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doi:10.3748/wjg.15.6102

World J Gastroenterol 2009 December 28; 15(48): 6102-6110
World Journal of Gastroenterology ISSN 1007-9327

BRIEF ARTICLE

Azithromycin-containing *versus* standard triple therapy for *Helicobacter pylori* eradication: A meta-analysis

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Received: July 19, 2009 Revised: September 1, 2009
Accepted: September 8, 2009
Published online: December 28, 2009

Key words: Azithromycin; *Helicobacter pylori*; Combination drug therapy; Adverse effects

Peer reviewers: Siegfried Wagner, Professor, Medical Clinic II, Klinikum Deggendorf, Perlasberger Str. 41, Deggendorf 94469, Germany; Özlem Yilmaz, PhD, Associate Professor of Microbiology, Department of Microbiology and Clinical Microbiology, Dokuz Eylul University, School of Medicine, Inciralti 35340, Izmir, Turkey

Dong J, Yu XF, Zou J. Azithromycin-containing *versus* standard triple therapy for *Helicobacter pylori* eradication: A meta-analysis. *World J Gastroenterol* 2009; 15(48): 6102-6110 Available from: URL: http://www.wjgnet.com/1007-9327/15/6102.asp DOI: http://dx.doi.org/10.3748/wjg.15.6102

Abstract

AIM: To evaluate whether adding azithromycin to first-line *Helicobacter pylori* (*H pylori*) eradication improved eradication and reduced side effects.

METHODS: Eligible articles were identified by searches of electronic databases. We included all randomized trials that compared azithromycin-containing with standard triple-therapy regimens for first-line treatment of *H pylori* infection. Statistical analysis was performed with Review Manager 5.0.10. Sub-analyses were also performed.

RESULTS: We identified 14 randomized trials (1431 patients). Pooled *H pylori* eradication rates were 72.01% (95% CI: 58.09%-85.93%) and 69.78% (95% CI: 66.47%-73.09%) for patients with or without azithromycin by intention-to-treat analysis, and the odds ratio (OR) was 1.17 (95% CI: 0.64-2.14). The occurrence of side effects differed significantly and was 15.81% (95% CI: 12.50%-19.12%) and 25.20% (95% CI: 21.44%-28.96%) for treatment with or without azithromycin, respectively, and the summary OR was 0.58 (95% CI: 0.41-0.82). Furthermore, the azithromycin-containing group had a lower occurrence of diarrhea, nausea and taste disturbance.

CONCLUSION: Our review suggests that azithromycin-containing triple-therapy regimens could be equally effective in eradication of *H pylori* compared with standard first-line triple-therapy regimens.

INTRODUCTION

Infection caused by *Helicobacter pylori* (*H pylori*), one of the most common pathogens worldwide, causes chronic gastritis and increases the risk of peptic ulcer and gastric cancer. Although some *H pylori*-positive individuals are asymptomatic, many experience symptoms such as dyspepsia. It is increasingly common to screen patients, even those with mild symptoms, for *H pylori* infection, and to treat them actively. The first-line treatment for *H pylori* infection, as recommended by the Maastricht III Consensus Report, is 7-d triple therapy that includes clarithromycin, amoxicillin and a proton-pump inhibitor (PPI)[1]. Even though this triple therapy is effective and its short duration helps maintain patient compliance, a considerable number of patients experience undesirable side effects.

In first-line therapy, eradication rates using combinations of PPI-based triple therapies range from 75% to 98%, with most of them near 80%[2]. This signifies that up to 20% of patients are expected to be treatment failures, a value which could be even higher in areas with a high prevalence of resistant *H pylori* strains. The recommended second-line therapy is a quadruple regimen composed of tetracycline, metronidazole, bismuth salts and a PPI; however, the efficacy of this regimen is limited by poor compliance, treatment duration, number and dose of the prescribed drugs, and bacterial antibiotic resistance.

Gastroenterologists and microbiologists continue the search for new therapies because of the increasing number of target subjects for *H pylori* and the physiological and pharmacoeconomic burden of a second course of therapy.

Among the new options against *H pylori* brought to light recently, azithromycin has attracted substantial interest. Azithromycin is a macrolide antibiotic that has been shown to reach high concentrations in gastric tissue after oral administration; furthermore, these high concentrations are maintained for several days, which make it potentially useful in the eradication of *H pylori*[3]. Clinical trials with triple therapy regimens that contain azithromycin have reported eradication rates of approximately 60%-80%, depending on the regimen and azithromycin dose used[4,5]. However, results from some other available trials utilizing azithromycin have yielded conflicting results. The primary aim of the present meta-analysis was to evaluate whether adding azithromycin to *H pylori* eradication regimens could improve eradication and reduce side effects.

MATERIALS AND METHODS

Selection of studies

Studies evaluating azithromycin-containing triple therapy for the eradication of *H pylori* were considered. For the meta-analysis, the selection criteria were as follows: (1) articles that reported comparative randomized controlled trials (RCTs); (2) studies had to include at least two branches of treatment that consisted of (a) triple first-line therapy (one PPI and two antibiotics) and (b) azithromycin-containing triple regimen; (3) study population consisted of subjects who had never been treated for *H pylori* infection previously; and (4) data for successful eradication and/or side effects were available.

Search strategy for identification of studies

Trials were identified by searching the Cochrane Controlled Trials Register (Issue 2, 2009), PubMed (1966 to May 2009), Embase (1980 to May 2009), Science Citation Index (1945 to May 2009) and the Chinese Biomedical Database (1981 to May 2009). A search strategy was constructed by using a combination of the following words: (*Helicobacter pylori* OR *H pylori*) AND (azithromycin). Articles published in any language were included. Reference lists from the trials selected by electronic searching were hand-searched to identify further relevant trials. We also conducted a manual search of abstracts from 1995 to May 2009 from the following congresses: International Workshop of the European Helicobacter Study Group, American Digestive Disease Week (DDW), and United European Gastroenterology Week (UEGW). Abstracts of the articles selected in each of these multiple searches were reviewed and those meeting the inclusion criteria were recorded. References of reviews on *H pylori* treatment with azithromycin, and from the articles selected for the study, were also examined for articles that met the inclusion criteria. Authors of some identified trials were asked whether they knew of additional studies, including unpublished randomized ones. In case of duplicate reports, or studies obviously reporting results from the same study population, only the latest published results were used.

Data extraction

Standardized data abstraction sheets were prepared.

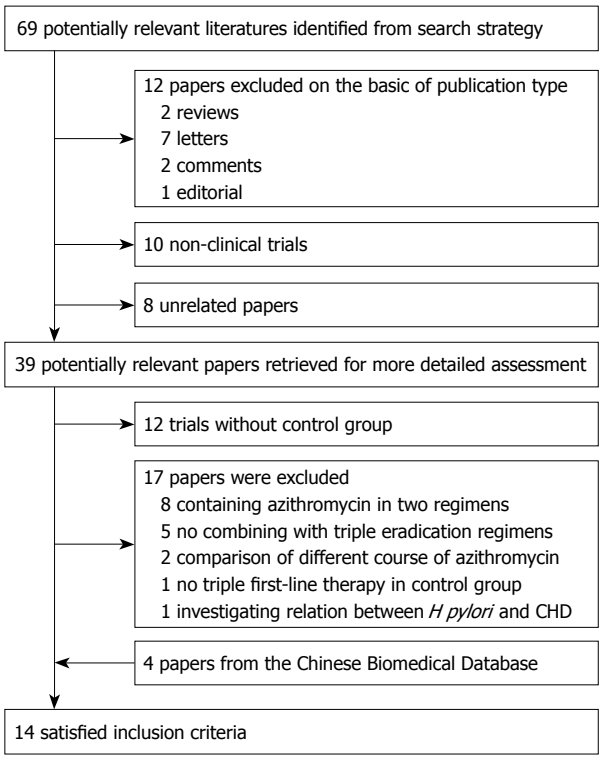


Figure 1 Flowchart of study selection. *H pylori*: *Helicobacter pylori*.

Data were exacted for study quality, dose and duration of azithromycin treatment, anti-*H pylori* regimens, and the number, sex and age of enrolled subjects, diagnostic methods of testing *H pylori* infection before enrolling and after completing the study, and scoring systems for assessing side effects. Key outcome data, such as eradication rates, occurrence of diarrhea, nausea, taste disturbance and abdominal pain were abstracted from all included studies. All articles were examined independently for eligibility by two reviewers. Disagreements were resolved by consulting a third reviewer. Quality was assessed using the Jadad score system based on three items, randomization, double blinding and description of withdrawals/dropouts. We considered that they were low quality when scores were < 3.

Data synthesis

Data were entered into the Cochrane Collaboration review manager programme RevMan 5.0.10 (released on May 16, 2008). The outcome measure examined was the OR of improving *H pylori* eradication rates and reducing side effects with azithromycin compared to without azithromycin-containing triple regimens. Categorical variables were compared with the χ^2 test, and $P < 0.05$ was considered statistically significant. Eradication rates and side effects were analyzed based on a fixed-effects model using the methods of Mantel-Haenszel[6], both by intention-to-treat and per-protocol. Heterogeneity between the studies was assessed by χ^2 test. Statistical significance of heterogeneity was set at 0.10. If significant heterogeneity existed, it would have been inappropriate to combine the data for further analysis using a fixed-effects model, while the random model was used for calculations.

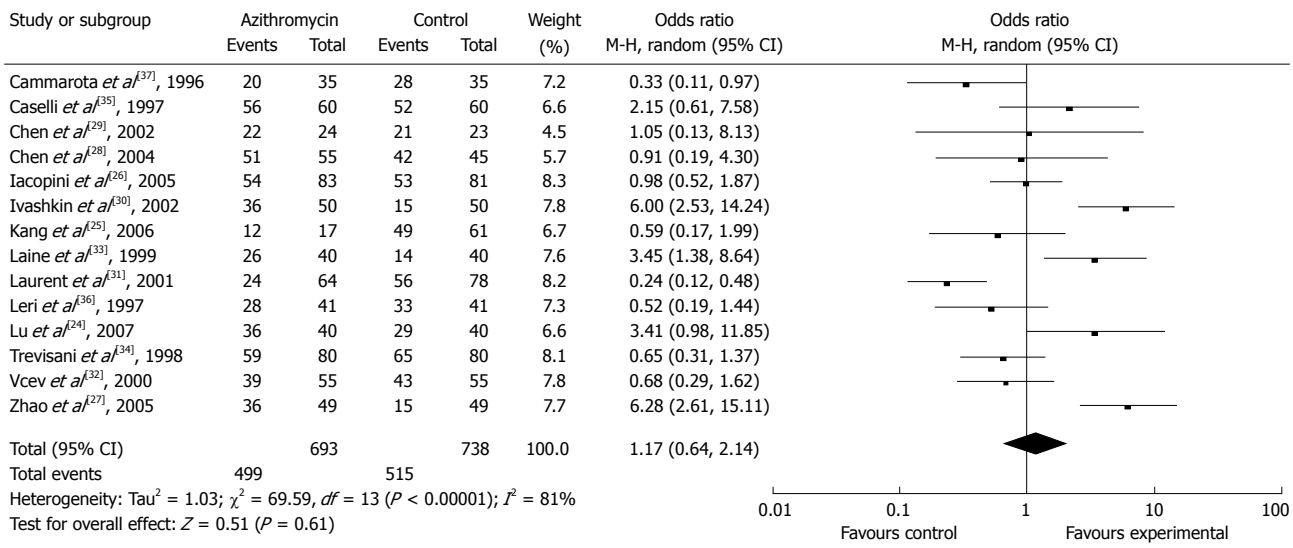


Figure 2 Effect of azithromycin-containing triple therapy *versus* standard triple therapy on eradication rates by intention-to-treat analysis.

Sub-analyses

In the meta-analysis, sub-analyses of *H pylori* eradication efficacy were planned, depending on: (1) the type of drugs co-prescribed with azithromycin (combination with amoxicillin and a PPI was the most widely prescribed); (2) the duration and dose of azithromycin therapy; (3) age of the subjects involved; and (4) quality of the studies (based on quality score proposed by Jadad, see appropriate section). Finally, we used funnel plot asymmetry to detect any publication bias in the meta-analysis, and Egger's regression test to measure funnel plot asymmetry.

RESULTS

Description of the studies

The bibliographical search yielded a total of 69 studies. Of these, 12 articles were excluded owing to publication type, i.e. two reviews, seven letters, two comments, and one editorial. We excluded 18 articles (10 non-clinical trials and eight unrelated articles) after examining the title and abstract, which left 39 potentially relevant articles for more detailed assessment. Of these potential eligible articles, 12 trials without a control group were excluded, and then we excluded another 17 articles, because of no combining with triple eradication regimens[7-11], containing azithromycin in two regimens[12-19], comparison of different treatment course of azithromycin[20,21], no triple first-line therapy in control group[22], and investigating relation between *H pylori* eradication and coronary heart disease[23]. Furthermore, we identified four additional articles from the Chinese Biomedical Database (1981 to May 2009). Finally, 14 RCTs met the inclusion criteria[24-37]. The flowchart of reviews showed the detailed process of selection (Figure 1). The characteristics of 14 trials included in the meta-analysis are summarized in Table 1, including quality score.

Eradication rates

Fourteen studies that described *H pylori* eradication rates were selected for the meta-analysis. Four of these reported significantly improved eradication rates, and the remaining 10 had similar efficacy for *H pylori* eradication. Pooled eradication rates were achieved in 499 of 693 patients with azithromycin supplementation (72.01%, 95% CI: 58.09%-85.93%) and in 515 of 738 patients with azithromycin without regimen (69.78%, 95% CI: 66.47%-73.09%) by intention-to-treat analysis, the OR was 1.17 (95% CI: 0.64-2.14) (Figure 2). Overall, per-protocol eradication rates were 75.81% (95% CI: 72.44%-79.18%) and 72.44% (95% CI: 69.05%-75.83%) for azithromycin supplementation and azithromycin without regimen, respectively (OR 1.22, 95% CI: 0.61-2.43).

Side effects

Total side effects were initially performed for meta-analysis. Data for the occurrence of side effects were obtained from 10 RCTs. Five of these studies reported a significant decrease in the occurrence of gastrointestinal side effects. The total number of side effects with azithromycin supplementation differed significantly from azithromycin without regimen: 15.81% (95% CI: 12.50%-19.12%) and 25.20% (95% CI: 21.44%-28.96%), and the summary OR was 0.58 (95% CI: 0.41-0.82) (Figure 3A). Individual symptoms during eradication therapy, such as nausea, diarrhea, abdominal pain, and taste disturbance were also analyzed. Incidence of diarrhea (2.13% *vs* 6.98%) (Figure 3B), nausea (3.85% *vs* 10.14%) (Figure 3C) and taste disturbance (3.17% *vs* 11.05%) (Figure 3D) were lower in the azithromycin supplementation group (OR: 0.33 *vs* 0.37 *vs* 0.28, 95% CI: 0.12-0.96 *vs* 0.14-0.96 *vs* 0.11-0.70).

Sub-analyses

Sub-analyses for the meta-analysis were planned depending on subject age, symptoms before enrollment, course of azithromycin, and choice of antibiotics. We divided all eligible trials into long- and short-course subgroups, Az+A subgroup, Az+Lev subgroup and Az+M/T subgroup. There was no significant difference between the long-course and short-course subgroups; the summary ORs were 0.89 (95% CI: 0.43-1.85) and 1.56 (95% CI:

Table 1 Characteristics of included studies comparing *Helicobacter pylori* (*H pylori*) eradication efficacy of azithromycin-containing triple therapy versus standard triple therapy

Authors	Country	Form	Trial design	Case No. (Az/con)	Patients	Diagnostic methods	Azithromycin regimen	% Eradication (*n*)	% Adverse effects (*n*)	Triple therapy	Days of antibiotics	% Eradication (*n*)	% Adverse effects (*n*)	Q
Lu *et al*[24], 2007	China	JA	Single centre RCT	85 (43/42)	*H pylori* positive	RUT/	O (20 mg *bid*)	ITT 84 (36/43)	26 (11/43)	O (20 mg *bid*)	7	ITT 69 (29/42)	19 (8/42)	3
					Chronic active gastritis	RUT (30 d later)	Lev (200 mg *bid*) Az (500 mg *o.d.*)	PP 90 (36/40)		A (1 g *bid*) C (500 mg *bid*)		PP 72.5 (29/40)		
Kang *et al*[25], 2006	Korea	JA	Single centre RCT	78 (17/61)	*H pylori* positive	Histology + RUT or UBT/	O (20 mg *bid*)	ITT 70.6 (12/17)	11.8 (2/17)	O (20 mg *bid*)	7	ITT 80.3 (49/61)	41.0 (25/61)	3
					Adults	Histology + RUT or UBT (8 wk later)	Lev (500 mg *o.d.*) Az (500 mg *o.d.*)	PP 70.6 (12/17)		A (1 g *bid*) C (500 mg *bid*)		PP 80.3 (49/61)		
Iacopini *et al*[26], 2005	Italy	JA	Single centre RCT	164 (83/81)	*H pylori* positive	Histology + UBT/	E (20 mg *o.d.*)	ITT 65 (54/83)	12 (9/77)	E (20 mg *bid*)	7	ITT 65 (53/81)	30 (22/70)	4
					Peptic ulcer and GERD adults	UBT + HpSA (8 wk later)	Lev (500 mg *o.d.*) Az (500 mg *o.d.*)	PP 70 (54/77)		A (1 g *bid*) C (500 mg *bid*)		PP 76 (53/70)		
Zhao *et al*[27], 2005	China	JA	Single centre RCT	98 (49/49)	*H pylori* positive	Histology + RUT/	O (20 mg *bid*)	ITT 73.5 (36/49)	/	O (20 mg *bid*)	7	ITT 30.6 (15/49)	/	3
					Active duodenal ulcer	RUT + Histology (4 wk later)	A (1 g *bid*) Az (1 g *o.d.*) 3 d	PP 76.6 (36/47)		A (1 g *bid*) M (500 mg *bid*)		PP 31.3 (15/48)		
Chen *et al*[28], 2004	China	JA	Single centre RCT	100 (55/45)	*H pylori* positive	Histology + UBT/	O (40 mg *o.d.*)	ITT 92.7 (51/55)	5 (3/55)	O (40 mg *o.d.*)	7	ITT 93.3 (42/45)	17.8 (8/45)	2
					Active duodenal ulcer	UBT (6 wk later)	A (1 g *bid*) Az (500 mg *o.d.*) 3 d	PP 92.7 (51/55)		A (1 g *bid*) C (500 mg *bid*)		PP 93.3 (42/45)		
Chen *et al*[29], 2002	China	JA	Single centre RCT	47 (24/23)	*H pylori* positive	Histology + RUT/	L (30 mg *o.d.*)	ITT 92 (22/24)	4 (1/24)	O (20 mg *bid*)	7	ITT 91 (21/23)	9 (2/23)	3
					Chronic gastritis adults	UBT (4 wk later)	M (400 mg *bid*) 3 d Az (500 mg *o.d.*) 3 d	PP 92 (22/24)		M (400 mg *bid*) C (500 mg *bid*)		PP 91 (21/23)		
Ivashkin *et al*[30], 2002	Russia	JA	Multicenter RCT	100 (50/50)	*H pylori* positive	Histology + RUT/	O (20 mg *bid*)	ITT 72 (36/50)	/	O (20 mg *bid*)	7	ITT 30 (15/50)	/	4
					Active duodenal Ulcer adults	Histology + RUT (8 wk later)	A (1 g *bid*) Az (1 g *o.d.*) 3 d	PP 75 (36/48)		A (1 g *bid*) M (500 mg *bid*)		PP 31 (15/49)		
Laurent *et al*[31], 2001	France	JA	Multicenter RCT	247 (64/78/70)	*H pylori* positive	Histology + RUT/	O (20 mg *bid*)	ITT 37.5 (24/64)	56.9 (33/58)	O (20 mg *bid*)	7	ITT 71.8/61.4 (56/78) (43/70)	57.7/66.1 (41/71) (41/62)	4
					Non-ulcer dyspepsia	UBT (4-6 wk later)	A (1 g *bid*) Az (500 mg *o.d.*) day 1 + (250 mg *o.d.*) days 2-5	PP 41.4 (24/58)		C (500 mg *bid*)/ C (250 mg *bid*) A (1 g *bid*)/ M (500 mg *bid*)		PP 78.9/69.4 (56/71) (43/62)		
Vcev *et al*[32], 2000	Croatia	JA	Single centre RCT	110 (55/55)	*H pylori* positive	Histology + RUT/	P (40 mg *bid*)	ITT 71 (39/55)	14 (7/50)	P (40 mg *bid*)	7	ITT 78 (43/55)	17 (9/53)	3
					Active duodenal ulcer	Histology + RUT (8 wk later)	A (1 g *bid*) Az (500 mg *o.d.*) 6 d	PP 78 (39/50)		A (1 g *bid*) C (500 mg *bid*)		PP 81 (43/53)		
Laine *et al*[33], 1999	USA	JA	Single centre RCT	120 (40/40/40)	*H pylori* positive	Histology or serology + UBT/	O (80 mg *o.d.*)	ITT 65 (26/40)	3 (1/38)	O (80 mg *o.d.*)	10	ITT 35/78 (14/40) (31/40)	8/15 (3/37) (5/33)	3
					Symptomatic and	UBT (6 wk later)	M (750 mg *o.d.*)	PP 66 (25/38)		M (750 mg *o.d.*)		PP 35/79 (13/37) (26/33)		

Trevisani *et al*[34], 1998	Italy	JA	Single centre RCT	160 (80/80)	Asymptomatic adults *H pylori* positive	RUT + Histology/ (4 wk later)	Az (500 mg *o.d.*) 7 d L (30 mg *bid*) days 1-4	ITT 73.3 (59/80)	1.3 (1/73)	A (1.5 g *o.d.*)/C (1 g *o.d.*) O (20 mg *o.d.*)	7	ITT 81.2 (65/80)	2.6 (2/76)	4
					Symptomatic adults	RUT + Histology (4 wk later)	T (2000 mg *o.d.*) day 3 Az (500 mg *o.d.*) days 2-4	PP 80.8 (59/73)		C (250 mg *bid*) T (500 mg *bid*)		PP 85.5 (65/76)		
Caselli *et al*[35], 1997	Italy	JA	Multicenter RCT	120 (60/60)	*H pylori* positive Gastritis with or without peptic ulcer	Histology + RUT/ Histology (7-8 wk later)	L (30 mg *o.d.*) M (250 mg *bid*) 3 d Az (500 mg *o.d.*) 3 d	ITT 93.3 (56/60) PP 93.3 (56/60)	/	O (20 mg *o.d.*) C (250 mg *bid*) T (500 mg *bid*)	7	ITT 86.7 (52/60) PP 91.2 (52/57)	/	3
Leri *et al*[36], 1997	Italy	Ab	Single centre RCT	123 (41/41/41)	*H pylori* positive	Histology + RUT	O (20 mg *bid*) M (500 mg *bid*) 10 d Az (500 mg *o.d.*) 6 d	ITT 68 (28/41)	/	O (20 mg *bid*) M (500 mg *bid*) 10 d A (1 g *bid*) / C (500 mg *t.d.*)	14	ITT 80/97 (33/41) (40/41)	/	2
Cammarota *et al*[37], 1996	Italy	JA	Single centre RCT	70 (35/35)	*H pylori* positive Symptomatic adults	Histology + RUT/ Histology + RUT (8 wk later)	L (30 mg *o.d.*) A (1 g *bid*) Az (500 mg *o.d.*) 3 d	ITT 57 (20/35) PP 61 (20/33)	18 (6/33)	L (30 mg *o.d.*) A (1 g *bid*) C (250 mg *bid*)	7	ITT 80 (28/35) PP 82 (28/34)	26 (9/34)	3

Ab: Abstract; JA: Journal article; C: Clarithromycin; A: Amoxicillin; Az: Azithromycin; M: Metronidazole; T: Tinidazole; Lev: Levofloxacin; E: Esomeprazole; P: Pantorazole; O: Omeprazole; L: Lanzoprazole; UBT: 13C-urea breath test; RUT: Rapid urease test; HpSA: *H pylori* stool antigen; Q: quality score; RCT: Randomized controlled trial; ITT: Intent-to-treat analysis; PP: Per-protocol analysis.

0.60-4.08), respectively (Figure 4A). For antibiotics sub-analysis, Az+A subgroup, Az+Lev subgroup and Az+M/T subgroup all had no significant difference; the summary ORs were 1.11 (95% CI: 0.32-3.89), 1.19 (95% CI: 0.51-2.81) and 1.20 (95% CI: 0.53-2.69), respectively (Figure 4B).

Publication bias

We found that the funnel plot had a slightly asymmetrical distribution, but Egger's regression test[38] suggested no significant asymmetry of the funnel plot ($P = 0.84$), which indicated no evidence of substantial publication bias.

DISCUSSION

For *H pylori* eradication therapy, clinical trails are undertaken to search for simpler but equally or more effective regimens. The modern macrolides are a focus of attention from that point of view. Azithromycin, a new-generation macrolide, has some special attributes that make it a promising compound in regimens for *H pylori* eradication. Following the administration of a single oral dose, azithromycin readily accumulates in the human gastric mucosa, subsequently redistributes from mucosal tissue to the mucus layer, and from the mucus to gastric juice. There, it reaches gastric tissue concentrations that persist above the minimal concentration for 90% inhibition (MIC_{90}) for *H pylori* (0.25 μg/mL) over a 5-d period, thus leading to exposure of the microorganism to consistent amounts of this drug. The high tissue affinity and the absorption of the drug after oral administration are reduced when given during or after a meal. The pharmacological properties of azithromycin make it possible to use shorter courses, therefore, the problem was to define an optimal dose and duration of azithromycin in triple therapy.

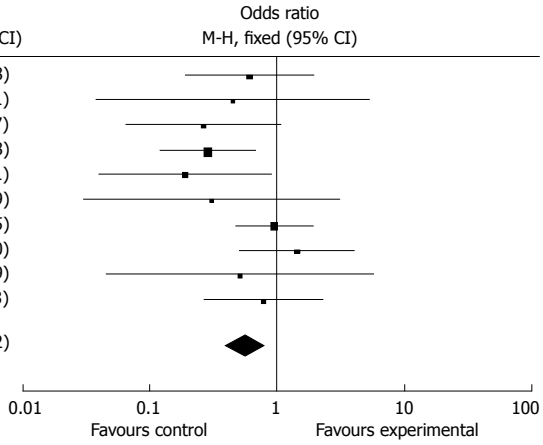
Azithromycin is able to reach high gastric concentrations that persist for several days, and therefore, it can be administered at a dose of 500 mg once daily for only 3 d during a 7-d triple eradication regimen. The published trials that have used this antibiotic have yielded conflicting results, and have reported a wide range of eradication rates. Administration with meals markedly reduces azithromycin absorption, therefore, this might account for the low eradication rates observed in some studies[21]. In treatment regimens in which azithromycin was given to fasting patients, the cure rate was in the range 86%-93%[13,37]. Recently, short-term treatments of only 3 d, using a PPI plus azithromycin 500 mg and tinidazole 1000-2000 mg daily, have been found to promote eradication in 81%-88% of cases[23,39]. In contrast with the results reported in early studies that have used azithromycin for 2 wk and in repeated daily doses[40], side effects are scarce if the drug is administered once daily for a few days. In subanalyses, we also found that *H pylori* eradication rate had no significant difference between the long-course and short course subgroups.

H pylori eradication depends on a number of factors, including patient compliance, side effects, bacterial resistance, poor drug distribution or concentration, geographic differences, and socio-economic conditions. Optimization of *H pylori* eradication therapy remains an

A

Study or subgroup	Azithromycin Events	Total	Control Events	Total	Weight (%)	Odds ratio M-H, fixed (95% CI)
Cammarota *et al*[37], 1996	6	33	9	34	8.9	0.62 (0.19, 1.98)
Chen *et al*[29], 2002	1	24	2	23	2.4	0.46 (0.04, 5.41)
Chen *et al*[28], 2004	3	55	8	45	10.2	0.27 (0.07, 1.07)
Iacopini *et al*[26], 2005	9	77	22	70	24.9	0.29 (0.12, 0.68)
Kang *et al*[25], 2006	2	17	25	61	11.8	0.19 (0.04, 0.91)
Laine *et al*[33], 1999	1	38	3	37	3.6	0.31 (0.03, 3.09)
Laurent *et al*[31], 2001	33	58	41	71	19.4	0.97 (0.48, 1.95)
Lu *et al*[24], 2007	11	43	8	42	7.4	1.46 (0.52, 4.10)
Trevisani *et al*[34], 1998	1	73	2	76	2.4	0.51 (0.05, 5.79)
Vcev *et al*[32], 2000	7	50	9	53	9.2	0.80 (0.27, 2.33)
Total (95% CI)		468		512	100.0	0.58 (0.41, 0.82)
Total events	74		129			

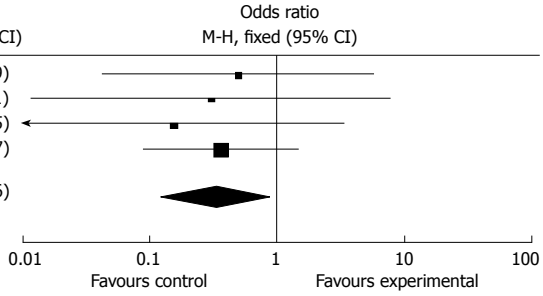
Heterogeneity: χ^2 = 11.46, *df* = 9 (*P* = 0.25); I^2 = 21%
Test for overall effect: *Z* = 3.02 (*P* = 0.002)



B

Study or subgroup	Azithromycin Events	Total	Control Events	Total	Weight (%)	Odds ratio M-H, fixed (95% CI)
Cammarota *et al*[37], 1996	1	33	2	34	14.5	0.50 (0.04, 5.79)
Chen *et al*[29], 2002	0	24	1	23	11.4	0.31 (0.01, 7.91)
Chen *et al*[28], 2004	0	55	2	45	20.6	0.16 (0.01, 3.35)
Iacopini *et al*[26], 2005	3	77	7	70	53.5	0.36 (0.09, 1.47)
Total (95% CI)		189		172	100.0	0.33 (0.12, 0.96)
Total events	4		12			

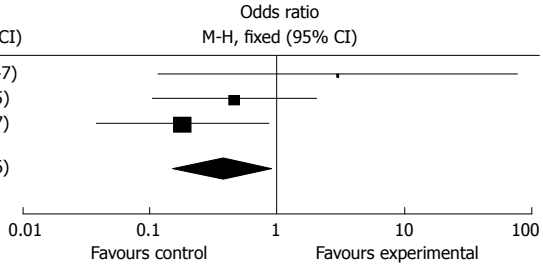
Heterogeneity: χ^2 = 0.36, *df* = 3 (*P* = 0.95); I^2 = 0%
Test for overall effect: *Z* = 2.03 (*P* = 0.04)



C

Study or subgroup	Azithromycin Events	Total	Control Events	Total	Weight (%)	Odds ratio M-H, fixed (95% CI)
Chen *et al*[29], 2002	1	24	0	23	3.2	3.00 (0.12, 77.47)
Chen *et al*[28], 2004	3	55	5	45	35.0	0.46 (0.10, 2.05)
Iacopini *et al*[26], 2005	2	77	9	70	61.8	0.18 (0.04, 0.87)
Total (95% CI)		156		138	100.0	0.37 (0.14, 0.96)
Total events	6		14			

Heterogeneity: χ^2 = 2.48, *df* = 2 (*P* = 0.29); I^2 = 19%
Test for overall effect: *Z* = 2.05 (*P* = 0.04)



D

Study or subgroup	Azithromycin Events	Total	Control Events	Total	Weight (%)	Odds ratio M-H, fixed (95% CI)
Cammarota *et al*[37], 1996	1	33	5	34	24.8	0.18 (0.02, 1.64)
Chen *et al*[29], 2002	1	24	2	23	10.1	0.46 (0.04, 5.41)
Chen *et al*[28], 2004	0	55	1	45	8.5	0.27 (0.01, 6.72)
Iacopini *et al*[26], 2005	4	77	11	70	56.6	0.29 (0.09, 0.97)
Total (95% CI)		189		172	100.0	0.28 (0.11, 0.70)
Total events	6		19			

Heterogeneity: χ^2 = 0.31, *df* = 3 (*P* = 0.96); I^2 = 0%
Test for overall effect: *Z* = 2.71 (*P* = 0.007)

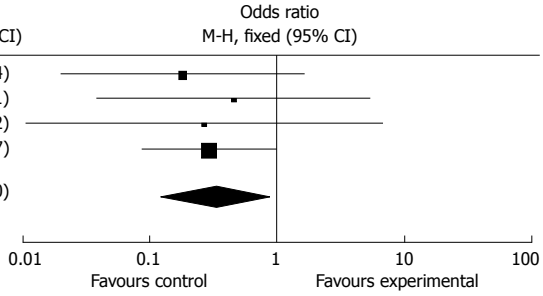
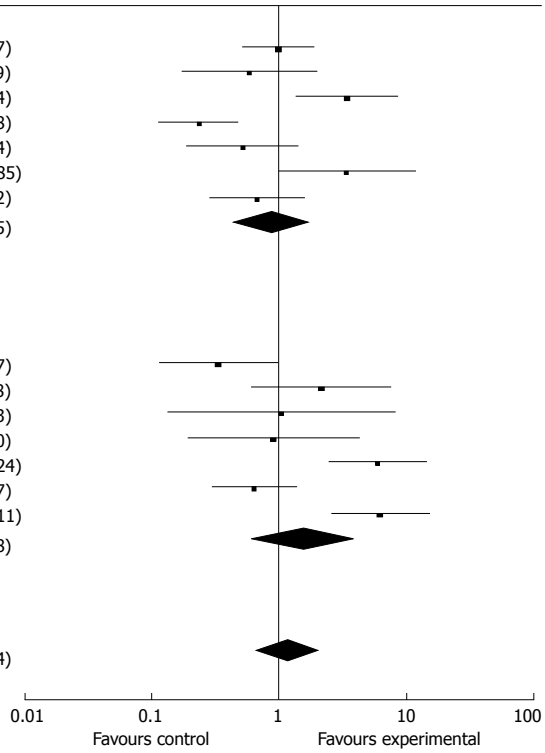


Figure 3 Effect of azithromycin-containing triple therapy *versus* standard triple therapy on the incidence of total side effects (A), diarrhea (B), nausea (C), and taste disturbance (D).

ongoing challenge worldwide. Although a great deal of research has focused on treatment of *H pylori* since the discovery of its crucial role in gastrointestinal disease, currently up to 25% of patients enrolled in clinical trials are treatment failures, even using the widely accepted and efficacious regimens that have gained inclusion in consensus guidelines[41]. A disappointing cure rate of < 80% after 7-d triple therapy was confirmed in the present study. Guidelines often suggest that an acceptable success rate for a particular therapy against *H pylori* infection should be > 80% on an intention-to-treat basis. However, clinical trials with azithromycin have displayed considerable variation with respect to the regimens used and the results obtained. Eradication rates varying between 93% and 22% have been reported[20,30,42]. The results of our meta-analysis demonstrated pooled

A

Study or subgroup	Azithromycin Events	Total	Control Events	Total	Weight (%)	Odds ratio M-H, random (95% CI)
3.1.1 Eradication rate-long						
Iacopini *et al*[26], 2005	54	83	53	81	8.3	0.98 (0.52, 1.87)
Kang *et al*[25], 2006	12	17	49	61	6.7	0.59 (0.17, 1.99)
Laine *et al*[33], 1999	26	40	14	40	7.6	3.45 (1.38, 8.64)
Laurent *et al*[31], 2001	24	64	56	78	8.2	0.24 (0.12, 0.48)
Leri *et al*[36], 1997	28	41	33	41	7.3	0.52 (0.19, 1.44)
Lu *et al*[24], 2007	36	40	29	40	6.6	3.41 (0.98, 11.85)
Vcev *et al*[32], 2000	39	55	43	55	7.8	0.68 (0.29, 1.62)
Subtotal (95% CI)		340		396	52.5	0.89 (0.43, 1.85)
Total events	219		277			
Heterogeneity: Tau^2 = 0.75; χ^2 = 27.89, *df* = 6 (*P* < 0.0001); I^2 = 78%						
Test for overall effect: *Z* = 0.31 (*P* = 0.75)						
3.1.2 Eradication rate-short						
Cammarota *et al*[37], 1996	20	35	28	35	7.2	0.33 (0.11, 0.97)
Caselli *et al*[35], 1997	56	60	52	60	6.6	2.15 (0.61, 7.58)
Chen *et al*[29], 2002	22	24	21	23	4.5	1.05 (0.13, 8.13)
Chen *et al*[28], 2004	51	55	42	45	5.7	0.91 (0.19, 4.30)
Ivashkin *et al*[30], 2002	36	50	15	50	7.8	6.00 (2.53, 14.24)
Trevisani *et al*[34], 1998	59	80	65	80	8.1	0.65 (0.31, 1.37)
Zhao *et al*[27], 2005	36	49	15	49	7.7	6.28 (2.61, 15.11)
Subtotal (95% CI)		353		342	47.5	1.56 (0.60, 4.08)
Total events	280		238			
Heterogeneity: Tau^2 = 1.31; χ^2 = 32.98, *df* = 6 (*P* < 0.0001); I^2 = 82%						
Test for overall effect: *Z* = 0.90 (*P* = 0.37)						
Total (95% CI)		693		738	100.0	1.17 (0.64, 2.14)
Total events	499		515			
Heterogeneity: Tau^2 = 1.03; χ^2 = 69.59, *df* = 13 (*P* < 0.00001); I^2 = 81%						
Test for overall effect: *Z* = 0.51 (*P* = 0.61)						
Test for subgroup differences: Not applicable						



B

Study or subgroup	Azithromycin Events	Total	Control Events	Total	Weight (%)	Odds ratio M-H, random (95% CI)
5.1.1 Eradication rate-A						
Cammarota *et al*[37], 1996	20	35	28	35	7.2	0.33 (0.11, 0.97)
Chen *et al*[28], 2004	51	55	42	45	5.7	0.91 (0.19, 4.30)
Ivashkin *et al*[30], 2002	36	50	15	50	7.8	6.00 (2.53, 14.24)
Laurent *et al*[31], 2001	24	64	56	78	8.2	0.24 (0.12, 0.48)
Vcev *et al*[32], 2000	39	55	43	55	7.8	0.68 (0.29, 1.62)
Zhao *et al*[27], 2005	36	49	15	49	7.7	6.28 (2.61, 15.11)
Subtotal (95% CI)		308		312	44.3	1.11 (0.32, 3.89)
Total events	206		199			
Heterogeneity: Tau^2 = 2.18; χ^2 = 54.20, *df* = 5 (*P* < 0.00001); I^2 = 91%						
Test for overall effect: *Z* = 0.17 (*P* = 0.87)						
5.1.2 Eradication rate-Lev						
Iacopini *et al*[26], 2005	54	83	53	81	8.3	0.98 (0.52, 1.87)
Kang *et al*[25], 2006	12	17	49	61	6.7	0.59 (0.17, 1.99)
Lu *et al*[24], 2007	36	40	29	40	6.6	3.41 (0.98, 11.85)
Subtotal (95% CI)		140		182	21.7	1.19 (0.51, 2.81)
Total events	102		131			
Heterogeneity: Tau^2 = 0.31; χ^2 = 4.32, *df* = 2 (*P* = 0.12); I^2 = 54%						
Test for overall effect: *Z* = 0.40 (*P* = 0.69)						
5.1.3 Eradication rate-M or T						
Caselli *et al*[35], 1997	56	60	52	60	6.6	2.15 (0.61, 7.58)
Chen *et al*[29], 2002	22	24	21	23	4.5	1.05 (0.13, 8.13)
Laine *et al*[33], 1999	26	40	14	40	7.6	3.45 (1.38, 8.64)
Leri *et al*[36], 1997	28	41	33	41	7.3	0.52 (0.19, 1.44)
Trevisani *et al*[34], 1998	59	80	65	80	8.1	0.65 (0.31, 1.37)
Subtotal (95% CI)		245		244	34.0	1.20 (0.53, 2.69)
Total events	191		185			
Heterogeneity: Tau^2 = 0.51; χ^2 = 11.01, *df* = 4 (*P* = 0.03); I^2 = 64%						
Test for overall effect: *Z* = 0.44 (*P* = 0.66)						
Total (95% CI)		693		738	100.0	1.17 (0.64, 2.14)
Total events	499		515			
Heterogeneity: Tau^2 = 1.03; χ^2 = 69.59, *df* = 13 (*P* < 0.00001); I^2 = 81%						
Test for overall effect: *Z* = 0.51 (*P* = 0.61)						
Test for subgroup differences: Not applicable						

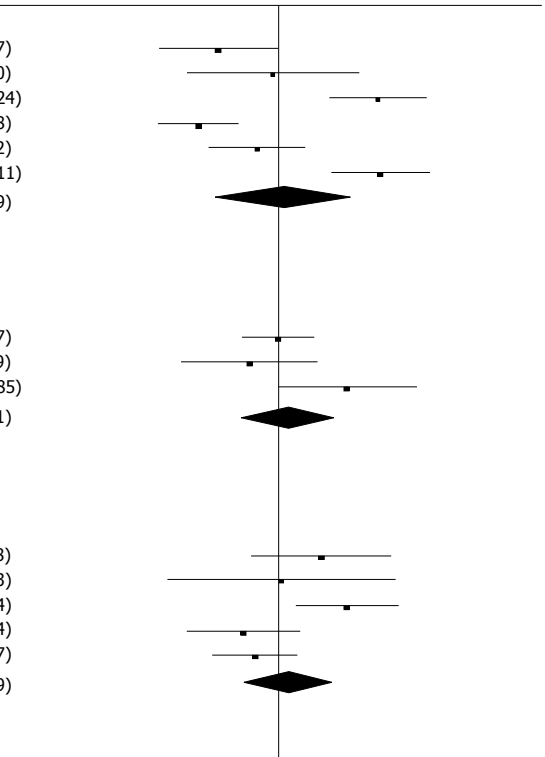


Figure 4 Meta-analysis of eradication rates by treatment course (A) and different antibiotics (B).

H pylori eradication rates were 72.01% and 69.78% for patients with or without azithromycin by intention-to-treat analysis, respectively, and no significant difference was observed between the two regimens.

H pylori has cross resistance to macrolides; e.g. a strain that is resistant to clarithromycin is resistant to every other macrolide. The level of clarithromycin resistance is unfortunately showing a tendency to increase. The effect of drug synergism is of great value in combination treatment to heal *H pylori* infection. Lepper *et al*[43] have demonstrated an *in vitro* synergistic effect of azithromycin and the PPI lansoprazole. They have speculated that this effect might enhance eradication rates even with macrolide-resistant *H pylori* strains, because of the unique pharmacological properties of the combination. Azithromycin could provide a potent anti-*H pylori* effect and could simplify the bulky triple therapy.

Antibiotic-associated gastrointestinal side effects such as diarrhea, nausea, vomiting, bloating and abdominal pain represent a serious drawback of anti-*H pylori* therapy, although they are mild in most cases, but usually result in non-compliance. The quadruple regimen is associated with a relatively high incidence of side effects. In contrast, azithromycin is generally well tolerated, and most side effects associated with its use are mild to moderate in severity and transient. In our systematic review, we found that the total number of side effects with azithromycin supplementation was significantly lower than with azithromycin without regimen: 15.81% *vs* 25.20%; the summary OR was 0.58 (95% CI: 0.41-0.82). Moreover, the incidence of diarrhea (2.13% *vs* 6.98%), nausea (3.85% *vs* 10.14%) and taste disturbance (3.17% *vs* 11.05%) were lower in the azithromycin supplementation group. Our results showed that azithromycin had a positive impact on some *H pylori* therapy-related side effects. Several methodological weaknesses may limit the validity and generalizability of our meta-analysis. For example, there were no studies involving patients from Africa and South America.

In summary, the conclusion of this systematic review and meta-analysis is that, for first-time treatment, azithromycin-containing triple therapy has equal efficacy to that of standard triple eradication therapy. A combination of azithromycin, amoxicillin and a PPI constitutes an encouraging empirical first-line strategy. Furthermore, azithromycin-containing triple therapy showed a lower occurrence of drug-related side effects.

COMMENTS

Background

Colonization with *Helicobacter pylori* (*H pylori*) causes a wide range of upper gastrointestinal disorders in humans. Unfortunately, eradication therapy is not always successful, and can even induce several side effects. Azithromycin has some special attributes that make it a promising compound in the regimens for *H pylori* eradication.

Research frontiers

In first-line therapy, *H pylori* eradication rates using proton-pump inhibitor (PPI)-based triple therapy are about 80%. This signifies that up to 20% of patients are expected to be treatment failures and it could be even higher in areas with a high prevalence of resistant *H pylori* strains. In this study, the authors demonstrated that, for first-time treatment, azithromycin-containing triple therapy has equal efficacy to standard triple eradication therapy.

Innovations and breakthroughs

Recent studies have shown that azithromycin is a promising compound in regimens for *H pylori* eradication. Our meta-analysis demonstrated that azithromycin-containing triple therapy has equal efficacy to standard triple eradication therapy, and has a lower occurrence of side effects. A combination of azithromycin, amoxycillin and a PPI constitutes an encouraging empirical first-line strategy.

Applications

By understanding the effect of azithromycin in *H pylori* eradication, this study represents a new encouraging strategy for first-time treatment, and it could decrease the physiological and pharmacoeconomic burden of second courses of therapy.

Terminology

Azithromycin is a new-generation macrolide and has some special attributes. It is able to reach high gastric concentrations that persist for several days, and therefore may be administered at a dose of 500 mg once daily for only 3 d during 7-d triple eradication therapy.

Peer review

The authors performed a meta-analysis and demonstrated that azithromycin-containing triple therapy has equal efficacy to standard triple *H pylori* eradication therapy. This was an original and good study.

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