP analysis were 66.6% (602/904) and 86.1% (733/851), respectively. There was a significant difference between the eradication rates of the two groups ($P<0.00001$), with statistical heterogeneity ($I^2=90.3\%$ and $I^2=93.4\%$ with ITT and PP, respectively). Pooled RRs of ITT and PP were 0.81 (95% CI: 0.69–0.94) and 0.81 (95% CI: 0.70–0.94), respectively.

Subgroup analysis showed comparable efficacy

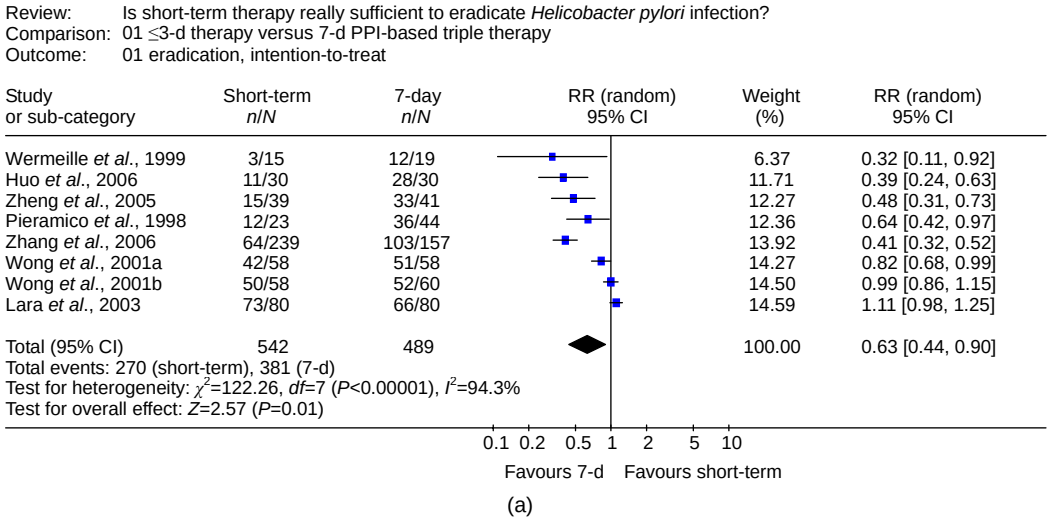


(a)

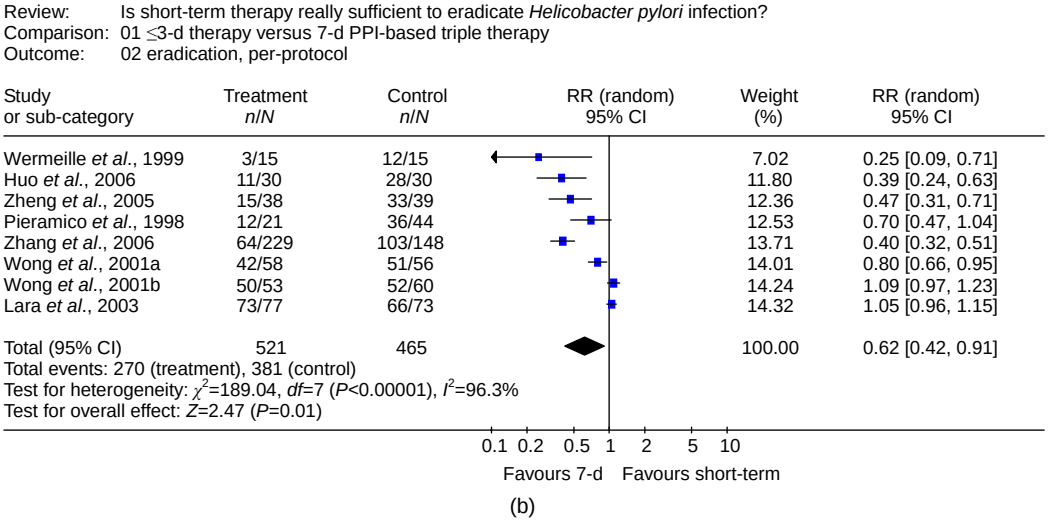


(b)

Fig. 2 Intention-to-treat (a) and per-protocol (b) eradication rates for short-term therapy vs. 7-d PPI-based triple protocol



(a)



(b)

Fig. 3 Intention-to-treat (a) and per-protocol (b) eradication rates for ultrashort-term therapy vs. 7-d PPI-based triple protocol

with ≥3-d therapy and 7-d standard therapy, with cumulative RR of ITT 0.95 (95% CI: 0.89–1.01, P=0.26) and PP 0.95 (95% CI: 0.90–1.00, P=0.10) respectively, without significant heterogeneity. But when the duration decreased to 3 d or less, lower eradication rates were found (49.8% vs. 77.9% and 51.8% vs. 81.9% with ITT and PP, respectively, P<0.00001).

To eliminate the potential influence of prolonged PPI use followed by a period after eradication therapy, we conducted sensitivity analysis by excluding these trials (Treiber *et al*., 1998; Trevisani *et al*., 1998; Isomoto *et al*., 2000; Yang *et al*., 2003; Wang *et al*., 2004; Giannini *et al*., 2006). The results, however, changed little [RR 0.67 (95% CI: 0.50–0.91, P< 0.00001)].

We also performed sensitivity analysis by excluding those with less than 40 cases in each group (Pieramico *et al*., 1998; Wermeille *et al*., 1999; Yang *et al*., 2003; Zheng *et al*., 2005; Huo *et al*., 2006), and the models did not notably change from the overall results. Pooled RRs of ITT and PP were 0.88 (95% CI: 0.76–1.02) and 0.89 (95% CI: 0.78–1.03), respectively.

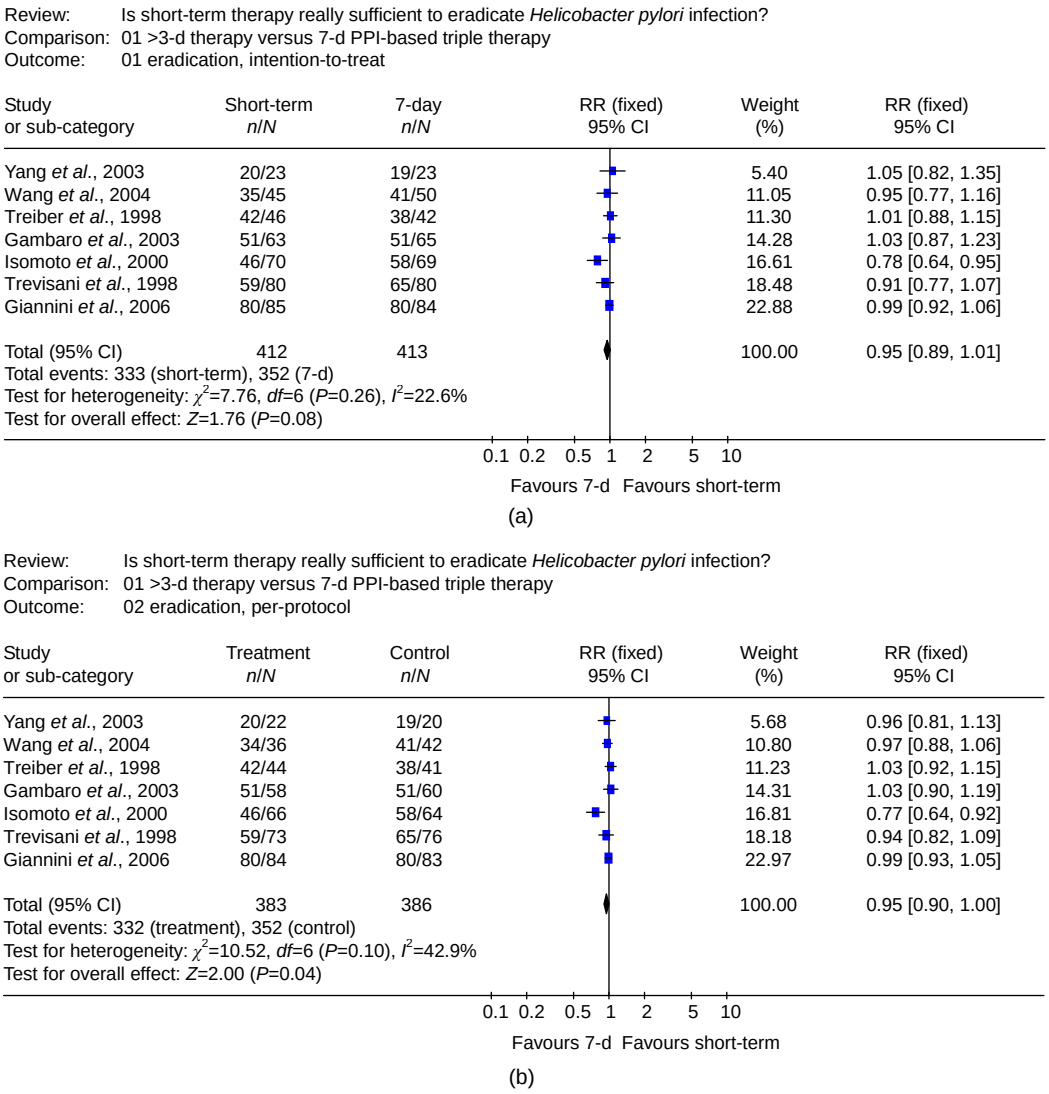


Fig. 4 Intention-to-treat (a) and per-protocol (b) eradication rates for >3 d therapy vs. 7-d PPI-based triple protocols

4 Discussion

Given the multiple options for anti-*H. pylori* treatment, no consensus on the optimal approach has been attained. The once well established 7-d triple therapy programs may no longer be the 'gold standard', mainly due to the high load of the bacteria and widespread prescription of antibiotics. Prolonging the duration can yield higher *H. pylori* eradication success, but the complexity and longer duration may lower compliance, with more adverse effects and costs. The increasing probability of antibiotics resistance is problematic as well. Controversy surrounds the optimal composition, dosage, and duration of therapies for more acceptable, rapid, and cost-effective eradication of *H. pylori* infection (Chu *et al*., 1998). Thus, consideration has been given to the possibility of shortening the treatment time without compromising its eradication efficacy of *H. pylori* infection, and in some instances (Wong *et al*., 2001b; Gambaro *et al*., 2003; Lara *et al*., 2003; Yang *et al*., 2003; Giannini *et al*., 2006), this has achieved equivalent results to those long-term combined protocols.

To date, few systematic reviews have investigated the efficacy of short-term (<1 week) protocols compared with that of long-term (≥1 week) protocols

in *H. pylori* eradication. The primary aim of the present analysis, thus, was to compare the shorter-than-usual durations of protocols vs. 7-d PPI-based triple protocols for the eradication of *H. pylori* infection (Vergara *et al*., 2003). The reason why we chose 7-d PPI-based triple protocols as control was based on management guidelines (i.e., Maastricht consensus). PPI in combination with two antimicrobial agents is still the most widely-used protocol with generally acceptable eradication rates. To make the study arms more comparable and better avoid selection bias, we defined relatively strict criteria, more so than those in Treiber (2000)'s analysis.

A stream of publications on short duration treatment of *H. pylori* infection exist, but qualified studies are limited for various reasons, such as lack of controls or unqualified controls, incomplete data, intravenous administration, and rescue therapy.

As mentioned by Tucci *et al*. (1993), the successful outcomes of short-term protocols for *H. pylori* infection might be attributed to the administration of high-dose drugs or a combination of two antibiotics with one or two non-antibiotic adjunctive agents. It has been reported that the rapid onset of anti-secretory action can potentiate the activity of combined antibiotics after the first day of anti-*Helicobacter* treatment (Gambaro *et al*., 2003) and inhibit bacterial urease to a greater degree, which reduces the possibility of *H. pylori* surviving in the low pH of gastric milieu, and strongly suppresses *H. pylori* motility.

Unfortunately, these intriguing results have not been extensively reproduced. In the present study, we found that short-term protocols could not meet predefined threshold cure rates, based on the following scale: A or excellent (95%–100%), B or good (90%–94%), C or fair (85%–89%), D or poor (81%–84%), and F or unacceptable (80%) (Graham *et al*., 2007). The effectiveness of triple protocols, containing of a PPI, has also been undermined (Graham *et al*., 2007). The plausible mechanism for the low eradication rates is that the phenotype and the load of *H. pylori* strain and/or the profile of host-immune responses are different among different groups (Namiot *et al*., 2000). The latent resistance to antibiotics cannot be ignored as well.

In this analysis, ≥3-d protocols had comparable efficacy with 7-d standard protocols. And head-to-head comparison illustrates the safety and less adverse profiles in short-term protocols. These protocols could be candidates for those who have low loads of *H. pylori* strain. So it's arbitrary to deny the therapy too early. This highlights some important aspects influencing short-term protocols, and can be at least used as a basis for sequential therapies. From the head-to-head comparison of adverse effects profiles, the advantage of short-term protocols can be seen. Additionally, patients may benefit by the reduced drug exposure and risks. Simplicity, convenience, lower expense, and high tolerance are also advantages of shorter protocols. Shorter protocols also are a consideration for those who have impaired renal and/or hepatic function.

Questions regarding recurrence of the infection after shorter protocol use have been raised. It has been reported that high recrudescence occurs after apparent successful eradication (Lai *et al*., 1996). Indeed, the relapse of *H. pylori* infection and symptom recurrence over time should not be neglected. Therefore, larger scale, rigorous double-blind regional RCTs should be carried out with longer follow-up. In fact, the follow-up period is critical for determining long term efficacy.

In any case, innovative anti-*H. pylori* protocols which reduce the duration of therapy for the benefit of patients are expected. To verify their efficacy, firstly, protocols should be tested according to the regional epidemiology of bacterial strains and resistance. Studies should be performed based on the relevant pharmacodynamics of the drugs used (Sugimoto *et al*., 2007). Drugs with immediate release, rapid absorption, gastric acid suppression, long half-lives, and higher doses with shorter intervals of dosing are especially required in short-term protocols. Secondly, more effective drug combinations, good cost-benefit ratios, and persistent high eradication rates also require further investigation. Moreover, the possible dose-related adverse effects and subsequent decreased compliance with increased daily dose must be assessed (Treiber, 1996). Finally, costs will always be a consideration.

Of note, several factors may contribute to the discrepant results obtained and the heterogeneity of the meta-analysis: (1) different demographic data (the baseline differences) in the studied populations; (2) study designs (the timing of drug dosing, the class of medicines, and improper choice of controls); (3) different levels of antibiotic resistance or transmission in

different regions; (4) small cohorts of patients. All above may jeopardize the comparison of results among these studies (Giannini *et al*., 2006).

We performed sensitivity analyses by excluding the protocol groups which had additional PPI or H2RA use for ulcer patients, considering that prolonged acid suppression might affect the eradication rate of *H. pylori* infection (Fischbach *et al*., 2002). There was a lower eradication rate (10% decrease) in the cohort without prolonged PPI use. More data are required to determine whether PPI use alone after eradication therapy will augment the treatment response or not. However, to differentiate the outcome, the best way is to calculate the eradication rate of *H. pylori* with peptic ulcer (PU) and non-ulcer dyspepsia (NUD), respectively. By excluding those trials with less than 40 cases in each group, which might undermine the overall results, the ITT and PP we recalculated were slightly higher than those in the total model.

This systematic review has several limitations. First, small-sized trials are insufficient. More results-based approaches are preferable and persuasive. Second, obtaining sustained cure rates is the optimal aim in *H. pylori* treatment, but few of included pilot studies had long-term follow-up. Third, the quality of the included trials was relatively poor, with only three of them having three Jadad scores, and none using double-blind methods. Three of 15 trials had clear and adequate allocation concealment. The use of concealed allocation should have limited patient selection bias in the current study (Li *et al*., 2008). Moreover, to predict the outcome of *H. pylori* eradication, the potential influencing factors should be analyzed jointly, which include characteristics of the population according to the geographical location, the prevalence of infection and microbial resistance, and the lead-time of reassessment. Baseline characteristics of the population among the different studies (concomitant symptoms, e.g., diameter of the ulcer, active or not, with or without bleeding; mean age; gender; body mass index; blood group; weather; drug use history; smoking and drinking habits; and antimicrobial susceptibility) (Zimmermann *et al*., 1992; Moshkowitz *et al*., 1994; Catalano *et al*., 1997; Misiewicz *et al*., 1997; Tucci *et al*., 1998; Ammon *et al*., 2000; Namiot *et al*., 2008) and test-and-treat strategies (the number of medications used, the dosage, frequency, duration of treatment) are also potential sources of treatment effect variation. Although logistic regression analysis demonstrated that patient's sex, age, smoking status, alcohol consumption, diagnosis (duodenal ulcer or gastritis), treatment with H2RA in the month before study entry, or the duration of the patient's disease had no significant effect on the eradication of *H. pylori* infection (Misiewicz *et al*., 1997; Wong *et al*., 2001b), when the set of drugs for *H. pylori* eradication is chosen, the above factors should all be taken into account. In addition, language barriers and resource restriction precluded review of all relevant literatures.

There were also some drawbacks in the included original trials. One of the flaws was that few studies (Wong *et al*., 2001a; 2001b) had focused on the impact of pre-treatment antimicrobial resistance on the outcome of the protocol, though high eradication rates were achieved even for metronidazole- or clarithromycin-resistant strains in some studies (Moshkowitz *et al*., 1994). It is preferable to prescribe antimicrobial agents according to the sensitivity status of the individual patient's *H. pylori*. The second flaw was that four out of nine studies (Pieramico *et al*., 1998; Trevisani *et al*., 1998; Isomoto *et al*., 2000; Wong *et al*., 2001a) did not assess the outcome of eradication therapy using the urea breath test (UBT), which is assumed to be the most sensitive modality (Ogura *et al*., 2001). The third flaw was that, although no bismuth compounds, antibiotics, PPI, and H2RA were given at least 4 weeks, 15 d or 7 d, respectively, before the study entry. It was unclear in some of the included studies whether the patients were *H. pylori* treatment-naive, which might have affected responses to the protocols (Moshkowitz *et al*., 1999). In addition, some sample sizes were too small to be persuasive (Wermeille *et al*., 1999; Huo *et al*., 2006). It was reported that randomization with an adequate number of subjects increases the likelihood that groups will have similar background risks (Fischbach *et al*., 2002). To have a power of 80% to detect a 20% difference in eradication rates, 40 cases would be required in each group (Scuderi *et al*., 2000). Finally, data on long-term follow-up were rare. If a higher frequency of re-infection is encountered in the long term, the primary scheme should seriously be questioned, and a more suitable approach with persistent *H. pylori* eradication is preferred. Some trials had

extremely low eradication rates with standard 7-d triple protocols (Wermeille *et al*., 1999; Zhang *et al*., 2006).

Putting the results of this meta-analysis into perspective, ultrashort (≤3 d) protocols are not sufficient to eradicate *H. pylori* infection. On the other hand, 4- to 6-d protocols are viable, and balance cure rate, adverse effects, compliance, and expenditure, though the efficacy needs to be improved. More data in this area are required.

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